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(54)名稱

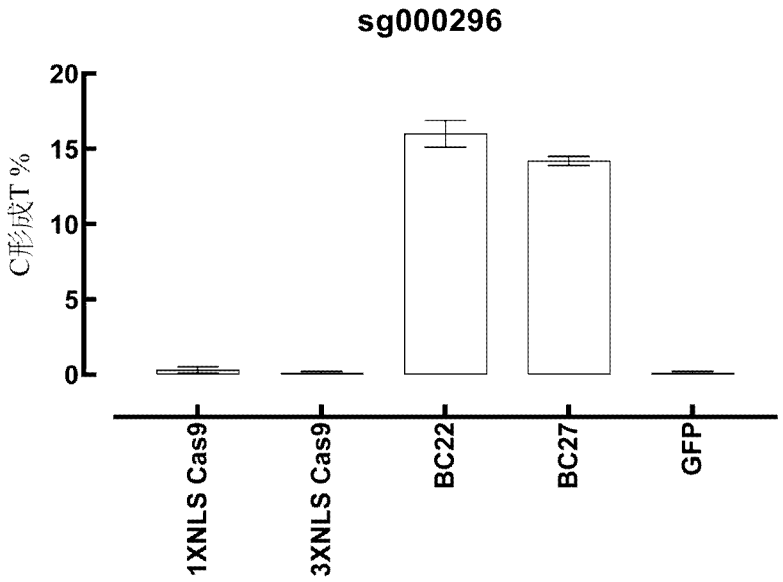
用於涉及去胺作用之基因體編輯之多核苷酸、組合物及方法

(57)摘要

本發明提供用於利用去胺作用之基因體編輯之多核苷酸、多肽、組合物及方法。本文提供一種含有編碼多肽之開讀框(ORF)之 mRNA。該多肽包括胞苷去胺酶及 RNA 導引之切口酶，且不包括尿嘧啶醣苷酶抑制劑(UGI)。本文所提供之組合物可包括兩種不同的 mRNA。第一 mRNA 包括編碼胞苷去胺酶及 RNA 導引之切口酶之 ORF，且第二 mRNA 包括編碼尿嘧啶醣苷酶抑制劑(UGI)之 ORF。

Polynucleotides, polypeptides, compositions, and methods for genome editing using deamination are provided. An mRNA containing an open reading frame (ORF) encoding a polypeptide is provided herein. The polypeptide includes a cytidine deaminase and an RNA-guided nickase, and does not include a uracil glycosylase inhibitor (UGI). A composition provided herein may include two different mRNAs. The first mRNA includes an ORF encoding a cytidine deaminase and an RNA-guided nickase, and the second mRNA includes an ORF encoding uracil glycosylase inhibitor (UGI).

指定代表圖：



【圖1A】

【發明摘要】

【中文發明名稱】

用於涉及去胺作用之基因體編輯之多核苷酸、組合物及方法

【英文發明名稱】

POLYNUCLEOTIDES, COMPOSITIONS, AND METHODS FOR GENOME EDITING INVOLVING DEAMINATION

【中文】

本發明提供用於利用去胺作用之基因體編輯之多核苷酸、多肽、組合物及方法。本文提供一種含有編碼多肽之開讀框(ORF)之mRNA。該多肽包括胞苷去胺酶及RNA導引之切口酶，且不包括尿嘧啶醣苷酶抑制劑(UGI)。本文所提供之組合物可包括兩種不同的mRNA。第一mRNA包括編碼胞苷去胺酶及RNA導引之切口酶之ORF，且第二mRNA包括編碼尿嘧啶醣苷酶抑制劑(UGI)之ORF。

【英文】

Polynucleotides, polypeptides, compositions, and methods for genome editing using deamination are provided. An mRNA containing an open reading frame (ORF) encoding a polypeptide is provided herein. The polypeptide includes a cytidine deaminase and an RNA-guided nickase, and does not include a uracil glycosylase inhibitor (UGI). A composition provided herein may include two different mRNAs. The first mRNA includes an ORF encoding a cytidine deaminase and an RNA-guided nickase, and the second mRNA includes an ORF encoding uracil glycosylase inhibitor (UGI).

【指定代表圖】

圖1A

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

用於涉及去胺作用之基因體編輯之多核苷酸、組合物及方法

【英文發明名稱】

POLYNUCLEOTIDES, COMPOSITIONS, AND METHODS FOR GENOME EDITING INVOLVING DEAMINATION

【技術領域】

【0001】 本發明係關於用於涉及去胺作用之基因體編輯之多核苷酸、組合物及方法。

【先前技術】

【發明內容】

【0002】 鹼基編輯為一種基因體編輯方法，其直接在基因體DNA之特定區內產生點突變而不引起雙股斷裂(double-stranded break；DSB)。DNA鹼基編輯器(editor；BE)包含催化受損Cas核酸酶與鹼基修飾酶之間的融合物。當前，胞苷形成胸苷(C形成T)編輯之效應子將胞苷去胺酶與切口酶及尿嘧啶醣苷酶抑制劑(UGI)融合。舉例而言，鹼基編輯器3 (BE3)由帶有突變之Cas9核酸酶組成，該突變將其轉化為融合至APOBEC1 (脂蛋白元mRNA編輯酶、催化多肽1)去胺酶及UGI之切口酶(nCas9) (例如，Wang等人，Cell Research 27:1289-1292 (2017))，且據報道，「nCas9融合UGI域對於實現鹼基編輯之高保真度仍十分重要，即使在存在高水平之自由UGI之情況下」。作為另一實例，已探究工程改造之人類APOBEC3A (A3A或脂蛋白元mRNA編輯酶、催化多肽3A)去胺酶替換原始BE3中之大鼠APOBEC1去胺酶(RAPO1) (Gehrke等人,Nature

Biotechnology，36: 977-982 (2018))，但應注意，鹼基編輯器「編輯其編輯視窗內之所有C之能力可潛在地具有不利影響」，且「在鹼基編輯器之背景下，人類A3A去胺酶中N57殘基之突變對於恢復其原生目標序列精確度且亦對降低其脫靶編輯活性極為關鍵」。實際上，APOBEC3A 2類Cas切口酶(D10A)鹼基編輯器已報導為：具有「較高程度之致突變性」，且展示Cas9獨立的脫靶鹼基編輯(Doman等人,Nature Biotechnology 38:620-628 (2020))。因此，需要用於使用胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶進行靶向C形成T鹼基編輯之改良組合物及方法。

【0003】 因此，本發明提供用於基因體編輯之多核苷酸、組合物及方法，該基因體編輯涉及在目標核苷酸處以較高保真度誘導C形成T轉化且可最小化旁觀者突變之胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶。本發明部分地基於以下發現：藉由將胞苷去胺酶(例如，APOBEC去胺酶)及RNA導引之切口酶系統與UGI以反式配對(例如，作為單獨mRNA)，有可能降低其他鹼基編輯(C形成A/G轉化、插入或缺失)之量且提高C形成T編輯之純度。

【0004】 因此，提供以下實施例。

【0005】 在一些實施例中，提供一種組合物，該組合物包含：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框，及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA。在一些實施例中，第一開讀框不包含編碼UGI之序列。在一些實施例中，組合物包含第一組合物及第二組合物，其中第一組合物包含含有編碼包含胞苷去胺酶及RNA導引之切口酶且不包含尿嘧啶醣苷酶抑制劑(UGI)之多肽的第一開讀框之第一

mRNA，且第二組合物包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中第二mRNA不同於第一mRNA。在一些實施例中，組合物包含脂質奈米粒子。

【0006】 在一些實施例中，提供一種修飾目標基因之方法，方法包含向細胞遞送：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之第一多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA；及至少一種導引RNA (gRNA)。

【0007】 在一些實施例中，提供一種修飾細胞中之目標基因內之至少一個胞苷的方法，方法包含在細胞中表現或使該細胞與以下接觸：(i)包含胞苷去胺酶及RNA導引之切口酶之第一多肽，其中第一多肽不包含尿嘧啶醣苷酶抑制劑(UGI)；(ii) UGI多肽；及(iii)至少一種導引RNA (gRNA)，其中第一多肽及gRNA與目標基因形成複合物其修飾目標基因中之至少一個胞苷。在一些實施例中，UGI多肽與第一多肽之比為10:1至50:1。

【0008】 在一些實施例中，提供一種含有編碼多肽之開讀框(open reading frame；ORF)之mRNA，該多肽包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶，其中多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。亦提供由mRNA編碼之多肽。在一些實施例中，提供一種修飾目標基因之方法，方法包含向細胞遞送本文中所描述之mRNA或多肽。

【0009】 在一些實施例中，組合物包含兩種不同mRNA，其中第一mRNA包含編碼胞苷去胺酶(例如，A3A)及RNA導引之切口酶之ORF，且

第二mRNA包含編碼尿嘧啶醣苷酶抑制劑(UGI)之ORF。在一些實施例中，組合物中之第一mRNA不包含編碼UGI之ORF。在一些實施例中，第二mRNA與第一mRNA之莫耳比為自1:1至30:1、自2:1至30:1、自7:1至22:1。在一些實施例中，第二mRNA與第一mRNA之莫耳比為22:1、7:1、2:1或1:1、1:4、1:11或1:33。

【0010】 通篇在申請專利範圍及圖式中提供且描述其他實施例。

【圖式簡單說明】

【0011】 圖1A至圖1E分別展示針對5個不同導引靶向序列剖析之C形成T轉化活性去胺酶編輯器。

【0012】 圖2A展示使用sg000296剖析之具有轉化為去胺酶編輯器之胸苷的4種目標胞嘧啶之經編輯讀數之百分比。

【0013】 圖2B展示使用sg0001373剖析之具有轉化為去胺酶編輯器之胸苷的5種目標胞嘧啶之經編輯讀數之百分比。

【0014】 圖2C展示使用sg001400剖析之具有轉化為去胺酶編輯器之胸苷的4種目標胞嘧啶之經編輯讀數之百分比。

【0015】 圖2D展示使用sg003018剖析之具有轉化為去胺酶編輯器之胸苷的6種目標胞嘧啶之經編輯讀數之百分比。

【0016】 圖2E展示使用sg005883剖析之具有轉化為去胺酶編輯器之胸苷的8種目標胞嘧啶中之至少6種之經編輯的讀數之百分比。

【0017】 圖3A至圖3E分別針對5種不同導引靶向序列展示鹼基位置之C形成T轉化百分比。

【0018】 圖4A至圖4B展示編輯型態為U-2OS細胞(圖4A)及HuH-7細胞(圖4B)中總讀數之百分比。

【0019】 圖5A至圖5B展示編輯型態為U-2OS細胞(圖5A)及HuH-7細胞(圖5B)中之經編輯讀數之百分比。

【0020】 圖6A至圖6B表示編輯型態為滴定UGI mRNA (SEQ ID NO: 25及34)後總讀數之百分比。

【0021】 圖7展示用與mRNA構築體及sgRNA之不同LNP組合治療之CD-1小鼠中之TTR編輯水準。圖7展示自CD-1小鼠採集之肝臟組織樣本提取之DNA序列(NGS定序)的C形成T轉化、C形成A/G轉化及插入/缺失之%編輯。

【0022】 圖8展示當將UGI序列以反式(單獨的mRNA)遞送時，自用與mRNA構築體及sgRNA之不同LNP組合治療之CD-1小鼠採集之肝臟組織中的TTR編輯水準。

【0023】 圖9A至圖9C展示在表示不存在反式UGI mRNA之情況下用sgRNA G000282及BC22n mRNA (圖9A)、在存在反式UGI mRNA之情況下用sgRNA G000282及BC22n mRNA (圖9B)或在反式UGI mRNA存在之情況下用Cas9 mRNA (圖9c)治療的小鼠肝臟樣本中統計學上顯著之(p. adj. < 0.05)差異基因表現事件(黑色點)的散佈圖。

【0024】 圖10展示用不同mRNA構築體及CIITA靶向sgRNA治療後T細胞中之編輯型態。

【0025】 圖11顯示藉由經不同mRNA構築體及CIITA導引RNA治療之T細胞之流式細胞量測術分析評定的MHC II類陰性細胞。

【0026】 圖12A至圖12B展示展示在用sgRNA G018076、UGI mRNA及Cas9 mRNA (圖12A)或BC22n mRNA (圖12B)治療之T細胞中統計學上顯著的(* = p. adj. < 0.05)差異基因表現事件(黑色點)之散佈圖。

【0027】 圖13A至圖13B展示展示在用sgRNA G018117、UGI mRNA及Cas9 mRNA (圖13A)或BC22n mRNA (圖13B)治療之T細胞中統計學上顯著的(* = p. adj. < 0.05)差異基因表現事件(黑色點)之散佈圖。

【0028】 圖14A至圖14B展示在用sgRNA G018076、UGI mRNA及Cas9 mRNA (圖14A)或BC22n mRNA (圖14B)治療之T細胞中差異表現基因之清單當中富集的蛋白質-蛋白質相互作用網路。

【0029】 圖15A至圖15B展示在用sgRNA G018117、UGI mRNA及Cas9 mRNA (圖15A)或BC22 mRNA (圖15B)治療之T細胞中差異表現基因之清單當中富集的蛋白質-蛋白質相互作用網路。

【0030】 圖16A至圖16C展示T細胞之編輯型態。靶上TRAC基因座(圖16A)以及先前已描述為APOBEC陽性腫瘤中之突變熱點的10個基因座(圖16B至圖16C)中之編輯型態。

【0031】 圖17A至圖17E展示當用不同含量之BC22n mRNA及Cas9 mRNA治療時T細胞之編輯型態。使用sgRNA G015995 (圖17A)、G016017 (圖17B)、G016206 (圖17C)、G018117 (圖17D)或G016086 (圖17E)編輯細胞。

【0032】 圖18A至圖18D展示同時使用不同含量之BC22n mRNA或Cas9 mRNA用四種導引物編輯之T細胞的編輯型態。每一經編輯基因座處之編輯型態分別表示：G015995 (圖18A)、G016017 (圖18B)、G016206 (圖18C)、G018117 (圖18D)。

【0033】 圖19A至圖19I將表型結果展示為對於抗體結合呈陰性之細胞之百分比，其中BC22n及Cas9樣本之總RNA增加。圖19A展示當B2M導引物G015995用於編輯時，B2M陰性細胞之百分比。圖19B展示當多種

導引物用於編輯時，B2M陰性細胞之百分比。圖19C展示當TRAC導引物G016017用於編輯時，CD3陰性細胞之百分比。圖19D展示當TRBC導引物G016206用於編輯時，CD3陰性細胞之百分比。圖19E展示當多種導引物用於編輯時，CD3陰性細胞之百分比。圖19F展示當CIITA導引物G018117用於編輯時，MHC II類陰性細胞之百分比。圖19G展示當多種導引物用於編輯時，MHC II類陰性細胞之百分比。圖19H展示當多種導引物用於編輯時，三(B2M、CD3、MHC II)陰性細胞之百分比。圖19I展示當CIITA導引物G016086用於編輯時，MHC II類陰性T細胞之百分比。

【0034】 圖20A至圖20C展示在使用不同含量之反式UGI mRNA及各種編輯器mRNA時，T細胞之編輯型態。圖20A展示BC22n mRNA在27.3 nM處之編輯百分比。圖20B展示BC22-2xUGI mRNA在24.7 nM處之編輯百分比。圖20C展示BE4Max mRNA在24.0 nM處之編輯百分比。

【0035】 圖21展示在使用不同含量之反式UGI mRNA與各種編輯器mRNA時，C形成T轉化作為經編輯讀數之百分比(BC22n處於27.3 nM、BC22-2xUGI處於24.7 nM、BE4Max處於24.0 nM)。

【0036】 圖22展示使用Cas9或BC22之若干導引物之對於MHC II 的細胞表面表現呈陰性的T細胞之平均百分比(「%MHC II陰性」)與展示為鹼基對(「bp」)之切割位點邊界核苷酸之間的距離之關係。正數值指示切割位點之剪接位點邊界核苷酸3'，而負數值指示切割位點之剪接位點邊界核苷酸5'。

【0037】 圖23A展示在可能二級結構中之例示性sgRNA (SEQ ID NO: 141，甲基化未展示)，其中標記標識sgRNA之保守區的個別核苷酸，包括下莖、隆突、上莖、連接區(其核苷酸依5'至3'方向分別可稱作

N1至N18)及髮夾區，該髮夾區包括髮夾1及髮夾2區。髮夾1與髮夾2之間的核苷酸標記為n。導引區可存在於sgRNA上且在此圖中指示為sgRNA之保守區之前的「(N)x」。

【0038】 圖23B在例示性sgRNA序列(SEQ ID NO: 141，甲基化未展示)中以1至10標記10個保守區YA位點。編號25、45、50、56、64、67及83指示YA位點1、5、6、7、8、9及10之嘧啶在sgRNA中的位置，其中引導區表示為$(N)_x$，例如其中x視情況為20。

【0039】 圖24A至圖24B展示三種CIITA導引物(G016086、G016092及G016067)在使用BC22編輯T細胞時的效率結果。圖24A展示C形成T轉化百分比。圖24B展示MHC II類陰性T細胞之百分比。

【0040】 圖25展示在用不同mRNA組合編輯之後B2M陰性T細胞之百分比。EP指示電穿孔。

【0041】 圖26展示單核苷酸變異體(SNV)之百分比，其為在B2M處用不同mRNA組合編輯之T細胞之總轉錄本中的C形成U轉化(n.s=不顯著)。

【0042】 圖27展示在用不同mRNA組合治療之後B2M陰性T細胞之百分比。

【0043】 圖28展示在用不同mRNA組合治療之後T細胞中之B2M基因座處的編輯型態。

【0044】 圖29顯示來自在B2M處用不同mRNA組合編輯之單個T細胞的擴增基因體DNA中作為C形成T轉化之SNV的百分比(n.s=不顯著)。

【0045】 圖30展示在用不同mRNA組合編輯之後B2M陰性eHap1細胞之百分比。

【0046】 圖31展示在用不同mRNA組合治療之後eHap1細胞中之B2M基因座的編輯型態。

【0047】 圖32展示在B2M處用不同mRNA組合編輯之純系地擴展之eHap1細胞中作為C形成T轉化的SNV之百分比(n.s=統計學上不顯著)。

【0048】 圖33展示在電穿孔或LNP遞送BC22n或Cas9編輯器及單個或多種導引物質後相對於未治療細胞之細胞活力。

【0049】 圖34展示在電穿孔或LNP遞送BC22n或Cas9編輯器及單個或多種導引物之後，每一細胞核之總γH2AX光點強度。

【0050】 圖35展示在LNP遞送BC22n或Cas9編輯器及單個或多種導引物之後，所關注之基因座處之編輯百分比。

【0051】 圖36展示在LNP遞送BC22n或Cas9編輯器及單個或多種導引物之後，所述表面蛋白質之陰性細胞的百分比。

【0052】 圖37展示在LNP遞送BC22n或Cas9編輯器及多種導引物之後，總獨特分子當中之染色體間易位的百分比。

【0053】 圖38展示用各種鹼基編輯器治療之後之小鼠肝臟中的平均編輯百分比。

【0054】 圖39展示針對經設計有各種去胺酶域之鹼基編輯器構築體的平均C形成T轉化活性百分比。

【0055】 圖40A至圖40K展示針對設計有各種連接子之鹼基編輯構築體含有至少1個C形成T轉化之總讀數的百分比。

【0056】 圖41展示在用使用各種連接子設計之鹼基編輯器構築體治療之後，Huh-7中SERPINA1處的平均編輯百分比。

【0057】 圖42展示經設計有各種連接子之鹼基編輯mRNA之

EC90。亦展示每一EC90值之95%信賴區間(confidence interval；CI)。

【0058】 圖43展示使用設計有各種連接子之鹼基編輯構築體在PHH中之ANAPC5基因座處的平均編輯百分比。

【0059】 圖44展示設計有各種連接子之鹼基編輯mRNA之EC95。亦展示每一EC95值之95%信賴區間(CI)。

【0060】 圖45展示使用設計有各種連接子之鹼基編輯構築體在PHH中之TRAC基因座處的平均編輯百分比。

【0061】 圖46展示設計有引起CD3之90%之最大(EC90)抑制基因表現之各種連接子的鹼基編輯器mRNA的質量。亦展示每一EC50值之95%信賴區間。

【0062】 圖47展示設計有引起CD3之90%之最大(EC90)抑制基因表現、HLA-A3及HLA-DR、DP、DQ (EC50)的各種連接子之BC22n mRNA的質量。亦展示每一EC50值之95%信賴區間(CI)。

【0063】 圖48展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中TRAC基因座處的平均編輯百分比。

【0064】 圖49A展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中TRBC1基因座處的平均編輯百分比。

【0065】 圖49B展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中TRBC2基因座處的平均編輯百分比。

【0066】 圖50展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中CIITA基因座處的平均編輯百分比。

【0067】 圖51展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中B2M基因座處的平均編輯百分比。

【0068】 圖52展示在用100聚體或91聚體格式中之sgRNA治療之T細胞中CD38基因座處的平均編輯百分比。

【0069】 圖53A展示在用靶向TRAC之100聚體或91聚體格式中之sgRNAs治療之後對於CD3表面受體呈陰性的CD8+T細胞之平均百分比。

【0070】 圖53B展示在用靶向TRBC之100聚體或91聚體格式中之sgRNAs治療之後對於CD3表面受體呈陰性的CD8+T細胞之平均百分比。

【0071】 圖54A展示在用靶向CIITA之100聚體或91聚體格式中之sgRNAs治療之後對於HLA-DR、DP、DQ表面受體呈陰性的CD8+T細胞之平均百分比。

【0072】 圖54B展示在用靶向HLA-A之100聚體或91聚體格式中之sgRNA治療之後對於HLA-A表面受體呈陰性的CD8+T細胞之平均百分比。

【0073】 圖55A展示在用靶向B2M之100聚體或91聚體格式中之sgRNA治療之後對於B2M表面受體呈陰性的CD8+T細胞之平均百分比。

【0074】 圖55B展示在用靶向CD38之100聚體或91聚體格式中之sgRNA治療之後對於CD38表面受體呈陰性的CD8+T細胞之平均百分比。

【0075】 圖56展示隨著UGI mRNA之量增加，小鼠肝臟中之ANAPC5基因座處之平均編輯百分比。

【0076】 圖57展示隨著UGI mRNA之量增加，編輯後小鼠肝臟中之ANAPC5基因座處之C形成T編輯純度百分比。

【0077】 圖58A展示在PHH細胞中之B2M處在不同BC22n-HiBiT mRNA濃度下之總編輯。

【0078】 圖58B展示在PHH細胞中之B2M處在不同UGI-HiBiT

mRNA濃度下之C形成T純度。

【0079】 圖58C展示在PHH細胞中之B2M處在不同BC22-2xUGI-HiBiT mRNA濃度下之總編輯。

【0080】 圖58D展示在PHH細胞中之B2M處在不同BC22-2xUGI-HiBiT mRNA濃度下之C形成T純度。

【0081】 圖59A展示在T細胞中在不同BC22n-HiBiT mRNA濃度下之總編輯。

【0082】 圖59B展示在T細胞中在不同UGI-HiBiT mRNA濃度下之C形成T純度。

【0083】 圖59C展示在T細胞中在不同BC22-2xUGI-HiBiT mRNA濃度下之總編輯。

【0084】 圖59D展示在T細胞中在不同BC22-2xUGI-HiBiT mRNA濃度下之C形成T純度。

【0085】 圖60展示用固定劑量之sgRNA及鹼基編輯器mRNA及不同劑量之UGI mRNA的LNP治療之CD-1小鼠採集之肝臟組織中的編輯。

【0086】 圖61顯示用固定劑量之sgRNA及鹼基編輯器mRNA及不同劑量之UGI mRNA的LNP治療之CD-1小鼠採集之肝臟組織中的C形成T純度。

【0087】 圖62展示由以不同效應子：靶(E:T)比用sgRNA及鹼基編輯器及UGI mRNA治療之NK細胞靶向之T細胞的溶解百分比。

【0088】 圖63展示用Spy鹼基編輯器編輯之高活性導引物在每一導引物核苷酸位置處之轉化率。

【0089】 圖64展示用Nme2鹼基編輯器編輯之高活性導引物在每一

導引核苷酸位置處之轉化率。

所揭示序列之簡要說明

SEQ ID NO	描述
1	編碼BC22n之mRNA
2	用於BC22n之開讀框
3	BC22n之胺基酸序列
4	編碼具有HiBit標籤之BC22n之mRNA
5	具有HiBit標籤之BC22n之開讀框
6	具有HiBit標籤之BC22n之胺基酸序列
7	未使用
8	用於Cas9之開讀框
9	用於Cas9之胺基酸序列
10	未使用
11	用於Cas9之開讀框
12	用於Cas9之胺基酸序列
13	編碼BE3之mRNA
14	用於BE3之開讀框
15	用於BE3之胺基酸序列
16	編碼BE3之mRNA
17	用於BE3之開讀框
18	用於BE3之胺基酸序列
19	編碼BC22之mRNA
20	用於BC22之開讀框
21	用於BC22之胺基酸序列
22	未使用
23	具有HiBit標籤之Cas9之開讀框
24	具有HiBit標籤之Cas9之胺基酸序列
25	編碼UGI之mRNA
26	用於UGI之開讀框
27	用於UGI之胺基酸序列
28	編碼具有2x UGI之BC22之mRNA
29	用於具有2x UGI之BC22之開讀框
30	用於具有2x UGI之BC22之胺基酸序列
31	編碼BE4MAX蛋白之mRNA
32	用於BE4MAX蛋白之開讀框
33	用於BE4MAX蛋白之胺基酸序列
34	編碼UGI之mRNA序列
35	用於UGI之開讀框
36	用於重組Cas9之胺基酸序列
37	未使用
38	未使用

39	未使用
40	智人(*H. sapiens*)APOBEC3A去胺酶(A3A)之胺基酸序列
41	褐家鼠(*R. norvegicus*)APOBEC1之胺基酸序列
42	用於UGI (SEQ ID No.43)之例示性編碼序列
43	用於例示性UGI之胺基酸序列
44	用於XTEN之例示性編碼序列(SEQ ID No.46)
45	用於XTEN之例示性編碼序列(SEQ ID No.46)
46	用於例示性XTEN之胺基酸序列
47	用於例示性XTEN之胺基酸序列
48	用於例示性XTEN之胺基酸序列
49	用於例示性連接子之胺基酸序列
50	用於例示性連接子之胺基酸序列
51	用於例示性連接子之胺基酸序列
52	用於例示性連接子之胺基酸序列
53	用於例示性連接子之胺基酸序列
54	用於例示性連接子之胺基酸序列
55	用於例示性連接子之胺基酸序列
56	用於例示性連接子之胺基酸序列
57	用於例示性連接子之胺基酸序列
58	用於例示性連接子之胺基酸序列
59	用於例示性連接子之胺基酸序列
60	用於例示性連接子之核酸序列
61	用於例示性連接子之胺基酸序列
62	用於SV40 NLS之核酸序列
63	用於SV40 NLS之胺基酸序列
64	pCl-Neo
65	篩選質體-恆定序列
66	pUC19
67	U6啟動子
68	CMV啟動子
69	來自人類白蛋白基因之3' UTR
70	Spy Cas9切口酶(D10A)之胺基酸序列，具有呈C末端7個胺基酸形式之1x NLS
71	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 70之Spy Cas9切口酶(D10A) ORF，具有起始及終止密碼子
72	使用如表3中所列出之最小尿苷密碼子編碼序列之Spy Cas9切口酶(D10A) ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
73	Spy Cas9切口酶之胺基酸序列(無NLS)
74	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 73之Spy Cas9切口酶ORF，具有起始及終止密碼子
75	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 73之Spy Cas9切口酶編碼序列(無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
76	Spy Cas9切口酶之胺基酸序列，具有兩個呈C末端胺基酸形式之核定位訊號

77	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 76之Spy Cas9切口酶ORF，具有起始及終止密碼子
78	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 76之Spy Cas9切口酶編碼序列(無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
79	使用表4之低A密碼子、具有起始及終止密碼子之Spy Cas9切口酶ORF
80	使用表4之低A密碼子、具有起始及終止密碼子且無NLS之Spy Cas9切口酶ORF
81	使用表4之低A密碼子、具有兩個C末端NLS序列及起始及終止密碼子之Spy Cas9切口酶ORF
82	使用表4之低A/U密碼子、具有起始及終止密碼子之Spy Cas9切口酶ORF
83	使用表4之低A/U密碼子、具有兩個C末端NLS序列及起始及終止密碼子之Spy Cas9切口酶ORF
84	使用表4之低A/U密碼子、具有起始及終止密碼子且無NLS之Spy Cas9切口酶ORF
85	使用表4之低A密碼子之Spy Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
86	使用表4之低A密碼子之Spy Cas9切口酶ORF (無NLS且無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
87	使用表4之低A密碼子、具有兩個C末端NLS序列之Spy Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
88	使用表4之低A/U密碼子之Spy Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
89	使用表4之低A/U密碼子、具有兩個C末端NLS序列之Spy Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
90	使用表4之低A/U密碼子之Spy Cas9切口酶ORF (無NLS且無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)
91	例示性5' UTR
92	例示性5' UTR
93	例示性5' UTR
94	例示性5' UTR
95	例示性5' UTR
96	例示性5' UTR
97	例示性5' UTR
98	例示性5' UTR
99	例示性3' UTR
100	例示性3' UTR
101	例示性3' UTR
102	例示性3' UTR
103	例示性3' UTR
104	例示性3' UTR
105	例示性3' UTR
106	例示性3' UTR
107	例示性Kozak序列
108	例示性Kozak序列

109	例示性poly-A序列
110	例示性NLS 1
111	例示性NLS 2
112	例示性NLS 3
113	例示性NLS 4
114	例示性NLS 5
115	例示性NLS 6
116	例示性NLS 7
117	例示性NLS 8
118	例示性NLS 9
119	例示性NLS 10
120	例示性NLS 11
121	替代SV40 NLS
122	核質蛋白NLS
123	用於SV40 NLS之例示性編碼序列
124	用於NLS1之例示性編碼序列
125	用於NLS2之例示性編碼序列
126	用於NLS3之例示性編碼序列
127	用於NLS4之例示性編碼序列
128	用於NLS5之例示性編碼序列
129	用於NLS6之例示性編碼序列
130	用於NLS7之例示性編碼序列
131	用於NLS8之例示性編碼序列
132	用於NLS9之例示性編碼序列
133	用於NLS10之例示性編碼序列
134	用於NLS11之例示性編碼序列
135	用於替代SV40 NLS之例示性編碼序列
136-138	未使用
139	在導引序列之3'端之後形成crRNA的例示性核苷酸序列
140	spyCas9 sgRNA之保守部分
141	經修飾之sgRNA圖案，其中N為編碼導引序列之核苷酸
142	例示性導引恆定區修飾模式(G282-C)
143	例示性導引修飾模式(G282-mN3Nx)
144	例示性導引修飾模式(G282-Nx)
145	例示性導引修飾模式(G282-N20)
147-150	未使用
151	例示性導引序列
152	用於B2M基因之例示性導引序列
153	用於TTR基因之例示性導引序列
154	用於TRAC基因之例示性導引序列
155	用於TRBC1/2基因之例示性導引序列
156	例示性導引序列
157	用於SERPINA1基因之例示性導引序列
158	用於SERPINA1基因之例示性導引序列

159	例示性導引|序列
160	用於CIITA基因之例示性導引|序列
161	用於CIITA基因之例示性導引|序列
162	用於CIITA基因之例示性導引|序列
163	用於CIITA基因之例示性導引|序列
164	用於CIITA基因之例示性導引|序列
165	用於CIITA基因之例示性導引|序列
166	用於CIITA基因之例示性導引|序列
167	用於CIITA基因之例示性導引|序列
168	用於CIITA基因之例示性導引|序列
169	用於CIITA基因之例示性導引|序列
170	用於CIITA基因之例示性導引|序列
171	用於CIITA基因之例示性導引|序列
172	用於CIITA基因之例示性導引|序列
173	用於CIITA基因之例示性導引|序列
174-176	未使用
177	靶向TRAC之G013009導引|RNA
178	靶向TRAC之G016016導引|RNA
179	靶向B2M之G015991導引|RNA
180	靶向B2M之G015996導引|RNA
181	G000297導引|RNA
182	靶向具有導引|序列SEQ ID NO: 152之B2M之G015995導引|RNA
183	靶向具有導引|序列SEQ ID NO: 153之TTR之G000282導引|RNA
184	靶向具有導引|序列SEQ ID NO: 154之TRAC之G016017導引|RNA
185	靶向具有導引|序列SEQ ID NO: 155之TRBC1/2之G016206導引|RNA
186	SG000296導引|RNA
187	靶向具有導引|序列SEQ ID NO: 157之SERPINA1之SG001373導引|RNA
188	靶向具有導引|序列SEQ ID NO: 158之SERPINA1之SG001400導引|RNA
189	SG005883導引|RNA
190	靶向具有導引|序列SEQ ID NO: 160之CIITA之SG003018導引|RNA
191	靶向具有導引|序列SEQ ID NO: 161之CIITA之G018075導引|RNA
192	靶向具有導引|序列SEQ ID NO: 162之CIITA之G018076導引|RNA
193	靶向具有導引|序列SEQ ID NO: 163之CIITA之G018077導引|RNA
194	靶向具有導引|序列SEQ ID NO: 164之CIITA之G018078導引|RNA
195	靶向具有導引|序列SEQ ID NO: 165之CIITA之G018081導引|RNA
196	靶向具有導引|序列SEQ ID NO: 166之CIITA之G018082導引|RNA
197	靶向具有導引|序列SEQ ID NO: 167之CIITA之G018084導引|RNA
198	靶向具有導引|序列SEQ ID NO: 168之CIITA之G018085導引|RNA
199	靶向具有導引|序列SEQ ID NO: 169之CIITA之G018091導引|RNA
200	靶向具有導引|序列SEQ ID NO: 170之CIITA之G018100導引|RNA
201	靶向具有導引|序列SEQ ID NO: 171之CIITA之G018117導引|RNA
202	靶向具有導引|序列SEQ ID NO: 172之CIITA之G018118導引|RNA
203	靶向具有導引|序列SEQ ID NO: 173之CIITA之G018120導引|RNA
204-210	未使用

211	用於例示性連接子之胺基酸序列
212	用於例示性連接子之胺基酸序列
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271	用於例示性連接子之胺基酸序列
272	用於例示性連接子之胺基酸序列
273-300	未使用
301	編碼APOBEC3A-Nme2D16A之例示性mRNA
302	用於APOBEC3A-Nme2D16A之例示性開讀框
303	用於APOBEC3A-Nme2D16A之例示性胺基酸序列
304	編碼APOBEC3A-Nme2D16A之例示性mRNA
305	用於APOBEC3A-Nme2D16A之例示性開讀框
306	用於APOBEC3A-Nme2D16A之例示性胺基酸序列
307	編碼APOBEC3A-Nme2D16A之例示性mRNA
308	用於APOBEC3A-Nme2D16A之例示性開讀框
309	用於APOBEC3A-Nme2D16A之例示性胺基酸序列
310	編碼APOBEC3A-Nme2D16A之例示性mRNA
311	用於APOBEC3A-Nme2D16A之例示性開讀框
312	用於APOBEC3A-Nme2D16A之例示性胺基酸序列
313	用於NLS-NLS-APOBEC3A-L070-Nme2D16A之例示性胺基酸序列
314	編碼具有C末端HiBiT標籤之BC22-2XUGI之mRNA (BC22-2XUGI-HibIT)
315	編碼BC22-Nme2D16A之mRNA (Nme2 BC22n)
316	編碼具有C末端HiBiT標籤之UGI之mRNA (UGI-HiBiT)
317-319	未使用
320	用於Nme2Cas9之胺基酸序列
321-337	用於具有連接子之鹼基編輯器之例示性胺基酸序列
340	編碼Nme2Cas9之mRNA
341-357	用於具有連接子之鹼基編輯器之例示性mRNA序列
360	編碼Nme2Cas9之開讀框
361-377	用於具有連接子之鹼基編輯器之例示性開讀框序列
378-386	未使用
387	用於D16A Nme2Cas9切口酶之例示性胺基酸序列

388	用於D16A Nme2Cas9切口酶之例示性編碼序列
389	用於D16A Nme2Cas9切口酶之例示性編碼序列
390	用於D16A Nme2Cas9切口酶之例示性編碼序列
391	用於D16A Nme2Cas9切口酶之例示性開讀框
392	用於D16A Nme2Cas9切口酶之例示性開讀框
393	用於D16A Nme2Cas9切口酶之例示性開讀框
394-400	未使用
401-416	靶向HLA-A之例示性導引RNA
417	未使用
418-422	靶向HLA-A之例示性導引RNA
423	未使用
424	靶向HLA-A之例示性導引RNA
425-426	未使用
429-435	靶向HLA-A之例示性導引RNA
436	未使用
437-443	靶向HLA-A之例示性導引RNA
444	未使用
445-453	靶向HLA-A之例示性導引RNA
454	未使用
455-495	靶向HLA-A之例示性導引RNA
496	靶向CD38基因之G023522例示性導引RNA
497	靶向ANAPC5之G019427例示性導引RNA
498	靶向B2M之G023519例示性導引RNA
499	靶向TRAC之G023520例示性導引RNA
500	靶向CIITA之G023521例示性導引RNA
501	靶向HLA-A之G023523例示性導引RNA
502	靶向TRBC1/2之G023524例示性導引RNA
503	G020073例示性Nme2Cas9 導引RNA
504	G020927例示性Nme2Cas9 導引RNA
505	G020928例示性Nme2Cas9 導引RNA
506	G020929例示性Nme2Cas9 導引RNA
507	G021237例示性Nme2Cas9 導引RNA
508	G021249例示性Nme2Cas9 導引RNA
509	G021321例示性Nme2Cas9 導引RNA
510	具有非肽連接子之G021844例示性Nme2Cas9 導引RNA
511	靶向TTR之G000502例示性導引RNA
512	例示性NmeCas9 sgRNA
513	例示性縮短NmeCas9 sgRNA之保守區
514	例示性縮短NmeCas9 sgRNA圖案之保守區
515	例示性縮短NmeCas9 sgRNA圖案之保守區
516	例示性縮短/經修飾NmeCas9 sgRNA圖案之保守區(Mod-77)
517	包含連接子之例示性縮短/經修飾NmeCas9 sgRNA之保守區(Mod-78)
518	包含連接子之例示性縮短NmeCas9 sgRNA
519	包含連接子之例示性縮短/經修飾NmeCas9 導引RNA

520	例示性縮短/經修飾SpyCas9 導引RNA
521	例示性縮短SpyCas9 導引RNA
522	例示性縮短/經修飾NmeCas9 導引RNA
523	包含連接子之例示性縮短/經修飾SpyCas9 導引RNA
524	包含連接子之例示性縮短SpyCas9 導引RNA
525-528	未使用
529	G016788例示性導引RNA
530-617	靶向CIITA之例示性導引RNA
618-705	用於TRBC基因之例示性導引序列
706-746	用於TRAC基因之例示性導引序列
747-762	用於TRAC基因之例示性導引RNA序列
763-800	未使用
801-852	用於TRBC基因之例示性導引RNA序列
853-868	用於TRAC基因之例示性導引RNA序列
869-956	用於CD38基因之例示性導引RNA
957-959	未使用
960-1023	胞苷去胺酶之例示性胺基酸序列
1024-1075	用於TRBC基因之例示性導引RNA序列
1076-1163	用於CIITA基因之例示性導引RNA序列

對於序列本身，參見下文序列表。轉錄本序列一般包括GGG作為供與ARCA一起使用的前三個核苷酸，或包括AGG作為供與CleanCap™一起使用的前三個核苷酸。因此，可對前三個核苷酸進行修飾以供與其他加端帽方法，諸如牛痘(*Vaccinia*)加端帽酶一起使用。啟動子及poly-A序列不包括於轉錄本序列中。諸如U6啟動子(SEQ ID NO: 67)之啟動子或CMV啟動子(SEQ ID NO: 68)及諸如SEQ ID NO: 109之poly-A序列可分別在5'端及3'端處附接至所揭示之轉錄本序列。大多數核苷酸序列以DNA形式提供，但可藉由將T變成U而容易轉化成RNA。

【實施方式】

【0090】 本申請案根據35 U.S.C. 119(e)主張2020年12月11日申請之美國臨時申請案第63/124,060號、2020年12月23日申請之美國臨時申請案第63/130,104號、2021年3月24日申請之美國臨時申請案第

63/165,636號及2021年11月3日申請之美國臨時申請案第63/275,424號的權益，該等申請案中之每一者以全文引用之方式併入本文中。

【0091】 現將詳細參考本發明之某些實施例，其實例在附圖中加以說明。儘管本發明將結合所說明之實施例描述，但應理解其並不意欲將本發明限於彼等實施例。相反，本發明意欲涵蓋所有替代方案、修改及等效物，其可如所附申請專利範圍所限定包括在本發明內。

【0092】 在詳細描述本發明教示內容之前，應理解，本發明不限於特定組合物或方法步驟，因此可加以改變。應注意，除非上下文另外明確規定，否則如本說明書及所附申請專利範圍中所用，單數形式「一(a/an)」及「該(the)」包括複數個提及物。因此，舉例而言，提及「結合物(a conjugate)」包括複數個結合物且提及「細胞(a cell)」包括複數個細胞及其類似者。

【0093】 數值範圍包括限定該範圍之數字。考慮到有效數位及與量測相關之誤差，實測值及可量測值應理解為近似值。此外，「包含(comprise/comprises/comprising)」、「含有(contain/contains/containing)」及「包括(include/includes/including)」之使用並不意欲為限制性的。應瞭解，前文一般描述與詳細說明僅具有例示性及解釋性且不限制教示內容。

【0094】 術語「約」或「大約」意謂如由一般熟習此項技術者所測定之特定值的可接受之誤差，其部分地取決於如何量測或判定該值、或變化程度不會實質上影響所述標的物之特性，或在此項技術中所接受之容限內，例如在10%、5%、2%或1%內。因此，除非有相反指示，否則以下說明書及所附申請專利範圍中所闡述之數值參數為可視設法獲得之所需特性

而變化的近似值。最低限度地，且不試圖限制等效物之原則對申請專利範圍之範疇的應用，每一數值參數至少應根據所報導之有效數位的數目且藉由應用一般捨入技術來解釋。

【0095】 除非以上說明書中具體指出，否則本說明書中敍述「包含」各種組分之實施例亦設想為「由所述組分組成」或「基本上由所述組分組成」；本說明書中敍述「由各種組分組成」之實施例亦設想為「包含」所述組分或「基本上由所述組分組成」；且本說明書中敍述「基本上由各種組分組成」之實施例亦設想為「由所述組分組成」或「包含」所述組分(此互換性並不適用於此等術語在申請專利範圍中之使用)。

【0096】 本文所用之章節標題僅出於組織目的而不應解釋為以任何方式限制所需主題。在以引用之方式併入之任何文獻與本說明書之表述內容(包括但不限於定義)相矛盾之情況下，以本說明書之表述內容為準。儘管本發明之教示係與各種實施例結合描述，但並不意欲使本發明之教示限制於此類實施例。相反，如熟習此項技術者將瞭解，本教示內容涵蓋各種替代方案、修改及等效物。

I. 定義

【0097】 除非另外說明，否則如本文所用之以下術語及片語意欲具有以下含義：

【0098】 如本文所用，術語「或其組合」係指在該術語前面所列項之所有排列及組合。舉例而言，「A、B、C或其組合」意欲包括以下中之至少一者：A、B、C、AB、AC、BC或ABC，且若在特定情況下順序為重要的，則亦包括BA、CA、CB、ACB、CBA、BCA、BAC或CAB。繼續此實例，明確地包括含有一或多個項或術語之重複的組合，諸如BB、

AAA、AAB、BBC、CBBA、CABA等等。熟習此項技術者應理解，除非另外自上下文顯而易知，否則通常不存在對任何組合中之項或術語之數目的限制。

【0099】 如本文所用，術語「套組」係指相關組分，諸如一或多種多核苷酸或組合物及一或多種相關材料，諸如遞送裝置(例如注射器)、溶劑、溶液、緩衝劑、說明書或乾燥劑之封裝組。

【0100】 除非本文另有規定，否則「或」係依包括性意義使用，亦即，等效於「及/或」。

【0101】 「多核苷酸」及「核酸」在本文中用於指代包含核苷或具有沿主鏈連接在一起的含氮雜環鹼基或鹼基類似物之核苷類似物的多聚化合物，其包括習知RNA、DNA、混合RNA-DNA及為其類似物之聚合物。核酸「主鏈」可由多個鍵聯構成，其包括糖-磷酸二酯鍵聯、肽-核酸鍵(「肽核酸」或PNA；PCT第WO 95/32305號)、硫代磷酸酯鍵聯、甲基膦酸酯鍵聯或其組合中之一或多者。核酸之糖部分可為核糖、去氧核糖或具有例如2'甲氧基或2'鹵基取代物之取代物之類似化合物。含氮鹼基可為習知鹼基(A、G、C、T、U)、其類似物(例如經修飾之尿苷，諸如5-甲氧基尿苷、假尿苷或N1-甲基假尿苷或其他)、肌苷、嘌呤或嘧啶之衍生物(例如N^4-甲基去氧鳥苷、去氮嘌呤或氮雜嘌呤、去氮嘧啶或氮雜嘧啶、在5位或6位處具有取代基之嘧啶鹼基(例如5-甲基胞嘧啶)、在2位、6位或8位處具有取代基之嘌呤鹼基、2-胺基-6-甲胺基嘌呤、O^6-甲基鳥嘌呤、4-硫基-嘧啶、4-胺基-嘧啶、4-二甲基肼-嘧啶，及O^4-烷基-嘧啶；美國專利第5,378,825號及PCT第WO 93/13121號)。對於一般論述，參見*The Biochemistry of the Nucleic Acids* 5-36，Adams等人編,第11版, 1992)。

核酸可包括一或多個「無鹼基」殘基，其中主鏈不包括針對聚合物位置之含氮鹼基(美國專利第5,585,481號)。核酸可僅包含習知RNA或DNA糖、鹼基及鍵聯，或可包括習知組分與取代(例如具有2'甲氧基鍵聯之習知鹼基，或含有習知鹼基與一或多個鹼基類似物的聚合物)。核酸包括「鎖定核酸」(LNA)，含有一或多個LNA核苷酸單體之類似物，其中雙環呋喃醣單元經鎖定於模擬糖構形之RNA中，由此增強針對互補RNA及DNA序列之雜交親和力(Vester及Wengel, 2004, *Biochemistry* 43(42):13233-41)。RNA及DNA具有不同糖部分且不同之處可為RNA中存在尿嘧啶或其類似物及DNA中存在胸腺嘧啶或其類似物。

【0102】 如本文所用，「多肽」係指包含可採用三維構形之胺基酸殘基之多聚化合物。多肽包括但不限於酶、酶前驅蛋白、調節蛋白、結構蛋白、受體、核酸結合蛋白、抗體等。多肽可未必包含轉譯後修飾、非天然胺基酸、輔基及類似物。

【0103】 如本文所用，「胞苷去胺酶」意謂能夠具有胞苷去胺酶活性之多肽或多肽複合物，其催化胞苷或去氧胞苷之水解去胺作用，通常產生尿苷或去氧尿苷。胞苷去胺酶涵蓋胞苷去胺酶超家族中之酶，且特定言之APOBEC家族之酶(酶之APOBEC1、APOBEC2、APOBEC4及APOBEC3子群)、活性誘導之胞苷去胺酶(AID或AICDA)及CMP去胺酶(參見例如Conticello等人，Mol. Biol. Evol. 22:367-77, 2005；Conticello，Genome Biol. 9:229, 2008；Muramatsu等人，J. Biol. Chem. 274: 18470-6, 1999；Carrington等人，Cells 9:1690 (2020))。在一些實施例中，涵蓋任何已知胞苷去胺酶或APOBEC蛋白之變異體。變異體包括具有與野生型蛋白質相差一個或若干個突變(即，取代、缺失、插入)之序列

之蛋白質，該一個或若干個突變諸如一個或若干個單點取代。舉例而言，縮短序列可例如藉由使N末端、C末端或內部胺基酸缺失，較佳缺失序列C末端處之一至四個胺基酸來使用。如本文所用，術語「變異體」係指與參考序列同源之等位基因變異體、剪接變異體及天然或人工突變。變異體為「功能性的」，因為其展示DNA編輯之催化活性。

【0104】 如本文所用，術語「APOBEC3A」係指胞苷去胺酶，諸如由人類A3A基因表現之蛋白質。APOBEC3A可具有催化DNA編輯活性。已描述APOBEC3A之胺基酸序列(UniPROT寄存ID: p31941)且作為SEQ ID NO: 40包括在本文中。在一些實施例中，APOBEC3蛋白質為人類APOBEC3蛋白質及/或野生型蛋白質。變異體包括具有與野生型APOBEC3A蛋白質相差一個或若干個突變(即，取代、缺失、插入)之序列之蛋白質，該一個或若干個突變諸如一個或若干個單點取代。舉例而言，可使用縮短之APOBEC3A序列，例如藉由使N末端、C末端或內部胺基酸缺失，較佳地使序列之C末端處之一至四個胺基酸缺失。如本文所用，術語「變異體」係指與APOBEC3A參考序列同源之對偶基因變異體、剪接變異體及天然或人工突變。變異體為「功能性的」，因為其展示DNA編輯之催化活性。在一些實施例中，APOBEC3A (諸如人類APOBEC3A)具有野生型胺基酸位置57 (如野生型序列中所編號)。在一些實施例中，APOBEC3A (諸如人類APOBEC3A)在胺基酸位置57 (如野生型序列中所編號)處具有天冬醯胺。

【0105】 如本文中所用，「切口酶」為在雙股DNA中產生單股斷裂(亦稱為「鏈裂」)之酶，亦即切割DNA雙螺旋之一股但不切割另一股。如本文中所用，「RNA導引之切口酶」意謂具有DNA切口酶活性之多肽或

多肽複合物，其中DNA切口酶活性為序列特定且取決於RNA之序列。例示性RNA導引之切口酶包括Cas切口酶。Cas切口酶包括但不限於：III型CRISPR系統之Csm或Cmr複合物之切口酶形式，其Cas10、Csm1或Cmr2次單元，I型CRISPR系統之級聯複合物，其Cas3次單元及2類Cas核酸酶。2類Cas切口酶包括2類Cas核酸酶變異體，其中兩個催化域中之僅一者失活，其具有RNA導引DNA切口酶活性。2類Cas切口酶包括例如Cas9(例如，H840A、D10A或SpyCas9之N863A變異體)、Cpf1、C2c1、C2c2、C2c3、HF Cas9（例如N497A、R661A、Q695A、Q926A變異體）、HypaCas9（例如N692A、M694A、Q695A、H698A變異體）、eSPCas9(1.0)（例如K810A、K1003A、R1060A變異體)及eSPCas9(1.1)(例如K848A、K1003A、R1060A變異體)蛋白質及其修飾。Cpf1蛋白質，Zetsche等人，*Cell*，163: 1-13 (2015)，與Cas9同源且含有RuvC樣蛋白質域。Zetsche之Cpf1序列以全文引用之方式併入。參見例如Zetsche，表S1及表S3。「Cas9」涵蓋化膿性鏈球菌(*S. pyogenes)* (Spy) Cas9，本文中所列出之Cas9之變異體及其等效物。參見例如Makarova等人，*Nat Rev Microbiol*，13(11): 722-36 (2015)；Shmakov等人，*Molecular Cell*，60:385-397 (2015)。

【0106】若干Cas9異種同源物已自以下獲得：腦膜炎雙球菌(*N. meningitidis*) (Esvelt等人，NAT. METHODS，第10卷，2013，1116 - 1121；Hou等人，PNAS，第110卷，2013，第15644 - 15649頁；Edraki等人，Mol. Cell 73:714-726, 2019) (Nme1Cas9、Nme2Cas9及Nme3Cas9)。Nme2Cas9直系同源物在哺乳動物細胞中有效地起作用，識別N4CC PAM，且可用於活體內編輯(Ran等人，NATURE，第520卷，

2015，第186至191頁；Kim等人，NAT. COMMUN.，第8卷，2017，第14500頁)。Nme2Cas9已展示為對脫靶編輯具有天然抗性(Lee等人，MOL. THER.，第24卷，2016，第645至654頁；Kim等人，2017)。亦參見例如，WO/2020081568 (例如，第28頁及42頁)，其描繪Nme2Cas9 D16A切口酶，該案之內容以全文引用的方式併入本文中。在全文中，「NmeCas9」為通用的且涵蓋任何類型之NmeCas9，包括Nme1Cas9、Nme2Cas9及Nme3Cas9。

【0107】 如本文所用，術語「融合蛋白質」係指包含來自至少兩種不同蛋白質或源之多肽之混合多肽。一個多肽可位於融合蛋白之胺基末端(N末端)部分處或羧基末端(C末端)蛋白處，因此分別形成「胺基末端融合蛋白」或「羧基末端融合蛋白」。本文所提供之任一蛋白質可藉由此項技術中已知之任何方法產生。舉例而言，本文所提供之蛋白質可經由重組蛋白表現及純化來產生，其尤其適合於包含肽連接子之融合蛋白。重組蛋白表現及純化之方法為熟知的，且包括由Green及Sambrook, Molecular Cloning: A Laboratory Manual (第4版, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012))描述之彼等方法，其全部內容以引用之方式併入本文中。

【0108】 如本文所用之術語「連接子」係指連接兩個相鄰分子或部分之化學基團或分子。通常，連接子安置於兩個基團、分子或其他部分之間或由兩個基團、分子或其他部分側接，且經由共價鍵彼此連接。在一些實施例中，連接子為一個胺基酸或複數個胺基酸(例如肽或蛋白質)，諸如16-胺基酸殘基「XTEN」連接子或其變異體(參見例如實例；及Schellenberger等人，A recombinant polypeptide extends the in vivo half-

life of peptides and proteins in a tunable manner. Nat. Biotechnol. 27, 1186-1190 (2009))。在一些實施例中，XTEN連接子包含序列SGSETPGTSESATPES (SEQ ID NO:46)、SGSETPGTSESA (SEQ ID NO:47)或SGSETPGTSESATPEGGSGGS (SEQ ID NO:48)。在一些實施例中，連接子包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列。

【0109】 如本文所用，術語「尿嘧啶醣苷酶抑制劑」、「尿嘧啶DNA醣苷酶抑制劑」或「UGI」係指能夠抑制尿嘧啶-DNA醣苷酶(UDG)鹼基-切除修復酶(例如，UniPROT ID:P14739；SEQ ID NO: 27；SEQ ID NO：43)之蛋白質。

【0110】 如本文所用，基因之「開讀框」或「ORF」係指由一系列密碼子組成的序列，該等密碼子指定該基因編碼之蛋白質的胺基酸序列。ORF一般開始於起始密碼子(例如DNA中之ATG或RNA中之AUG)且以終止密碼子結束，例如DNA中之TAA、TAG或TGA或RNA中之UAA、UAG或UGA)。

【0111】 「導引RNA」、「gRNA」及「導引物」在本文中互換使用以指crRNA（亦稱為CRISPR RNA)，或crRNA與trRNA（亦稱為tracrRNA)之組合。crRNA及trRNA可以單個RNA分子(單導引RNA，sgRNA)或以兩個獨立RNA分子(雙導引RNA，dgRNA)形式締合。「導引RNA」或「gRNA」係指各類型。trRNA可為天然存在之序列或與天然存在之序列相比具有修飾或變異之trRNA序列。

【0112】 如本文中所用，「導引序列」或「導引區」或「間隔件」或「間隔件序列」及其類似物係指gRNA內與目標序列互補且用於藉由

RNA導引之切口酶將gRNA導向至目標序列以用於結合或修飾(例如，裂解)之序列。導引序列之長度可為20個核苷酸，例如，在化膿性鏈球菌(亦即，Spy Cas9 (亦稱為SpCas9))及相關Cas9同源物/異種同源物之情況下。較短或較長序列亦可用作例如長度為15、16、17、18、19、21、22、23、24或25個核苷酸之導引物。導引序列之長度可為20至25個核苷酸，例如，在Nme Cas9之情況下，例如，長度為20、21、22、23、24或25個核苷酸。舉例而言，長度為24個核苷酸之導引序列可與Nme Cas9一起使用，例如，Nme2 Cas9。

【0113】 在一些實施例中，目標序列處於例如基因中或染色體上，且與導引序列互補。在一些實施例中，導引序列與其相應目標序列之間的互補性或一致性程度可為約75%、80%、85%、90%、95%或100%。在一些實施例中，導引序列與目標區域可為100%互補或一致的。在其他實施例中，導引序列與目標區域可含有至少一個錯配。舉例而言，導引序列及目標序列可含有1、2、3或4個錯配，其中目標序列之總長度為至少17、18、19、20個或更多個鹼基對。在一些實施例中，導引序列及目標區域可含有1至4個錯配，其中導引序列包含至少17、18、19、20個或更多個核苷酸。在一些實施例中，導引序列與目標區域可含有1、2、3或4個錯配，其中導引序列包含20個核苷酸。

【0114】 如本文所用，「目標序列」或「基因體目標序列」係指目標基因中與gRNA之引導序列具有互補性的核酸序列。目標序列與導引序列之相互作用導引經RNA導引之DNA結合劑結合，且在目標序列中潛在地鏈裂或裂解(視試劑活性而定)。針對Cas蛋白質之目標序列包括基因體DNA之正股及負股兩者(亦即給定序列及該序列之反向補體)，因為Cas蛋

白質之核酸底物為雙股核酸。因此，在據稱「導引序列與目標序列互補」之情況下，應理解，導引序列可導引經RNA導引之DNA結合劑(例如dCas9或受損Cas9)以結合至目標序列之反向補體。因此，在一些實施例中，在導引序列結合目標序列之反向補體之情況下，導引序列與目標序列(例如不包括PAM之目標序列)之某些核苷酸一致，不同之處在於導引序列中U取代T。

【0115】 如本文所用，若第一序列與第二序列之比對顯示整個第二序列之X%或更多位置與第一序列匹配，則第一序列視為「包含與第二序列具有至少X%一致性的序列」。舉例而言，序列AAGA包含與序列AAG具有100%一致性之序列，此係因為第二序列之全部三個位置均存在匹配，因此比對將得到100%一致性。RNA與DNA之間的差異(通常而言，尿苷更換為胸苷或反之亦然)及核苷類似物(諸如經修飾之尿苷)的存在不會造成多核苷酸之間一致性或互補性的差異，只要相關核苷酸(諸如胸苷、尿苷或經修飾之尿苷)具有相同互補序列(例如針對胸苷、尿苷或經修飾之尿苷均為腺苷；另一實例為胞嘧啶及5-甲基胞嘧啶，這兩者均以鳥苷作為互補序列)即可。因此，舉例而言，序列5'-AXG (其中X為任何經修飾之尿苷，諸如假尿苷、N1-甲基假尿苷或5-甲氧基尿苷)視為與AUG具有100%一致性，因為兩者與同一序列(5'-CAU)完美互補。例示性比對演算法為此項技術中熟知的Smith-Waterman及Needleman-Wunsch演算法。熟習此項技術者應理解選擇何種演算法及參數設置才適合於所要比對之一對指定序列；對於具有一般類似長度及預期胺基酸有>50%一致性或核苷酸有>75%一致性的序列而言，由EBI於www.ebi.ac.uk網站伺服器提供的Needleman-Wunsch演算法介面之具有默認設置的Needleman-Wunsch演

算法通常為合適的。

【0116】「mRNA」在本文中用於指一種多核苷酸，其不為DNA且包含可轉譯成多肽(亦即，可充當供核糖體及胺基醯基化tRNA轉譯的受質)之開讀框。mRNA可包含包括核糖殘基或其類似物，例如2'-甲氧基核糖殘基之磷酸酯-糖主鏈。在一些實施例中，mRNA磷酸酯-糖主鏈中之糖類基本上由核糖殘基、2'-甲氧基核糖殘基或其組合組成。通常而言，mRNA不含顯著量的胸苷殘基(例如0個殘基或小於30、20、10、5、4、3或2個胸苷殘基；或小於10%、9%、8%、7%、6%、5%、4%、3%、2%、1%、0.5%、0.2%或0.1%的胸苷含量)。mRNA可在其一些或全部尿苷位置處含有經修飾之尿苷。

【0117】「經修飾之尿苷」在本文中用於指代除胸苷外的與尿苷具有相同氫鍵受體且與尿苷存在一或多種結構差異的核苷。在一些實施例中，經修飾之尿苷為經取代之尿苷，亦即其中一或多個非質子取代基(例如烷氧基，諸如甲氧基)替代質子之尿苷。在一些實施例中，經修飾之尿苷為假尿苷。在一些實施例中，經修飾之尿苷為經取代之假尿苷，亦即其中一或多個非質子取代(例如烷基，諸如甲基)代替質子之假尿苷。在一些實施例中，經修飾之尿苷為經取代之尿苷、假尿苷或經取代之假尿苷中之任一者。

【0118】如本文所用，「尿苷位置」係指多核苷酸中由尿苷或經修飾之尿苷佔據之位置。因此，舉例而言，其中「100%之尿苷位置為經修飾之尿苷」之多核苷酸在相同序列之習知RNA (其中所有鹼基均為標準A、U、C或G鹼基)中應為尿苷的每一位置處均含有經修飾之尿苷。除非另外指明，否則本發明中或附隨本發明的序列表(sequence table/sequence

listing)之多核苷酸序列中之U可為尿苷或經修飾之尿苷。

【0119】 如本文中所用，給定胺基酸之「最小尿苷密碼子」為具有最少尿苷之密碼子(通常0個或1個，除了苯丙胺酸之密碼子以外，其中最小尿苷密碼子具有2個尿苷)。出於評估尿苷含量之目的，經修飾之尿苷殘基視為等效於尿苷。

【0120】 如本文中所用，「尿苷二核苷酸(UU)含量」可以絕對術語表示為ORF中之UU二核苷酸之計數或基於比率，表示為尿苷二核苷酸之尿苷所佔據的位置之百分比(例如，AUUAU之尿苷二核苷酸含量將為40%，因為尿苷二核苷酸之尿苷佔據了5個位置中之2個)。出於評估尿苷二核苷酸含量之目的，經修飾之尿苷殘基視為等效於尿苷。

【0121】 如本文中所用，給定胺基酸之「最小腺嘌呤密碼子」為具有最少腺嘌呤之密碼子(通常為0或1個，除了離胺酸及天冬醯胺之密碼子以外，其中最小腺嘌呤密碼子具有2個腺嘌呤)。出於評估腺嘌呤含量之目的，經修飾之腺嘌呤殘基視為等效於腺嘌呤。

【0122】 如本文中所用，ORF之「腺嘌呤二核苷酸含量」可以絕對術語表現為ORF中之AA二核苷酸計數或基於比率，表現為腺嘌呤二核苷酸之腺嘌呤所佔據之位置的百分比(例如，UAAUA之腺嘌呤二核苷酸含量將為40%，因為腺嘌呤二核苷酸之腺嘌呤佔據5個位置中之2個)。出於評估腺嘌呤二核苷酸含量之目的，經修飾之腺嘌呤殘基視為等效於腺嘌呤。

【0123】 如本文所用，「插入/缺失」係指由多種核苷酸組成之插入/缺失突變，該等核苷酸例如在目標核酸中之雙股斷裂(DSB)位點處進行插入或缺失。

【0124】 如本文所用，「抑制基因表現(knockdown)」係指特定基

因產物(例如蛋白質、mRNA或兩者)之表現降低。可藉由偵測由組織或細胞群(例如在血清或細胞培養基中)分泌之蛋白質或藉由偵測來自相關組織或細胞群的蛋白質之總細胞量來量測蛋白質之抑制基因表現。用於量測將mRNA阻斷基因表現之方法為已知的，且包括對自所關注之組織或細胞群分離之mRNA進行定序。在一些實施例中，「抑制基因表現」可指一些特定基因產物之表現損失，例如經轉錄之mRNA的量下降或由細胞群(包括活體內細胞群，諸如組織中所發現的彼等者)表現或分泌的蛋白質之量下降。

【0125】 如本文所用，「基因剔除(knockout)」係指細胞中之特定蛋白質之表現損失。基因剔除可藉由偵測由組織或細胞群(例如血清或細胞培養基中)分泌之蛋白質之量或藉由偵測來自組織或細胞群的蛋白質之總細胞量來量測。在一些實施例中，本發明之方法在一或多種細胞(例如在細胞群，包括活體內細胞群，諸如彼等出現在組織中者)「基因剔除」目標蛋白。在一些實施例中，基因剔除並非例如由插入/缺失產生之目標蛋白之突變的形成，而是目標蛋白在細胞中之表現之完全損失，亦即，表現下降至所用測定之偵測水平之下。

【0126】 如本文中所用，術語「核定位訊號」(NLS)或「核定域序列」係指誘導包含此類序列或連接至此類序列之分子輸送至真核細胞之細胞核的胺基酸序列。核定位訊號可形成待輸送之分子之一部分。在一些實施例中，NLS可藉由共價鍵、氫鍵或離子相互作用融合至分子。在一些實施例中，NLS可經由連接子融合至分子。

【0127】 如本文中所用，「β2M」或「B2M」係指「β-2微球蛋白」之核酸序列或蛋白質序列；人類基因具有寄存編號NC_000015 (範圍

44711492..44718877)，參考GRCh38.p13。B2M蛋白與MHC I類分子締合為成核細胞表面上之異二聚體且為MHC I類蛋白質表現所需。

【0128】如本文所使用，「*CIITA*」或「CIITA」或「C2TA」係指「II類主要組織相容複合物反式活化子」之核酸序列或蛋白質序列；人類基因具有寄存編號NC_000016.10 (範圍10866208..10941562)，參考GRCh38.p13。細胞核中之CIITA蛋白充當MHC II類基因轉錄之正調控劑且為MHC II類蛋白質表現所需。

【0129】如本文所用，「MHC」或「MHC分子」或「MHC蛋白質」或「MHC複合物」係指一個主要組織相容複合物分子(或多個)，且包括例如MHC I類及MHC II類分子。在人類中，MHC分子稱為「人類白血球抗原」複合物或「HLA分子」或「HLA蛋白質」。術語「MHC」及「HLA」之使用不意欲為限制性的；如本文所用，術語「MHC」可用於指人類MHC分子，亦即HLA分子。因此，術語「MHC」及「HLA」在本文中可互換使用。

【0130】如本文所用，HLA-A蛋白之上下文中的術語「HLA-A」係指MHC I類蛋白質分子，其為由重鏈(由HLA-A基因編碼)及輕鏈(亦即β-2微球蛋白)組成之異二聚體。如本文所用，在核酸之上下文中的術語「HLA-A」或「HLA-A基因」係指編碼HLA-A蛋白分子之重鏈的基因。HLA-A基因亦稱為「HLA I類組織相容，A α鏈」；人類基因具有寄存編號NC_000006.12 (29942532..29945870)。已知HLA-A基因跨群體具有數千種不同型式(亦稱為「等位基因」) (且個體可接受HLA-A基因之兩種不同等位基因)。H-LAA等位基因之公共資料庫(包括序列資訊)可訪問IPD-IMGT/HLA: https://www.ebi.ac.uk/ipd/imgt/hla/。HLA-A之所有等位基

因均由術語「HLA-A」及「HLA-A基因」涵蓋。

【0131】 如本文在核酸之上下文中所用之術語「HLA-B」係指編碼HLA-B蛋白分子之重鏈的基因。HLA-B基因亦稱為「HLA I類組織相容，B α鏈」；人類基因具有寄存編號NC_000006.12 (31353875..31357179)。

【0132】 如本文在核酸之上下文中所用的術語「HLA-C」係指編碼HLA-C蛋白分子之重鏈的基因。HLA-C基因亦稱為「HLA I類組織相容，C α鏈」；人類基因具有寄存編號NC_000006.12 (31268749..31272092)。

【0133】 如本文在核酸之上下文中所用之「TRBC1」及「TRBC2」係指編碼T細胞受體β-鏈的兩個同源基因。「TRBC」或「TRBC1/2」在本文中用以指代TRBC1及TRBC2。人類野生型TRBC1序列可以NCBI基因ID：28639；Ensembl: ENSG00000211751獲得。T細胞受體β恆定區、V_segment轉譯產物、BV05S1J2.2、TCRBC1及TCRB為TRBC1之基因同義詞。人類野生型TRBC2序列可以NCBI基因ID：28638；Ensembl: ENSG00000211772獲得。T細胞受體β恆定區、V_segment轉譯產物、及TCRBC2為TRBC2之基因同義詞。

【0134】 如本文在核酸之上下文中所用，「TRAC」係指編碼T細胞受體α鏈之基因。人類野生型TRAC序列可以NCBI基因ID：28755；Ensembl: ENSG00000277734獲得。T細胞受體α恆定區、TCRA、IMD7、TRCA及TRA為TRAC之基因同義詞。

【0135】 如本文所用，術語「同型組合」係指具有特定基因之兩個相同等位基因。

【0136】 如本文所用，「治療(treatment)」係指投與或施用用於個體之疾病或病症的治療劑，且包括抑制疾病、遏制其發展、減輕疾病之一

或多種症狀、治癒疾病或預防疾病之一或多種症狀，包括症狀復發。

【0137】 如本文中所用，「遞送」及「投與」可互換地使用，且包括活體外及活體內應用。

【0138】 如本文中所用，共同投與意謂複數種物質在時間上足夠接近地一起投與，以使得與藥劑一起作用。共同投與涵蓋在單個調配物中一起投與物質及在單獨調配物中在時間上足夠接近地投與物質以使得藥劑一起作用。

【0139】 如本文中所用，片語「醫藥學上可接受」意謂在製備藥物組合物時有用的，該藥物組合物通常無毒且在生物學上並非不合需要且在其他方面對於醫藥用途並非不可接受的。醫藥學上可接受之物質通常係指非熱解物質。醫藥學上可接受可指無菌物質，尤其對於注射或輸注用之醫藥物質。

【0140】 如本文所用，「個體」係指動物界之任何成員。在一些實施例中，「個體」係指人類。在一些實施例中，「個體」係指非人類動物。在一些實施例中，「個體」係指靈長類動物。在一些實施例中，個體包括但不限於哺乳動物、鳥、爬行動物、兩棲動物、魚、昆蟲及/或蠕蟲。在某些實施例中，非人類個體為哺乳動物(例如嚙齒動物、小鼠、大鼠、兔、猴、犬、貓、綿羊、牛、靈長類動物及/或豬)。在一些實施例中，個體可為基因轉殖動物、經基因工程改造之動物及/或純系。在本發明之某些實施例中，個體為成年人、青年或嬰兒。在一些實施例中，使用術語「個體(individual)」或「患者」且希望可與「個體(subject)」互換。

【0141】 如本文所用，細胞上蛋白質之表現「降低或消除」係指相對於未經修飾之細胞而言，蛋白質之表現部分或完全損失。在一些實施例

中，藉由流動式細胞量測術量測細胞上蛋白質之表面表現，且相對於未經修飾之細胞具有「降低或消除之」表面表現，如藉由用針對蛋白質之相同抗體染色後螢光訊號之減少所證明。藉由流動式細胞量測術相對於未經修飾之細胞具有「降低或消除之」蛋白質表面表現的細胞可稱作對於彼蛋白質之表現為「陰性的」，如藉由類似於用同型對照抗體染色之細胞的螢光訊號所證明。「降低或消除之」蛋白質表現係利用熟習此項技術者已知之適當對照，藉由此項技術中之其他已知技術來量測。

II. 例示性組合物及方法

【0142】 在一些實施例中，提供一種核酸，該核酸包含編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶之多肽之開讀框，其中多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。在一些實施例中，核酸為DNA或RNA。在一些實施例中，核酸為mRNA。在一些實施例中，提供一種由mRNA編碼之多肽。

【0143】 在一些實施例中，提供一種多肽或編碼多肽之mRNA，該多肽包含胞苷去胺酶及RNA導引之切口酶，其中多肽不包含UGI。在一些實施例中，胞苷去胺酶為A3A。在一些實施例中，RNA導引之切口酶不包含尿嘧啶醣苷酶抑制劑(UGI)。在一些實施例中，提供一種組合物，其包含：第一多肽或編碼第一多肽之mRNA，該第一多肽包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶；及第二多肽或編碼第二多肽之mRNA，該第二多肽包含尿嘧啶醣苷酶抑制劑(UGI)，其中第二多肽不同於第一多肽。

【0144】 在一些實施例中，提供一種組合物，其包含：第一核酸，其包含編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶之多肽的第

一開讀框；及第二核酸，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二核酸不同於第一核酸。在一些實施例中，第一核酸編碼不包含UGI之多肽。

【0145】 在一些實施例中，提供一種修飾目標基因之方法，其包含投與本文所描述之組合物。在一些實施例中，該方法包含向細胞遞送：第一核酸，其包含編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶之第一多肽的第一開讀框；及第二核酸，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二核酸不同於第一核酸。

【0146】 在一些實施例中，方法包含向細胞遞送包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶之多肽或編碼多肽之核酸，且單獨地(例如，不經由同一核酸構築體)向細胞遞送尿嘧啶醣苷酶抑制劑(UGI)或編碼UGI之核酸。

【0147】 在一些實施例中，編碼UGI之mRNA於編碼胞苷去胺酶(例如，A3A)及RNA導引之切口酶之mRNA的莫耳比為約1:35至約30:1。在一些實施例中，莫耳比為約1:25至約25:1。在一些實施例中，莫耳比為約1:20至約25:1。在一些實施例中，莫耳比為約1:10至約22:1。在一些實施例中，莫耳比為約1:5至約25:1。在一些實施例中，莫耳比為約1:1至約30:1。在一些實施例中，莫耳比為約2:1至約10:1。在一些實施例中，莫耳比為約5:1至約20:1。在一些實施例中，莫耳比為約1:1至約25:1。在一些實施例中，莫耳比可為約1:35、1:34、1:33、1:32、1:31、1:30、1:32、1:31、1:30、1:29、1:28、1:27、1:26、1:25、1:24、1:23、1:22、1:21、1:20、1:19、1:18、1:17、1:16、1:15、1:14、1:13、1:12、1:11、1:10、1:9、1:8、1:7、1:6、1:5、1:4、1:3、1:2、1:1、

2:1、3:1、4:1、5:1、6:1、7:1、8:1、9:1、10:1、11:1、12:1、13:1、14:1、15:1、16:1、17:1、18:1、19:1、20:1、21:1、22:1、23:1、24:1、25:1、26:1、27:1、28:1、29:1或30:1。在一些實施例中，莫耳比等於或大於約1:1。在一些實施例中，莫耳比約為1:1。在一些實施例中，莫耳比約為2:1。在一些實施例中，莫耳比約為3:1。在一些實施例中，莫耳比約為4:1。在一些實施例中，莫耳比約為5:1。在一些實施例中，莫耳比約為6:1。在一些實施例中，莫耳比約為7:1。在一些實施例中，莫耳比約為8:1。在一些實施例中，莫耳比約為9:1。在一些實施例中，莫耳比約為10:1。在一些實施例中，莫耳比約為11:1。在一些實施例中，莫耳比約為12:1。在一些實施例中，莫耳比約為13:1。在一些實施例中，莫耳比約為14:1。在一些實施例中，莫耳比約為15:1。在一些實施例中，莫耳比約為16:1。在一些實施例中，莫耳比約為17:1。在一些實施例中，莫耳比約為18:1。在一些實施例中，莫耳比約為19:1。在一些實施例中，莫耳比約為20:1。在一些實施例中，莫耳比約為21:1。在一些實施例中，莫耳比約為22:1。在一些實施例中，莫耳比約為23:1。在一些實施例中，莫耳比約為24:1。在一些實施例中，莫耳比約為25:1。

【0148】 類似地，在一些實施例中，若遞送蛋白質，則上文關於編碼UGI蛋白質之mRNA與編碼胞苷去胺酶(例如A3A)及RNA導引之切口酶之mRNA所論述之莫耳比類似。

【0149】 舉例而言，在一些實施例中，將遞送之待遞送至胞苷去胺酶(例如，A3A)及RNA導引之切口酶的UGI蛋白質之莫耳比為約1:35至約30:1。在一些實施例中，莫耳比為約1:1至約30:1。

【0150】 在一些實施例中，UGI肽與胞苷去胺酶(例如，A3A)及

RNA導引之切口酶之莫耳比為約10:1至約50:1。在一些實施例中，莫耳比可為約10:1、11:1、12:1、13:1、14:1、15:1、16:1、17:1、18:1、19:1、20:1、21:1、22:1、23:1、24:1、25:1、26:1、27:1、28:1、29:1、30:1、31:1、32:1、33:1、34:1、35:1、36:1、37:1、38:1、39:1、40:1、41:1、42:1、43:1、44:1、45:1、46:1、47:1、48:1、49:1或50:1。在一些實施例中，莫耳比為約10:1至約40:1。在一些實施例中，莫耳比為約10:1至約30:1。在一些實施例中，莫耳比約為2:1。在一些實施例中，莫耳比為約10:1至約20:1。在一些實施例中，莫耳比為約10:1至約15:1。在一些實施例中，莫耳比約為15:1至約50:1。在一些實施例中，莫耳比約為6:1。在一些實施例中，莫耳比約為20:1至約50:1。在一些實施例中，莫耳比約為8:1。在一些實施例中，莫耳比約為30:1至約50:1。在一些實施例中，莫耳比約為30:1至約40:1。在一些實施例中，莫耳比約為11:1。在一些實施例中，莫耳比約為20:1至約30:1。

【0151】在一些實施例中，本文中所描述之組合物進一步包含至少一種gRNA。在一些實施例中，提供一種組合物，其包含本文所述之mRNA及至少一種gRNA。在一些實施例中，gRNA為單導引gRNA (sgRNA)。在一些實施例中，gRNA為雙導引gRNA (dgRNA)。

【0152】在一些實施例中，組合物在投與個體之後能夠實現基因體編輯。

A. UGI

【0153】在不受任何理論束縛之情況下，提供UGI以及包含去胺酶之多肽可藉由抑制細胞DNA修復機構(例如UDG及下游修復效應子)而有助於本文所描述之方法，該等機構將識別DNA中之尿嘧啶作為DNA損傷

形式或以其他方式將切除或修飾尿嘧啶及/或周圍核苷酸。應理解，UGI之用途可提高能夠對C殘基進行去胺之酶之編輯效率。

【0154】本文中提供適合的UGI蛋白質及核苷酸序列，且其他適合UGI序列為熟習此技術者已知的，且包括例如以下所揭示：Wang等人，Uracil-DNA glycosylase inhibitor gene of bacteriophage PBS2 encodes a binding protein specific for uracil-DNA glycosylase. J. Biol. Chem. 264: 1163-1171(1989)；Lundquist等人，Site-directed mutagenesis and characterization of uracil-DNA glycosylase inhibitor protein. Role of specific carboxylic amino acids in complex formation with Escherichia coli uracil-DNA glycosylase. J. Biol. Chem. 272:21408-21419(1997)；Ravishankar等人，X-ray analysis of a complex of Escherichia coli uracil DNA glycosylase (EcUDG) with a proteinaceous inhibitor. The structure elucidation of a prokaryotic UDG. Nucleic Acids Res. 26:4880-4887(1998)；及Putnam等人，Protein mimicry of DNA from crystal structures of the uracil-DNA glycosylase inhibitor protein and its complex with Escherichia coli uracil-DNA glycosylase. J. Mol. Biol. 287:331-346(1999)，各者之全部內容以引用的方式併入本文中。應瞭解，能夠抑制尿嘧啶-DNA醣苷酶鹼基-切除修復酶之任何蛋白質均在本發明之範疇內。另外，阻斷或抑制鹼基切除修復之任何蛋白質亦在本發明之範疇內。在一些實施例中，尿嘧啶醣苷酶抑制劑為結合尿嘧啶之蛋白質。在一些實施例中，尿嘧啶醣苷酶抑制劑為結合DNA中之尿嘧啶之蛋白質。在一些實施例中，尿嘧啶醣苷酶抑制劑為單股結合蛋白。在一些實施例中，尿嘧啶醣苷酶抑制劑為無催化活性尿嘧啶DNA-醣苷酶蛋白質。在一些實施例

中，尿嘧啶醣苷酶抑制劑為不自DNA切除尿嘧啶之無催化活性尿嘧啶DNA-醣苷酶蛋白質。在一些實施例中，尿嘧啶醣苷酶抑制劑為無催化活性UDG。

【0155】在一些實施例中，本文中所揭示之尿嘧啶醣苷酶抑制劑(UGI)包含與SEQ ID NO: 27或43具有至少80%一致性之胺基酸序列。在一些實施例中，前述一致性水準中之任一者為至少90%、至少95%、至少98%、至少99%或100%。在一些實施例中，UGI包含與SEQ ID NO: 27或43具有至少90%一致性之胺基酸序列。在一些實施例中，UGI包含與SEQ ID NO: 27或43具有至少95%一致性之胺基酸序列。在一些實施例中，UGI包含與SEQ ID NO: 27或43具有至少98%一致性之胺基酸序列。在一些實施例中，UGI包含與SEQ ID NO: 27或43具有至少99%一致性之胺基酸序列。在一些實施例中，UGI包含SEQ ID NO: 27或43之胺基酸序列。

B. 胞苷去胺酶

【0156】胞苷去胺酶涵蓋胞苷去胺酶超家族中之酶，且特定言之APOBEC家族之酶(酶之APOBEC1、APOBEC2、APOBEC4及APOBEC3子群)、活性誘導之胞苷去胺酶(AID或AICDA)及CMP去胺酶(參見例如Conticello等人，Mol. Biol. Evol. 22:367-77, 2005；Conticello，Genome Biol. 9:229, 2008；Muramatsu等人，J. Biol. Chem. 274: 18470-6, 1999；及Carrington等人，Cells 9:1690 (2020))。

【0157】在一些實施例中，本文揭示之胞苷去胺酶係APOBEC家族之酶。在一些實施例中，本文所揭示之胞苷去胺酶為APOBEC1、APOBEC2、APOBEC4及APOBEC3子群之酶。在一些實施例中，本文揭示之胞苷去胺酶為APOBEC3子群之酶。在一些實施例中，本文揭示之胞

苷去胺酶為APOBEC3A去胺酶(A3A)。

【0158】 在一些實施例中，胞苷去胺酶為：

(i) APOBEC家族之酶，視情況為APOBEC3子群之酶；

(ii)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iii)包含與SEQ ID NO: 40、41及960至1013中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iv)包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；或

(v)包含與SEQ ID NO: 40、976、981、984、986及1014至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶。

【0159】 在一些實施例中，胞苷去胺酶為包含與SEQ ID NO: 40、41及960至1023具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列之胞苷去胺酶。在一些實施例中，胞苷去胺酶為包含與SEQ ID NO: 40、41及960至1013中之任一者至少80%、85%、87%、90%、95%、98%、99%或100%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，胞苷去胺酶為包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少80%、85%、87%、90%、95%、98%、99%或100%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，胞苷去胺酶為包含與SEQ ID NO: 40、976、981、984、986及1014至1023中之任一者至少80%、85%、87%、90%、95%、98%、99%或100%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，

胞苷去胺酶為包含與SEQ ID NO: 976、977、993至1006及1009至少80%、85%、87%、90%、95%、98%、99%或100%一致之胺基酸序列的胞苷去胺酶。

1. APOBEC3A去胺酶

【0160】在一些實施例中，本文中所揭示之APOBEC3A去胺酶(A3A)為人類A3A。在一些實施例中，A3A為野生型A3A。

【0161】在一些實施例中，A3A為A3A變異體。A3A變異體與野生型A3A或其片段共享同源性。在一些實施例中，A3A變異體與野生型A3A具有至少約80%一致性、至少約85%一致性、至少約90%一致性、至少約95%一致性、至少約96%一致性、至少約97%一致性、至少約98%一致性、至少約99%一致性、至少約99.5%一致性或至少約99.9%一致性。在一些實施例中，與野生型A3A相比較，A3A變異體可具有1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、21、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50個或更多個胺基酸改變。在一些實施例中，A3A變異體包含A3A之片段，使得該片段與野生型A3A之對應片段具有至少約80%一致性、至少約90%一致性、至少約95%一致性、至少約96%一致性、至少約97%一致性、至少約98%一致性、至少約99%一致性、至少約99.5%一致性或至少約99.9%一致性。

【0162】在一些實施例中，A3A變異體為具有與野生型A3A蛋白質相差一個或若干個突變之序列之蛋白質，該一個或若干個突變諸如取代、缺失、插入、一個或若干個單點取代。在一些實施例中，縮短A3A序列可

例如，藉由使N末端、C末端或內部胺基酸確實來使用。在一些實施例中，使用縮短的A3A序列，其中序列之C末端處之一至四個胺基酸缺失。在一些實施例中，APOBEC3A (諸如人類APOBEC3A)具有野生型胺基酸位置57 (如野生型序列中所編號)。在一些實施例中，APOBEC3A (諸如人類APOBEC3A)在胺基酸位置57 (如野生型序列中所編號)處具有天冬醯胺。

【0163】 在一些實施例中，野生型A3A為人類A3A (UniPROT寄存ID: p319411, SEQ ID NO: 40)。

【0164】 在一些實施例中，本文中所揭示之A3A包含與SEQ ID NO: 40具有至少80%一致性之胺基酸序列。在一些實施例中，一致性水準為至少85%、至少87%、至少90%、至少95%、至少98%、至少99%或100%。在一些實施例中，A3A包含與SEQ ID NO: 40具有至少87%一致性之胺基酸序列。在一些實施例中，A3A包含與SEQ ID NO: 40具有至少90%一致性之胺基酸序列。在一些實施例中，A3A包含與SEQ ID NO: 40具有至少95%一致性之胺基酸序列。在一些實施例中，A3A包含與SEQ ID NO: 40具有至少98%一致性之胺基酸序列。在一些實施例中，A3A包含與A3A ID NO: 40具有至少99%一致性之胺基酸序列。在一些實施例中，A3A包含SEQ ID NO: 40之胺基酸序列。

C. 連接子

【0165】 在一些實施例中，包含本文中所描述之A3A及RNA導引之切口酶的多肽進一步包含連接A3A與RNA導引之切口酶之連接子。在一些實施例中，連接子為有機分子、聚合物或化學部分。在一些實施例中，連接子為肽連接子。在一些實施例中，編碼包含A3A及RNA導引之切口

酶之多肽的核酸進一步包含編碼肽連接子之序列。提供編碼A3A-連接子-RNA-導引之切口酶融合蛋白質之mRNA。

【0166】在一些實施例中，肽連接子為具有至少1個、至少2個、至少3個、至少4個、至少5個、至少6個、至少7個、至少8個、至少9個、至少10個、至少15個、至少20個、至少25個、至少30個、至少40個、至少50個或更多個胺基酸之任一段胺基酸。

【0167】在一些實施例中，肽連接子為16個殘基「XTEN」連接子或其變異體(參見例如實例；及Schellenberger等人，A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner. Nat. Biotechnol. 27, 1186-1190 (2009))。在一些實施例中，XTEN連接子包含為SGSETPGTSESATPES (SEQ ID NO: 46)、SGSETPGTSESA (SEQ ID NO: 47)或SGSETPGTSESATPEGGSGGS (SEQ ID NO: 48)中之任一者之序列。在一些實施例中，XTEN連接子由序列SGSETPGTSESATPES (SEQ ID NO: 46)、SGSETPGTSESA (SEQ ID NO: 47)或SGSETPGTSESATPEGGSGGS (SEQ ID NO: 48)組成。

【0168】在一些實施例中，肽連接子包含$(GGGGS)_n$ (例如，SEQ ID NO: 212、216、221、240)、$(G)_n$、$(EAAAK)_n$ (e.g., SEQ ID NOs: 213、219、267)、$(GGS)_n$、SGSETPGTSESATPES (SEQ ID NO: 46)模體(參見例如Guilinger J P、Thompson D B、Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82；其全部內容以引用的方式併入本文中)，或$(XP)_n$模體，或此等中之任一者之組合，其中n獨立地為1與30之間的整數。參見WO2015089406，例如段落[0012]，其全部

內容以引用的方式併入本文中。

【0169】在一些實施例中，肽連接子包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列。在一些實施例中，肽連接子包含選自SEQ ID NO: 46、SEQ ID NO: 47、SEQ ID NO: 48、SEQ ID NO: 268、SEQ ID NO: 269、SEQ ID NO: 270、SEQ ID NO: 271及SEQ ID NO: 272之一或多個序列。在一些實施例中，肽連接子包含序列SEQ ID NO: 268。

D. RNA導引之切口酶

【0170】在一些實施例中，本文中所揭示之RNA導引之切口酶為Cas切口酶。在一些實施例中，RNA導引之切口酶來自特異性Cas核酸酶，其中其催化域未活化。在一些實施例中，RNA導引之切口酶為2類Cas切口酶，諸如Cas9切口酶或Cpf1切口酶。在一些實施例中，RNA導引之切口酶為化膿性鏈球菌Cas9切口酶。在一些實施例中，RNA導引之切口酶為腦膜炎雙球菌(*Neisseria meningitidis*) Cas9切口酶。

【0171】在一些實施例中，RNA導引之切口酶為經修飾之2類Cas蛋白質或衍生自2類Cas蛋白質。在一些實施例中，RNA導引之切口酶經修飾或衍生自Cas蛋白質，諸如2類Cas核酸酶(其可例如，為II型、V型或VI型Cas核酸酶)。2類Cas核酸酶包括例如Cas9、Cpf1、C2c1、C2c2及C2c3蛋白質及其修飾。Cas9核酸酶之實例包括化膿性鏈球菌、金黃色葡萄球菌(*S. aureus*)及其他原核生物(參見例如下一段落中之清單)之II型CRISPR系統之彼等及其經修飾(例如，經工程改造或突變)之型式。參見例如US2016/0312198 A1；US 2016/0312199 A1，其以全文引用的方式併入本文中。Cas核酸酶之其他實例包括III型CRISPR系統之Csm或Cmr複合物

或其Cas10、Csm1或Cmr2次單元；及I型CRISPR系統之級聯複合物或其Cas3次單元。在一些實施例中，Cas核酸酶可來自第IIA型、第IIB型或第IIC型系統。關於各種CRISPR系統及Cas核酸酶之論述，參見例如Makarova等人，NAT. REV. MICROBIOL. 9:467-477 (2011)；Makarova等人，NAT. REV. MICROBIOL, 13: 722-36 (2015)；Shmakov等人，MOLECULAR CELL, 60:385-397 (2015)。

【0172】本文中所描述之Cas切口酶可為來自包括但不限於以下物種之Cas核酸酶之切口酶形式：釀膿鏈球菌(Streptococcus pyogenes)、嗜熱鏈球菌(Streptococcus thermophiles)、鏈球菌屬、金黃色葡萄球菌(Staphylococcus aureus)、無害李氏菌(Listeria innocua)、加氏乳桿菌(Lactobacillus gasseri)、新兇手弗朗西斯氏菌(Francisella novicida)、產琥珀酸沃廉菌(Wolinella succinogenes)、華德薩特菌(Sutterella wadsworthensis)、伽馬變形菌(Gammaproteobacterium)、腦膜炎雙球菌、空腸彎曲桿菌(Campylobacter jejuni)、多殺巴斯德菌(Pasteurella multocida)、產琥珀酸纖維桿菌(Fibrobacter succinogene)、深紅紅螺菌(Rhodospirillum rubrum)、達松維爾擬諾卡氏菌(Nocardiopsis dassonvillei)、始旋鏈黴菌(Streptomyces pristinaespiralis)、產綠色鏈黴菌(*Streptomyces viridochromogenes*)、粉紅鏈孢囊菌(*Streptosporangium roseum*)、嗜酸熱脂環桿菌(Alicyclobacillus acidocaldarius)、假蕈狀芽孢桿菌(Bacillus pseudomycoides)、砷還原芽孢桿菌(Bacillus selenitireducens)、西伯利亞微小桿菌(Exiguobacterium sibiricum)、戴白氏乳桿菌(Lactobacillus delbrueckii)、唾液乳桿菌(Lactobacillus salivarius)、布氏乳桿菌(Lactobacillus buchneri)、齒垢密螺旋體

(Treponema denticola)、海洋微顫菌(Microscilla marina)、伯克霍爾德氏細菌(Burkholderiales bacterium)、食萘極地單胞菌(Polaromonas naphthalenivorans)、單胞菌屬(Polaromonas sp.)、瓦氏鱷球藻(Crocosphaera watsonii)、鱷球藻屬、銅綠微囊藻(Microcystis aeruginosa)、聚球藻屬(Synechococcus sp.)、阿拉伯糖醋桿菌(Acetohalobium arabaticum)、根制氨菌(Ammonifex degensii)、熱解纖維素菌(Caldicelulosiruptor becscii)、輻射合成細菌(Candidatus Desulforudis)、肉毒梭菌(Clostridium botulinum)、艱難梭菌(Clostridium difficile)、大芬戈爾德菌(Finegoldia magna)、嗜熱鹽鹼厭氧菌(Natranaerobius thermophiles)、嗜熱丙酸厭氧腸狀菌(Pelotomaculum thermopropionicum)、嗜酸性喜溫硫桿菌(Acidithiobacillus caldus)、嗜酸氧化亞鐵硫桿菌(Acidithiobacillus ferrooxidans)、酒色異著色菌(Allochromatium vinosum)、海桿菌屬(Marinobacter sp.)、嗜鹽亞硝化球菌(Nitrosococcus halophilus)、瓦氏亞硝化球菌(Nitrosococcus watsoni)、遊海假交替單胞菌(Pseudoalteromonas haloplanktis)、Ktedonobacter racemifer、發現甲烷耐鹽菌(Methanohalobium evestigatum)、變異念珠藻(Anabaena variabilis)、泡沫節球藻(Nodularia spumigena)、念珠藻屬(Nostoc sp.)、極大節旋藻(Arthrospira maxima)、鈍頂節旋藻(Arthrospira platensis)、節旋藻屬(Arthrospira sp.)、螺旋藻屬(Lyngbya sp.)、原型微鞘藻(Microcoleus chthonoplastes)、顫藻屬(Oscillatoria sp.)、運動石袍菌(Petrotoga mobilis)、非洲高熱桿菌(Thermosipho africanus)、巴氏鏈球菌(Streptococcus pasteurianus)、灰色奈瑟球菌(Neisseria cinerea)、紅嘴

鷗彎曲桿菌(Campylobacter lari)、食清潔劑細小棒菌(Parvibaculum lavamentivorans)、白喉棒狀桿菌(Corynebacterium diphtheria)、胺基酸球菌屬(Acidaminococcus sp.)、毛螺科菌(Lachnospiraceae bacterium) ND2006或海洋無核氯菌(Acaryochloris marina)。

【0173】在一些實施例中，Cas切口酶為來自釀膿鏈球菌之Cas9核酸酶之切口酶形式。在一些實施例中，Cas切口酶為來自嗜熱鏈球菌之Cas9核酸酶之切口酶形式。在一些實施例中，Cas切口酶為來自腦膜炎雙球菌之Cas9核酸酶之切口酶形式。參見例如WO/2020081568，描繪Nme2Cas9 D16A切口酶。在一些實施例中，Cas切口酶為來自金黃色葡萄球菌之Cas9核酸酶之切口酶形式。在一些實施例中，Cas切口酶為來自新兇手弗朗西斯氏菌之Cpf1核酸酶之切口酶形式。在一些實施例中，Cas切口酶為來自胺基酸球菌屬之Cpf1核酸酶之切口酶形式。在一些實施例中，Cas切口酶為來自毛螺科菌ND2006之Cpf1核酸酶之切口酶形式。在其他實施例中，Cas切口酶為來自以下之Cpf1核酸酶之切口酶形式：土拉文氏桿菌(*Francisella tularensis*)、毛螺科菌、瘤胃溶纖維丁酸弧菌(*Butyrivibrio proteoclasticus*)、佩氏細菌(*Peregrinibacteria bacterium*)、帕庫氏菌(*Parcubacteria bacterium*)、史密斯氏菌(*Smithella*)、胺基酸球菌屬、白蟻甲烷支原體菌候選種(*Candidatus Methanoplasma termitum*)、挑剔真桿菌(*Eubacterium eligens*)、牛眼莫拉菌(*Moraxella bovoculi*)、稻田鉤端螺旋體(*Leptospira inadai*)、狗口腔卟啉單胞菌(*Porphyromonas crevioricanis*)、解糖胨普雷沃菌(*Prevotella disiens*)或獼猴卟啉單胞菌(*Porphyromonas macacae*)。在某些實施例中，Cas切口酶為來自胺基酸球菌屬或毛螺菌科之Cpf1核酸酶之切口酶形式。

如別處所論述，切口酶可衍生自(亦即，相關於)特異性Cas核酸酶，因為切口酶為核酸酶之形式，其中其兩個催化域中之一者例如，藉由使核溶解必不可少之活性位點殘基突變，諸如Spy Cas9中之D10、H840或N863而失活。熟習此項技術者將熟悉容易地識別其他Cas蛋白質中之對應殘基之技術，諸如序列比對及結構比對，其將在下文詳細論述。

【0174】 在其他實施例中，Cas切口酶可係關於I型CRISPR/Cas系統。在一些實施例中，Cas切口酶可為I型CRISPR/Cas系統之級聯複合物之組分。在一些實施例中，Cas切口酶可為Cas3蛋白質。在一些實施例中，Cas切口酶可來自III型CRISPR/Cas系統。

【0175】 在一些實施例中，Cas切口酶為其中例如，藉由催化域中之一或多個變化(例如，點突變)使核酸內切酶活性位點不活化的Cas核酸酶或經修飾之Cas核酸酶之切口酶形式。參見例如關於Cas切口酶及例示性催化域改變之論述之美國專利第8,889,356號。

【0176】 野生型化膿性鏈球菌Cas9具有兩個催化域：RuvC及HNH。RuvC域裂解非目標DNA股，且HNH域裂解DNA之目標股。在一些實施例中，Cas核酸酶可在RuvC或類RuvC核酸酶域中包含胺基酸取代。RuvC或類RuvC核酸酶域中之例示性胺基酸取代包括D10A (基於化膿性鏈球菌Cas9蛋白質)。參見例如Zetsche等人(2015) *Cell* 10月22:163(3):759-771。在一些實施例中，Cas核酸酶可包含HNH或類HNH核酸酶域中之胺基酸取代。HNH或類HNH核酸酶域中之例示性胺基酸取代包括E762A、H840A、N863A、H983A及D986A (基於化膿性鏈球菌Cas9蛋白質)。參見例如Zetsche等人(2015)。其他例示性胺基酸取代包括D917A、E1006A及D1255A (基於新兇手弗朗西斯氏菌U112 Cpf1 (FnCpf1)序列

(UniProtKB-A0Q7Q2(CPF1_FRATN))。

【0177】 在一些實施例中，Cas切口酶，諸如Cas9切口酶具有非活性的RuvC或HNH域。在一些實施例中，使用具有活性降低之RuvC域之切口酶。在一些實施例中，使用具有非活性RuvC域之切口酶。在一些實施例中，使用具有活性降低之HNH域之切口酶。在一些實施例中，使用具有非活性HNH域之切口酶。

【0178】 在一些實施例中，Cas9切口酶具有活性HNH核酸酶域且能夠裂解DNA之非靶向股，亦即與gRNA結合之股，且具有非活性RuvC核酸酶域且不能裂解DNA之靶向股，亦即需要去胺酶進行鹼基編輯之股。

【0179】 例示性Cas9切口酶胺基酸序列提供為SEQ ID NO: 70。包括起始及終止密碼子之例示性Cas9切口酶mRNAORF序列提供為SEQ ID NO: 71。適合於包括於融合蛋白質中之例示性Cas9切口酶mRNA編碼序列提供為SEQ ID NO: 72。

【0180】 在一些實施例中，RNA導引之切口酶為本文中所描述之2類Cas切口酶。在一些實施例中，RNA導引之切口酶為本文中所描述之Cas9切口酶。

【0181】 在一些實施例中，RNA導引之切口酶為本文中所描述之化膿性鏈球菌Cas9切口酶。

【0182】 在一些實施例中，RNA導引之切口酶為本文中所描述之D10A SpyCas9切口酶。在一些實施例中，RNA導引之切口酶包含與SEQ ID NO: 70、73或76具有至少80%、90%、95%、98%或99%一致性之胺基酸序列。在一些實施例中，RNA導引之切口酶包含SEQ ID NO: 70之胺基酸序列。

【0183】 在一些實施例中，mRNA ORF序列包含編碼RNA導引之切口酶，其包括起始及終止密碼子，包含與SEQ ID NO: 71、74或77中之任一者之核苷酸序列具有至少80%、90%、95%、98%、99%或100%一致性的核苷酸序列。在一些實施例中，編碼RNA導引之切口酶之mRNA序列包含與SEQ ID NO: 72、75或78中之任一者之核苷酸序列具有至少80%、90%、95%、98%、99%或100%一致性的核苷酸序列。在一些實施例中，一致性水準為至少90%。在一些實施例中，一致性水準為至少95%。在一些實施例中，一致性水準為至少98%。在一些實施例中，一致性水準為至少99%。在一些實施例中，一致性水準為至少100%。在一些實施例中，編碼RNA導引之切口酶之序列包含SEQ ID NO: 71、72、74、75、77或78中之任一者之核苷酸序列。

【0184】 在一些實施例中，RNA導引之切口酶為本文中所描述之腦膜炎雙球菌(Nme) Cas9切口酶。

【0185】 在一些實施例中，RNA導引之切口酶為本文中所描述之D16A NmeCas9切口酶。在一些實施例中，D16A NmeCas9切口酶為D16A Nme2Cas9切口酶。在一些實施例中，D16A Nme2Cas9切口酶包含與SEQ ID NO: 387至少80%、90%、95%、98%、99%或100%一致之胺基酸序列。在一些實施例中，編碼D16A Nme2Cas9之序列包含與SEQ ID NO: 388至393中之任一者至少80%、90%、95%、98%、99%或100%一致的核苷酸序列。

E. 包含胞苷去胺酶及RNA導引之切口酶的組合物

【0186】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA，其中多肽不包含尿嘧啶醣苷酶抑制劑

(UGI)。

1. 例示性組合物

【0187】 如本文所描述，提供包含mRNA之組合物、方法及用途，該mRNA包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框，其中多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。對於下文描述之每一例示性組合物，mRNA不包含UGI。

【0188】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA。在一些實施例中，提供APOBEC家族之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC1子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC2子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC4子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC3子群之酶及RNA導引之切口酶。

【0189】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA。在一些實施例中，提供APOBEC家族之酶及D10A SpyCas9切口酶。在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶。在一些實施例中，多肽包含APOBEC2子群之酶及D10A SpyCas9切口酶。在一些實施例中，多肽包含APOBEC4子群之酶及D10A SpyCas9切口酶。在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶。

【0190】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA。在一些實施例中，提供APOBEC家族之酶及D16A NmeCas9切口酶。在一些實施例中，提供APOBEC家族之酶及

D16A Nme2Cas9切口酶。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶。在一些實施例中，多肽包含APOBEC2子群之酶及D16A Nme2Cas9切口酶。在一些實施例中，多肽包含APOBEC4子群之酶及D16A Nme2Cas9切口酶。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶。

【0191】 在一些實施例中，多肽缺少UGI。

【0192】 在一些實施例中，胞苷去胺酶及RNA導引之切口酶經由連接子連接。在一些實施例中，胞苷去胺酶及RNA導引之切口酶經由肽連接子連接。在一些實施例中，肽連接子包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列。

【0193】 在一些實施例中，多肽進一步包含一或多個額外異源功能域。在一些實施例中，多肽在多肽之C末端或多肽之N末端進一步包含一或多個核定位序列(NLS) (本文中所描述)。

【0194】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA。在一些實施例中，提供APOBEC家族之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC1子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC2子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC4子群之酶及RNA導引之切口酶。在一些實施例中，多肽包含APOBEC3子群之酶及RNA導引之切口酶。

【0195】 在一些實施例中，提供一種編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的mRNA。在一些實施例中，APOBEC家族之酶及D10A SpyCas9切口酶，其中APOBEC家族之酶及D10A SpyCas9切口酶

經由連接子融合。在一些實施例中，多肽包含APOBEC家族之酶及D10A SpyCas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC家族之酶及D10A SpyCas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC家族之酶及D10A SpyCas9切口酶，其中APOBEC家族之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。在一些實施例中，多肽包含APOBEC家族之酶及D10A SpyCas9切口酶，其中APOBEC家族之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。

【0196】在一些實施例中，多肽包含APOBEC家族之酶及D16A NmeCas9切口酶，其中APOBEC家族之酶及D16A NmeCas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC家族之酶及D16A Nme2Cas9切口酶，其中APOBEC家族之酶及D16A Nme2Cas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC家族之酶及D16A Nme2Cas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC家族之酶及D16A Nme2Cas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC家族之酶及D16A Nme2Cas9切口酶，其中APOBEC家族之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D16A Nme2Cas9切口酶之C末端。在一些實施例中，多肽包含APOBEC家族之酶及D16A Nme2Cas9切口酶，其中APOBEC家族之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至

D16A Nme2Cas9切口酶之C末端。

【0197】在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶，其中APOBEC1子群之酶及D10A SpyCas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶，其中APOBEC1子群之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。在一些實施例中，多肽包含APOBEC1子群之酶及D10A SpyCas9切口酶，其中APOBEC1子群之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。

【0198】在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶，其中APOBEC1子群之酶及D16A Nme2Cas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶，其中APOBEC1子群之酶及D16A Nme2Cas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶，其中APOBEC1子群之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至

D16A Nme2Cas9切口酶之C末端。在一些實施例中，多肽包含APOBEC1子群之酶及D16A Nme2Cas9切口酶，其中APOBEC1子群之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D16A Nme2Cas9切口酶之C末端。

【0199】在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶，其中APOBEC3子群之酶及D10A SpyCas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶，其中APOBEC3子群之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。在一些實施例中，多肽包含APOBEC3子群之酶及D10A SpyCas9切口酶，其中APOBEC3子群之酶及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。

【0200】在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶，其中APOBEC3子群之酶及D16A Nme2Cas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶，其中APOBEC3子群之酶及D16A Nme2Cas9切口酶經由連接子融合。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶以及

位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶，其中APOBEC3子群之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D16A Nme2Cas9切口酶之C末端。在一些實施例中，多肽包含APOBEC3子群之酶及D16A Nme2Cas9切口酶，其中APOBEC3子群之酶及D16A Nme2Cas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D16A Nme2Cas9切口酶之C末端。

【0201】在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 268之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 269之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 270之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 271之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 272之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致

之胺基酸序列的胞苷去胺酶。在前述實施例中之任一者中，D10A SpyCas9切口酶可包含與SEQ ID NO: 70、73或76中之任一者至少85%、至少90%、至少95%、至少98%、至少99%或100%一致的胺基酸序列。

【0202】在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 268之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 269之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 270之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 271之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 272之連接子及包含與SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少85%一致之胺基酸序列的胞苷去胺酶。在前述實施例中之任一者中，D16A Nme2Cas9切口酶可包含與SEQ ID NO: 387至少85%、至少90%、至少95%、至少98%、至少99%或100%一致之胺基酸序列。

【0203】在一些實施例中，多肽包含D10A SpyCas9切口酶、包含

胺基酸序列SEQ ID NO: 268之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 269之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 270之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 271之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D10A SpyCas9切口酶、包含胺基酸序列SEQ ID NO: 272之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在前述實施例中之任一者中，D10A SpyCas9包含與SEQ ID NO: 70、73或76中之任一者至少85%、至少90%、至少95%、至少98%、至少99%或100%一致的胺基酸序列。

【0204】 在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 268之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 269之連接子及包含選自SEQ ID NO:

40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 270之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 271之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在一些實施例中，多肽包含D16A Nme2Cas9切口酶、包含胺基酸序列SEQ ID NO: 272之連接子及包含選自SEQ ID NO: 40、41、976、977、979、980、984至987、993至1006及1009中之任一者之胺基酸序列的胞苷去胺酶。在前述實施例中之任一者中，D16A Nme2Cas9切口酶包含與SEQ ID NO: 387至少85%、至少90%、至少95%、至少98%、至少99%或100%一致之胺基酸序列。

【0205】 多肽可以多種方式組織以形成單鏈。NLS可為N末端或C末端，或同時為N末端及C末端，且與RNA導引之切口酶相比，胞苷去胺酶可為N末端或C末端。在一些實施例中，多肽自N末端至C末端包含胞苷去胺酶、視情況存在之連接子、RNA導引之切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含RNA導引之切口酶、視情況存在之連接子、胞苷去胺酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子及胞苷去胺酶。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子及胞苷去

胺酶及視情況存在之NLS。

【0206】在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、APOBEC家族之酶、視情況存在之連接子、RNA導引之切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC家族之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC家族之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC家族之酶及視情況存在之NLS。

【0207】在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、APOBEC3子群之酶、視情況存在之連接子、RNA導引之切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC3子群之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC3子群之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子、APOBEC3子群之酶及視情況存在之NLS。

【0208】在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、APOBEC家族之酶、視情況存在之連接子、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或

D16A Nme2Cas9切口酶、視情況存在之連接子、APOBEC家族之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶、視情況存在之連接子、APOBEC家族之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶、視情況存在之連接子及APOBEC家族之酶及視情況存在之NLS。

【0209】 在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、APOBEC3子群之酶、視情況存在之連接子、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶、視情況存在之連接子、APOBEC3子群之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶、視情況存在之連接子、APOBEC3子群之酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、D10A SpyCas9切口酶或D16A Nme2Cas9切口酶、視情況存在之連接子及APOBEC3子群之酶及視情況存在之NLS。

【0210】 在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、APOBEC3子群之酶、視情況存在之連接子、D16A Nme2Cas9切口酶。

【0211】 在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii)包含與SEQ ID NO: 40、41及960至1023中之任一者至少

80%一致之胺基酸序列的胞苷去胺酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；以及(v)視情況存在之NLS。

【0212】 在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

【0213】 在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

【0214】 在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv)包含與SEQ ID NO:40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

【0215】 在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；以及(v)視情況存在之NLS。

【0216】在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

【0217】在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；(iv)包含與SEQ ID NO: 40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

【0218】在一些實施例中，多肽自N末端至C末端包含：(i)視情況存在之NLS；(ii) D10A SpyCas9切口酶或D16A Nme2Cas9切口酶；(iii)包含選自SEQ ID NO: 46至59、61及211至272之一或多個序列的連接子；及(iv)包含與SEQ ID NO:40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；以及(v)視情況存在之NLS。

2. 包含APOBEC3A去胺酶及RNA導引之切口酶的組合物

【0219】在一些實施例中，提供一種編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的mRNA。在一些實施例中，多肽包含人類A3A及RNA導引之切口酶。在一些實施例中，多肽包含野生型A3A及RNA導引之切口酶。在一些實施例中，多肽包含A3A變異體及RNA導引之切口酶。在一些實施例中，多肽包含A3A及Cas9切口酶。在一些實施例中，多肽包含A3A及D10A SpyCas9切口酶。在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶。在一些實施例中，多肽包含A3A

變異體及D10A SpyCas9切口酶。在一些實施例中，多肽缺少UGI。在一些實施例中，A3A及RNA導引之切口酶經由連接子連接。在一些實施例中，多肽進一步包含一或多個額外異源功能域。在一些實施例中，多肽在多肽之C末端或多肽之N末端處進一步包含核定位序列(NLS) (本文中所描述)。

【0220】 在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶，其中人類A3A及D10A SpyCas9切口酶經由連接子融合。在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶以及位於融合多肽之C末端處的核定位序列(NLS)。在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶以及位於融合多肽之N末端處的NLS。在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶，其中人類A3A及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。在一些實施例中，多肽包含人類A3A及D10A SpyCas9切口酶，其中人類A3A及D10A SpyCas9切口酶經由連接子融合，且NLS視情況經由連接子融合至D10A SpyCas9切口酶之C末端。

【0221】 多肽可以多種方式組織以形成單鏈。NLS可為N末端或C末端，或同時為N末端及C末端，且與RNA導引之切口酶相比，A3A可為N末端或C末端。在一些實施例中，多肽自N末端至C末端包含A3A、視情況存在之連接子、RNA導引之切口酶及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含RNA導引之切口酶、視情況存在之連接子、A3A及視情況存在之NLS。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子及

A3A。在一些實施例中，多肽自N末端至C末端包含視情況存在之NLS、RNA導引之切口酶、視情況存在之連接子及A3A及視情況存在之NLS。

【0222】 在前述實施例中之任一者中，多肽可包含與SEQ ID NO: 3或6具有至少80%一致性之胺基酸序列。在一些實施例中，前述一致性水準中之任一者為至少85%、至少90%、至少95%、至少98%、至少99%或100%。在一些實施例中，本文揭示之多肽可包含與SEQ ID NO: 3或6具有至少90%一致性之胺基酸序列。在一些實施例中，本文揭示之多肽可包含與SEQ ID NO: 3或6具有至少95%一致性之胺基酸序列。在一些實施例中，本文揭示之多肽可包含與SEQ ID NO: 3或6具有至少98%一致性之胺基酸序列。在一些實施例中，本文揭示之多肽可包含與SEQ ID NO: 3或6具有至少99%一致性之胺基酸序列。在一些實施例中，本文揭示之多肽可包含SEQ ID NO: 3或6之胺基酸序列。

【0223】 在前述實施例中之任一者中，包含編碼本文揭示之多肽之開讀框的核酸序列可包含與SEQ ID NO: 2或5具有至少80%一致性之核酸序列。在一些實施例中，前述一致性水準中之任一者為至少85%、至少90%、至少95%、至少98%、至少99%或100%。

【0224】 在前述實施例中之任一者中，編碼本文揭示之多肽的mRNA序列可包含與SEQ ID NO: 1或4具有至少80%一致性之核酸序列。在一些實施例中，前述一致性水準中之任一者為至少85%、至少90%、至少95%、至少98%、至少99%或100%。

【0225】 在以上實施例中之任一者中，多肽可包含與SEQ ID NO: 303、306、309或312具有至少80%、至少90%、至少95%、至少98%、至少99%或100%一致性之胺基酸序列。在一些實施例中，本文揭示之多肽

可包含SEQ ID NO: 303、306、309或312之胺基酸序列。在前述實施例中之任一者中，包含編碼本文揭示之多肽之開讀框的核酸序列可包含與SEQ ID NO: 302、305、308或311具有至少80%、至少90%、至少95%、至少98%、至少99%或100%一致性之核酸序列。在一些實施例中，包含編碼本文揭示之多肽之開讀框的核酸序列包含SEQ ID NO: 302、305、308或311之核酸序列。在前述實施例中之任一者中，編碼本文揭示之多肽的mRNA序列可包含與SEQ ID NO: 301、304、307或310具有至少80%、至少90%、至少95%、至少98%、至少99%或100%一致性的核酸序列。在前述實施例中之任一者中，編碼本文揭示之多肽的mRNA序列可包含SEQ ID NO: 301、304、307或310之核酸序列。

【0226】 在以上實施例中之任一者中，A3A可包含與SEQ ID NO: 40具有至少80%一致性之胺基酸序列。在一些實施例中，一致性水準為至少85%、至少87%、至少90%、至少95%、至少98%、至少99%或100%。在一些實施例中，A3A包含SEQ ID NO: 40之胺基酸序列。

【0227】 在以上實施例中之任一者中，RNA導引之切口酶可包含與SEQ ID NO: 70、73或76中之任一者具有至少80%、90%、95%、98%或99%一致性之胺基酸序列。在一些實施例中，一致性水準為至少85%、至少87%、至少90%、至少95%、至少98%、至少99%或100%。在一些實施例中，RNA導引之切口酶包含SEQ ID NO: 70之胺基酸序列。在一些實施例中，RNA導引之切口酶包含SEQ ID NO: 73之胺基酸序列。在一些實施例中，RNA導引之切口酶包含SEQ ID NO: 76之胺基酸序列。

【0228】 在以上實施例中之任一者中，A3A可包含與SEQ ID NO: 40具有至少80%一致性之胺基酸序列，且RNA導引之切口酶可包含與SEQ

ID NO: 70、73或76中之任一者具有至少80%、90%、95%、98%或99%一致性之胺基酸序列。在一些實施例中，A3A包含SEQ ID NO: 40之胺基酸序列，且RNA導引之切口酶包含SEQ ID NO: 70之胺基酸序列。

F. 額外特徵

1. 密碼子-最佳化

【0229】 在一些實施例中，包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶的UGI或多肽由包含經密碼子最佳化之核酸序列的開讀框(ORF)編碼。在一些實施例中，經密碼子最佳化之核酸序列包含最少腺嘌呤密碼子及/或最少尿苷密碼子。

【0230】 可例如藉由在ORF之足夠多的一部分中使用最小尿苷密碼子來降低給定ORF之尿苷含量或尿苷二核苷酸含量。舉例而言，可藉由將胺基酸轉化成密碼子而將本文中所描述之多肽的胺基酸序列轉譯回ORF序列，其中ORF中之一些或全部使用以下所示之例示性最小尿苷密碼子。在一些實施例中，ORF中至少約50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表1中所列出之密碼子。

表1.例示性最小尿苷密碼子

	胺基酸	最小尿苷密碼子
A	丙胺酸	GCA或GCC或GCG
G	甘胺酸	GGA或GGC或GGG
V	纈胺酸	GUC或GUA或GUG
D	天冬胺酸	GAC
E	麩胺酸	GAA或GAG
I	異白胺酸	AUC或AUA
T	蘇胺酸	ACA或ACC或ACG
N	天冬醯胺酸	AAC
K	離胺酸	AAG或AAA
S	絲胺酸	AGC
R	精胺酸	AGA或AGG

L	白胺酸	CUG或CUA或CUC
P	脯胺酸	CCG或CCA或CCC
H	組胺酸	CAC
Q	麩醯胺酸	CAG或CAA
F	苯丙胺酸	UUC
Y	酪胺酸	UAC
C	半胱胺酸	UGC
W	色胺酸	UGG
M	甲硫胺酸	AUG

【0231】 在一些實施例中，ORF可由一組密碼子組成，其中至少約75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表1中所列出之密碼子。

【0232】 可例如藉由在ORF之足夠多的一部分中使用最小腺嘌呤密碼子來降低給定ORF之腺嘌呤含量或腺嘌呤二核苷酸含量。舉例而言，可藉由將胺基酸轉化成密碼子而將本文中所描述之多肽的胺基酸序列轉譯回ORF序列，其中ORF中之一些或全部使用以下所示之例示性最小腺嘌呤密碼子。在一些實施例中，ORF中至少約50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表2中所列出之密碼子。

表2.例示性最小腺嘌呤密碼子

	胺基酸	最小腺嘌呤密碼子
A	丙胺酸	GCU或GCC或GCG
G	甘胺酸	GGU或GGC或GGG
V	纈胺酸	GUC或GUU或GUG
D	天冬胺酸	GAC或GAU
E	麩胺酸	GAG
I	異白胺酸	AUC或AUU
T	蘇胺酸	ACU或ACC或ACG
N	天冬醯胺酸	AAC或AAU
K	離胺酸	AAG
S	絲胺酸	UCU或UCC或UCG
R	精胺酸	CGU或CGC或CGG
L	白胺酸	CUG或CUC或CUU
P	脯胺酸	CCG或CCU或CCC

H	組胺酸	CAC或CAU
Q	麩醯胺酸	CAG
F	苯丙胺酸	UUC或UUU
Y	酪胺酸	UAC或UAU
C	半胱胺酸	UGC或UGU
W	色胺酸	UGG
M	甲硫胺酸	AUG

【0233】 在一些實施例中，ORF可由一組密碼子組成，其中至少約75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表2中所列出之密碼子。

【0234】 就可行性而言，上文關於低腺嘌呤含量所描述之特徵中之任一者可與上文關於低尿苷含量所描述之特徵中之任一者組合。尿苷及腺嘌呤二核苷酸亦如此。類似地，ORF中之尿苷核苷酸及腺嘌呤二核苷酸之含量可如上文所闡述。類似地，ORF中之尿苷二核苷酸及腺嘌呤核苷酸之含量可如上文所闡述。

【0235】 可例如藉由在ORF之足夠多的一部分中使用最小尿苷及腺嘌呤密碼子來降低給定ORF之尿苷及腺嘌呤核苷酸及/或二核苷酸含量。舉例而言，可藉由將胺基酸轉化成密碼子而將本文所描述之多肽的胺基酸序列轉譯回ORF序列，其中ORF中之一些或全部使用以下所示之例示性最小尿苷及腺嘌呤密碼子。在一些實施例中，ORF中至少約50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表3中所列出之密碼子。

表3.例示性最小尿苷及腺嘌呤密碼子

	胺基酸	最小尿苷及腺嘌呤密碼子
A	丙胺酸	GCC或GCG
G	甘胺酸	GGC或GGG
V	纈胺酸	GUC或GUG
D	天冬胺酸	GAC
E	麩胺酸	GAG
I	異白胺酸	AUC

T	蘇胺酸	ACC或ACG
N	天冬醯胺酸	AAC
K	離胺酸	AAG
S	絲胺酸	AGC或UCC或UCG
R	精胺酸	CGC或CGG
L	白胺酸	CUG或CUC
P	脯胺酸	CCG或CCC
H	組胺酸	CAC
Q	麩醯胺酸	CAG
F	苯丙胺酸	UUC
Y	酪胺酸	UAC
C	半胱胺酸	UGC
W	色胺酸	UGG
M	甲硫胺酸	AUG

【0236】 在一些實施例中，ORF可由一組密碼子組成，其中至少約75%、80%、85%、90%、95%、98%、99%或100%之密碼子為表3中所列出之密碼子。如表3中可見，三個所列出絲胺酸密碼子中之每一者含有一個A或一個U。在一些實施例中，對於絲胺酸，藉由使用AGC密碼子來優先化進行尿苷最小化。在一些實施例中，對於絲胺酸，藉由使用UCC及/或UCG密碼子優先化進行腺嘌呤最小化。

【0237】 在一些實施例中，ORF可具有增加哺乳動物(諸如人類)中之轉譯的密碼子。在其他實施例中，mRNA包含具有增加哺乳動物(例如，人類)之器官，諸如肝臟中之轉譯的密碼子之ORF。在其他實施例中，ORF可具有增加哺乳動物(例如，人類)之細胞型，諸如肝臟細胞中之轉譯的密碼子。哺乳動物、細胞型、哺乳動物之器官、人類、人類之器官等中之轉譯的增加可相對於ORF之轉譯野生型序列的程度或相對於具有匹配衍生ORF之生物體或含有處於胺基酸水準之最相似ORF的生物體之密碼子分佈的密碼子分佈之ORF來測定。替代地，在一些實施例中，哺乳動物、細胞型、哺乳動物之器官、人類、人類之器官等中之Cas9序列的轉譯之增加係相對於具有SEQ ID NO: 2或5之序列的ORF之轉譯測定，其中

所有其他方面相同，包括任何適用的點突變、異源域及類似者。在一些實施例中，ORF中至少約75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為對應於哺乳動物(諸如人類)中的高度表現之tRNA (例如，針對各胺基酸之表現最高之tRNA)的密碼子。在一些實施例中，ORF中至少75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為對應於哺乳動物器官(諸如人類器官)中的高度表現之tRNA (例如，針對各胺基酸之表現最高之tRNA)的密碼子。

【0238】 可替代地，通常可使用對應於生物體(例如，人類)中之高度表現之tRNA的密碼子。

【0239】 前述密碼子選擇方法中之任一者與上文所示之最小尿苷及/或腺嘌呤密碼子可例如藉由以下進行組合：以表1、表2或表3之密碼子開始，且隨後在可利用多於一種選擇之情況下，使用對應於一般生物體(例如，人類)中，或相關器官或細胞型(例如，人類肝臟或人類肝臟細胞)中之較高度表現之tRNA的密碼子。

【0240】 在一些實施例中，ORF中至少75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為來自表4中所示之密碼子組(例如，低U 1、低A或低A/U密碼子組)的密碼子。低U 1、低G、低A及低A/U組中之密碼子使用將所指定之核苷酸減至最小之密碼子，同時在可利用多於一種選擇之情況下，亦使用對應於高度表現之tRNA的密碼子。在一些實施例中，ORF中至少75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為來自表4中所示之低U 1密碼子組的密碼子。在一些實施例中，ORF中至少75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為來自表4中所示之低A

密碼子組的密碼子。在一些實施例中，ORF中至少75%、80%、85%、90%、95%、96%、97%、98%、99%或100%之密碼子為來自表4中所示之低A/U密碼子組的密碼子。

表4.例示性密碼子組.

胺基酸	低U 1	低U 2	低A	低A/U
Gly	GGC	GGG	GGC	GGC
Glu	GAG	GAA	GAG	GAG
Asp	GAC	GAC	GAC	GAC
Val	GTG	GTA	GTG	GTG
Ala	GCC	GCG	GCC	GCC
Arg	AGA	CGA	CGG	CGG
Ser	AGC	AGC	TCC	AGC
Lys	AAG	AAA	AAG	AAG
Asn	AAC	AAC	AAC	AAC
Met	ATG	ATG	ATG	ATG
Ile	ATC	ATA	ATC	ATC
Thr	ACC	ACG	ACC	ACC
Trp	TGG	TGG	TGG	TGG
Cys	TGC	TGC	TGC	TGC
Tyr	TAC	TAC	TAC	TAC
Leu	CTG	CTA	CTG	CTG
Phe	TTC	TTC	TTC	TTC
Gln	CAG	CAA	CAG	CAG
His	CAC	CAC	CAC	CAC

2. 異源功能域；核定位訊號(NLS)

【0241】 在一些實施例中，包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶的多肽進一步包含一或多個額外異源功能域(例如，為或包含三元或更高階融合多肽)。

【0242】 在一些實施例中，異源功能域可促進多肽轉運至細胞核中。舉例而言，異源功能域可為核定位訊號(NLS)。在一些實施例中，多肽可與1至10個NLS融合。在一些實施例中，多肽可與1至5個NLS融合。在一些實施例中，多肽可與一個NLS融合。在使用一個NLS之情況下，NLS可在多肽序列之N末端或C末端處融合。在一些實施例中，多肽可C末端融合至至少一個NLS。NLS亦可插入多肽序列內。在其他實施例中，多

肽可與多於一個NLS融合。在一些實施例中，多肽可與2、3、4或5個NLS融合。在一些實施例中，多肽可與兩個NLS融合。在某些情況下，兩個NLS可相同(例如，兩個SV40 NLS)或不同。在一些實施例中，多肽在羧基端處融合至兩個SV40 NLS序列。在一些實施例中，多肽可與兩個NLS融合，一個NLS位於N末端處且一個位於C末端處。在一些實施例中，多肽可與3個NLS融合。在一些實施例中，多肽可不與NLS融合。在一些實施例中，NLS可為單聯(monopartite)序列，諸如SV40 NLS、PKKKRKV (SEQ ID NO: 63)或PKKKRRV (SEQ ID NO: 121)。在一些實施例中，NLS可為雙聯序列，諸如核質蛋白之NLS、KRPAATKKAGQAKKKK (SEQ ID NO: 122)。在一特定實施例中，單一PKKKRKV (SEQ ID NO: 63) NLS可在多肽之C末端處融合。一或多個連接子視情況包括在融合位點處(例如，在多肽與NLS之間)。在一些實施例中，根據前述實施例中之任一者之一或多個NLS與一或多個額外異源功能域(諸如下文所描述之異源功能域中之任一者)組合存在於多肽中。

【0243】 在本文所揭示之mRNA的一些實施例中，胞苷去胺酶(例如，A3A)位於多肽中之RNA導引之切口酶的N末端。在本文所揭示之mRNA的一些實施例中，經編碼之RNA導引之切口酶包含核定位訊號(NLS)。在一些實施例中，NLS與RNA導引之切口酶之C末端融合。在一些實施例中，NLS經由連接子融合至RNA導引之切口酶的C末端。在一些實施例中，NLS與RNA導引之切口酶之N末端融合。在一些實施例中，NLS經由連接子(例如，SEQ ID NO: 61)與RNA導引之切口酶之N末端融合。在一些實施例中，NLS包含與SEQ ID NO: 63及110至122中之任一者具有至少80%、85%、90%或95%一致性之序列。在一些實施例中，NLS

包含SEQ ID NO: 63及110至122中之任一者的序列。在一些實施例中，NLS由與SEQ ID NO: 63及110至122中之任一者之序列具有至少80%、85%、90%、95%、98%或100%一致性的序列編碼。

【0244】 在一些實施例中，異源功能域可能能夠修飾多肽中之A3A及/或RNA導引之切口酶的胞內半衰期。在一些實施例中，可增加多肽中之A3A及/或RNA導引之切口酶的半衰期。在一些實施例中，可減少多肽中之A3A及/或RNA導引之切口酶的半衰期。在一些實施例中，異源功能域可能能夠增加多肽中之A3A及/或RNA導引之切口酶的穩定性。在一些實施例中，異源功能域可能能夠降低多肽中之A3A及/或RNA導引之切口酶的穩定性。在一些實施例中，異源功能域可充當蛋白質降解之訊號肽。在一些實施例中，蛋白質降解可由蛋白水解酶，諸如蛋白酶體、溶酶體蛋白酶或鈣蛋白酶蛋白酶媒介。在一些實施例中，異源功能域可包含PEST序列。在一些實施例中，多肽可藉由添加泛素或多聚泛素鏈來修飾。在一些實施例中，泛素可為類泛素蛋白質(UBL)。類泛素蛋白質之非限制性實例包括小類泛素修飾因子(SUMO)、泛素交叉反應蛋白(UCRP，亦稱為干擾素刺激基因-15 (ISG15))、泛素相關修飾因子-1 (URM1)、神經元-前驅體-細胞表現之發育下調蛋白-8 (NEDD8，在釀酒酵母(*S . cerevisiae*)中亦稱作Rub1)、人類白血球抗原F相關(FAT10)、自噬-8 (ATG8)及自噬-12 (ATG12)、Fau類泛素蛋白(FUB1)、膜錨定UBL (MUB)、泛素摺疊修飾因子-1 (UFM1)及類泛素蛋白-5 (UBL5)。

【0245】 在一些實施例中，異源功能域可為標記域。標記域之非限制性實例包括螢光蛋白、純化標籤、抗原決定基標籤及報導基因序列。在一些實施例中，標記域可為螢光蛋白。任何已知的螢光蛋白均可用作標記

域，諸如GFP、YFP、EBFP、ECFP、DsRed或任何其他適合的螢光蛋白。在一些實施例中，標記域可為純化標籤及/或抗原決定基標籤。非限制性例示性標籤包括麩胱甘肽-S-轉移酶(GST)、殼質結合蛋白(CBP)、麥芽糖結合蛋白(MBP)、硫氧還蛋白(TRX)、聚(NANP)、串聯親和純化(TAP)標籤、myc、AcV5、AU1、AU5、E、ECS、E2、FLAG、HA、nus、Softag 1、Softag 3、Strep、SBP、Glu-Glu、HSV、KT3、S、S1、T7、V5、VSV-G、6×His、8×His、生物素羧基載體蛋白(BCCP)、聚His及調鈣蛋白。在一些實施例中，標記域可為報導基因。非限制性例示性報導基因包括麩胱甘肽-S-轉移酶(GST)、辣根過氧化酶(HRP)、氯黴素乙醯基轉移酶(CAT)、β-半乳糖苷酶、β-葡糖醛酸酶、螢光素酶或螢光蛋白。

【0246】 在額外實施例中，異源功能域可使多肽靶向至特定細胞器、細胞型、組織或器官。在一些實施例中，異源功能域可將多肽靶向至粒線體。

3. UTR；Kozak序列

【0247】 在一些實施例中，本文揭示之核酸(例如，mRNA)包含來自羥基類固醇17-β去氫酶4 (HSD17B4或HSD)或球蛋白之5' UTR、3' UTR或5'及3' UTR，球蛋白諸如人類α球蛋白(HBA)、人類β球蛋白(HBB)、有爪蟾蜍(*Xenopus laevis*)、β球蛋白(XBG)、牛生長激素、巨細胞病毒(CMV)、小鼠Hba-al、熱休克蛋白90 (Hsp90)、甘油醛3-磷酸酯去氫酶(GAPDH)、β肌動蛋白、α微管蛋白、腫瘤蛋白(p53)或表皮成長因子受體(EGFR)。

【0248】 在一些實施例中，本文揭示之核酸包含來自HSD之5'UTR及來自人類白蛋白基因之3'UTR。在一些實施例中，本文揭示之mRNA包

含與SEQ ID NO: 93中之任一者具有至少90%一致性的5'UTR及與SEQ ID NO: 69中之任一者具有至少90%一致性的3'UTR。

【0249】 在一些實施例中，本文揭示之核酸包含5' UTR，其與SEQ ID NO: 91至98中之任一者具有至少90%一致性。在一些實施例中，本文揭示之mRNA包含與SEQ ID NO: 69、99至106中之任一者具有至少90%一致性之3' UTR。在一些實施例中，前述一致性水準中之任一者為至少95%、至少98%、至少99%或100%。在一些實施例中，本文揭示之mRNA包含具有SEQ ID NO: 91至98中之任一者之序列的5' UTR。在一些實施例中，本文揭示之mRNA包含具有SEQ ID NO: 69、99至106中之任一者之序列的3' UTR。在一些實施例中，mRNA包含來自同一來源之5' UTR及3' UTR。

【0250】 在一些實施例中，本文中所描述之核酸不包含5' UTR，例如5'端帽與起始密碼子之間不存在額外核苷酸。在一些實施例中，mRNA在5'端帽與起始密碼子之間包含Kozak序列(下文所描述)，但不具有任何額外5' UTR。在一些實施例中，mRNA不包含3' UTR，例如在終止密碼子與poly-A尾之間不存在額外核苷酸。

【0251】 在一些實施例中，本文之核酸包含Kozak序列。Kozak序列可影響轉譯起始及由mRNA轉譯之多肽的總產率。Kozak序列包括可充當起始密碼子之甲硫胺酸密碼子。最小Kozak序列為NNNRUGN，其中以下中之至少一者成立：第一個N為A或G且第二個N為G。在核苷酸序列之情形下，R意謂嘌呤(A或G)。在一些實施例中，Kozak序列為RNNRUGN、NNNRUGG、RNNRUGG、RNNAUGN、NNNAUGG、RNNAUGG或GCCACCAUG。在一些實施例中，Kozak序列為

rccRUGg、rccAUGg、gccAccAUG、gccRccAUGG (SEQ ID NO: 107)或gccgccRccAUGG (SEQ ID NO: 108)，具有零錯配或與小寫字母之位置具有多達一或兩個錯配。

4. Poly-A尾

【0252】 在一些實施例中，本文揭示之核酸進一步包含聚腺苷酸化(poly-A)尾。poly-A尾可包含至少8個連續腺嘌呤核苷酸，但亦包含一或多個非腺嘌呤核苷酸。如本文所使用，「非腺嘌呤核苷酸」指不包含腺嘌呤之任何天然或非天然核苷酸。鳥嘌呤、胸腺嘧啶及胞嘧啶核苷酸為例示性非腺嘌呤核苷酸。因此，本文中所描述之核酸上的poly-A尾可包含位於編碼所關注多肽之核苷酸3'處的連續腺嘌呤核苷酸。在一些情況下，mRNA上之poly-A尾包含非連續腺嘌呤核苷酸，其位於編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶或所關注序列之多肽的3'核苷酸上，其中非腺嘌呤核苷酸以規則或不規則隔開之間隔中斷腺嘌呤核苷酸。

【0253】 在一些實施例中，poly-A尾編碼於用於活體外轉錄mRNA之質體中且變成轉錄本之一部分。編碼於質體中之poly-A序列，亦即poly-A序列中之連續腺嘌呤核苷酸之數目可能並不精確，例如質體中之100 poly-A序列可能不會在經轉錄之mRNA中產生恰好100 poly-A序列。在一些實施例中，poly-A尾未編碼於質體中，且藉由PCR加尾或酶促加尾，例如使用大腸桿菌(*E. coli*) poly(A)聚合酶來添加。

【0254】 在一些實施例中，一或多個非腺嘌呤核苷酸定位成中斷連續腺嘌呤核苷酸，以使得poly(A)結合蛋白可結合至一段連續腺嘌呤核苷酸。在一些實施例中，一或多個非腺嘌呤核苷酸位於至少8、9、10、11或12個連續腺嘌呤核苷酸之後。在一些實施例中，一或多個非腺嘌呤核苷

酸位於8至50個連續腺嘌呤核苷酸之後。在一些實施例中，一或多個非腺嘌呤核苷酸位於8至100個連續腺嘌呤核苷酸之後。

【0255】 在一些實施例中，poly-A尾包含或含有一個非腺嘌呤核苷酸或2至10個非腺嘌呤核苷酸之一個連續段。

【0256】 在一些實施例中，非腺嘌呤核苷酸為鳥嘌呤、胞嘧啶或胸腺嘧啶。在其中存在多於一個非腺嘌呤核苷酸之一些情況下，非腺嘌呤核苷酸可選自：a)鳥嘌呤及胸腺嘧啶核苷酸；b)鳥嘌呤及胞嘧啶核苷酸；c)胸腺嘧啶及胞嘧啶核苷酸；或d)鳥嘌呤、胸腺嘧啶及胞嘧啶核苷酸。包含非腺嘌呤核苷酸之例示性poly-A尾提供為SEQ ID NO: 109。

5. 經修飾之核苷酸

【0257】 在一些實施例中，本文揭示之核酸在一些或所有尿苷位置處包含經修飾之尿苷。在一些實施例中，經修飾之尿苷為在5位處，例如用鹵素或C1-C3烷氧基修飾之尿苷。在一些實施例中，經修飾之尿苷為在1位處，例如用C1-C3烷基修飾之假尿苷。經修飾之尿苷可為例如假尿苷、N1-甲基假尿苷、5-甲氧基尿苷、5-碘尿苷或其組合。

【0258】 在一些實施例中，本文所揭示之核酸中至少10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、98%、99%或100%之尿苷位置為經修飾之尿苷。在一些實施例中，本文揭示之mRNA中10%至25%、15%至25%、25%至35%、35%至45%、45%至55%、55%至65%、65%至75%、75%至85%、85%至95%或90%至100%之尿苷位置為經修飾之尿苷，例如5-甲氧基尿苷、5-碘尿苷、N1-甲基假尿苷、假尿苷或其組合。

【0259】 在一些實施例中，至少10%之尿苷由經修飾之尿苷取代。

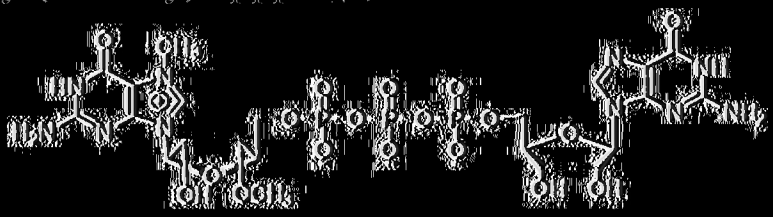
在一些實施例中，15%至45%之尿苷由經修飾之尿苷取代。在一些實施例中，至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%或100%之尿苷由經修飾之尿苷取代。

6. 5'端帽

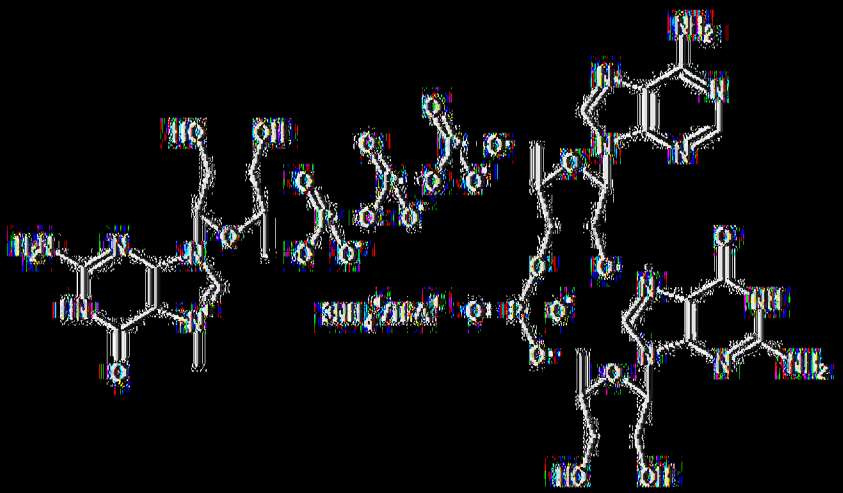
【0260】在一些實施例中，本文揭示之核酸包含5'端帽，諸如Cap0、Cap1或Cap2。5'端帽通常為經由5'-三磷酸連接至核酸之5'至3'鏈之第一核苷酸之5'位的7-甲基鳥嘌呤核糖核苷酸(其可進一步修飾，如下文例如相對於ARCA所論述)，亦即第一端帽近端核苷酸。在Cap0中，mRNA之第一與第二端帽近端核苷酸之核糖均包含2'-羥基。在Cap1中，mRNA之第一及第二轉錄核苷酸之核糖分別包含2'-甲氧基及2'-羥基。在Cap2中，mRNA之第一及第二端帽近端核苷酸之核糖均包含2'-甲氧基。參見例如Katibah等人(2014) *Proc Natl Acad Sci USA* 111(33):12025-30；Abbas等人(2017) *Proc Natl Acad Sci USA* 114(11):E2106-E2115。包括哺乳動物核酸(諸如人類核酸)之大多數內源性高等真核核酸包含Cap1或Cap2。歸因於藉由先天免疫系統之組分，諸如IFIT-1及IFIT-5識別為「非自體(non-self)」，Cap0及與Cap1及Cap2不同的其他端帽結構在哺乳動物，諸如人類中可呈免疫原性，其可導致包括I型干擾素之細胞介素含量升高。先天免疫系統之組分，諸如IFIT-1及IFIT-5亦可與eIF4E競爭結合具有除Cap1或Cap2外之端帽的核酸，從而潛在地抑制核酸轉譯。

【0261】端帽可以共轉錄方式包括。舉例而言，ARCA (抗反向端帽類似物；Thermo Fisher Scientific目錄號AM8045)為包含連接至鳥嘌呤核糖核苷酸之5'位的7-甲基鳥嘌呤3'-甲氧基-5'-三磷酸之端帽類似物，其可在一開始時活體外併入轉錄本中。ARCA產生Cap0端帽或類Cap0端

帽，其中第一個端帽近端核苷酸之2'位為羥基。參見例如Stepinski等人，(2001)「Synthesis and properties of mRNAs containing the novel "anti-reverse" cap analogs 7-methyl(3'-O-methyl)GpppG and 7-methyl(3'deoxy)GpppG」，*RNA* 7: 1486-1495。ARCA結構展示如下。



[0262] CleanCap™ AG (m7G(5')ppp(5')(2'OMeA)pG；TriLink Biotechnologies ||| 貨號 N-7113) 或 CleanCap™ GG (m7G(5')ppp(5')(2'OMeG)pG；TriLink Biotechnologies]|貨號N-7133)可用於以共轉錄方式提供Cap1結構。CleanCap™ AG及CleanCap™ GG之3'-O-甲基化形式亦可分別以||貨號N-7413及N-7433購自TriLink Biotechnologies。CleanCap™ AG結構展示如下。CleanCap™結構在本文中有時會使用上文所列出的||貨號之最後三個數位來指代(例如，對於TriLink Biotechnologies||貨號N-7113，使用「CleanCap™ 113」指代)。



[0263] 替代地，可以轉錄後方式將端帽添加至RNA。舉例而言，牛痘加端帽酶可自市面上購得(New England Biolabs]|貨號M2080S)，其

具有由其D1次單元提供之RNA三磷酸酶及鳥苷酸轉移酶活性及由其D12次單元提供之鳥嘌呤甲基轉移酶。因此，在S-腺苷甲硫胺酸及GTP存在下，可將7-甲基鳥嘌呤添加至RNA，以產生Cap0。參見例如Guo, P.及Moss, B. (1990) *Proc. Natl. Acad. Sci. USA* 87, 4023-4027；Mao, X.及Shuman, S. (1994) *J. Biol. Chem.* 269, 24472-24479。關於端帽及加端帽方法之額外論述，參見例如WO2017/053297及Ishikawa等人, *Nucl. Acids. Symp. Ser.* (2009) No. 53, 129-130。

G. 導引RNA (gRNA)

【0264】在一些實施例中，組合物包含至少一種導引RNA (gRNA)，且方法包含遞送至少一種gRNA，其中gRNA將編輯器導向至所要基因位置。在一些實施例中，組合物包含本文所描述之mRNA及至少一種gRNA。在一些實施例中，組合物包含本文所描述之多肽及至少一種gRNA。在一些實施例中，gRNA為單導引gRNA (sgRNA)。在一些實施例中，gRNA為雙導引gRNA (dgRNA)。

【0265】本文揭示之gRNA可包含導引序列，其將包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶之多肽導向至位於用於胞嘧啶(C)至胸腺嘧啶(T)轉化(「C形成T轉化」)之基因之任何區中(例如，在基因之編碼區內)的胞嘧啶(C)。

【0266】在一些實施例中，C形成T轉化改變DNA序列，諸如人類基因序列。在一些實施例中，C形成T轉化改變基因之編碼序列。在一些實施例中，C形成T轉化產生終止密碼子，例如基因編碼區內之過早終止密碼子。在一些實施例中，C形成T轉化消除終止密碼子。在一些實施例中，C形成T轉化改變基因(例如，基因啟動子或基因抑制因子)之調節序

列。在一些實施例中，C形成T轉化改變基因之剪接。在一些實施例中，C形成T轉化校正與疾病或病症相關之遺傳缺陷。

【0267】 在一些實施例中，導引RNA (gRNA)包含導引序列，該導引序列將包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶的多肽導向至基因中之剪接供體或受體位點。在一些實施例中，剪接供體或受體為剪接供體位點。在一些實施例中，剪接供體或受體位點為剪接受體位點。

【0268】 在一些實施例中，導引RNA (gRNA)包含導引序列，該導引序列將包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶的多肽導向至受體剪接位點邊界。在一些實施例中，導引RNA (gRNA)包含導引序列，該導引序列將包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶的多肽導向至供體剪接位點邊界。

【0269】 在一些實施例中，導引RNA (gRNA)包含導引序列，該導引序列導向包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶的多肽，以在受體剪接位點邊界之切割位點3'或受體剪接位點邊界之5'處對基因進行單股切割。在此論述及以下論述中，3'及5'指示在所切割的股的意義上之方向。

【0270】 在一些實施例中，本文揭示之導引RNA (gRNA)包含導引序列，該引導序列導向包含胞苷去胺酶(例如，APOBEC3A去胺酶)及RNA導引之切口酶的多肽，以在作為供體剪接位點邊界之3'或供體剪接位點邊界之5'的切割位點處對基因進行單股切割。

【0271】 如本文所使用，「剪接位點」係指構成受體剪接位點或供體剪接位點(下文所定義)或此項技術中已知為剪接位點之一部分的任何其

他核苷酸的三個核苷酸。參見例如Burset等人, Nucleic Acids Research 28(21):4364-4375 (2000) (描述哺乳基因體中之典型及非典型剪接位點)。構成「受體剪接位點」之三個核苷酸為內含子之3'處的兩個保守殘基(例如，人類AG) 及邊界核苷酸(亦即，AG之外顯子3'的第一個核苷酸)。構成「供體剪接位點」之三個核苷酸為內含子之5'端處的兩個保守殘基(例如，人類中之GT (基因)或GU (在RNA中，諸如前mRNA))及邊界核苷酸(亦即，GT之外顯子5'的第一個核苷酸)。

【0272】 在一些實施例中，包含至少一種gRNA之組合物與本文揭示之核酸(例如，mRNA)組合提供。在一些實施例中，一或多種gRNA提供為與本文揭示之核酸(例如，mRNA)分離之分子。在一些實施例中，gRNA提供為本文揭示之核酸之一部分，諸如UTR之一部分。

【0273】 在一些實施例中，提供一種包含多肽及gRNA之組合物，該多肽包含胞苷去胺酶及RNA導引之切口酶。在一些實施例中，提供一種核糖核蛋白複合物(RNP)，RNP包含含有胞苷去胺酶及RNA導引之切口酶的多肽以及gRNA。在一些實施例中，多肽不包含UGI。

【0274】 gRNA包含靶向特定基因或基因序列之導引序列。在一些實施例中，gRNA為Cas切口酶導引。在一些實施例中，gRNA為2類切口酶導引。在其他實施例中，gRNA為Cpf1或Cas9導引。在一些實施例中，gRNA為Nme切口酶導引。在一些實施例中，Nme切口酶為Nme1、Nme2或Nme3切口酶。在一些實施例中，gRNA包含RNA之導引序列5'，其形成兩個或更多個髮夾或莖環結構。CRISPR/Cas gRNA結構為此項技術中已知的且隨其同源Cas核酸酶而變化。一般而言，與本文所描述之任何特定Cas9或Nme切口酶一起使用之gRNA必須與該切口酶一起起作用。舉例

而言，當本文揭示之多肽包含SpyCas9切口酶時，所提供之gRNA為SpyCas9導引RNA (如本文所描述)。當本文揭示之多肽包含NmeCas9切口酶時，導引RNA為NmeCas9導引RNA (如本文所描述)。

【0275】 在一些實施例中，gRNA包含將RNA導引之切口酶(例如，Cas9切口酶)導向至目標基因座(諸如目標基因)中之目標DNA序列的導引序列。靶向各基因之目標及例示性目標序列在本文中例示且包括但不限於以下中所揭示之目標及導引序列：WO2017185054 (針對轉錄因子四中三核苷酸重複序列(*TCF4*))；WO 2018119182 A1 (靶向*SERPINA1*)；WO 2019/067872 (靶向甲狀腺素運載蛋白(*TTR*))；WO 2020/028327 A1 (靶向羥酸氧化酶1 (*HAO1*))，該等文獻中之各者之內容特此以全文引用之方式併入。熟習此項技術者將熟悉用於靶向所關注之其他基因或基因座之適合的導引序列。

【0276】 gRNA可包含含有導引序列之17、18、19、20、21、22、23、24或25個連續核苷酸的crRNA。gRNA可進一步包含trRNA。在本文所描述之各組合物及方法實施例中，crRNA及trRNA可結合為單一RNA (sgRNA)或可處於單獨的RNA (dgRNA)上。在sgRNA之情形下，crRNA與trRNA組分可例如經由磷酸二酯鍵或其他共價鍵共價連接。

【0277】 在本文所描述之組合物、用途及方法實施例中之每一者中，gRNA可包含呈「雙導引RNA」或「dgRNA」形式之兩種RNA分子。dgRNA包含含有crRNA之第一RNA分子及包含trRNA之第二RNA分子，該第一RNA分子包含導引序列。第一及第二RNA分子可不共價連接，但可經由crRNA與trRNA之部分之間的鹼基配對形成RNA雙螺旋。

【0278】 在本文所描述之組合物、用途及方法實施例中之每一者

中，gRNA可包含呈「單導引RNA」或「sgRNA」形式之單個RNA分子。sgRNA可包含crRNA (或其部分)，其包含共價連接至例如trRNA之導引序列。sgRNA可包含導引序列之17、18、19、20、21、22、23、24或25個連續核苷酸。在一些實施例中，crRNA及trRNA經由連接子共價連接。在一些實施例中，sgRNA經由crRNA與trRNA之部分之間的鹼基配對形成莖-環結構。在一些實施例中，crRNA及trRNA經由不為磷酸二酯鍵之一或多個鍵共價連接。

【0279】在一些實施例中，trRNA可包含來源於天然存在之CRISPR/Cas系統之trRNA序列之全部或一部分。在一些實施例中，trRNA包含經截短或經修飾之野生型trRNA。trRNA之長度視所使用CRISPR/Cas系統而定。在一些實施例中，trRNA包含或由以下組成：5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、40、50、60、70、80、90、100或大於100個核苷酸。在一些實施例中，trRNA可包含某些二級結構，諸如一或多種髮夾結構或莖環結構或一或多種隆突結構。

【0280】本文提供之gRNA可適用於識別(例如，雜交至)基因中之目標序列。在一些實施例中，一或多種gRNA之選擇基於基因內之目標序列而判定。在一些實施例中，與目標基因座內之目標序列互補或具有互補性之gRNA用於將包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶之多肽導向至基因座中之特定位置。目標基因座可藉由包含gRNA之Cas切口酶識別及切口。

【0281】在一些實施例中，導引序列與目標序列至少99%、98%、97%、96%、95%、94%、93%、92%、91%或90%一致。在一些實施例

中，目標序列可與gRNA之導引序列互補。在一些實施例中，gRNA之導引序列與其對應目標序列之間的互補性或一致性可為約50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或100%。在一些實施例中，gRNA之目標序列與導引序列可具有100%互補性或一致性。在其他實施例中，gRNA之目標序列及導引序列可含有至少一個錯配。舉例而言，gRNA之目標序列及導引序列可含有1、2、3、4、5、6、7、8、9或10個錯配，其中目標序列之總長度為至少約17、18、19、20或更多個鹼基對。在一些實施例中，gRNA之目標序列及導引序列可含有1、2、3、4、5或6個錯配，其中導引序列為20個核苷酸。

【0282】 gRNA可包含連接至額外核苷酸以形成crRNA之導引序列，例如其3'端處之導引序列之後具有以下例示性核苷酸序列：GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO:139)。

【0283】 在sgRNA之情況下，導引序列可連接至額外核苷酸以形成sgRNA，例如在導引序列之3'端之後具有以下例示性核苷酸序列：5'至3'位向之GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 140)。

【0284】 在一些實施例中，sgRNA包含以下在SEQ ID NO:141中所示之修飾模式，其中N為天然或非天然核苷酸，且其中N'之總體包含如本文所描述之導引序列，且經修飾sgRNA包含以下序列：mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCA

mAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmG mUmCmGmGmUmGmCmU*mU*mU*mU (SEQ ID NO: 141)，其中「N」可為任何天然或非天然核苷酸。舉例而言，SEQ ID NO: 141涵蓋在本文中，其中N'經本文所揭示之導引序列中之任一者置換。儘管導引之核苷酸用N'取代，但該等修飾保持如SEQ ID NO: 141中所示。亦即，儘管導引之核苷酸置換「N'」，但前三個核苷酸仍為經2'OMe修飾的，且在第一核苷酸與第二核苷酸、第二核苷酸與第三核苷酸及第三核苷酸與第四核苷酸之間存在硫代磷酸酯鍵。

【0285】 圖23A展示在可能二級結構中之例示性sgRNA (SEQ ID NO: 141，甲基化未展示)，其中標記標識sgRNA之保守區的個別核苷酸，包括下莖、隆突、上莖、連接區(其核苷酸依5'至3'方向分別可稱作N1至N18)及髮夾區，該髮夾區包括髮夾1及髮夾2區。髮夾1與髮夾2之間的核苷酸標記為n。導引區可存在於sgRNA上且在此圖中指示為sgRNA之保守區之前的「(N)x」。在一些實施例中，sgRNA可進一步包含下莖與隆突區之間、隆突與上莖區之間、上莖與連接之間或連接與髮夾1區之間或髮夾1與髮夾2區之間的一或多個核苷酸。

【0286】 在一些實施例中，sgRNA之保守部分為spyCas9或spyCas9等效物之保守區。在一些實施例中，sgRNA之保守部分不來自化膿性鏈球菌Cas9，諸如金黃色葡萄球菌Cas9(「saCas9」)。例示性sgRNA之區之進一步描述提供於2019年12月12日公開之WO2019/237069中，其全部內容以引用的方式併入本文中。

【0287】 SpyCas9 gRNA可包含內部連接子。在一些實施例中，內部連接子可具有約3個至30、視情況12至21個原子之橋接長度，且連接子

取代gRNA之至少2個核苷酸。在一些實施例中，內部連接子具有約6至18個原子，視情況約6至12個原子之橋接長度，且連接子取代gRNA之至少2個核苷酸。在一些實施例中，內部連接子包含至少兩個彼此共價連接之乙二醇次單元。在一些實施例中，內部連接子包含PEG-連接子。

【0288】 在一些實施例中，內部連接子包含具有1至10個乙二醇單元之PEG-連接子。在一些實施例中，內部包連接子包含具有3至6個乙二醇單元之PEG-連接子。在一些實施例中，內部連接子包含具有3個乙二醇單元之PEG-連接子。在一些實施例中，內部連接子包含具有6個乙二醇單元之PEG-連接子。

【0289】 在一些實施例中，spyCas9導引RNA之保守部分包含重複抗重複區、髮夾1區及髮夾2區，且進一步包含以下中之至少一者：

1)第一內部連接子，其取代sgRNA之重複抗重複區之上莖區的至少2個核苷酸；

2)第二內部連接子，其取代sgRNA之髮夾1之1或2個核苷酸；或

3)第三內部連接子，其取代sgRNA之髮夾2之至少2個核苷酸。

【0290】 spyCas9 導引RNA中之連接子的例示性位置如以下中所示 ： NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUA(**L1**)UAGCAAGUUAAAAUAAGGC**U**AGUCCGUUAUCAACUU(**L1**)AAGUGGCACCGAGUCGGUGCUUUUU (SEQ ID NO: 524)，其中N為編碼導引序列之核苷酸。

【0291】 如本文所使用，「連接子1」或「L1」係指具有約15至21個原子之橋連長度的內部連接子。如本文所使用，「連接子2」或「L2」係指具有約6至12個原子之橋連長度的內部連接子。

【0292】在一些實施例中，包含內部連接子之spyCas9導引RNA可經化學修飾。例示性修飾包括以下序列之修飾模式：mA*mC*mG*CAAAUAUCAGUCCAGCGGUUUUAGAmGmCmUmA(L1)mUmAmGmCAAGUUAAAAUAAGGC(L2)GUCCGUUAUCAC(L1)GGGCACCGAGUCGG*mU*mG*mC (SEQ ID NO: 523)。

【0293】在一些實施例中，gRNA包含3'尾。在一些實施例中，3'尾由包含尿嘧啶或經修飾之尿嘧啶的核苷酸組成。在一些實施例中，3'末端核苷酸為經修飾之核苷酸。在一些實施例中，其中3'尾包含存在於3'尾中之核苷酸中之任何一或多者的修飾。在其他實施例中，其中3'尾之修飾為經2'-O-甲基(2'-OMe)修飾之核苷酸及核苷酸之間的硫代磷酸酯(PS)鍵中之一或多者。

1. 短單導引RNA (短sgRNA)

【0294】在一些實施例中，本文所提供之sgRNA為短單導引RNA (短sgRNA)，例如包含含有髮夾區之sgRNA的保守部分，其中髮夾區缺少至少5至10個核苷酸或6至10個核苷酸。在一些實施例中，5至10個核苷酸或6至10個核苷酸為鄰接的。

【0295】在一些實施例中，短sgRNA缺少spyCas9 sgRNA之保守部分的至少核苷酸54至58 (AAAAA)。在一些實施例中，短sgRNA為缺少與spyCas9保守部分之核苷酸54至58 (AAAAA)對應之核苷酸的非spyCas9 sgRNA，如藉由例如成對或結構比對所測定。

【0296】結構比對在分子共用類似結構(儘管存在相當大的序列變化)時為有用的。結構比對涉及藉由以下鑑別兩個(或更多個)序列上之對應殘基：(i)使用第二序列之已知結構，對第一序列之結構模型化或(ii)比

較均已知之第一與第二序列的結構；以及鑑別第一序列中與第二序列中之所關注殘基最相似地定位的殘基。在一些算法中，基於重疊結構中之給定位置(例如，多核苷酸之戊糖環的核鹼基位置1或1'碳，或多肽之α碳)的距離最小化，鑑別出對應殘基(例如，哪一組成對位置為比對提供最小化均方根偏差)。當鑑別非spyCas9 gRNA中之與關於spyCas9 gRNA所描述之位置對應的位置時，spyCas9 gRNA可為「第二」序列。在所關注之非spyCas9 gRNA不具有可獲得之已知結構、但與具有已知結構之另一種非spyCas9 gRNA更密切相關的情況下，最有效的可以為使用緊密相關之非spyCas9 gRNA之已知結構將所關注之非spyCas9 gRNA模型化，且接著比較該模型與spyCas9 gRNA結構以鑑別出所關注之非spyCas9 gRNA中的所需對應殘基。關於蛋白質之結構模型化及比對，存在大量的文獻；代表性揭示內容包括US 6859736；US 8738343；及Aslam等人, Electronic Journal of Biotechnology 20 (2016) 9-13中所引述之彼等文獻。關於基於一或多種已知相關結構將結構模型化之論述，參見例如Bordoli等人, *Nature Protocols* 4 (2009) 1-13，及其中引述之參考文獻。關於核酸比對，亦參見Nishimasu等人, *Cell* 162(5): 1113-1126 (2015)之圖2(F)。

【0297】 在一些實施例中，本文所描述之短sgRNA包含含有髮夾區之保守部分，其中髮夾區缺少5、6、7、8、9、10、11或12個核苷酸。在一些實施例中，缺少核苷酸為5至10個缺少核苷酸或6至10個缺少核苷酸。在一些實施例中，缺少核苷酸為鄰接的。在一些實施例中，缺少核苷酸跨越髮夾1之至少一部分及髮夾2之一部分。在一些實施例中，5至10個缺少核苷酸包含SEQ ID NO: 140之核苷酸54至58、54至61或53或60或由其組成。

【0298】 在一些實施例中，本文中所描述之短sgRNA進一步包含連接區，其中連接區缺少至少一個核苷酸(例如，連接區中之1、2、3、4、5、6、7、8、9或10個核苷酸)。在一些實施例中，短sgRNA缺少連接區中之各核苷酸。

【0299】 在一些實施例中，本文中所描述之SpyCas9 短sgRNA包含NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGUGCU (SEQ ID NO: 521)之序列。在一些實施例中，本文中所描述之短sgRNA包含SEQ ID NO:520中所示之修飾模式：mN*mN*mN*GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU (SEQ ID NO: 520)，其中除非另外規定，否則A、C、G、U及N分別為腺嘌呤、胞嘧啶、鳥嘌呤、尿嘧啶及任何核糖核苷酸。m指示2'O-甲基修飾，且*指示核苷酸之間的硫代磷酸酯鍵。

【0300】 在一些實施例中，本文中所描述之gRNA為腦膜炎雙球菌Cas9 (NmeCas9) gRNA，其包含含有重複/抗重複區、髮夾1區及髮夾2區之保守部分，其中重複/抗重複區、髮夾1區及髮夾2區中之一或多者經縮短。例示性野生型NmeCas9導引RNA包含$(N)_{20-25}$GUUGUAGCUCCCUUUCUCAUUUCGGAAACGAAAUGAGAACCGUUGCUACAAUAAGGCCGUCUGAAAAGAUGUGCCGCAACGCUCUGCCCCUUAAAGCUUCUGCUUUAAGGGGCAUCGUUUA (SEQ ID NO: 512)之序列。如本文所使用之$(N)_{20-25}$表示20至25，亦即20、21、22、23、24或25鄰接N。A、C、G及U分別表示具有腺嘌呤、胞嘧啶、鳥嘌呤

及尿嘧啶鹼基之核苷酸。在一些實施例中，$(N)_{20-25}$長度為24個核苷酸。N為任何天然或非天然核苷酸，且其中N'之總體包含導引序列。

【0301】 在一些實施例中，NmeCas9短gRNA之保守部分包含：

(a)經縮短之重複/抗重複區，其中經縮短之重複/抗重複區缺少2至24個核苷酸，其中

(i)核苷酸37至48及53至64中之一或多者缺失，且視情況核苷酸37至64中之一或多者相對於SEQ ID NO: 512經取代；及

(ii)核苷酸36藉由至少2個核苷酸連接至核苷酸65；或

b)經縮短之髮夾1區，其中經縮短之髮夾1缺少2至10個、視情況2至8個核苷酸，其中

(i)核苷酸82至86及91至95中之一或多者缺失，且視情況位置82至96中之一或多者相對於SEQ ID NO: 512經取代，及

(ii)核苷酸81藉由至少4個核苷酸連接至核苷酸96；或

(c)經縮短之髮夾2區，其中經縮短之髮夾2缺少2至18個、視情況2至16個核苷酸，其中

(i)核苷酸113至121及126至134中之一或多者缺失，且視情況核苷酸113至134中之一或多者相對於SEQ ID NO: 512經取代；且

(ii)核苷酸112藉由至少4個核苷酸連接至核苷酸135；

其中一個或兩個核苷酸144至145視情況相對於SEQ ID NO:512缺失；且其中至少10個核苷酸為經修飾之核苷酸。

【0302】 在一些實施例中，NmeCas9短gRNA包含5'至3'位向之以下序列中之一者：

$(N)_{20-25}$ GUUGUAGCUCCCUGAAACCGUUGCUACAAUAAGGCC

GUCGAAAGAUGUGCCGCAACGCUCUGCCUUCUGGCAUCGUU (SEQ ID NO: 513)；

$(N)_{20-25}$ GUUGUAGCUCCCUGAAACCGUUGCUACAAUAAGGCCGUCGAAAGAUGUGCCGCAACGCUCUGCCUUCUGGCAUCGUUUAU U (SEQ ID NO: 514)；

$(N)_{20-25}$ GUUGUAGCUCCCUGGAAACCCGUUGCUACAAUAAGGCCGUCGAAAGAUGUGCCGCAACGCUCUGCCUUCUGGCAUCGUUU AUU (SEQ ID NO: 515)。

【0303】 在一些實施例中，NmeCas9短sgRNA之保守部分之至少10個核苷酸為經修飾之核苷酸。

【0304】 在一些實施例中，NmeCas9 短sgRNA包含含有5'至3'位向之以下序列中之一者的保守區：

GUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU (SEQ ID NO: 516)；或

GUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGmCAAmCGCUCUmGmCCmUmUmCmUGGCAUCG*mU*mU (SEQ ID NO: 517)。

【0305】 經縮短之NmeCas9 gRNA可包含本文揭示之內部連接子。

【0306】 如本文所使用之「內部連接子」描述接合導引RNA內之兩個核苷酸的非核苷酸片段。若gRNA含有間隔區，則內部連接子位於間隔

區外部(例如，gRNA之骨架或保守區中)。對於V型導引件，應理解，最後一個髮夾為結構中之唯一髮夾，亦即重複抗重複區。在一些實施例中，內部連接子包含本文揭示之PEG-連接子。

【0307】 連接子之例示性位置如以下所示：

$(N)_{20-25}$ GUUGUAGCUCCCUUC(**L1**)GACCGUUGCUACAAUAAGGCCGUC(**L1**)GAUGUGCCGCAACGCUCUGCC(**L1**)GGCAUCGUU (SEQ ID NO: 518)。如本文所使用，(L1)係指具有約15至21個原子之橋連長度的內部連接子。

【0308】 在一些實施例中，包含內部連接子之經縮短之NmeCas9導引RNA可經化學修飾。例示性修飾包括以下序列之修飾模式：mN*mN*mN*mNmNNNmNmNNmNNmNNNNNmNNNNmNNNmGUUGmUmAmGmCUCCCmUmUmC(L1)mGmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmC(L1)mGmAmUGUGCmCGmCAAmCGCUCUmGmCC(L1)GGCAUCG*mU*mU (SEQ ID NO: 519)。

2. 修飾

【0309】 在一些實施例中，gRNA (例如，sgRNA、短sgRNA、dgRNA或crRNA)經修飾。在本文所描述之gRNA的上下文中，術語「經修飾」或「修飾」包括上文所描述之修飾，包括例如(a)端修飾，例如5'端修飾或3'端修飾，包括5'或3'保護端修飾；(b)核鹼基(或「鹼基」)修飾，包括鹼基置換或移除；(c)糖修飾，包括2'、3'及/或4'位置處之修飾；(d)核苷間連接修飾；及(e)主鏈修飾，其可包括磷酸二酯鍵及/或核糖之修飾或置換。核苷酸在給定位置之修飾包括緊接著核苷酸之糖之3'的磷酸二酯鍵之修飾或置換。因此，舉例而言，包含5'端之第一糖與第二糖之間之硫

代磷酸酯的核酸視為包含位置1處之修飾。術語「經修飾之gRNA」通常係指對鹼基、糖及磷酸二酯鍵或主鏈部分中之一或多者的化學結構進行修飾之gRNA，包括核苷酸磷酸酯，全部如本文詳述及例示(參見例如SEQ ID NO:142至145、181至185及191至203中所示之修飾模式)。

【0310】 其他描述及例示性修飾模式提供於2019年12月12日公開之WO2019/237069的表1中，其全部內容以引用之方式併入本文中。

【0311】 在一些實施例中，gRNA包含在1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16或更多個YA位點處之修飾。在一些實施例中，YA位點之嘧啶包含修飾(其包括改變緊接嘧啶之糖之3'的核苷間鍵之修飾)。在一些實施例中，YA位點之腺嘌呤包含修飾(其包括改變緊接腺嘌呤之糖之3'的核苷間鍵之修飾)。在一些實施例中，YA位點之嘧啶及腺嘌呤包含修飾，諸如糖、鹼基或核苷間鍵修飾。YA修飾可為本文所闡述之任何類型的修飾。在一些實施例中，YA修飾包含硫代磷酸酯、2'-OMe或2'-氟中之一或多者。在一些實施例中，YA修飾包含嘧啶修飾，包含硫代磷酸酯、2'-OMe、2'-H、肌苷或2'-氟中之一或多者。在一些實施例中，YA修飾在含有一或多個YA位點的RNA雙螺旋區內包含雙環核糖類似物(例如，LNA、BNA或ENA)。在一些實施例中，YA修飾在含有YA位點的RNA雙螺旋區內包含雙環核糖類似物(例如，LNA、BNA或ENA)，其中YA修飾位於YA位點遠端。

【0312】 在一些實施例中，gRNA之導引序列(或導引區)包含1、2、3、4、5或更多個可包含YA修飾之YA位點(「導引區YA位點」)。在一些實施例中，位於相對於5'末端之5'端之5端、6端、7端、8端、9端或10端處的一或多個YA位點(其中「5端」等係指相對於導引區之3'端的位

置5，亦即，導引區中之最多3'核苷酸)包含YA修飾。經修飾之導引區YA位點包含YA修飾。

【0313】 在一些實施例中，經修飾之導引區YA位點位於導引區之3'末端核苷酸之20、19、18、17、16、15、14、13、12、11、10或9個核苷酸內。舉例而言，若經修飾之導引區YA位點位於導引區之3'末端核苷酸之10個核苷酸內且導引區具有20個核苷酸長度，則經修飾之導引區YA位點中之經修飾核苷酸位於位置11至20中之任一位置處。在一些實施例中，經修飾之導引區YA位點位於相對於5'末端之5'端的核苷酸4、5、6、7、8、9、10或11處或其之後。

【0314】 在一些實施例中，經修飾之導引區YA位點不同於5'端修飾。舉例而言，sgRNA可包含如本文所描述之5'端修飾且進一步包含經修飾之導引區YA位點。替代地，sgRNA可包含未經修飾之5'端及經修飾之導引區YA位點。替代地，短sgRNA可包含經修飾之5'端及未經修飾之導引區YA位點。

【0315】 在一些實施例中，經修飾之導引區YA位點包含位於導引區YA位點之5'之至少一個核苷酸不包含的修飾。舉例而言，若核苷酸1至3包含硫代磷酸酯，核苷酸4僅包含2'-OMe修飾，且核苷酸5為YA位點之嘧啶且包含硫代磷酸酯，則經修飾之導引區YA位點包含位於導引區YA位點之5'之至少一個核苷酸(核苷酸4)不包含的修飾(硫代磷酸酯)。在另一實例中，若核苷酸1至3包含硫代磷酸酯，且核苷酸4為YA位點之嘧啶且包含2'-OMe，則經修飾之導引區YA位點包含位於導引區YA位點之5'之至少一個核苷酸(核苷酸1至3中之任一者)不包含的修飾(2'-OMe)。若未經修飾之核苷酸位於經修飾之導引區YA位點之5'，則亦始終滿足此條件。

【0316】 在一些實施例中，經修飾之導引區YA位點包含如上文針對YA位點所描述之修飾。gRNA之導引區可根據任何實施例修飾，其包含本文所闡述之經修飾導引區。

【0317】 保守區YA位點1至10說明於圖23B中。在一些實施例中，1、2、3、4、5、6、7、8、9或10個保守區YA位點包含修飾。在一些實施例中，保守區YA位點1、8或1及8包含YA修飾。在一些實施例中，保守區YA位點1、2、3、4及10包含YA修飾。在一些實施例中，YA位點2、3、4、8及10包含YA修飾。在一些實施例中，保守區YA位點1、2、3及10包含YA修飾。在一些實施例中，YA位點2、3、8及10包含YA修飾。在一些實施例中，YA位點1、2、3、4、8及10包含YA修飾。在一些實施例中，1、2、3、4、5、6、7或8個其他保守區YA位點包含YA修飾。

【0318】 在一些實施例中，經修飾之保守區YA位點包含如上文針對YA位點所描述之修飾。在可行的情況下，本發明在別處闡述之任何實施例可與前述實施例中之任一者組合。

【0319】 在一些實施例中，gRNA之5'及/或3'末端區經修飾。

【0320】 在一些實施例中，3'末端區中之末端(亦即，最後) 1、2、3、4、5、6或7個核苷酸經修飾。在全篇中，此修飾可稱為「3'端修飾」。在一些實施例中，3'末端區中之末端(亦即，最後) 1、2、3、4、5、6或7個核苷酸包含超過一個修飾。在一些實施例中，3'端修飾包含或進一步包含以下中之任何一或多者：選自2'-O-甲基(2'-O-Me)修飾之核苷酸、2'-O-(2-甲氧基乙基) (2'-O-moe)修飾之核苷酸、2'-氟(2'-F)修飾之核苷酸、核苷酸之間的硫代磷酸酯(PS)鍵、倒轉無鹼基修飾之核苷酸或其組合的經修飾之核苷酸。在一些實施例中，3'端修飾包含或進一步包含

gRNA之3'端之1、2、3、4、5、6或7個核苷酸的修飾。在一些實施例中，3'端修飾包含或進一步包含一個PS鍵，其中該鍵介於最後一個核苷酸與倒數第二個核苷酸之間。在一些實施例中，3'端修飾包含或進一步包含最後三個核苷酸之間的兩個PS鍵。在一些實施例中，3'端修飾包含或進一步包含最後四個核苷酸之間的四個PS鍵。在一些實施例中，3'端修飾包含或進一步包含最後2、3、4、5、6或7個核苷酸中之任何一或多者之間的PS鍵。在一些實施例中，包含3'端修飾之gRNA包含或進一步包含3'尾，其中該3'尾包含存在於3'尾中之核苷酸中之任何一或多者的修飾。在一些實施例中，3'尾完全被修飾。在一些實施例中，3'尾包含1、2、3、4、5、6、7、8、9、10、1至2個、1至3個、1至4個、1至5個、1至6個、1至7個、1至8個、1至9個或1至10個核苷酸，視情況其中此等核苷酸中之任何一或多者經修飾。在一些實施例中，提供包含3'端修飾之gRNA，其中3'端修飾包含如SEQ ID NO: 141至145中之任一者中所示的3'端修飾。在一些實施例中，提供包含3'保護端修飾之gRNA。在一些實施例中，3'尾包含1至約20個核苷酸、1至約15個核苷酸、1至約10個核苷酸、1至約5個核苷酸、1至約4個核苷酸、1至約3個核苷酸及1至約2個核苷酸。在一些實施例中，gRNA不包含3'尾。

【0321】 在一些實施例中，5'末端區經修飾，例如gRNA中之前1、2、3、4、5、6或7個核苷酸經修飾。在全篇中，此修飾可稱為「5'端修飾」。在一些實施例中，5'末端區中之前1、2、3、4、5、6或7個核苷酸包含超過一個修飾。在一些實施例中，5'端之末端(亦即，前) 1、2、3、4、5、6或7個核苷酸中的至少一者經修飾。在一些實施例中，gRNA之5'及3'端區(例如，端)兩者均經修飾。在一些實施例中，僅gRNA之5'端區經

修飾。在一些實施例中，僅gRNA保守部分中之3'末端區(加或減3'尾)經修飾。在一些實施例中，gRNA包含在gRNA之5'末端區處之前7個核苷酸中之1、2、3、4、5、6或7者處的修飾。在一些實施例中，gRNA包含在3'末端區處之7個末端核苷酸中之1、2、3、4、5、6或7者處的修飾。在一些實施例中，5'末端區處之前4個核苷酸中之2、3或4者，及/或3'末端區處之末端4個核苷酸中之2、3或4者經修飾。在一些實施例中，5'末端區處之前4個核苷酸中的2、3或4者經由硫代磷酸酯(PS)鍵連接。在一些實施例中，對5'端及/或3'端之修飾包含2'-O-甲基(2'-O-Me)或2'-O-(2-甲氧基乙基) (2'-O-moe)修飾。在一些實施例中，修飾包含對核苷酸之2'-氟(2'-F)修飾。在一些實施例中，修飾包含核苷酸之間的硫代磷酸酯(PS)鍵。在一些實施例中，修飾包含倒轉無鹼基核苷酸。在一些實施例中，修飾包含保護端修飾。在一些實施例中，修飾包含超過一個修飾，其選自保護端修飾、2'-O-Me、2'-O-moe、2'-氟(2'-F)、核苷酸之間的硫代磷酸酯(PS)鍵及倒轉無鹼基核苷酸。在一些實施例中，包涵等效修飾。在一些實施例中，提供包含5'端修飾之gRNA，其中5'端修飾包含如SEQ ID NO: 141至145中之任一者中所示的5'端修飾。

【0322】 在一些實施例中，提供包含5'端修飾及3'端修飾之gRNA。在一些實施例中，gRNA包含不處於5'或3'端處之經修飾之核苷酸。

【0323】 在一些實施例中，提供包含上莖修飾之sgRNA，其中上莖修飾包含對上莖區中之US1至US12中之任何一或多者的修飾。在一些實施例中，提供包含上莖修飾之sgRNA，其中上莖修飾包含對上莖區中之至少1、2、3、4、5、6、7、8、9、10、11或所有12個核苷酸的修飾。在一些實施例中，提供包含上莖修飾之sgRNA，其中上莖修飾包含YA位點

中之1、2、3、4或5個YA修飾。在一些實施例中，上莖修飾包含2'-OMe修飾之核苷酸、2'-O-moe修飾之核苷酸、2'-F修飾之核苷酸及/或其組合。本文中所描述之其他修飾，諸如5'端修飾及/或3'端修飾可與上莖修飾組合。

【0324】 在一些實施例中，sgRNA包含髮夾區中之修飾。在一些實施例中，髮夾區修飾包含至少一個經修飾之核苷酸，其選自2'-O-甲基(2'-OMe)修飾之核苷酸、2'-氟(2'-F)修飾之核苷酸及/或其組合。在一些實施例中，髮夾區修飾處於髮夾1區中。在一些實施例中，髮夾區修飾處於髮夾2區中。在一些實施例中，髮夾修飾包含YA位點中之1、2或3個YA修飾。在一些實施例中，髮夾修飾包含至少1、2、3、4、5或6個YA修飾。本文中所描述之其他修飾，諸如上莖修飾、5'端修飾及/或3'端修飾可與髮夾區中之修飾組合。

【0325】 在一些實施例中，gRNA包含經取代且視情況經縮短之髮夾1區，其中以下核苷酸對中之至少一者在經取代及視情況經縮短之髮夾1中經沃森-克里克配對核苷酸(Watson-Crick pairing nucleotide)取代：H1-1及H1-12、H1-2及H1-11、H1-3及H1-10及/或H1-4及H1-9。「沃森-克里克配對核苷酸」包括能夠形成沃森-克里克鹼基對之任何對，包括A-T、A-U、T-A、U-A、C-G及G-C對，及包括具有相同鹼基配對偏好之前述核苷酸中之任一者的經修飾型式的對。在一些實施例中，髮夾1區缺少H1-5至H1-8中之任一者或兩者。在一些實施例中，髮夾1區缺少以下核苷酸對中之一者、兩者或三者：H1-1及H1-12、H1-2及H1-11、H1-3及H1-10及/或H1-4及H1-9。在一些實施例中，髮夾1區缺少髮夾1區之1至8個核苷酸。在前述實施例中之任一者中，缺少核苷酸可使得經沃森-克里克配

對核苷酸(H1-1及H1-12、H1-2及H1-11、H1-3及H1-10及/或H1-4及H1-9)取代之一或多個核苷酸對在gRNA中形成鹼基對。

【0326】 在一些實施例中，gRNA進一步包含缺少至少1個核苷酸之上莖區，例如美國申請案第62/946,905號之表7中指示的經縮短之上莖區中之任一者，其內容以全文引用的方式併入本文中或描述於本文中之其他地方，該等上莖區可與本文所描述之經縮短或經取代的髮夾1區中之任一者組合。

【0327】 在一些實施例中，本文所描述之gRNA進一步包含連接區，其中連接區缺少至少一個核苷酸。

3. gRNA之化學修飾

【0328】 在一些實施例中，gRNA經化學修飾。包含一或多個經修飾之核苷或核苷酸之gRNA稱為「經修飾之」gRNA或「經化學修飾之」gRNA，用於描述替代或外加典型A、G、C及U殘基使用之一或多種非天然及/或天然存在之組分或組態之存在。經修飾之核苷及核苷酸可包括以下中之一或多者：(i)磷酸二酯主鏈鍵中之一或兩個非連接磷酸酯氧及/或一或多個連接磷酸酯氧的變化，例如置換(例示性主鏈修飾)；(ii)核糖組分(例如，核糖上之2'羥基)之變化，例如置換(例示性糖修飾)；(iii)用「去磷酸化」連接子成批置換磷酸酯部分(例示性主鏈修飾)；(iv)天然存在之核鹼基的修飾或置換，包括用非典型核鹼基修飾或置換(例示性鹼基修飾)；(v)核糖-磷酸酯主鏈之置換或修飾(例示性主鏈修飾)；(vi)寡核苷酸之3'端或5'端之修飾，例如末端磷酸酯基之移除、修飾或置換，或部分、端帽或連接子之結合(此類3'或5'端帽修飾可包含糖及/或主鏈修飾)；及(vii)糖之修飾或置換(例示性糖修飾)。

【0329】 化學修飾(諸如以上列出之彼等)可經組合以得到經修飾之gRNA，其包含可具有兩個、三個、四個或更多個修飾之核苷及核苷酸(統稱為「殘基」)。舉例而言，經修飾之殘基可具有經修飾之糖及經修飾之核鹼基。在一些實施例中，gRNA之每一鹼基經修飾，例如所有鹼基均具有諸如硫代磷酸酯基之經修飾之磷酸酯基。在某些實施例中，gRNA分子之所有或實質上所有磷酸酯基經硫代磷酸酯基置換。在一些實施例中，經修飾之gRNA在RNA之5'端處或其附近包含至少一個經修飾之殘基。在一些實施例中，經修飾之gRNA在RNA之3'端處或附近包含至少一個經修飾之殘基。

【0330】 在一些實施例中，gRNA包含一個、二個、三個或更多個經修飾之殘基。在一些實施例中，經修飾之gRNA中至少5% (例如至少5%、至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或100%)之位置為經修飾之核苷或核苷酸。

【0331】 在主鏈修飾之一些實施例中，經修飾之殘基中的磷酸酯基可藉由用不同取代基置換一或多個氧而經修飾。另外，經修飾之殘基，例如存在於經修飾之核酸中之經修飾之殘基可包括用如本文所描述之經修飾之磷酸酯基批量置換未經修飾之磷酸酯部分。在一些實施例中，磷酸酯主鏈之主鏈修飾可包括產生不帶電連接子或具有不對稱電荷分佈之帶電連接子的變化。

【0332】 經修飾之磷酸酯基的實例包括硫代磷酸酯、硒代磷酸酯、硼烷磷酸酯、硼烷磷酸酯、氫膦酸酯、胺基磷酸酯、烷基或芳基膦酸酯及

磷酸三酯。

【0333】 亦可構築可模擬核酸之骨架，其中磷酸酯連接子及核糖經耐核酸酶性核苷或核苷酸替代物置換。此類修飾可包含主鏈及糖修飾。在一些實施例中，核鹼基可藉由替代主鏈繫栓。實例可包括(但不限於) N-嗎啉基、環丁基、吡咯啶及肽核酸(PNA)核苷替代物。

【0334】 經修飾之核苷及經修飾之核苷酸可包括對糖基之一或多個修飾，亦即糖修飾。舉例而言，2'羥基(OH)可經修飾，例如經多個不同「氧基」或「去氧」取代基置換。在一些實施例中，對2'羥基之修飾可增強核酸之穩定性，因為羥基可不再經去質子化以形成2'-烷氧離子。2'羥基修飾之實例可包括烷氧基或芳氧基(OR，其中「R」可為例如烷基、環烷基、芳基、芳烷基、雜芳基或糖)；聚乙二醇(PEG)、$O(CH_2CH_2O)_nCH_2CH_2OR$，其中R可為例如H或視情況經取代之烷基，且n可為0至20之整數。在一些實施例中，2'羥基修飾可為2'-O-Me。在一些實施例中，2'羥基修飾可為2'-氟修飾，其用氟化物置換2'羥基。在一些實施例中，2'羥基修飾可包括「鎖定」核酸LAA，其中2'羥基可例如藉由C_{1-6}亞烷基或C_{1-6}雜亞烷基橋連接至同一核糖之4'碳，其中例示性橋可包括亞甲基、丙烯、乙醚或胺基橋。在一些實施例中，2'羥基修飾可包括「未鎖定」核酸(UNA)，其中核糖環缺少C2'-C3'鍵。在一些實施例中，2'羥基修飾可包括甲氧基乙基(MOE)($OCH_2CH_2OCH_3$，例如PEG衍生物)。

【0335】 「去氧」2'修飾可包括氫(亦即，去氧核糖，例如在部分dsRNA之突出部分處)；鹵基(例如溴基、氯基、氟基或碘基)；胺基(其中胺基可為例如NH_2；烷基胺基、二烷基胺基、雜環基、芳基胺基、二芳基胺基、雜芳胺基、二雜芳胺基或胺基酸)；$NH(CH_2CH_2NH)_nCH_2CH_2$-胺基

(其中胺基可例如如本文所描述)、-NHC(O)R (其中R可為例如烷基、環烷基、芳基、芳烷基、雜芳基或糖)、氰基；巯基；烷基-硫基-烷基；硫代烷氧基；及可視情況經例如如本文所描述之胺基取代的烷基、環烷基、芳基、烯基及炔基。

【0336】 糖修飾可包含亦可含有一或多個碳之糖基，其具有與核糖中之對應碳相反的立體化學組態。因此，經修飾之核酸可包括含有例如阿拉伯糖作為糖的核苷酸。經修飾之核酸亦可包括無鹼基糖。此等無鹼基糖亦可進一步在成分糖原子中之一或多者處經修飾。經修飾之核酸亦可包括一或多種呈L形式之糖，例如L-核苷。

【0337】 可併入至經修飾之核酸中之本文所描述的經修飾之核苷及經修飾之核苷酸可包括經修飾之核鹼基，亦稱為核鹼基。核鹼基之實例包括但不限於腺嘌呤(A)、鳥嘌呤(G)、胞嘧啶(C)及尿嘧啶(U)。此等核鹼基可經修飾或全部被置換以提供可併入經修飾之核酸中的經修飾之殘基。核苷酸之核鹼基可獨立地選自嘌呤、嘧啶、嘌呤類似物或嘧啶類似物。在一些實施例中，核鹼基可包括例如天然存在之鹼基衍生物及合成鹼基衍生物。

【0338】 在使用雙重導引RNA的實施例中，crRNA及tracr RNA中的每一者可含有修飾。該等修飾可處於crRNA及/或tracr RNA之一端或兩端處。在包含sgRNA之實施例中，sgRNA之一端或兩端處的一或多個殘基可經化學修飾，或整個sgRNA可經化學修飾。某些實施例包含5'端修飾。某些實施例包含3'端修飾。在某些實施例中，gRNA分子之單股突出中之一或多個或所有核苷酸為去氧核苷酸。

【0339】 在一些實施例中，本文所揭示之gRNA包含2018年6月14

日公開之WO2018/107028 A1中所揭示之修飾模式中之一者，該案之內容特此以全文引用之方式併入。

【0340】 術語「mA」、「mC」、「mU」或「mG」可用於表示經2'-O-Me修飾之核苷酸。術語「fA」、「fC」、「fU」或「fG」可用於表示經2'-F取代之核苷酸。「*」可用於描述PS修飾。術語A*、C*、U*或G*可用於表示經PS鍵連接至下一個(例如3')核苷酸之核苷酸。術語「mA*」、「mC*」、「mU*」或「mG*」可用於表示已經2'-O-Me取代且經PS鍵連接至下一個(例如3')核苷酸之核苷酸。

H. 脂質；調配物；遞送

【0341】 本文揭示使用包含本文中所描述之核酸或組合物之脂質核酸組裝組合物的各種實施例。在一些實施例中，脂質核酸組裝組合物包含核酸(例如，mRNA)，該核酸包含編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶的第一多肽之開讀框。在一些實施例中，脂質核酸組裝組合物包含第一核酸及編碼UGI之第二核酸，該第一核酸包含編碼包含胞苷去胺酶(例如，A3A)及RNA導引之切口酶的第一多肽之開讀框。

【0342】 如本文所用，「脂質核酸組裝組合物」係指基於脂質之遞送組合物，包括脂質奈米粒子(LNP)及脂質複合物。LNP係指<100nM之脂質奈米粒子。LNP係藉由將脂質組分(例如於乙醇中)與水性核酸組分精確混合而形成，且LNP之大小均一。脂質複合物為藉由使脂質與核酸組分大量混合而形成之粒子且大小在約100 nm與1微米之間。在某些實施例中，脂質核酸組裝體為LNP。如本文所用，「脂質核酸組裝體」包含複數個(亦即，超過一個)藉由分子間力以物理方式彼此締合之脂質分子。脂質核酸組裝體可包含pKa值為<7.5或<7之生物可用脂質。脂質核酸組裝體係

藉由混合含水性核酸溶液與基於有機溶劑之脂質溶液(例如，100%乙醇)形成。適合溶液或溶劑包括或可含有：水、PBS、Tris緩衝液、NaCl、檸檬酸鹽緩衝液、乙醇、氯仿、二乙醚、環己烷、四氫呋喃、甲醇、異丙醇。醫藥學上可接受之緩衝液可視情況包含於包含脂質核酸組裝體之醫藥調配物中，例如用於離體療法。在一些實施例中，水溶液包含RNA，諸如mRNA或gRNA。在一些實施例中，水溶液包含編碼經RNA導引之DNA結合劑(諸如Cas9)的mRNA。

【0343】 如本文所使用，脂質奈米粒子(LNP)係指包含複數個(亦即，超過一個)藉由分子間力以物理方式彼此締合之脂質分子的粒子。LNP可例如為微球體(包括單層及多層囊泡，例如「脂質體」—在一些實施例中為實質上球形之層狀相脂質雙層—且在更特定實施例中可包含水性核心，例如包含大部分RNA分子)、乳液中之分散相、微胞或懸浮液中之內相。乳液、微胞及懸浮液可為用於局部及/或表面遞送之適合組合物。亦參見例如WO2017173054A1，其內容特此以全文引用之方式併入。熟習此項技術者已知能夠將核苷酸遞送至個體之任何LNP可與導引RNA及編碼RNA導引之切口酶之核酸及編碼本文所描述之胞苷去胺酶的核酸一起使用。

【0344】 在一些實施例中，水溶液包含編碼包含A3A及RNA導引之切口酶之多肽的核酸。包含脂質核酸組裝組合物之醫藥調配物可視情況包含醫藥學上可接受之緩衝液。

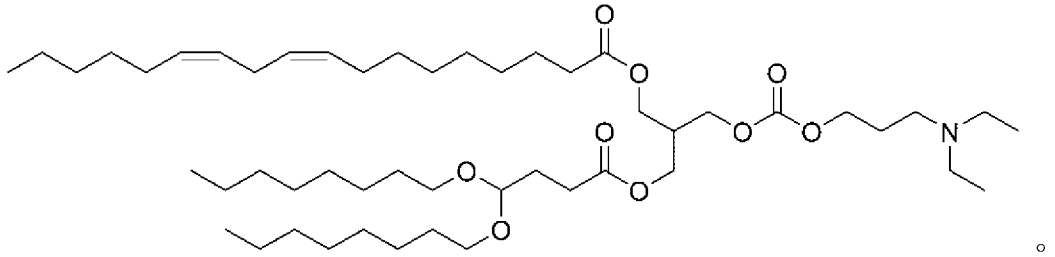
【0345】 在一些實施例中，脂質核酸組裝組合物包括「胺脂質」(在本文中或其他地方有時描述為「可離子化脂質」或「可生物降解脂質」)，以及視情況存在之「輔助脂質」、「中性脂質」及隱形脂質，諸

如PEG脂質。在一些實施例中，取決於pH，胺脂質或可離子化脂質為陽離子型的。

1. 胺脂質

【0346】 在一些實施例中，脂質核酸組裝組合物包含「胺脂質」，其為例如可離子化脂質，諸如脂質A或其等效物，包括脂質A之縮醛類似物。

【0347】 在一些實施例中，胺脂質為脂質A，其為十八-9,12-二烯酸(9Z,12Z)-3-((4,4-雙(辛氧基)丁醯基)氧基)-2-((((3-(二乙胺基)丙氧基)羰基)氧基)甲基)丙酯，亦稱作(9Z,12Z)-十八-9,12-二烯酸3-((4,4-雙(辛氧基)丁醯基)氧基)-2-((((3-(二乙胺基)丙氧基)羰基)氧基)甲基)丙酯。脂質A可描繪為：



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【0348】 可根據WO2015/095340 (例如第84至86頁)合成脂質A。在一些實施例中，胺脂質為脂質A之等效物。

【0349】 在一些實施例中，胺脂質為脂質A之類似物。在一些實施例中，脂質A類似物為脂質A之縮醛類似物。在特定脂質核酸組裝組合物中，縮醛類似物為C4-C12縮醛類似物。在一些實施例中，縮醛類似物為C5-C12縮醛類似物。在額外實施例中，縮醛類似物為C5-C10縮醛類似物。在其他實施例中，縮醛類似物係選自C4、C5、C6、C7、C9、C10、C11及C12縮醛類似物。

【0350】 適用於本文所描述之脂質核酸組裝體的胺脂質及其他「可

生物降解脂質」為活體內或離體可生物降解的。胺脂質具有低毒性(例如，以大於或等於10 mg/kg之量在動物模型中得到耐受而不具有不良作用)。在一些實施例中，包含胺脂質之脂質核酸組裝體包括其中在8、10、12、24或48小時或3、4、5、6、7或10天內自血漿或工程化細胞清除至少75%胺脂質的脂質核酸組裝體。在一些實施例中，包含胺脂質之脂質核酸組裝體包括其中在8、10、12、24或48小時或3、4、5、6、7或10天內自血漿清除至少50%核酸，例如mRNA或gRNA的脂質核酸組裝體。在一些實施例中，包含胺脂質之脂質核酸組裝體包括其中在8、10、12、24或48小時或3、4、5、6、7或10天內自血漿清除至少50%脂質核酸組裝體之脂質核酸組裝體，例如藉由量測脂質(例如，胺脂質)、核酸(例如，RNA/mRNA)或其他組分。在一些實施例中，量測脂質核酸組裝體之經脂質囊封相對於游離脂質、RNA或核酸組分。

【0351】可生物降解脂質包括例如WO/2020/219876、WO/2020/118041、WO/2020/072605、WO/2019/067992、WO/2017/173054、WO2015/095340及WO2014/136086之可生物降解脂質，且LNP包括其中所描述之LNP組合物，其脂質及組合物特此以引用之方式併入。

【0352】脂質清除率可如文獻中所描述來量測。參見Maier, M.A.等人Biodegradable Lipids Enabling Rapidly Eliminated Lipid Nanoparticles for Systemic Delivery of RNAi Therapeutics. *Mol. Ther.* 2013, 21(8), 1570-78 (「*Maier*」)。舉例而言，在*Maier*中，以0.3 mg/kg藉由靜脈內推注注射經由外側尾部靜脈向六至八週齡雄性C57BL/6小鼠投與含有靶向螢光素酶之siRNA的LNP-siRNA系統。在給藥後0.083、0.25、0.5、1、2、

4、8、24、48、96及168小時收集血液、肝臟及脾臟樣本。在收集組織之前向小鼠灌注生理鹽水且處理血液樣本以獲得血漿。處理且藉由LC-MS分析所有樣本。此外，*Maier*描述了一種用於評定投與LNP-siRNA調配物之後的毒性之程序。舉例而言，以0、1、3、5及10 mg/kg (5隻動物/組)經由單一靜脈內推注注射以5 mL/kg之劑量體積向雄性史泊格-多利大鼠(Sprague-Dawley rat)投與靶向螢光素酶之siRNA。24小時之後，自清醒的動物之頸靜脈獲得約1 mL血液且分離血清。在給藥後72小時，將所有動物安樂死以用於屍體剖檢。進行臨床症狀、體重、血清化學、器官重量及組織病理學之評定。儘管*Maier*描述了用於評定siRNA-LNP調配物之方法，但此等方法可適用於評定本發明之脂質核酸組裝組合物之投藥的清除率、藥物動力學及毒性。

【0353】 此項技術中已知用於核酸之LNP遞送的可離子化及生物可用脂質為適合的。脂質可取決於其所存在之介質的pH而離子化。舉例而言，在弱酸性介質中，脂質，諸如胺脂質可經質子化且因此帶有正電荷。相反地，在弱鹼性介質，諸如其中pH為大約7.35之血液中，脂質，諸如胺脂質可不經質子化且因此不帶電荷。

【0354】 脂質攜帶電荷之能力與其固有pKa有關。在一些實施例中，本發明之胺脂質可各自獨立地具有在約5.1至約7.4範圍內之pKa。在一些實施例中，本發明之生物可用脂質可各自獨立地具有在約5.1至約7.4，諸如約5.5至約6.6、約5.6至約6.4、約5.8至約6.2或約5.8至約6.5範圍內之pKa。舉例而言，本發明之胺脂質可各自獨立地具有在約5.8至約6.5範圍內之pKa。pKa在約5.1至約7.4範圍內之脂質有效用於活體內遞送負荷，例如遞送至肝臟。另外，已發現，pKa在約5.3至約6.4範圍內之脂

質對活體內遞送至例如腫瘤為有效的。參見例如WO2014/136086。

2. 額外脂質

【0355】 適用於本發明之脂質核酸組裝組合物中的「中性脂質」包括例如多種中性、不帶電荷或兩性離子型脂質。適用於本發明之中性磷脂之實例包括但不限於：5-十七基苯-1,3-二醇(間苯二酚)、二軟脂醯基磷脂醯膽鹼(DPPC)、二硬脂醯基磷脂醯膽鹼(DSPC)、磷酸膽鹼(DOPC)、二肉豆蔻醯基磷脂醯膽鹼(DMPC)、磷脂醯膽鹼(PLPC)、1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DAPC)、磷脂醯乙醇胺(PE)、卵磷脂醯膽鹼(EPC)、二月桂醯基磷脂醯膽鹼(DLPC)、二肉豆蔻醯基磷脂醯膽鹼(DMPC)、1-肉豆蔻醯基-2-軟脂醯基磷脂醯膽鹼(MPPC)、1-軟脂醯基-2-肉豆蔻醯基磷脂醯膽鹼(PMPC)、1-軟脂醯基-2-硬脂醯基磷脂醯膽鹼(PSPC)、1,2-二花生醯基-sn-甘油-3-磷酸膽鹼(DBPC)、1-硬脂醯基-2-軟脂醯基磷脂醯膽鹼(SPPC)、1,2-二十碳烯醯基-sn-甘油-3-磷酸膽鹼(DEPC)、軟脂醯油醯基磷脂醯膽鹼(POPC)、溶血磷脂醯基膽鹼、二油醯基磷脂醯乙醇胺(DOPE)、二亞油醯基磷脂醯膽鹼二硬脂醯基磷脂醯乙醇胺(DSPE)、二肉豆蔻醯基磷脂醯乙醇胺(DMPE)、二軟脂醯基磷脂醯乙醇胺(DPPE)、軟脂醯油醯基磷脂醯乙醇胺(POPE)、溶血磷脂醯乙醇胺及其組合。在一個實施例中，中性磷脂可選自由以下組成之群：二硬脂醯基磷脂醯膽鹼(DSPC)及二肉豆蔻醯基磷脂醯乙醇胺(DMPE)。在另一實施例中，中性磷脂可為二硬脂醯基磷脂醯膽鹼(DSPC)。

【0356】 「輔助脂質」包括類固醇、固醇及烷基間苯二酚。適用於本發明中之輔助脂質包括但不限於膽固醇、5-十七基間苯二酚及膽固醇半丁二酸酯。在一個實施例中，輔助脂質可為膽固醇。在一個實施例中，輔

助脂質可為膽固醇半丁二酸酯。

【0357】「隱形脂質」為改變奈米粒子可在活體內(例如血液中)存在之時長的脂質。隱形脂質可藉由例如減少粒子聚集且控制粒度來輔助調配過程。本文使所用之隱形脂質可調節脂質核酸組裝體之藥物動力學特性或有助於奈米粒子離體穩定性。適用於本發明之脂質核酸組裝組合物之隱形脂質包括但不限於具有連接至脂質部分之親水性頭基的隱形脂質。適用於本發明之脂質核酸組裝組合物之隱形脂質及關於此類脂質之生物化學的資訊可見於Romberg等人, Pharmaceutical Research, 第25卷, 第1期, 2008, 第55至71頁及Hoekstra等人, Biochimica et Biophysica Acta 1660 (2004) 41-52。額外適合PEG脂質揭示於例如WO 2006/007712中。

【0358】在一個實施例中，隱形脂質之親水性頭基包含選自基於PEG之聚合物的聚合物部分。隱形脂質可包含脂質部分。在一些實施例中，隱形脂質為PEG脂質。

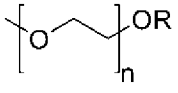
【0359】在一個實施例中，隱形脂質包含選自基於以下之聚合物的聚合物部分：PEG (有時稱作聚(環氧乙烷))、聚(噁唑啉)、聚(乙烯醇)、聚(甘油)、聚(N-乙烯基吡咯啶酮)、聚胺基酸及聚[N-(2-羥丙基)甲基丙烯醯胺]。

【0360】在一個實施例中，PEG脂質包含基於PEG (有時稱作聚(環氧乙烷))之聚合物部分。

【0361】PEG脂質進一步包含脂質部分。在一些實施例中，脂質部分可源自二醯基甘油或二醯基甘油醯胺、包括包含具有獨立地包含約C4至約C40飽和或不飽和碳原子之烷基鏈長度的二烷基甘油或二烷基甘油醯胺基之彼等者，其中該鏈可包含一或多個官能基，諸如醯胺或酯。在一些

實施例中，烷基鏈長度包含約C10至C20。二烷基甘油或二烷基甘油醯胺基可進一步包含一或多個經取代之烷基。鏈長可為對稱或不對稱的。

【0362】 除非另外指示，否則如本文所使用，術語「PEG」意謂任何聚乙二醇或其他聚伸烷醚聚合物。在一個實施例中，PEG為乙二醇或環氧乙烷的視情況經取代之直鏈或分支鏈聚合物。在一個實施例中，PEG為未經取代的。在一個實施例中，PEG經例如一或多個烷基、烷氧基、醯基、羥基、或芳基取代。在一個實施例中，該術語包括PEG共聚物，諸如PEG-聚胺基甲酸酯或PEG-聚丙烯(參見例如J. Milton Harris, Poly(ethylene glycol) chemistry: biotechnical and biomedical applications (1992))；在另一實施例中，該術語不包括PEG共聚物。在一個實施例中，PEG之分子量為約130至約50,000，在子實施例中，約150至約30,000，在子實施例中，約150至約20,000，在子實施例中，約150至約15,000，在子實施例中，約150至約10,000，在子實施例中，約150至約6,000，在子實施例中，約150至約5,000，在子實施例中，約150至約4,000，在子實施例中，約150至約3,000，在子實施例中，約300至約3,000，在子實施例中，約1,000至約3,000，及在子實施例中，約1,500至約2,500。

【0363】 在一些實施例中，PEG (例如，與脂質部分或脂質，諸如隱形脂質結合)為「PEG-2K」，亦稱為「PEG 2000」，其平均分子量為約2,000道爾頓。PEG-2K在本文中由下式(I)表示，其中n為45，意謂經數目平均化之聚合度包含約45個次單元：  (I)。然而，可使用此項技術中已知之其他PEG實施例，包括例如其中經數目平均化之聚合度包含約23個次單元(n=23)及/或68個次單元(n=68)之彼等。在一些實施例

中，n可在約30至約60範圍內。在一些實施例中，n可在約35至約55範圍內。在一些實施例中，n可在約40至約50範圍內。在一些實施例中，n可在約42至約48範圍內。在一些實施例中，n可為45。在一些實施例中，R可選自H、經取代之烷基及未經取代之烷基。在一些實施例中，R可為未經取代之烷基。在一些實施例中，R可為甲基。

【0364】 在本文所描述之實施例中之任一者中，PEG脂質可選自：PEG-二月桂醯甘油、PEG-二肉豆蔻醯甘油(PEG-DMG) (目錄號GM-020，獲自NOF, Tokyo, Japan)、PEG-二棕櫚醯甘油、PEG-二硬脂醯甘油(PEG-DSPE) (目錄號DSPE-020CN，NOF, Tokyo, Japan)、PEG-二月桂基甘油醯胺、PEG-二肉豆蔻基甘油醯胺、PEG-二軟酯醯甘油醯胺及PEG-二硬脂醯甘油醯胺、PEG-膽固醇(1-[8'-(膽甾-5-烯-3[β]-氧基)甲醯胺基-3',6'-二氧雜辛基]胺甲醯基-[ω]-甲基-聚(乙二醇)、PEG-DMB (3,4-二-十四氧基苯甲基-[ω]-甲基-聚(乙二醇)醚)、1,2-二肉豆蔻醯基-sn-丙三氧基-3-磷酸乙醇胺-N-[甲氧基(聚乙二醇)-2000] (PEG2k-DMG) (目錄號880150P，獲自Avanti Polar Lipids, Alabaster, Alabama, USA)、1,2-二硬脂醯基-sn-丙三氧基-3-磷酸乙醇胺-N-[甲氧基(聚乙二醇)-2000] (PEG2k-DSPE) (目錄號880120C，獲自Avanti Polar Lipids, Alabaster, Alabama, USA)、1,2-二硬脂醯基-sn-甘油, 甲氧基聚乙二醇(PEG2k-DSG；GS-020，NOF Tokyo, Japan)、聚(乙二醇)-2000-二甲基丙烯酸酯(PEG2k-DMA)及1,2-二硬脂醯氧基丙基-3-胺-N-[甲氧基(聚乙二醇)-2000] (PEG2k-DSA)。在一個實施例中，PEG脂質可為PEG2k-DMG。在一些實施例中，PEG脂質可為PEG2k-DSG。在一個實施例中，PEG脂質可為PEG2k-DSPE。在一個實施例中，PEG脂質可為PEG2k-DMA。在一個實

施例中，PEG脂質可為PEG2k-C-DMA。在一個實施例中，PEG脂質可為化合物S027，其揭示於WO2016/010840(第[00240]至[00244]段)中。在一個實施例中，PEG脂質可為PEG2k-DSA。在一個實施例中，PEG脂質可為PEG2k-C11。在一些實施例中，PEG脂質可為PEG2k-C14。在一些實施例中，PEG脂質可為PEG2k-C16。在一些實施例中，PEG脂質可為PEG2k-C18。

3. 調配物

【0365】 脂質核酸組裝體可含有(i)可生物降解脂質，(ii)視情況存在之中性脂質，(iii)輔助脂質，及(iv)隱形脂質，諸如PEG脂質。脂質核酸組裝體可含有可生物降解的脂質及中性脂質、輔助脂質及隱形脂質(諸如PEG脂質)中之一或多者。

【0366】 脂質核酸組裝體可含有(i)用於囊封及用於核內體逃逸(endosomal escape)之胺脂質，(ii)用於穩定之中性脂質、(iii)亦用於穩定之輔助脂質及(iv)隱形脂質，諸如PEG脂質。脂質核酸組裝體可含有胺脂質及中性脂質、亦用於穩定之輔助脂質及隱形脂質(諸如PEG脂質)中之一或多者。

【0367】 達成本文所描述之所描述功能效應所需的mRNA可以一或多種脂質核酸組裝組合物遞送至細胞。舉例而言，一種脂質核酸組裝組合物可經調配以用於遞送，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之多肽的mRNA以及編碼例如一或多種UGI及一或多種gRNA之額外mRNA。替代地，編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之mRNA、編碼一或多個UGI之mRNA及編碼一或多種gRNA之mRNA可調配於單獨的

脂質核酸組裝組合物中。因此，一或多種脂質核酸組裝組合物可活體外或活體內遞送至細胞。

【0368】 在一些實施例中，提供一種修飾細胞中之目標基因之方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，該一或多種脂質核酸組裝組合物包含：

(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之多肽的第一開讀框；

(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)一或多種導引RNA。

【0369】 在一些實施例中，部分(a)及(b)在單獨的脂質核酸組裝組合物中。在一些實施例中，部分(a)及(b)在同一脂質核酸組裝組合物中。在一些實施例中，部分(a)及(c)在單獨的脂質核酸組裝組合物中。在一些實施例中，部分(a)及(c)在同一脂質核酸組裝組合物中。在一些實施例中，部分(b)及(c)在單獨的脂質核酸組裝組合物中。在一些實施例中，部分(a)及(c)在同一脂質核酸組裝組合物中，且部分(b)在單獨的脂質核酸組裝組合物中。在一些實施例中，部件(a)、(b)及(c)各自在單獨的脂質核酸組裝組合物中。在一些實施例中，部件(a)、(b)及(c)在同一脂質核酸組裝組合物中。在一些實施例中，一或多種導引RNA各自在單獨的脂質核酸組裝組合物中。

【0370】 在一些實施例中，該方法進一步包含遞送一或多種脂質核酸組裝組合物中之一或多種導引RNA，該一或多種脂質核酸組裝組合物與包含A3A及UGI之脂質核酸組裝組合物分離。

【0371】 在一些實施例中，向細胞遞送至少2種、3種、4種、5種、6種、7種、8種、9種或10種脂質核酸組裝組合物。在一些實施例中，至少一種脂質核酸組裝組合物包含脂質奈米粒子(LNP)。在一些實施例中，所有脂質核酸組裝組合物包含LNP。在一些實施例中，至少一種脂質核酸組裝組合物為脂質複合物組合物。

【0372】 在一些實施例中，脂質核酸組裝組合物，例如LNP組合物包含編碼多肽之mRNA，該多肽包含如本文所描述之胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶。在一些實施例中，脂質核酸組裝組合物，例如LNP組合物包含：編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的mRNA；及gRNA。

【0373】 在一些實施例中，脂質核酸組裝組合物包含含有mRNA之第一脂質核酸組裝組合物，該mRNA編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的第一多肽。在一些實施例中，脂質核酸組裝組合物進一步包含含有gRNA之第二脂質核酸組裝組合物。

【0374】 在一些實施例中，脂質核酸組裝組合物包含：第一組合物，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的第一多肽之mRNA；及編碼尿嘧啶醣苷酶抑制劑(UGI)之一或多個第二mRNA。在一些實施例中，脂質核酸組裝組合物進一步包含一或多種gRNA。

【0375】 在一些實施例中，脂質核酸組裝組合物進一步包含含有gRNA之第二脂質核酸組裝組合物。在一些實施例中，脂質核酸組裝組合物包含第一及第二脂質核酸組裝組合物，其中第一組合物包含編碼包含胞

苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之多肽的mRNA；且第二組合物包含編碼尿嘧啶醣苷酶抑制劑(UGI)之一或多個mRNA。在一些實施例中，第一脂質核酸組裝組合物或第二脂質核酸組裝組合物進一步包含一或多種gRNA。在一些實施例中，脂質核酸組裝組合物進一步包含含有一或多種gRNA之第三脂質核酸組裝組合物。

【0376】 在一些實施例中，脂質核酸組裝組合物包含：包含mRNA之第一脂質核酸組裝組合物，該mRNA包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之第一多肽的開讀框；及包含一或多種導引RNA (gRNA)之第二脂質核酸組裝組合物。

【0377】 在一些實施例中，脂質核酸組裝組合物包含：包含第一mRNA之第一組合物，該第一mRNA包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之第一多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之一或多個第二開讀框。在一些實施例中，脂質核酸組裝組合物進一步包含一或多種gRNA。在一些實施例中，脂質核酸組裝組合物進一步包含含有一或多種gRNA之第二脂質核酸組裝組合物。

【0378】 在一些實施例中，脂質核酸組裝組合物包含第一及第二脂質核酸組裝組合物，其中第一組合物包含含有編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之第一多肽的第一開讀框之第一mRNA；第二組合物包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。在一些實施例中，第一脂質核酸組裝組合物或第二脂質核酸組裝組合物進一步包含gRNA。在一些實施例中，脂質核酸組裝組合物進一步包含含有gRNA之第三脂質核酸組裝組合物。

【0379】在一些實施例中，脂質核酸組裝組合物包含：包含第一mRNA之第一組合物，該第一mRNA包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之第一多肽的第一開讀框；及包含尿嘧啶醣苷酶抑制劑(UGI)之第二組合物。在一些實施例中，第一脂質核酸組裝組合物或第二脂質核酸組裝組合物進一步包含gRNA。在一些實施例中，脂質核酸組裝組合物進一步包含含有gRNA之第三脂質核酸組裝組合物。

【0380】在一些實施例中，脂質核酸組裝組合物包含第一及第二脂質核酸組裝組合物，其中第一組合物包含含有胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽；且第二組合物包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。在一些實施例中，第一脂質核酸組裝組合物或第二脂質核酸組裝組合物進一步包含gRNA。在一些實施例中，脂質核酸組裝組合物進一步包含含有gRNA之第三脂質核酸組裝組合物。

【0381】在一些實施例中，脂質核酸組裝組合物可包含胺mRNA、視情況gRNA、胺脂質、輔助脂質、中性脂質及隱形脂質。在某些脂質核酸組裝組合物中，輔助脂質為膽固醇。在其他脂質核酸組裝組合物中，中性脂質為DSPC。在其他實施例中，隱形脂質為PEG2k-DMG或PEG2k-C11。在某些實施例中，脂質核酸組裝組合物包含脂質A或脂質A之等效物；輔助脂質；中性脂質；隱形脂質。在某些組合物中，胺脂質為脂質A。在某些組合物中，胺脂質為脂質A或其縮醛類似物；輔助脂質為膽固醇；中性脂質為DSPC；且隱形脂質為PEG2k-DMG。

【0382】本發明之實施例亦提供根據胺脂質(N)之帶正電胺基與待

囊封之核酸之帶負電磷酸酯基(P)之間的莫耳比描述之核酸組裝組合物。此可由方程式N/P數學表示。在一些實施例中，脂質核酸組裝組合物可包含脂質組分，其包含胺脂質、輔助脂質、中性脂質及PEG脂質；及核酸組分，其中N/P比為約3至10。在一些實施例中，脂質核酸組裝組合物可包含脂質組分，其包含胺脂質、輔助脂質及PEG脂質；及核酸組分，其中N/P比為約3至10。在一些實施例中，脂質核酸組裝組合物可包含脂質組分，其包含胺脂質、輔助脂質、中性脂質及輔助脂質；及RNA組分，其中N/P比為約3至10。在一些實施例中，脂質核酸組裝組合物可包含脂質組分，其包含胺脂質、輔助脂質及PEG脂質；及RNA組分，諸如mRNA或gRNA，其中N/P比為約3至10。在一個實施例中，N/P比可為約5至7。在一個實施例中，N/P比可為約3至7。在一個實施例中，N/P比可為約4.5至8。在一個實施例中，N/P比可為約6。在一個實施例中，N/P比可為6 ± 1。在一個實施例中，N/P比可為6 ± 0.5。在一些實施例中，N/P比將為目標N/P比之±30%、±25%、±20%、±15%、±10%、±5%或±2.5%。在某些實施例中，LNP批次間變化將低於15%、低於10%或小於5%。

【0383】 在一些實施例中，脂質核酸組裝組合物藉由混合水性RNA溶液與基於有機溶劑之脂質溶液(例如，100%乙醇)形成。適合溶液或溶劑包括或可含有：水、PBS、Tris緩衝液、NaCl、檸檬酸鹽緩衝液、乙醇、氯仿、二乙醚、環己烷、四氫呋喃、甲醇、異丙醇。可使用醫藥學上可接受之緩衝液，例如用於活體內投與脂質核酸組裝組合物。在某些實施例中，緩衝液用於將包含脂質核酸組裝組合物之組合物的pH維持處於或高於pH 6.5。在某些實施例中，緩衝液用於將包含LNP之組合物的pH維持處於或高於pH 7.0。在某些實施例中，組合物之pH在約7.2至約7.7範圍

內。在額外實施例中，組合物之pH在約7.3至約7.7範圍內或約7.4至約7.6範圍內。在其他實施例中，組合物之pH為約7.2、7.3、7.4、7.5、7.6或7.7。組合物之pH可用微型pH探針進行量測。在某些實施例中，組合物中包括低溫保護劑。低溫保護劑之非限制性實例包括蔗糖、海藻糖、甘油、DMSO及乙二醇。例示性組合物可包括至多10%低溫保護劑，諸如蔗糖。在某些實施例中，脂質核酸組裝組合物可包括約1%、2%、3%、4%、5%、6%、7%、8%、9%或10%低溫保護劑。在某些實施例中，脂質核酸組裝組合物可包括約1%、2%、3%、4%、5%、6%、7%、8%、9%或10%蔗糖。在一些實施例中，脂質核酸組裝組合物可包括緩衝液。在一些實施例中，緩衝液可包含磷酸鹽緩衝液(PBS)、Tris緩衝液、檸檬酸鹽緩衝液及其混合物。在某些例示性實施例中，緩衝液包含NaCl。在某些實施例中，省略NaCl。NaCl之例示性量可在約20 mM至約45 mM範圍內。NaCl之例示性量可在約40 mM至約50 mM範圍內。在一些實施例中，NaCl之量為約45 mM。在一些實施例中，緩衝液為Tris緩衝液。Tris之例示性量可在約20 mM至約60 mM範圍內。Tris之例示性量可在約40 mM至約60 mM範圍內。在一些實施例中，Tris之量為約50 mM。在一些實施例中，緩衝液包含NaCl及Tris。脂質核酸組裝組合物之某些例示性實施例含有5%蔗糖及含45 mM NaCl之Tris緩衝液。在其他例示性實施例中，組合物含有呈約5% w/v之量的蔗糖、約45 mM NaCl及約50 mM Tris (pH 7.5)。鹽、緩衝液及低溫保護劑量可有所變化以使得總調配物之滲透重量莫耳濃度得以維持。舉例而言，最終滲透重量莫耳濃度可維持低於450 mOsm/L。在其他實施例中，滲透重量莫耳濃度在350與250 mOsm/L之間。某些實施例之最終滲透重量莫耳濃度為300 +/- 20 mOsm/L。

【0384】 在一些實施例中，使用微流混合、T型混合或交叉混合。在某些態樣中，流動速率、接頭大小、接頭幾何結構、接頭形狀、管徑、溶液及/或核酸及脂質濃度可有所變化。脂質核酸組裝組合物可例如經由滲析、切向流過濾或層析得到濃縮或純化。脂質核酸組裝組合物可以例如懸浮液、乳液或凍乾粉末形式儲存。在一些實施例中，脂質核酸組裝組合物儲存在2至8℃下，在某些態樣中，LNP組合物儲存在室溫下。在額外實施例中，脂質核酸組裝組合物冷凍儲存，例如在-20℃或-80℃下。在其他實施例中，脂質核酸組裝組合物儲存在約0℃至約-80℃範圍內之溫度下。冷凍的脂質核酸組裝組合物可在使用之前例如在冰上、在室溫下或在25℃下解凍。

【0385】 脂質核酸組裝組合物可為例如微球體、於乳液中之分散相、微胞或懸浮液中之內相。

【0386】 此外，在一些實施例中，脂質核酸組裝組合物為可生物降解的，此係因為其不會在治療有效劑量下活體內積聚至細胞毒性水準。在一些實施例中，脂質核酸組裝組合物不在治療劑量水準下引起導致重大副作用之先天性免疫反應。在一些實施例中，本文提供之脂質核酸組裝組合物不會在治療劑量水準下引起毒性。

【0387】 本文揭示之LNP的大小(例如，Z平均直徑)為約1至約150 nm。在一些實施例中，LNP之大小為約10至約200 nm。在一些實施例中，LNP之大小為約50至約100 nm。在一些實施例中，LNP之大小為約60至約100 nm。在一些實施例中，LNP之大小為約75至約100 nm。在一些實施例中，LNP組合物包含平均直徑為約20至100 nm之LNP群體。在一些實施例中，LNP組合物包含平均直徑為約50至100 nm之LNP群體。

在一些實施例中，LNP組合物包含平均直徑為約60至100 nm之LNP群體。在一些實施例中，LNP組合物包含平均直徑為或約75至100 nm之LNP群體。除非另外指明，否則本文所提及之所有大小為完全成形奈米粒子之平均大小(直徑)，如藉由Malvern Zetasizer上之動態光散射所量測。奈米粒子樣本稀釋於磷酸鹽緩衝鹽水(PBS)中，以使得計數率為大致200至400 kcps。資料呈現為強度量度之加權平均值(Z平均直徑)。

【0388】 在一些實施例中，LNP經形成而具有介於約50%至約100%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於約50%至約70%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於約70%至約90%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於約90%至約100%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於約75%至約95%範圍內的平均囊封效率。

【0389】 在一些實施例中，LNP經形成而具有介於約1.00E+05 g/mol至約1.00E+10 g/mol範圍內的平均分子量。在一些實施例中，LNP經形成而具有介於約5.00E+05 g/mol至約7.00E+07 g/mol範圍內的平均分子量。在一些實施例中，LNP經形成而具有介於約1.00E+06 g/mol至約1.00E+10 g/mol範圍內的平均分子量。在一些實施例中，LNP經形成而具有介於約1.00E+07 g/mol至約1.00E+09 g/mol範圍內的平均分子量。在一些實施例中，LNP經形成而具有介於約5.00E+06 g/mol至約5.00E+09 g/mol範圍內的平均分子量。

【0390】 在一些實施例中，多分散性(Mw/Mn；重量平均莫耳質量(Mw)與數目平均莫耳質量(Mn)之比)可在約1.000至約2.000範圍內。在一些實施例中，Mw/Mn可在約1.00至約1.500範圍內。在一些實施例中，

Mw/Mn可在約1.020至約1.400範圍內。在一些實施例中，Mw/Mn可在約1.010至約1.100範圍內。在一些實施例中，Mw/Mn可在約1.100至約1.350範圍內。

【0391】 可使用動態光散射(「DLS」)來表徵本發明之LNP的多分散性指數(「pdi」)及大小。DLS量測由將樣本置於光源下而產生的光之散射。如根據DLS量測所測定，PDI表示群體中粒度之分佈(平均粒度周圍)，其中完全均一群體之PDI為零。在一些實施例中，pdi可在0.005至0.75範圍內。在一些實施例中，pdi可在0.01至0.5範圍內。在一些實施例中，pdi可在0.02至0.4範圍內。在一些實施例中，pdi可在0.03至0.35範圍內。在一些實施例中，pdi可在0.1至0.35範圍內。在一些實施例中，pdi可在約零至約0.4範圍內，諸如約零至約0.35。在一些實施例中，pdi可在約零至約0.35、約零至約0.3、約零至約0.25或約零至約0.2範圍內。在一些實施例中，pdi小於約0.08、0.1、0.15、0.2或0.4。

【0392】 在一些實施例中，本文揭示之LNP之大小為1至250 nm。在一些實施例中，LNP之大小為10至200 nm。在其他實施例中，LNP之大小為20至150nm。在一些實施例中，LNP之大小為50至150 nm。在一些實施例中，LNP之大小為50至100 nm。在一些實施例中，LNP之大小為50至120 nm。在一些實施例中，LNP之大小為75至150 nm。在一些實施例中，LNP之大小為30至200 nm。除非另外指明，否則本文所提及之所有大小為完全成形奈米粒子之平均大小(直徑)，如藉由Malvern Zetasizer上之動態光散射所量測。奈米粒子樣本稀釋於磷酸鹽緩衝鹽水(PBS)中，以使得計數率為大致200至400 kcts。資料呈現為強度量度之加權平均值。在一些實施例中，LNP經形成而具有介於50%至100%範圍內

的平均囊封效率。在一些實施例中，LNP經形成而具有介於50%至70%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於70%至90%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於90%至100%範圍內的平均囊封效率。在一些實施例中，LNP經形成而具有介於75%至95%範圍內的平均囊封效率。

【0393】 電穿孔亦為遞送負荷之熟知手段，且任何電穿孔方法可用於遞送本文揭示之RNA中之任一者。

【0394】 在一些實施例中，方法包含將包含本文揭示之mRNA的組合物遞送至離體細胞之方法，其中mRNA囊封於LNP中。在一些實施例中，組合物包含囊封於LNP中之mRNA及一或多種本文揭示之額外RNA。

【0395】 在一些實施例中，脂質核酸組裝組合物包含脂質組分，其中脂質組分包含胺脂質、中性脂質、輔助脂質及隱形脂質；且其中N/P比為約1至10。

【0396】 在一些情況下，脂質組分包含脂質A或其縮醛類似物、膽固醇、DSPC及PEG-DMG；且其中N/P比為約1至10。在一些實施例中，脂質組分包含：約40至60 mol%胺脂質；約5至15 mol%中性脂質；及約1.5至10 mol% PEG脂質，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至10。在一些實施例中，脂質組分包含：約50至60 mol%胺脂質；約8至10 mol%中性脂質；及約2.5至4 mol% PEG脂質，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至8。在一些情況下，脂質組分包含：約50至60 mol%胺脂質；約5至15 mol% DSPC；及約2.5至4 mol% PEG脂質，其中脂質組分之其餘部分為膽固醇，且其中脂質核酸組裝組合物之N/P比為約3至8。

在一些情況下，脂質組分包含：48至53 mol%脂質A；約8至10 mol% DSPC；及1.5至10 mol% PEG脂質，其中脂質組分之其餘部分為膽固醇，且其中脂質核酸組裝組合物之N/P比為3至8 ±0.2。

【0397】在一些實施例中，脂質組分包含：約50至60 mol%胺脂質，諸如脂質A；約8至10 mol%中性脂質；及約2.5至4 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，脂質組分包含：約50至60 mol%胺脂質，諸如脂質A；約27至39.5 mol%輔助脂質；約8至10 mol%中性脂質；及約2.5至4 mol%隱形脂質(例如，PEG脂質)，其中脂質核酸組裝組合物之N/P比為約5至7 (例如，約6)。在一些實施例中，脂質組分包含：約50至60 mol%胺脂質，諸如脂質A；約5至15 mol%中性脂質；及約2.5至4 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至10。在一些實施例中，脂質組分包含：約40至60 mol%胺脂質，諸如脂質A；約5至15 mol%中性脂質；及約2.5至4 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，脂質組分包含：約50至60 mol%胺脂質，諸如脂質A；約5至15 mol%中性脂質；及約1.5至10 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，脂質組分包含：約40至60 mol%胺脂質，諸如脂質A；約0至10 mol%中性脂質；及約1.5至10 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至10。在一些實施例中，脂質組分包含：約

40至60 mol%胺脂質，諸如脂質A；小於約1 mol%中性脂質；及約1.5至10 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至10。在一些實施例中，脂質組分包含約40至60 mol%胺脂質，諸如脂質A；及約1.5至10 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，其中脂質核酸組裝組合物之N/P比為約3至10，且其中脂質核酸組裝組合物基本上不含或不含中性磷脂。在一些實施例中，脂質組分包含：約50至60 mol%胺脂質，諸如脂質A；約8至10 mol%中性脂質；及約2.5至4 mol%隱形脂質(例如，PEG脂質)，其中脂質組分之其餘部分為輔助脂質，且其中脂質核酸組裝組合物之N/P比為約3至7。

【0398】 在一些實施例中，胺脂質以約50 mol%存在。在一些實施例中，中性脂質以約9 mol%存在。在一些實施例中，隱形脂質以約3 mol%存在。在一些實施例中，輔助脂質以約38 mol%存在。

【0399】 在一些實施例中，脂質組分包含以下、基本上由以下組成或由以下組成：約50 mol%胺脂質，諸如脂質A；約9 mol%中性脂質，諸如DSPC；約3 mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，胺脂質為脂質A。在一些實施例中，中性脂質為DSPC。在一些實施例中，隱形脂質為PEG脂質。在一些實施例中，隱形脂質為PEG2k-DMG脂質。在一些實施例中，輔助脂質為膽固醇。在一些實施例中，脂質包含脂質組分且脂質組分包含：約50 mol%脂質A；約9 mol% DSPC；約3 mol% PEG2k-DMG，且脂質組分之其餘部分為膽固醇，其中脂質核酸組裝組合物之N/P比為約6。

【0400】在一些實施例中，脂質組分包含以下、基本上由以下組成或由以下組成：約25至45 mol%胺脂質，諸如脂質A；約10至30 mol%中性脂質，諸如DSPC；約1.5至3.5 mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG；及約25至65 mol%輔助脂質，諸如膽固醇，其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，脂質組分包含以下、基本上由以下組成或由以下組成：約35 mol%胺脂質，諸如脂質A；約15 mol%中性脂質，諸如DSPC；約2.5 mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中脂質核酸組裝組合物之N/P比為約6。在一些實施例中，胺脂質為脂質A。在一些實施例中，中性脂質為DSPC。在一些實施例中，隱形脂質為PEG脂質。在一些實施例中，隱形脂質為PEG2k-DMG脂質。在一些實施例中，輔助脂質為膽固醇。在一些實施例中，脂質包含脂質組分且脂質組分包含：約35 mol%脂質A；約15 mol% DSPC；約2.5 mol% PEG2k-DMG，且脂質組分之其餘部分為膽固醇，其中脂質核酸組裝組合物之N/P比為約6。

I. 例示性用途、方法及治療

【0401】在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物用於基因體編輯，例如編輯目標基因，或修飾目標基因。在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物用於修飾目標基因，例如改變其序列或表觀遺傳狀態。在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物用於製造用於基因體編輯或修飾目標基因之藥劑。

【0402】在一些實施例中，提供本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物之用途，其用於製備用於基因體編輯，例如編輯目標基因之藥劑。在一些實施例中，提供核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物之用途，其用於製備用於修飾目標基因，例如改變其序列或表觀遺傳狀態之藥劑。在一些實施例中，提供本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物之用途，其用於製備用於引起目標基因內之C形成T轉化之藥劑。

【0403】在一些實施例中，提供一種基因體編輯或修飾目標基因之方法，該方法包含向細胞遞送本文所描述之mRNA、組合物或脂質奈米粒子。

【0404】在一些實施例中，該方法產生目標基因內之胞嘧啶(C)至胸腺嘧啶(T)轉化。

【0405】在一些實施例中，相對於目標序列中之總編輯，該方法引起至少50%的C形成T轉化。如本文所使用，「目標序列中之總編輯」為各讀數與插入/缺失或至少一個轉化之總和，其中插入/缺失可包含多於一個核苷酸。插入/缺失經計算為在20 bp評分區內插入或缺失一或多個鹼基之定序讀數之總數目除以定序讀數(包括野生型)之總數目。在包括20 bp sgRNA目標序列之上游10 bp及下游10 bp之40 bp區中對C形成T轉化或C形成A/G轉化進行評分。可使用允許讀取自野生型比對發散之序列的任何定序方法(例如，NGS)。在一些實施例中，相對於目標序列中之總編輯，該方法引起至少50%、至少55%、至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的C形成T轉化。

【0406】 在一些實施例中，C形成T轉化與非預期編輯之比大於1:1。如本文中所使用，「非預期編輯」為目標區中之不為C形成T轉化之任何編輯。在一些實施例中，C形成T轉化與非預期編輯之比大於2:1、大於3:1、大於4:1、大於5:1、大於6:1、大於7:1或大於8:1。在一些實施例中，C形成T轉化與非預期編輯之比為2:1至99:1。在一些實施例中，C形成T轉化與非預期編輯之比為2:1、3:1、4:1、5:1、6:1、7:1或8:1。

【0407】 在一些實施例中，該方法使A3A進行對應於相對於導引序列之5'端的位置-1至位置10中之任何一者的鹼基編輯。

【0408】 在一些實施例中，該方法使A3A在距導引序列之5'端的1、2、3、4、5、6、7、8、9或10個核苷酸的位置處進行鹼基編輯。

【0409】 在一些實施例中，切口酶為SpyCas9切口酶，且該方法使胞苷去胺酶在距導引序列之5'端的1、2、3、4、5、6、7、8、9、10或11個核苷酸的位置處存在的胞苷處進行鹼基編輯。

【0410】 在一些實施例中，切口酶為NmeCas9切口酶，且該方法使胞苷去胺酶在距導引序列之5'端的4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19或20個核苷酸的位置處存在的胞苷處進行鹼基編輯。

【0411】 在一些實施例中，組合物包含：第一mRNA，其包含編碼包含A3A及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及gRNA；且第一mRNA、第二mRNA及gRNA (若存在)以約6:2:3(w:w:w)之比遞送。在一些實施例中，目標基因處於個體，諸如哺乳動物，諸如人類中。

【0412】 在一些實施例中，提供用於修飾目標基因之方法，其包含

向細胞遞送：第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之第一多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA；及至少一種導引RNA (gRNA)。

【0413】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA。在一些實施例中，一或多種導引RNA各自在單獨的脂質核酸組裝組合物中。

【0414】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，及/或靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA，及/或靶向降低或消除內源性TCR表現之基因的一種gRNA。

【0415】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，

APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自以下之至少兩種gRNA：靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

【0416】 在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

【0417】 在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向降低或消除細胞表面上之HLA-A表現之基因的一種gRNA，及/或靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA，及/或靶向降低或消除內源性TCR表現之基因的

一種gRNA。

【0418】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自以下之至少兩種gRNA：靶向降低或消除細胞表面上之HLA-A表現之基因的一種gRNA，靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

【0419】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向降低或消除細胞表面上之HLA-A表現之基因的一種gRNA，靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因之一種gRNA。

【0420】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)

第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自靶向TRAC、TRBC、B2M、HLA-A或CIITA之gRNA的一種gRNA。在一些實施例中，一種gRNA靶向TRAC。在一些實施例中，一種gRNA靶向TRBC。在一些實施例中，一種gRNA靶向B2M。在一些實施例中，一種gRNA靶向HLA-A。在一些實施例中，一種gRNA靶向CIITA。

【0421】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自靶向TRAC、TRBC或B2M之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0422】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自靶向TRAC、TRBC或HLA-A之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0423】在一些實施例中，提供用於修飾細胞中之目標基因的方

法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含選自靶向TRAC、TRBC、HLA-A之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0424】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0425】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向B2M之一種導引RNA及靶向CIITA之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0426】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向HLA-A之一種導引RNA及靶向CIITA之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。在一些實施例中，細胞對HLA-B為同型組合的且對HLA-C為同型組合的。

【0427】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向B2M之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0428】在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向TRAC之一種導引RNA及靶向

TRBC之一種gRNA及靶向HLA-A之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。在一些實施例中，細胞對HLA-B為同型組合的且對HLA-C為同型組合的。

【0429】 在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA，靶向B2M之一種gRNA及靶向CIITA之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。

【0430】 在一些實施例中，提供用於修飾細胞中之目標基因的方法，其包含向細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：(a)第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶的多肽之第一開讀框；(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及(c)一或多種導引RNA，其中該方法包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向HLA-A之一種gRNA及靶向CIITA之一種gRNA。在一些實施例中，gRNA各自在單獨的脂質核酸組裝組合物中。在一些實施例中，細胞對HLA-B為同型組合的且對HLA-C為同型組合的。

【0431】 在一些實施例中，提供一種包含組合物之細胞，該組合物包含：第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺

酶(A3A))及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA。

【0432】 在一些實施例中，提供一種包含至少一種鹼基編輯及/或插入/缺失之經工程改造之細胞，其中該鹼基編輯及/或插入/缺失藉由使細胞與組合物接觸而進行，該組合物包含：第一mRNA，其包含編碼包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA。

【0433】 在一些實施例中，細胞為人類細胞。在一些實施例中，經基因修飾之細胞稱為經工程改造之細胞。經工程改造之細胞係指包含經工程改造之基因修飾之細胞(或細胞後代)，例如已與基因編輯系統接觸且經基因編輯系統基因修飾。術語「經工程改造之細胞」及「經基因修飾之細胞」通篇可互換使用。經工程改造之細胞可為本文揭示之例示性細胞類型中之任一者。在一些實施例中，細胞為同種異體細胞。

【0434】 在一些實施例中，細胞為免疫細胞。如本文所使用，「免疫細胞」係指免疫系統之細胞，包括例如淋巴細胞(例如，T細胞、B細胞、自然殺手細胞(「NK細胞」及NKT細胞或iNKT細胞))、單核球、巨噬細胞、肥大細胞、樹突狀細胞或顆粒球(例如，嗜中性球、嗜酸性球及嗜鹼性球)。在一些實施例中，細胞為原代免疫細胞。在一些實施例中，免疫系統細胞可選自CD3+、CD4+及CD8+ T細胞、調節T細胞(Treg)、B細胞、NK細胞及樹突狀細胞(DC)。在一些實施例中，免疫細胞為同種異體的。在一些實施例中，該細胞為淋巴細胞。在一些實施例中，該細胞為

適應性免疫細胞。在一些實施例中，該細胞為T細胞。在一些實施例中，該細胞為B細胞。在一些實施例中，該細胞為NK細胞。在一些實施例中，淋巴細胞為同種異體的。

【0435】 在一些實施例中，目標基因之基因體編輯或修飾係在活體內進行。在一些實施例中，目標基因之基因體編輯或修飾係在經分離或經培養之細胞中進行。

【0436】 在一些實施例中，目標基因處於器官，諸如肝臟，諸如哺乳動物肝臟，諸如人類肝臟中。在一些實施例中，目標基因處於肝臟細胞，諸如哺乳動物肝臟細胞，諸如人類肝臟細胞中。在一些實施例中，目標基因處於肝細胞，諸如哺乳動物肝細胞，諸如人類肝細胞中。在一些實施例中，肝臟細胞或肝細胞處於原位。在一些實施例中，肝臟細胞或肝細胞分離於例如培養物中，諸如原代培養物中。

【0437】 在一些實施例中，目標基因之基因體編輯或修飾使剪接供體或剪接受體位點失活。

【0438】 亦提供對應於本文揭示之用途的方法，其包含向個體投與本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物，或使細胞(諸如上文所描述之細胞)與本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物接觸。

【0439】 在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物經靜脈內投與，以用於上文關於原位生物體、器官或細胞論述之用途中的任一者。

【0440】 在涉及個體之前述實施例中之任一者中，個體可為哺乳動物。在涉及個體之前述實施例中之任一者中，個體可為人類。在涉及個體

之前述實施例中之任一者中，個體可為牛、豬、猴、綿羊、狗、貓、魚或家禽。

【0441】在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物經靜脈內投與或用於靜脈內投與。

【0442】在一些實施例中，目標基因之基因體編輯或修飾阻斷目標基因之表現。在一些實施例中，目標基因之基因體編輯或修飾將目標基因之表現阻斷至少50%、55%、60%、65%、70%、75%或80%。在一些實施例中，目標基因之基因體編輯或修飾在基因中產生錯義突變。

【0443】在一些實施例中，單次投與本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物足以阻斷目標基因產物之表現。在一些實施例中，單次投與本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物足以阻斷目標基因產物的表現。在其他實施例中，超過一次投與本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物可有益於經由累積效應使編輯最大化。

【0444】在一些實施例中，本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物的治療功效可見於遞送之後1年、2年、3年、4年、5年或10年。

【0445】在一些實施例中，治療會減緩或中斷疾病進展。

【0446】在一些實施例中，治療會引起器官功能或器官之疾病的症狀得到改善、穩定或減緩其變化。

【0447】在一些實施例中，治療功效藉由個體之存活時間增加來量測。

1. 用於TRAC及TRBC編輯之例示性導引RNA、組合物、方法及經工程

改造之細胞

【0448】 本發明提供靶向TRAC之導引RNA。靶向TRAC基因之導引序列以SEQ ID NO:706至721展示於表5A中。

【0449】 本發明提供靶向TRBC之導引RNA。靶向TRBC基因之導引序列以SEQ ID NO: 618至669展示於表5B中。

【0450】 在一些實施例中，導引RNA序列與根據來自人類參考基因體hg38座標之下表中所示之對應基因體區互補。其他實施例之導引序列可與表5A及表5B中之任何一者所列出之基因體座標附近的序列互補。舉例而言，其他實施例之導引序列可與包含表5A及表5B中之任一者中所列出之基因體座標之15個連續核苷酸±10個核苷酸的序列互補。

【0451】 如前述部分中所描述，表5A及表5B中所示之導引序列中之每一者可進一步包含額外核苷酸以形成crRNA，例如在其3'端處之導引序列之後具有以下例示性核苷酸序列：5'至3'位向之GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO:139)。在sgRNA之情況下，導引序列可進一步包含額外核苷酸以形成sgRNA，例如在導引序列之3'端後具有以下例示性核苷酸序列：5'至3'位向之GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 140) 或 GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 146)。

【0452】 在一些實施例中，sgRNA包含以下在SEQ ID NO:141中所

示之修飾模式，其中N為天然或非天然核苷酸，且其中N'之總體包含如本文所描述之導引序列，且經修飾sgRNA包含以下序列：mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU (SEQ ID NO: 141)，其中「N」可為任何天然或非天然核苷酸。舉例而言，SEQ ID NO: 141涵蓋在本文中，其中N'經本文所揭示之導引序列中之任一者置換。儘管導引之核苷酸用N'取代，但該等修飾保持如SEQ ID NO: 141中所示。亦即，儘管導引之核苷酸置換「N'」，但前三個核苷酸仍為經2'OMe修飾的，且在第一核苷酸與第二核苷酸、第二核苷酸與第三核苷酸及第三核苷酸與第四核苷酸之間存在硫代磷酸酯鍵。

【0453】 在一些實施例中，靶向TRAC之gRNA包含選自以下之導引序列：i) SEQ ID NO: 706至721；ii)選自SEQ ID NO: 706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 706至721之序列至少95%、90%或85%一致之導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致之導引序列。

【0454】 表5A TRAC導引序列、導引RNA序列及染色體座標

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G016019	706	AACAAAUGUGUCACAAGUA	AACAAAUGUGUCACAAAGUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mA*mC*AAAUGUGUCACAAAGUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmU*mU*mU*mU	chr14:22547596-22547616
G016016	707	UUUCAAACCUGUCAGUGAU	UUUCAAAACCUGUCAGUGAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mU*mU*CAAAACCUGUCAGUGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmU*mU*mU*mU	chr14:22550570-22550590
G016026	708	CUUACCUGGGCUGGGGAAGA	CUUACCUGGGCUGGGGAAGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mU*ACCUGGGCUGGGGAAGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmU*mU*mU*mU	chr14:22547763-22547783

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G016013	709	CCGAAUCCUCCUCCUGAAAG	CCGAAUCCUCCUCCUGAAAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mG*AAUCCUCCUCCUGAAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22550596-22550616
G016022	710	CUGACAGGUUUUGAAAGUUU	CUGACAGGUUUUGAAAGUUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mG*ACAGGUUUUGAAAGUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22550566-22550586
G016023	711	CUGGGGAAGAAGGUGUCUUC	CUGGGGAAGAAGGUGUCUUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mG*GGGAAGAAGGUGUCUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22547753-22547773

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G016010	712	UCCUCCUCCUGAAGUGGCC	UCCUCCUCCUGAAAGUGGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mC*UCCUCCUGAAAGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22550601-22550621
G016014	713	CCACUUUCAGGAGGAGGAU	CCACUUUCAGGAGGAGGAUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mA*CUUUCAGGAGGAGGAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22550599-22550619
G016020	714	AUUUGUUUGAGAAUCAAAAU	AUUUGUUUGAGAAUCAAAAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mU*mU*UGUUUGAGAAUCAAAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmGmUmGmCmU*mU*mU*mU	chr14:22547583-22547603

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G015998	715	CUUCAAGAGCAACAGUGCUG	CUUCAAGAGCAACAGUGCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mU*CAAGAGCAACAGUGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmCmU*mU*mU*mU	chr14:22547671-22547691
G016025	716	AGCUGCCCUUACCUGGGCUG	AGCUGCCCUUACCUGGGCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mC*UGCCCUUACCUGGGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmCmU*mU*mU*mU	chr14:22547770-22547790
G015997	717	AGAGCAACAGUGCUGUGGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mA*GCAACAGUGCUGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmCmU*mU*mU*mU	chr14:22547676-22547696

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G016029	718	AAAGCUGCCCUUACCUGGGC	AAAGCUGCCCUUACCUGGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mA*mA*GCUGCCCUUACCUGGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr14:22547772-22547792
G016028	719	AAGCUGCCCUUACCUGGGCU	AAGCUGCCCUUACCUGGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mA*mG*CUGCCCUUACCUGGGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr14:22547771-22547791
G016021	720	UGGAAUAAUGCUGUUGUUGA	UGGAAUAAUGCUGUUGUUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mG*AAUAAUGCUGUUGUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr14:22547733-22547753

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 747至762)	例示性Mod序列(SEQ ID NO: 853至868)	基因體座標(hg38)
G016015	721	CACCAAAGCUGCCCUUACCU	CACCAAAGCUGCCCUUACCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mC*CAAAGCUGCCCUUACCUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr14:22547776-22547796

【0455】 在一些實施例中，導引序列包含SEQ ID NO: 706。在一些實施例中，導引序列包含SEQ ID NO: 707。在一些實施例中，導引序列包含SEQ ID NO: 708。在一些實施例中，導引序列包含SEQ ID NO: 709。在一些實施例中，導引序列包含SEQ ID NO: 710。在一些實施例中，導引序列包含SEQ ID NO: 711。在一些實施例中，導引序列包含SEQ ID NO: 712。在一些實施例中，導引序列包含SEQ ID NO: 713。在一些實施例中，導引序列包含SEQ ID NO: 714。在一些實施例中，導引序列包含SEQ ID NO: 715。在一些實施例中，導引序列包含SEQ ID NO: 716。在一些實施例中，導引序列包含SEQ ID NO: 717。在一些實施例中，導引序列包含SEQ ID NO: 718。在一些實施例中，導引序列包含SEQ ID NO: 719。在一些實施例中，導引序列包含SEQ ID NO: 720。在一些實施例中，導引序列包含SEQ ID NO: 721。

【0456】 在一些實施例中，靶向TRBC之gRNA包含選自以下之導引序列：i) SEQ ID NO: 618至669；ii)選自SEQ ID NO: 618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 618至669之序列至少95%、90%或85%一致之導引序列；iv)包含表5B中所列出之基

因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致之導引序列。

【0457】 表5B TRBC導引序列、導引RNA序列及染色體座標

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016200	618	CCACACCCAAAAGGCCAC	CCACACCCAAAAGGCCACACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mA*CACCCAAAAGGCCACACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791757-142791777 chr7:142801104-142801124
G016174	619	CCCACCAGCUCAGCUCCACG	CCCACCAGCUCAGCUCCACGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mC*ACCAGCUCAGCUCCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791811-142791831; chr7:142801158-142801178
G016263	620	UCCCUAGCAGGAUCUCAUAG	UCCCUAGCAGGAUCUCAUAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mC*CUAGCAGGAUCUCAUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792728-142792748

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016270	621	GGCUCAACACAGCGACCUC	GGCUCAAACACAGCGACCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*UCAAACACAGCGACCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791719-142791739
G016212	622	GGCACACCAGUGUGGCCUUUU	GGCACACCAGUGUGGCCUUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*ACACCAGUGUGGCCUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791766-142791786; chr7: 142801113-142801133
G016207	623	AGGUGGCCGAGACCCUCAGG	AGGUGGCCGAGACCCUCAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mG*UGGCCGAGACCCUCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791928-142791948; chr7: 142801275-142801295

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016205	624	ACCUGCUCUACCCAGGCCU	ACCUGCUCUACCCCAGGCCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mC*UGCUCUACCCCAGGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792062-142792082;chr7:142801409-142801429
G016245	625	CAUAGAGGAUGGUGGCAG	CAUAGAGGAUGGUGGCAGACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mU*AGAGGAUGGUGGCAGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792713-142792733;chr7:142802126-142802146
G016232	626	CCACGUGGAGCUGAGCUGGUGU	CCACGUGGAGCUGAGCUGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mA*CGUGGAGCUGAGCUGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791808-142791828;chr7:142801155-142801175

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016227	627	GGAGAAUGACGAGUGGACCC	GGAGAAUGACGAGUGGACCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mA*GAAUGACGAGUGGACCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792003-142792023;chr7:142801350-142801370
G016273	628	CCAGUGUGGCCUUU UGGGUG	CCAGUGUGGCCUUUUGGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mA*GUGUGGCCUUUUGGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791760-142791780
G016251	629	CAAACACAGCGACCUCGGGU	CAAACACAGCGACCUCGGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mA*ACACAGCGACCUCGGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791715-142791735

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016276	630	UACCAUGGCCAUCAACACAA	UACCAUGGCCAUCAACACAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mA*mC*CAUGGCCAUCAACACAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142792781-142792801
G016167	631	GCGCUGACGAUCUGGGUGACC	GCGCUGACGAUCUGGGUGACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mG*CUGACGAUCUGGGUGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142792040-142792060; chr7: 142801387-142801407
G016253	632	CACGGACCCGCAGCCCCU	CACGGACCCGCAGCCCCUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mC*GGACCCGCAGCCCCUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791862-142791882

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016272	633	UCAAACACAGCGACCUCGG	UCAAACACAGCGACCUCGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mA*AACACAGCGACCUCGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791716-142791736
G016258	634	CAGGGAAGAAGCCUGUGG	CAGGGAAGAAGCCUGUGGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mG*GGAAGAAGCCUGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791787-142791807
G016183	635	CAGUGUGGCCUUUUGGGUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CAGUGUGGCCUUUUGGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7: 142791759-142791779; chr7: 142801106-142801126

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016222	636	ACCACGUGGAGCUGAGCUGG	ACCACGUGGAGCUGAGCUGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mC*ACGUGGAGCUGAGCUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791807-142791827;chr7:142801154-142801174
G016233	637	GAGGGCGGGCUGCUCCUUGA	GAGGGCGGGCUGCUCCUUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mG*GGCGGGCUGCUCCUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791879-142791899;chr7:142801226-142801246
G016264	638	AGCUCAGCUCCACGUGGUCA	AGCUCAGCUCCACGUGGUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mC*UCAGCUCCACGUGGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791805-142791825

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016255	639	GAACAAGGUGUUCCCACCCGG	GAACAAGGUGUUCCCACCCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mA*CAAGGUGUUCCCACCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791700-142791720
G016177	640	GCACACCAGUGUGGCCUUUUGUUUUAG	GCACACCAGUGUGGCCUUUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mA*CACCAGUGUGGCCUUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791765-142791785; chr7: 142801112-142801132
G016283	641	GAGCUGGUGGGUGAAUGGGAG	GAGCUGGUGGGUGAAUGGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mG*CUGGUGGGUGAAUGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791820-142791840

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016194	642	GGCUGCUCCUGAGGGGCU G	GGCUGCUCCUUGAGGGGCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*UGCUCCUUGAGGGGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791872-142791892; chr7: 142801219-142801239
G016266	643	CGGGUGGGAACACCUUGUUC	CGGGUGGGAACACCUUGUUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mG*GUGGGAACACCUUGUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791700-142791720
G016196	644	CAGCUCAGCUCCACGUGGUC	CAGCUCAGCUCCACGUGGUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mG*CUCAGCUCCACGUGGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791806-142791826; chr7: 142801153-142801173

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016274	645	GACGAUCUGGGUGACGGGUU	GACGAUCUGGGUGACGGGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mC*GAUCUGGGUGACGGGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792035-142792055
G016282	646	UAGCAGGAUCUCAUAGAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	UAGCAGGAUCUCAUAGAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mA*mG*CAGGAUCUCAUAGAGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792724-142792744
G016267	647	GACCAGCACAGCAUACAGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	GACCAGCACAGCAUACAGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mC*CAGCACAGCAUACAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792754-142792774

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016261	648	CUGACCACGUGGAGCUGAGC	CUGACCACGUGGAGCUGAGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mG*ACCACGUGGAGCUGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791804-142791824
G016277	649	CCAACAGUGUCCUACCAGCA	CCAACAGUGUCCUACCAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mA*ACAGUGUCCUACCAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792684-142792704
G016285	650	CUGGUGGGUGAAUGGGAAGG	CUGGUGGGUGAAUGGGAAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mG*GUGGGUGAAUGGGAAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791823-142791843

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016275	651	CUAUGAGAUCCUGCUAGGGA	CUAUGAGAUCCUGCUAGGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mA*UGAGAUCCUGCUAGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792728-142792748
G016281	652	CAGGAUCUCAUAGAGGAUGGGA	CAGGAUCUCAUAGAGGAUGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mG*GAUCUCAUAGAGGAUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792721-142792741
G016280	653	GGCCACCCUGUAUGCUGU	GGCCACCCUGUAUGCUGUGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*CACCCUGUAUGCUGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792749-142792769

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016279	654	CAACAGUGUCCUACCAGCAA	CAACAGUGUCCUACCAGCAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mA*CAGUGUCCUACCAGCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7:142792685-142792705
G016250	655	AGCUGAGCUGGUGGGUGAAU	AGCUGAGCUGGUGGGUGAAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mC*UGAGCUGGUGGGUGAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7:142791816-142791836;chr7:142801163-142801183
G016278	656	AACAGUGUCCUACCAGCAAG	AACAGUGUCCUACCAGCAAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mA*mC*AGUGUCCUACCAGCAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU	chr7:142792686-142792706

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016259	657	AGGCUUCUUCCCUGACCACG	AGGCUUCUUCCCUGACCACGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mG*CUUCUUCCCUGACCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791793-142791813
G016284	658	UCUUCUGCAGGUCAAGAGAA	UCUUCUGCAGGUCAAGAGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mU*UCUGCAGGUCAAGAGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142793110-142793130
G016249	659	GAGCUGAGCUGGUGGGUGAA	GAGCUGAGCUGGUGGGUGAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mG*CUGAGCUGGUGGGUGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791815-142791835; chr7:142801162-142801182

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016256	660	GGUCAGCGCCCUUG UGU UGA	GGUCAGCGCCCUUGUGUUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mU*CAGCGCCCUUGUGUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142792770-142792790
G016190	661	AGAUCGUCAGCGCCGAGGCCGA GGCC	AGAUCGUCAGCGCCGAGGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mA*UCGUCAGCGCCGAGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142792047-142792067; chr7: 142801394-142801414
G016248	662	GCUGCUCCUUGAG GGG CUGC	GCUGCUCCUUGAGGGGCUGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mU*GCUCCUUGAGGGGCUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7: 142791871-142791891; chr7: 142801218-142801238

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016257	663	GUAUCUGGAGUCAUUGAGGGG	GUAUCUGGAGUCAUUGAGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mU*mA*UCUGGAGUCAUUGAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791894-142791914
G016260	664	AUCCUCUAUGAGAUCCUGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AUCCUCUAUGAGAUCCUGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	mA*mU*mC*CUCUAUGAGAUCCUGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792723-142792743
G016262	665	UCCUCUAUGAGAUCCUGCUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	UCCUCUAUGAGAUCCUGCUAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	mU*mC*mC*UCUAUGAGAUCCUGCUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792724-142792744

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016242	666	GCAGUAUCUGGAGUCAUUGA	GCAGUAUCUGGAGUCAUUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mA*GUAUCUGGAGUCAUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142791897-142791917;chr7:142801244-142801264
G016268	667	GCUGACCAGCACAGCAUACA	GCUGACCAGCACAGCAUACAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mU*GACCAGCACAGCAUACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792757-142792777
G016265	668	ACAGGGUGGCCUUCCCUAGC	ACAGGGUGGCCUUCCCUAGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mA*GGGUGGCCUUCCCUAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792740-142792760

導引ID	導引序列之SEQ ID NO	導引序列	例示性全序列(SEQ ID NO: 1024至1075)	例示性Mod序列(SEQ ID NO: 801至852)	基因體座標(hg38)
G016254	669	CGCUGACCAGCACAGCAUAC	CGCUGACCAGCACAGCAUACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mC*UGACCAGCACAGCAUACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr7:142792758-142792778

【0458】在一些實施例中，導引序列包含SEQ ID NO: 618。在一些實施例中，導引序列包含SEQ ID NO: 619。在一些實施例中，導引序列包含SEQ ID NO: 620。在一些實施例中，導引序列包含SEQ ID NO: 621。在一些實施例中，導引序列包含SEQ ID NO: 622。在一些實施例中，導引序列包含SEQ ID NO: 623。在一些實施例中，導引序列包含SEQ ID NO: 624。在一些實施例中，導引序列包含SEQ ID NO: 625。在一些實施例中，導引序列包含SEQ ID NO: 626。在一些實施例中，導引序列包含SEQ ID NO: 627。在一些實施例中，導引序列包含SEQ ID NO: 628。在一些實施例中，導引序列包含SEQ ID NO: 629。在一些實施例中，導引序列包含SEQ ID NO: 630。在一些實施例中，導引序列包含SEQ ID NO: 631。在一些實施例中，導引序列包含SEQ ID NO: 632。在一些實施例中，導引序列包含SEQ ID NO: 633。在一些實施例中，導引序列包含SEQ ID NO: 634。在一些實施例中，導引序列包含SEQ ID NO: 635。在一些實施例中，導引序列包含SEQ ID NO: 636。在一些實施例中，導引序列包含SEQ ID NO: 637。在一些實施例中，導引序列包含SEQ ID NO: 638。在一些實施例中，導引序列包含SEQ ID NO: 639。在

一些實施例中，導引序列包含SEQ ID NO: 640。在一些實施例中，導引序列包含SEQ ID NO: 641。在一些實施例中，導引序列包含SEQ ID NO: 642。在一些實施例中，導引序列包含SEQ ID NO: 643。在一些實施例中，導引序列包含SEQ ID NO: 644。在一些實施例中，導引序列包含SEQ ID NO: 645。在一些實施例中，導引序列包含SEQ ID NO: 646。在一些實施例中，導引序列包含SEQ ID NO: 647。在一些實施例中，導引序列包含SEQ ID NO: 648。在一些實施例中，導引序列包含SEQ ID NO: 649。在一些實施例中，導引序列包含SEQ ID NO: 650。在一些實施例中，導引序列包含SEQ ID NO: 651。在一些實施例中，導引序列包含SEQ ID NO: 652。在一些實施例中，導引序列包含SEQ ID NO: 653。在一些實施例中，導引序列包含SEQ ID NO: 654。在一些實施例中，導引序列包含SEQ ID NO:655。在一些實施例中，導引序列包含SEQ ID NO: 656。在一些實施例中，導引序列包含SEQ ID NO: 657。在一些實施例中，導引序列包含SEQ ID NO: 658。在一些實施例中，導引序列包含SEQ ID NO: 659。在一些實施例中，導引序列包含SEQ ID NO: 660。在一些實施例中，導引序列包含SEQ ID NO: 661。在一些實施例中，導引序列包含SEQ ID NO: 662。在一些實施例中，導引序列包含SEQ ID NO: 663。在一些實施例中，導引序列包含SEQ ID NO: 664。在一些實施例中，導引序列包含SEQ ID NO: 665。在一些實施例中，導引序列包含SEQ ID NO: 666。在一些實施例中，導引序列包含SEQ ID NO: 667。在一些實施例中，導引序列包含SEQ ID NO: 668。在一些實施例中，導引序列包含SEQ ID NO: 669。

【0459】在一些實施例中，本發明提供一種改變TRAC基因內之

DNA序列的方法，其包含向細胞遞送本文揭示之組合物。組合物可包含：

a.包含選自以下之導引序列的gRNA：i)SEQ ID NO: 706至721；ii)選自SEQ ID NO: 706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b.編碼(a.)之gRNA的核酸。

【0460】 在一些實施例中，本發明提供一種降低TRAC基因之表現的方法，其包含向細胞遞送本文揭示之組合物。組合物可包含：

a.包含選自以下之導引序列的gRNA：i)SEQ ID NO: 706至721；ii)選自SEQ ID NO: 706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b.編碼(a.)之gRNA的核酸。

【0461】 在一些實施例中，本發明提供一種免疫療法之方法，其包含向個體、其自體細胞及/或同種異體細胞投與本文揭示之組合物。組合物可包含：

a.包含選自以下之導引序列的gRNA：i)SEQ ID NO: 706至721；ii)選自SEQ ID NO: 706至721之序列之至少17、18、19或20個連續核苷酸；

iii)與選自SEQ ID NO: 706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

【0462】 在一些實施例中，提供一種藉由本文揭示之方法改變的細胞。細胞可離體改變。細胞可為T細胞、$CD4^+$或$CD8^+$細胞。細胞可為哺乳動物、靈長類動物或人類細胞。細胞可用於個體之免疫療法。

【0463】 在一些實施例中，提供一種組合物，其包含：包含選自以下之導引序列的gRNA：i) SEQ ID NO: 706至721；ii)選自SEQ ID NO: 706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。組合物可視情況進一步包含本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物中之任一者。

【0464】 在某些實施例中，本文揭示之組合物係用於改變細胞中TRAC基因內之DNA序列。在某些實施例中，本文揭示之組合物係用於降低細胞中TRAC基因之表現。在一些實施例中，本文揭示之組合物係用於個體之免疫療法。

【0465】 在一些實施例中，本發明提供一種改變TRBC1及/或TRBC2基因內之DNA序列的方法，其包含向細胞遞送本文揭示之組合

物。組合物可包含：

a. 包含選自以下之導引序列的gRNA：i) SEQ ID NO: 618至669；ii)選自SEQ ID NO: 618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

【0466】 在一些實施例中，本發明提供一種降低TRBC1及/或TRBC2基因之表現的方法，其包含向細胞遞送本文揭示之組合物。組合物可包含：

a. 包含選自以下之導引序列的gRNA：i) SEQ ID NO: 618至669；ii)選自SEQ ID NO: 618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5C中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

【0467】 在一些實施例中，本發明提供一種免疫療法之方法，其包含向個體、其自體細胞及/或同種異體細胞投與本文揭示之組合物。組合物可包含：

a. 包含選自以下之導引序列的gRNA：i) SEQ ID NO: 618至669；ii)選自SEQ ID NO: 618至669之序列之至少17、18、19或20個連續核苷酸；

iii)與選自SEQ ID NO: 618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

【0468】 在一些實施例中，可提供一種藉由本文揭示之方法改變的細胞。細胞可離體改變。細胞為T細胞、$CD4^+$或$CD8^+$細胞。細胞可為哺乳動物、靈長類動物或人類細胞。細胞可用於個體之免疫療法。

【0469】 在一些實施例中，提供一種組合物，其包含：包含選自以下之導引序列的gRNA：i) SEQ ID NO: 618至669；ii)選自SEQ ID NO: 618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO: 618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。組合物可視情況進一步包含本文揭示之核酸(例如，mRNA)、多肽、組合物或脂質核酸組裝組合物中之任一者。

【0470】 在某些實施例中，本文揭示之組合物係用於改變細胞中TRBC1及/或TRBC2基因內之DNA序列。在某些實施例中，本文揭示之組合物係用於降低細胞中TRBC1及/或TRBC2基因之表現。在一些實施例中，本文揭示之組合物係用於個體之免疫療法。

J. 例示性DNA分子、載體、表現構築體、宿主細胞及產生方法

【0471】 在某些實施例中，本發明提供包含編碼本文所描述之多肽

之序列的DNA分子。在一些實施例中，DNA分子進一步包含不編碼多肽之核酸。不編碼本文揭示之多肽的核酸包括但不限於啟動子、強化子、調節序列及編碼gRNA之核酸。

【0472】在一些實施例中，DNA分子進一步包含編碼crRNA、trRNA或crRNA及trRNA之核苷酸序列。在一些實施例中，編碼crRNA、trRNA或crRNA及trRNA之核苷酸序列包含或由以下組成：藉由來自天然存在之CRISPR/Cas系統的重複序列之全部或一部分側接的引導序列。包含或由crRNA、trRNA或crRNA及trRNA組成之核酸可進一步包含載體序列，其中該載體序列包含或由以下組成：不會與crRNA、trRNA或crRNA及trRNA一起經天然發現的核酸。在一些實施例中，crRNA及trRNA由一個載體中之非連續核酸編碼。在其他實施例中，crRNA及trRNA可由連續核酸編碼。在一些實施例中，crRNA及trRNA由單一核酸之相對鏈編碼。在其他實施例中，crRNA及trRNA由單一核酸之相同鏈編碼。

【0473】在一些實施例中，DNA分子進一步包含可操作地連接於編碼mRNA中之任一者的序列之啟動子，該等mRNA編碼本文所描述之多肽。在一些實施例中，DNA分子為適用於在哺乳動物細胞，例如人類細胞或小鼠細胞，諸如人類肝細胞或嚙齒動物(例如，小鼠)肝細胞中表現之表現構築體。在一些實施例中，DNA分子為適用於在哺乳動物器官，例如人類肝臟或嚙齒動物(例如，小鼠)肝臟之細胞中表現之表現構築體。在一些實施例中，DNA分子為質體或游離基因體。在一些實施例中，DNA分子包含於宿主細胞，諸如細菌或經培養之真核細胞中。例示性細菌包括變形菌門，諸如大腸桿菌。例示性經培養之真核細胞包括初級肝細胞，包括嚙齒動物(例如，小鼠)或人源之肝細胞；肝細胞細胞株，包括嚙齒動物

(例如，小鼠)或人源之肝細胞；人類細胞株；嚙齒動物(例如，小鼠)細胞株；CHO細胞；微生物真菌，諸如裂殖或出芽酵母，例如酵母菌，諸如釀酒酵母；及昆蟲細胞。

【0474】 在一些實施例中，提供一種製造本文所揭示之mRNA的方法。在一些實施例中，此類方法包含使本文所描述之DNA分子與RNA聚合酶在容許轉錄之條件下接觸。在一些實施例中，活體外，例如在無細胞系統中進行接觸。在一些實施例中，RNA聚合酶為噬菌體源之RNA聚合酶，諸如T7 RNA聚合酶。在一些實施例中，提供包括至少一種如上文所論述之經修飾之核苷酸的NTP。在一些實施例中，NTP包括至少一種如上文所論述之經修飾之核苷酸且不包含UTP。

【0475】 在一些實施例中，單獨或與一或多種gRNA一起之本文所揭示之mRNA可包含於一或多個載體之載體系統內或由其遞送。在一些實施例中，載體中之一或多者或所有載體可為DNA載體。在一些實施例中，載體中之一或多者或所有載體可為RNA載體。在一些實施例中，載體中之一或多者或所有載體可為環狀的。在其他實施例中，載體中之一或多者或所有載體可為線性的。在一些實施例中，載體中之一或多者或所有載體可包封於脂質奈米粒子、脂質體、非脂質奈米粒子或病毒衣殼中。非限制性例示性載體包括質體、噬菌粒、黏質體、人工染色體、袖珍染色體、轉位子、病毒載體及表現載體。

【0476】 非限制性例示性病毒載體包括腺相關病毒(AAV)載體、慢病毒載體、腺病毒載體、輔助依賴型腺病毒載體(HDAd)、單純疱疹病毒(HSV-1)載體、噬菌體T4、桿狀病毒載體及反轉錄病毒載體。在一些實施例中，病毒載體可為AAV載體。在其他實施例中，病毒載體可為慢病毒

載體。在一些實施例中，慢病毒可為非整合性的。在一些實施例中，病毒載體可為腺病毒載體。在一些實施例中，腺病毒可為高選殖容量或「無腸(gutless)」腺病毒，其中除5'及3'倒轉末端重複序列(ITR)之外的病毒編碼區及封裝訊號(『I』)自病毒缺失以增加其封裝容量。在又其他實施例中，病毒載體可為HSV-1載體。在一些實施例中，HSV-1類載體為輔助依賴型，且在其他實施例中，其為非輔助依賴型。舉例而言，僅保留封裝序列之擴增子載體需要具有結構性組分之輔助病毒用於封裝，而移除非必需病毒功能之缺失30kb之HSV-1載體不需要輔助病毒。在額外實施例中，病毒載體可為噬菌體T4。在一些實施例中，當清空病毒頭部時，噬菌體T4可能能夠封裝任何線性或環狀DNA或RNA分子。在其他實施例中，病毒載體可為桿狀病毒載體。在又其他實施例中，病毒載體可為反轉錄病毒載體。在使用具有較小選殖容量之AAV或慢病毒載體之實施例中，可能需要使用多於一個載體以遞送如本文揭示之載體系統的全部組分。舉例而言，一個AAV載體可含有編碼Cas蛋白之序列，而第二AAV載體可含有一或多個導引序列。

【0477】 在一些實施例中，載體可能夠驅動細胞中一或多個編碼序列，諸如本文揭示之mRNA之編碼序列的表現。在一些實施例中，細胞可為原核細胞，諸如細菌細胞。在一些實施例中，細胞可為真核細胞，諸如酵母、植物、昆蟲或哺乳動物細胞。在一些實施例中，真核細胞可為哺乳動物細胞。在一些實施例中，真核細胞可為嚙齒動物細胞。在一些實施例中，真核細胞可為人類細胞。驅動不同類型細胞中之表現的適合啟動子為此項技術中已知的。在一些實施例中，啟動子可為野生型。在其他實施例中，啟動子可經修飾以供較高效或較有效表現。在又其他實施例中，啟動

子可經截短但仍保留其功能。舉例而言，啟動子可具有正常大小或適用於將載體適當封裝於病毒中的減小之大小。

【0478】 在一些實施例中，載體系統可包含編碼本文揭示之多肽的核苷酸序列之一個複本。在其它實施例中，載體系統可包含編碼本文揭示之多肽的核苷酸序列之多於一個複本。在一些實施例中，編碼本文揭示之多肽的核苷酸序列可操作地連接於至少一個轉錄或轉譯控制序列。在一些實施例中，編碼蛋白質之核苷酸序列可操作地連接於至少一個啟動子。

【0479】 在一些實施例中，啟動子可為組成性、誘導性或組織特異性的。在一些實施例中，啟動子可為組成性啟動子。非限制性例示性的組成性啟動子包括細胞巨大病毒即刻早期啟動子(CMV)、猴病毒(SV40)啟動子、腺病毒主要晚期啟動子(MLP)、勞斯肉瘤病毒(RSV)啟動子、小鼠乳腺腫瘤病毒(MMTV)啟動子、磷酸甘油酸激酶(PGK)啟動子、延長因子-α (EF1a)啟動子、泛素啟動子、肌動蛋白啟動子、微管蛋白啟動子、免疫球蛋白啟動子、其功能性片段或前述中之任一者之組合。在一些實施例中，啟動子可為CMV啟動子。在一些實施例中，啟動子可為經截短之CMV啟動子。在其他實施例中，啟動子可為EF1a啟動子。在一些實施例中，啟動子可為誘導性啟動子。非限制性例示性的誘導性啟動子包括可藉由熱衝擊、光、化學物質、肽、金屬、類固醇、抗生素或醇誘導之誘導性啟動子。在一些實施例中，誘導性啟動子可為具有低基礎(非經誘導)表現量之誘導性啟動子，諸如Tet-On®啟動子(Clontech)。

【0480】 在一些實施例中，啟動子可為組織特異性啟動子，例如對肝臟中之表現具有特異性的啟動子。

【0481】 載體可進一步包含編碼至少一個gRNA之核苷酸序列。在

一些實施例中，載體包含gRNA之一個複本。在其他實施例中，載體包含gRNA之多於一個複本。在具有多於一個gRNA之實施例中，gRNA可為不相同的以使得其靶向不同目標序列，或可為相同的，此係因為其靶向相同目標序列。在其中載體包含多於一個gRNA之一些實施例中，各gRNA可具有其他不同屬性，諸如在與包含胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))及本文揭示之RNA導引之切口酶的多肽之複合物內的活性或穩定性。在一些實施例中，編碼gRNA之核苷酸序列可操作地連接於至少一個轉錄或轉譯控制序列，諸如啟動子、3' UTR或5' UTR。在一個實施例中，啟動子可為tRNA啟動子，例如tRNALys3或tRNA嵌合體。參見Mefferd等人, RNA. 2015 21:1683-9；Scherer等人, Nucleic Acids Res. 2007 35: 2620-2628。在一些實施例中，啟動子可藉由RNA聚合酶III (Pol III)識別。Pol III啟動子之非限制性實例包括U6及H1啟動子。在一些實施例中，編碼gRNA之核苷酸序列可以可操作地連接於小鼠或人類U6啟動子。在其他實施例中，編碼gRNA之核苷酸序列可以可操作地連接於小鼠或人類H1啟動子。在具有多於一個gRNA之實施例中，用於驅動表現之啟動子可相同或不同。在一些實施例中，編碼gRNA之crRNA的核苷酸及編碼gRNA之trRNA的核苷酸可提供於相同載體上。在一些實施例中，編碼crRNA之核苷酸及編碼trRNA之核苷酸可藉由同一啟動子驅動。在一些實施例中，crRNA及trRNA可轉錄為單一轉錄本。舉例而言，crRNA及trRNA可由單一轉錄本進行處理以形成雙分子gRNA。或者，crRNA及trRNA可轉錄為單分子gRNA。在其他實施例中，crRNA及trRNA可藉由其處於相同載體上之對應啟動子來驅動。在又其他實施例中，crRNA及trRNA可藉由不同載體編碼。

【0482】 在一些實施例中，組合物包含載體系統，其中該系統包含多於一個載體。在一些實施例中，載體系統可包含一個單一載體。在其他實施例中，載體系統可包含兩個載體。在額外實施例中，載體系統可包含三個載體。當將不同gRNA用於多工(multiplexing)時或當使用gRNA之多個複本時，載體系統可包含多於三個載體。

【0483】 在一些實施例中，載體系統可包含誘導性啟動子，以便僅在其遞送至目標細胞之後開始表現。非限制性例示性的誘導性啟動子包括可藉由熱衝擊、光、化學物質、肽、金屬、類固醇、抗生素或醇誘導之誘導性啟動子。在一些實施例中，誘導性啟動子可為具有低基礎(非經誘導)表現量之誘導性啟動子，諸如Tet-On®啟動子(Clontech)。

【0484】 在額外實施例中，載體系統可包含組織特異性啟動子，以便僅在其遞送至特定組織中之後開始表現。

【0485】 在一些實施例中，可全身遞送載體。在一些實施例中，載體可遞送於肝循環中。

表5C.序列表

【0486】 以下序列表提供本文揭示之某些序列的清單。應理解，若相對於RNA提及DNA序列(包含Ts)，則Ts應經Us (取決於上下文，其可經修飾或未經修飾)置換，且反之亦然。在下表及通篇中，術語「mA」、「mC」、「mU」或「mG」用於指示已經2'-O-Me修飾之核苷酸。在下表中，「*」用於描繪PS修飾。在本申請案中，術語A*、C*、U*或G*可用於表示經PS鍵連接至下一(例如3')核苷酸之核苷酸。* = PS鍵；'m' = 2'-O-Me核苷酸。在下表中，使用單胺基酸字母編碼來提供肽序列。

SEQ ID NO	描述	序列

1	編碼BC22n之mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACC UGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGG AGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGU GCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCU ACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGG AGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGA UGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCC UGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAAGAAGUACU CCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGU UCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGA CCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGG AGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGG ACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGA UCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGC UGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCG CCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCA ACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGC UGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGG CCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGC CCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGG AGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGG AGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCA UCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGA UCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCA CCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCA AGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGC UGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCG UGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACA AGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGG AGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGU ACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACA UCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA

		AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCG UGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGG AGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGU ACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACG UGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCU UCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCA AGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGA AGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGG GCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGA AGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGA UCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGA CCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGA AGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGG AGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGA AGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGC AGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGG UGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGG CCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCG ACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGA CCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGACUAGCACCAG CCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGU AGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAA AACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAUAUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAACG UAAAAAAAAAAAACUCAAAAAAAAAAAAAGAUAAAAAAAAAAAACCUAAAAAAAAAAAAUGUAAAAAAAAAAAGGGAA AAAAAAAAAACGCAAAAAAAAAAAAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAUCUAAAAA AAAAAAACGAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAGUUAAAAAAAAA AAACUGAAAAAAAAAAAUUUAAAAAAAAAAAUCUAG

2	用於BC22n之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUC GGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGG GGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUG GUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGG GGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUAC GACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGAC GAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCC GAGUCCGCCACCCCCGAGUCCGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUG AUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAAC CUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUAC ACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUC CACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGAC GAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCC GACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAAC GCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAG CUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCC AACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCC CAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUG CGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGC UACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGAC GGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUC CCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAAC CGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUC GCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCC CAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUG UCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAG GACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGC ACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGAC AUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGAC GACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUC CGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAG CACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUG

		AAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAG AAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCC GUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAG GAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUC GACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAG CGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCAC GUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUC ACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCAC CACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUC GUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCC AAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUG CUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCC AAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACC GUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUG GGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUG AAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCC GCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAG AUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUAC AACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCC CCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACC CUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCC CCCAAGAAGAAGCGGAAGGUGUGA

3	BC22n之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDL VPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYD EFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAV ITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFF HRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNP DNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSI PHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASA QSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFD DKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHP VENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILP KRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEV KKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

4	編碼具有Hibit標籤之BC22n之mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACC UGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGG AGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGU GCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCU ACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGG AGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGA UGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCC UGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAAGAAGUACU CCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGU UCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGA CCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGG AGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGG ACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGA UCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGC UGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCG CCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCA ACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGC UGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGG CCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGC CCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGG AGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGG AGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCA UCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGA UCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCA CCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCA AGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGC UGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCG UGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACA AGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGG AGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGU ACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACA UCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA

		AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCG UGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGG AGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGU ACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACG UGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCU UCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCA AGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGA AGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGG GCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGA AGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGA UCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGA CCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGA AGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGG AGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGA AGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGC AGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGG UGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGG CCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCG ACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGA CCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUCCGAGUCCGCCA CCCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAAGAUCUCCUGACUAGCACCAGCCUCAAGAACACCCGAAUGGA GUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUA AUAAAAAGAAAGUUUCUUCACAUUCUCUCGAGAAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAAAAAAGGUA AAAAAAAAAAAUAUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAAAACGUAAAAAAAAAAAACUCAAAAA AAAAAAAGAUAAAAAAAAAAAAACCUAAAAAAAAAAAAAUGUAAAAAAAAAAAAAGGGAAAAAAAAAAAACGCAAAAAAAA AAAACACAAAAAAAAAAAAAUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAACGAAAAAAAAAAAA CCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAUUU AAAAAAAAAAAUCUAG

5	具有Hibit標籤之BC22n之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUC GGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGG GGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUG GUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGG GGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUAC GACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGAC GAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCC GAGUCCGCCACCCCCGAGUCCGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUG AUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAAC CUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUAC ACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUC CACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGAC GAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCC GACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAAC GCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAG CUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCC AACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCC CAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUG CGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGC UACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGAC GGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUC CCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAAC CGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUC GCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCC CAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUG UCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAG GACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGC ACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGAC AUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGAC GACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUC CGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAG CACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUG

		AAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAG AAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCC GUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAG GAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUC GACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAG CGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCAC GUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUC ACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCAC CACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUC GUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCC AAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUG CUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCC AAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACC GUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUG GGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUG AAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCC GCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAG AUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUAC AACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCC CCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACC CUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCC CCCAAGAAGAAGCGGAAGGUGUCCGAGUCCGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAAGAUCUCC UGA

6	具有Hibit標籤之BC22n之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDL VPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYD EFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAV ITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFF HRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNP DNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSI PHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASA QSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFD DKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHP VENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILP KRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEV KKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSITGLYETRIDLSQLGGDGGGSPKKKRKVSESATPESVSGWRLFKKIS
7	未使用	

8	用於Cas9之開讀框	AUGGACAAGAAGUACAGCAUCGGACUGGACAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAG GUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUG UUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGA AUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGC UUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAA AAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGAC AAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCA AAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAG AACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAA GACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUAC GCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUG GUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGAC GGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUG GUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUG GGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAG AUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGA AUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUC UACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAG GCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUC GAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAG CUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGA AAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUG ACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCA GGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACAC AAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUG CAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGA CUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACA AGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGA CAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAA CUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGAC AGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUG

		GUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUAC CUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAG GUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGC AACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAAC GGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUC AACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAG CUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUG GUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAA AGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUC AAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAG GGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGC CCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGC GAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAG CCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUAC UUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUC ACAGGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAGGAGGAAGCCCGAAGAAGAAGAGAAAG GUCUAG
9	用於Cas9之胺基酸序列	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV*
10	未使用	

11	用於Cas9之開讀框	AUGGACAAGAAGUACUCCAUCGGCCUGGACAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAG GUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUG UUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGG AUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCC UUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAG AAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUG GCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGAC AAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCC AAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAG AACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAG GACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUAC GCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUC ACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUG GUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGAC GGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUG GUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUG GGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAG AUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAG UCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGG AUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUG UACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAG GCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUC GAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACC CUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAG CUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGC AAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUG ACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCC GGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCAC AAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGG AUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUG CAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGG CUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACC CGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGG CAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAG CUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGAC UCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUG

		GUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUAC CUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAG GUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCC AACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAAC GGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUG AACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAG CUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUG GUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAG CGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUC AAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAG GGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCC CCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCC GAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAG CCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUAC UUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUC ACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAG GUGUGA
12	用於Cas9之胺基酸序列	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

13	編碼BE3之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUG UGUCGUUGCAGGCCUUAUUCGGAUCCGCCACCAUGAGCAGCGAAACAGGACCGGUCGCAGUCGACCCGACACUGAGAA GAAGAAUCGAACCGCACGAAUUCGAAGUCUUCUUCGACCCGAGAGAACUGAGAAAGGAAACAUGCCUGCUGUACGAAA UCAACUGGGGAGGAAGACACAGCAUCUGGAGACACACAAGCCAGAACACAAACAAGCACGUCGAAGUCAACUUCAUCG AAAAGUUCACAACAGAAAGAUACUUCUGCCCGAACACAAGAUGCAGCAUCACAUGGUUCCUGAGCUGGAGCCCGUGCG GAGAAUGCAGCAGAGCAAUCACAGAAUUCCUGAGCAGAUACCCGCACGUCACACUGUUCAUCUACAUCGCAAGACUGU ACCACCACGCAGACCCGAGAAACAGACAGGGACUGAGAGACCUGAUCAGCAGCGGAGUCACAAUCCAGAUCAUGACAG AACAGGAAAGCGGAUACUGCUGGAGAAACUUCGUCAACUACAGCCCGAGCAACGAAGCACACUGGCCGAGAUACCCGC ACCUGUGGGUCAGACUGUACGUCCUGGAACUGUACUGCAUCAUCCUGGGACUGCCGCCGUGCCUGAACAUCCUGAGAA GAAAGCAGCCGCAGCUGACAUUCUUCACAAUCGCACUGCAGAGCUGCCACUACCAGAGACUGCCGCCGCACAUCCUGU GGGCAACAGGACUGAAGAGCGGAAGCGAAACACCGGGAACAAGCGAAAGCGCAACACCGGAAAGCGACAAGAAGUACA GCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGU UCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAA CAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGG AAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAG ACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCU ACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGA UCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGC UGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCG CAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAA ACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGC UGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGG CAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGA GCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGC CGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGG AAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAG AAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAA UCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAA UCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCA CACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACA AGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAA AGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGC UGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCG UCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACA AGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAG AAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAU ACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACU

		UCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACA UCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCA AGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCG UCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAG AAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGU ACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACG UCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACA GAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAA AGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAU UCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAA AGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAA AGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCG GAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAA AGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCU UCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAA UCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGA CAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGA AGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCG AAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAA AGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACA GCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCAC UGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAAC AGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAG UCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGG CAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCG ACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAA CAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAG GAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAA GCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAU ACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGA AGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUG AAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCU UUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAU

14	用於BE3之開讀框	AUGAGCAGCGAAACAGGACCGGUCGCAGUCGACCCGACACUGAGAAGAAGAAUCGAACCGCACGAAUUCGAAGUCUUC UUCGACCCGAGAGAACUGAGAAAGGAAACAUGCCUGCUGUACGAAAUCAACUGGGGAGGAAGACACAGCAUCUGGAGA CACACAAGCCAGAACACAAACAAGCACGUCGAAGUCAACUUCAUCGAAAAGUUCACAACAGAAAGAUACUUCUGCCCG AACACAAGAUGCAGCAUCACAUGGUUCCUGAGCUGGAGCCCGUGCGGAGAAUGCAGCAGAGCAAUCACAGAAUUCCUG AGCAGAUACCCGCACGUCACACUGUUCAUCUACAUCGCAAGACUGUACCACCACGCAGACCCGAGAAACAGACAGGGA CUGAGAGACCUGAUCAGCAGCGGAGUCACAAUCCAGAUCAUGACAGAACAGGAAAGCGGAUACUGCUGGAGAAACUUC GUCAACUACAGCCCGAGCAACGAAGCACACUGGCCGAGAUACCCGCACCUGUGGGUCAGACUGUACGUCCUGGAACUG UACUGCAUCAUCCUGGGACUGCCGCCGUGCCUGAACAUCCUGAGAAGAAAGCAGCCGCAGCUGACAUUCUUCACAAUC GCACUGCAGAGCUGCCACUACCAGAGACUGCCGCCGCACAUCCUGUGGGCAACAGGACUGAAGAGCGGAAGCGAAACA CCGGGAACAAGCGAAAGCGCAACACCGGAAAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUC GGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGC AUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCA AGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGAC GACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGA AACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACA GACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGA GACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAA AACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAAC CUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCG AACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGAC AACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUG AGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACAC CACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAG AGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUG GAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGAC AACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUC CUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGA AACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAG GGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAG CACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAG CCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAG CAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAAC GCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGAC AUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCA CACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUG AUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAAC UUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGAC

		AGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUC GACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACA CAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUG AAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUG UACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAG GACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAA GUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUG ACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAG AUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAA GUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUC AACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUG GAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGA AAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACA GUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAA AGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUC GACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUC AAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGA UACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGA AUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCAC UACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUC CUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACA AACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUC CUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGAC AGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUG AUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAA AGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGC AACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUC

15	用於BE3之胺基酸序列	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERYFCP NTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNF VNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGSET PGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTA RRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLEN LIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILL SDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPIL EKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARG NSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRK PAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENED ILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTT QKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLK DDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQ ITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKL ESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFAT VRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSV KELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLT NLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESIL MLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

16	編碼BE3之mRNA	GGGUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGCCUUAUUCGGAUCCACCAUGAG CUCAGAGACUGGCCCAGUGGCUGUGGACCCCACAUUGAGACGGCGGAUCGAGCCCCAUGAGUUUGAGGUAUUCUUCGA UCCGAGAGAGCUCCGCAAGGAGACCUGCCUGCUUUACGAAAUUAAUUGGGGGGGCCGGCACUCCAUUUGGCGACAUAC AUCACAGAACACUAACAAGCACGUCGAAGUCAACUUCAUCGAGAAGUUCACGACAGAAAGAUAUUUCUGUCCGAACAC AAGGUGCAGCAUUACCUGGUUUCUCAGCUGGAGCCCAUGCGGCGAAUGUAGUAGGGCCAUCACUGAAUUCCUGUCAAG GUAUCCCCACGUCACUCUGUUUAUUUACAUCGCAAGGCUGUACCACCACGCUGACCCCCGCAAUCGACAAGGCCUGCG GGAUUUGAUCUCUUCAGGUGUGACUAUCCAAAUUAUGACUGAGCAGGAGUCAGGAUACUGCUGGAGAAACUUUGUGAA UUAUAGCCCGAGUAAUGAAGCCCACUGGCCUAGGUAUCCCCAUCUGUGGGUACGACUGUACGUUCUUGAACUGUACUG CAUCAUACUGGGCCUGCCUCCUUGUCUCAACAUUCUGAGAAGGAAGCAGCCACAGCUGACAUUCUUUACCAUCGCUCU UCAGUCUUGUCAUUACCAGCGACUGCCCCCACACAUUCUCUGGGCCACCGGGUUGAAAAGCGGCAGCGAGACUCCGGG CACCUCAGAGUCCGCCACACCCGAAAGUGAUAAGAAGUACUCAAUCGGGCUGGCCAUCGGAACUAAUUCCGUGGGUUG GGCAGUGAUCACGGAUGAAUACAAAGUGCCGUCCAAGAAGUUCAAGGUCCUGGGGAACACCGAUAGACACAGCAUCAA GAAAAAUCUCAUCGGAGCCCUGCUGUUUGACUCCGGCGAAACCGCAGAAGCGACCCGGCUCAAACGUACCGCGAGGCG ACGCUACACCCGGCGGAAGAAUCGCAUCUGCUAUCUGCAAGAGAUCUUUUCGAACGAAAUGGCAAAGGUCGACGACAG CUUCUUCCACCGCCUGGAAGAAUCUUUCCUGGUGGAGGAGGACAAGAAGCAUGAACGGCAUCCUAUCUUUGGAAACAU CGUCGACGAAGUGGCGUACCACGAAAAGUACCCGACCAUCUACCAUCUGCGGAAGAAGUUGGUUGACUCAACUGACAA GGCCGACCUCAGAUUGAUCUACUUGGCCCUCGCCCAUAUGAUCAAAUUCCGCGGACACUUCCUGAUCGAAGGCGAUCU GAACCCUGAUAACUCCGACGUGGAUAAGCUUUUCAUUCAACUGGUGCAGACCUACAACCAACUGUUCGAAGAAAACCC AAUCAAUGCUAGCGGCGUCGAUGCCAAGGCCAUCCUGUCCGCCCGGCUGUCGAAGUCGCGGCGCCUCGAAAACCUGAU CGCACAGCUGCCGGGAGAGAAAAAGAACGGACUUUUCGGCAACUUGAUCGCUCUCUCACUGGGACUCACUCCCAAUUU CAAGUCCAAUUUUGACCUGGCCGAGGACGCGAAGCUGCAACUCUCAAAGGACACCUACGACGACGACUUGGACAAUUU GCUGGCACAAAUUGGCGAUCAGUACGCGGAUCUGUUCCUUGCCGCUAAGAACCUUUCGGACGCAAUCUUGCUGUCCGA UAUCCUGCGCGUGAACACCGAAAUAACCAAAGCGCCGCUUAGCGCCUCGAUGAUUAAGCGGUACGACGAGCAUCACCA GGAUCUCACGCUGCUCAAAGCGCUCGUGAGACAGCAACUGCCUGAAAAGUACAAGGAGAUCUUCUUCGACCAGUCCAA GAAUGGGUACGCAGGGUACAUCGAUGGAGGCGCUAGCCAGGAAGAGUUCUAUAAGUUCAUCAAGCCAAUCCUGGAAAA GAUGGACGGAACCGAAGAACUGCUGGUCAAGCUGAACAGGGAGGAUCUGCUCCGGAAACAGAGAACCUUUGACAACGG AUCCAUUCCCCACCAGAUCCAUCUGGGUGAGCUGCACGCCAUCUUGCGGCGCCAGGAGGACUUUUACCCAUUCCUCAA GGACAACCGGGAAAAGAUCGAGAAAAUUCUGACGUUCCGCAUCCCGUAUUACGUGGGCCCACUGGCGCGCGGCAAUUC GCGCUUCGCGUGGAUGACUAGAAAAUCAGAGGAAACCAUCACUCCUUGGAAUUUCGAGGAAGUUGUGGAUAAGGGAGC UUCGGCACAAAGCUUCAUCGAACGAAUGACCAACUUCGACAAGAAUCUCCCAAACGAGAAGGUGCUUCCUAAGCACAG CCUCCUUUACGAAUACUUCACUGUCUACAACGAACUGACUAAAGUGAAAUACGUUACUGAAGGAAUGAGGAAGCCGGC CUUUCUGUCCGGAGAACAGAAGAAAGCAAUUGUCGAUCUGCUGUUCAAGACCAACCGCAAGGUGACCGUCAAGCAGCU UAAAGAGGACUACUUCAAGAAGAUCGAGUGUUUCGACUCAGUGGAAAUCAGCGGGGUGGAGGACAGAUUCAACGCUUC GCUGGGAACCUAUCAUGAUCUCCUGAAGAUCAUCAAGGACAAGGACUUCCUUGACAACGAGGAGAACGAGGACAUCCU GGAAGAUAUCGUCCUGACCUUGACCCUUUUCGAGGAUCGCGAGAUGAUCGAGGAGAGGCUUAAGACCUACGCUCAUCU CUUCGACGAUAAGGUCAUGAAACAACUCAAGCGCCGCCGGUACACUGGUUGGGGCCGCCUCUCCCGCAAGCUGAUCAA CGGUAUUCGCGAUAAACAGAGCGGUAAAACUAUCCUGGAUUUCCUCAAAUCGGAUGGCUUCGCUAAUCGUAACUUCAU

		GCAAUUGAUCCACGACGACAGCCUGACCUUUAAGGAGGACAUCCAAAAAGCACAAGUGUCCGGACAGGGAGACUCACU CCAUGAACACAUCGCGAAUCUGGCCGGUUCGCCGGCGAUUAAGAAGGGAAUUCUGCAAACUGUGAAGGUGGUCGACGA GCUGGUGAAGGUCAUGGGACGGCACAAACCGGAGAAUAUCGUGAUUGAAAUGGCCCGAGAAAACCAGACUACCCAGAA GGGCCAGAAAAACUCCCGCGAAAGGAUGAAGCGGAUCGAAGAAGGAAUCAAGGAGCUGGGCAGCCAGAUCCUGAAAGA GCACCCGGUGGAAAACACGCAGCUGCAGAACGAGAAGCUCUACCUGUACUAUUUGCAAAAUGGACGGGACAUGUACGU GGACCAAGAGCUGGACAUCAAUCGGUUGUCUGAUUACGACGUGGACCACAUCGUUCCACAGUCCUUUCUGAAGGAUGA CUCGAUCGAUAACAAGGUGUUGACUCGCAGCGACAAGAACAGAGGGAAGUCAGAUAAUGUGCCAUCGGAGGAGGUCGU GAAGAAGAUGAAGAAUUACUGGCGGCAGCUCCUGAAUGCGAAGCUGAUUACCCAGAGAAAGUUUGACAAUCUCACUAA AGCCGAGCGCGGCGGACUCUCAGAGCUGGAUAAGGCUGGAUUCAUCAAACGGCAGCUGGUCGAGACUCGGCAGAUUAC CAAGCACGUGGCGCAGAUCUUGGACUCCCGCAUGAACACUAAAUACGACGAGAACGAUAAGCUCAUCCGGGAAGUGAA GGUGAUUACCCUGAAAAGCAAACUUGUGUCGGACUUUCGGAAGGACUUUCAGUUUUACAAAGUGAGAGAAAUCAACAA CUACCAUCACGCGCAUGACGCAUACCUCAACGCUGUGGUCGGUACCGCCCUGAUCAAAAAGUACCCUAAACUUGAAUC GGAGUUUGUGUACGGAGACUACAAGGUCUACGACGUGAGGAAGAUGAUAGCCAAGUCCGAACAGGAAAUCGGGAAAGC AACUGCGAAAUACUUCUUUUACUCAAACAUCAUGAACUUUUUCAAGACUGAAAUUACGCUGGCCAAUGGAGAAAUCAG GAAGAGGCCACUGAUCGAAACUAACGGAGAAACGGGCGAAAUCGUGUGGGACAAGGGCAGGGACUUCGCAACUGUUCG CAAAGUGCUCUCUAUGCCGCAAGUCAAUAUUGUGAAGAAAACCGAAGUGCAAACCGGCGGAUUUUCAAAGGAAUCGAU CCUCCCAAAGAGAAAUAGCGACAAGCUCAUUGCACGCAAGAAAGACUGGGACCCGAAGAAGUACGGAGGAUUCGAUUC GCCGACUGUCGCAUACUCCGUCCUCGUGGUGGCCAAGGUGGAGAAGGGAAAGAGCAAAAAGCUCAAAUCCGUCAAAGA GCUGCUGGGGAUUACCAUCAUGGAACGAUCCUCGUUCGAGAAGAACCCGAUUGAUUUCCUCGAGGCGAAGGGUUACAA GGAGGUGAAGAAGGAUCUGAUCAUCAAACUCCCCAAGUACUCACUGUUCGAACUGGAAAAUGGUCGGAAGCGCAUGCU GGCUUCGGCCGGAGAACUCCAAAAAGGAAAUGAGCUGGCCUUGCCUAGCAAGUACGUCAACUUCCUCUAUCUUGCUUC GCACUACGAAAAACUCAAAGGGUCACCGGAAGAUAACGAACAGAAGCAGCUUUUCGUGGAGCAGCACAAGCAUUAUCU GGAUGAAAUCAUCGAACAAAUCUCCGAGUUUUCAAAGCGCGUGAUCCUCGCCGACGCCAACCUCGACAAAGUCCUGUC GGCCUACAAUAAGCAUAGAGAUAAGCCGAUCAGAGAACAGGCCGAGAACAUUAUCCACUUGUUCACCCUGACUAACCU GGGAGCCCCAGCCGCCUUCAAGUACUUCGAUACUACUAUCGAUCGCAAAAGAUACACGUCCACCAAGGAAGUUCUGGA CGCGACCCUGAUCCACCAAAGCAUCACUGGACUCUACGAAACUAGGAUCGAUCUGUCGCAGCUGGGUGGCGAUUCUGG UGGUUCUACUAAUCUGUCAGAUAUUAUUGAAAAGGAGACCGGUAAGCAACUGGUUAUCCAGGAAUCCAUCCUCAUGCU CCCAGAGGAGGUGGAAGAAGUCAUUGGGAACAAGCCGGAAAGCGAUAUACUCGUGCACACCGCCUACGACGAGAGCAC CGACGAGAAUGUCAUGCUUCUGACUAGCGACGCCCCUGAAUACAAGCCUUGGGCUCUGGUCAUACAGGAUAGCAACGG UGAGAACAAGAUUAAGAUGCUCUCUGGUGGUUCUCCCAAGAAGAAGAGGAAAGUCUAAUAGUCUAGCCAUCACAUUUA AAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGU UGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAA UAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAA AAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAU

17	用於BE3之開讀框	AUGAGCUCAGAGACUGGCCCAGUGGCUGUGGACCCCACAUUGAGACGGCGGAUCGAGCCCCAUGAGUUUGAGGUAUUC UUCGAUCCGAGAGAGCUCCGCAAGGAGACCUGCCUGCUUUACGAAAUUAAUUGGGGGGGCCGGCACUCCAUUUGGCGA CAUACAUCACAGAACACUAACAAGCACGUCGAAGUCAACUUCAUCGAGAAGUUCACGACAGAAAGAUAUUUCUGUCCG AACACAAGGUGCAGCAUUACCUGGUUUCUCAGCUGGAGCCCAUGCGGCGAAUGUAGUAGGGCCAUCACUGAAUUCCUG UCAAGGUAUCCCCACGUCACUCUGUUUAUUUACAUCGCAAGGCUGUACCACCACGCUGACCCCCGCAAUCGACAAGGC CUGCGGGAUUUGAUCUCUUCAGGUGUGACUAUCCAAAUUAUGACUGAGCAGGAGUCAGGAUACUGCUGGAGAAACUUU GUGAAUUAUAGCCCGAGUAAUGAAGCCCACUGGCCUAGGUAUCCCCAUCUGUGGGUACGACUGUACGUUCUUGAACUG UACUGCAUCAUACUGGGCCUGCCUCCUUGUCUCAACAUUCUGAGAAGGAAGCAGCCACAGCUGACAUUCUUUACCAUC GCUCUUCAGUCUUGUCAUUACCAGCGACUGCCCCCACACAUUCUCUGGGCCACCGGGUUGAAAAGCGGCAGCGAGACU CCGGGCACCUCAGAGUCCGCCACACCCGAAAGUGAUAAGAAGUACUCAAUCGGGCUGGCCAUCGGAACUAAUUCCGUG GGUUGGGCAGUGAUCACGGAUGAAUACAAAGUGCCGUCCAAGAAGUUCAAGGUCCUGGGGAACACCGAUAGACACAGC AUCAAGAAAAAUCUCAUCGGAGCCCUGCUGUUUGACUCCGGCGAAACCGCAGAAGCGACCCGGCUCAAACGUACCGCG AGGCGACGCUACACCCGGCGGAAGAAUCGCAUCUGCUAUCUGCAAGAGAUCUUUUCGAACGAAAUGGCAAAGGUCGAC GACAGCUUCUUCCACCGCCUGGAAGAAUCUUUCCUGGUGGAGGAGGACAAGAAGCAUGAACGGCAUCCUAUCUUUGGA AACAUCGUCGACGAAGUGGCGUACCACGAAAAGUACCCGACCAUCUACCAUCUGCGGAAGAAGUUGGUUGACUCAACU GACAAGGCCGACCUCAGAUUGAUCUACUUGGCCCUCGCCCAUAUGAUCAAAUUCCGCGGACACUUCCUGAUCGAAGGC GAUCUGAACCCUGAUAACUCCGACGUGGAUAAGCUUUUCAUUCAACUGGUGCAGACCUACAACCAACUGUUCGAAGAA AACCCAAUCAAUGCUAGCGGCGUCGAUGCCAAGGCCAUCCUGUCCGCCCGGCUGUCGAAGUCGCGGCGCCUCGAAAAC CUGAUCGCACAGCUGCCGGGAGAGAAAAAGAACGGACUUUUCGGCAACUUGAUCGCUCUCUCACUGGGACUCACUCCC AAUUUCAAGUCCAAUUUUGACCUGGCCGAGGACGCGAAGCUGCAACUCUCAAAGGACACCUACGACGACGACUUGGAC AAUUUGCUGGCACAAAUUGGCGAUCAGUACGCGGAUCUGUUCCUUGCCGCUAAGAACCUUUCGGACGCAAUCUUGCUG UCCGAUAUCCUGCGCGUGAACACCGAAAUAACCAAAGCGCCGCUUAGCGCCUCGAUGAUUAAGCGGUACGACGAGCAU CACCAGGAUCUCACGCUGCUCAAAGCGCUCGUGAGACAGCAACUGCCUGAAAAGUACAAGGAGAUCUUCUUCGACCAG UCCAAGAAUGGGUACGCAGGGUACAUCGAUGGAGGCGCUAGCCAGGAAGAGUUCUAUAAGUUCAUCAAGCCAAUCCUG GAAAAGAUGGACGGAACCGAAGAACUGCUGGUCAAGCUGAACAGGGAGGAUCUGCUCCGGAAACAGAGAACCUUUGAC AACGGAUCCAUUCCCCACCAGAUCCAUCUGGGUGAGCUGCACGCCAUCUUGCGGCGCCAGGAGGACUUUUACCCAUUC CUCAAGGACAACCGGGAAAAGAUCGAGAAAAUUCUGACGUUCCGCAUCCCGUAUUACGUGGGCCCACUGGCGCGCGGC AAUUCGCGCUUCGCGUGGAUGACUAGAAAAUCAGAGGAAACCAUCACUCCUUGGAAUUUCGAGGAAGUUGUGGAUAAG GGAGCUUCGGCACAAAGCUUCAUCGAACGAAUGACCAACUUCGACAAGAAUCUCCCAAACGAGAAGGUGCUUCCUAAG CACAGCCUCCUUUACGAAUACUUCACUGUCUACAACGAACUGACUAAAGUGAAAUACGUUACUGAAGGAAUGAGGAAG CCGGCCUUUCUGUCCGGAGAACAGAAGAAAGCAAUUGUCGAUCUGCUGUUCAAGACCAACCGCAAGGUGACCGUCAAG CAGCUUAAAGAGGACUACUUCAAGAAGAUCGAGUGUUUCGACUCAGUGGAAAUCAGCGGGGUGGAGGACAGAUUCAAC GCUUCGCUGGGAACCUAUCAUGAUCUCCUGAAGAUCAUCAAGGACAAGGACUUCCUUGACAACGAGGAGAACGAGGAC AUCCUGGAAGAUAUCGUCCUGACCUUGACCCUUUUCGAGGAUCGCGAGAUGAUCGAGGAGAGGCUUAAGACCUACGCU CAUCUCUUCGACGAUAAGGUCAUGAAACAACUCAAGCGCCGCCGGUACACUGGUUGGGGCCGCCUCUCCCGCAAGCUG AUCAACGGUAUUCGCGAUAAACAGAGCGGUAAAACUAUCCUGGAUUUCCUCAAAUCGGAUGGCUUCGCUAAUCGUAAC UUCAUGCAAUUGAUCCACGACGACAGCCUGACCUUUAAGGAGGACAUCCAAAAAGCACAAGUGUCCGGACAGGGAGAC

		UCACUCCAUGAACACAUCGCGAAUCUGGCCGGUUCGCCGGCGAUUAAGAAGGGAAUUCUGCAAACUGUGAAGGUGGUC GACGAGCUGGUGAAGGUCAUGGGACGGCACAAACCGGAGAAUAUCGUGAUUGAAAUGGCCCGAGAAAACCAGACUACC CAGAAGGGCCAGAAAAACUCCCGCGAAAGGAUGAAGCGGAUCGAAGAAGGAAUCAAGGAGCUGGGCAGCCAGAUCCUG AAAGAGCACCCGGUGGAAAACACGCAGCUGCAGAACGAGAAGCUCUACCUGUACUAUUUGCAAAAUGGACGGGACAUG UACGUGGACCAAGAGCUGGACAUCAAUCGGUUGUCUGAUUACGACGUGGACCACAUCGUUCCACAGUCCUUUCUGAAG GAUGACUCGAUCGAUAACAAGGUGUUGACUCGCAGCGACAAGAACAGAGGGAAGUCAGAUAAUGUGCCAUCGGAGGAG GUCGUGAAGAAGAUGAAGAAUUACUGGCGGCAGCUCCUGAAUGCGAAGCUGAUUACCCAGAGAAAGUUUGACAAUCUC ACUAAAGCCGAGCGCGGCGGACUCUCAGAGCUGGAUAAGGCUGGAUUCAUCAAACGGCAGCUGGUCGAGACUCGGCAG AUUACCAAGCACGUGGCGCAGAUCUUGGACUCCCGCAUGAACACUAAAUACGACGAGAACGAUAAGCUCAUCCGGGAA GUGAAGGUGAUUACCCUGAAAAGCAAACUUGUGUCGGACUUUCGGAAGGACUUUCAGUUUUACAAAGUGAGAGAAAUC AACAACUACCAUCACGCGCAUGACGCAUACCUCAACGCUGUGGUCGGUACCGCCCUGAUCAAAAAGUACCCUAAACUU GAAUCGGAGUUUGUGUACGGAGACUACAAGGUCUACGACGUGAGGAAGAUGAUAGCCAAGUCCGAACAGGAAAUCGGG AAAGCAACUGCGAAAUACUUCUUUUACUCAAACAUCAUGAACUUUUUCAAGACUGAAAUUACGCUGGCCAAUGGAGAA AUCAGGAAGAGGCCACUGAUCGAAACUAACGGAGAAACGGGCGAAAUCGUGUGGGACAAGGGCAGGGACUUCGCAACU GUUCGCAAAGUGCUCUCUAUGCCGCAAGUCAAUAUUGUGAAGAAAACCGAAGUGCAAACCGGCGGAUUUUCAAAGGAA UCGAUCCUCCCAAAGAGAAAUAGCGACAAGCUCAUUGCACGCAAGAAAGACUGGGACCCGAAGAAGUACGGAGGAUUC GAUUCGCCGACUGUCGCAUACUCCGUCCUCGUGGUGGCCAAGGUGGAGAAGGGAAAGAGCAAAAAGCUCAAAUCCGUC AAAGAGCUGCUGGGGAUUACCAUCAUGGAACGAUCCUCGUUCGAGAAGAACCCGAUUGAUUUCCUCGAGGCGAAGGGU UACAAGGAGGUGAAGAAGGAUCUGAUCAUCAAACUCCCCAAGUACUCACUGUUCGAACUGGAAAAUGGUCGGAAGCGC AUGCUGGCUUCGGCCGGAGAACUCCAAAAAGGAAAUGAGCUGGCCUUGCCUAGCAAGUACGUCAACUUCCUCUAUCUU GCUUCGCACUACGAAAAACUCAAAGGGUCACCGGAAGAUAACGAACAGAAGCAGCUUUUCGUGGAGCAGCACAAGCAU UAUCUGGAUGAAAUCAUCGAACAAAUCUCCGAGUUUUCAAAGCGCGUGAUCCUCGCCGACGCCAACCUCGACAAAGUC CUGUCGGCCUACAAUAAGCAUAGAGAUAAGCCGAUCAGAGAACAGGCCGAGAACAUUAUCCACUUGUUCACCCUGACU AACCUGGGAGCCCCAGCCGCCUUCAAGUACUUCGAUACUACUAUCGAUCGCAAAAGAUACACGUCCACCAAGGAAGUU CUGGACGCGACCCUGAUCCACCAAAGCAUCACUGGACUCUACGAAACUAGGAUCGAUCUGUCGCAGCUGGGUGGCGAU UCUGGUGGUUCUACUAAUCUGUCAGAUAUUAUUGAAAAGGAGACCGGUAAGCAACUGGUUAUCCAGGAAUCCAUCCUC AUGCUCCCAGAGGAGGUGGAAGAAGUCAUUGGGAACAAGCCGGAAAGCGAUAUACUCGUGCACACCGCCUACGACGAG AGCACCGACGAGAAUGUCAUGCUUCUGACUAGCGACGCCCCUGAAUACAAGCCUUGGGCUCUGGUCAUACAGGAUAGC AACGGUGAGAACAAGAUUAAGAUGCUCUCUGGUGGUUCUCCCAAGAAGAAGAGGAAAGUCUAA

18	用於BE3之胺基酸序列	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERYFCP NTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNF VNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGSET PGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTA RRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLEN LIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILL SDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPIL EKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARG NSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRK PAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENED ILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTT QKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLK DDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQ ITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKL ESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFAT VRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSV KELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLT NLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESIL MLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

19	編碼BC22之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUG UGUCGUUGCAGGCCUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGC ACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACA ACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACG GAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGAGUCACAU GGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACG UCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCC CGUUCCAGCCGUGGGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGG GAAACAGCGGAAGCGAAACACCGGGAACAAGCGAAAGCGCAACACCGGAAAGCGACAAGAAGUACAGCAUCGGACUGG CCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGG GAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAA CAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCA ACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACG AAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAA AGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAG GACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAU ACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCA AGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCAC UGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACA CAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACC UGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGA UCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACA AGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACA AGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGA GAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGAC AGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACG UCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACU UCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGA ACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACG UCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAA ACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCG GAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGG ACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAG AAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGG GAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCG ACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCAC

		AGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCC UGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGG CAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGG AACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACC UGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCG UCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCG ACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACAC AGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGAC AGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAA ACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGU UCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGA UCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAA AGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAA UCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACA AGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGA CAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACC CGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGA GCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCG ACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAAC UGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGU ACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGU UCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAG ACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCA UCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAU ACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUC UGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGG UCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGG UCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGG CACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGG UCUAAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGC UUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUG CCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA GCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAU

20	用於BC22之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUC GGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGA GGAUUCCUGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUG GUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGG GGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUAC GACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAUCAUGACAUACGAC GAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACAGCGGAAGCGAAACACCGGGAACAAGC GAAAGCGCAACACCGGAAAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUC AUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAAC CUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUAC ACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUC CACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGAC GAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGAC CUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCG GACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAAC GCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAG CUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGC AACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCA CAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUG AGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUG ACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGA UACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGAC GGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUC CCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAAC AGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUC GCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCA CAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUG UACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUG AGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAA GACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGA ACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGAC AUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGAC GACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUC AGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUG AUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAA CACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUC

		AAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAG AAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCG GUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAG GAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUC GACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAG AUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAG AGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCAC GUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUC ACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCAC CACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUC GUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCA AAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGA CCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUC CUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCG AAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACA GUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUG GGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUC AAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGC GCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUAC GAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAA AUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUAC AACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCA CCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACA CUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGC ACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAA GAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAA AACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAAC AAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

21	用於BC22之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDL VPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYD EFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAV ITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFF HRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNP DNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSI PHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASA QSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFD DKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHP VENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILP KRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEV KKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDE NVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV
22	未使用	

23	具有Hibit標籤之Cas9之開讀框	AUGGACAAGAAGUACUCCAUCGGCCUGGACAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAG GUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUG UUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGG AUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCC UUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAG AAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUG GCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGAC AAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCC AAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAG AACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAG GACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUAC GCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUC ACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUG GUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGAC GGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUG GUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUG GGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAG AUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAG UCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGG AUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUG UACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAG GCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUC GAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACC CUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAG CUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGC AAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUG ACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCC GGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCAC AAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGG AUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUG CAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGG CUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACC CGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGG CAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAG CUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGAC UCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUG

		GUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUAC CUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAG GUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCC AACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAAC GGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUG AACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAG CUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUG GUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAG CGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUC AAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAG GGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCC CCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCC GAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAG CCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUAC UUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUC ACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAG GUGUCCGAGUCCGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAAGAUCUCCUGA
24	具有Hibit標籤之Cas9之胺基酸序列	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKVSESATPESVSGWRLFKKIS*

25	編碼UGI之mRNA	GGGAGACCCAAGCUGGCUAGCUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGCCUU AUUCGGAUCCGCCACCAUGGGACCGAAGAAGAAGAGAAAGGUCGGAGGAGGAAGCACAAACCUGUCGGACAUCAUCGA AAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAUCGAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAA CAAGCCGGAAUCGGACAUCCUGGUCCACACAGCAUACGACGAAUCGACAGACGAAAACGUCAUGCUGCUGACAUCGGA CGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACUCGAACGGAGAAAACAAGAUCAAGAUGCUGUGAUAGUC UAGACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCU CUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCU CUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGUCUAG
26	用於UGI之開讀框	AUGGGACCGAAGAAGAAGAGAAAGGUCGGAGGAGGAAGCACAAACCUGUCGGACAUCAUCGAAAAGGAAACAGGAAAG CAGCUGGUCAUCCAGGAAUCGAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAUCGGAC AUCCUGGUCCACACAGCAUACGACGAAUCGACAGACGAAAACGUCAUGCUGCUGACAUCGGACGCACCGGAAUACAAG CCGUGGGCACUGGUCAUCCAGGACUCGAACGGAGAAAACAAGAUCAAGAUGCUGUGA
27	用於UGI之胺基酸序列	MTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGE NKIKMLSGGSKRTADGSEFESPKKKRKVE

28	編碼具有2x UGI之BC22之mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACC UGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGG AGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGU GCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCU ACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGG AGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGA UGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCC UGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAAGAAGUACU CCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGU UCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGA CCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGG AGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGG ACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGA UCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGC UGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCG CCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCA ACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGC UGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGG CCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGC CCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGG AGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGG AGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCA UCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGA UCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCA CCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCA AGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGC UGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCG UGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACA AGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGG AGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGU ACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACA UCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA

		AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCG UGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGG AGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGU ACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACG UGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCU UCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCA AGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGA AGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGG GCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGA AGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGA UCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGA CCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGA AGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGG AGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGA AGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGC AGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGG UGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGG CCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCG ACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGA CCCGGAUCGACCUGUCCCAGCUGGGCGGCGACUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACCUGUCCGACA UCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGA UCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGA CCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGU CCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACCUGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGA UCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGC ACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCC UGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCG AGUUCGAGCCCAAGAAGAAGCGGAAGGUGUGAUAGCUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUA CAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAG UUUCUUCACAUUCUCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAAGGUAAAAAAAAAAAU AUAAAAAAAAAAAACAUAAAAAAAAAAAACGAAAAAAAAAAAACGUAAAAAAAAAAAACUCAAAAAAAAAAAGAUAA AAAAAAAAACCUAAAAAAAAAAAUGUAAAAAAAAAAAGGGAAAAAAAAAAACGCAAAAAAAAAACACAAAAA

		AAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAAACGAAAAAAAAAAAAACCCAAAAAAAAAA AAAGACAAAAAAAAAAAAAUAGAAAAAAAAAAAAAGUUAAAAAAAAAAAAACUGAAAAAAAAAAAAAUUUAAAAAAAAAAAA UCUAG

29	用於具有2x UGI之BC22之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUC GGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGG GGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUG GUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGG GGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUAC GACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGAC GAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCC GAGUCCGCCACCCCCGAGUCCGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUG AUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAAC CUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUAC ACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUC CACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGAC GAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCC GACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAAC GCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAG CUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCC AACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCC CAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUG CGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGC UACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGAC GGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUC CCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAAC CGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUC GCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCC CAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUG UCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAG GACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGC ACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGAC AUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGAC GACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUC CGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAG CACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUG

		AAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAG AAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCC GUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAG GAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUC GACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAG CGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCAC GUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUC ACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCAC CACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUC GUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCC AAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUG CUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCC AAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACC GUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUG GGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUG AAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCC GCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAG AUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUAC AACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCC CCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACC CUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACUCCGGCGGCUCC GGCGGCUCCGGCGGCUCCACCAACCUGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCC AUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUAC GACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAG GACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACCUGUCCGAC AUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUG AUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGCUG ACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUG UCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAGCCCAAGAAGAAGCGGAAGGUGUGAUAG

30	用於具有2x UGI之BC22之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDL VPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYD EFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAV ITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFF HRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNP DNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSI PHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASA QSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFD DKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHP VENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILP KRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEV KKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDAT LIHQSITGLYETRIDLSQLGGDSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAY DESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEV IGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSKRTADGSEFEPKKKRKV

31	編碼BE4MAX蛋白之mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGAAGCGGACCGCCGACGGCUCCGAGUUCGAGU CCCCCAAGAAGAAGCGGAAGGUGUCCUCCGAGACCGGCCCCGUGGCCGUGGACCCCACCCUGCGGCGGCGGAUCGAGC CCCACGAGUUCGAGGUGUUCUUCGACCCCCGGGAGCUGCGGAAGGAGACCUGCCUGCUGUACGAGAUCAACUGGGGCG GCCGGCACUCCAUCUGGCGGCACACCUCCCAGAACACCAACAAGCACGUGGAGGUGAACUUCAUCGAGAAGUUCACCA CCGAGCGGUACUUCUGCCCCAACACCCGGUGCUCCAUCACCUGGUUCCUGUCCUGGUCCCCCUGCGGCGAGUGCUCCC GGGCCAUCACCGAGUUCCUGUCCCGGUACCCCCACGUGACCCUGUUCAUCUACAUCGCCCGGCUGUACCACCACGCCG ACCCCCGGAACCGGCAGGGCCUGCGGGACCUGAUCUCCUCCGGCGUGACCAUCCAGAUCAUGACCGAGCAGGAGUCCG GCUACUGCUGGCGGAACUUCGUGAACUACUCCCCCUCCAACGAGGCCCACUGGCCCCGGUACCCCCACCUGUGGGUGC GGCUGUACGUGCUGGAGCUGUACUGCAUCAUCCUGGGCCUGCCCCCCUGCCUGAACAUCCUGCGGCGGAAGCAGCCCC AGCUGACCUUCUUCACCAUCGCCCUGCAGUCCUGCCACUACCAGCGGCUGCCCCCCCACAUCCUGUGGGCCACCGGCC UGAAGUCCGGCGGCUCCUCCGGCGGCUCCUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCU CCGGCGGCUCCUCCGGCGGCUCCGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCG UGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGA ACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGU ACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCU UCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGG ACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCG ACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACC CCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCA ACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCC AGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGU CCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGG CCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCC UGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACC UGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACG GCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGG ACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCA UCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACA ACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGU UCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCG CCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGC UGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCC UGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGG AGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGG GCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGG ACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCG ACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCA

		UCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGC UGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACG AGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGG UGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCC AGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACC CCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACC AGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCA UCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGA AGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCG AGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGC ACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGA UCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACC ACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGU UCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCG CCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGC GGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGG UGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGC CCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCA CCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGC UGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGG UGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCU CCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACU ACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACG AGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCU ACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCG CCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCA CCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACUCCGGCGGCU CCGGCGGCUCCGGCGGCUCCACCAACCUGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGU CCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCU ACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCC AGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACCUGUCCG ACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGG UGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGC UGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGC UGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAGCCCAAGAAGAAGCGGAAGGUGUGAUAGCUAGCAC CAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAA UGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUCUCGAGAAAAAAAAAAAAUGGAAAAAAA

		AAAAACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAA ACGUAAAAAAAAAAAAACUCAAAAAAAAAAAAAGAUAAAAAAAAAAAAACCUAAAAAAAAAAAAAUGUAAAAAAAAAAAGG GAAAAAAAAAAAACGCAAAAAAAAAAAAACACAAAAAAAAAAAAAUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAA AAAAAAAAAACGAAAAAAAAAAAAACCCAAAAAAAAAAAAAGACAAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAA AAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

32	用於BE4MAX蛋白之開讀框	AUGAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGUGUCCUCCGAGACCGGCCCCGUG GCCGUGGACCCCACCCUGCGGCGGCGGAUCGAGCCCCACGAGUUCGAGGUGUUCUUCGACCCCCGGGAGCUGCGGAAG GAGACCUGCCUGCUGUACGAGAUCAACUGGGGCGGCCGGCACUCCAUCUGGCGGCACACCUCCCAGAACACCAACAAG CACGUGGAGGUGAACUUCAUCGAGAAGUUCACCACCGAGCGGUACUUCUGCCCCAACACCCGGUGCUCCAUCACCUGG UUCCUGUCCUGGUCCCCCUGCGGCGAGUGCUCCCGGGCCAUCACCGAGUUCCUGUCCCGGUACCCCCACGUGACCCUG UUCAUCUACAUCGCCCGGCUGUACCACCACGCCGACCCCCGGAACCGGCAGGGCCUGCGGGACCUGAUCUCCUCCGGC GUGACCAUCCAGAUCAUGACCGAGCAGGAGUCCGGCUACUGCUGGCGGAACUUCGUGAACUACUCCCCCUCCAACGAG GCCCACUGGCCCCGGUACCCCCACCUGUGGGUGCGGCUGUACGUGCUGGAGCUGUACUGCAUCAUCCUGGGCCUGCCC CCCUGCCUGAACAUCCUGCGGCGGAAGCAGCCCCAGCUGACCUUCUUCACCAUCGCCCUGCAGUCCUGCCACUACCAG CGGCUGCCCCCCCCACAUCCUGUGGGCCACCGGCCUGAAGUCCGGCGGCUCCUCCGGCGGCUCCUCCGGCUCCGAGACC CCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCUCCGGCGGCUCCUCCGGCGGCUCCGACAAGAAGUACUCCAUCGGC CUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUG CUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAG GCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUC UCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAG CACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUG CGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUC CGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAG ACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUG UCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUC GCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAG GACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAG AACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCC AUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAG UACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUC UACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUG CUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGG CGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUAC UACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGG AACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUG CCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAG UACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAG ACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUC UCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUC CUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUC GAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGC UGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAG

		UCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAG GCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGC AUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAG AUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUC AAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUAC UACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCAC AUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAG UCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUC ACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAG CGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGAC GAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUC CAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCC CUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUC GCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACC GAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGG GACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUG CAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGG GACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGC AAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCC AUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUC GAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCC AAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAG CUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUG GCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAAC AUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAG CGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUC GACCUGUCCCAGCUGGGCGGCGACUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCCACCAACCUGUCCGACAUCAUCGAG AAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAAC AAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGAC GCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGC UCCGGCGGCUCCGGCGGCUCCACCAACCUGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAG UCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCC UACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUC CAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAG CCCAAGAAGAAGCGGAAGGUGUGAUAG

33	用於BE4MAX蛋白之胺基酸序列	MKRTADGSEFESPKKKRKVSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNK HVEVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSG VTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQ RLPPHILWATGLKSGGSSGGSSGSETPGTSESATPESSGGSSGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKV LGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKK HERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQ TYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSK DTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNL PNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEI SGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTG WGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKG ILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLY YLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLI TQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDF QFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDW DPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLF ELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVIL ADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRI DLSQLGGDSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSD APEYKPWALVIQDSNGENKIKMLSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTA YDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSKRTADGSEFEPKKKRKV**
34	編碼UGI之mRNA序列	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGACCAACCUGUCCGACAUCAUCGAGAAGGAGA CCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCG AGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCG AGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCAAGC GGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGUGGAGUGAUAGCUAGCACCAGCCUCAAGAA CACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCG UAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAA AAAAAAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAAACGUAAAAAAAA AAAACUCAAAAAAAAAAAAAGAUAAAAAAAAAAAACCUAAAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAAAAAAA ACGCAAAAAAAAAAAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAAAAAAAAAAAACG AAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAAAAAAACUGAAA AAAAAAAAUUUAAAAAAAAAAAUCUAG

35	用於UGI之開讀框	AUGACCAACCUGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCC GAGGAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGAC GAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAG AACAAGAUCAAGAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGCGG AAGGUGGAGUGA
36	用於重組Cas9-NLS之胺基酸序列	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV
37	未使用	未使用
38	未使用	未使用
39	未使用	未使用
40	智人(H. sapiens) APOBEC3A去胺酶(A3A)之胺基酸序列，參見表58、BC22	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDL VPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYD EFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGN
41	褐家鼠Apobec1之胺基酸序列，參見表58、BC27	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERYFCP NTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNF VNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLK

42	用於UGI之例示性編碼序列(SEQ ID NO: 43)	ACTAATCTGTCAGATATTATTGAAAAGGAGACCGGTAAGCAACTGGTTATCCAGGAATCCATCCTCATGCTCCCAGAG GAGGTGGAAGAAGTCATTGGGAACAAGCCGGAAAGCGATATACTCGTGCACACCGCCTACGACGAGAGCACCGACGAG AATGTCATGCTTCTGACTAGCGACGCCCCTGAATACAAGCCTTGGGCTCTGGTCATACAGGATAGCAACGGTGAGAAC AAGATTAAGATGCTC
43	例示性UGI	TNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGEN KIKML
44	用於XTEN SEQ ID NO. 46之例示性編碼序列	AGCGGCAGCGAGACTCCGGGCACCTCAGAGTCCGCCACACCCGAAAGT
45	用於XTEN SEQ ID NO. 46之例示性編碼序列	AGCGGAAGCGAAACACCGGGAACAAGCGAAAGCGCAACACCGGAAAGC
46	例示性XTEN	SGSETPGTSESATPES
47	例示性XTEN	SGSETPGTSESA
48	例示性XTEN	SGSETPGTSESATPEGGSGGS
49	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAK
50	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGS
51	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAK
52	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSGGGGS
53	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKEAAAK
54	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSGGGGS
55	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKGGGGSGGGGS

56	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKEAAAK
57	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKGGGGSEAAAK
58	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSGGGGSGGGGS
59	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSGGGGSEAAAK
60	用於例示性連接子SSGS之核酸序列	TCTGGTGGTTCT
61	用於例示性連接子SGGS之胺基酸序列	SGGS
62	用於SV40 NLS之核酸序列	CCCAAGAAGAAGAGGAAAGTC
63	用於SV40 NLS之胺基酸序列	PKKKRKV

64	pCl-Neo	TCAATATTGGCCATTAGCCATATTATTCATTGGTTATATAGCATAAATCAATATTGGCTATTGGCCATTGCATACGTT GTATCTATATCATAATATGTACATTTATATTGGCTCATGTCCAATATGACCGCCATGTTGGCATTGATTATTGACTAG TTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAA TGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAAT AGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATAT GCCAAGTCCGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTACGGGA CTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACACCAATGG GCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCA AAATCAACGGGACTTTCCAAAATGTCGTAACAACTGCGATCGCCCGCCCCGTTGACGCAAATGGGCGGTAGGCGTGTA CGGTGGGAGGTCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCACTAGAAGCTTTATTGCGGTAGTTTATCAC AGTTAAATTGCTAACGCAGTCAGTGCTTCTGACACAACAGTCTCGAACTTAAGCTGCAGTGACTCTCTTAAGGTAGCC TTGCAGAAGTTGGTCGTGAGGCACTGGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCAATAGAAACT GGGCTTGTCGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTATTGGTCTTACTGACATCCACTTTGCCTTTCT CTCCACAGGTGTCCACTCCCAGTTCAATTACAGCTCTTAAGGCTAGAGTACTTAATACGACTCACTATAGGCTAGCCT CGAGAATTCACGCGTGGTACCTCTAGAGTCGACCCGGGCGGCCGCTTCCCTTTAGTGAGGGTTAATGCTTCGAGCAGA CATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTG TGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATTCATTTTATGTT TCAGGTTCAGGGGGAGATGTGGGAGGTTTTTTAAAGCAAGTAAAACCTCTACAAATGTGGTAAAATCCGATAAGGATC GATCCGGGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGG ACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCC TAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGG GGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTA GTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCC AAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGT TAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTTCCTGATGCGGTA TTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGCGGATCTGCGCAGCACCATGGCCTGAAATAACCTCT GAAAGAGGAACTTGGTTAGGTACCTTCTGAGGCGGAAAGAACCAGCTGTGGAATGTGTGTCAGTTAGGGTGTGGAAAG TCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTAGTCAGCAACCAGGTGTGGAAAGTCCCCA GGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCC GAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT GATTCTTCTGACACAACAGTCTCGAACTTAAGGCTAGAGCCACCATGATTGAACAAGATGGATTGCACGCAGGTTCTC CGGCCGCTTGGGTGGAGAGGCTATTCGGCTATGACTGGGCACAACAGACAATCGGCTGCTCTGATGCCGCCGTGTTCC GGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGCCCTGAATGAACTGCAGGACGAGG CAGCGCGGCTATCGTGGCTGGCCACGACGGGCGTTCCTTGCGCAGCTGTGCTCGACGTTGTCACTGAAGCGGGAAGGG ACTGGCTGCTATTGGGCGAAGTGCCGGGGCAGGATCTCCTGTCATCTCACCTTGCTCCTGCCGAGAAAGTATCCATCA TGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGCCCATTCGACCACCAAGCGAAACATCGCATCG

		AGCGAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCAGGATGATCTGGACGAAGAGCATCAGGGGCTCGCGCCAG CCGAACTGTTCGCCAGGCTCAAGGCGCGCATGCCCGACGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGC CGAATATCATGGTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGCGGACCGCTATCAGG ACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGTGCTTTACGGTA TCGCCGCTCCCGATTCGCAGCGCATCGCCTTCTATCGCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTGGGGTTCGA AATGACCGACCAAGCGACGCCCAACCTGCCATCACGATGGCCGCAATAAAATATCTTTATTTTCATTACATCTGTGTG TTGGTTTTTTGTGTGAATCGATAGCGATAAGGATCCGCGTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCAT AGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACA GACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGG GCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGG GAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCT GATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTG CGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCAC GAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGA TGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCA TACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAG AATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGG AGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCA TACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTAC TTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCC TTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGC CAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGA TCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATT TAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTG AGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAA TCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTC CGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCA AGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGT GTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACAC AGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCG AAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAA ACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGG GGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGG CTCGACAGATCT

65	篩選質體-恆定序列	GATAAGAAGTACTCAATCGGGCTGGATATCGGAACTAATTCCGTGGGTTGGGCAGTGATCACGGATGAATACAAAGTG CCGTCCAAGAAGTTCAAGGTCCTGGGGAACACCGATAGACACAGCATCAAGAAAAATCTCATCGGAGCCCTGCTGTTT GACTCCGGCGAAACCGCAGAAGCGACCCGGCTCAAACGTACCGCGAGGCGACGCTACACCCGGCGGAAGAATCGCATC TGCTATCTGCAAGAGATCTTTTCGAACGAAATGGCAAAGGTCGACGACAGCTTCTTCCACCGCCTGGAAGAATCTTTC CTGGTGGAGGAGGACAAGAAGCATGAACGGCATCCTATCTTTGGAAACATCGTCGACGAAGTGGCGTACCACGAAAAG TACCCGACCATCTACCATCTGCGGAAGAAGTTGGTTGACTCAACTGACAAGGCCGACCTCAGATTGATCTACTTGGCC CTCGCCCATATGATCAAATTCCGCGGACACTTCCTGATCGAAGGCGATCTGAACCCTGATAACTCCGACGTGGATAAG CTTTTCATTCAACTGGTGCAGACCTACAACCAACTGTTCGAAGAAAACCCAATCAATGCTAGCGGCGTCGATGCCAAG GCCATCCTGTCCGCCCGGCTGTCGAAGTCGCGGCGCCTCGAAAACCTGATCGCACAGCTGCCGGGAGAGAAAAAGAAC GGACTTTTCGGCAACTTGATCGCTCTCTCACTGGGACTCACTCCCAATTTCAAGTCCAATTTTGACCTGGCCGAGGAC GCGAAGCTGCAACTCTCAAAGGACACCTACGACGACGACTTGGACAATTTGCTGGCACAAATTGGCGATCAGTACGCG GATCTGTTCCTTGCCGCTAAGAACCTTTCGGACGCAATCTTGCTGTCCGATATCCTGCGCGTGAACACCGAAATAACC AAAGCGCCGCTTAGCGCCTCGATGATTAAGCGGTACGACGAGCATCACCAGGATCTCACGCTGCTCAAAGCGCTCGTG AGACAGCAACTGCCTGAAAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAATGGGTACGCAGGGTACATCGATGGA GGCGCTAGCCAGGAAGAGTTCTATAAGTTCATCAAGCCAATCCTGGAAAAGATGGACGGAACCGAAGAACTGCTGGTC AAGCTGAACAGGGAGGATCTGCTCCGGAAACAGAGAACCTTTGACAACGGATCCATTCCCCACCAGATCCATCTGGGT GAGCTGCACGCCATCTTGCGGCGCCAGGAGGACTTTTACCCATTCCTCAAGGACAACCGGGAAAAGATCGAGAAAATT CTGACGTTCCGCATCCCGTATTACGTGGGCCCACTGGCGCGCGGCAATTCGCGCTTCGCGTGGATGACTAGAAAATCA GAGGAAACCATCACTCCTTGGAATTTCGAGGAAGTTGTGGATAAGGGAGCTTCGGCACAAAGCTTCATCGAACGAATG ACCAACTTCGACAAGAATCTCCCAAACGAGAAGGTGCTTCCTAAGCACAGCCTCCTTTACGAATACTTCACTGTCTAC AACGAACTGACTAAAGTGAAATACGTTACTGAAGGAATGAGGAAGCCGGCCTTTCTGTCCGGAGAACAGAAGAAAGCA ATTGTCGATCTGCTGTTCAAGACCAACCGCAAGGTGACCGTCAAGCAGCTTAAAGAGGACTACTTCAAGAAGATCGAG TGTTTCGACTCAGTGGAAATCAGCGGGGTGGAGGACAGATTCAACGCTTCGCTGGGAACCTATCATGATCTCCTGAAG ATCATCAAGGACAAGGACTTCCTTGACAACGAGGAGAACGAGGACATCCTGGAAGATATCGTCCTGACCTTGACCCTT TTCGAGGATCGCGAGATGATCGAGGAGAGGCTTAAGACCTACGCTCATCTCTTCGACGATAAGGTCATGAAACAACTC AAGCGCCGCCGGTACACTGGTTGGGGCCGCCTCTCCCGCAAGCTGATCAACGGTATTCGCGATAAACAGAGCGGTAAA ACTATCCTGGATTTCCTCAAATCGGATGGCTTCGCTAATCGTAACTTCATGCAATTGATCCACGACGACAGCCTGACC TTTAAGGAGGACATCCAAAAAGCACAAGTGTCCGGACAGGGAGACTCACTCCATGAACACATCGCGAATCTGGCCGGT TCGCCGGCGATTAAGAAGGGAATTCTGCAAACTGTGAAGGTGGTCGACGAGCTGGTGAAGGTCATGGGACGGCACAAA CCGGAGAATATCGTGATTGAAATGGCCCGAGAAAACCAGACTACCCAGAAGGGCCAGAAAAACTCCCGCGAAAGGATG AAGCGGATCGAAGAAGGAATCAAGGAGCTGGGCAGCCAGATCCTGAAAGAGCACCCGGTGGAAAACACGCAGCTGCAG AACGAGAAGCTCTACCTGTACTATTTGCAAAATGGACGGGACATGTACGTGGACCAAGAGCTGGACATCAATCGGTTG TCTGATTACGACGTGGACCACATCGTTCCACAGTCCTTTCTGAAGGATGACTCGATCGATAACAAGGTGTTGACTCGC AGCGACAAGAACAGAGGGAAGTCAGATAATGTGCCATCGGAGGAGGTCGTGAAGAAGATGAAGAATTACTGGCGGCAG CTCCTGAATGCGAAGCTGATTACCCAGAGAAAGTTTGACAATCTCACTAAAGCCGAGCGCGGCGGACTCTCAGAGCTG GATAAGGCTGGATTCATCAAACGGCAGCTGGTCGAGACTCGGCAGATTACCAAGCACGTGGCGCAGATCTTGGACTCC CGCATGAACACTAAATACGACGAGAACGATAAGCTCATCCGGGAAGTGAAGGTGATTACCCTGAAAAGCAAACTTGTG

		TCGGACTTTCGGAAGGACTTTCAGTTTTACAAAGTGAGAGAAATCAACAACTACCATCACGCGCATGACGCATACCTC AACGCTGTGGTCGGTACCGCCCTGATCAAAAAGTACCCTAAACTTGAATCGGAGTTTGTGTACGGAGACTACAAGGTC TACGACGTGAGGAAGATGATAGCCAAGTCCGAACAGGAAATCGGGAAAGCAACTGCGAAATACTTCTTTTACTCAAAC ATCATGAACTTTTTCAAGACTGAAATTACGCTGGCCAATGGAGAAATCAGGAAGAGGCCACTGATCGAAACTAACGGA GAAACGGGCGAAATCGTGTGGGACAAGGGCAGGGACTTCGCAACTGTTCGCAAAGTGCTCTCTATGCCGCAAGTCAAT ATTGTGAAGAAAACCGAAGTGCAAACCGGCGGATTTTCAAAGGAATCGATCCTCCCAAAGAGAAATAGCGACAAGCTC ATTGCACGCAAGAAAGACTGGGACCCGAAGAAGTACGGAGGATTCGATTCGCCGACTGTCGCATACTCCGTCCTCGTG GTGGCCAAGGTGGAGAAGGGAAAGAGCAAAAAGCTCAAATCCGTCAAAGAGCTGCTGGGGATTACCATCATGGAACGA TCCTCGTTCGAGAAGAACCCGATTGATTTCCTCGAGGCGAAGGGTTACAAGGAGGTGAAGAAGGATCTGATCATCAAA CTCCCCAAGTACTCACTGTTCGAACTGGAAAATGGTCGGAAGCGCATGCTGGCTTCGGCCGGAGAACTCCAAAAAGGA AATGAGCTGGCCTTGCCTAGCAAGTACGTCAACTTCCTCTATCTTGCTTCGCACTACGAAAAACTCAAAGGGTCACCG GAAGATAACGAACAGAAGCAGCTTTTCGTGGAGCAGCACAAGCATTATCTGGATGAAATCATCGAACAAATCTCCGAG TTTTCAAAGCGCGTGATCCTCGCCGACGCCAACCTCGACAAAGTCCTGTCGGCCTACAATAAGCATAGAGATAAGCCG ATCAGAGAACAGGCCGAGAACATTATCCACTTGTTCACCCTGACTAACCTGGGAGCCCCAGCCGCCTTCAAGTACTTC GATACTACTATCGATCGCAAAAGATACACGTCCACCAAGGAAGTTCTGGACGCGACCCTGATCCACCAAAGCATCACT GGACTCTACGAAACTAGGATCGATCTGTCGCAGCTGGGTGGCGATTCTGGTGGTTCTACTAATCTGTCAGATATTATT GAAAAGGAGACCGGTAAGCAACTGGTTATCCAGGAATCCATCCTCATGCTCCCAGAGGAGGTGGAAGAAGTCATTGGG AACAAGCCGGAAAGCGATATACTCGTGCACACCGCCTACGACGAGAGCACCGACGAGAATGTCATGCTTCTGACTAGC GACGCCCCTGAATACAAGCCTTGGGCTCTGGTCATACAGGATAGCAACGGTGAGAACAAGATTAAGATGCTCTCTGGT GGTTCTCCCAAGAAGAAGAGGAAAGTCTAATAG

66	pUC19	GCCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGA GACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCA ACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGC AACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAA CGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGA AGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGA TGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCG GCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGA AAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCT TTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGG AAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATAC ATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAA GAAACCATTATTATCATGACATTAACCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTCTCGCGCGTTTCGGTGAT GACGGTGAAAACCTCTGACACATGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAA GCCCGTCAGGGCGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTAACTATGCGGCATCAGAGCAGATTGTACTG AGAGTGCACCATATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCCATTCGCCATTC AGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCT GCAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTCGAGCTC GGTACCCGGGGATCCTCTAGAGTCGACCTGCAGGCATGCAAGCTTGGCGTAATCATGGTCATAGCTGTTTCCTGTGTG AAATTGTTATCCGCTCACAATTCCACACAACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGT GAGCTAACTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCATTAATG AATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTC GGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGC AGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAG GCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATA CCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTT TCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAA GCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCC GGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTAC AGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGT TACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAA GCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAA CGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATG AAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTAT CTCAGCGATCTGTCTATTTCGTTCATCCATAGTT

67	U6啟動子	TTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTGGAATTAATTTGACTGTAAAC ACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTT AAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACG
68	CMV啟動子	ATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCC GCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGAC TTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAG TCCGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTACGGGACTTTCC TACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACACCAATGGGCGTGG ATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCA ACGGGACTTTCCAAAATGTCGTAACAACTGCGATCGCCCGCCCCGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGG GAGGTCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATC
69	來自人類白蛋白基因之3' UTR	CAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUU UUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGU GCUUCAAUUAAUAAAAAAUGGAAAGAA
70	Cas9切口酶(D10A)之胺基酸序列，具有呈C末端7個胺基酸形式之1x NLS	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

71	使用如表3中所列出之最小尿苷密碼子之編碼SEQ ID NO: 70之Cas9切口酶(D10A)mRNA ORF，具有起始及終止密碼子	AUGGACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAG GUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUG UUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGA AUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGC UUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAA AAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGAC AAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCA AAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAG AACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAA GACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUAC GCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUG GUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGAC GGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUG GUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUG GGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAG AUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGA AUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUC UACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAG GCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUC GAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAG CUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGA AAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUG ACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCA GGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACAC AAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUG CAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGA CUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACA AGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGA CAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAA CUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGAC AGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUG

		GUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUAC CUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAG GUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGC AACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAAC GGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUC AACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAG CUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUG GUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAA AGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUC AAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAG GGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGC CCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGC GAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAG CCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUAC UUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUC ACAGGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAGGAGGAAGCCCGAAGAAGAAGAGAAAG GUCUAG

72	使用如表3中所列出之最小尿苷密碼子的Cas9切口酶(D10A) mRNA編碼序列(無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUC CCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUC GACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUC CUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAG UACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCA CUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAG CUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAG GCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAAC GGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCA GACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACA AAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUC AGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGA GGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUC AAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGA GAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGC GAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUG ACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUAC AACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCA AUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAA UGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAG AUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUG AAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAG ACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACA UUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGA AGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAG CCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUG AAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUG AGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGA AGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAG CUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUG GACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGC AGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUC

		AGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUC UACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAAC AUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGA GAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAAC AUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUG AUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUC GUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAG CUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGA AACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCG GAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAA UUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCG AUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUC GACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAGGAGGAAGCCCGAAGAAGAAGAGAAAGGUC
73	Cas9切口酶之胺基酸序列(無NLS)	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKK NGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEI TKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELL VKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK SEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKK AIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRER MKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLT RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILD SRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYK VYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQV NIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGS PEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKY FDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD

74	使用如表3中所列出之最小尿苷密碼子之編碼SEQ ID NO: 73之Cas9切口酶mRNA ORF，具有起始及終止密碼子	AUGGACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAG GUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUG UUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGA AUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGC UUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAA AAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGAC AAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCA AAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAG AACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAA GACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUAC GCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUG GUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGAC GGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUG GUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUG GGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAG AUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGA AUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUC UACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAG GCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUC GAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAG CUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGA AAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUG ACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCA GGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACAC AAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUG CAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGA CUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACA AGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGA CAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAA CUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGAC AGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUG

		GUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUAC CUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAG GUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGC AACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAAC GGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUC AACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAG CUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUG GUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAA AGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUC AAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAG GGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGC CCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGC GAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAG CCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUAC UUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUC ACAGGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACUAG

75	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 73的Cas9切口酶編碼序列(無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUC CCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUC GACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUC CUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAG UACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCA CUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAG CUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAG GCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAAC GGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCA GACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACA AAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUC AGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGA GGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUC AAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGA GAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGC GAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUG ACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUAC AACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCA AUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAA UGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAG AUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUG AAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAG ACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACA UUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGA AGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAG CCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUG AAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUG AGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGA AGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAG CUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUG GACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGC AGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUC

		AGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUC UACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAAC AUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGA GAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAAC AUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUG AUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUC GUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAG CUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGA AACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCG GAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAA UUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCG AUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUC GACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGAC
76	Cas9切口酶之胺基酸序列，具有呈C末端胺基酸形式之兩個核定位訊號	DKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRI CYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKN GLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEIT KAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLV KLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKS EETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKA IVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTL FEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLT FKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERM KRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTR SDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDS RMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKV YDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMER SSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSP EDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYF DTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGSGSPKKKRKVDGSPKKKRKVDSG

77	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 76之Cas9切口酶mRNA ORF，具有起始及終止密碼子	AUGGACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAG GUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUG UUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGA AUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGC UUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAA AAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGAC AAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCA AAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAG AACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAA GACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUAC GCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUG GUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGAC GGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUG GUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUG GGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAG AUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGA AUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUC UACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAG GCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUC GAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUG AAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAG CUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGA AAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUG ACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCA GGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACAC AAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUG CAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGA CUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACA AGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGA CAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAA CUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGAC AGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUG

		GUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUAC CUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAG GUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGC AACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAAC GGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUC AACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAG CUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUG GUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAA AGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUC AAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAG GGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGC CCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGC GAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAG CCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUAC UUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUC ACAGGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAAGCGGAAGCCCGAAGAAGAAGAGAAAG GUCGACGGAAGCCCGAAGAAGAAGAGAAAGGUCGACAGCGGAUAG

78	使用如表3中所列出之最小尿苷密碼子編碼SEQ ID NO: 76之Cas9切口酶編碼序列(無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGUACAGCAUCGGACUGGCAAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUC CCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUC GACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUC CUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAG UACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCA CUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAG CUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAG GCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAAC GGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCA GACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACA AAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUC AGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGA GGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUC AAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGA GAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGC GAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUG ACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUAC AACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCA AUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAA UGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAG AUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUG AAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAG ACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACA UUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGA AGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAG CCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUG AAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUG AGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGA AGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAG CUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUG GACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGC AGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUC

		AGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUC UACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAAC AUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGA GAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAAC AUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUG AUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUC GUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAG CUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGA AACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCG GAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAA UUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCG AUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUC GACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAAGCGGAAGCCCGAAGAAGAAGAGAAAGGUC GACGGAAGCCCGAAGAAGAAGAGAAAGGUCGACAGCGGA

79	使用表4之低A密碼子、具有起始及終止密碼子之Cas9切口酶ORF	ATGGACAAGAAGTACTCCATCGGCCTGGCCATCGGCACCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTACAAG GTGCCCTCCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCGCCCTGCTG TTCGACTCCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGG ATCTGCTACCTGCAGGAGATCTTCTCCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCACCGGCTGGAGGAGTCC TTCCTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAG AAGTACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAGGCCGACCTGCGGCTGATCTACCTG GCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACTCCGACGTGGAC AAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCTCCGGCGTGGACGCC AAGGCCATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAG AACGGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCCTGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGAG GACGCCAAGCTGCAGCTGTCCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTAC GCCGACCTGTTCCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAACACCGAGATC ACCAAGGCCCCCCTGTCCGCCTCCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTG GTGCGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCTACGCCGGCTACATCGAC GGCGGCGCCTCCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTG GTGAAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCTCCATCCCCCACCAGATCCACCTG GGCGAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAG ATCCTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACTCCCGGTTCGCCTGGATGACCCGGAAG TCCGAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGG ATGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCGTG TACAACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAGAAGAAG GCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATC GAGTGCTTCGACTCCGTGGAGATCTCCGGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCTACCACGACCTGCTG AAGATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACC CTGTTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAG CTGAAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGC AAGACCATCCTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACTCCCTG ACCTTCAAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAGGGCGACTCCCTGCACGAGCACATCGCCAACCTGGCC GGCTCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCAC AAGCCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCCCGGGAGCGG ATGAAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTG CAGAACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGG CTGTCCGACTACGACGTGGACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCCATCGACAACAAGGTGCTGACC CGGTCCGACAAGAACCGGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGG CAGCTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGTCCGAG CTGGACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGAC TCCCGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCTG

		GTGTCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACTCC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGTCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAGGGCTCC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCTCC GAGTTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGTCCATC ACCGGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACGGCGGCGGCTCCCCCAAGAAGAAGCGGAAG GTGTGA

80	Cas9 nickase ORF 使用表4之低A密碼子，具有起始及終止密碼子且無NLS	ATGGACAAGAAGTACTCCATCGGCCTGGCCATCGGCACCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTACAAG GTGCCCTCCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCGCCCTGCTG TTCGACTCCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGG ATCTGCTACCTGCAGGAGATCTTCTCCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCACCGGCTGGAGGAGTCC TTCCTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAG AAGTACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAGGCCGACCTGCGGCTGATCTACCTG GCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACTCCGACGTGGAC AAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCTCCGGCGTGGACGCC AAGGCCATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAG AACGGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCCTGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGAG GACGCCAAGCTGCAGCTGTCCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTAC GCCGACCTGTTCCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAACACCGAGATC ACCAAGGCCCCCCTGTCCGCCTCCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTG GTGCGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCTACGCCGGCTACATCGAC GGCGGCGCCTCCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTG GTGAAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCTCCATCCCCCACCAGATCCACCTG GGCGAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAG ATCCTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACTCCCGGTTCGCCTGGATGACCCGGAAG TCCGAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGG ATGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCGTG TACAACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAGAAGAAG GCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATC GAGTGCTTCGACTCCGTGGAGATCTCCGGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCTACCACGACCTGCTG AAGATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACC CTGTTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAG CTGAAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGC AAGACCATCCTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACTCCCTG ACCTTCAAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAGGGCGACTCCCTGCACGAGCACATCGCCAACCTGGCC GGCTCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCAC AAGCCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCCCGGGAGCGG ATGAAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTG CAGAACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGG CTGTCCGACTACGACGTGGACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCCATCGACAACAAGGTGCTGACC CGGTCCGACAAGAACCGGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGG CAGCTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGTCCGAG CTGGACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGAC TCCCGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCTG

		GTGTCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACTCC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGTCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAGGGCTCC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCTCC GAGTTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGTCCATC ACCGGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACTGA

81	使用表4之低A密碼子、具有兩個C末端NLS序列以及起始及終止密碼子之Cas9切口酶ORF	ATGGACAAGAAGTACTCCATCGGCCTGGCCATCGGCACCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTACAAG GTGCCCTCCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCGCCCTGCTG TTCGACTCCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGG ATCTGCTACCTGCAGGAGATCTTCTCCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCACCGGCTGGAGGAGTCC TTCCTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAG AAGTACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAGGCCGACCTGCGGCTGATCTACCTG GCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACTCCGACGTGGAC AAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCTCCGGCGTGGACGCC AAGGCCATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAG AACGGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCCTGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGAG GACGCCAAGCTGCAGCTGTCCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTAC GCCGACCTGTTCCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAACACCGAGATC ACCAAGGCCCCCCTGTCCGCCTCCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTG GTGCGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCTACGCCGGCTACATCGAC GGCGGCGCCTCCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTG GTGAAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCTCCATCCCCCACCAGATCCACCTG GGCGAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAG ATCCTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACTCCCGGTTCGCCTGGATGACCCGGAAG TCCGAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGG ATGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCGTG TACAACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAGAAGAAG GCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATC GAGTGCTTCGACTCCGTGGAGATCTCCGGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCTACCACGACCTGCTG AAGATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACC CTGTTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAG CTGAAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGC AAGACCATCCTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACTCCCTG ACCTTCAAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAGGGCGACTCCCTGCACGAGCACATCGCCAACCTGGCC GGCTCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCAC AAGCCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCCCGGGAGCGG ATGAAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTG CAGAACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGG CTGTCCGACTACGACGTGGACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCCATCGACAACAAGGTGCTGACC CGGTCCGACAAGAACCGGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGG CAGCTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGTCCGAG CTGGACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGAC TCCCGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCTG

		GTGTCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACTCC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGTCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAGGGCTCC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCTCC GAGTTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGTCCATC ACCGGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACGGCTCCGGCTCCCCCAAGAAGAAGCGGAAG GTGGACGGCTCCCCCAAGAAGAAGCGGAAGGTGGACTCCGGCTGA

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		GTGAGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGAGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGC GAGTTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATC ACCGGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGACGGCGGCGGCAGCCCCAAGAAGAAGCGGAAG GTGTGA

83	使用表4之低A/U密碼子、具有兩個C末端NLS序列以及起始及終止密碼子之Cas9切口酶ORF	ATGGACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACAGCGTGGGCTGGGCCGTGATCACCGACGAGTACAAG GTGCCCAGCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGCGCCCTGCTG TTCGACAGCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGG ATCTGCTACCTGCAGGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACCGGCTGGAGGAGAGC TTCCTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAG AAGTACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTACCTG GCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACGTGGAC AAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCAGCGGCGTGGACGCC AAGGCCATCCTGAGCGCCCGGCTGAGCAAGAGCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAG AACGGCCTGTTCGGCAACCTGATCGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAG GACGCCAAGCTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTAC GCCGACCTGTTCCTGGCCGCCAAGAACCTGAGCGACGCCATCCTGCTGAGCGACATCCTGCGGGTGAACACCGAGATC ACCAAGGCCCCCCTGAGCGCCAGCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTG GTGCGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACATCGAC GGCGGCGCCAGCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTG GTGAAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGATCCACCTG GGCGAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAG ATCCTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACAGCCGGTTCGCCTGGATGACCCGGAAG AGCGAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCAGCGCCCAGAGCTTCATCGAGCGG ATGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTG TACAACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGAGCGGCGAGCAGAAGAAG GCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATC GAGTGCTTCGACAGCGTGGAGATCAGCGGCGTGGAGGACCGGTTCAACGCCAGCCTGGGCACCTACCACGACCTGCTG AAGATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACC CTGTTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAG CTGAAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGAGCGGC AAGACCATCCTGGACTTCCTGAAGAGCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACAGCCTG ACCTTCAAGGAGGACATCCAGAAGGCCCAGGTGAGCGGCCAGGGCGACAGCCTGCACGAGCACATCGCCAACCTGGCC GGCAGCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCAC AAGCCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACAGCCGGGAGCGG ATGAAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCAGCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTG CAGAACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGG CTGAGCGACTACGACGTGGACCACATCGTGCCCCAGAGCTTCCTGAAGGACGACAGCATCGACAACAAGGTGCTGACC CGGAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCAGCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGG CAGCTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGAGCGAG CTGGACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGAC AGCCGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGAGCAAGCTG

		GTGAGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGAGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGC GAGTTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATC ACCGGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGACGGCAGCGGCAGCCCCAAGAAGAAGCGGAAG GTGGACGGCAGCCCCAAGAAGAAGCGGAAGGTGGACAGCGGCTGA

84	使用表4之低A/U密碼子、具有起始及終止密碼子且無NLS的Cas9切口酶ORF	ATGGACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACAGCGTGGGCTGGGCCGTGATCACCGACGAGTACAAG GTGCCCAGCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGCGCCCTGCTG TTCGACAGCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGG ATCTGCTACCTGCAGGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACCGGCTGGAGGAGAGC TTCCTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAG AAGTACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTACCTG GCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACGTGGAC AAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCAGCGGCGTGGACGCC AAGGCCATCCTGAGCGCCCGGCTGAGCAAGAGCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAG AACGGCCTGTTCGGCAACCTGATCGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAG GACGCCAAGCTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTAC GCCGACCTGTTCCTGGCCGCCAAGAACCTGAGCGACGCCATCCTGCTGAGCGACATCCTGCGGGTGAACACCGAGATC ACCAAGGCCCCCCTGAGCGCCAGCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTG GTGCGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACATCGAC GGCGGCGCCAGCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTG GTGAAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGATCCACCTG GGCGAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAG ATCCTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACAGCCGGTTCGCCTGGATGACCCGGAAG AGCGAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCAGCGCCCAGAGCTTCATCGAGCGG ATGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTG TACAACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGAGCGGCGAGCAGAAGAAG GCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATC GAGTGCTTCGACAGCGTGGAGATCAGCGGCGTGGAGGACCGGTTCAACGCCAGCCTGGGCACCTACCACGACCTGCTG AAGATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACC CTGTTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAG CTGAAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGAGCGGC AAGACCATCCTGGACTTCCTGAAGAGCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACAGCCTG ACCTTCAAGGAGGACATCCAGAAGGCCCAGGTGAGCGGCCAGGGCGACAGCCTGCACGAGCACATCGCCAACCTGGCC GGCAGCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCAC AAGCCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACAGCCGGGAGCGG ATGAAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCAGCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTG CAGAACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGG CTGAGCGACTACGACGTGGACCACATCGTGCCCCAGAGCTTCCTGAAGGACGACAGCATCGACAACAAGGTGCTGACC CGGAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCAGCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGG CAGCTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGAGCGAG CTGGACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGAC AGCCGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGAGCAAGCTG

		GTGAGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTAC CTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAG GTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGC AACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAAC GGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTG AACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAG CTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTG GTGGTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAG CGGAGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAG GGCAACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGC CCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGC GAGTTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAG CCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTAC TTCGACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATC ACCGGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGACTGA

85	使用表4之低A密碼子之Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGTACTCCATCGGCCTGGCCATCGGCACCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTG CCCTCCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCGCCCTGCTGTTC GACTCCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGGATC TGCTACCTGCAGGAGATCTTCTCCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCACCGGCTGGAGGAGTCCTTC CTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAG TACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAGGCCGACCTGCGGCTGATCTACCTGGCC CTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACTCCGACGTGGACAAG CTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCTCCGGCGTGGACGCCAAG GCCATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAAC GGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCCTGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGAGGAC GCCAAGCTGCAGCTGTCCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTCCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAACACCGAGATCACC AAGGCCCCCCTGTCCGCCTCCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTGGTG CGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCTACGCCGGCTACATCGACGGC GGCGCCTCCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTGGTG AAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCTCCATCCCCCACCAGATCCACCTGGGC GAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAGATC CTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACTCCCGGTTCGCCTGGATGACCCGGAAGTCC GAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGGATG ACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCGTGTAC AACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAGAAGAAGGCC ATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATCGAG TGCTTCGACTCCGTGGAGATCTCCGGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCTACCACGACCTGCTGAAG ATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACCCTG TTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAGCTG AAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAG ACCATCCTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACTCCCTGACC TTCAAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAGGGCGACTCCCTGCACGAGCACATCGCCAACCTGGCCGGC TCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCACAAG CCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCCCGGGAGCGGATG AAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTGCAG AACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGGCTG TCCGACTACGACGTGGACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCCATCGACAACAAGGTGCTGACCCGG TCCGACAAGAACCGGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGGCAG CTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGTCCGAGCTG GACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGACTCC CGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCTGGTG

		TCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGACTACAAGGTG TACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACTCCAAC ATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAACGGC GAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCCCAGGTGAAC ATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCCGACAAGCTG ATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCCGTGCTGGTG GTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATCATGGAGCGG TCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATCAAG CTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCAGAAGGGC AACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAGGGCTCCCCC GAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCTCCGAG TTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGGGACAAGCCC ATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTACTTC GACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGTCCATCACC GGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACGGCGGCGGCTCCCCCAAGAAGAAGCGGAAGGTG

86	使用表4之低A密碼子之Cas9切口酶ORF (無NLS且無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGTACTCCATCGGCCTGGCCATCGGCACCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTG CCCTCCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCGCCCTGCTGTTC GACTCCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGGATC TGCTACCTGCAGGAGATCTTCTCCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCACCGGCTGGAGGAGTCCTTC CTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAG TACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAGGCCGACCTGCGGCTGATCTACCTGGCC CTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACTCCGACGTGGACAAG CTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCTCCGGCGTGGACGCCAAG GCCATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAAC GGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCCTGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGAGGAC GCCAAGCTGCAGCTGTCCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTCCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAACACCGAGATCACC AAGGCCCCCCTGTCCGCCTCCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTGGTG CGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCTACGCCGGCTACATCGACGGC GGCGCCTCCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTGGTG AAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCTCCATCCCCCACCAGATCCACCTGGGC GAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAGATC CTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACTCCCGGTTCGCCTGGATGACCCGGAAGTCC GAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGGATG ACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCGTGTAC AACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAGAAGAAGGCC ATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATCGAG TGCTTCGACTCCGTGGAGATCTCCGGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCTACCACGACCTGCTGAAG ATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACCCTG TTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAGCTG AAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAG ACCATCCTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACTCCCTGACC TTCAAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAGGGCGACTCCCTGCACGAGCACATCGCCAACCTGGCCGGC TCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCACAAG CCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCCCGGGAGCGGATG AAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTGCAG AACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGGCTG TCCGACTACGACGTGGACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCCATCGACAACAAGGTGCTGACCCGG TCCGACAAGAACCGGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGGCAG CTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGTCCGAGCTG GACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGACTCC CGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCTGGTG

		TCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGACTACAAGGTG TACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACTCCAAC ATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAACGGC GAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCCCAGGTGAAC ATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCCGACAAGCTG ATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCCGTGCTGGTG GTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATCATGGAGCGG TCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATCAAG CTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCAGAAGGGC AACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAGGGCTCCCCC GAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCTCCGAG TTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGGGACAAGCCC ATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTACTTC GACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGTCCATCACC GGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGAC

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		AAGCTGGTGTCCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGAC GCCTACCTGAACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGCGAC TACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTC TACTCCAACATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAG ACCAACGGCGAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGTCCATGCCC CAGGTGAACATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATCCTGCCCAAGCGGAACTCC GACAAGCTGATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACTCCCCCACCGTGGCCTACTCC GTGCTGGTGGTGGCCAAGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCGTGAAGGAGCTGCTGGGCATCACCATC ATGGAGCGGTCCTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTG ATCATCAAGCTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTG CAGAAGGGCAACGAGCTGGCCCTGCCCTCCAAGTACGTGAACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGAAG GGCTCCCCCGAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAG ATCTCCGAGTTCTCCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAACAAGCACCGG GACAAGCCCATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTC AAGTACTTCGACACCACCATCGACCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAG TCCATCACCGGCCTGTACGAGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACGGCTCCGGCTCCCCCAAGAAGAAG CGGAAGGTGGACGGCTCCCCCAAGAAGAAGCGGAAGGTGGACTCCGGC

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		AGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAGGTG TACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGCAAC ATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAACGGC GAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTGAAC ATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAGCTG ATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTGGTG GTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAGCGG AGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATCAAG CTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAGGGC AACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGCCCC GAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAG TTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAGCCC ATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTACTTC GACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACC GGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGACGGCGGCGGCAGCCCCAAGAAGAAGCGGAAGGTG

89	使用表4之低A/U密碼子、具有兩個C末端NLS序列之Cas9切口酶ORF (無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACAGCGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTG CCCAGCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGCGCCCTGCTGTTC GACAGCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGGATC TGCTACCTGCAGGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACCGGCTGGAGGAGAGCTTC CTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAG TACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTACCTGGCC CTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACGTGGACAAG CTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCAGCGGCGTGGACGCCAAG GCCATCCTGAGCGCCCGGCTGAGCAAGAGCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAAC GGCCTGTTCGGCAACCTGATCGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGAC GCCAAGCTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTCCTGGCCGCCAAGAACCTGAGCGACGCCATCCTGCTGAGCGACATCCTGCGGGTGAACACCGAGATCACC AAGGCCCCCCTGAGCGCCAGCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTGGTG CGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACATCGACGGC GGCGCCAGCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTGGTG AAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGATCCACCTGGGC GAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAGATC CTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACAGCCGGTTCGCCTGGATGACCCGGAAGAGC GAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCAGCGCCCAGAGCTTCATCGAGCGGATG ACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTGTAC AACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGAGCGGCGAGCAGAAGAAGGCC ATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATCGAG TGCTTCGACAGCGTGGAGATCAGCGGCGTGGAGGACCGGTTCAACGCCAGCCTGGGCACCTACCACGACCTGCTGAAG ATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACCCTG TTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAGCTG AAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGAGCGGCAAG ACCATCCTGGACTTCCTGAAGAGCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACAGCCTGACC TTCAAGGAGGACATCCAGAAGGCCCAGGTGAGCGGCCAGGGCGACAGCCTGCACGAGCACATCGCCAACCTGGCCGGC AGCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCACAAG CCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACAGCCGGGAGCGGATG AAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCAGCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTGCAG AACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGGCTG AGCGACTACGACGTGGACCACATCGTGCCCCAGAGCTTCCTGAAGGACGACAGCATCGACAACAAGGTGCTGACCCGG AGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCAGCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGGCAG CTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGAGCGAGCTG GACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGACAGC CGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGAGCAAGCTGGTG

		AGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAGGTG TACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGCAAC ATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAACGGC GAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTGAAC ATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAGCTG ATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTGGTG GTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAGCGG AGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATCAAG CTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAGGGC AACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGCCCC GAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAG TTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAGCCC ATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTACTTC GACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACC GGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGACGGCAGCGGCAGCCCCAAGAAGAAGCGGAAGGTG GACGGCAGCCCCAAGAAGAAGCGGAAGGTGGACAGCGGC

90	使用表4之低A/U密碼子之Cas9切口酶ORF(無NLS且無起始或終止密碼子；適合於包括於融合蛋白質編碼序列中)	GACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACAGCGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTG CCCAGCAAGAAGTTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGCGCCCTGCTGTTC GACAGCGGCGAGACCGCCGAGGCCACCCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGGCGGAAGAACCGGATC TGCTACCTGCAGGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACCGGCTGGAGGAGAGCTTC CTGGTGGAGGAGGACAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAG TACCCCACCATCTACCACCTGCGGAAGAAGCTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTACCTGGCC CTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACGTGGACAAG CTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAGAACCCCATCAACGCCAGCGGCGTGGACGCCAAG GCCATCCTGAGCGCCCGGCTGAGCAAGAGCCGGCGGCTGGAGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAAC GGCCTGTTCGGCAACCTGATCGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGAC GCCAAGCTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTCCTGGCCGCCAAGAACCTGAGCGACGCCATCCTGCTGAGCGACATCCTGCGGGTGAACACCGAGATCACC AAGGCCCCCCTGAGCGCCAGCATGATCAAGCGGTACGACGAGCACCACCAGGACCTGACCCTGCTGAAGGCCCTGGTG CGGCAGCAGCTGCCCGAGAAGTACAAGGAGATCTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACATCGACGGC GGCGCCAGCCAGGAGGAGTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATGGACGGCACCGAGGAGCTGCTGGTG AAGCTGAACCGGGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGATCCACCTGGGC GAGCTGCACGCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCTGAAGGACAACCGGGAGAAGATCGAGAAGATC CTGACCTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGGGCAACAGCCGGTTCGCCTGGATGACCCGGAAGAGC GAGGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTGGACAAGGGCGCCAGCGCCCAGAGCTTCATCGAGCGGATG ACCAACTTCGACAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTGTAC AACGAGCTGACCAAGGTGAAGTACGTGACCGAGGGCATGCGGAAGCCCGCCTTCCTGAGCGGCGAGCAGAAGAAGGCC ATCGTGGACCTGCTGTTCAAGACCAACCGGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTTCAAGAAGATCGAG TGCTTCGACAGCGTGGAGATCAGCGGCGTGGAGGACCGGTTCAACGCCAGCCTGGGCACCTACCACGACCTGCTGAAG ATCATCAAGGACAAGGACTTCCTGGACAACGAGGAGAACGAGGACATCCTGGAGGACATCGTGCTGACCCTGACCCTG TTCGAGGACCGGGAGATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGTTCGACGACAAGGTGATGAAGCAGCTG AAGCGGCGGCGGTACACCGGCTGGGGCCGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGAGCGGCAAG ACCATCCTGGACTTCCTGAAGAGCGACGGCTTCGCCAACCGGAACTTCATGCAGCTGATCCACGACGACAGCCTGACC TTCAAGGAGGACATCCAGAAGGCCCAGGTGAGCGGCCAGGGCGACAGCCTGCACGAGCACATCGCCAACCTGGCCGGC AGCCCCGCCATCAAGAAGGGCATCCTGCAGACCGTGAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCGGCACAAG CCCGAGAACATCGTGATCGAGATGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACAGCCGGGAGCGGATG AAGCGGATCGAGGAGGGCATCAAGGAGCTGGGCAGCCAGATCCTGAAGGAGCACCCCGTGGAGAACACCCAGCTGCAG AACGAGAAGCTGTACCTGTACTACCTGCAGAACGGCCGGGACATGTACGTGGACCAGGAGCTGGACATCAACCGGCTG AGCGACTACGACGTGGACCACATCGTGCCCCAGAGCTTCCTGAAGGACGACAGCATCGACAACAAGGTGCTGACCCGG AGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCAGCGAGGAGGTGGTGAAGAAGATGAAGAACTACTGGCGGCAG CTGCTGAACGCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGACCAAGGCCGAGCGGGGCGGCCTGAGCGAGCTG GACAAGGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGGCAGATCACCAAGCACGTGGCCCAGATCCTGGACAGC CGGATGAACACCAAGTACGACGAGAACGACAAGCTGATCCGGGAGGTGAAGGTGATCACCCTGAAGAGCAAGCTGGTG

		AGCGACTTCCGGAAGGACTTCCAGTTCTACAAGGTGCGGGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTGGTGGGCACCGCCCTGATCAAGAAGTACCCCAAGCTGGAGAGCGAGTTCGTGTACGGCGACTACAAGGTG TACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTACTTCTTCTACAGCAAC ATCATGAACTTCTTCAAGACCGAGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCCCCTGATCGAGACCAACGGC GAGACCGGCGAGATCGTGTGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGGTGCTGAGCATGCCCCAGGTGAAC ATCGTGAAGAAGACCGAGGTGCAGACCGGCGGCTTCAGCAAGGAGAGCATCCTGCCCAAGCGGAACAGCGACAAGCTG ATCGCCCGGAAGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTACAGCGTGCTGGTG GTGGCCAAGGTGGAGAAGGGCAAGAGCAAGAAGCTGAAGAGCGTGAAGGAGCTGCTGGGCATCACCATCATGGAGCGG AGCAGCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCCAAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATCAAG CTGCCCAAGTACAGCCTGTTCGAGCTGGAGAACGGCCGGAAGCGGATGCTGGCCAGCGCCGGCGAGCTGCAGAAGGGC AACGAGCTGGCCCTGCCCAGCAAGTACGTGAACTTCCTGTACCTGGCCAGCCACTACGAGAAGCTGAAGGGCAGCCCC GAGGACAACGAGCAGAAGCAGCTGTTCGTGGAGCAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAG TTCAGCAAGCGGGTGATCCTGGCCGACGCCAACCTGGACAAGGTGCTGAGCGCCTACAACAAGCACCGGGACAAGCCC ATCCGGGAGCAGGCCGAGAACATCATCCACCTGTTCACCCTGACCAACCTGGGCGCCCCCGCCGCCTTCAAGTACTTC GACACCACCATCGACCGGAAGCGGTACACCAGCACCAAGGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACC GGCCTGTACGAGACCCGGATCGACCTGAGCCAGCTGGGCGGCGAC
91	例示性5' UTR	ACATTTGCTTCTGACACAACTGTGTTCACTAGCAACCTCAAACAGACACC
92	例示性5' UTR	CATAAACCCTGGCGCGCTCGCGGCCCGGCACTCTTCTGGTCCCCACAGACTCAGAGAGAACCCACC
93	例示性5' UTR	AAGCTCAGAATAAACGCTCAACTTTGGCC
94	例示性5' UTR	CAGGGTCCTGTGGACAGCTCACCAGCT
95	例示性5' UTR	TCCCGCAGTCGGCGTCCAGCGGCTCTGCTTGTTCGTGTGTGTGTCGTTGCAGGCCTTATTC
96	例示性5' UTR	CAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCAT
97	例示性5' UTR	AGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGG
98	例示性5' UTR	TGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACTCACCG
99	例示性3' UTR	GCTCGCTTTCTTGCTGTCCAATTTCTATTAAAGGTTCCTTTGTTCCCTAAGTCCAACTACTAAACTGGGGGATATTAT GAAGGGCCTTGAGCATCTGGATTCTGCCTAATAAAAAACATTTATTTTCATTGC
100	例示性3' UTR	GCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCACCCGTACCCC CGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC
101	例示性3' UTR	ACCAGCCTCAAGAACACCCGAATGGAGTCTCTAAGCTACATAATACCAACTTACACTTTACAAAATGTTGTCCCCCAA AATGTAGCCATTCGTATCTGCTCCTAATAAAAAGAAAGTTTCTTCACATTCT
102	例示性3' UTR	TTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTA ATAAAATGAGGAAATTGCATCGCA
103	例示性3' UTR	GCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTCTCTCCCTTGCACCTGTACCTCTTGGTCTTTGAATAA AGCCTGAGTAGGAAG

104	例示性3' UTR	CTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCA GGTATGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAATGCAGC TCAAAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACTAA GCTATACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACC
105	例示性3' UTR	CAAGCACGCAGCAATGCAGCTCAAAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCA ATAAACGAAAGTTTAACTAAGCTATACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTGGTACTGCATGC ACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCAGGTATGCTCCCACC TCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCC
106	例示性3' UTR	ACCAGCCTCAAGAACACCCGAATGGAGTCTCTAAGCTACATAATACCAACTTACACTTTACAAAATGTTGTCCCCCAA AATGTAGCCATTCGTATCTGCTCCTAATAAAAAGAAAGTTTCTTCACATTCTACCAGCCTCAAGAACACCCGAATGGA GTCTCTAAGCTACATAATACCAACTTACACTTTACAAAATGTTGTCCCCCAAAATGTAGCCATTCGTATCTGCTCCTA ATAAAAAGAAAGTTTCTTCACATTCT
107	例示性Kozak序列	GCCRCCAUGG
108	例示性Kozak序列	GCCGCCRCCAUGG
109	例示性poly-A序列	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAA
110	例示性NLS 1	LAAKRSRTT
111	例示性NLS 2	QAAKRSRTT
112	例示性NLS 3	PAPAKRERTT
113	例示性NLS 4	QAAKRPRTT
114	例示性NLS 5	RAAKRPRTT
115	例示性NLS 6	AAAKRSWSMAA
116	例示性NLS 7	AAAKRVWSMAF
117	例示性NLS 8	AAAKRSWSMAF
118	例示性NLS 9	AAAKRKYFAA
119	例示性NLS 10	RAAKRKAFAA
120	例示性NLS 11	RAAKRKYFAV
121	替代SV40 NLS	PKKKRRV
122	核質蛋白NLS	KRPAATKKAGQAKKKK
123	用於SV40 NLS之例示性編碼序列	CCGAAGAAGAAGAGAAAGGTC

124	用於NLS1之例示性編碼序列	CTGGCAGCAAAGAGAAGCAGAACAACA
125	用於NLS2之例示性編碼序列	CAGGCAGCAAAGAGAAGCAGAACAACA
126	用於NLS3之例示性編碼序列	CCGGCACCGGCAAAGAGAGAAAGAACAACA
127	用於NLS4之例示性編碼序列	CAGGCAGCAAAGAGACCGAGAACAACA
128	用於NLS5之例示性編碼序列	AGAGCAGCAAAGAGACCGAGAACAACA
129	用於NLS6之例示性編碼序列	GCAGCAGCAAAGAGAAGCTGGAGCATGGCAGCA
130	用於NLS7之例示性編碼序列	GCAGCAGCAAAGAGAGTCTGGAGCATGGCATTC
131	用於NLS8之例示性編碼序列	GCAGCAGCAAAGAGAAGCTGGAGCATGGCATTC
132	用於NLS9之例示性編碼序列	GCAGCAGCAAAGAGAAAGTACTTCGCAGCA
133	用於NLS10之例示性編碼序列	AGAGCAGCAAAGAGAAAGGCATTCGCAGCA
134	用於NLS11之例示性編碼序列	AGAGCAGCAAAGAGAAAGTACTTCGCAGTC
135	用於替代SV40 NLS之例示性編碼序列	CCGAAGAAGAAGAGAAGAGTC
136-138	未使用	未使用
139	在導引序列之3'端之後形成crRNA的例示性核苷酸序列	GUUUUAGAGCUAUGCUGUUUUG

140	spyCas9 sgRNA之保守部分	GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC
141	經修飾之sgRNA圖案，其中N為編碼導引序列之核苷酸	mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
142	例示性導引恆定區修飾模式(G282-C)	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
143	例示性導引修飾模式(G282-mN3Nx)	mN*mN*mN*(N)xGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
144	例示性導引修飾模式(G282-Nx)	(N)xGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
145	例示性導引修飾模式(G282-N20)	mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
146		GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
147-150		未使用
151	例示性導引序列	UAAGGCCAGUGGAAAGAAUU
152	用於B2M基因之例示性導引序列	UUACCCCACUUAACUAUCUU
153	用於TTR基因之例示性導引序列	UUACAGCCACGUCUACAGCA
154	用於TRAC基因之例示性導引序列	UUCAAAACCUGUCAGUGAUU
155	用於TRBC1/2基因之例示性導引序列	CGCUGUCAAGUCCAGUUCUA
156	例示性導引序列	CCUUCCGAAAGAGGCCCCCC
157	用於SERPINA1基因之例示性導引序列	UCCCUGGCUGAGGAUCCCCA

158	用於SERPINA1基因之例示性導引序列	ACUCACGAUGAAAUCCUGGA
159	例示性導引序列	CCCCCCGCCGUGUUUGUGGG
160	用於CIITA基因之例示性導引序列	GAGCCCCCCACUGUGGUGAC
161	用於CIITA基因之例示性目標序列	ACCGGCUCUGCAAAGGCCAG
162	用於CIITA基因之例示性目標序列	CACCGGCUCUGCAAAGGCCA
163	用於CIITA基因之例示性目標序列	CCACCGGCUCUGCAAAGGCC
164	用於CIITA基因之例示性目標序列	CUGCUCCACCGGCUCUGCAA
165	用於CIITA基因之例示性目標序列	CUGUGUCACCCGUUUCAGGU
166	用於CIITA基因之例示性目標序列	UGUGUCACCCGUUUCAGGUG
167	用於CIITA基因之例示性目標序列	ACCCGUUUCAGGUGGGGUGA
168	用於CIITA基因之例示性目標序列	CCCGUUUCAGGUGGGGUGAG
169	用於CIITA基因之例示性目標序列	UGUGCAGACUCAGAGGUGAG
170	用於CIITA基因之例示性目標序列	CAGCGCAUCCAGGCUGCAGG
171	用於CIITA基因之例示性目標序列	GCGUCCACAUCCUGCAAGGG
172	用於CIITA基因之例示性目標序列	GGCGUCCACAUCCUGCAAGG

173	用於CIITA基因之例示性目標序列	UGGGCGUCCACAUCCUGCAA
174-176	未使用	
177	靶向TRAC之G013009導引RNA	mU*mA*mG*GCAGACAGACUUGUCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
178	靶向TRAC之G016016導引RNA	mU*mU*mU*CAAAACCUGUCAGUGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
179	靶向B2M之G015991導引RNA	mA*mC*mU*CACGCUGGAUAGCCUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
180	靶向B2M之G015996導引RNA	mC*mU*mU*ACCCCACUUAACUAUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
181	G000297導引RNA	mU*mA*mA*GGCCAGUGGAAAGAAUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmU*mU*mU*U
182	G015995導引RNA	mU*mU*mA*CCCCACUUAACUAUCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
183	G000282導引RNA	mU*mU*mA*CAGCCACGUCUACAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
184	靶向具有導引序列SEQ ID NO: 154之TRAC之G016017導引RNA	mU*mU*mC*AAAACCUGUCAGUGAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
185	靶向具有導引序列SEQ ID NO: 155之TRBC1/2之G016206導引RNA	mC*mG*mC*UGUCAAGUCCAGUUCUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
186	SG000296導引RNA	CCUUCCGAAAGAGGCCCCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
187	SG001373導引RNA	UCCCUGGCUGAGGAUCCCCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
188	SG001400導引RNA	ACUCACGAUGAAAUCCUGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU

189	SG005883導引RNA	CCCCCCGCCGUGUUUGUGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
190	靶向具有導引序列SEQ ID NO: 160之CIITA之SG003018導引RNA	GAGCCCCCCACUGUGGUGACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
191	靶向具有導引序列SEQ ID NO: 161之CIITA之G018075導引RNA	mA*mC*mC*GGCUCUGCAAAGGCCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
192	靶向具有導引序列SEQ ID NO: 162之CIITA之G018076導引RNA	mC*mA*mC*CGGCUCUGCAAAGGCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
193	靶向具有導引序列SEQ ID NO: 163之CIITA之G018077導引RNA	mC*mC*mA*CCGGCUCUGCAAAGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
194	靶向具有導引序列SEQ ID NO: 164之CIITA之G018078導引RNA	mC*mU*mG*CUCCACCGGCUCUGCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
195	靶向具有導引序列SEQ ID NO: 165之CIITA之G018081導引RNA	mC*mU*mG*UGUCACCCGUUUCAGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
196	靶向具有導引序列SEQ ID NO: 166之CIITA之G018082導引RNA	mU*mG*mU*GUCACCCGUUUCAGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

197	靶向具有導引序列SEQ ID NO: 167之CIITA之G018084導引RNA	mA*mC*mC*CGUUUCAGGUGGGGUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
198	靶向具有導引序列SEQ ID NO: 168之CIITA之G018085導引RNA	mC*mC*mC*GUUUCAGGUGGGGUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
199	靶向具有導引序列SEQ ID NO: 169之CIITA之G018091導引RNA	mU*mG*mU*GCAGACUCAGAGGUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
200	靶向具有導引序列SEQ ID NO: 170之CIITA之G018100導引RNA	mC*mA*mG*CGCAUCCAGGCUGCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
201	靶向具有導引序列SEQ ID NO: 171之CIITA之G018117導引RNA	mG*mC*mG*UCCACAUCCUGCAAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
202	靶向具有導引序列SEQ ID NO: 172之CIITA之G018118導引RNA	mG*mG*mC*GUCCACAUCCUGCAAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
203	靶向具有導引序列SEQ ID NO: 173之CIITA之G018120導引RNA	mU*mG*mG*GCGUCCACAUCCUGCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
204-210		未使用

211	用於例示性連接子之胺基酸序列	GGS
212	用於例示性連接子之胺基酸序列	GGGGS
213	用於例示性連接子之胺基酸序列	EAAAK
214	用於例示性連接子之胺基酸序列	SEGSA
215	用於例示性連接子之胺基酸序列	SEGSAGTST
216	用於例示性連接子之胺基酸序列	GGGGSGGGGS
217	用於例示性連接子之胺基酸序列	GGGGSEAAAK
218	用於例示性連接子之胺基酸序列	EAAAKGGGGS
219	用於例示性連接子之胺基酸序列	EAAAKEAAAK
220	用於例示性連接子之胺基酸序列	SEGSAGTSTESEGSA
221	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGS
222	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAK
223	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGS
224	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAK

225	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGS
226	用於例示性連接子之胺基酸序列	SEGSAGTSTESEGSAGTSTE
227	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSEAAAK
228	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKGGGGS
229	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSEAAAK
230	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKGGGGS
231	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKEAAAK
232	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSGGGGS
233	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSEAAAK
234	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKGGGGS
235	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKEAAAK
236	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSGGGGS
237	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSEAAAK
238	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKGGGGS

239	用於例示性連接子之胺基酸序列	SEGSAGTSTESEGSAGTSTESEGSA
240	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSGGGGSGGGGS
241	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSGGGGSEAAAK
242	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSEAAAKGGGGS
243	用於例示性連接子之胺基酸序列	GGGGSGGGGSGGGGSEAAAKEAAAK
244	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKGGGGSGGGGS
245	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKGGGGSEAAAK
246	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKEAAAKGGGGS
247	用於例示性連接子之胺基酸序列	GGGGSGGGGSEAAAKEAAAKEAAAK
248	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSGGGGSGGGGS
249	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSGGGGSEAAAK
250	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSEAAAKGGGGS
251	用於例示性連接子之胺基酸序列	GGGGSEAAAKGGGGSEAAAKEAAAK
252	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKGGGGSGGGGS

253	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKEAAAKGGGGS
254	用於例示性連接子之胺基酸序列	GGGGSEAAAKEAAAKEAAAKEAAAK
255	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSGGGGSGGGGS
256	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSGGGGSEAAAK
257	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSEAAAKGGGGS
258	用於例示性連接子之胺基酸序列	EAAAKGGGGSGGGGSEAAAKEAAAK
259	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKGGGGSGGGGS
260	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKGGGGSEAAAK
261	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKEAAAKGGGGS
262	用於例示性連接子之胺基酸序列	EAAAKGGGGSEAAAKEAAAKEAAAK
263	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSEAAAKGGGGS
264	用於例示性連接子之胺基酸序列	EAAAKEAAAKGGGGSEAAAKEAAAK
265	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKGGGGSEAAAK
266	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKEAAAKGGGGS

267	用於例示性連接子之胺基酸序列	EAAAKEAAAKEAAAKEAAAKEAAAK
268	用於例示性連接子之胺基酸序列	GTKDSTKDIPETPSKD
269	用於例示性連接子之胺基酸序列	GRDVRQPEVKEEKPES
270	用於例示性連接子之胺基酸序列	EGKSSGSGSESKSTAG
271	用於例示性連接子之胺基酸序列	TPGSPAGSPTSTEEGT
272	用於例示性連接子之胺基酸序列	GSEPATSGSETPGTST
273-300		未使用

301	編碼APOBEC3A-Nme2D16A之例示性mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGC CUGGCCAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGGCGUGCGGG UGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCCGUGCGGCGGCUGACCCGGCGGCG GGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCC CUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCA AGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAAGGGCGUGGCCAACAACGC CCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGG GGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACG UGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUGGGCCA CUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGCUGACCAAGCUGAACAACCUGCGG AUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACG CCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAU GGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUGAACCUGUCCUCCGAGCUG CAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGG AGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAA GCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCCGCC GACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGUGCGGCGGUACGGCUCCCCCGCCC GGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCG GGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAG CAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGGAGAUCGACCACGCCCUGC CCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAACAAGGGCAACCAGACCCCCUACGA GUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGG AUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCGUGG CCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAACCUGCUGCGGGGCUUCUGGGGCCU GCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACC CGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCC CCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGAGGCCGACACCCC CGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGACCCCCCUGUUCGUGUCCCGGGCC CCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGG UGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAGGC

		CCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAAGGGCGGCCAGCUGGUGAAGGCC GUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGG ACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGA CAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUCCAGAAGGACGAG AAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUGGCACGACAAGGGCUCCAAGGAGC AGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAA GAAGCGGCCCCCCGUGCGGUCCGGAAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGUGGAGUAGUGACUA GCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAU UCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCU

302	用於APOBEC3A-Nme2D16A之例示性開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCC CCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAU CGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCC AUGGCCCGGCGGCUGGCCCGGUCCGUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGG GCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCG GAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACC GCCGACAAGGAGCUGGGCGCCCUGCUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGG CCCUGAACAAGUUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGA GCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACC CAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCU ACACCGCCGAGCGGUUCAUCUGGCUGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCG GGCCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUC AAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGG AGGGCCUGAAGGACAAGAAGUCCCCCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGA GGACAUCACCGGCCGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUC UCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACG GCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGC CCGGAAGGUGAUCAACGGCGUGGUGCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAG GACCGGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCG UGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCU GGUGCGGCUGAACGAGAAGGGCUACGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUG GUGCUGGGCUCCGAGAACCAGAACAAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCA AGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAA CCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUC GCCUCCAACGGCCAGAUCACCAACCUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACG CCGUGGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGAC CAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUG UUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGC CCGAGGCCGUGCACGAGUACGUGACCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUC CGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUG AACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACC

		CCAAGGACAACCCCUUCUACAAGAAGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAA GAAGAACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUC AUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCU GCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUC CAACGGCCGGUUCUACCUGGCCUGGCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAG UACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUCCGGAAAGCGGACCGCCGACGGCU CCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGUGGAGUAG
303	用於APOBEC3A-Nme2D16A之例示性胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNSGSETPGTSESATPESAAFKPNPINYILGLAIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLA MARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGET ADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMT QRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFF KGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQI SLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFK DRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVL VLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVF ASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRV FGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMV NYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKGKNQYF IVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQK YQVNELGKEIRPCRLKKRPPVRSGKRTADGSEFESPKKKRKVE*

304	編碼APOBEC3A-Nme2D16A之例示性mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGA GGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGC CCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGC GGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCG GCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCC CCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCU ACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCA CUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUG CGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAA AUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCG GCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCC GUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCG ACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUC CGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUG CUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGU CCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCA GAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGAC GCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGC UGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUA CCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGAC AACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCC CCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGA CCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUC GUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGA UCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGU GCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGG CAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACA UCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUA CGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAAC AAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGU UCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAA CCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAAC CUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCG UGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGU GCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCC GAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGA CCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAA

		CGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUC GAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGA AGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGA CAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAG GUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACC UGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUG GCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAG GAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUCCGGAAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGA AGCGGAAGGUGGAGUAGUGACUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAAAAU GUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCU

305	用於APOBEC3A-Nme2D16A之例示性開讀框	AUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGAGGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGA AGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAA CAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGC UUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGC UGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCU GCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGG GACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGC CCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCC CGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCC GUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGC CCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCCGUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGC CCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAG CUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCC AGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGA CUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUC UCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGG GCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGA GCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGCUGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAG CGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGG GCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGC CAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCC UUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCU CCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGC CGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUG GUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGUGCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCC GGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUU CCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUG UACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACG ACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAACAAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAA CUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGAC GAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCG GCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAACCUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAA CGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAG AUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCG CCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCU GGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGACCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGC GCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGC

		UGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGG CAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAAGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAG GAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACA AGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCG GAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCC UACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUGGCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCC AGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUC CGGAAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGUGGAGUAG
306	用於APOBEC3A-Nme2D16A之例示性胺基酸序列	MDGSGGGSPKKKRKVEDKRPAATKKAGQAKKKKGGSGGGEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRG FLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLR DAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESAAFKPNPINYILGLAIGIAS VGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQ LRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTF SRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSE RPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTA FSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPV VLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCL YSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFD EDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKE MNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSG AHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQ ESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFA YYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPPVRSGKRTADGSEFESPKKKRKVE*

307	編碼APOBEC3A-Nme2D16A之例示性mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGA GGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGC CCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGC GGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCG GCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCC CCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCU ACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCA CUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUG CGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAA AUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCG GCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCC GUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCG ACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUC CGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUG CUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGU CCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCA GAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGAC GCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGC UGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUA CCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGAC AACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCC CCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGA CCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUC GUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGA UCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGU GCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGG CAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACA UCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUA CGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAAC AAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGU UCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAA CCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAAC CUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCG UGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGU GCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCC GAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGA CCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAA

		CGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUC GAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGA AGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGA CAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAG GUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACC UGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUG GCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAG GAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGGAGGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGA AGAAGUACCCCUACGACGUGCCCGACUACGCCGGCUACCCCUACGACGUGCCCGACUACGCCGGCUCCUACCCCUACGACGUGCCCGACUA CGCCGCCGCCCCCGCCGCCAAGAAGAAGAAGCUGGACUAGCUAGUGACUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUAC AUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCU

308	用於APOBEC3A-Nme2D16A之例示性開讀框	AUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGAGGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGA AGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAA CAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGC UUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGC UGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCU GCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGG GACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGC CCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCC CGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCC GUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGC CCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCCGUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGC CCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAG CUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCC AGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGA CUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUC UCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGG GCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGA GCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGCUGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAG CGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGG GCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGC CAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCC UUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCU CCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGC CGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUG GUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGUGCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCC GGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUU CCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUG UACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACG ACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAACAAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAA CUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGAC GAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCG GCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAACCUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAA CGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAG AUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCG CCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCU GGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGACCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGC GCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGC

		UGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGG CAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAAGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAG GAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACA AGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCG GAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCC UACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUGGCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCC AGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGGA GGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGUACCCCUACGACGUGCCCGACUACGCCGGCUACCCCUAC GACGUGCCCGACUACGCCGGCUCCUACCCCUACGACGUGCCCGACUACGCCGCCGCCCCCGCCGCCAAGAAGAAGAAGCUGGACU
309	用於APOBEC3A-Nme2D16A之例示性胺基酸序列	MDGSGGGSPKKKRKVEDKRPAATKKAGQAKKKKGGSGGGEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRG FLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLR DAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESAAFKPNPINYYILGLAIGIAS VGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQ LRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTF SRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSE RPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTA FSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPV VLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCL YSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFD EDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKE MNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSG AHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQ ESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFA YYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPPVREDKRPAATKKAGQAKKKKYPYDVPDYAGYPY DVPDYAGSYPYDVPDYAAAPAAKKKKLD

310	編碼APOBEC3A-NME2D16A之例示性MRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGA GGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGC CCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGC GGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCG GCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCC CCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCU ACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCA CUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUG CGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAA AUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCG GCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCC GUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCG ACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUC CGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUG CUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGU CCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCA GAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGAC GCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGC UGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUA CCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGAC AACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCC CCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGA CCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUC GUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGA UCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGU GCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGG CAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACA UCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUA CGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAAC AAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGU UCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAA CCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAAC CUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCG UGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGU GCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCC GAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGA CCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAA

		CGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUC GAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGA AGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGA CAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAG GUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACC UGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUG GCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAG GAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUAGUGACUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUA CAUAAUACCAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUC U

311	用於APOBEC3A-Nme2D16A之例示性開讀框	AUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGAGGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGA AGAAGAAGGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAA CAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGC UUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGC UGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCU GCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGG GACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGC CCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCC CGGCACCUCCGAGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGCAUCGCCUCC GUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGC CCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCCGUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGC CCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAG CUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCC AGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAAGGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGA CUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUC UCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGG GCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGA GCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGCUGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAG CGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGG GCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGC CAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUGAACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCC UUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCU CCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGC CGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUG GUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGUGCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCC GGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUU CCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUG UACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGGAGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACG ACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAACAAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAA CUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGAC GAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCG GCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAACCUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAA CGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAG AUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCG CCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCU GGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGACCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGC GCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGC

		UGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGG CAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAAGGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAG GAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACA AGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCG GAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCC UACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUGGCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCC AGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUA G
312	用於APOBEC3A-Nme2D16A之例示性胺基酸序列	MDGSGGGSPKKKRKVEDKRPAATKKAGQAKKKKGGSGGGEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRG FLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLR DAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGNSGSETPGTSESATPESAAFKPNPINYILGLAIGIAS VGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQ LRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTF SRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSE RPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTA FSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPV VLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCL YSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFD EDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKE MNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSG AHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQ ESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFA YYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPPVR*

313	用於NLS-NLS-APOBEC3A-L070-Nme2D16A之例示性胺基酸序列	MDGSGGGSPKKKRKVEDKRPAATKKAGQAKKKKGGSGGGEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYE VERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVR AFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQAL SGRLRAILQNQGNGTKDSTKDIPETPSKDAAFKPNPINYILGLAIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEV PKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLE WSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSH TFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFI WLTKLNNLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAY HAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVP LMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREVG KSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEID HALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGF KECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVA MQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAE KLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIEL YEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVD KKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAW HDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPPVR

314	編碼具有C末端HiBiT標籤之BC22-2XUGI之mRNA (BC22-2XUGI-HibIT)	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCC CGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCU GUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACA ACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCC UCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUG GGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCC GGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCC AUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCC CUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCA ACUCCGGCUCCGAGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAAGAAGUACUCCAUCGGCC UGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUC AAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGG CGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCU GCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAG UCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGC CUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACC UGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUG AACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGA GAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCU GGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCC UGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGAC ACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGC CAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCC UGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGG CAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGA CGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGG AGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCC CACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGA CAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCA ACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUG GACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAA GGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACG UGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUC

		AAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACU CCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCCUGGGCACCUACCACGACCUGCUGAAGAUC AUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGAC CCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGA UGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGG GACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCA GCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACU CCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGG AGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAG GAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCU GUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACG ACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCC GACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGC GGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGC CUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGU GGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUC AACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCC CAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCC GAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGA GAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCG UGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAG AAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAU CGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGC UGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGA AGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUG GCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCU GGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGC ACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCC AACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAU CAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCG

		GAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACG AGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACC UGUCCGACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAG GAGGUGGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCAC CGACGAGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACU CCAACGGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCGGCGGCUCCGGCGGCUCCACCAACCUGUCC GACAUCAUCGAGAAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGU GGAGGAGGUGAUCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACG AGAACGUGAUGCUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAAC GGCGAGAACAAGAUCAAGAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAGCCCAA GAAGAAGCGGAAGGUGUCCGAGUCCGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAAGAUCU CCUGAUAGCUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUU UACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUU CUCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAUAUA AAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAAAA GAUAAAAAAAAAAAACCUAAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAAAAAAAAACGCAAAAAA AAAAAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAAAAAAAAAAAACGAA AAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAAAAAAA ACUGAAAAAAAAAAAUUUAAAAAAAAAAAUCUAG

315	編碼BC22-Nme2D16A之mRNA (Nme2 BC22n)	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGACGGCUCCGGCGGCGGCUCCCCC AAGAAGAAGCGGAAGGUGGAGGACAAGCGGCCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAA GGGCGGCUCCGGCGGCGGCGAGGCCUCCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCAC CUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACG GCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUC UACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUA CCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCC UGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUG CUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGG CCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCCCCGGCACCUCCG AGUCCGCCACCCCCGAGUCCGCAGCGUUCAAACCAAAUCCCAUCAACUACAUCCUGGGCCUGGCCAUCGGC AUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGAUCGACCUGGG CGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCC GGUCCGUGCGGCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAG GGCGUGCUGCAGGCCGCCGACUUCGACGAGAACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCU GCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCGUGCUGCUGCACCUGAUCAAGC ACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAAG GGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAG UUCGAGAAGGAGUCCGGCCACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCU GCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGGAGUUCGGCAACCCCCACGUGUCCGGCGGCCUGA AGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGUGCAGAAGAUGCUG GGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUG GCUGACCAAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGG CCACCCUGAUGGACGAGCCCUACCGGAAGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUG GAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGCCGAGGCCUCCACCCUGAUGGAGAU GAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUGAACC UGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGC CGGCUGAAGGACCGGGUGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGU GCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCCCCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCU GCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUACCUGCCCCCCAUCCCC GCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGU GCGGCGGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACC

		GGAAGGAGAUCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGA GUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUGAAGCUGCGGCUGUACGAGCAGCAGC ACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGGAGAU CGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCG AGAACCAGAACAAGGGCAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAG GAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCCCGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUU CGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGCUUCCUGUGCCAGUUCG UGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAAC CUGCUGCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGU GGUGGUGGCCUGCUCCACCGUGGCCAUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACG CCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGCACCAGAAGACCCACUUCCCCCAGCCC UGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUUCGAGGA GGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACG AGUACGUGACCCCCCUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUG CGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGAAGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAA GCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCUGUACGAGGCCCUGAAG GCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAA GGGCGGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAG AACGCCUACACCAUCGCCGACAACGGCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGG CAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGCCGAGAACAUCCUGCCCGACAUCGACU GCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUCGCCUUC CAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUA CCUGGCCUGGCACGACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCC AGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAUCCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGG UAGUGACUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUA CAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUC UCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAGGUAAAAAAAAAAAAUAUAAAAA AAAAAACAUAAAAAAAAAAAACGAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAAAGAUAAA AAAAAAAAACCUAAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAAAAAAAACGCAAAAAAAAAAAACA CAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAAAAAAAAAAAACGAAAAAAAAA AACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAA AAAAAAUUUAAAAAAAAAAAUCUAG

316	編碼具有C末端HiBiT標籤之UGI之mRNA (UGI-HiBiT)	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGACCAACCUGUCCGACAUCAUCGAG AAGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGA UCGGCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCGCCUACGACGAGUCCACCGACGAGAACGUGAUG CUGCUGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUCCAGGACUCCAACGGCGAGAACAA GAUCAAGAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAGUUCGAGUCCCCCAAGAAGAAGC GGAAGGUGGAGUCCGAGUCCGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAAGAUCUCCUGA UAGCUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUUACACUUUACAA AAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUCUCG AGAAAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAAUAUAAAAAAA AAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAAAAAGAUAAA AAAAAAAAACCUAAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAAAAAAAAACGCAAAAAAAAAAAAC ACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAAAAAAAAAAAACGAAAAAAAAA AAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAA AAAAAAAAUUUAAAAAAAAAAAUCUAG
317-319		未使用
320	用於Nme2Cas9之胺基酸序列	MDGSGGGSPKKKRKVEDKRPAATKKAGQAKKKKGGSGGGAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPK TGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQR KNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGI ETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGL EDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISF DKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETARE VGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDS FNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHILLTGK GKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQ EVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLA DLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDKK GKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQN LVLIQKYQVNELGKEIRPCRLKKRPPVR

321	用於具有連接子L070之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGTKDSTKDIPETPSKDDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETA EATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNL IALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAIL RRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLL YEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKD FLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQL IHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKD FQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR PLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDR KRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV
322	用於具有連接子L071之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGRDVRQPEVKEEKPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETA EATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNL IALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAIL RRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLL YEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKD FLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQL IHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKD FQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR PLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDR KRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

323	用於具有連接子L072之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEGKSSGSGSESKSTAGDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETA EATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNL IALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAIL RRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLL YEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKD FLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQL IHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKD FQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR PLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDR KRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV
324	用於具有連接子L073之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNTPGSPAGSPTSTEEGTDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETA EATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNL IALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAIL RRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLL YEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKD FLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQL IHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKD FQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR PLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDR KRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

325	用於具有連接子L074之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGSEPATSGSETPGTSTDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETA EATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNL IALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAIL RRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLL YEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKD FLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQL IHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEG IKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKD FQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKR PLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDR KRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV
326	用於具有連接子L019之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAE ATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADL RLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLI ALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDF LDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLI HDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDF QFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRP LIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKG KSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYE KLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRK RYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDGGGSPKKKRKV

327	用於具有連接子L015之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGGGGSEAAAKEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAE ATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADL RLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLI ALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDF LDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLI HDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDF QFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRP LIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKG KSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYE KLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRK RYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDEN VMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

328	用於具有連接子L016之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAE ATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADL RLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLI ALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDF LDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLI HDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDF QFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRP LIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKG KSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYE KLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRK RYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDEN VMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV*

329	用於具有連接子 L019 之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAE ATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADL RLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLI ALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDF LDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLI HDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGI KELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDF QFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRP LIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKG KSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYE KLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRK RYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDEN VMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV*

330	用於具有連接子L021之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGGGGSGGGGSGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDS GETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGL FGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEH HQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGEL HAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKII KDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKR IEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEE VVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGE IRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVA KVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDE STDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

331	用於具有連接子 L024 之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGGGGSGGGGSEAAAKEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDS GETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGL FGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEH HQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGEL HAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKII KDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKR IEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEE VVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGE IRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVA KVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDE STDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV*

332	用於具有連接子L025之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGGGGSEAAAKGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDS GETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGL FGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEH HQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGEL HAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKII KDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKR IEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEE VVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGE IRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVA KVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDE STDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

333	用於具有連接子L036之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKEAAAKEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDS GETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDST DKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGL FGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEH HQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGEL HAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKII KDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKR IEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEE VVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGE IRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVA KVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYL ASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDE STDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

334	用於具有連接子 L051 之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNGGGGSEAAAKEAAAKGGGGSEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGA LLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKK LVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGE KKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIK RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNE KVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHD LLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDG FANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSR ERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDN VPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYS VLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVH TAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

335	用於具有連接子L062之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKGGGGSGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGA LLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKK LVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGE KKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIK RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNE KVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHD LLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDG FANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSR ERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDN VPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYS VLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVH TAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

336	用於具有連接子L063之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKGGGGSGGGGSEAAAKDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGA LLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKK LVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGE KKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIK RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNE KVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHD LLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDG FANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSR ERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDN VPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYS VLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVH TAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV

337	用於具有連接子L066之鹼基編輯器之胺基酸序列	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYR VTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEH SQALSGRLRAILQNQGNEAAAKEAAAKEAAAKGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGA LLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKK LVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGE KKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIK RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI HLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNE KVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHD LLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDG FANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSR ERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDN VPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKS KLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYS VLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYV NFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAF KYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVH TAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV
338-339		未使用

340	Nme2 Cas9 切口酶之 mRNA	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAUCUGCCACCAUGGACGGCUCCGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGGA GGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGAAGAAGAAGGGCGGCUCCGGCGGCGGCGCCGCCUUCAAGCCCAACCCC AUCAACUACAUCCUGGGCCUGGACAUCGGCAUCGCCUCCGUGGGCUGGGCCAUGGUGGAGAUCGACGAGGAGGAGAACCCCAUCCGGCUGA UCGACCUGGGCGUGCGGGUGUUCGAGCGGGCCGAGGUGCCCAAGACCGGCGACUCCCUGGCCAUGGCCCGGCGGCUGGCCCGGUCCGUGCG GCGGCUGACCCGGCGGCGGGCCCACCGGCUGCUGCGGGCCCGGCGGCUGCUGAAGCGGGAGGGCGUGCUGCAGGCCGCCGACUUCGACGAG AACGGCCUGAUCAAGUCCCUGCCCAACACCCCCUGGCAGCUGCGGGCCGCCGCCCUGGACCGGAAGCUGACCCCCCUGGAGUGGUCCGCCG UGCUGCUGCACCUGAUCAAGCACCGGGGCUACCUGUCCCAGCGGAAGAACGAGGGCGAGACCGCCGACAAGGAGCUGGGCGCCCUGCUGAA GGGCGUGGCCAACAACGCCCACGCCCUGCAGACCGGCGACUUCCGGACCCCCGCCGAGCUGGCCCUGAACAAGUUCGAGAAGGAGUCCGGC CACAUCCGGAACCAGCGGGGCGACUACUCCCACACCUUCUCCCGGAAGGACCUGCAGGCCGAGCUGAUCCUGCUGUUCGAGAAGCAGAAGG AGUUCGGCAACCCCCACGUGUCCGGCGGCCUGAAGGAGGGCAUCGAGACCCUGCUGAUGACCCAGCGGCCCGCCCUGUCCGGCGACGCCGU GCAGAAGAUGCUGGGCCACUGCACCUUCGAGCCCGCCGAGCCCAAGGCCGCCAAGAACACCUACACCGCCGAGCGGUUCAUCUGGCUGACC AAGCUGAACAACCUGCGGAUCCUGGAGCAGGGCUCCGAGCGGCCCCUGACCGACACCGAGCGGGCCACCCUGAUGGACGAGCCCUACCGGA AGUCCAAGCUGACCUACGCCCAGGCCCGGAAGCUGCUGGGCCUGGAGGACACCGCCUUCUUCAAGGGCCUGCGGUACGGCAAGGACAACGC CGAGGCCUCCACCCUGAUGGAGAUGAAGGCCUACCACGCCAUCUCCCGGGCCCUGGAGAAGGAGGGCCUGAAGGACAAGAAGUCCCCCCUG AACCUGUCCUCCGAGCUGCAGGACGAGAUCGGCACCGCCUUCUCCCUGUUCAAGACCGACGAGGACAUCACCGGCCGGCUGAAGGACCGGG UGCAGCCCGAGAUCCUGGAGGCCCUGCUGAAGCACAUCUCCUUCGACAAGUUCGUGCAGAUCUCCCUGAAGGCCCUGCGGCGGAUCGUGCC CCUGAUGGAGCAGGGCAAGCGGUACGACGAGGCCUGCGCCGAGAUCUACGGCGACCACUACGGCAAGAAGAACACCGAGGAGAAGAUCUAC CUGCCCCCCAUCCCCGCCGACGAGAUCCGGAACCCCGUGGUGCUGCGGGCCCUGUCCCAGGCCCGGAAGGUGAUCAACGGCGUGGUGCGGC GGUACGGCUCCCCCGCCCGGAUCCACAUCGAGACCGCCCGGGAGGUGGGCAAGUCCUUCAAGGACCGGAAGGAGAUCGAGAAGCGGCAGGA GGAGAACCGGAAGGACCGGGAGAAGGCCGCCGCCAAGUUCCGGGAGUACUUCCCCAACUUCGUGGGCGAGCCCAAGUCCAAGGACAUCCUG AAGCUGCGGCUGUACGAGCAGCAGCACGGCAAGUGCCUGUACUCCGGCAAGGAGAUCAACCUGGUGCGGCUGAACGAGAAGGGCUACGUGG AGAUCGACCACGCCCUGCCCUUCUCCCGGACCUGGGACGACUCCUUCAACAACAAGGUGCUGGUGCUGGGCUCCGAGAACCAGAACAAGGG CAACCAGACCCCCUACGAGUACUUCAACGGCAAGGACAACUCCCGGGAGUGGCAGGAGUUCAAGGCCCGGGUGGAGACCUCCCGGUUCCCC CGGUCCAAGAAGCAGCGGAUCCUGCUGCAGAAGUUCGACGAGGACGGCUUCAAGGAGUGCAACCUGAACGACACCCGGUACGUGAACCGGU UCCUGUGCCAGUUCGUGGCCGACCACAUCCUGCUGACCGGCAAGGGCAAGCGGCGGGUGUUCGCCUCCAACGGCCAGAUCACCAACCUGCU GCGGGGCUUCUGGGGCCUGCGGAAGGUGCGGGCCGAGAACGACCGGCACCACGCCCUGGACGCCGUGGUGGUGGCCUGCUCCACCGUGGCC AUGCAGCAGAAGAUCACCCGGUUCGUGCGGUACAAGGAGAUGAACGCCUUCGACGGCAAGACCAUCGACAAGGAGACCGGCAAGGUGCUGC ACCAGAAGACCCACUUCCCCCAGCCCUGGGAGUUCUUCGCCCAGGAGGUGAUGAUCCGGGUGUUCGGCAAGCCCGACGGCAAGCCCGAGUU CGAGGAGGCCGACACCCCCGAGAAGCUGCGGACCCUGCUGGCCGAGAAGCUGUCCUCCCGGCCCGAGGCCGUGCACGAGUACGUGACCCCC CUGUUCGUGUCCCGGGCCCCCAACCGGAAGAUGUCCGGCGCCCACAAGGACACCCUGCGGUCCGCCAAGCGGUUCGUGAAGCACAACGAGA AGAUCUCCGUGAAGCGGGUGUGGCUGACCGAGAUCAAGCUGGCCGACCUGGAGAACAUGGUGAACUACAAGAACGGCCGGGAGAUCGAGCU GUACGAGGCCCUGAAGGCCCGGCUGGAGGCCUACGGCGGCAACGCCAAGCAGGCCUUCGACCCCAAGGACAACCCCUUCUACAAGAAGGGC GGCCAGCUGGUGAAGGCCGUGCGGGUGGAGAAGACCCAGGAGUCCGGCGUGCUGCUGAACAAGAAGAACGCCUACACCAUCGCCGACAACG GCGACAUGGUGCGGGUGGACGUGUUCUGCAAGGUGGACAAGAAGGGCAAGAACCAGUACUUCAUCGUGCCCAUCUACGCCUGGCAGGUGGC CGAGAACAUCCUGCCCGACAUCGACUGCAAGGGCUACCGGAUCGACGACUCCUACACCUUCUGCUUCUCCCUGCACAAGUACGACCUGAUC GCCUUCCAGAAGGACGAGAAGUCCAAGGUGGAGUUCGCCUACUACAUCAACUGCGACUCCUCCAACGGCCGGUUCUACCUGGCCUGGCACG ACAAGGGCUCCAAGGAGCAGCAGUUCCGGAUCUCCACCCAGAACCUGGUGCUGAUCCAGAAGUACCAGGUGAACGAGCUGGGCAAGGAGAU

		CCGGCCCUGCCGGCUGAAGAAGCGGCCCCCCGUGCGGUAGCUAGCACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUAC CAACUUACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUCUCUCGAGA AAAAAAAAAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAA AAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAAAAGAUAAAAAAAAAAAAACCUAAAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAA AAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUAAAAAAAAAAAACGAAAAAA AAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAGUUAAAAAAAAAAAAACUGAAAAAAAAAAAUUUAAAAAAAAA AAAUCUAG

341	編碼具有連接子L070之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACggcaccaaggacuccaccaaggacaucccccgagacccccuccaaggacGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAAC UCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGA AGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUC CUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGG CCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUC GAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCG CCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGA CCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCC GACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAA GGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCC AUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAA GAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGU GACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACC GUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCC UGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCU GACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCA GGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGG GCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAA CACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUG UCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCA

		GCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACC CGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCA CGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUG UACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAA GGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCC AAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCC CCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAG CUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUU CGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGAC AAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGG GCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCA CCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUG UGACUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaaugu agccauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAA AAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAAACGAAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAA AAGAUAAAAAAAAAAAAAACCUAAAAAAAAAAAAAAUGUAAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAA AUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAU AGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

342	編碼具有連接子L071之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACggccgggacgugcggcagcccgaggugaaggaggagaagcccgaguccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAAC UCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGA AGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUC CUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGG CCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUC GAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCG CCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGA CCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCC GACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAA GGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCC AUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAA GAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGU GACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACC GUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCC UGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCU GACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCA GGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGG GCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAA CACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUG UCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCA

		GCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACC CGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCA CGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUG UACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAA GGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCC AAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCC CCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAG CUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUU CGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGAC AAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGG GCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCA CCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUG UGACUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaaugu agccauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAA AAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAAACGAAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAA AAGAUAAAAAAAAAAAAAACCUAAAAAAAAAAAAAAUGUAAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAA AUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAU AGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

343	編碼具有連接子L072之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACgagggcaaguccuccggcuccggcuccgaguccaaguccaccgccggcGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAAC UCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGA AGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUC CUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGG CCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUC GAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCG CCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGA CCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCC GACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAA GGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCC AUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAA GAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGU GACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACC GUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCC UGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCU GACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCA GGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGG GCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAA CACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUG UCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCA

		GCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACC CGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCA CGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUG UACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAA GGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCC AAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCC CCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAG CUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUU CGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGAC AAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGG GCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCA CCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUG UGACUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaaugu agccauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAA AAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAAACGAAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAA AAGAUAAAAAAAAAAAAAACCUAAAAAAAAAAAAAAUGUAAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAA AUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAU AGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

344	編碼具有連接子L073之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACaccccggcucccccgccggcucccccaccuccaccgaggagggcaccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAAC UCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGA AGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUC CUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGG CCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUC GAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCG CCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGA CCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCC GACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAA GGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCC AUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAA GAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGU GACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACC GUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCC UGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCU GACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCA GGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGG GCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAA CACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUG UCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCA

		GCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACC CGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCA CGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUG UACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAA GGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCC AAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCC CCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAG CUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUU CGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGAC AAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGG GCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCA CCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUG UGACUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaaugu agccauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAA AAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAAACGAAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAA AAGAUAAAAAAAAAAAAAACCUAAAAAAAAAAAAAAUGUAAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAA AUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAU AGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

345	編碼具有連接子L074之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACggcuccgagcccgccaccuccggcuccgagacccccggcaccuccaccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAAC UCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGA AGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUC CUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCU ACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGG CCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUC GAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCG CCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGA CCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCC GACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGU CCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAA GGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCC AUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAA GAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACA AGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGU GACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACC GUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCC UGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCU GACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACU UCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCA GGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAG GUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGG GCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAA CACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUG UCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACC GGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCA

		GCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACC CGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGG UGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCA CGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUG UACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAA GGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCC AAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCC CCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCAC CAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAG CUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUU CGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGAC AAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGG GCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCA CCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUG UGACUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaaugu agccauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAA AAAAGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAAACAUAAAAAAAAAAAAAACGAAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAA AAGAUAAAAAAAAAAAAAACCUAAAAAAAAAAAAAAUGUAAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAA AUGCAAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAU AGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

346	編碼具有連接子L019之鹼基編輯器之mRNA	GGGaagcucagaauaaacgcucaacuuuggccggaucugccacCAUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCA CAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGG ACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGC CGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAG GAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACC ACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGG CAACgaggccgccgccaaggaggccgccgccaaggaggccgccgccaagGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCC GUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGA ACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAA GAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUG GUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACC ACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCA CUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAG GAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCC AGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCU GGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGAC CUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCG CCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGA GAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUC CUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCA UCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAU CGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAG GAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGA ACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGAC CGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUG AAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGG GCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGAC CCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAG CGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCC UGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGU GUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUG GUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCC AGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACAC CCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCC GACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGG GCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCG

		GAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGG CAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGA UCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGA CGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUAC GACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCA AGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGG CCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAG GAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCA CCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAU CAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUG CCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGC CCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGU GGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAG GUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCG CCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCA GUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA CUAGCaccagccucaagaacacccgaauggagucucuaagcuacauaauaccaacuuacacuuuacaaaauguuguccccccaaaauguagc cauucguaucugcuccuaauaaaaagaaaguuucuucacauucuCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAACGGAAAAAAAAAAA AGGUAAAAAAAAAAAAAUAUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAAAAAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAAAAAG AUAAAAAAAAAAAAACCUAAAAAAAAAAAAAUGUAAAAAAAAAAAAAGGGAAAAAAAAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAAAAUG CAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGA AAAAAAAAAAAGUUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG

347	編碼具有連接子L015之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGAGGAGGAGGAAGCGAAGCA GCAGCAAAGGAAGCAGCAGCAAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACG AAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGA CAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAA AUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAA GACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAG CACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAAC CCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAG UCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGG ACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUG AGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGA GCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGA ACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAAC GGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAG AACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGA ACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUC CCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCG AAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCC GAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUC CUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCA AGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAU CAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAA AUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAA GACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAG AAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCAC GAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGG GAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAA GAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUAC CUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCC CGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGA

		AGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCA GAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGA UCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAG CGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGA ACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGA GCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGG AGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAG GUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACA GCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGU CGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAG AACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGG AAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUA CCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGAC GAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACA GAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGA CACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACA AGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCA UCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGA CGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAA AACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUAC CAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAA CAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAU

348	編碼具有連接子L016之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAGGCCGCCGCCAAGGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACG AAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGA CAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAA AUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAA GACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAG CACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAAC CCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAG UCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGG ACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUG AGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGA GCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGA ACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAAC GGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAG AACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGA ACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUC CCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCG AAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCC GAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUC CUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCA AGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAU CAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAA AUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAA GACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAG AAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCAC GAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGG GAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAA GAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUAC CUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCC CGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGA

		AGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCA GAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGA UCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAG CGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGA ACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGA GCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGG AGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAG GUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACA GCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGU CGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAG AACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGG AAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUA CCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGAC GAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACA GAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGA CACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACA AGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCA UCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGA CGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAA AACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUAC CAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAA CAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAU

349	編碼具有連接子L019之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAGGCCGCCGCCAAGGAGGCC GCCGCCAAGGAGGCCGCCGCCAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACG AAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGA CAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAA AUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAA GACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAG CACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAAC CCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAG UCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGG ACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUG AGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGA GCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGA ACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAAC GGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAG AACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGA ACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUC CCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCG AAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCC GAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUC CUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCA AGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAU CAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAA AUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAA GACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAG AAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCAC GAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGG GAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAA GAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUAC CUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCC CGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGA

		AGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCA GAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGA UCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAG CGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGA ACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGA GCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGG AGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAG GUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACA GCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGU CGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAG AACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGG AAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUA CCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGAC GAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACA GAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGA CACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACA AGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCA UCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGA CGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAA AACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUAC CAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAA CAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAU

350	編碼具有連接子L021之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGG CAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGG AGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAG ACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAA GAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUC GAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGA UCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGG AGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGG CAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAU CAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUC GACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGA UGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCA GAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCA CACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAA CGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUG AGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGA AGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCA CGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAU ACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGA CGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAG GGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAAC UGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAG CAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACG UCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGA

		CAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGAC AACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAA AGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAA GAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAA AGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAU CACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUC GCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCC UGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUA CAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACA GCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUA CGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCAC AAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCG CAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGC AUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAG GAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGU CCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAG GACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAA AGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAAC ACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAU

351	編碼具有連接子L024之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGCGGCGGCGGCAGCGGAGGA GGAGGAAGCGAAGCCGCCGCCAAAGAGGCCGCCGCCAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGG CAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGG AGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAG ACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAA GAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUC GAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGA UCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGG AGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGG CAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAU CAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUC GACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGA UGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCA GAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCA CACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAA CGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUG AGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGA AGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCA CGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAU ACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGA CGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAG GGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAAC UGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAG CAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACG UCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGA

		CAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGAC AACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAA AGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAA GAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAA AGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAU CACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUC GCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCC UGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUA CAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACA GCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUA CGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCAC AAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCG CAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGC AUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAG GAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGU CCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAG GACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAA AGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAAC ACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAU

352	編碼具有連接子L025之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGCGGCGGCGGAAGCGAGGCC GCUGCCAAAGGCGGAGGAGGAAGCGGAGGAGGCGGCAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGG CAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGG AGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAG ACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAA GAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUC GAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGA UCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGG AGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGG CAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAU CAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUC GACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGA UGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCA GAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCA CACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAA CGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUG AGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGA AGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCA CGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAU ACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGA CGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAG GGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAAC UGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAG CAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACG UCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGA

		CAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGAC AACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAA AGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAA GAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAA AGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAU CACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUC GCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCC UGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUA CAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACA GCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUA CGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCAC AAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCG CAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGC AUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAG GAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGU CCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAG GACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAA AGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAAC ACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAU

353	編碼具有連接子L036之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAGGCCGCCGCCAAGGAGGCC GCCGCCAAGGAGGCCGCCGCCAAGGAGGCCGCCGCCAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGG CAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGG AGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUC UGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAG ACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAA GAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUC GAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGA UCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGG AGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGAC GCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGG CAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAU CAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUC GACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGA UGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCA GAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUC CUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCA CACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAA CGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUG AGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGA AGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCA CGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUG UUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAU ACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGA CGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAG GGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAAC UGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAG CAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAG AACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACG UCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGA

		CAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGAC AACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAA AGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAA GAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUG AACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAA AGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAU CACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUC GCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCC UGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUA CAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGA AGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACA GCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUA CGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCAC AAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCG CAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGC AUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACA GGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAG GAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGU CCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAG GACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUAGACAUCACAUUUAAA AGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAAC ACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAU

354	編碼具有連接子L051之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGAGGAGGAGGAAGCGAAGCC GCCGCCAAAGAGGCCGCCGCCAAGGGAGGCGGCGGCAGCGAGGCCGCCGCCAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAA ACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAA GAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGA AGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCU UCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAU CUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGA GGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGU UCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAU CGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUC GACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACG CAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCU GAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUAC AAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGC CGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGG AAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAA AAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGA GCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGA CAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUAC GUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCA CAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAG CCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUC CUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGC UGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGA CUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCA CAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCA AGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAA GGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAA AACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGAC UGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAA

		CAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACA CAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAA CAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAA GGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCA CACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGG UCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUU CUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGAC AAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCA GCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAG CCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUC ACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCA AGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGC ACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUG UUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGG ACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCU GGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUC CACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCA UCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGA AAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGG GCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUA GACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGU UGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAA GAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAU

355	編碼具有連接子L062之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAGGCCGCCGCCAAGGAGGCC GCCGCCAAGGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAA ACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAA GAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGA AGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCU UCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAU CUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGA GGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGU UCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAU CGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUC GACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACG CAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCU GAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUAC AAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGC CGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGG AAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAA AAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGA GCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGA CAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUAC GUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCA CAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAG CCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUC CUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGC UGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGA CUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCA CAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCA AGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAA GGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAA AACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGAC UGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAA

		CAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACA CAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAA CAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAA GGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCA CACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGG UCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUU CUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGAC AAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCA GCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAG CCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUC ACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCA AGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGC ACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUG UUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGG ACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCU GGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUC CACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCA UCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGA AAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGG GCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUA GACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGU UGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAA GAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAU

356	編碼具有連接子L063之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAAGCAGCAGCAAAGGAAGCA GCAGCAAAGGGAGGAGGAGGAAGCGGAGGAGGAGGAAGCGAAGCAGCAGCAAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAA ACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAA GAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGA AGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCU UCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAU CUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGA GGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGU UCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAU CGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUC GACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACG CAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCU GAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUAC AAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGC CGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGG AAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAA AAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGA GCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGA CAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUAC GUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCA CAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAG CCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUC CUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGC UGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGA CUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCA CAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCA AGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAA GGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAA AACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGAC UGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAA

		CAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACA CAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAA CAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAA GGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCA CACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGG UCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUU CUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGAC AAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCA GCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAG CCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUC ACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCA AGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGC ACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUG UUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGG ACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCU GGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUC CACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCA UCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGA AAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGG GCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUA GACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGU UGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAA GAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAU

357	編碼具有連接子L066之鹼基編輯器之mRNA	GGGAGACCCAAGCUGGCUAGCGUUUAAACUUAAGCUUUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGC CUUAUUCGGAUCCGCCACCAUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCC UGCACAACCAGGCAAAGAACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGA CCCGGCACAGAUCUACAGAGUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAG GAAAACACACACGUCAGACUGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACG CAGGAGCACAGGUCAGCAUCAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUG GGACGGACUGGACGAACACAGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAAGCAGCAGCAAAGGAAGCA GCAGCAAAGGAAGCAGCAGCAAAGGGAGGAGGAGGAAGCGGAGGAGGAGGAAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAA ACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAA GAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGA AGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCU UCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAU CUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGA GGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGU UCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAU CGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUC GACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACG CAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCU GAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUAC AAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGC CGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGG AAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAA AAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGA GCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGA CAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUAC GUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCA CAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAG CCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUC CUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGC UGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGA CUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCA CAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCA AGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAA GGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAA AACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGAC UGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAA

		CAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACA CAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAA CAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAA GGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCA CACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGG UCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUU CUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGAC AAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCA GCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAG CCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUC ACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCA AGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGC ACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUG UUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGG ACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCU GGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUC CACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCA UCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGA AAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGG GCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAGUCUA GACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGU UGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAA GAACCUCGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCGAAAAAAAAAAAAAAAAAAAAAAAAAAAACCGAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAU
358-359		未使用

360	用於 Nme2 Cas9之開讀框	atgGACGGCTCCGGCGGCGGCTCCCCCAAGAAGAAGCGGAAGGTGGAGGACAAGCGGCCCGCCGCCACCAAGAAGGCCGGCCAGGCCAAGA AGAAGAAGGGCGGCTCCGGCGGCGGCgccgccttcaagcccaaccccatcaactacatcctgggcctggacatcggcatcgcctccgtggg ctgggccatggtggagatcgacgaggaggagaaccccatccggctgatcgacctgggcgtgcgggtgttcgagcgggccgaggtgcccaag accggcgactccctggccatggcccggcggctggcccggtccgtgcggcggctgacccggcggcgggcccaccggctgctgcgggcccggc ggctgctgaagcgggagggcgtgctgcaggccgccgacttcgacgagaacggcctgatcaagtccctgcccaacacccccctggcagctgcg ggccgccgccctggaccggaagctgacccccctggagtggtccgccgtgctgctgcacctgatcaagcaccggggctacctgtcccagcgg aagaacgagggcgagaccgccgacaaggagctgggcgccctgctgaagggcgtggccaacaacgcccacgccctgcagaccggcgacttcc ggaccccccgccgagctggccctgaacaagttcgagaaggagtccggccacatccggaaccagcggggcgactactcccacaccttctcccg gaaggacctgcaggccgagctgatcctgctgttcgagaagcagaaggagttcggcaacccccacgtgtccggcggcctgaaggagggcatc gagaccctgctgatgacccagcggcccgccctgtccggcgacgccgtgcagaagatgctgggccactgcaccttcgagcccgccgagccca aggccgccaagaacacctacaccgccgagcggttcatctggctgaccaagctgaacaacctgcggatcctggagcagggctccgagcggcc cctgaccgacaccgagcgggccaccctgatggacgagccctaccggaagtccaagctgacctacgcccaggcccggaagctgctgggcctg gaggacaccgccttcttcaagggcctgcggtacggcaaggacaacgccgaggcctccaccctgatggagatgaaggcctaccacgccatct cccgggccctggagaaggagggcctgaaggacaagaagtccccccctgaacctgtcctccgagctgcaggacgagatcggcaccgccttctc cctgttcaagaccgacgaggacatcaccggccggctgaaggaccgggtgcagcccgagatcctggaggccctgctgaagcacatctccttc gacaagttcgtgcagatctccctgaaggccctgcggcggatcgtgcccctgatggagcagggcaagcggtacgacgaggcctgcgccgaga tctacggcgaccactacggcaagaagaacaccgaggagaagatctacctgccccccatccccgccgacgagatccggaaccccgtggtgct gcgggccctgtcccaggcccggaaggtgatcaacggcgtggtgcggcggtacggctcccccgcccggatccacatcgagaccgcccgggag gtgggcaagtccttcaaggaccggaaggagatcgagaagcggcaggaggagaaccggaaggaccgggagaaggccgccgccaagttccggg agtacttccccaacttcgtgggcgagcccaagtccaaggacatcctgaagctgcggctgtacgagcagcagcacggcaagtgcctgtactc cggcaaggagatcaacctggtgcggctgaacgagaagggctacgtggagatcgaccacgccctgcccttctcccggacctgggacgactcc ttcaacaacaaggtgctggtgctgggctccgagaaccagaacaagggcaaccagacccctacgagtacttcaacggcaaggacaactccc gggagtggcaggagttcaaggcccgggtggagacctcccggttcccccggtccaagaagcagcggatcctgctgcagaagttcgacgagga cggcttcaaggagtgcaacctgaacgacacccggtacgtgaaccggttcctgtgccagttcgtggccgaccacatcctgctgaccggcaag ggcaagcggcgggtgttcgcctccaacggccagatcaccaacctgctgcggggcttctggggcctgcggaaggtgcgggccgagaacgacc ggcaccacgccctggacgccgtggtggtggcctgctccaccgtggccatgcagcagaagatcacccggttcgtgcggtacaaggagatgaa cgccttcgacggcaagaccatcgacaaggagaccggcaaggtgctgcaccagaagacccacttcccccagccctgggagttcttcgcccag gaggtgatgatccgggtgttcggcaagcccgacggcaagcccgagttcgaggaggccgacaccccgagaagctgcggaccctgctggccg agaagctgtcctcccggcccgaggccgtgcacgagtacgtgaccccctgttcgtgtcccgggcccccaaccggaagatgtccggcgccca caaggacaccctgcggtccgccaagcggttcgtgaagcacaacgagaagatctccgtgaagcgggtgtggctgaccgagatcaagctggcc gacctggagaacatggtgaactacaagaacggccgggagatcgagctgtacgaggccctgaaggcccggctggaggcctacggcggcaacg ccaagcaggccttcgaccccaaggacaacccccttctacaagaagggcggccagctggtgaaggccgtgcgggtggagaagacccaggagtc cggcgtgctgctgaacaagaagaacgcctacaccatcgccgacaacggcgacatggtgcgggtggacgtgttctgcaaggtggacaagaag ggcaagaaccagtacttcatcgtgcccatctacgcctggcaggtggccgagaacatcctgcccgacatcgactgcaagggctaccggatcg acgactcctacaccttctgcttctccctgcacaagtacgacctgatcgccttccagaaggacgagaagtccaaggtggagttcgcctacta catcaactgcgactcctccaacggccggttctacctggcctggcacgacaagggctccaaggagcagcagttccggatctccacccagaac ctggtgctgatccagaagtaccaggtgaacgagctgggcaaggagatccggccctgccggctgaagaagcggcccccccgtgcggtag

361	用於具有連接子L070之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACggcaccaaggacuccaccaaggacaucccgagacccccu ccaaggacGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUC CAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCC GAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGA UGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGG CAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACG UGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAU CCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUG AUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACG ACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCU GUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACA UCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCU GAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCC CCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAA GGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGA AGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUU CGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGAC UUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGC UGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCU GAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACC UGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGA GAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGC AUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAA GGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGU

		CCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAU GAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGAC UUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGA AGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGG CAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCC AGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGC CCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAG GGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCC UGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCG GAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGA UCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCG GGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGG AAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCC AGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

362	用於具有連接子L071之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACggccgggacgugcggcagcccgaggugaaggaggagaagc ccgaguccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUC CAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCC GAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGA UGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGG CAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACG UGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAU CCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUG AUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACG ACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCU GUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACA UCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCU GAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCC CCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAA GGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGA AGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUU CGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGAC UUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGC UGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCU GAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACC UGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGA GAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGC AUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAA GGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGU

		CCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAU GAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGAC UUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGA AGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGG CAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCC AGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGC CCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAG GGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCC UGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCG GAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGA UCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCG GGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGG AAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCC AGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

363	用於具有連接子L072之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACgagggcaaguccuccggcuccggcuccgaguccaaguccca ccgccggcGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUC CAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCC GAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGA UGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGG CAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACG UGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAU CCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUG AUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACG ACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCU GUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACA UCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCU GAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCC CCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAA GGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGA AGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUU CGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGAC UUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGC UGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCU GAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACC UGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGA GAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGC AUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAA GGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGU

		CCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAU GAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGAC UUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGA AGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGG CAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCC AGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGC CCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAG GGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCC UGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCG GAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGA UCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCG GGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGG AAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCC AGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

364	用於具有連接子L073之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACaccccccggcucccccgccggcucccccaccuccaccgaggg agggcaccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUC CAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCC GAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGA UGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGG CAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACG UGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAU CCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUG AUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACG ACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCU GUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACA UCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCU GAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCC CCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAA GGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGA AGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUU CGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGAC UUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGC UGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCU GAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACC UGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGA GAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGC AUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAA GGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGU

		CCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAU GAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGAC UUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGA AGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGG CAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCC AGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGC CCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAG GGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCC UGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCG GAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGA UCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCG GGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGG AAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCC AGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

365	用於具有連接子L074之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACggcuccgagcccgccaccuccggcuccgagacccccggca ccuccaccGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUC CAAGAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCC GAGGCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGA UGGCCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGG CAACAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGAC CUGCGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACG UGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAU CCUGUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUG AUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACG ACGACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCU GUCCGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUG ACCCUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACA UCGACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCU GAACCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCC CCCUGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAA GGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUG UACGAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGA AGAAGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUU CGACUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGAC UUCCUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGC UGAAGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCU GAUCAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUG AUCCACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACC UGGCCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGA GAACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGC AUCAAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAA GGACGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAG AUGAAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGU

		CCGAGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAU GAACACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGAC UUCCAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGA AGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGG CAAGGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGG CCCCUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCC AGGUGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGC CCGGAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAG GGCAAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCC UGGAGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCG GAUGCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUAC GAGAAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGA UCUCCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCG GGAGCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGG AAGCGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCC AGCUGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

366	用於具有連接子 L019 之鹼基編輯器之開讀框	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUCAACAACGGCAUCGGCCGGCACAAGA CCUACCUGUGCUACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGAA CCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGGACCCCGCCCAGAUCUACCGG GUGACCUGGUUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGCGGC UGCGGAUCUUCGCCGCCCGGAUCUACGACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGGACGCCGGCGCCCAGGUGUCCAU CAUGACCUACGACGAGUUCAAGCACUGCUGGGACACCUUCGUGGACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACGAGCAC UCCCAGGCCCUGUCCGGCCGGCUGCGGGCCAUCCUGCAGAACCAGGGCAACgaggccgccgccaaggaggccgccgccaaggaggccgccg ccaagGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGUGCCCUCCAA GAAGUUCAAGGUGCUGGGCAACACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAG GCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUCCAACGAGAUGG CCAAGGUGGACGACUCCUUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAA CAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGACAAGGCCGACCUG CGGCUGAUCUACCUGGCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGAGGGCGACCUGAACCCCGACAACUCCGACGUGG ACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGACGCCAAGGCCAUCCU GUCCGCCCGGCUGUCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCUGAUC GCCCUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCCAAGGACACCUACGACG ACGACCUGGACAACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUC CGACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAGCACCACCAGGACCUGACC CUGCUGAAGGCCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUCG ACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAGGAGCUGCUGGUGAAGCUGAA CCGGGAGGACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUGCGG CGGCAGGAGGACUUCUACCCCUUCCUGAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGGAUCCCCUACUACGUGGGCCCCC UGGCCCGGGGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGACAAGGG CGCCUCCGCCCAGUCCUUCAUCGAGCGGAUGACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUGCUGCCCAAGCACUCCCUGCUGUAC GAGUACUUCACCGUGUACAACGAGCUGACCAAGGUGAAGUACGUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAGCAGAAGA AGGCCAUCGUGGACCUGCUGUUCAAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGACUACUUCAAGAAGAUCGAGUGCUUCGA CUCCGUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUC CUGGACAACGAGGAGAACGAGGACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGA AGACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCCCGGAAGCUGAU CAACGGCAUCCGGGACAAGCAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUC CACGACGACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCACAUCGCCAACCUGG CCGGCUCCCCCGCCAUCAAGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGAA CAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGGAUCGAGGAGGGCAUC AAGGAGCUGGGCUCCCAGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGAACG GCCGGGACAUGUACGUGGACCAGGAGCUGGACAUCAACCGGCUGUCCGACUACGACGUGGACCACAUCGUGCCCCAGUCCUUCCUGAAGGA CGACUCCAUCGACAACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUG AAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCCGAGCGGGGCGGCCUGUCCG

		AGCUGGACAAGGCCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUGAA CACCAAGUACGACGAGAACGACAAGCUGAUCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUGUCCGACUUCCGGAAGGACUUC CAGUUCUACAAGGUGCGGGAGAUCAACAACUACCACCACGCCCACGACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAGAAGU ACCCCAAGCUGGAGUCCGAGUUCGUGUACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCCAAGUCCGAGCAGGAGAUCGGCAA GGCCACCGCCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAGCGGCCC CUGAUCGAGACCAACGGCGAGACCGGCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUGCGGAAGGUGCUGUCCAUGCCCCAGG UGAACAUCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUGAUCGCCCG GAAGAAGGACUGGGACCCCAAGAAGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGC AAGUCCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCGACUUCCUGG AGGCCAAGGGCUACAAGGAGGUGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAU GCUGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCUCCCACUACGAG AAGCUGAAGGGCUCCCCCGAGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCU CCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACAAGCCCAUCCGGGA GCAGGCCGAGAACAUCAUCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUUCAAGUACUUCGACACCACCAUCGACCGGAAG CGGUACACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAUCGACCUGUCCCAGC UGGGCGGCGACGGCGGCGGCUCCCCCAAGAAGAAGCGGAAGGUGUGA

367	用於具有連接子 L015 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGGAGGAGGAGGAAGCGAAGCAGCAGCAAAGGAAGCAGCAG CAAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAA GAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAA GCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGG CAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAA CAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUG AGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCG ACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCU GAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUC GCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACG ACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAG CGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACA CUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCG ACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAA CAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGA AGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGC UGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGG AGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUAC GAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGA AGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGA CAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUC CUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGA AGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAU CAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUC CACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGG CAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAA CAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUC AAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACG GAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGA CGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUG AAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCG

		AACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAA CACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUC CAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGU ACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAA GGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCG CUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGG UCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAG AAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGA AAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGG AAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAU GCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAA AAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCA GCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGA ACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAG AGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGC UGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAU GCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAAC GUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGA GCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUA

368	用於具有連接子 L016 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACgaggccgccgccaagggcggcggcggcagcggcggcggcg gcagcGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAA GAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAA GCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGG CAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAA CAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUG AGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCG ACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCU GAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUC GCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACG ACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAG CGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACA CUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCG ACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAA CAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGA AGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGC UGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGG AGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUAC GAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGA AGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGA CAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUC CUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGA AGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAU CAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUC CACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGG CAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAA CAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUC AAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACG GAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGA CGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUG AAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCG

		AACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAA CACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUC CAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGU ACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAA GGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCG CUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGG UCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAG AAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGA AAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGG AAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAU GCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAA AAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCA GCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGA ACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAG AGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGC UGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAU GCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAAC GUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGA GCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAG

369	用於具有連接子 L019 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACgaggccgccgccaaggaggccgccgccaaggaggccgccg ccaagGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUACAAGGUCCCGAGCAA GAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAA GCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCUUCAGCAACGAAAUGG CAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGAAA CAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACAGACAAGGCAGACCUG AGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGGACAACAGCGACGUCG ACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGACGCAAAGGCAAUCCU GAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAACCUGAUC GCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCAAGGACACAUACGACG ACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUCCUGCUGAG CGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACACCACCAGGACCUGACA CUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCAGGAUACAUCG ACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACUGCUGGUCAAGCUGAA CAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCACGCAAUCCUGAGA AGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGUACUACGUCGGACCGC UGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAAGUCGUCGACAAGGG AGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAGCACAGCCUGCUGUAC GAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGAGCGGAGAACAGAAGA AGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGA CAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUCAAGGACAAGGACUUC CUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUGA AGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACUGAGCAGAAAGCUGAU CAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUGAUC CACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAACACAUCGCAAACCUGG CAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCGGAAAA CAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGAAUCGAAGAAGGAAUC AAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCUGCAGAACG GAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCAGAGCUUCCUGAAGGA CGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUCAAGAAGAUG AAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGAGAGGAGGACUGAGCG

		AACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGACAGCAGAAUGAA CACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGACUUCAGAAAGGACUUC CAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUCAAGAAGU ACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGAACAGGAAAUCGGAAA GGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGAAAGAGACCG CUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGG UCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAGCUGAUCGCAAG AAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGA AAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCGAUCGACUUCCUGG AAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGAAU GCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUGGCAAGCCACUACGAA AAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAAUCAUCGAACAGAUCA GCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGACAAGCCGAUCAGAGA ACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACAACAAUCGACAGAAAG AGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAAUCGAUCUGAGCCAGC UGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGCAUCCUGAU GCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAAAGCACAGACGAAAAC GUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUCAAGAUGCUGA GCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAG

370	用於具有連接子 L021 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACggcggcggcggcagcggcggcggcggcagcggcggcggcg gcagcggcggcggcggcagcGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUA CAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGC GGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCU UCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACA CCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACA GACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGG ACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGA CGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUG UUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCA AGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGA CGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACAC CACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAU ACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACU GCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUG CACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGU ACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGA AGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAG CACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGA GCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAA GAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGA UCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACU GAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAAC UUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAAC ACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAG ACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGA AUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGU ACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCA GAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAA GUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGA

		GAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCU GGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGAC UUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAG CACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGA ACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCC UGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGA CAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCA AAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACC CGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAA CGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAA UCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGA CAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACA ACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAA UCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCA GGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAA AGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACA AGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAAUAG

371	用於具有連接子L024之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACggcggcggcggcagcggaggaggaggaagcgaagccgccg ccaaagaggccgccgccaagGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUA CAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGC GGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCU UCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACA CCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACA GACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGG ACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGA CGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUG UUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCA AGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGA CGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACAC CACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAU ACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACU GCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUG CACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGU ACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGA AGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAG CACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGA GCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAA GAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGA UCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACU GAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAAC UUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAAC ACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAG ACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGA AUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGU ACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCA GAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAA GUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGA

		GAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCU GGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGAC UUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAG CACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGA ACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCC UGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGA CAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCA AAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACC CGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAA CGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAA UCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGA CAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACA ACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAA UCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCA GGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAA AGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACA AGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

372	用於具有連接子 L025 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACggcggcggcggaagcgaggccgcugccaaaggcggaggag gaagcggaggaggcggcagcGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUA CAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGC GGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCU UCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACA CCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACA GACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGG ACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGA CGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUG UUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCA AGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGA CGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACAC CACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAU ACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACU GCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUG CACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGU ACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGA AGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAG CACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGA GCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAA GAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGA UCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACU GAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAAC UUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAAC ACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAG ACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGA AUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGU ACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCA GAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAA GUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGA

		GAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCU GGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGAC UUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAG CACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGA ACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCC UGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGA CAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCA AAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACC CGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAA CGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAA UCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGA CAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACA ACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAA UCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCA GGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAA AGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACA AGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

373	用於具有連接子L036之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACgaggccgccgccaaggaggccgccgccaaggaggccgccg ccaaggaggccgccgccaagGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAAUA CAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCACUGCUGUUCGACAGC GGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAAAUCU UCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAAGAAGCACGAAAGACA CCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGACAGCACA GACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAGGAGACCUGAACCCGG ACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGCGGAGUCGA CGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAAAAGAAGAACGGACUG UUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUGCAGCUGAGCA AGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGCAAAGAACCUGAGCGA CGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGAUACGACGAACAC CACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACCAGAGCAAGAACGGAU ACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGACGGAACAGAAGAACU GCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUCCACCUGGGAGAACUG CACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGACAUUCAGAAUCCCGU ACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACCGUGGAACUUCGAAGA AGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAAAAGGUCCUGCCGAAG CACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUGA GCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGAAGACUACUUCAAGAA GAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCGAAGACAGAGAAAUGA UCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGAAGACU GAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGAUUCGCAAACAGAAAC UUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUGCACGAAC ACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGUCAAGGUCAUGGGAAG ACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGAAUGAAGAGA AUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACGAAAAGCUGUACCUGU ACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGACCACAUCGUCCCGCA GAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAACGUCCCGAGCGAAGAA GUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUGACAAAGGCAGAGA

		GAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCACGUCGCACAGAUCCU GGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGCAAGCUGGUCAGCGAC UUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACGCAGUCGUCGGAACAG CACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUCGCAAAGAGCGA ACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACAGUCAGAAAGGUCC UGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGCGA CAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGCGUCCUGGUCGUCGCA AAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACC CGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCUGUUCGAACUGGAAAA CGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGCACUACCUGGACGAAA UCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGAGA CAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUCAAGUACUUCGACACA ACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGACUGUACGAAACAAGAA UCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCA GGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACAGCAUACGACGAA AGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACAGCAACGGAGAAAACA AGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

374	用於具有連接子 L051 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACggaggaggaggaagcgaagccgccgccaaagaggccgccg ccaagggaggcggcggcagcgaggccgccgccaagGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGU CAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCA CUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCU ACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAA GAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAG CUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAG GAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAA CGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAA AAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAA AGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGC AAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAG AGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACC AGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGA CGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUC CACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGA CAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACC GUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAA AAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAA AGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGA AGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGAC CUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCG AAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACAC AGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGA UUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAG ACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGU CAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGA GAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACG AAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGA CCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAAC GUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACC

		UGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCA CGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGC AAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACG CAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAU GAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACA CUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAA CAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCC GAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGC GUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCA GCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCU GUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUC AACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGC ACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUA CAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUC AAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGAC UGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAA GCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCAC ACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACA GCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

375	用於具有連接子 L062 之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACgaggccgccgccaaggaggccgccgccaagggcggcggcg gcagcggcggcggcggcagcggcggcggcggcagcGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGU CAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCA CUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCU ACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAA GAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAG CUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAG GAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAA CGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAA AAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAA AGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGC AAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAG AGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACC AGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGA CGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUC CACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGA CAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACC GUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAA AAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAA AGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGA AGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGAC CUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCG AAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACAC AGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGA UUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAG ACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGU CAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGA GAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACG AAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGA CCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAAC GUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACC

		UGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCA CGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGC AAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACG CAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAU GAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACA CUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAA CAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCC GAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGC GUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCA GCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCU GUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUC AACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGC ACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUA CAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUC AAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGAC UGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAA GCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCAC ACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACA GCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

376	用於具有連接子L063之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAAGCAGCAGCAAAGGAAGCAGCAGCAAAGGGAGGAGGAG GAAGCGGAGGAGGAGGAAGCGAAGCAGCAGCAAAGGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGU CAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCA CUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCU ACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAA GAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAG CUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAG GAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAA CGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAA AAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAA AGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGC AAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAG AGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACC AGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGA CGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUC CACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGA CAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACC GUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAA AAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAA AGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGA AGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGAC CUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCG AAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACAC AGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGA UUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAG ACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGU CAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGA GAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACG AAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGA CCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAAC GUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACC

		UGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCA CGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGC AAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACG CAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAU GAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACA CUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAA CAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCC GAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGC GUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCA GCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCU GUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUC AACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGC ACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUA CAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUC AAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGAC UGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAA GCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCAC ACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACA GCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA

377	用於具有連接子L066之鹼基編輯器之開讀框	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUGAUGGACCCGCACAUCUUCACAAGCAACUUCAACAACGGAAUCGGAAGACACAAGA CAUACCUGUGCUACGAAGUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUGGACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAGAA CCUGCUGUGCGGAUUCUACGGAAGACACGCAGAACUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUGGACCCGGCACAGAUCUACAGA GUCACAUGGUUCAUCAGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGAGAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUCAGAC UGAGAAUCUUCGCAGCAAGAAUCUACGACUACGACCCGCUGUACAAGGAAGCACUGCAGAUGCUGAGAGACGCAGGAGCACAGGUCAGCAU CAUGACAUACGACGAAUUCAAGCACUGCUGGGACACAUUCGUCGACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGACUGGACGAACAC AGCCAGGCACUGAGCGGAAGACUGAGAGCAAUCCUGCAGAACCAGGGAAACGAAGCAGCAGCAAAGGAAGCAGCAGCAAAGGAAGCAGCAG CAAAGGGAGGAGGAGGAAGCGGAGGAGGAGGAAGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGAACAAACAGCGUCGGAUGGGCAGU CAUCACAGACGAAUACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGAAACACAGACAGACACAGCAUCAAGAAGAACCUGAUCGGAGCA CUGCUGUUCGACAGCGGAGAAACAGCAGAAGCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUACACAAGAAGAAAGAACAGAAUCUGCU ACCUGCAGGAAAUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGCUUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAAGAAGACAA GAAGCACGAAAGACACCCGAUCUUCGGAAACAUCGUCGACGAAGUCGCAUACCACGAAAAGUACCCGACAAUCUACCACCUGAGAAAGAAG CUGGUCGACAGCACAGACAAGGCAGACCUGAGACUGAUCUACCUGGCACUGGCACACAUGAUCAAGUUCAGAGGACACUUCCUGAUCGAAG GAGACCUGAACCCGGACAACAGCGACGUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUACAACCAGCUGUUCGAAGAAAACCCGAUCAA CGCAAGCGGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUGAGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAGCUGCCGGGAGAA AAGAAGAACGGACUGUUCGGAAACCUGAUCGCACUGAGCCUGGGACUGACACCGAACUUCAAGAGCAACUUCGACCUGGCAGAAGACGCAA AGCUGCAGCUGAGCAAGGACACAUACGACGACGACCUGGACAACCUGCUGGCACAGAUCGGAGACCAGUACGCAGACCUGUUCCUGGCAGC AAAGAACCUGAGCGACGCAAUCCUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUCACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAG AGAUACGACGAACACCACCAGGACCUGACACUGCUGAAGGCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAGGAAAUCUUCUUCGACC AGAGCAAGAACGGAUACGCAGGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUCUACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGA CGGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAAGACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGAAGCAUCCCGCACCAGAUC CACCUGGGAGAACUGCACGCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUCCUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUGA CAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCAAGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAGAGCGAAGAAACAAUCACACC GUGGAACUUCGAAGAAGUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUCGAAAGAAUGACAAACUUCGACAAGAACCUGCCGAACGAA AAGGUCCUGCCGAAGCACAGCCUGCUGUACGAAUACUUCACAGUCUACAACGAACUGACAAAGGUCAAGUACGUCACAGAAGGAAUGAGAA AGCCGGCAUUCCUGAGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUGUUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUGAAGGA AGACUACUUCAAGAAGAUCGAAUGCUUCGACAGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAACGCAAGCCUGGGAACAUACCACGAC CUGCUGAAGAUCAUCAAGGACAAGGACUUCCUGGACAACGAAGAAAACGAAGACAUCCUGGAAGACAUCGUCCUGACACUGACACUGUUCG AAGACAGAGAAAUGAUCGAAGAAAGACUGAAGACAUACGCACACCUGUUCGACGACAAGGUCAUGAAGCAGCUGAAGAGAAGAAGAUACAC AGGAUGGGGAAGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGACAAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAGAGCGACGGA UUCGCAAACAGAAACUUCAUGCAGCUGAUCCACGACGACAGCCUGACAUUCAAGGAAGACAUCCAGAAGGCACAGGUCAGCGGACAGGGAG ACAGCCUGCACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCAAUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUCGACGAACUGGU CAAGGUCAUGGGAAGACACAAGCCGGAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAGACAACACAGAAGGGACAGAAGAACAGCAGA GAAAGAAUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGGAAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACACACAGCUGCAGAACG AAAAGCUGUACCUGUACUACCUGCAGAACGGAAGAGACAUGUACGUCGACCAGGAACUGGACAUCAACAGACUGAGCGACUACGACGUCGA CCACAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAUCGACAACAAGGUCCUGACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAAC GUCCCGAGCGAAGAAGUCGUCAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAACGCAAAGCUGAUCACACAGAGAAAGUUCGACAACC

		UGACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGACAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACAAGACAGAUCACAAAGCA CGUCGCACAGAUCCUGGACAGCAGAAUGAACACAAAGUACGACGAAAACGACAAGCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGC AAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAGGUCAGAGAAAUCAACAACUACCACCACGCACACGACGCAUACCUGAACG CAGUCGUCGGAACAGCACUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUACGGAGACUACAAGGUCUACGACGUCAGAAAGAU GAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUCAAGACAGAAAUCACA CUGGCAAACGGAGAAAUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAA CAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGCAAGGAAAGCAUCCUGCC GAAGAGAAACAGCGACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGC GUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUCACAAUCAUGGAAAGAAGCA GCUUCGAAAAGAACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGCCU GUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUGGCACUGCCGAGCAAGUACGUC AACUUCCUGUACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAACAGCACAAGC ACUACCUGGACGAAAUCAUCGAACAGAUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAACCUGGACAAGGUCCUGAGCGCAUA CAACAAGCACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUCCACCUGUUCACACUGACAAACCUGGGAGCACCGGCAGCAUUC AAGUACUUCGACACAACAAUCGACAGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGACGCAACACUGAUCCACCAGAGCAUCACAGGAC UGUACGAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGACAGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAAAAGGAAACAGGAAA GCAGCUGGUCAUCCAGGAAAGCAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAAGCGACAUCCUGGUCCAC ACAGCAUACGACGAAAGCACAGACGAAAACGUCAUGCUGCUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACA GCAACGGAGAAAACAAGAUCAAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGAAAGGUCUAA
378-386未使用		
387	用於D16A Nme2Cas9切口酶之胺基酸序列	MAAFKPNPINYILGLAIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAH RLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETAD KELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVS GGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDTERATL MDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQD EIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNT EEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAK FREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQ NKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHILLT GKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKET GKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKM SGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNP FYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDID CKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVN ELGKEIRPCRLKKRPPVR

388	用於 D16A Nme2Cas9 切口酶之編碼序列	GCTGCTTTTAAGCCTAATCCTATTAATTATATTCTTGGTCTTGCTATTGGTATTGCTTCTGTTGGTTGGGCTATG GTTGAGATTGATGAGGAGGAGAATCCTATTCGTCTTATTGATCTTGGTGTTCGTGTTTTTGAGCGTGCTGAGGT TCCTAAGACTGGTGATTCTCTTGCTATGGCTCGTCGTCTTGCTCGTTCTGTTCGTCGTCTTACTCGTCGTCGTGCT CATCGTCTTCTTCGTGCTCGTCGTCTTCTTAAGCGTGAGGGTGTTCTTCAGGCTGCTGATTTTGATGAGAATGGT CTTATTAAGTCTCTTCCTAATACTCCTTGGCAGCTTCGTGCTGCTGCTCTTGATCGTAAGCTTACTCCTCTTGAG TGGTCTGCTGTTCTTCTTCATCTTATTAAGCATCGTGGTTATCTTTCTCAGCGTAAGAATGAGGGTGAGACTGCT GATAAGGAGCTTGGTGCTCTTCTTAAGGGTGTTGCTAATAATGCTCATGCTCTTCAGACTGGTGATTTTCGTAC TCCTGCTGAGCTTGCTCTTAATAAGTTTGAGAAGGAGTCTGGTCATATTCGTAATCAGCGTGGTGATTATTCTC ATACTTTTTCTCGTAAGGATCTTCAGGCTGAGCTTATTCTTCTTTTTGAGAAGCAGAAGGAGTTTGGTAATCCTC ATGTTTCTGGTGGTCTTAAGGAGGGTATTGAGACTCTTCTTATGACTCAGCGTCCTGCTCTTTCTGGTGATGCTG TTCAGAAGATGCTTGGTCATTGTACTTTTGAGCCTGCTGAGCCTAAGGCTGCTAAGAATACTTATACTGCTGAG CGTTTTATTTGGCTTACTAAGCTTAATAATCTTCGTATTCTTGAGCAGGGTTCTGAGCGTCCTCTTACTGATACT GAGCGTGCTACTCTTATGGATGAGCCTTATCGTAAGTCTAAGCTTACTTATGCTCAGGCTCGTAAGCTTCTTGG TCTTGAGGATACTGCTTTTTTTAAGGGTCTTCGTTATGGTAAGGATAATGCTGAGGCTTCTACTCTTATGGAGAT GAAGGCTTATCATGCTATTTCTCGTGCTCTTGAGAAGGAGGGTCTTAAGGATAAGAAGTCTCCTCTTAATCTTT CTTCTGAGCTTCAGGATGAGATTGGTACTGCTTTTTCTCTTTTTAAGACTGATGAGGATATTACTGGTCGTCTTA AGGATCGTGTTCAGCCTGAGATTCTTGAGGCTCTTCTTAAGCATATTTCTTTTGATAAGTTTGTTCAGATTTCTC TTAAGGCTCTTCGTCGTATTGTTCCTCTTATGGAGCAGGGTAAGCGTTATGATGAGGCTTGTGCTGAGATTTAT GGTGATCATTATGGTAAGAAGAATACTGAGGAGAAGATTTATCTTCCTCCTATTCCTGCTGATGAGATTCGTAA TCCTGTTGTTCTTCGTGCTCTTTCTCAGGCTCGTAAGGTTATTAATGGTGTTGTTCGTCGTTATGGTTCTCCTGCT CGTATTCATATTGAGACTGCTCGTGAGGTTGGTAAGTCTTTTAAGGATCGTAAGGAGATTGAGAAGCGTCAGG AGGAGAATCGTAAGGATCGTGAGAAGGCTGCTGCTAAGTTTCGTGAGTATTTTCCTAATTTTGTTGGTGAGCCT AAGTCTAAGGATATTCTTAAGCTTCGTCTTTATGAGCAGCAGCATGGTAAGTGTCTTTATTCTGGTAAGGAGAT TAATCTTGTTCGTCTTAATGAGAAGGGTTATGTTGAGATTGATCATGCTCTTCCTTTTTCTCGTACTTGGGATGA TTCTTTTAATAATAAGGTTCTTGTTCTTGGTTCTGAGAATCAGAATAAGGGTAATCAGACTCCTTATGAGTATTT TAATGGTAAGGATAATTCTCGTGAGTGGCAGGAGTTTAAGGCTCGTGTTGAGACTTCTCGTTTTCCTCGTTCTA AGAAGCAGCGTATTCTTCTTCAGAAGTTTGATGAGGATGGTTTTAAGGAGTGTAATCTTAATGATACTCGTTAT GTTAATCGTTTTCTTTGTCAGTTTGTTGCTGATCATATTCTTCTTACTGGTAAGGGTAAGCGTCGTGTTTTTGCTT CTAATGGTCAGATTACTAATCTTCTTCGTGGTTTTTGGGGTCTTCGTAAGGTTCGTGCTGAGAATGATCGTCATC ATGCTCTTGATGCTGTTGTTGTTGCTTGTTCTACTGTTGCTATGCAGCAGAAGATTACTCGTTTTGTTCGTTATA AGGAGATGAATGCTTTTGATGGTAAGACTATTGATAAGGAGACTGGTAAGGTTCTTCATCAGAAGACTCATTT TCCTCAGCCTTGGGAGTTTTTTGCTCAGGAGGTTATGATTCGTGTTTTTGGTAAGCCTGATGGTAAGCCTGAGTT TGAGGAGGCTGATACTCCTGAGAAGCTTCGTACTCTTCTTGCTGAGAAGCTTTCTTCTCGTCCTGAGGCTGTTC

		ATGAGTATGTTACTCCTCTTTTTGTTTCTCGTGCTCCTAATCGTAAGATGTCTGGTGCTCATAAGGATACTCTTC GTTCTGCTAAGCGTTTTGTTAAGCATAATGAGAAGATTTCTGTTAAGCGTGTTTGGCTTACTGAGATTAAGCTT GCTGATCTTGAGAATATGGTTAATTATAAGAATGGTCGTGAGATTGAGCTTTATGAGGCTCTTAAGGCTCGTCT TGAGGCTTATGGTGGTAATGCTAAGCAGGCTTTTGATCCTAAGGATAATCCTTTTTATAAGAAGGGTGGTCAGC TTGTTAAGGCTGTTCGTGTTGAGAAGACTCAGGAGTCTGGTGTTCTTCTTAATAAGAAGAATGCTTATACTATT GCTGATAATGGTGATATGGTTCGTGTTGATGTTTTTTGTAAGGTTGATAAGAAGGGTAAGAATCAGTATTTTAT TGTTCCTATTTATGCTTGGCAGGTTGCTGAGAATATTCTTCCTGATATTGATTGTAAGGGTTATCGTATTGATGA TTCTTATACTTTTTGTTTTTCTCTTCATAAGTATGATCTTATTGCTTTTCAGAAGGATGAGAAGTCTAAGGTTGA GTTTGCTTATTATATTAATTGTGATTCTTCTAATGGTCGTTTTTATCTTGCTTGGCATGATAAGGGTTCTAAGGA GCAGCAGTTTCGTATTTCTACTCAGAATCTTGTTCTTATTCAGAAGTATCAGGTTAATGAGCTTGGTAAGGAGA TTCGTCCTTGTCGTCTTAAGAAGCGTCCTCCTGTTCGT

389	用於 D16A Nme2Cas9 切口酶之編碼序列	GCCGCCTTCAAGCCCAACCCCATCAACTACATCCTGGGCCTGGCCATCGGCATCGCCTCCGTGGGCTGGGCCAT GGTGGAGATCGACGAGGAGGAGAACCCCATCCGGCTGATCGACCTGGGCGTGCGGGTGTTCGAGCGGGCCGA GGTGCCCAAGACCGGCGACTCCCTGGCCATGGCCCGGCGGCTGGCCCGGTCCGTGCGGCGGCTGACCCGGCGG CGGGCCCACCGGCTGCTGCGGGCCCGGCGGCTGCTGAAGCGGGAGGGCGTGCTGCAGGCCGCCGACTTCGAC GAGAACGGCCTGATCAAGTCCCTGCCCAACACCCCCTGGCAGCTGCGGGCCGCCGCCCTGGACCGGAAGCTGA CCCCCCTGGAGTGGTCCGCCGTGCTGCTGCACCTGATCAAGCACCGGGGCTACCTGTCCCAGCGGAAGAACGA GGGCGAGACCGCCGACAAGGAGCTGGGCGCCCTGCTGAAGGGCGTGGCCAACAACGCCCACGCCCTGCAGAC CGGCGACTTCCGGACCCCCGCCGAGCTGGCCCTGAACAAGTTCGAGAAGGAGTCCGGCCACATCCGGAACCA GCGGGGCGACTACTCCCACACCTTCTCCCGGAAGGACCTGCAGGCCGAGCTGATCCTGCTGTTCGAGAAGCAG AAGGAGTTCGGCAACCCCCACGTGTCCGGCGGCCTGAAGGAGGGCATCGAGACCCTGCTGATGACCCAGCGG CCCGCCCTGTCCGGCGACGCCGTGCAGAAGATGCTGGGCCACTGCACCTTCGAGCCCGCCGAGCCCAAGGCCG CCAAGAACACCTACACCGCCGAGCGGTTCATCTGGCTGACCAAGCTGAACAACCTGCGGATCCTGGAGCAGGG CTCCGAGCGGCCCCTGACCGACACCGAGCGGGCCACCCTGATGGACGAGCCCTACCGGAAGTCCAAGCTGACC TACGCCCAGGCCCGGAAGCTGCTGGGCCTGGAGGACACCGCCTTCTTCAAGGGCCTGCGGTACGGCAAGGACA ACGCCGAGGCCTCCACCCTGATGGAGATGAAGGCCTACCACGCCATCTCCCGGGCCCTGGAGAAGGAGGGCCT GAAGGACAAGAAGTCCCCCCTGAACCTGTCCTCCGAGCTGCAGGACGAGATCGGCACCGCCTTCTCCCTGTTC AAGACCGACGAGGACATCACCGGCCGGCTGAAGGACCGGGTGCAGCCCGAGATCCTGGAGGCCCTGCTGAAG CACATCTCCTTCGACAAGTTCGTGCAGATCTCCCTGAAGGCCCTGCGGCGGATCGTGCCCCTGATGGAGCAGG GCAAGCGGTACGACGAGGCCTGCGCCGAGATCTACGGCGACCACTACGGCAAGAAGAACACCGAGGAGAAG ATCTACCTGCCCCCCATCCCCGCCGACGAGATCCGGAACCCCGTGGTGCTGCGGGCCCTGTCCCAGGCCCGGA AGGTGATCAACGGCGTGGTGCGGCGGTACGGCTCCCCCGCCCGGATCCACATCGAGACCGCCCGGGAGGTGG GCAAGTCCTTCAAGGACCGGAAGGAGATCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCC GCCGCCAAGTTCCGGGAGTACTTCCCCAACTTCGTGGGCGAGCCCAAGTCCAAGGACATCCTGAAGCTGCGGC TGTACGAGCAGCAGCACGGCAAGTGCCTGTACTCCGGCAAGGAGATCAACCTGGTGCGGCTGAACGAGAAGG GCTACGTGGAGATCGACCACGCCCTGCCCTTCTCCCGGACCTGGGACGACTCCTTCAACAACAAGGTGCTGGT GCTGGGCTCCGAGAACCAGAACAAGGGCAACCAGACCCCCTACGAGTACTTCAACGGCAAGGACAACTCCCG GGAGTGGCAGGAGTTCAAGGCCCGGGTGGAGACCTCCCGGTTCCCCCGGTCCAAGAAGCAGCGGATCCTGCTG CAGAAGTTCGACGAGGACGGCTTCAAGGAGTGCAACCTGAACGACACCCGGTACGTGAACCGGTTCCTGTGCC AGTTCGTGGCCGACCACATCCTGCTGACCGGCAAGGGCAAGCGGCGGGTGTTCGCCTCCAACGGCCAGATCAC CAACCTGCTGCGGGGCTTCTGGGGCCTGCGGAAGGTGCGGGCCGAGAACGACCGGCACCACGCCCTGGACGC CGTGGTGGTGGCCTGCTCCACCGTGGCCATGCAGCAGAAGATCACCCGGTTCGTGCGGTACAAGGAGATGAAC GCCTTCGACGGCAAGACCATCGACAAGGAGACCGGCAAGGTGCTGCACCAGAAGACCCACTTCCCCCAGCCCT GGGAGTTCTTCGCCCAGGAGGTGATGATCCGGGTGTTCGGCAAGCCCGACGGCAAGCCCGAGTTCGAGGAGG

		CCGACACCCCCGAGAAGCTGCGGACCCTGCTGGCCGAGAAGCTGTCCTCCCGGCCCGAGGCCGTGCACGAGTA CGTGACCCCCCTGTTCGTGTCCCGGGCCCCCAACCGGAAGATGTCCGGCGCCCACAAGGACACCCTGCGGTCC GCCAAGCGGTTCGTGAAGCACAACGAGAAGATCTCCGTGAAGCGGGTGTGGCTGACCGAGATCAAGCTGGCC GACCTGGAGAACATGGTGAACTACAAGAACGGCCGGGAGATCGAGCTGTACGAGGCCCTGAAGGCCCGGCTG GAGGCCTACGGCGGCAACGCCAAGCAGGCCTTCGACCCCAAGGACAACCCCTTCTACAAGAAGGGCGGCCAG CTGGTGAAGGCCGTGCGGGTGGAGAAGACCCAGGAGTCCGGCGTGCTGCTGAACAAGAAGAACGCCTACACC ATCGCCGACAACGGCGACATGGTGCGGGTGGACGTGTTCTGCAAGGTGGACAAGAAGGGCAAGAACCAGTAC TTCATCGTGCCCATCTACGCCTGGCAGGTGGCCGAGAACATCCTGCCCGACATCGACTGCAAGGGCTACCGGA TCGACGACTCCTACACCTTCTGCTTCTCCCTGCACAAGTACGACCTGATCGCCTTCCAGAAGGACGAGAAGTCC AAGGTGGAGTTCGCCTACTACATCAACTGCGACTCCTCCAACGGCCGGTTCTACCTGGCCTGGCACGACAAGG GCTCCAAGGAGCAGCAGTTCCGGATCTCCACCCAGAACCTGGTGCTGATCCAGAAGTACCAGGTGAACGAGCT GGGCAAGGAGATCCGGCCCTGCCGGCTGAAGAAGCGGCCCCCCGTGCGG

390	用於 D16A Nme2Cas9 切口酶之編碼序列	GCCGCCTTCAAGCCCAACCCCATCAACTACATCCTGGGCCTGGCCATCGGCATCGCCTCCGTGGGCTGGGCCAT GGTGGAGATCGACGAGGAGGAGAACCCCATCCGGCTGATCGACCTGGGCGTGCGGGTGTTCGAGCGGGCCGA GGTGCCCAAGACCGGCGACTCCCTGGCCATGGCCCGGCGGCTGGCCCGGTCCGTGCGGCGGCTGACCCGGCGG CGGGCCCACCGGCTGCTGCGGGCCCGGCGGCTGCTGAAGCGGGAGGGCGTGCTGCAGGCCGCCGACTTCGAC GAGAACGGCCTGATCAAGTCCCTGCCCAACACCCCCTGGCAGCTGCGGGCCGCCGCCCTGGACCGGAAGCTGA CCCCCCTGGAGTGGTCCGCCGTGCTGCTGCACCTGATCAAGCACCGGGGCTACCTGTCCCAGCGGAAGAACGA GGGCGAGACCGCCGACAAGGAGCTGGGCGCCCTGCTGAAGGGCGTGGCCAACAACGCCCACGCCCTGCAGAC CGGCGACTTCCGGACCCCCGCCGAGCTGGCCCTGAACAAGTTCGAGAAGGAGTCCGGCCACATCCGGAACCA GCGGGGCGACTACTCCCACACCTTCTCCCGGAAGGACCTGCAGGCCGAGCTGATCCTGCTGTTCGAGAAGCAG AAGGAGTTCGGCAACCCCCACGTGTCCGGCGGCCTGAAGGAGGGCATCGAGACCCTGCTGATGACCCAGCGG CCCGCCCTGTCCGGCGACGCCGTGCAGAAGATGCTGGGCCACTGCACCTTCGAGCCCGCCGAGCCCAAGGCCG CCAAGAACACCTACACCGCCGAGCGGTTCATCTGGCTGACCAAGCTGAACAACCTGCGGATCCTGGAGCAGGG CTCCGAGCGGCCCCTGACCGACACCGAGCGGGCCACCCTGATGGACGAGCCCTACCGGAAGTCCAAGCTGACC TACGCCCAGGCCCGGAAGCTGCTGGGCCTGGAGGACACCGCCTTCTTCAAGGGCCTGCGGTACGGCAAGGACA ACGCCGAGGCCTCCACCCTGATGGAGATGAAGGCCTACCACGCCATCTCCCGGGCCCTGGAGAAGGAGGGCCT GAAGGACAAGAAGTCCCCCCTGAACCTGTCCTCCGAGCTGCAGGACGAGATCGGCACCGCCTTCTCCCTGTTC AAGACCGACGAGGACATCACCGGCCGGCTGAAGGACCGGGTGCAGCCCGAGATCCTGGAGGCCCTGCTGAAG CACATCTCCTTCGACAAGTTCGTGCAGATCTCCCTGAAGGCCCTGCGGCGGATCGTGCCCCTGATGGAGCAGG GCAAGCGGTACGACGAGGCCTGCGCCGAGATCTACGGCGACCACTACGGCAAGAAGAACACCGAGGAGAAG ATCTACCTGCCCCCCATCCCCGCCGACGAGATCCGGAACCCCGTGGTGCTGCGGGCCCTGTCCCAGGCCCGGA AGGTGATCAACGGCGTGGTGCGGCGGTACGGCTCCCCCGCCCGGATCCACATCGAGACCGCCCGGGAGGTGG GCAAGTCCTTCAAGGACCGGAAGGAGATCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGAAGGCC GCCGCCAAGTTCCGGGAGTACTTCCCCAACTTCGTGGGCGAGCCCAAGTCCAAGGACATCCTGAAGCTGCGGC TGTACGAGCAGCAGCACGGCAAGTGCCTGTACTCCGGCAAGGAGATCAACCTGGTGCGGCTGAACGAGAAGG GCTACGTGGAGATCGACCACGCCCTGCCCTTCTCCCGGACCTGGGACGACTCCTTCAACAACAAGGTGCTGGT GCTGGGCTCCGAGAACCAGAACAAGGGCAACCAGACCCCCTACGAGTACTTCAACGGCAAGGACAACTCCCG GGAGTGGCAGGAGTTCAAGGCCCGGGTGGAGACCTCCCGGTTCCCCCGGTCCAAGAAGCAGCGGATCCTGCTG CAGAAGTTCGACGAGGACGGCTTCAAGGAGTGCAACCTGAACGACACCCGGTACGTGAACCGGTTCCTGTGCC AGTTCGTGGCCGACCACATCCTGCTGACCGGCAAGGGCAAGCGGCGGGTGTTCGCCTCCAACGGCCAGATCAC CAACCTGCTGCGGGGCTTCTGGGGCCTGCGGAAGGTGCGGGCCGAGAACGACCGGCACCACGCCCTGGACGC CGTGGTGGTGGCCTGCTCCACCGTGGCCATGCAGCAGAAGATCACCCGGTTCGTGCGGTACAAGGAGATGAAC GCCTTCGACGGCAAGACCATCGACAAGGAGACCGGCAAGGTGCTGCACCAGAAGACCCACTTCCCCCAGCCCT GGGAGTTCTTCGCCCAGGAGGTGATGATCCGGGTGTTCGGCAAGCCCGACGGCAAGCCCGAGTTCGAGGAGG

		CCGACACCCCCGAGAAGCTGCGGACCCTGCTGGCCGAGAAGCTGTCCTCCCGGCCCGAGGCCGTGCACGAGTA CGTGACCCCCCTGTTCGTGTCCCGGGCCCCCAACCGGAAGATGTCCGGCGCCCACAAGGACACCCTGCGGTCC GCCAAGCGGTTCGTGAAGCACAACGAGAAGATCTCCGTGAAGCGGGTGTGGCTGACCGAGATCAAGCTGGCC GACCTGGAGAACATGGTGAACTACAAGAACGGCCGGGAGATCGAGCTGTACGAGGCCCTGAAGGCCCGGCTG GAGGCCTACGGCGGCAACGCCAAGCAGGCCTTCGACCCCAAGGACAACCCCTTCTACAAGAAGGGCGGCCAG CTGGTGAAGGCCGTGCGGGTGGAGAAGACCCAGGAGTCCGGCGTGCTGCTGAACAAGAAGAACGCCTACACC ATCGCCGACAACGGCGACATGGTGCGGGTGGACGTGTTCTGCAAGGTGGACAAGAAGGGCAAGAACCAGTAC TTCATCGTGCCCATCTACGCCTGGCAGGTGGCCGAGAACATCCTGCCCGACATCGACTGCAAGGGCTACCGGA TCGACGACTCCTACACCTTCTGCTTCTCCCTGCACAAGTACGACCTGATCGCCTTCCAGAAGGACGAGAAGTCC AAGGTGGAGTTCGCCTACTACATCAACTGCGACTCCTCCAACGGCCGGTTCTACCTGGCCTGGCACGACAAGG GCTCCAAGGAGCAGCAGTTCCGGATCTCCACCCAGAACCTGGTGCTGATCCAGAAGTACCAGGTGAACGAGCT GGGCAAGGAGATCCGGCCCTGCCGGCTGAAGAAGCGGCCCCCCGTGCGG

391	用於 D16A Nme2Cas9 切口酶之開讀框	ATGGCTGCTTTTAAGCCTAATCCTATTAATTATATTCTTGGTCTTGCTATTGGTATTGCTTCTGTTGGTTGGGCT ATGGTTGAGATTGATGAGGAGGAGAATCCTATTCGTCTTATTGATCTTGGTGTTCGTGTTTTTGAGCGTGCTGA GGTTCCTAAGACTGGTGATTCTCTTGCTATGGCTCGTCGTCTTGCTCGTTCTGTTCGTCGTCTTACTCGTCGTCG TGCTCATCGTCTTCTTCGTGCTCGTCGTCTTCTTAAGCGTGAGGGTGTTCTTCAGGCTGCTGATTTTGATGAGAA TGGTCTTATTAAGTCTCTTCCTAATACTCCTTGGCAGCTTCGTGCTGCTGCTCTTGATCGTAAGCTTACTCCTCTT GAGTGGTCTGCTGTTCTTCTTCATCTTATTAAGCATCGTGGTTATCTTTCTCAGCGTAAGAATGAGGGTGAGAC TGCTGATAAGGAGCTTGGTGCTCTTCTTAAGGGTGTTGCTAATAATGCTCATGCTCTTCAGACTGGTGATTTTC GTACTCCTGCTGAGCTTGCTCTTAATAAGTTTGAGAAGGAGTCTGGTCATATTCGTAATCAGCGTGGTGATTAT TCTCATACTTTTTCTCGTAAGGATCTTCAGGCTGAGCTTATTCTTCTTTTTGAGAAGCAGAAGGAGTTTGGTAAT CCTCATGTTTCTGGTGGTCTTAAGGAGGGTATTGAGACTCTTCTTATGACTCAGCGTCCTGCTCTTTCTGGTGAT GCTGTTCAGAAGATGCTTGGTCATTGTACTTTTGAGCCTGCTGAGCCTAAGGCTGCTAAGAATACTTATACTGC TGAGCGTTTTATTTGGCTTACTAAGCTTAATAATCTTCGTATTCTTGAGCAGGGTTCTGAGCGTCCTCTTACTGA TACTGAGCGTGCTACTCTTATGGATGAGCCTTATCGTAAGTCTAAGCTTACTTATGCTCAGGCTCGTAAGCTTC TTGGTCTTGAGGATACTGCTTTTTTTAAGGGTCTTCGTTATGGTAAGGATAATGCTGAGGCTTCTACTCTTATGG AGATGAAGGCTTATCATGCTATTTCTCGTGCTCTTGAGAAGGAGGGTCTTAAGGATAAGAAGTCTCCTCTTAAT CTTTCTTCTGAGCTTCAGGATGAGATTGGTACTGCTTTTTCTCTTTTTAAGACTGATGAGGATATTACTGGTCGT CTTAAGGATCGTGTTCAGCCTGAGATTCTTGAGGCTCTTCTTAAGCATATTTCTTTTGATAAGTTTGTTCAGATT TCTCTTAAGGCTCTTCGTCGTATTGTTCCTCTTATGGAGCAGGGTAAGCGTTATGATGAGGCTTGTGCTGAGAT TTATGGTGATCATTATGGTAAGAAGAATACTGAGGAGAAGATTTATCTTCCTCCTATTCCTGCTGATGAGATTC GTAATCCTGTTGTTCTTCGTGCTCTTTCTCAGGCTCGTAAGGTTATTAATGGTGTTGTTCGTCGTTATGGTTCTCC TGCTCGTATTCATATTGAGACTGCTCGTGAGGTTGGTAAGTCTTTTAAGGATCGTAAGGAGATTGAGAAGCGTC AGGAGGAGAATCGTAAGGATCGTGAGAAGGCTGCTGCTAAGTTTCGTGAGTATTTTCCTAATTTTGTTGGTGA GCCTAAGTCTAAGGATATTCTTAAGCTTCGTCTTTATGAGCAGCAGCATGGTAAGTGTCTTTATTCTGGTAAGG AGATTAATCTTGTTCGTCTTAATGAGAAGGGTTATGTTGAGATTGATCATGCTCTTCCTTTTTCTCGTACTTGGG ATGATTCTTTTAATAATAAGGTTCTTGTTCTTGGTTCTGAGAATCAGAATAAGGGTAATCAGACTCCTTATGAG TATTTTAATGGTAAGGATAATTCTCGTGAGTGGCAGGAGTTTAAGGCTCGTGTTGAGACTTCTCGTTTTCCTCG TTCTAAGAAGCAGCGTATTCTTCTTCAGAAGTTTGATGAGGATGGTTTTAAGGAGTGTAATCTTAATGATACTC GTTATGTTAATCGTTTTCTTTGTCAGTTTGTTGCTGATCATATTCTTCTTACTGGTAAGGGTAAGCGTCGTGTTTT TGCTTCTAATGGTCAGATTACTAATCTTCTTCGTGGTTTTTGGGGTCTTCGTAAGGTTCGTGCTGAGAATGATCG TCATCATGCTCTTGATGCTGTTGTTGTTGCTTGTTCTACTGTTGCTATGCAGCAGAAGATTACTCGTTTTGTTCG TTATAAGGAGATGAATGCTTTTGATGGTAAGACTATTGATAAGGAGACTGGTAAGGTTCTTCATCAGAAGACT CATTTTCCTCAGCCTTGGGAGTTTTTTGCTCAGGAGGTTATGATTCGTGTTTTTGGTAAGCCTGATGGTAAGCCT GAGTTTGAGGAGGCTGATACTCCTGAGAAGCTTCGTACTCTTCTTGCTGAGAAGCTTTCTTCTCGTCCTGAGGC

		TGTTCATGAGTATGTTACTCCTCTTTTTGTTTCTCGTGCTCCTAATCGTAAGATGTCTGGTGCTCATAAGGATAC TCTTCGTTCTGCTAAGCGTTTTGTTAAGCATAATGAGAAGATTTCTGTTAAGCGTGTTTGGCTTACTGAGATTAA GCTTGCTGATCTTGAGAATATGGTTAATTATAAGAATGGTCGTGAGATTGAGCTTTATGAGGCTCTTAAGGCTC GTCTTGAGGCTTATGGTGGTAATGCTAAGCAGGCTTTTGATCCTAAGGATAATCCTTTTTATAAGAAGGGTGGT CAGCTTGTTAAGGCTGTTCGTGTTGAGAAGACTCAGGAGTCTGGTGTTCTTCTTAATAAGAAGAATGCTTATAC TATTGCTGATAATGGTGATATGGTTCGTGTTGATGTTTTTTGTAAGGTTGATAAGAAGGGTAAGAATCAGTATT TTATTGTTCCTATTTATGCTTGGCAGGTTGCTGAGAATATTCTTCCTGATATTGATTGTAAGGGTTATCGTATTG ATGATTCTTATACTTTTTGTTTTTCTCTTCATAAGTATGATCTTATTGCTTTTCAGAAGGATGAGAAGTCTAAGG TTGAGTTTGCTTATTATATTAATTGTGATTCTTCTAATGGTCGTTTTTATCTTGCTTGGCATGATAAGGGTTCTA AGGAGCAGCAGTTTCGTATTTCTACTCAGAATCTTGTTCTTATTCAGAAGTATCAGGTTAATGAGCTTGGTAAG GAGATTCGTCCTTGTCGTCTTAAGAAGCGTCCTCCTGTTCGTUGA

392	用於 D16A Nme2Cas9 切口酶之開讀框	ATGGCCGCCTTCAAGCCCAACCCCATCAACTACATCCTGGGCCTGGCCATCGGCATCGCCTCCGTGGGCTGGG CCATGGTGGAGATCGACGAGGAGGAGAACCCCATCCGGCTGATCGACCTGGGCGTGCGGGTGTTCGAGCGGG CCGAGGTGCCCAAGACCGGCGACTCCCTGGCCATGGCCCGGCGGCTGGCCCGGTCCGTGCGGCGGCTGACCCG GCGGCGGGCCCACCGGCTGCTGCGGGCCCGGCGGCTGCTGAAGCGGGAGGGCGTGCTGCAGGCCGCCGACTT CGACGAGAACGGCCTGATCAAGTCCCTGCCCAACACCCCCTGGCAGCTGCGGGCCGCCGCCCTGGACCGGAAG CTGACCCCCCTGGAGTGGTCCGCCGTGCTGCTGCACCTGATCAAGCACCGGGGCTACCTGTCCCAGCGGAAGA ACGAGGGCGAGACCGCCGACAAGGAGCTGGGCGCCCTGCTGAAGGGCGTGGCCAACAACGCCCACGCCCTGC AGACCGGCGACTTCCGGACCCCCGCCGAGCTGGCCCTGAACAAGTTCGAGAAGGAGTCCGGCCACATCCGGA ACCAGCGGGGCGACTACTCCCACACCTTCTCCCGGAAGGACCTGCAGGCCGAGCTGATCCTGCTGTTCGAGAA GCAGAAGGAGTTCGGCAACCCCCACGTGTCCGGCGGCCTGAAGGAGGGCATCGAGACCCTGCTGATGACCCA GCGGCCCGCCCTGTCCGGCGACGCCGTGCAGAAGATGCTGGGCCACTGCACCTTCGAGCCCGCCGAGCCCAAG GCCGCCAAGAACACCTACACCGCCGAGCGGTTCATCTGGCTGACCAAGCTGAACAACCTGCGGATCCTGGAGC AGGGCTCCGAGCGGCCCCTGACCGACACCGAGCGGGCCACCCTGATGGACGAGCCCTACCGGAAGTCCAAGC TGACCTACGCCCAGGCCCGGAAGCTGCTGGGCCTGGAGGACACCGCCTTCTTCAAGGGCCTGCGGTACGGCAA GGACAACGCCGAGGCCTCCACCCTGATGGAGATGAAGGCCTACCACGCCATCTCCCGGGCCCTGGAGAAGGA GGGCCTGAAGGACAAGAAGTCCCCCCTGAACCTGTCCTCCGAGCTGCAGGACGAGATCGGCACCGCCTTCTCC CTGTTCAAGACCGACGAGGACATCACCGGCCGGCTGAAGGACCGGGTGCAGCCCGAGATCCTGGAGGCCCTG CTGAAGCACATCTCCTTCGACAAGTTCGTGCAGATCTCCCTGAAGGCCCTGCGGCGGATCGTGCCCCTGATGG AGCAGGGCAAGCGGTACGACGAGGCCTGCGCCGAGATCTACGGCGACCACTACGGCAAGAAGAACACCGAGG AGAAGATCTACCTGCCCCCCATCCCCGCCGACGAGATCCGGAACCCCGTGGTGCTGCGGGCCCTGTCCCAGGC CCGGAAGGTGATCAACGGCGTGGTGCGGCGGTACGGCTCCCCCGCCCGGATCCACATCGAGACCGCCCGGGA GGTGGGCAAGTCCTTCAAGGACCGGAAGGAGATCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGA AGGCCGCCGCCAAGTTCCGGGAGTACTTCCCCAACTTCGTGGGCGAGCCCAAGTCCAAGGACATCCTGAAGCT GCGGCTGTACGAGCAGCAGCACGGCAAGTGCCTGTACTCCGGCAAGGAGATCAACCTGGTGCGGCTGAACGA GAAGGGCTACGTGGAGATCGACCACGCCCTGCCCTTCTCCCGGACCTGGGACGACTCCTTCAACAACAAGGTG CTGGTGCTGGGCTCCGAGAACCAGAACAAGGGCAACCAGACCCCCTACGAGTACTTCAACGGCAAGGACAAC TCCCGGGAGTGGCAGGAGTTCAAGGCCCGGGTGGAGACCTCCCGGTTCCCCCGGTCCAAGAAGCAGCGGATCC TGCTGCAGAAGTTCGACGAGGACGGCTTCAAGGAGTGCAACCTGAACGACACCCGGTACGTGAACCGGTTCCT GTGCCAGTTCGTGGCCGACCACATCCTGCTGACCGGCAAGGGCAAGCGGCGGGTGTTCGCCTCCAACGGCCAG ATCACCAACCTGCTGCGGGGCTTCTGGGGCCTGCGGAAGGTGCGGGCCGAGAACGACCGGCACCACGCCCTG GACGCCGTGGTGGTGGCCTGCTCCACCGTGGCCATGCAGCAGAAGATCACCCGGTTCGTGCGGTACAAGGAGA TGAACGCCTTCGACGGCAAGACCATCGACAAGGAGACCGGCAAGGTGCTGCACCAGAAGACCCACTTCCCCC AGCCCTGGGAGTTCTTCGCCCAGGAGGTGATGATCCGGGTGTTCGGCAAGCCCGACGGCAAGCCCGAGTTCGA

		GGAGGCCGACACCCCCGAGAAGCTGCGGACCCTGCTGGCCGAGAAGCTGTCCTCCCGGCCCGAGGCCGTGCA CGAGTACGTGACCCCCCTGTTCGTGTCCCGGGCCCCCAACCGGAAGATGTCCGGCGCCCACAAGGACACCCTG CGGTCCGCCAAGCGGTTCGTGAAGCACAACGAGAAGATCTCCGTGAAGCGGGTGTGGCTGACCGAGATCAAG CTGGCCGACCTGGAGAACATGGTGAACTACAAGAACGGCCGGGAGATCGAGCTGTACGAGGCCCTGAAGGCC CGGCTGGAGGCCTACGGCGGCAACGCCAAGCAGGCCTTCGACCCCAAGGACAACCCCTTCTACAAGAAGGGC GGCCAGCTGGTGAAGGCCGTGCGGGTGGAGAAGACCCAGGAGTCCGGCGTGCTGCTGAACAAGAAGAACGCC TACACCATCGCCGACAACGGCGACATGGTGCGGGTGGACGTGTTCTGCAAGGTGGACAAGAAGGGCAAGAAC CAGTACTTCATCGTGCCCATCTACGCCTGGCAGGTGGCCGAGAACATCCTGCCCGACATCGACTGCAAGGGCT ACCGGATCGACGACTCCTACACCTTCTGCTTCTCCCTGCACAAGTACGACCTGATCGCCTTCCAGAAGGACGAG AAGTCCAAGGTGGAGTTCGCCTACTACATCAACTGCGACTCCTCCAACGGCCGGTTCTACCTGGCCTGGCACG ACAAGGGCTCCAAGGAGCAGCAGTTCCGGATCTCCACCCAGAACCTGGTGCTGATCCAGAAGTACCAGGTGA ACGAGCTGGGCAAGGAGATCCGGCCCTGCCGGCTGAAGAAGCGGCCCCCCGTGCGGUGA

393	用於 D16A Nme2Cas9 切口酶之開讀框	ATGGCCGCCTTCAAGCCCAACCCCATCAACTACATCCTGGGCCTGGCCATCGGCATCGCCTCCGTGGGCTGGG CCATGGTGGAGATCGACGAGGAGGAGAACCCCATCCGGCTGATCGACCTGGGCGTGCGGGTGTTCGAGCGGG CCGAGGTGCCCAAGACCGGCGACTCCCTGGCCATGGCCCGGCGGCTGGCCCGGTCCGTGCGGCGGCTGACCCG GCGGCGGGCCCACCGGCTGCTGCGGGCCCGGCGGCTGCTGAAGCGGGAGGGCGTGCTGCAGGCCGCCGACTT CGACGAGAACGGCCTGATCAAGTCCCTGCCCAACACCCCCTGGCAGCTGCGGGCCGCCGCCCTGGACCGGAAG CTGACCCCCCTGGAGTGGTCCGCCGTGCTGCTGCACCTGATCAAGCACCGGGGCTACCTGTCCCAGCGGAAGA ACGAGGGCGAGACCGCCGACAAGGAGCTGGGCGCCCTGCTGAAGGGCGTGGCCAACAACGCCCACGCCCTGC AGACCGGCGACTTCCGGACCCCCGCCGAGCTGGCCCTGAACAAGTTCGAGAAGGAGTCCGGCCACATCCGGA ACCAGCGGGGCGACTACTCCCACACCTTCTCCCGGAAGGACCTGCAGGCCGAGCTGATCCTGCTGTTCGAGAA GCAGAAGGAGTTCGGCAACCCCCACGTGTCCGGCGGCCTGAAGGAGGGCATCGAGACCCTGCTGATGACCCA GCGGCCCGCCCTGTCCGGCGACGCCGTGCAGAAGATGCTGGGCCACTGCACCTTCGAGCCCGCCGAGCCCAAG GCCGCCAAGAACACCTACACCGCCGAGCGGTTCATCTGGCTGACCAAGCTGAACAACCTGCGGATCCTGGAGC AGGGCTCCGAGCGGCCCCTGACCGACACCGAGCGGGCCACCCTGATGGACGAGCCCTACCGGAAGTCCAAGC TGACCTACGCCCAGGCCCGGAAGCTGCTGGGCCTGGAGGACACCGCCTTCTTCAAGGGCCTGCGGTACGGCAA GGACAACGCCGAGGCCTCCACCCTGATGGAGATGAAGGCCTACCACGCCATCTCCCGGGCCCTGGAGAAGGA GGGCCTGAAGGACAAGAAGTCCCCCCTGAACCTGTCCTCCGAGCTGCAGGACGAGATCGGCACCGCCTTCTCC CTGTTCAAGACCGACGAGGACATCACCGGCCGGCTGAAGGACCGGGTGCAGCCCGAGATCCTGGAGGCCCTG CTGAAGCACATCTCCTTCGACAAGTTCGTGCAGATCTCCCTGAAGGCCCTGCGGCGGATCGTGCCCCTGATGG AGCAGGGCAAGCGGTACGACGAGGCCTGCGCCGAGATCTACGGCGACCACTACGGCAAGAAGAACACCGAGG AGAAGATCTACCTGCCCCCCATCCCCGCCGACGAGATCCGGAACCCCGTGGTGCTGCGGGCCCTGTCCCAGGC CCGGAAGGTGATCAACGGCGTGGTGCGGCGGTACGGCTCCCCCGCCCGGATCCACATCGAGACCGCCCGGGA GGTGGGCAAGTCCTTCAAGGACCGGAAGGAGATCGAGAAGCGGCAGGAGGAGAACCGGAAGGACCGGGAGA AGGCCGCCGCCAAGTTCCGGGAGTACTTCCCCAACTTCGTGGGCGAGCCCAAGTCCAAGGACATCCTGAAGCT GCGGCTGTACGAGCAGCAGCACGGCAAGTGCCTGTACTCCGGCAAGGAGATCAACCTGGTGCGGCTGAACGA GAAGGGCTACGTGGAGATCGACCACGCCCTGCCCTTCTCCCGGACCTGGGACGACTCCTTCAACAACAAGGTG CTGGTGCTGGGCTCCGAGAACCAGAACAAGGGCAACCAGACCCCCTACGAGTACTTCAACGGCAAGGACAAC TCCCGGGAGTGGCAGGAGTTCAAGGCCCGGGTGGAGACCTCCCGGTTCCCCCGGTCCAAGAAGCAGCGGATCC TGCTGCAGAAGTTCGACGAGGACGGCTTCAAGGAGTGCAACCTGAACGACACCCGGTACGTGAACCGGTTCCT GTGCCAGTTCGTGGCCGACCACATCCTGCTGACCGGCAAGGGCAAGCGGCGGGTGTTCGCCTCCAACGGCCAG ATCACCAACCTGCTGCGGGGCTTCTGGGGCCTGCGGAAGGTGCGGGCCGAGAACGACCGGCACCACGCCCTG GACGCCGTGGTGGTGGCCTGCTCCACCGTGGCCATGCAGCAGAAGATCACCCGGTTCGTGCGGTACAAGGAGA TGAACGCCTTCGACGGCAAGACCATCGACAAGGAGACCGGCAAGGTGCTGCACCAGAAGACCCACTTCCCCC AGCCCTGGGAGTTCTTCGCCCAGGAGGTGATGATCCGGGTGTTCGGCAAGCCCGACGGCAAGCCCGAGTTCGA

		GGAGGCCGACACCCCCGAGAAGCTGCGGACCCTGCTGGCCGAGAAGCTGTCCTCCCGGCCCGAGGCCGTGCA CGAGTACGTGACCCCCCTGTTCGTGTCCCGGGCCCCCAACCGGAAGATGTCCGGCGCCCACAAGGACACCCTG CGGTCCGCCAAGCGGTTCGTGAAGCACAACGAGAAGATCTCCGTGAAGCGGGTGTGGCTGACCGAGATCAAG CTGGCCGACCTGGAGAACATGGTGAACTACAAGAACGGCCGGGAGATCGAGCTGTACGAGGCCCTGAAGGCC CGGCTGGAGGCCTACGGCGGCAACGCCAAGCAGGCCTTCGACCCCAAGGACAACCCCTTCTACAAGAAGGGC GGCCAGCTGGTGAAGGCCGTGCGGGTGGAGAAGACCCAGGAGTCCGGCGTGCTGCTGAACAAGAAGAACGCC TACACCATCGCCGACAACGGCGACATGGTGCGGGTGGACGTGTTCTGCAAGGTGGACAAGAAGGGCAAGAAC CAGTACTTCATCGTGCCCATCTACGCCTGGCAGGTGGCCGAGAACATCCTGCCCGACATCGACTGCAAGGGCT ACCGGATCGACGACTCCTACACCTTCTGCTTCTCCCTGCACAAGTACGACCTGATCGCCTTCCAGAAGGACGAG AAGTCCAAGGTGGAGTTCGCCTACTACATCAACTGCGACTCCTCCAACGGCCGGTTCTACCTGGCCTGGCACG ACAAGGGCTCCAAGGAGCAGCAGTTCCGGATCTCCACCCAGAACCTGGTGCTGATCCAGAAGTACCAGGTGA ACGAGCTGGGCAAGGAGATCCGGCCCTGCCGGCTGAAGAAGCGGCCCCCCGTGCGGUAA
394-400		未使用
401	G018932	mC*mG*mC*ACGGGUACCAGGGGCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
402	G018933	mG*mC*mA*CGGGUACCAGGGGCCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
403	G018934	mC*mA*mC*GGGUACCAGGGGCCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
404	G018935	mG*mG*mG*AGGCGCCCCGUGGCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
405	G018936	mG*mC*mG*AUCAGGGAGGCGCCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
406	G018937	mC*mG*mG*GCUGGCCUCCCCACAAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
407	G018938	mC*mU*mC*CUUGUGGGAGGCCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
408	G018939	mG*mG*mC*UGGCCUCCCACAAGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
409	G018940	mU*mU*mG*UCUCCCCUCCUUGUGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
410	G018941	mC*mC*mA*CAAGGAGGGGAGACAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

411	G018942	mC*mA*mC*AAGGAGGGGAGACAAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
412	G018943	mC*mA*mA*UUGUCUCCCCUCCUUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
413	G018944	mC*mC*mA*AUUGUCUCCCCUCCUUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
414	G018945	mA*mU*mC*CCUCGAAUACUGAUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
415	G018946	mA*mA*mC*CACUCAUCAGUAUUCGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
416	G018947	mG*mA*mA*CCACUCAUCAGUAUUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
417		未使用
418	G018949	mG*mG*mC*CCGUGACUUUUCCUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
419	G018950	mU*mG*mC*UUCACACUCAAUGUGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
420	G018951	mG*mC*mU*UCACACUCAAUGUGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
421	G018952	mC*mU*mU*CACACUCAAUGUGUGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
422	G018953	mU*mU*mC*ACACUCAAUGUGUGUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
423		未使用
424	G018955	mA*mG*mG*GGCCCUGACCCUGCUAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
425		未使用
426		未使用
427	G018958	mU*mG*mA*GAUUUCUUGUCUCACUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
428	G018959	mG*mA*mG*AUUUCUUGUCUCACUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
429	G018960	mU*mA*mA*AGCACCUGUUAAAAUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

430	G018961	mA*mA*mU*CUGUCCUUCAUUUUAACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
431	G018962	mG*mU*mC*ACAGGGGAAGGUCCCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
432	G018963	mA*mA*mC*AUGAAGAAAGCAGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
433	G018964	mA*mA*mA*CAUGAAGAAAGCAGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
434	G018965	mU*mC*mA*GGAAACAUGAAGAAAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
435	G018966	mU*mG*mU*CCUGUGAGAUACCAGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
436		未使用
437	G018968	mA*mG*mG*CUGAUGCCUGAGGUCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
438	G018969	mG*mG*mC*UGAUGCCUGAGGUCCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
439	G018970	mC*mA*mC*AAUAUCCCAAGGACCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
440	G018971	mG*mG*mU*CCUUGGGAUAUUGUGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
441	G018972	mG*mU*mC*CUUGGGAUAUUGUGUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
442	G018973	mC*mU*mC*CCAAACACAAUAUCCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
443	G018974	mU*mC*mC*UCUAGCCACAUCUUCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
444		未使用
445	G018976	mC*mC*mU*CUAGCCACAUCUUCUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
446	G018977	mC*mC*mC*ACAGAAGAUGUGGCUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
447	G018978	mG*mU*mC*AGAUCCCACAGAAGAUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
448	G018979	mA*mU*mC*UUCUGUGGGAUCUGACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

449	G018980	mC*mC*mC*AGGCAGUGACAGUGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
450	G018981	mC*mU*mG*GGCACUGUCACUGCCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
451	G018982	mC*mC*mU*GGGCACUGUCACUGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
452	G018983	mU*mG*mG*AGGGCCUGAUGUGUGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
453	G018984	mG*mC*mC*UGAUGUGUGUUGGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
454		未使用
455	G018986	mC*mC*mC*AACACCCAACACACAUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
456	G018987	mU*mU*mG*GGUGUUGGGCGGAACAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
457	G018988	mU*mG*mG*AUGUAUUGAGCAUGCGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
458	G018989	mG*mG*mA*UGUAUUGAGCAUGCGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
459	G018990	mA*mC*mG*GCCAUCCUCGGCGUCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
460	G018991	mG*mA*mC*GGCCAUCCUCGGCGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
461	G018992	mG*mA*mC*GCCGAGGAUGGCCGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
462	G018993	mU*mG*mA*CGGCCAUCCUCGGCGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
463	G018994	mG*mG*mC*GCCAUGACGGCCAUCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
464	G018995	mA*mC*mA*GCGACGCCGCGAGCCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
465	G018996	mC*mG*mA*CGCCGCGAGCCAGAGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
466	G018997	mC*mG*mA*GCCAGAGGAUGGAGCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

467	G018998	mC*mG*mG*CUCCAUCCUCUGGCUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
468	G018999	mG*mA*mG*CCAGAGGAUGGAGCCGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
469	G019000	mG*mC*mG*CCCGCGGCUCCAUCCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
470	G019001	mG*mC*mC*CGUCCGUGGGGGAUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
471	G019002	mU*mC*mA*UCCCCCACGGACGGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
472	G019003	mA*mU*mC*UCGGACCCGGAGACUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
473	G019004	mG*mG*mG*GUCCCGCGGCUUCGGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
474	G019005	mC*mU*mC*GGGGUCCCGCGGCUUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
475	G019006	mU*mC*mU*CGGGGUCCCGCGGCUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
476	G019007	mG*mU*mC*UCGGGGUCCCGCGGCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
477	G019008	mG*mC*mA*AGGGUCUCGGGGUCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
478	G019009	mG*mG*mA*CCCCGAGACCCUUGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
479	G019010	mG*mA*mC*CCCGAGACCCUUGCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
480	G019011	mC*mG*mA*GACCCUUGCCCCGGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
481	G019012	mC*mU*mC*CCGGGGCAAGGGUCUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
482	G019013	mU*mC*mU*CCCGGGGCAAGGGUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
483	G019014	mC*mU*mC*UCCCGGGGCAAGGGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
484	G019015	mC*mC*mU*UGCCCCGGGAGAGGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

485	G019016	mC*mU*mG*GGCCUCUCCCGGGGCAAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
486	G019017	mC*mC*mU*GGGCCUCUCCCGGGGCAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
487	G019018	mA*mG*mG*CGCCUGGGCCUCUCCCGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
488	G019019	mU*mU*mU*AGGCCAAAAAUCCCCCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
489	G021205	mA*mG*mG*CAUUUUGCAUCUGUCAUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
490	G021206	mC*mA*mG*GCAUUUUGCAUCUGUCAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
491	G021207	mC*mC*mC*UGGGCACUGUCACUGCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
492	G021208	mC*mG*mC*UGCAGCGCACGGGUACCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
493	G021209	mG*mC*mU*GCAGCGCACGGGUACCAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
494	G021210	mC*mU*mG*CAGCGCACGGGUACCAGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
495	G021211	mU*mC*mC*UUGUGGGAGGCCAGCCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
496	G023522 靶向 CD38 之導引 RNA	mC*mU*mU*GACGCAUCGCGCCAGGAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
497	G019427 靶向 ANAPC5之導引RNA	mA*mA*mU*CCUAAUUGCCUCCUGCAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
498	G023519 靶向 B2M 之導引 RNA	mA*mC*mU*CACGCUGGAUAGCCUCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU

499	G023520 靶向 TRAC 之導引 RNA	mU*mU*mC*AAAACCUGUCAGUGAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
500	G023521 靶向 CIITA 之導引 RNA	mC*mG*mC*CCAGGUCCUCACGUCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
501	靶向 HLA-A 之 G023523 導引RNA	mG*mC*mU*GCAGCGCACGGGUACCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
502	靶向 TRBC1/2 之 G023524 導引RNA	mC*mC*mA*CACCCAAAAGGCCACACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
503	G020073	mG*mUGUGUCCCmUCUmCCCCACCCGUCCmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCAACGCUCUmGmCCmUmUmCmUGGCAUCGmU*mU
504	G020927	mA*mU*mC*UGCCUUUAUAGGGCACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
505	G020928	mA*mG*mU*CACGAUGCCUUUAUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
506	G020929	mG*mG*mU*UGCAAGGAAUGAGAACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
507	G021237	mG*mGGGCCAGCmUUCmAGACACAAAUACmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU
508	G021249	mC*mAGAAUUGAmGAGmACUCAGCCCAGGmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU
509	G021321	mG*mAGAAGCCGmUCAmCACAGAUCCACAmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU
510	G021844	mC*mC*mA*mAmGUGmUmCUmUCmCAGUAmCGAUmUUGmGUUGmUmAmGmCUCCCmUmUmC(L1)mGmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmC(L1)mGmAmUGUGCmCGmCAAmCGCUCUmGmCC(L1)GGCAUCG*mU*mU

511	G000502	mA*mC*mA*CAAAUACCAGUCCAGCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
512	野生型NmeCas9導引RNA	NNNNNNNNNNNNNNNNNNNNNNNNNGUUGUAGCUCCCUUUCUCAUUUCGGAAACGAAAUGAGAACCGUUGCUACAAUAAGGCCGUCUGAAAAGAUGUGCCGCAACGCUCUGCCCCUUAAAGCUUCUGCUUUAAGGGGCAUCGUUUA
513	縮短/未經修飾之NmeCas9導引RNA	$(N)_{20-25}$ GUUGUAGCUCCCUGAAACCGUUGCUACAAUAAGGCCGUCGAAAGAUGUGCCGCAACGCUCUGCCUUCUGGCAUCGUU
514	縮短/未經修飾之NmeCas9導引RNA	$(N)_{20-25}$ GUUGUAGCUCCCUGAAACCGUUGCUACAAUAAGGCCGUCGAAAGAUGU GCCGCAACGCUCUGCCUUCUGGCAUCGUUUAUU
515	縮短/未經修飾之NmeCas9導引RNA	$(N)_{20-25}$ GUUGUAGCUCCCUGGAAACCCGUUGCUACAAUAAGGCCGUCGAAAGA UGUGCCGCAACGCUCUGCCUUCUGGCAUCGUUUAUU
516	僅Mod-N77保守部分	GUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU
517	僅Mod-N78保守部分	GUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGmCAAmCGCUCUmGmCCmUmUmCmUGGCAUCG*mU*mU
518	包含連接子之縮短/未經修飾之NmeCas9導引RNA	$(N)_{20-25}$ GUUGUAGCUCCCUUC(L1)GACCGUUGCUACAAUAAGGCCGUC(L1)GAUGUGCCGCAACGCUCUGCC(L1)GGCAUCGUU

519	包含連接子之縮短/經修飾NmeCas9導引RNA	mN*mN*mN*mNmNNNmNmNNmNNmNNNNNmNNNNmNNNmGUUGmUmAmGmCUCCCmUmUmC(L1)mGmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmC(L1)mGmAmUGUGCmCGmCAAmCGCUCUmGmCC(L1)GGCAUCG*mU*mU
520	縮短之SpyCas9導引RNA	mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU
521	縮短之SpyCas9導引RNA (未經修飾)	NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGUGCU
522	縮短之NmeCas9導引RNA	mN*mNNNNNNNNmNNNmNNNNNNNNNNNNNmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU
523	包含內部連接子之縮短/經修飾spyCas9導引RNA	mA*mC*mG*CAAAUAUCAGUCCAGCGGUUUUAGAmGmCmUmA(L1)mUmAmGmCAAGUUAAAAUAAGGC(L2)GUCCGUUAUCAC(L1)GGGCACCGAGUCGG*mU*mG*mC
524	包含內部連接子之縮短之spyCas9導引RNA	NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUA(L1)UAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU(L1)AAGUGGCACCGAGUCGGUGCUUUUU
525-528		未使用
529	G016788	mU*mU*mC*CCGGCCUUUUUACCUUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
530	G016030	mU*mC*mA*ACUGCGACCAGUUCAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

531	G016031	mA*mG*mC*GCAGGCAGUGGCAGGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
532	G016032	mA*mC*mC*UGCAACAACAGGAUUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
533	G016033	mC*mC*mA*GGAACACCUGCAACAACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
534	G016034	mC*mA*mG*CAGCAAGAGCCUGGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
535	G016035	mG*mC*mA*GCAGCAAGAGCCUGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
536	G016036	mC*mA*mA*UCUCUUCUUCUCCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
537	G016037	mA*mG*mC*AGCUCGCUGCCAGCCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
538	G016038	mA*mG*mC*UCGCUGCCAGCCUUCGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
539	G016039	mC*mU*mC*UGGACCAGGCGGCCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
540	G016040	mG*mC*mA*GCCCUCGACAGCCCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
541	G016041	mC*mA*mG*CCCUCGACAGCCCCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
542	G016042	mA*mG*mC*CAAGUACCCCCUCCCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
543	G016043	mC*mA*mG*CCAACAGCACCUCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
544	G016044	mU*mG*mC*CGCGCCCGCAGUGUCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
545	G016045	mC*mG*mA*CAGCCCCCCCCGGGGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
546	G016046	mG*mG*mC*AGCGAGCUGCUGGGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
547	G016047	mG*mC*mC*AGCUCUGCCAGGGCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
548	G016048	mA*mG*mC*GAGCGAAGGCAGGGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

549	G016049	mA*mA*mG*GCUGGCAGCGAGCUGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
550	G016050	mA*mG*mC*CCUCGACAGCCCCCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
551	G016051	mG*mG*mA*UGCAGCGAGCGAAGGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
552	G016052	mU*mC*mC*ACCGAGGCAGCCGCCGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
553	G016053	mU*mC*mU*CCAACAAGCUUCCAAAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
554	G016054	mA*mG*mC*AGCCCCCGGAGGGAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
555	G016055	mG*mC*mC*ACAGCCCUACUUUGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
556	G016056	mC*mU*mG*CGCCCACGAGGCCGAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
557	G016057	mC*mA*mG*CCGCCGAUGGCCCGAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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559	G016059	mC*mU*mC*AACGAGGAACUGGAGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
560	G016060	mC*mC*mA*CAGCCCUACUUUGUGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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562	G016062	mG*mA*mC*UGCCAGUCACCACAGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
563	G016063	mG*mC*mC*CACGAGGCCGAGGAGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
564	G016064	mA*mU*mC*AGCCCAGCCAGAAAGCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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566	G016066	mU*mG*mG*GAGUCCCUGCAGCAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

567	G016067	mC*mA*mG*CAGGCUGUUGUGUGACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
568	G016068	mC*mU*mG*GUCAGGGCAAGAGCUAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
569	G016069	mC*mA*mG*GUUCAGGCAUGCUGGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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571	G016071	mA*mG*mG*CCGAGGAGGCUGGAAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
572	G016072	mC*mA*mG*UGGCUGAUGGAGCGAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
573	G016073	mG*mG*mG*AUGCAGCGAGCGAAGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
574	G016074	mA*mA*mG*CUGCCCUCCACGCUCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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578	G016078	mU*mC*mC*CUGGACCUCCGCAGCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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582	G016082	mC*mG*mU*CCUCCCCAAGCUCCAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
583	G016083	mC*mC*mA*GCUCCUCGAAGCCGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
584	G016084	mC*mU*mU*UUCCUCCCCUGCAGCAUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

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589	G016089	mU*mC*mG*GACUCUGCGGCCCGCGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
590	G016090	mC*mU*mU*CCCCCAGCUGAAGUCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
591	G016091	mG*mC*mC*CAGCUCCCAGGCCAGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
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593	G016093	mG*mC*mC*CUCCAGCCAGUUGUCAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
594	G016094	mC*mC*mC*UGACGCUCCUCCGGGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
595	G016095	mC*mA*mC*ACUGCCCGGCACAAAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
596	G016096	mC*mA*mG*CUCACAGUGUGCCACCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
597	G016097	mA*mG*mC*UCGGACUCUGCGGCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
598	G016098	mG*mA*mC*GCCCUAUUUGAGCUGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
599	G016099	mG*mC*mC*AGUGCUGCGGAGGUCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
600	G016100	mA*mG*mG*GCUCCCAGGCAGCGGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
601	G016101	mG*mC*mC*GAGCCCGCAGGCCCGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
602	G016102	mG*mC*mU*CCCAGGCAGCGGGCGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

603	G016103	mC*mC*mU*CUCCAGCUGCCGGGCAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
604	G016104	mA*mG*mG*CUUUCCCCAAACUGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
605	G016105	mC*mC*mA*UCUCCACUCUGCCCCAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
606	G016106	mU*mC*mC*UCCUCACAGCCCGGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
607	G016107	mC*mC*mA*CUCUGCCCCAUGGGCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
608	G016108	mC*mA*mG*CCUCCCGCCCGCUGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
609	G016109	mC*mC*mC*GGCCGCCUCUCUUUUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
610	G016110	mC*mC*mU*GGGCCCACAGCCACUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
611	G016111	mU*mC*mC*CCGGCUGCAGCCGCUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
612	G016112	mC*mG*mC*GUUCUGCUCAUCCUAGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
613	G016113	mU*mU*mC*CACAUCCUUCAGGGACUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
614	G016114	mC*mU*mC*UCCAGCUGCCGGGCAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
615	G016115	mG*mG*mG*CCCACAGCCACUCGUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
616	G016116	mC*mC*mC*CGGCCGCCUCUCUUUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
617	G016117	mU*mC*mC*AGCUGCCGGGCAUUGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCm UmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

618	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:618之TRBC之G016200導引RNA)	CCACACCCAAAAGGCCACAC
619	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:619之TRBC之G016174導引RNA)	CCCACCAGCUCAGCUCCACG
620	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:620之TRBC之G016263導引RNA)	UCCCUAGCAGGAUCUCAUAG

621	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:621之TRBC之G016270導引RNA)	GGCUCAAACACAGCGACCUC
622	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:622之TRBC之G016212導引RNA)	GGCACACCAGUGUGGCCUUU
623	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:623之TRBC之G016207導引RNA)	AGGUGGCCGAGACCCUCAGG

624	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:624之TRBC之G016205導引RNA)	ACCUGCUCUACCCCAGGCCU
625	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:625之TRBC之G016245導引RNA)	CAUAGAGGAUGGUGGCAGAC
626	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:626之TRBC之G016232導引RNA)	CCACGUGGAGCUGAGCUGGU

627	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:627之TRBC之G016227導引RNA)	GGAGAAUGACGAGUGGACCC
628	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:628之TRBC之G016273導引RNA)	CCAGUGUGGCCUUUUGGGUG
629	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:629之TRBC之G016251導引RNA)	CAAACACAGCGACCUCGGGU

630	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:630之TRBC之G016276導引RNA)	UACCAUGGCCAUCAACACAA
631	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:631之TRBC之G016167導引RNA)	GCGCUGACGAUCUGGGUGAC
632	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:632之TRBC之G016253導引RNA)	CACGGACCCGCAGCCCCUCA

633	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:633之TRBC之G016272導引RNA)	UCAAACACAGCGACCUCGGG
634	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:634之TRBC之G016258導引RNA)	CAGGGAAGAAGCCUGUGGCC
635	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:635之TRBC之G016183導引RNA)	CAGUGUGGCCUUUUGGGUGU

636	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:636之TRBC之G016222導引RNA)	ACCACGUGGAGCUGAGCUGG
637	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:637之TRBC之G016233導引RNA)	GAGGGCGGGCUGCUCCUUGA
638	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:638之TRBC之G016264導引RNA)	AGCUCAGCUCCACGUGGUCA

639	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:639之TRBC之G016255導引RNA)	GAACAAGGUGUUCCCACCCG
640	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:640之TRBC之G016177導引RNA)	GCACACCAGUGUGGCCUUUU
641	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:641之TRBC之G016283導引RNA)	GAGCUGGUGGGUGAAUGGGA

642	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:642之TRBC之G016194導引RNA)	GGCUGCUCCUUGAGGGGCUG
643	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:643之TRBC之G016266導引RNA)	CGGGUGGGAACACCUUGUUC
644	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:644之TRBC之G016196導引RNA)	CAGCUCAGCUCCACGUGGUC

645	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:645之TRBC之G016274導引RNA)	GACGAUCUGGGUGACGGGUU
646	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:646之TRBC之G016282導引RNA)	UAGCAGGAUCUCAUAGAGGA
647	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:647之TRBC之G016267導引RNA)	GACCAGCACAGCAUACAGGG

648	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:648之TRBC之G016261導引RNA)	CUGACCACGUGGAGCUGAGC
649	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:649之TRBC之G016277導引RNA)	CCAACAGUGUCCUACCAGCA
650	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:650之TRBC之G016285導引RNA)	CUGGUGGGUGAAUGGGAAGG

651	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:651之TRBC之G016275導引RNA)	CUAUGAGAUCCUGCUAGGGA
652	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:652之TRBC之G016281導引RNA)	CAGGAUCUCAUAGAGGAUGG
653	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:653之TRBC之G016280導引RNA)	GGCCACCCUGUAUGCUGUGC

654	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:654之TRBC之G016279導引RNA)	CAACAGUGUCCUACCAGCAA
655	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:655之TRBC之G016250導引RNA)	AGCUGAGCUGGUGGGUGAAU
656	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:656之TRBC之G016278導引RNA)	AACAGUGUCCUACCAGCAAG

657	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:657之TRBC之G016259導引RNA)	AGGCUUCUUCCCUGACCACG
658	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:658之TRBC之G016284導引RNA)	UCUUCUGCAGGUCAAGAGAA
659	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:659之TRBC之G016249導引RNA)	GAGCUGAGCUGGUGGGUGAA

660	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:660之TRBC之G016256導引RNA)	GGUCAGCGCCCUUGUGUUGA
661	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:661之TRBC之G016190導引RNA)	AGAUCGUCAGCGCCGAGGCC
662	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:662之TRBC之G016248導引RNA)	GCUGCUCCUUGAGGGGCUGC

663	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:663之TRBC之G016257導引RNA)	GUAUCUGGAGUCAUUGAGGG
664	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:664之TRBC之G016260導引RNA)	AUCCUCUAUGAGAUCCUGCU
665	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:665之TRBC之G016262導引RNA)	UCCUCUAUGAGAUCCUGCUA

666	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:666之TRBC之G016242導引RNA)	GCAGUAUCUGGAGUCAUUGA
667	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:667之TRBC之G016268導引RNA)	GCUGACCAGCACAGCAUACA
668	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:668之TRBC之G016265導引RNA)	ACAGGGUGGCCUUCCCUAGC

669	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:669之TRBC之G016254導引RNA)	CGCUGACCAGCACAGCAUAC
670	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:670之TRBC之G013015導引RNA)	AGAGAUCUCCCACACCCAAA
671	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:671之TRBC之G014832導引RNA)	GGCUCUCGGAGAAUGACGAG

672	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:672之TRBC之G016168導引RNA)	UGUGGCCAGGCACACCAGUG
673	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:673之TRBC之G016171導引RNA)	GCGGCUGCUCAGGCAGUAUC
674	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:674之TRBC之G016172導引RNA)	ACACUGGUGUGCCUGGCCAC

675	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:675之TRBC之G016179導引RNA)	CGUAGAACUGGACUUGACAG
676	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:676之TRBC之G016180導引RNA)	CUUGACAGCGGAAGUGGUUG
677	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:677之TRBC之G016181導引RNA)	ACUGGACUUGACAGCGGAAG

678	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:678之TRBC之G016187導引RNA)	UGAGGGUCUCGGCCACCUUC
679	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:679之TRBC之G016188導引RNA)	AGUCCAGUUCUACGGGCUCU
680	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:680之TRBC之G016189導引RNA)	CACCCAGAUCGUCAGCGCCG

681	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:681之TRBC之G016191導引RNA)	GAUCGUCAGCGCCGAGGCCU
682	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:682之TRBC之G016192導引RNA)	AUCGUCAGCGCCGAGGCCUG
683	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:683之TRBC之G016193導引RNA)	ACUGCCUGAGCAGCCGCCUG

684	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:684之TRBC之G016195導引RNA)	GAGCAGCCGCCUGAGGGUCU
685	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:685之TRBC之G016197導引RNA)	AGGGCGGGCUGCUCCUUGAG
686	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:686之TRBC之G016199導引RNA)	GCUGUCAAGUCCAGUUCUAC

687	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:687之TRBC之G016201導引RNA)	AGGCCUCGGCGCUGACGAUC
688	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:688之TRBC之G016203導引RNA)	CUGCCUGAGCAGCCGCCUGA
689	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:689之TRBC之G016204導引RNA)	AGACCCUCAGGCGGCUGCUC

690	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:690之TRBC之G016206導引RNA)	CGCUGUCAAGUCCAGUUCUA
691	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:691之TRBC之G016211導引RNA)	AAAGGCCACACUGGUGUGCC
692	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:692之TRBC之G016214導引RNA)	UUGACAGCGGAAGUGGUUGC

693	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:693之TRBC之G016216導引RNA)	CCACUCACCUGCUCUACCCC
694	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:694之TRBC之G016217導引RNA)	UGGCUCAAACACAGCGACCU
695	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:695之TRBC之G016219導引RNA)	UGGCAGACAGGACCCCUUGC

696	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:696之TRBC之G016228導引RNA)	GUUGCGGGGGUUCUGCCAGA
697	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:697之TRBC之G016230導引RNA)	UGAGGGCGGGCUGCUCCUUG
698	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:698之TRBC之G016238導引RNA)	UCUCCGAGAGCCCGUAGAAC

699	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:699之TRBC之G016239導引RNA)	GGCCUCGGCGCUGACGAUCU
700	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:700之TRBC之G016240導引RNA)	AUGACGAGUGGACCCAGGAU
701	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:701之TRBC之G016241導引RNA)	UGACGAGUGGACCCAGGAUA

702	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:702之TRBC之G016243導引RNA)	GCGGGGGUUCUGCCAGAAGG
703	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:703之TRBC之G016252導引RNA)	GGUGCACAGUGGGGUCAGCA
704	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:704之TRBC之G016269導引RNA)	GGCGCUGACGAUCUGGGUGA

705	用於TRBC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:705之TRBC之G016271導引RNA)	AGACAGGACCCCUUGCUGGU
706	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:706之TRAC之G016019導引RNA)	AACAAAUGUGUCACAAAGUA
707	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:707之TRAC之G016016導引RNA)	UUUCAAAACCUGUCAGUGAU

708	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:708之TRAC之G016026導引RNA)	CUUACCUGGGCUGGGGAAGA
709	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:709之TRAC之G016013導引RNA)	CCGAAUCCUCCUCCUGAAAG
710	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:710之TRAC之G016022導引RNA)	CUGACAGGUUUUGAAAGUUU

711	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:711之TRAC之G016023導引RNA)	CUGGGGAAGAAGGUGUCUUC
712	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:712之TRAC之G016010導引RNA)	UCCUCCUCCUGAAAGUGGCC
713	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:713之TRAC之G016014導引RNA)	CCACUUUCAGGAGGAGGAUU

714	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:714之TRAC之G016020導引RNA)	AUUUGUUUGAGAAUCAAAAU
715	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:715之TRAC之G015998導引RNA)	CUUCAAGAGCAACAGUGCUG
716	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:716之TRAC之G016025導引RNA)	AGCUGCCCUUACCUGGGCUG

717	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:717之TRAC之G015997導引RNA)	AGAGCAACAGUGCUGUGGCC
718	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:718之TRAC之G016029導引RNA)	AAAGCUGCCCUUACCUGGGC
719	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:719之TRAC之G016028導引RNA)	AAGCUGCCCUUACCUGGGCU

720	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO: 720之TRAC之G016021導引RNA)	UGGAAUAAUGCUGUUGUUGA
721	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:721之TRAC之G016015導引RNA)	CACCAAAGCUGCCCUUACCU
722	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:722之TRAC之G012086導引RNA)	AGAGUCUCUCAGCUGGUACA

723	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:723之TRAC之G013004導引RNA)	ACACGGCAGGGUCAGGGUUC
724	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:724之TRAC之G013005導引RNA)	AGCUGGUACACGGCAGGGUC
725	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:725之TRAC之G013006導引RNA)	CUCUCAGCUGGUACACGGCA

726	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:726之TRAC之G013007導引RNA)	UCUCUCAGCUGGUACACGGC
727	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:727之TRAC之G013008導引RNA)	UGGAUUUAGAGUCUCUCAGC
728	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:728之TRAC之G013009導引RNA)	UAGGCAGACAGACUUGUCAC

729	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:729之TRAC之G014831導引RNA)	UUCGGAACCCAAUCACUGAC
730	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:730之TRAC之G015999導引RNA)	GCUGGUACACGGCAGGGUCA
731	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:731之TRAC之G016000導引RNA)	ACAAAACUGUGCUAGACAUG

732	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:732之TRAC之G016001導引RNA)	GAGAAUCAAAAUCGGUGAAU
733	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:733之TRAC之G016002導引RNA)	AAGUUCCUGUGAUGUCAAGC
734	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:734之TRAC之G016003導引RNA)	UGCUCAUGACGCUGCGGCUG

735	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:735之TRAC之G016004導引RNA)	UUAAUCUGCUCAUGACGCUG
736	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:736之TRAC之G016005導引RNA)	GAUUAAACCCGGCCACUUUC
737	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:737之TRAC之G016006導引RNA)	CUCGACCAGCUUGACAUCAC

738	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:738之TRAC之G016007導引RNA)	UAAACCCGGCCACUUUCAGG
739	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:739之TRAC之G016008導引RNA)	ACCCGGCCACUUUCAGGAGG
740	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:740之TRAC之G016009導引RNA)	AAAGUCAGAUUUGUUGCUCC

741	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:741之TRAC之G016011導引RNA)	GCACCAAAGCUGCCCUUACC
742	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:742之TRAC之G016012導引RNA)	AUCCUCCUCCUGAAAGUGGC
743	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:743之TRAC之G016017導引RNA)	UUCAAAACCUGUCAGUGAUU

744	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:744之TRAC之G016018導引RNA)	UGUGCUAGACAUGAGGUCUA
745	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:745之TRAC之G016024導引RNA)	CGUCAUGAGCAGAUUAAACC
746	用於TRAC基因之例示性導引序列(靶向具有導引序列SEQ ID NO:746之TRAC之G016027導引RNA)	UCAAGGCCCCUCACCUCAGC

763-800		未使用
801	靶向具有導引序列SEQ ID NO:618之TRBC之G016200導引RNA	mC*mC*mA*CACCCAAAAGGCCACACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
802	靶向具有導引序列SEQ ID NO:619之TRBC之G016174導引RNA	mC*mC*mC*ACCAGCUCAGCUCCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
803	靶向具有導引序列SEQ ID NO:620之TRBC之G016263導引RNA	mU*mC*mC*CUAGCAGGAUCUCAUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
804	靶向具有導引序列SEQ ID NO:621之TRBC之G016270導引RNA	mG*mG*mC*UCAAACACAGCGACCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

805	靶向具有導引序列SEQ ID NO:622之TRBC之G016212導引RNA	mG*mG*mC*ACACCAGUGUGGCCUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
806	靶向具有導引序列SEQ ID NO:623之TRBC之G016207導引RNA	mA*mG*mG*UGGCCGAGACCCUCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
807	靶向具有導引序列SEQ ID NO:624之TRBC之G016205導引RNA	mA*mC*mC*UGCUCUACCCCAGGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
808	靶向具有導引序列SEQ ID NO:625之TRBC之G016245導引RNA	mC*mA*mU*AGAGGAUGGUGGCAGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
809	靶向具有導引序列SEQ ID NO:626之TRBC之G016232導引RNA	mC*mC*mA*CGUGGAGCUGAGCUGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

810	靶向具有導引序列SEQ ID NO:627之TRBC之G016227導引RNA	mG*mG*mA*GAAUGACGAGUGGACCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
811	靶向具有導引序列SEQ ID NO:628之TRBC之G016273導引RNA	mC*mC*mA*GUGUGGCCUUUUGGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
812	靶向具有導引序列SEQ ID NO:629之TRBC之G016251導引RNA	mC*mA*mA*ACACAGCGACCUCGGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
813	靶向具有導引序列SEQ ID NO:630之TRBC之G016276導引RNA	mU*mA*mC*CAUGGCCAUCAACACAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
814	靶向具有導引序列SEQ ID NO:631之TRBC之G016167導引RNA	mG*mC*mG*CUGACGAUCUGGGUGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

815	靶向具有導引序列SEQ ID NO:632之TRBC之G016253導引RNA	mC*mA*mC*GGACCCGCAGCCCCUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
816	靶向具有導引序列SEQ ID NO:633之TRBC之G016272導引RNA	mU*mC*mA*AACACAGCGACCUCGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
817	靶向具有導引序列SEQ ID NO:634之TRBC之G016258導引RNA	mC*mA*mG*GGAAGAAGCCUGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
818	靶向具有導引序列SEQ ID NO:635之TRBC之G016183導引RNA	mC*mA*mG*UGUGGCCUUUUGGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
819	靶向具有導引序列SEQ ID NO:636之TRBC之G016222導引RNA	mA*mC*mC*ACGUGGAGCUGAGCUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

820	靶向具有導引序列SEQ ID NO:637之TRBC之G016233導引RNA	mG*mA*mG*GGCGGGCUGCUCCUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
821	靶向具有導引序列SEQ ID NO:638之TRBC之G016264導引RNA	mA*mG*mC*UCAGCUCCACGUGGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
822	靶向具有導引序列SEQ ID NO:639之TRBC之G016255導引RNA	mG*mA*mA*CAAGGUGUUCCCACCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
823	靶向具有導引序列SEQ ID NO:640之TRBC之G016177導引RNA	mG*mC*mA*CACCAGUGUGGCCUUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
824	靶向具有導引序列SEQ ID NO:641之TRBC之G016283導引RNA	mG*mA*mG*CUGGUGGGUGAAUGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

825	靶向具有導引序列SEQ ID NO:642之TRBC之G016194導引RNA	mG*mG*mC*UGCUCCUUGAGGGGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
826	靶向具有導引序列SEQ ID NO:643之TRBC之G016266導引RNA	mC*mG*mG*GUGGGAACACCUUGUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
827	靶向具有導引序列SEQ ID NO:644之TRBC之G016196導引RNA	mC*mA*mG*CUCAGCUCCACGUGGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
828	靶向具有導引序列SEQ ID NO:645之TRBC之G016274導引RNA	mG*mA*mC*GAUCUGGGUGACGGGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
829	靶向具有導引序列SEQ ID NO:646之TRBC之G016282導引RNA	mU*mA*mG*CAGGAUCUCAUAGAGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

830	靶向具有導引序列SEQ ID NO:647之TRBC之G016267導引RNA	mG*mA*mC*CAGCACAGCAUACAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
831	靶向具有導引序列SEQ ID NO:648之TRBC之G016261導引RNA	mC*mU*mG*ACCACGUGGAGCUGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
832	靶向具有導引序列SEQ ID NO:649之TRBC之G016277導引RNA	mC*mC*mA*ACAGUGUCCUACCAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
833	靶向具有導引序列SEQ ID NO:650之TRBC之G016285導引RNA	mC*mU*mG*GUGGGUGAAUGGGAAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
834	靶向具有導引序列SEQ ID NO:651之TRBC之G016275導引RNA	mC*mU*mA*UGAGAUCCUGCUAGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

835	靶向具有導引序列SEQ ID NO:652之TRBC之G016281導引RNA	mC*mA*mG*GAUCUCAUAGAGGAUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
836	靶向具有導引序列SEQ ID NO:653之TRBC之G016280導引RNA	mG*mG*mC*CACCCUGUAUGCUGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
837	靶向具有導引序列SEQ ID NO:654之TRBC之G016279導引RNA	mC*mA*mA*CAGUGUCCUACCAGCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
838	靶向具有導引序列SEQ ID NO:655之TRBC之G016250導引RNA	mA*mG*mC*UGAGCUGGUGGGUGAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
839	靶向具有導引序列SEQ ID NO:656之TRBC之G016278導引RNA	mA*mA*mC*AGUGUCCUACCAGCAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

840	靶向具有導引序列SEQ ID NO:657之TRBC之G016259導引RNA	mA*mG*mG*CUUCUUCCCUGACCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
841	靶向具有導引序列SEQ ID NO:658之TRBC之G016284導引RNA	mU*mC*mU*UCUGCAGGUCAAGAGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
842	靶向具有導引序列SEQ ID NO:659之TRBC之G016249導引RNA	mG*mA*mG*CUGAGCUGGUGGGUGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
843	靶向具有導引序列SEQ ID NO:660之TRBC之G016256導引RNA	mG*mG*mU*CAGCGCCCUUGUGUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
844	靶向具有導引序列SEQ ID NO:661之TRBC之G016190導引RNA	mA*mG*mA*UCGUCAGCGCCGAGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

845	靶向具有導引序列SEQ ID NO:662之TRBC之G016248導引RNA	mG*mC*mU*GCUCCUUGAGGGGCUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
846	靶向具有導引序列SEQ ID NO:663之TRBC之G016257導引RNA	mG*mU*mA*UCUGGAGUCAUUGAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
847	靶向具有導引序列SEQ ID NO:664之TRBC之G016260導引RNA	mA*mU*mC*CUCUAUGAGAUCCUGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
848	靶向具有導引序列SEQ ID NO:665之TRBC之G016262導引RNA	mU*mC*mC*UCUAUGAGAUCCUGCUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
849	靶向具有導引序列SEQ ID NO:666之TRBC之G016242導引RNA	mG*mC*mA*GUAUCUGGAGUCAUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

850	靶向具有導引序列SEQ ID NO:667之TRBC之G016268導引RNA	mG*mC*mU*GACCAGCACAGCAUACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
851	靶向具有導引序列SEQ ID NO:668之TRBC之G016265導引RNA	mA*mC*mA*GGGUGGCCUUCCCUAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
852	靶向具有導引序列SEQ ID NO:669之TRBC之G016254導引RNA	mC*mG*mC*UGACCAGCACAGCAUACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
853	靶向具有導引序列SEQ ID NO:706之TRAC之G016019導引RNA	mA*mA*mC*AAAUGUGUCACAAAGUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
854	靶向具有導引序列SEQ ID NO:707之TRAC之G016016導引RNA	mU*mU*mU*CAAAACCUGUCAGUGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

855	靶向具有導引序列SEQ ID NO:708之TRAC之G016026導引RNA	mC*mU*mU*ACCUGGGCUGGGGAAGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
856	靶向具有導引序列SEQ ID NO:709之TRAC之G016013導引RNA	mC*mC*mG*AAUCCUCCUCCUGAAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
857	靶向具有導引序列SEQ ID NO:710之TRAC之G016022導引RNA	mC*mU*mG*ACAGGUUUUGAAAGUUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
858	靶向具有導引序列SEQ ID NO:711之TRAC之G016023導引RNA	mC*mU*mG*GGGAAGAAGGUGUCUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
859	靶向具有導引序列SEQ ID NO:712之TRAC之G016010導引RNA	mU*mC*mC*UCCUCCUGAAAGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

860	靶向具有導引序列SEQ ID NO:713之TRAC之G016014導引RNA	mC*mC*mA*CUUUCAGGAGGAGGAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
861	靶向具有導引序列SEQ ID NO:714之TRAC之G016020導引RNA	mA*mU*mU*UGUUUGAGAAUCAAAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
862	靶向具有導引序列SEQ ID NO:715之TRAC之G015998導引RNA	mC*mU*mU*CAAGAGCAACAGUGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
863	靶向具有導引序列SEQ ID NO:716之TRAC之G016025導引RNA	mA*mG*mC*UGCCCUUACCUGGGCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
864	靶向具有導引序列SEQ ID NO:717之TRAC之G015997導引RNA	mA*mG*mA*GCAACAGUGCUGUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

865	靶向具有導引序列SEQ ID NO:718之TRAC之G016029導引RNA	mA*mA*mA*GCUGCCCUUACCUGGGCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
866	靶向具有導引序列SEQ ID NO:719之TRAC之G016028導引RNA	mA*mA*mG*CUGCCCUUACCUGGGCUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
867	靶向具有導引序列SEQ ID NO:720之TRAC之G016021導引RNA	mU*mG*mG*AAUAAUGCUGUUGUUGAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
868	靶向具有導引序列SEQ ID NO:721之TRAC之G016015導引RNA	mC*mA*mC*CAAAGCUGCCCUUACCUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
869	靶向CD38之G019761導引RNA	mG*mA*mU*CCUCGUCGUGGUGCUCGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
870	靶向CD38之G019762導引RNA	mC*mC*mU*CGUCGUGGUGCUCGCGGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

871	靶向CD38之G019763導引RNA	mG*mC*mA*UCGCGCCAGGACGGUCUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
872	靶向CD38之G019764導引RNA	mU*mG*mU*ACUUGACGCAUCGCGCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
873	靶向CD38之G019765導引RNA	mC*mA*mC*CGGGCUGAACUCGCAGUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
874	靶向CD38之G019766導引RNA	mU*mC*mG*CGGUGGUCGUCCCGAGGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
875	靶向CD38之G019767導引RNA	mC*mC*mA*CCGCGAGCACCACGACGGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
876	靶向CD38之G019768導引RNA	mC*mA*mU*CGCGCCAGGACGGUCUCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
877	靶向CD38之G019769導引RNA	mG*mA*mC*GGUCUCGGGAAAGCGCUGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
878	靶向CD38之G019770導引RNA	mG*mC*mG*CUUUCCCGAGACCGUCCGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
879	靶向CD38之G019771導引RNA	mC*mU*mU*GACGCAUCGCGCCAGGAGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

880	靶向CD38之G019772導引RNA	mU*mG*mC*GAGUUCAGCCCGGUGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
881	靶向CD38之G019773導引RNA	mU*mG*mC*UCGCGGUGGUCGUCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
882	靶向CD38之G019774導引RNA	mA*mG*mG*GUUUGUCCCCGGACACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
883	靶向CD38之G019775導引RNA	mG*mC*mG*AGUUCAGCCCGGUGUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
884	靶向CD38之G019776導引RNA	mG*mG*mU*CUCGGGAAAGCGCUUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
885	靶向CD38之G019777導引RNA	mC*mG*mA*GUUCAGCCCGGUGUCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
886	靶向CD38之G019778導引RNA	mC*mC*mG*GCAGCAGGGUUUGUCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
887	靶向CD38之G019779導引RNA	mG*mU*mU*GGGCUCUCCUAGAGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
888	靶向CD38之G019780導引RNA	mC*mG*mA*GCACCACGACGAGGAUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

889	靶向CD38之G019781導引RNA	mG*mG*mC*CAACUGCGAGUUCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
890	靶向CD38之G019782導引RNA	mU*mA*mC*UGACGCCAAGACAGAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
891	靶向CD38之G019783導引RNA	mU*mC*mG*CCAACCCACCUCAUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
892	靶向CD38之G019784導引RNA	mC*mC*mG*GGGACAAACCCUGCUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
893	靶向CD38之G019785導引RNA	mG*mG*mA*AAGCGCUUGGUGGUGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
894	靶向CD38之G019786導引RNA	mU*mC*mU*CCUAGAGAGCCGGCAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
895	靶向CD38之G019787導引RNA	mC*mG*mC*CAGCAGUGGAGCGGUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
896	靶向CD38之G019788導引RNA	mC*mU*mC*CACUGCUGGCGCCACCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
897	靶向CD38之G019789導引RNA	mC*mA*mG*GGUUUGUCCCCCGGACACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

898	靶向CD38之G019790導引RNA	mC*mU*mG*UCUUGGCGUCAGUAUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
899	靶向CD38之G019791導引RNA	mU*mG*mC*CCGGACCGCUCCACUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
900	靶向CD38之G019792導引RNA	mC*mU*mC*CUAGAGAGCCGGCAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
901	靶向CD38之G019793導引RNA	mC*mC*mU*GGUCCUGAUCCUCGUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
902	靶向CD38之G019794導引RNA	mU*mC*mC*CGAGGUGGCGCCAGCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
903	靶向CD38之G019795導引RNA	mG*mC*mG*CCAGCAGUGGAGCGGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
904	靶向CD38之G019796導引RNA	mU*mC*mC*ACUGCUGGCGCCACCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
905	靶向CD38之G019797導引RNA	mA*mG*mG*AGAGCCCAACUCUGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
906	靶向CD38之G019798導引RNA	mA*mC*mU*GACGCCAAGACAGAGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

907	靶向CD38之G019799導引RNA	mA*mA*mC*CCUGCUGCCGGCUCUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
908	靶向CD38之G019800導引RNA	mU*mA*mU*CAGCCACUAAUGAAGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
909	靶向CD38之G019801導引RNA	mU*mG*mA*AAGCAUCCCAUACACUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
910	靶向CD38之G019802導引RNA	mC*mC*mC*CCAAUUACCUUGUUGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
911	靶向CD38之G019803導引RNA	mA*mU*mG*UAGACUGCCAAAGUGUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
912	靶向CD38之G019804導引RNA	mA*mA*mG*UGUAUGGGAUGCUUUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
913	靶向CD38之G019805導引RNA	mA*mA*mU*UACCUUGUUGCAAGGUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
914	靶向CD38之G019806導引RNA	mU*mG*mA*GUUCCCAACUUCAUUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
915	靶向CD38之G019807導引RNA	mU*mG*mU*AGACUGCCAAAGUGUAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

916	靶向CD38之G019808導引RNA	mA*mG*mU*GUAUGGGAUGCUUUCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
917	靶向CD38之G019809導引RNA	mC*mU*mA*UCAGCCACUAAUGAAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
918	靶向CD38之G019810導引RNA	mU*mC*mU*UCUUCAGUAAUGUUGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
919	靶向CD38之G019811導引RNA	mU*mC*mU*GGCCCAUCAGUUCACACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
920	靶向CD38之G019812導引RNA	mG*mC*mG*GGACAUGUUCACCCUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
921	靶向CD38之G019813導引RNA	mC*mC*mA*GCGGGACAUGUUCACCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
922	靶向CD38之G019814導引RNA	mA*mG*mC*CUAGCAGCGUGUCCUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
923	靶向CD38之G019815導引RNA	mU*mG*mA*AUUCACCACACCAUGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
924	靶向CD38之G019816導引RNA	mA*mU*mC*AGUUCACACAGGUCCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

925	靶向CD38之G019817導引RNA	mG*mC*mU*GAUGACCUCACAUGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
926	靶向CD38之G019818導引RNA	mG*mC*mC*UAGCAGCGUGUCCUCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
927	靶向CD38之G019819導引RNA	mA*mC*mC*AUGUGAGGUCAUCAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
928	靶向CD38之G019820導引RNA	mU*mC*mA*GUUCACACAGGUCCAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
929	靶向CD38之G019821導引RNA	mC*mC*mA*GGGUGAACAUGUCCCGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
930	靶向CD38之G019822導引RNA	mG*mC*mU*GGACCUGUGUGAACUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
931	靶向CD38之G019823導引RNA	mA*mC*mC*CUGGAGGACACGCUGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
932	靶向CD38之G019824導引RNA	mC*mU*mG*GACCUGUGUGAACUGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
933	靶向CD38之G019825導引RNA	mU*mC*mU*GGAAAACGGUUUCCCGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

937	靶向CD38之G019829導引RNA	mG*mU*mU*UUCCAGAAUACUGAAACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
938	靶向CD38之G019830導引RNA	mG*mG*mG*AUCCAUUGAGCAUCACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
939	靶向CD38之G019831導引RNA	mC*mA*mU*CACAUGGACCACAUCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
940	靶向CD38之G019832導引RNA	mG*mU*mG*GUCCAUGUGAUGCUCAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
941	靶向CD38之G019833導引RNA	mA*mG*mA*GAAGGUUCAGACACUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
942	靶向CD38之G019834導引RNA	mU*mC*mU*AGUGUCUGAACCUUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
943	靶向CD38之G019835導引RNA	mG*mG*mU*UCAGACACUAGAGGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
944	靶向CD38之G019836導引RNA	mC*mC*mA*UAAUUUGCAACCAGAGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
945	靶向CD38之G019837導引RNA	mC*mC*mU*UCUCUGGUUGCAAAUUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

946	靶向CD38之G019838導引RNA	mA*mG*mG*UUCAGACACUAGAGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
947	靶向CD38之G019839導引RNA	mC*mU*mA*GAGGCCUGGGUGAUACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
948	靶向CD38之G019840導引RNA	mU*mU*mU*UAGCACUUUUGGGAGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
949	靶向CD38之G019841導引RNA	mU*mC*mU*UCCACCAUGUAUCACCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
950	靶向CD38之G019842導引RNA	mC*mU*mU*CCCCAGAGACUUAUGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
951	靶向CD38之G019843導引RNA	mU*mU*mA*CCUGUAGAUAUUCUUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
952	靶向CD38之G019844導引RNA	mG*mC*mU*CUUUUAUGGUGGGAUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
953	靶向CD38之G019845導引RNA	mG*mG*mA*UCCCACCAUAAAAGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
954	靶向CD38之G019846導引RNA	mC*mG*mA*UUCCAGCUCUUUUAUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

955	靶向CD38之G019847導引RNA	mG*mA*mU*UCCAGCUCUUUUAUGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
956	靶向CD38之G019848導引RNA	mA*mA*mU*CGAUUCCAGCUCUUUUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
957-959		未使用
960	例示性胞苷去胺酶之胺基酸序列；參見表58，BC01	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSVWRHTSQNTSNHVEVNFLEKFTTERYFRPNTRCSITWFLSWSPCGECSRAITEFLSRHPYVTLF
961	例示性胞苷去胺酶之胺基酸序列；參見表58，BC02	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSVWRHTSQNTSNHVEVNFLEKFTTERYFRPNTRCSITWFLSWSPCGECSRAITEFLSRHPYVTLFIYIARLYH
962	例示性胞苷去胺酶之胺基酸序列；參見表58，BC03	MNWNALRSKAIEVSRHAYAPYSGFPVGAAALVDDGRTVTGCNVENVSYGLGLCAECAVVCALHSGGGGRLVALSCVGPDGGVLMPCGRCRQVLLEHGGPELLIDHAHGPRPLRELLPDAFGPDDLGRR
963	例示性胞苷去胺酶之胺基酸序列；參見表58，BC04	MTHHALIEAAKAARFKAYAPYSNFKVGAALVTNDGKVFHGCNVENASYGLCNCAERTALFSALAAGYRPGEFAAIAVVGETHGPIAPCGACRQVMIELGKPTLEVVLTNMQGDVRVTSAGDLLPDAFYLA

964	例示性胞苷去胺酶之胺基酸序列；參見表58，BC05	MPDIDWKQLRDKATQVAAGAYAPYSRFPVGAAALVDDGRVVTGCNVENVSYGLALCAECGVVCALHATGGGRLVALACVDGRGAPLMPCGR CRQLLFEHGGPELLVDHLAGPRRLGDLLPEPFHADLTGEPT
965	例示性胞苷去胺酶之胺基酸序列；參見表58，BC06	MNSKQLIQEAIEARKQAYVPYSKFQVGAALLTQDGKVYRGCNVENASYGLCNCAERTALFKAVSEGDKEFVAIAIVADTKRPVPPCGACRQ VMVELCKQDTKVYLSNLHGDVQETTVGELLPGAFLAEDLHE
966	例示性胞苷去胺酶之胺基酸序列；參見表58，BC07	MPDVDWNMLRGNATQAAAGAYVPYSRFAVGAAALVDDGRVVTGCNVENVSYGLTLCAECAVVCALHSTGGGRLLALACVDGHGSVLMPCGR CRQVLLEHGGSELLIDHPVRPRRLGDLLPDAFGLDDLPRERR
967	例示性胞苷去胺酶之胺基酸序列；參見表58，BC08	MGDVNWDTLQKAAVAARANSYAPYSNFPVGVAGFVNDGRLITGVNVENASYGLALCAECSMISALYATGGGRLVAVYCVDGNGDSLMPCGR CRQLLYEHGGPELKIMTPKGVQTMAQLLPQAFNPQERIFGNDE
968	例示性胞苷去胺酶之胺基酸序列；參見表58，BC09	MNRQELITEALKARDMAYAPYSKFQVGAALLTKDGKVYRGCNIENAAYSMCNCAERTALFKAVSEGDTEFQMLAVAADTPGPVSPCGACRQ VISELCTKDVIVVLTNLQGQIKEMTVEELLPGAFSSEDLHDERKL
969	例示性胞苷去胺酶之胺基酸序列；參見表58，BC10	MKVGGIEDRQLEALKRAALKACELSYSPYSHFRVGCSILTNNDVIFTGANVENASYSNCICAERSAMIQVLMAGHRSGWKCMVICGDSEDQ CVSPCGVCRQFINEFVVKDFPIVMLNSTGSRSKVMTMGELLPMAFGPSHLN

970	例示性胞苷去胺酶之胺基酸序列；參見表58，BC11	MNIEQQLYDVVKQLIEQRYPNDWGGAAAIRVEDGTIYTSVAPDVINASTELCMETGAILEAHKFQKKVTHSICLARENEHSELKVLSPCGV CQERLFYWGPEVQCAITNAKQDIIFKPLKELQPYHWTEAYHDEMVKEWSTR
971	例示性胞苷去胺酶之胺基酸序列；參見表58，BC12	MAQERPSCAVEPEHVQRLLLSSREAKKSAYCPYSRFPVGAALLTGDGRIFSGCNIENACYPLGVCAERTAIQKAISEGYKDFRAIAISSDL QEEFISPCGACRQVMREFGTDWAVYMTKPDGTFVVRTVQELLPASFGPEDLQKIQ
972	例示性胞苷去胺酶之胺基酸序列；參見表58，BC13	MAQKRPACTLKPECVQQLLVCSQEAKKSAYCPYSHFPVGAALLTQEGRIFKGCNIENACYPLGICAERTAIQKAVSEGYKDFRAIAIASDM QDDFISPCGACRQVMREFGTNWPVYMTKPDGTYIVMTVQELLPSSFGPEDLQKTQ
973	例示性胞苷去胺酶之胺基酸序列；參見表58，BC14	MVTGGMASKWDQKGMDIAYEEAALGYKEGGVPIGGCLINNKDGSVLGRGHNMRFQKGSATLHGEISTLENCGRLEGKVYKDTTLYTTLSPC DMCTGAIIMYGIPRCVVGENVNFKSKGEKYLQTRGHEVVVVDDERCKKIMKQFIDERPQDWFEDIGE
974	例示性胞苷去胺酶之胺基酸序列；參見表58，BC15	MTTTKANLTEFEQQLVDKAIGAMENAYCKYSNFKVGAALVCDDGEIIIGANHENASYGATICAERSAIVTALTKGHRKFKYIVVATELEAP CSPCGVCRQVLIEFGDYKVILGSSTSDQIIETTTYELLPYAFTPKSLDDHEKETEERKHHNDHNNKE
975	例示性胞苷去胺酶之胺基酸序列；參見表58，BC16	MAANSLPQDISDVELVHLARAAMKRAHCPYSKFPVGAALLTESGEIVQGCNVENASYGGTICAERSAIVSAVSQGYTKFRAIAVVTELSEP ASPCGLCRQFLVEFGDYKVVVGTASNNKILITSTRALLPFAFTPESLDTFEQEKASEAKGLKQDDATEHNVTVVS

976	例示性胞苷去胺酶之胺基酸序列；參見表58，BC17	MNPQIRNPMKAMYPGTFYFQFKNLWEANDRNETWLCFTVEGIKRRSVVSWKTGVFRNQVDSETHCHAERCFLSWFCDDILSPNTKYQVTWY TSWSPCPDCAGEVAEFLARHSNVNLTIFTARLYYFQYPCYQEGLRSLSQEGVAVEIMDYEDFKYCWENFVYNDNEPFKPWKGLKTNFRLLK RRLRESLQ
977	例示性胞苷去胺酶之胺基酸序列；參見表58，BC18	MNPQIRNPMEAMYPHIFYFHFKNLLKACGRNESWLCFTMEVTKHHSAVFRKRGVFRNQVDPETHCHAERCFLSWFCDDILSPNTNYEVTWY TSWSPCPECAGEVAEFLARHSNVNLTIFTARLCYFWDTDYQEGLCSLSQEGASVKIMGYKDFVSCWKNFVYSDDEPFKPWKGLQTNFRLLK RRLREILQ
978	例示性胞苷去胺酶之胺基酸序列；參見表58，BC19	MNDALHIGLPPFLVQANNEPRVLAAPEARMGYVLELVRANIAADGGPFAAAVFERDSGLLIAAGTNRVVPGRCSAAHAEILALSLAQAKLD THDLSADGLPACELVTSAEPCVMCFGAVIWSGVRSLVCAARSDDVEAIGFDEGPRPENWMGGLEARGITVTTGLLRDAACALLREYNACNG VIYNARCGVHK
979	例示性胞苷去胺酶之胺基酸序列；參見表58，BC20	MDSLLMNRRKFLYQFKNVRWAKGRRETYLCYVVKRRDSATSFSLDFGYLRNKNGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCA RHVADFLRGNPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIAIMTFKDYFYCWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLP LYEVDDLRDAFRTLGL
980	例示性胞苷去胺酶之胺基酸序列；參見表58，BC21	MDSLLMKQKKFLYHFKNVRWAKGRHETYLCYVVKRRDSATSCSLDFGHLRNKSGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCA RHVAEFLRWNPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIGIMTFKDYFYCWNTFVENRERTFKAWEGLHENSVRLTRQLRRILLP LYEVDDLRDAFRMLGF
981	例示性胞苷去胺酶之胺基酸序列；參見表58，BC23	MALLTAETFRLQFNNKRRLRRPYYPRKALLCYQLTPQNGSTPTRGYFENKKKCHAEICFINEIKSMGLDETQCYQVTCYLTWSPCSSCAWE LVDFIKAHDHLNLGIFASRLYYHWCKPQQKGLRLLCGSQVPVEVMGFPKFADCWENFVDHEKPLSFNPYKMLEELDKNSRAIKRRLERIKI PGVRAQGRYMDILCDAEV

982	例示性胞苷去胺酶之胺基酸序列；參見表58，BC24	MAQKEEAAVATEAASQNGEDLENLDDPEKLKELIELPPFEIVTGERLPANFFKFQFRNVEYSSGRNKTFLCYVVEAQGKGGQVQASRGYLE DEHAAAHAEEAFFNTILPAFDPALRYNVTWYVSSSPCAACADRIIKTLSKTKNLRLLILVGRLFMWEEPEIQAALKKLKEAGCKLRIMKPQ DFEYVWQNFVEQEEGESKAFQPWEDIQENFLYYEEKLADILK
983	例示性胞苷去胺酶之胺基酸序列；參見表58，BC25	MAQKEEAAEAAAPASQNGDDLENLEDPEKLKELIDLPPFEIVTGVRLPVNFFKFQFRNVEYSSGRNKTFLCYVVEVQSKGGQAQATQGYLE DEHAGAHAEEAFFNTILPAFDPALKYNVTWYVSSSPCAACADRILKTLSKTKNLRLLILVSRLFMWEEPEVQAALKKLKEAGCKLRIMKPQ DFEYIWQNFVEQEEGESKAFEPWEDIQENFLYYEEKLADILK
984	例示性胞苷去胺酶之胺基酸序列；參見表58，BC26	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSVWRHTSQNTSNHVEVNFLEKFTTERYFRPNTRCSITWFLSWS PCGECSRAITEFLSRHPYVTLFIYIARLYHHTDQRNRQGLRDLISSGVTIQIMTEQEYCYCWRNFVNYPPSNEAYWPRYPHLWVKLYVLEL YCIILGLPPCLKILRRKQPQLTFFTITLQTCHYQRIPPHLLWATGLK
985	例示性胞苷去胺酶之胺基酸序列；參見表58，BC28	MNSKTGPSVGDATLRRRIKPWEFVAFFNPQELRKETCLLYEIKWGNQNIWRHSNQNTSQHAEINFMEKFTAERHFNSSVRCSITWFLSWSP CWECSKAIRKFLDHYPNVTLAIFISRLYWHMDQQHRQGLKELVHSGVTIQIMSYSEYHYCWRNFVDYPQGEEDYWPKYPYLWIMLYVLELH CIILGLPPCLKISGSHSNQLALFSLDLQDCHYQKIPYNVLVATGLVQPFVTWR
986	例示性胞苷去胺酶之胺基酸序列；參見表58，BC29	MTSEKGPSTGDPTLRRRIEPWEFDVFYDPRELRKEACLLYEIKWGMSRKIWRSSGKNTTNHVEVNFIKKFTSERDFHPSMSCSITWFLSWS PCWECSQAIREFLSRHPGVTLVIYVARLFWHMDQQNRQGLRDLVNSGVTIQIMRASEYYHCWRNFVNYPPGDEAHWPQYPPLWMMLYALEL HCIILSLPPCLKISRRWQNHLTFFRLHLQNCHYQTIPPHILLATGLIHPSVAWR
987	例示性胞苷去胺酶之胺基酸序列；參見表58，BC30	MASEKGPSNKDYTLRRRIEPWEFEVFFDPQELRKEACLLYEIKWGASSKTWRSSGKNTTNHVEVNFLEKLTSEGRLGPSTCCSITWFLSWS PCWECSMAIREFLSQHPGVTLIIFVARLFQHMDRRNRQGLKDLVTSGVTVRVMSVSEYCYCWENFVNYPPGKAAQWPRYPPRWMLMYALEL YCIILGLPPCLKISRRHQKQLTFFSLTPQYCHYKMIPPYILLATGLLQPSVPWR

988	例示性胞苷去胺酶之胺基酸序列；參見表58，BC31	MKVSLAGQTVDVKKILNEIPKRTVTAALLEGGEIVAVEEADDEHAERKLVRRHDVEGKVVFVTARPCLYCARELAEAGVAGVVYLGRGRGL GPYYLARSGVEVVEVHPDEPLGYDPVDRLDVLLTFGGNPYLTEEDVAARVYCLLTGRGFDADIAPAPENLSGRVEIMVTRGDPDEAVELLK EELPVFRIRRFLISGEFDRDELRERILEDIEPRILDPFAVRARIARAGAFSSSREAEVFIGDVLTSVGREVNLNDPRTVVTVDVLGPRVSV GVEKR
989	例示性胞苷去胺酶之胺基酸序列；參見表58，BC32	MHPRFQTAFAQLADNLQSALEPILADKYFPALLTGEQVSSLKSATGLDEDALAFALLPLAAACARTPLSNFNVGAIARGVSGTWYFGANME FIGATMQQTVHAEQSAISHAWLSGEKALAAITVNYTPCGHCRQFMNELNSGLDLRIHLPGREAHALRDYLPDAFGPKDLEIKTLLMDEQDH GYALTGDALSQAAIAAANRSHMPYSKSPSGVALECKDGRIFSGSYAENAAFNPTLPPLQGALILLNLKGYDYPDIQRAVLAEKADAPLIQW DATSATLKALGCHSIDRVLLA
990	例示性胞苷去胺酶之胺基酸序列；參見表58，BC33	MRNRIEQALQQMPASFAPYLRELVLAKDFDATFSAEQYQQLLTLSGLEDADLRVALLPIAAAYSYAPISEFYVGAIVRGISGRLYLGANME FTGAQLGQTVHAEQCAISHAWMKGEKGVADITINFSPCGHCRQFMNELTTASSLKIQLPKRAAKTLQEYLPESFGPADLGIDSGLMSPVNH GKTSDDDEELIQQALRAMNISHSPYTQNFSGVALKMRSGAIYLGAYAENAAFNPSLPPLQVALAQAMMMGESFEDIEAAALVESATGKISH LADTQATLEVINPDIPLSYLSL
991	例示性胞苷去胺酶之胺基酸序列；參見表58，BC34	MSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRLLTNFRYQD SKLQEILRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWS PCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRR IKESWGLQDLVNDFGNLQLGPPMS
992	例示性胞苷去胺酶之胺基酸序列；參見表58，BC35	MDKPSFVIQSKEAESAAKQLGVSVIQLLPSLVKPAQSYARTPISKFNVAVVGLGSSGRIFLGVNVEFPNLPLHHSIHAEQFLVTNLTLNGE RHLNFFAVSAAPCGHCRQFLQEIRDAPEIKILITDPNNSADSDSAADSDGFLRLGSFLPHRFGPDDLLGKDHPLLLESHDNHLKISDLDSI CNGNTDSSADLKQTALAAANRSYAPYSLCPSGVSLVDCDGKVYRGWYMESAAYNPSMGPVQAALVDYVANGGGGGYERIVGAVLVEKEDAV VRQEHTARLLLETISPKCEFKVFHCYEA
993	例示性胞苷去胺酶之胺基酸序列；參見表58，BC36	MVEPMDPRTFVSNFNNRPILSGLNTVWLCCEVKTKDPSGPPLDAKIFQGKVYSKAKYHPEMRFLRWFHKWRQLHHDQEYKVTWYVSWSPCT RCANSVATFLAKDPKVTLTIFVARLYYFWKPDYQQALRILCQKRGGPHATMKIMNYNEFQDCWNKFVDGRGKPFKPRNNLPKHYTLLQATL GELLRHLMDPGTFTSNFNNKPWVSGQHETYLCYKVERLHNDTWVPLNQHRGFLRNQAPNIHGFPKGRHAELCFLDLIPFWKLDGQQYRVTC FTSWSPCFSCAQEMAKFISNNEHVSLCIFAARIYDDQGRYQEGLRALHRDGAKIAMMNYSEFEYCWDTFVDRQGRPFQPWDGLDEHSQALS GRLRAI

994	例示性胞苷去胺酶之胺基酸序列；參見表58，BC37	MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPRLDAKIFRGQVYSQPEHHAEMCFLSWFCGNQLPAYKCFQITWFV SWTPCPDCVAKLAEFLAEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVKIMDDEEFAYCWENFVYSEGQPFMPWYKFDDNYAFLHR TLKEILRNPMEAMYPHIFYFHFKNLRKAYGRNESWLCFTMEVVKHHSPVSWKRGVFRNQVDPETHCHAERCFLSWFCDDILSPNTNYEVTW YTSWSPCPECAGEVAEFLARHSNVNLTIFTARLYYFWDTDYQEGLRSLSQEGASVEIMGYKDFKYCWENFVYNDDEPFKPWKGLKYNFLFL DSKLQEILE
995	例示性胞苷去胺酶之胺基酸序列；參見表58，BC38	MNPQIRNMVEQMEPDIFVYYFNNRPILSGRNTVWLCYEVKTKDPSGPPLDANIFQGKLYPEAKDHPEMKFLHWFRKWRQLHRDQEYEVTWY VSWSPCTRCANSVATFLAEDPKVTLTIFVARLYYFWKPDYQQALRILCQERGGPHATMKIMNYNEFQHCWNEFVDGQGKPFKPRKNLPKHY TLLHATLGELLRHVMDPGTFTSNFNNKPWVSGQRETYLCYKVERSHNDTWVLLNQHRGFLRNQAPDRHGFPKGRHAELCFLDLIPFWKLDD QQYRVTCFTSWSPCFSCAQKMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLHRDGAKIAVMNYSEFEYCWDTFVDRQGRPFQPWDGLD EHSQALSGRLRAI
996	例示性胞苷去胺酶之胺基酸序列；參見表58，BC39	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGQVYFKPQYHAEMCFLSWFCGNQLPAYKCFQITWF VSWTPCPDCVAKLAEFLSEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVTIMDYEEFAYCWENFVYNEGQQFMPWYKFDENYAFLH RTLKEILRYLMDPDTFTFNFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIY RVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGCPFQPWDGLEE HSQALSGRLRAILQNQGN
997	例示性胞苷去胺酶之胺基酸序列；參見表58，BC40	MKPQIRNMVEPMDPRTFVSNFNNRPILSGLDTVWLCCEVKTKDPSGPPLDAKIFQGKVYPKAKYHPEMRFLRWFHKWRQLHHDQEYKVTWY VSWSPCTRCANSVATFLAKDPKVTLTIFVARLYYFWKPDYQQALRILCQKRDGPHATMKIMNYNEFQDCWNKFVDGRGKPFKPWNNLPKHY TLLQATLGELLRHLMDPGTFTSNFNNKPWVSGQHETYLCYKVERLHNDTWVPLNQHRGFLRNQAPNIHGFPKGRHAELCFLDLIPFWKLDG QQYRVTCFTSWSPCFSCAQEMAKFISNNEHVSLCIFAARIYDDQGRYQEGLRTLHRDGAKIAMMNYSEFEYCWDTFVDRQGRPFQPWDGLD EHSQALSGRLRAILQNQGN
998	例示性胞苷去胺酶之胺基酸序列；參見表58，BC41	MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSELKYHPEMRFFHWFSKWRKLHRDQEYEVTWY ISWSPCTKCTRDMATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDL DQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGL DEHSQDLSGRLRAILQNQEN
999	例示性胞苷去胺酶之胺基酸序列；參見表58，BC42	MKPHFRNPVERMYQDTFSDNFYNRPILSHRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSKLKYHPEMRFFHWFSKWRKLHRDQEYEVTWY ISWSPCTKCTRDVATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTSNFNNELWVRGRHETYLCYEVERLHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDL HQDYRVTCFTSWSPCFSCAQEMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLAKAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGL EEHSQALSGRLRAILQNQGN

1000	例示性胞苷去胺酶之胺基酸序列；參見表58，BC43	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGPVLPKRQSNHRQEVYFRFENHAEMCFLSWFCGNR LPANRRFQITWFVSWNPCLPCVVKVTKFLAEHPNVTLTISAARLYYYRDRDWRWVLLRLHKAGARVKIMDYEDFAYCWENFVCNEGQPFMP WYKFDDNYASLHRTLKEILRNPMEAMYPHIFYFHFKNLLKACGRNESWLCFTMEVTKHHSAVFRKRGVFRNQVDPETHCHAERCFLSWFCD DILSPNTNYEVTWYTSWSPCPECAGEVAEFLARHSNVNLTIFTARLCYFWDTDYQEGLCSLSQEGASVKIMGYKDFVSCWKNFVYSDDEPF KPWKGLQTNFRLLKRRLREILQ
1001	例示性胞苷去胺酶之胺基酸序列；參見表58，BC44	MQPQRLGPRAGMGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWF HDKVLKVLSPREEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDN GGRRFRPWKRLLTNFRYQDSKLQEILRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKGKQHAEILFLD KIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPF WPWKGLEIISRRTQRRLRRIKESRSHAS
1002	例示性胞苷去胺酶之胺基酸序列；參見表58，BC45	MQPQRLGPRAGMGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWF HDKVLKVLSPREEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDN GGRRFRPWKRLLTNFRYQDSKLQEILRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKGKQHAEILFLD KIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPF WPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
1003	例示性胞苷去胺酶之胺基酸序列；參見表58，BC46	MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWFHDKVLKVLSPR EEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRL LTNFRYQDSKLQEILRPCYISVPSSSSSTLSNICLTKGLPETRFWVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQ APLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILV DVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
1004	例示性胞苷去胺酶之胺基酸序列；參見表58，BC47	MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWFHDKVLKVLSPR EEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRL LTNFRYQDSKLQEILRPCYIPVPSSSSSTLSNICLTKGLPETRFCVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQ APLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILV DVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
1005	例示性胞苷去胺酶之胺基酸序列；參見表58，BC48	MQPQRLGPRAGMGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWF HDKVLKVLSPREEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDN GGRRFRPWKRLLTNFRYQDSKLQEILRPCYISVPSSSSSTLSNICLTKGLPETRFWVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPY LCYQLEQFNGQAPLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKG LCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKEVRTTLLQGPAS

1006	例示性胞苷去胺酶之胺基酸序列；參見表58，BC49	MQPQRLGPRAGMGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWF HDKVLKVLSPREEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDN GGRRFRPWKRLLTNFRYQDSKLQEILRPCYISVPSSSSSTLSNICLTKGLPETRFWVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPY LCYQLEQFNGQAPLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKG LCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
1007	例示性胞苷去胺酶之胺基酸序列；參見表58，BC50	MKETDQMQSLEGSGAERSVGTQTGSMTGQIPRLSKVNLFTLLSLWMELFPGVEAQGQKSQKTEEESRGPLGDNEELTRVSTEKKQVKKTGL VVVKNMKIIGLHCSSEDLHTGQIALIKHGSRLKNCDLYFSRKPCSACLKMIVNAGVNRISYWPSDPEISLLTEASSSEDAKLDAKAAERLK SNSRAHVCVLLQPLVCYMVQFVEETSYKCDFIQKTAKALPGADTDFYSECKQERIKEYEMLFLVSNEERHKQILMTIGLESLCEDPYFSNL RQNMKDLILLLATVASSVPNLKHFGFYCSSPEQINEIHNQSLPQEVARHCMVQARLLAYRTEDHKTGVGAVIWAEAKSRSCDGTGAMYFIG CGYNAFPVGSEYADFPHMDDKHKDREIRKFRYIIHAEQNALTFRCQDIKPEERSMIFVTKCPCDECVPLIKGAGIKQIYAGDVDVGKKKAD ISYMKFGELEGVRKFTWQLNPSEAYSLDPNEPERRENGVLRRRSAKDEQRSSKRPRLETRSAGSATTACF
1008	例示性胞苷去胺酶之胺基酸序列；參見表58，BC51	MSNNALQTIINARLPGEEGLWQIHLQDGKISAIDAQSGVMPITENSLDAEQGLVIPPFVEPHIHLDTTQTAGQPNWNQSGTLFEGIERWAE RKALLTHDDVKQRAWQTLKWQIANGIQHVRTHVDVSDATLTALKAMLEVKQEVAPWIDLQIVAFPQEGILSYPNGEALLEEALRLGADVVG AIPHFEFTREYGVESLHKTFALAQKYDRLIDVHCDEIDDEQSRFVETVAALAHHEGMGARVTASHTTAMHSYNGAYTSRLFRLLKMSGINF VANPLVNIHLQGRFDTYPKRRGITRVKEMLESGINVCFGHDDVFDPWYPLGTANMLQVLHMGLHVCQLMGYGQINDGLNLITHHSARTLNL QDYGIAAGNSANLIILPAENGFDALRRQVPVRYSVRGGKVIASTQPAQTTVYLEQPEAIDYKR
1009	例示性胞苷去胺酶之胺基酸序列；參見表58，BC52	MALLTAKTFSLQFNNKRRVNKPYYPRKALLCYQLTPQNGSTPTRGHLKNKKKDHAEIRFINKIKSMGLDETQCYQVTCYLTWSPCPSCAGE LVDFIKAHRHLNLRIFASRLYYHWRPNYQEGLLLLCGSQVPVEVMGLPEFTDCWENFVDHKEPPSFNPSEKLEELDKNSQAIKRRLERIKS RSVDVLENGLRSLQLGPVTPSSSIRNSR
1010	例示性胞苷去胺酶之胺基酸序列；參見表58，BC53	MEKDINLKIFKGNLIFTKTSDKFTIMKDSYIVVIDGKIASVSSNLPDKYKGNPIIDFRNNIIIPGMNDLHAHASQYKNLGIGMDKELLPWL NNYTFPEEAKFLNVDYAKKTYGRLIKDLIKNGTTRVALFATLHKDSTIELFNMLIKSGIGAYVGKVNMDYNCPDYLTENYITSLNDTEEII LKYKDKSNIVKPIITPRFVPSCSNELMDGLGKLSYKYRLPVQSHLSENLDEIAVVKSLHKKSNFYGEVYDKFGLFGNTPTLMAHCIHSSKE EINLIKRNNVTIVHCPTSNFNLGSGMMPVRKYLNLGINVVLGSDISAGHTCSLFKVIAYAIQNSKIKWQESGKKDMFLSTSEAFYMATKKG GSFFGKVGSFEEGYDFDALVINDSNLYPEDYDLTERLERFIYLGDDRNIMKRYVCGNEIFGPKF
1011	例示性胞苷去胺酶之胺基酸序列；參見表58，BC54	MKIINARLRRQEALFTLDLQDGIIHRITAQAAMQTADAGAIDAQGRLAIPPFVEPHIHLDATLTAGEPEWNRSGTLFEGITRWSQRKASIT PEDTRQRALKTIGMLRDFGVQHVRTHVDVTDPSLAALQALLAVKQEAADLIDLQIVAFPQEGIESYPNGRELMTRAIEMGADVVGGIPHYE NTRDKGVSSVMFLMDLAQRYGRLVDVHCDEIDDPQSRFLEVLAEEARVRGMGAQVTASHTCAMGSYDNAYCSKLFRLLKASGINFISCPTE SIHLQGRFDSWPKRRGVTRVAELDRAGINVCFAQDSIQDPWYPLGNGNILRILDAGLHICHMLGYDDLQRCLDFVTDNSARALCLGDNYGL AEGRPANLLILDAENDYEAVRRQARVLTSIRHGKVILQREVEHIRYPA

1012	例示性胞苷去胺酶之胺基酸序列；參見表58，BC55	MGRKLDPTKEKRGPGRKARKQKGAETELVRFLPAVSDENSKRLSSRARKRAAKRRLGSVEAPKTNKSPEAKPLPGKLPKGISAGAVQTAGK KGPQSLFNAPRGKKRPAPGSDEEEEEEDSEEDGMVNHGDLWGSEDDADTVDDYGADSNSEDEEEGEALLPIERAARKQKAREAAAGIQWSE EETEDEEEEKEVTPESGPPKVEEADGGLQINVDEEPFVLPPAGEMEQDAQAPDLQRVHKRIQDIVGILRDFGAQREEGRSRSEYLNRLKKD LAIYYSYGDFLLGKLMDLFPLSELVEFLEANEVPRPVTLRTNTLKTRRRDLAQALINRGVNLDPLGKWSKTGLVVYDSSVPIGATPEYLAG HYMLQGASSMLPVMALAPQEHERILDMCCAPGGKTSYMAQLMKNTGVILANDANAERLKSVVGNLHRLGVTNTIISHYDGRQFPKVVGGFD RVLLDAPCSGTGVISKDPAVKTNKDEKDILRCAHLQKELLLSAIDSVNATSKTGGYLVYCTCSITVEENEWVVDYALKKRNVRLVPTGLDF GQEGFTRFRERRFHPSLRSTRRFYPHTHNMDGFFIAKFKKFSNSIPQSQTGNSETATPTNVDLPQVIPKSENSSQPAKKAKGAAKTKQQLQ KQQHPKKASFQKLNGISKGADSELSTVPSVTKTQASSSFQDSSQPAGKAEGIREPKVTGKLKQRSPKLQSSKKVAFLRQNAPPKGTDTQTP AVLSPSKTQATLKPKDHHQPLGRAKGVEKQQLPEQPFEKAAFQKQNDTPKGPQPPTVSPIRSSRPPPAKRKKSQSRGNSQLLLS
1013	例示性胞苷去胺酶之胺基酸序列；參見表58，BC56	MGRRSRGRRLQQQQRPEDAEDGAEGGGKRGEAGWEGGYPEIVKENKLFEHYYQELKIVPEGEWGQFMDALREPLPATLRITGYKSHAKEIL HCLKNKYFKELEDLEVDGQKVEVPQPLSWYPEELAWHTNLSRKILRKSPHLEKFHQFLVSETESGNISRQEAVSMIPPLLLNVRPHHKILD MCAAPGSKTTQLIEMLHADMNVPFPEGFVIANDVDNKRCYLLVHQAKRLSSPCIMVVNHDASSIPRLQIDVDGRKEILFYDRILCDVPCSG DGTMRKNIDVWKKWTTLNSLQLHGLQLRIATRGAEQLAEGGRMVYSTCSLNPIEDEAVIASLLEKSEGALELADVSNELPGLKWMPGITQW KVMTKDGQWFTDWDAVPHSRHTQIRPTMFPPKDPEKLQAMHLERCLRILPHHQNTGGFFVAVLVKKSSMPWNKRQPKLQGKSAETRESTQL SPADLTEGKPTDPSKLESPSFTGTGDTEIAHATEDLENNGSKKDGVCGPPPSKKMKLFGFKEDPFVFIPEDDPLFPPIEKFYALDPSFPRM NLLTRTTEGKKRQLYMVSKELRNVLLNNSEKMKVINTGIKVWCRNNSGEEFDCAFRLAQEGIYTLYPFINSRIITVSMEDVKILLTQENPF FRKLSSETYSQAKDLAKGSIVLKYEPDSANPDALQCPIVLCGWRGKASIRTFVPKNERLHYLRMMGLEVLGEKKKEGVILTNESAASTGQP DNDVTEGQRAGEPNSPDAEEANSPDVTAGCDPAGVHPPR
1014	例示性APOBEC家族去胺酶之胺基酸序列	MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWFHDKVLKVLSPR EEFKITWYMSWSPCFECAEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRL LTNFRYQDSKLQEILRPCYIPVPSSSSSTLSNICLTKGLPETRFCVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQ APLKGCLLSEKGKQHAEILFLDKIRSMELSQVTITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILV DVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
1015	例示性APOBEC家族去胺酶之胺基酸序列	MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLRYAIDRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNIHAEICFLYWFHDKVLKVLSPR EEFKITWYMSWSPCFECAEQVLRFLATHHNLSLDIFSSRLYNIRDPENQQNLCRLVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKKL LTNFRYQDSKLQEILRPCYIPVPSSSSSTLSNICLTKGLPETRFCVERRRVHLLSEEEFYSQFYNQRVKHLCYYHGVKPYLCYQLEQFNGQ APLKGCLLSEKGKQHAEILFLDKIRSMELSQVIITCYLTWSPCPNCAWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSGILV DVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLHRIKESWGLQDLVNDFGNLQLGPPMS
1016	例示性APOBEC家族去胺酶之胺基酸序列	MVEPMDPRTFVSNFNNRPILSGLNTVWLCCEVKTKDPSGPPLDAKIFQGKVYSKAKYHPEMRFLRWFHKWRQLHHDQEYKVTWYVSWSPCT RCANSVATFLAKDPKVTLTIFVARLYYFWKPDYQQALRILCQKRGGPHATMKIMNYNEFQDCWNKFVDGRGKPFKPRNNLPKHYTLLQATL GELLRHLMDPGTFTSNFNNKPWVSGQHETYLCYKVERLHNDTWVPLNQHRGFLRNQAPNIHGFPKGRHAELCFLDLIPFWKLDGQQYRVTC FTSWSPCFSCAQEMAKFISNNEHVSLCIFAARIYDDQGRYQEGLRALHRDGAKIAMMNYSEFEYCWDTFVDRQGRPFQPWDGLDEHSQALS GRLRAI

1017	例示性APOBEC家族去胺酶之胺基酸序列	MKPHFRNPVERMYQDTFSDNFYNRPILSHRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSKLKYHPEMRFFHWFSKWRKLHRDQEYEVTWY ISWSPCTKCTRDVATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTSNFNNELWVRGRHETYLCYEVERLHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDL HQDYRVTCFTSWSPCFSCAQEMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLAKAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGL EEHSQALSGRLRAILQNQGN
1018	例示性APOBEC家族去胺酶之胺基酸序列	MNPQIRNMVEQMEPDIFVYYFNNRPILSGRNTVWLCYEVKTKDPSGPPLDANIFQGKLYPEAKDHPEMKFLHWFRKWRQLHRDQEYEVTWY VSWSPCTRCANSVATFLAEDPKVTLTIFVARLYYFWKPDYQQALRILCQERGGPHATMKIMNYNEFQHCWNEFVDGQGKPFKPRKNLPKHY TLLHATLGELLRHVMDPGTFTSNFNNKPWVSGQRETYLCYKVERSHNDTWVLLNQHRGFLRNQAPDRHGFPKGRHAELCFLDLIPFWKLDD QQYRVTCFTSWSPCFSCAQKMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLHRDGAKIAVMNYSEFEYCWDTFVDRQGRPFQPWDGLD EHSQALSGRLRAI
1019	例示性APOBEC家族去胺酶之胺基酸序列	MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSELKYHPEMRFFHWFSKWRKLHRDQEYEVTWY ISWSPCTKCTRDMATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYY ILLHIMLGEILRHSMDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDL DQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGL DEHSQDLSGRLRAILQNQEN
1020	例示性APOBEC家族去胺酶之胺基酸序列	MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPRLDAKIFRGQVYSQPEHHAEMCFLSWFCGNQLPAYKCFQITWFV SWTPCPDCVAKLAEFLAEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVKIMDDEEFAYCWENFVYSEGQPFMPWYKFDDNYAFLHR TLKEILRNPMEAMYPHIFYFHFKNLRKAYGRNESWLCFTMEVVKHHSPVSWKRGVFRNQVDPETHCHAERCFLSWFCDDILSPNTNYEVTW YTSWSPCPECAGEVAEFLARHSNVNLTIFTARLYYFWDTDYQEGLRSLSQEGASVEIMGYKDFKYCWENFVYNDDEPFKPWKGLKYNFLFL DSKLQEILE
1021	例示性APOBEC家族去胺酶之胺基酸序列	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGQVYFKPQYHAEMCFLSWFCGNQLPAYKCFQITWF VSWTPCPDCVAKLAEFLSEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVTIMDYEEFAYCWENFVYNEGQQFMPWYKFDENYAFLH RTLKEILRYLMDPDTFTFNFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIY RVTWFISWSPCFSWGCAGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGCPFQPWDGLEE HSQALSGRLRAILQNQGN
1022	例示性APOBEC家族去胺酶之胺基酸序列	MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGPVLPKRQSNHRQEVYFRFENHAEMCFLSWFCGNR LPANRRFQITWFVSWNPCLPCVVKVTKFLAEHPNVTLTISAARLYYYRDRDWRWVLLRLHKAGARVKIMDYEDFAYCWENFVCNEGQPFMP WYKFDDNYASLHRTLKEILRNPMEAMYPHIFYFHFKNLLKACGRNESWLCFTMEVTKHHSAVFRKRGVFRNQVDPETHCHAERCFLSWFCD DILSPNTNYEVTWYTSWSPCPECAGEVAEFLARHSNVNLTIFTARLCYFWDTDYQEGLCSLSQEGASVKIMGYKDFVSCWKNFVYSDDEPF KPWKGLQTNFRLLKRRLREILQ
1023	例示性APOBEC家族去胺酶之胺基酸序列	MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERYFCPNTRCSITWFLSWS PCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVL ELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLK

1076	靶向CIITA基因之G018021導引RNA	mU*mC*mC*UACCUGUCAGAGCCCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1077	靶向CIITA基因之G018022導引RNA	mG*mA*mG*CCCCAAGGUAAAAAGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1078	靶向CIITA基因之G018023導引RNA	mA*mG*mC*CCCAAGGUAAAAAGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1079	靶向CIITA基因之G018024導引RNA	mU*mU*mU*CCCGGCCUUUUUACCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1080	靶向CIITA基因之G018025導引RNA	mC*mU*mU*UCCCGGCCUUUUUACCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1081	靶向CIITA基因之G018026導引RNA	mA*mC*mA*CUGUGAGCUGCCUGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1082	靶向CIITA基因之G018027導引RNA	mC*mA*mC*ACUGUGAGCUGCCUGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1083	靶向CIITA基因之G018028導引RNA	mG*mU*mG*GCACACUGUGAGCUGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1084	靶向CIITA基因之G018029導引RNA	mG*mA*mG*AUUGAGCUCUACUCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1085	靶向CIITA基因之G018030導引RNA	mA*mG*mA*UUGAGCUCUACUCAGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1086	靶向CIITA基因之G018031導引RNA	mC*mA*mG*GUGGGCCCUCCUCCCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1087	靶向CIITA基因之G018032導引RNA	mC*mG*mG*AAGAGACCAGAGGGAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1088	靶向CIITA基因之G018033導引RNA	mU*mA*mC*CGGAAGAGACCAGAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1089	靶向CIITA基因之G018034導引RNA	mA*mG*mG*GAGGCUUAUGCCAAUAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1090	靶向CIITA基因之G018035導引RNA	mG*mG*mC*UUAUGCCAAUAUCGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1091	靶向CIITA基因之G018036導引RNA	mU*mG*mA*CUGCGCUUUUCCUUGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1092	靶向CIITA基因之G018037導引RNA	mG*mA*mC*UGCGCUUUUCCUUGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1093	靶向CIITA基因之G018038導引RNA	mG*mC*mU*UUUCCUUGUCUGGGCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1094	靶向CIITA基因之G018039導引RNA	mC*mC*mA*GUUCCGCUGCCCAGACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1095	靶向CIITA基因之G018040導引RNA	mG*mA*mC*CUGAAGCACUGGAAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1096	靶向CIITA基因之G018041導引RNA	mG*mC*mA*CUGGAAGCCAGGUGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1097	靶向CIITA基因之G018042導引RNA	mC*mA*mC*UGGAAGCCAGGUGUGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1098	靶向CIITA基因之G018043導引RNA	mG*mG*mA*AGCCAGGUGUGCAGGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1099	靶向CIITA基因之G018044導引RNA	mA*mG*mC*CAGGUGUGCAGGGCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1100	靶向CIITA基因之G018045導引RNA	mG*mC*mC*CACCUGCCCUGCACACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1101	靶向CIITA基因之G018046導引RNA	mG*mG*mG*CUCAGCUGUGAGGAAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1102	靶向CIITA基因之G018047導引RNA	mG*mG*mG*GCUCAGCUGUGAGGAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1103	靶向CIITA基因之G018048導引RNA	mG*mA*mC*CAGAUUCCCAGUAUGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1104	靶向CIITA基因之G018049導引RNA	mC*mC*mA*GAUUCCCAGUAUGUUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1105	靶向CIITA基因之G018050導引RNA	mC*mA*mG*AUUCCCAGUAUGUUAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1106	靶向CIITA基因之G018051導引RNA	mU*mC*mC*CAGUAUGUUAGGGGGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1107	靶向CIITA基因之G018052導引RNA	mU*mC*mC*AAGCCCCCUAACAUACUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1108	靶向CIITA基因之G018053導引RNA	mC*mU*mC*CAAGCCCCCUAACAUACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1109	靶向CIITA基因之G018054導引RNA	mA*mA*mA*GGCACUGCAAGAGACAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1110	靶向CIITA基因之G018055導引RNA	mU*mC*mC*AGUAUAUUCAUCUACCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1111	靶向CIITA基因之G018056導引RNA	mU*mU*mC*AUCUACCAUGGUGAGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1112	靶向CIITA基因之G018057導引RNA	mU*mC*mA*UCUACCAUGGUGAGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1113	靶向CIITA基因之G018058導引RNA	mC*mA*mU*CUACCAUGGUGAGUGCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1114	靶向CIITA基因之G018059導引RNA	mA*mC*mC*AUGGUGAGUGCGGGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1115	靶向CIITA基因之G018060導引RNA	mG*mC*mC*AGGCCCCGCACUCACCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1116	靶向CIITA基因之G018061導引RNA	mC*mC*mA*CUCUCCACCCCCAAUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1117	靶向CIITA基因之G018062導引RNA	mC*mU*mC*CACCCCCAAUGUAGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1118	靶向CIITA基因之G018063導引RNA	mC*mA*mC*CUCACCUACAUUGGGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1119	靶向CIITA基因之G018064導引RNA	mG*mG*mG*CACCUCACCUACAUUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1120	靶向CIITA基因之G018065導引RNA	mU*mG*mG*GGCACCUCACCUACAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1121	靶向CIITA基因之G018066導引RNA	mC*mU*mG*GGGCACCUCACCUACAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1122	靶向CIITA基因之G018067導引RNA	mA*mC*mC*UCCCGAGCAAACAUGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1123	靶向CIITA基因之G018068導引RNA	mC*mC*mG*AGCAAACAUGACAGGUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1124	靶向CIITA基因之G018069導引RNA	mG*mU*mA*CCUCUCACAGGCCCUAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1125	靶向CIITA基因之G018070導引RNA	mA*mG*mU*ACCUCUCACAGGCCCUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1126	靶向CIITA基因之G018071導引RNA	mG*mA*mC*GUCUUGUGCUCUGGAGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1127	靶向CIITA基因之G018072導引RNA	mA*mA*mC*AAGCUUCCAAAAUGGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1128	靶向CIITA基因之G018073導引RNA	mG*mA*mG*AUCCCGCAUCACUCACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1129	靶向CIITA基因之G018074導引RNA	mG*mC*mC*CCUGGCCUUUGCAGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1130	靶向CIITA基因之G018079導引RNA	mU*mC*mA*GCUGUGUCACCCGUUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1131	靶向CIITA基因之G018080導引RNA	mG*mC*mU*GUGUCACCCGUUUCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1132	靶向CIITA基因之G018083導引RNA	mC*mA*mC*CCGUUUCAGGUGGGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1133	靶向CIITA基因之G018086導引RNA	mG*mU*mC*UGAGGCCCUCCCUCCACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1134	靶向CIITA基因之G018087導引RNA	mU*mC*mU*GAGGCCCUCCCUCCACAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1135	靶向CIITA基因之G018088導引RNA	mC*mA*mA*GGCAGCCCUGUGGAGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1136	靶向CIITA基因之G018089導引RNA	mG*mC*mU*CAAGGCAGCCCUGUGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1137	靶向CIITA基因之G018090導引RNA	mC*mG*mC*UCAAGGCAGCCCUGUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1138	靶向CIITA基因之G018092導引RNA	mU*mA*mA*CAUUGCCUGUUCUCUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1139	靶向CIITA基因之G018093導引RNA	mC*mU*mU*CUCGUCCUGGAGAGAACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1140	靶向CIITA基因之G018094導引RNA	mU*mU*mC*CGAGGAACUUCUCGUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1141	靶向CIITA基因之G018095導引RNA	mA*mC*mC*CUUGCUCUUUGCCUCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1142	靶向CIITA基因之G018096導引RNA	mU*mU*mG*CUCUUUGCCUCCUAGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1143	靶向CIITA基因之G018097導引RNA	mU*mG*mC*UCUUUGCCUCCUAGGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1144	靶向CIITA基因之G018098導引RNA	mC*mC*mU*GAGACAGGGCCCAGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1145	靶向CIITA基因之G018099導引RNA	mA*mU*mC*UGAUUCCACCUGCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1146	靶向CIITA基因之G018101導引RNA	mA*mC*mU*CAGCGCAUCCAGGCUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1147	靶向CIITA基因之G018102導引RNA	mA*mA*mA*CCCUCAAGUGAGUGAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1148	靶向CIITA基因之G018103導引RNA	mA*mA*mC*CCUCAAGUGAGUGAGCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1149	靶向CIITA基因之G018104導引RNA	mG*mG*mC*CCAGCUCACUCACUUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1150	靶向CIITA基因之G018105導引RNA	mA*mG*mG*CCCAGCUCACUCACUUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1151	靶向CIITA基因之G018106導引RNA	mC*mA*mG*ACUGCGGGGACACAGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1152	靶向CIITA基因之G018107導引RNA	mC*mU*mG*CAUCCCUGCUCAGGCUAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1153	靶向CIITA基因之G018108導引RNA	mC*mC*mU*GCUCAGGCUAAGGUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1154	靶向CIITA基因之G018109導引RNA	mC*mU*mG*CUCAGGCUAAGGUGAGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1155	靶向CIITA基因之G018110導引RNA	mC*mA*mG*CACCUGACCGGUAUCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1156	靶向CIITA基因之G018111導引RNA	mG*mU*mA*CAAGCUGUCGGAAACAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1157	靶向CIITA基因之G018112導引RNA	mG*mG*mA*GACGCUGGCGUAAGUCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1158	靶向CIITA基因之G018113導引RNA	mG*mG*mC*GUAAGUCCAGGCAACCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1159	靶向CIITA基因之G018114導引RNA	mC*mU*mC*CACCCACCAGGGUUGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

1160	靶向CIITA基因之G018115導引RNA	mU*mG*mA*GUCCCAUCCCCCCUUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1161	靶向CIITA基因之G018116導引RNA	mC*mC*mA*CAUCCUGCAAGGGGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1162	靶向CIITA基因之G018119導引RNA	mG*mG*mG*CGUCCACAUCCUGCAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1163	靶向CIITA基因之G018121導引RNA	mG*mU*mG*GGCGUCCACAUCCUGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU

(在上表中或本文中所描述之序列中之每一者中，經修飾序列可未經修飾或以替代性方式經修飾)

實例

【0487】 提供以下實例以說明某些所揭示實施例且不應解釋為以任何方式限制本發明之範疇。

【0488】 如以下實例中所使用，術語「編輯器」係指包含能夠使DNA分子內之鹼基去胺之多肽的試劑且其為鹼基編輯器。編輯器可能夠使DNA中之胞苷(C)去胺。編輯器可包括藉由視情況選用之連接子融合至胞苷去胺酶(例如，APOBEC3A去胺酶(A3A))之RNA導引之切口酶(例如，Cas9切口酶)。在一些情況下，編輯器包括UGI。在一些實施例中，編輯器缺少UGI。

【0489】 用於以下實例中之例示性編輯器為BC22n (SEQ ID NO:3)，其由藉由XTEN連接子融合至化膿性鏈球菌-D10A SpyCas9切口酶之智人APOBEC3A及編碼BC22n之mRNA組成。亦使用編碼BC22n (SEQ ID NO: 1)之mRNA。

實例1.一般方法

1.1.製備脂質奈米粒子

【0490】 一般而言，以各種莫耳比將脂質組分溶解於100%乙醇中。將RNA負荷(例如，Cas9 mRNA及sgRNA)溶解於25 mM檸檬酸鹽緩衝液、100 mM NaCl (pH 5.0)中，產生大約0.45 mg/mL之RNA負荷濃度。

【0491】 除非另外規定，否則脂質核酸組裝體含有分別為50:38:9:3莫耳比之可離子化脂質A (十八碳-9,12-二烯酸(9Z,12Z)-3-((4,4-雙(辛氧基)丁醯基)氧基)-2-((((3-(二乙胺基)丙氧基)羰基)氧基)甲基)丙酯，亦稱為(9Z,12Z)-十八碳-9,12-二烯酸3-((4,4-雙(辛氧基)丁醯基)氧基)-2-((((3-(二

乙胺基)丙氧基)羰基)氧基)甲基)丙酯)、膽固醇、DSPC及PEG2k-DMG。除非另外規定，否則脂質核酸組裝體用約6之脂質胺與RNA磷酸酯(N:P)莫耳比及按重量計1:1之gRNA與mRNA之比調配。

【0492】 使用交叉流技術，利用含脂質之乙醇與兩個體積之RNA溶液及一個體積之水的衝擊射流混合來製備LNP。經由混合交叉使含脂質之乙醇與兩個體積之RNA溶液混合。經由線內T形管將第四水流與十字管之出口流混合(參見WO2016010840圖2)。將LNP在室溫下保持1小時且進一步用水稀釋(大約1:1 v/v)。使用切向流過濾在平板濾筒(Sartorius, 100kD MWCO)上濃縮LNP，且使用PD-10去鹽管柱(GE)將其緩衝液交換至50 mM Tris、45 mM NaCl、5% (w/v)蔗糖，pH 7.5 (TSS)中。替代地，視情況使用100 kDa Amicon旋轉過濾器濃縮LNP，且使用PD-10去鹽管柱(GE)將其緩衝液交換至TSS中。所得混合物接著使用0.2 μm無菌過濾器過濾。在進一步使用之前，將最終LNP儲存於4℃或-80℃下。

1.2.mRNA之活體外轉錄(「IVT」)

【0493】 含有N1-甲基假-U之經封端及聚腺苷酸化mRNA係藉由使用經線性化質體DNA模板及T7 RNA聚合酶之活體外轉錄產生。藉由在以下條件下與XbaI一起在37℃下培育2小時來線性化含有T7啟動子、轉錄序列及聚腺苷酸化區之質體DNA：200 ng/μL質體、2 U/μL XbaI (NEB)及1x反應緩衝液。藉由在65℃下加熱反應物20分鐘來使XbaI失活。由酶及緩衝液鹽純化經線性化質體。用以產生經修飾mRNA之IVT反應係藉由在以下條件下在37℃下培育1.5-4小時來進行：50 ng/μL經線性化質體；各2-5 mM之GTP、ATP、CTP及N1-甲基假-UTP (Trilink)；10-25 mM ARCA (Trilink)；5 U/μL T7 RNA聚合酶(NEB)；1 U/μL鼠類核糖核酸酶

抑制劑(NEB)；0.004 U/μL無機大腸桿菌焦磷酸酶(NEB)；及1x反應緩衝液。將TURBO去氧核糖核酸酶(ThermoFisher)添加至0.01 U/μL之最終濃度，且將反應物再培育30分鐘以移除DNA模板。根據製造商之方案，使用MegaClear Transcription Clean-up套組(ThermoFisher)或RNeasy Maxi套組(Qiagen)來純化mRNA。替代地，經由沈澱方案(在一些情況下，其繼之以基於HPLC之純化)來純化mRNA。簡言之，在去氧核糖核酸酶消化之後，使用LiCl沈澱、乙酸銨沈澱及乙酸鈉沈澱來純化mRNA。對於經HPLC純化之mRNA，在LiCl沈澱及復原之後，藉由RP-IP HPLC純化mRNA (參見例如Kariko等人，Nucleic Acids Research, 2011, 第39卷, 第21期e142)。合併選擇用於彙集之溶離份且藉由如上文所描述之乙酸鈉/乙醇沈澱來去鹽。在另一替代方法中，mRNA用LiCl沈澱法純化，隨後藉由切向流過濾進一步純化。藉由量測260 nm處之吸光度(Nanodrop)來測定RNA濃度，且藉由毛細管電泳用Bioanlayzer (Agilent)來分析轉錄本。

【0494】 自編碼根據SEQ ID NOs: 360 (參見**表5C**中之序列)之開讀框的質體DNA產生Nme2Cas9 mRNA。自編碼根據SEQ ID NOs: 8、11或23 (參見**表5C**中之序列)之開讀框的質體DNA產生化膿性鏈球菌(「Spy」)Cas9 mRNA。自編碼根據SEQ ID NOs: 2或5之開讀框之質體DNA產生BC22n mRNA。自編碼根據SEQ ID NO: 20之開讀框之質體DNA產生BC22 mRNA。自編碼根據SEQ ID No: 29之開讀框之質體DNA產生具有2x UGI mRNA之BC22。自編碼根據SEQ ID NOs: 26或35之開讀框之質體DNA產生UGI mRNA。自編碼根據SEQ ID NO: 14或17之開讀框之質體DNA產生BE3 mRNA。自編碼根據SEQ ID NO: 32之開讀框之質體DNA產生BE4Max mRNA。當本段中引用的序列在下文中針對RNA提及時，

應理解，T應替換為U (其為如上文所描述之N1-甲基假尿苷)。用於實例中之信使RNA包括5'端帽及3'聚腺苷酸化區，例如，高達100 nts。

1.3.用於靶上編輯效率之下一代定序(「NGS」)及分析

【0495】 根據製造商之方案，使用QuickExtract™ DNA提取溶液(Lucigen，目錄號QE09050)提取基因體DNA。為了定量地測定基因體中之目標位置處之編輯效率，使用深度定序來鑑別藉由基因編輯引入之插入及缺失的存在。圍繞所關注基因(例如，TRAC)內之目標位點設計PCR引子，且擴增所關注基因體區域。按本領域中之標準進行引子序列設計。

【0496】 根據製造商之方案(Illumina)執行額外PCR以添加化學物質以進行定序。在Illumina MiSeq儀器上對擴增子定序。在消除具有低品質評分之讀數之後，將讀數與人類參考基因體(例如，hg38)比對。將與所關注目標區重疊之讀數與局部基因體序列重新比對以改良該比對。接著，計算野生型讀數之數目相對於含有C形成T突變、C形成A/G突變或插入/缺失之讀數之數目。在以所預測之Cas9裂解位點為中心的20 bp區中對插入及缺失進行評分。插入/缺失百分比定義為在20 bp評分區內插入或缺失一或多個鹼基之定序讀數之總數目除以定序讀數(包括野生型)之總數目。在包括20 bp sgRNA目標序列之上游10 bp及下游10 bp之40 bp區中對C形成T突變或C形成A/G突變進行評分。C形成T編輯百分比定義為在40 bp區內具有一或多個C形成T突變之定序讀數之總數目除以定序讀數(包括野生型)之總數目。類似地計算C形成A/G突變之百分比。

實例1A - C形成T轉化

【0497】 評估APOBEC3A去胺酶-Cas9D10A編輯器之C形成T轉化活性之效率及C形成T轉化視窗之跨度。將C形成T轉化活性及視窗結果與

編碼BE3之構築體BC27進行比較(Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016;533(7603):420-424)。構築體各自在單一實驗中針對5種sgRNA一式三份地評估。

【0498】 使用pUC19主鏈(GenBank®登錄號U47119)之質體A表現來自U6啟動子之化膿性鏈球菌單導引RNA (sgRNA)。稱為pCI之質體B表現來自CMV啟動子之鹼基編輯器構築體，其由藉由XTEN連接子融合至化膿性鏈球菌-D10A-Cas9之候選去胺酶構成，該XTEN連接子隨後融合至UGI之一個複本及SV40 NLS之一個複本。使用Mirus *Trans*IT-X2®，用質體A及質體B各100 ng對在96孔板中在補充有10%胎牛血清(FBS)之Dulbecco改良Eagle培養基(DMEM)中生長之U-2OS細胞進行轉染。在初始轉染之後24小時，細胞經洗滌且再懸浮於新鮮培養基中。在額外48小時之後，移除培養基且用QuickExtract™ DNA提取溶液(Lucigen，目錄號QE09050)溶解細胞。

【0499】 與編碼具有多於一種導引物(sg000296：P值0.0303；sg001373，P值0.0263)之大鼠APOBEC1去胺酶(Uniprot ID P38483)之BC27相比，在融合物中編碼智人*APOBEC3A*去胺酶(Uniprot ID P31941)之構築體BC22具有顯著更大C形成T轉化活性。在所有導引物中，BC22之平均活性與BC27之平均活性相當(表6，圖1A至圖1E)。

【0500】 在所有5種經測試之sgRNA中，BC22比BC27顯著更可能將所有目標胞嘧啶轉化成胸苷(表7，圖2A至圖2E，P值<0.005)。目標胞嘧啶為原型間隔區目標序列之位置1至10內(帶下劃線)或目標序列之第一位置5'中之任何胞嘧啶。sg000296之導引序列為

CCUUCCGAAAGAGGCCCCCC (SEQ ID NO: 156)，且基因座具有4個目標胞嘧啶。sg001373之目標導引序列為**UCCCUGGCUGAGGAUCCCCA** (SEQ ID NO: 157)，且基因座具有5個目標胞嘧啶，包括目標序列之第一位置5'。sg001400之目標導引序列為**ACUCACGAUGAAAUCCUGGA** (SEQ ID NO: 158)，且基因座具有4個目標胞嘧啶，包括目標序列之第一位置5'。sg003018之目標導引序列為**GAGCCCCCCCACUGUGGUGAC** (SEQ ID NO: 160)，且基因座具有6個目標胞嘧啶。sg005883之導引序列為**CCCCCCGCCGUGUUUGUGGG** (SEQ ID NO: 159)，且基因座具有8個目標胞嘧啶。

【0501】 與BC27相比，BC22轉化之目標胞嘧啶之比率及位置範圍顯著更大(圖3A至圖3E)。與BC27相比，轉化之目標胞嘧啶之比率及位置範圍顯著更大(圖3A至圖3E)。此較寬C形成T轉化視窗甚至適用於BC22在諸如sg001400、sg003018上具有較小總C形成T轉化活性之導引(表7，圖3C至圖3E)。

【0502】 表6.含有至少1個胞嘧啶至胸苷轉化之總讀數之百分比。(n=3)

	sg000296		**sg0001373**		**sg001400**		**sg003018**		**sg005883**	
構築體	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**
1XNLS Cas9	0.3	0.2	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.1
3XNLS Cas9	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0
BC22	16.0	0.9	20.3	2.6	24.2	1.1	12.6	1.7	46.0	7.7
BC27	14.2	0.3	13.0	2.6	30.6	1.4	19.6	1.9	40.8	5.2
GFP	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.1

【0503】 表7.所有目標胞嘧啶已轉化為胸苷之C形成T編輯讀數的百分比(sg000296、sg001373、sg001400、sg003018)。對於sg005883，8種目標胞嘧啶中之至少6種已轉化為胸苷之編輯讀數的百分比。(n/d =未進行)

	sg000296		sg001373		sg001400		sg003018		sg005883	
構築體	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
1XNLS Cas9	0	0	n/d	n/d	0	0	0	0	9.4	9.5
3XNLS Cas9	0	0	0	0	0	0	0	0	7.0	3.9
BC22	45.1	2.1	34.6	5.5	11.1	0.9	80.2	1.4	61.8	10.1
BC27	0.6	0	3.3	0.3	0.1	0.2	43.2	6.7	15.2	4.8
GFP	0	0	n/d	n/d	0	0	0	0	0	0

實例2 - 鹼基切除修復基因對編輯之影響

【0504】 在各種細胞株中研究相對於非所要鹼基切除修復活性，額外反式UGI基因表現對C形成T轉化活性之影響。

【0505】 使用Mirus *Trans*IT-X2®，用100 ng BC22或BC27、100 ng另一CMV驅動過度表現質體(pcDNA3.1)或對照質體(pMAX)及6.25 pmol單導引G000297對在96孔板中在補充有10% FBS之Dulbecco改良Eagle培養基(DMEM)中生長之U-2OS及HuH-7細胞進行共轉染。與BC22及BC27串聯測試之ORF為綠色螢光蛋白(pMAX-GFP，陰性對照)、尿嘧啶DNA醣苷酶(pCDNA3.1-UNG)、單股-選擇性單官能尿嘧啶-DNA醣苷酶1 (pcDNA3.1-SMUG1)及尿嘧啶醣苷酶抑制劑(pCDNA3.1-UGI)。UNG及SMUG1為自DNA移除尿嘧啶之鹼基切除修復蛋白。UGI為結合及抑制UDG之小蛋白。據報導，當UGI融合至構築體時，相對於C形成A/G突變及插入/缺失之其他結果，其增加C形成T突變之比率(Liu等人，Nature 2016)。為判定添加UNG轉錄本阻斷是否進一步富集僅C形成T編輯，額外轉染條件包括BC22或BC27、pcDNA3.1-UGI、G000297及靶向UNG之siRNA池(Dharmacon, # M-011795-00)。在轉染之後三天，移除培養基且用QuickExtract™ DNA提取溶液(Lucigen, 目錄號QE09050)溶解細胞。

【0506】 在HuH-7細胞中，當與陰性對照GFP之過度表現相比時，用BC22或BC27過度表現鹼基切除修復蛋白UNG或SMUG1導致C形成A/G突變及插入/缺失相對於僅C形成T突變之比率顯著增加1.3至1.7倍(表11，

圖5B)。相反，用UGI過度表現阻斷UNG導致含有C形成A/G突變及插入/缺失之讀數減少4.5至10.8倍，其中僅C形成T突變顯著增加1.56至2.2倍(表11，圖5B)。額外UGI過度表現導致無論使用BC22還是BC27，平均94%之總編輯為僅C形成T編輯(圖4B)。U-2OS可見類似趨勢(表8，圖4A、圖5A)，其中一個突出的差異為SMUG1及UNG過度表現未導致編輯結果之相對比率之顯著變化。在兩個細胞株中，將靶向UNG基因之siRNA添加至UGI過度表現質體不增加僅C形成T編輯相對於單獨UGI過度表現之比率(表8)。最後，在兩個細胞株中，BC22總C形成T轉化活性高於BC27 (圖4A、圖4B)，表明BC22之先天性C形成T轉化活性高於BC27。

【0507】 表8 -編輯作為U-2OS細胞中總讀數之% (n=3)

U-2OS		C形成**T %**		C形成**A/G %**		**插入/缺失%**	
構築體	**過度表現/siRNA**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**
BC27	GFP+	1.57	0.99	0.86	0.14	1.18	0.16
	SMUG1+	2.13	0.45	2.4	0.39	2.59	0.09
	UDG+	0.3	0.26	0.36	0.22	1.05	0.04
	UGI+	4.77	0.75	0.29	0.08	0.8	0.34
	siUDG, UGI+	4.9	0.75	0.22	0.05	0.76	0.03
BC22	GFP+	10.87	1.58	1.78	0.61	1.64	0.8
	SMUG1+	6.17	0.4	6.21	1.42	4.85	0.9
	UDG+	1.57	0.06	0.4	0.13	1.21	0.32
	UGI+	12.7	1.93	0.24	0.13	0.86	0.05
	siUDG, UGI+	16.97	0.93	0.36	0.25	0.9	0.04

【0508】 表9. U-2OS細胞中編輯讀數之%相對於GFP的倍數變化

構築體	**過度表現/siRNA**	C形成**T**	**P值**	C形成**A/G**或插入/缺失	**P值**
BC27	GFP+	不適用			
	SMUG1+	-1.37	0.1953	1.20	0.1953
	UDG+	-1.75	0.0864	1.31	0.0864
	UGI+	1.92	0.0091	-3.09	0.0091
	siUDG, UGI+	1.97	0.0042	-3.48	0.0042
BC22	GFP+	不適用			
	SMUG1+	-2.08	0.0004	2.67	0.0004
	UDG+	-1.52	0.0031	2.10	0.0031
	UGI+	1.21	0.0048	-2.97	0.0048
	siUDG, UGI+	1.22	0.0041	-3.46	0.0041

【0509】 表10. HuH-7細胞中不同DNA修復途徑條件下之編輯百分比

HuH-7		C形成T %		C形成A/G %		插入/缺失%	
構築體	過度表現/ siRNA	平均	SD	平均	SD	平均	SD
BC27	GFP+	18.70	0.70	13.24	0.95	10.55	1.11
	SMUG1+	9.57	1.91	14.78	1.64	13.23	1.24
	UDG+	4.57	0.46	7.45	0.23	7.74	0.49
	UGI+	42.40	2.10	0.82	0.34	1.88	0.47
	siUDG, UGI+	41.37	2.73	0.94	0.37	1.32	0.30
BC22	GFP+	41.77	2.30	15.02	0.73	15.00	1.06
	SMUG1+	19.20	1.61	21.89	2.17	25.98	1.86
	UDG+	12.97	1.89	8.27	0.82	12.11	1.14
	UGI+	64.53	1.32	2.50	0.30	4.05	1.45
	siUDG, UGI+	65.33	2.28	2.05	1.45	4.24	1.53

【0510】 表11. Huh-7細胞中編輯讀數之%相對於GFP的倍數變化

構築體	過度表現/ siRNA	C形成T	P值	C形成A/G或插入/缺失	P值
BC27	GFP+	不適用			
	SMUG1+	-1.73	0.0014	1.33	0.001
	UDG+	-1.86	<0.0001	1.37	<0.0001
	UGI+	2.13	<0.0001	-9.30	<0.0001
	siUDG, UGI+	2.15	<0.0001	-10.81	<0.0001
BC22	GFP+	不適用			
	SMUG1+	-2.03	<0.0001	1.71	<0.0001
	UDG+	-1.50	0.0001	1.46	0.0001
	UGI+	1.56	<0.0001	-4.53	<0.0001
	siUDG, UGI+	1.57	<0.0001	-4.76	<0.0001

實例3 - T細胞中之UGI mRNA滴定

【0511】 mRNA編碼融合蛋白BC22n (SEQ ID NO: 3)，其自N端至C端為智人APOBEC3A、XTEN連接子、D10ACas9切口酶、連接子及SV40 NLS。值得注意地，BC22n多肽缺少UGI。使用BC22n及可變量之UGI mRNA編輯T細胞以判定反式UGI含量對編輯型態之影響。使用各自使用不同開讀框(SEQ ID Nos: 26及35)編碼相同蛋白質之2種不同UGI mRNA進行此實驗。

3.1 T細胞製備

【0512】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)及Plasmalyte A (Baxter目錄號2B2522X)之1:1調配物中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞基礎培養基中：X-VIVO 15™無血清造血細胞培養基(Lonza Bioscience)，含有5% (v/v)胎牛血清、50 μM 2-巰基乙醇、10 mM N-乙醯基-L-(+)-半胱胺酸、10 U/mL青黴素-鏈黴素，外加1X細胞介素(200 U/mL重組人類介白素-2、5 μg/mL重組人類介白素-7及5 μg/mL重組人類介白素-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec)活化T細胞。細胞在電穿孔之前在T細胞基礎培養基中擴展72小時。

3.2使用mRNA及sgRNA電穿孔T細胞

【0513】 在無菌水中製備含有編碼BC22n (SEQ ID NO: 2)之mRNA及一種UGI (SEQ ID NO: 26或35)之溶液。將50 μM靶向sgRNA G016017 (SEQ ID NO: 184)之TRAC自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng BC22n mRNA、20 pmols sgRNA及在0.02 ng至26 ng (稀釋因子12.24)範圍內之UGI mRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此mRNA + sgRNA + T細胞混合物一式三

份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL T細胞基礎培養基中靜置10分鐘，隨後轉移至含有額外100 μL具有2X濃度之細胞介素的T細胞基礎培養基之新平底96孔板中。經電穿孔之T細胞隨後額外培養3天且如實例1中所描述收集用於NGS定序。

【0514】 200 ng BC22n mRNA之恆定劑量引起所有條件下之高總編輯(>92%) (表12及表13，插入/缺失、C形成A/G及C形成T之總和)。僅C形成T之編輯比率以對電穿孔中之UGI mRNA濃度之劑量反應方式增加。在最高劑量之UGI mRNA SEQ ID NOs: 25或34下，含有插入/缺失及C形成A/G突變之定序讀數之百分比分別下降至7.4±0.4、7.4±0.6及2.9±0.2、3.6±0.3 (表12及表13)。

【0515】 表12 -編輯作為具有UGI mRNA (SEQ ID NO: 26)之總讀數之百分比

UGI mRNA (ng)	%編輯					
	插入/缺失		C形成A/G		C形成T	
	平均	SD	平均	SD	平均	SD
未處理	0.2	0.1	2.1	0.0	0.2	0.0
0.000	51.2	0.8	27.2	0.4	18.3	0.3
0.025	50.0	1.1	28.2	0.6	18.6	0.6
0.051	48.2	2.0	28.4	0.3	19.0	1.0
0.102	49.8	0.5	28.1	0.3	18.7	0.8
0.203	49.5	1.1	27.9	0.6	18.7	0.3
0.406	47.7	2.0	27.5	0.5	19.4	0.7
0.813	47.8	0.6	28.0	0.5	19.5	0.9
1.625	47.9	0.1	26.6	0.5	21.5	0.3
3.250	41.9	0.6	24.7	0.8	28.9	0.7
6.500	30.0	0.5	21.1	0.6	44.1	1.0
13.000	18.7	2.6	15.5	0.6	58.3	1.0
26.000	7.4	0.4	7.4	0.6	80.1	2.1

【0516】 表13 -編輯作為具有UGI mRNA (SEQ ID NO: 35)之總讀數之百分比

UGI mRNA (ng)	%编辑					
	插入/缺失		C形成A/G		C形成T	
	平均	SD	平均	SD	平均	SD
未處理	0.2	0.1	2.1	0.0	0.2	0.0
0.000	51.2	0.8	27.2	0.4	18.3	0.3
0.025	48.2	1.7	27.0	0.7	19.0	0.5
0.051	48.7	1.3	27.3	0.7	19.4	0.4
0.102	47.5	2.3	27.1	0.2	18.5	0.5
0.203	49.7	1.3	27.4	0.9	18.7	0.7
0.406	49.4	0.7	28.0	0.6	19.4	0.4
0.813	47.1	2.3	26.6	2.2	19.6	0.5
1.625	43.8	2.5	27.3	2.0	25.2	1.0
3.250	33.1	3.0	22.8	0.8	38.4	0.7
6.500	24.0	0.4	18.2	0.3	53.9	0.8
13.000	11.2	1.9	10.5	0.6	73.1	1.6
26.000	2.9	0.2	3.6	0.3	89.1	1.6

實例4：用順式UGI進行活體內編輯

【0517】 用編輯器mRNA及sgRNA G000282以1:1 RNA重量比調配之LNP測試活體內編輯功效及編輯結果。實驗組包括：僅TSS緩衝液；編碼裂解酶-spCas9 (SEQ ID NO: 8)之mRNA；編碼包括融合至D10A SpyCas9之人類APOBEC3A及一個UGI複本(SEQ ID NO: 20)之BC22的mRNA；及編碼包括融合至D10A SpyCas9之大鼠APOBEC1及一個UGI複本(SEQ ID NOs: 14及17)之BE3的mRNA。

【0518】 在此研究中使用6-10週齡範圍內之CD-1雌性小鼠(n=5/組)。經由尾部靜脈注射以1 mg/kg總RNA相對於體重之劑量靜脈內投與LNP。在給藥後至少24小時，定期觀測動物之不良反應。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集血液及肝臟組織用於下游分析。將血液收集至血清分離管中或含有緩衝檸檬酸鈉的管中以得到血漿。收集重量在5與15 mg之間的肝臟穿孔以分離基因體DNA及總RNA。

【0519】 表14及圖7A描述小鼠肝臟中之編輯結果。含有人類APOBEC3A (BC22)之構築體展示與Cas9裂解酶構築體之總編輯水準相當

的總編輯水準，而大鼠APOBEC1 (BE3)構築體展示小於總編輯活性的一半。與大鼠APOBEC1構築體(BE3)相比，含有人類APOBEC3A之構築體亦達成超過兩倍之C形成T鹼基轉化之絕對百分比。

【0520】 表14.肝臟組織中之TTR編輯(Indel =插入或缺失；SD =標準差)

	%編輯					
	C形成T		C形成A/G		插入/缺失	
編輯器	平均	SD	平均	SD	平均	SD
TSS	0.15	0.04	1.95	0.26	0.31	0.11
Cas9 (SEQ ID NO: 8)	0.05	0.02	0.72	0.23	69.59	1.28
BE3 (SEQ ID NO: 14)	16.53	7.49	8.69	3.01	4.31	1.79
BE3 (SEQ ID NO: 17)	10.23	2.72	7.41	1.90	4.71	1.92
BC22 (SEQ ID NO: 20)	45.75	1.17	4.98	0.49	22.0	1.82

實例5 -用反式UGI進行活體內編輯

【0521】 當將UGI反式(作為單獨的mRNA)遞送時，將含有去胺酶之構築體之活體內編輯型態與Cas9進行比較。所使用之構築體編碼包括D10A SpyCas9與去胺酶之融合蛋白。另外，此等編輯條件之間的基因表現差異係經由總轉錄本分析來分析。

5.1藉由NGS測定之活體內編輯

【0522】 在此研究中使用6-10週齡範圍內之四十五隻可商購CD-1雌性小鼠(n=5/組)。給藥前對動物稱重以進行給藥計算。在LNP中分別調配每一RNA物種。以6:3:2 (編輯器mRNA:sgRNA:UGI mRNA)之RNA負荷之w/w比混合含有編輯器mRNA、UGI mRNA及sgRNA之調配物。第3組調配物混合物僅含有編輯器mRNA及sgRNA且此等以2:1 (編輯器mRNA:sgRNA)之w/w比混合。除僅用TSS緩衝液給藥之陰性對照組之

外，所有組均接受sgRNA G000282。根據表15中所列出之劑量，經由尾部靜脈注射靜脈內投與調配物。在給藥後至少24小時，定期觀測動物之不良反應。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集肝臟組織用於下游分析。收集重量在5與15 mg之間的肝臟穿孔以分離基因體DNA及總RNA。用NGS定序分析基因體DNA樣本，如實例1中所描述。

【0523】 表15 -動物組及各別LNP。

樣本	LNP負荷	編輯器mRNA + sgRNA劑量(mg/kg)
TSS	無	0
Cas9, UGI	Cas9 (SEQ ID NO: 11)	0.3 mg/kg
	UGI (SEQ ID NO: 26)	
	G0000282	
BC22n	BC22n (SEQ ID NO: 2)	0.3 mg/kg
	G0000282	
BC22n, UGI	BC22n (SEQ ID NO: 2)	0.3 mg/kg 或 0.1 mg/kg
	UGI (SEQ ID NO: 26)	
	G0000282	

【0524】 編輯資料展示於表16及圖8中。用Cas9 mRNA處理導致58.2%之*Ttr*基因編輯。在不存在UGI mRNA之情況下，用反式BC22n mRNA處理之動物顯示29.26%之C形成T轉化及28%之插入/缺失，而用BC22n及UGI mRNA處理之動物展示較高C形成T編輯純度(56.67%之C形成T轉化及僅5.6%之插入/缺失)。

【0525】 將脂質劑量自0.3降低至0.1 mg/kg導致較低編輯水準(31.39%之C形成T轉化及3.67%之插入/缺失)。

【0526】 表16 -用不同LNP組合處理之小鼠中之Ttr編輯水準(SD = 標準差)。

		mRNA(s)	TSS	Cas9, UGI	BC22n	BC22n, UGI	BC22n, UGI
		劑量(編輯器+sgRNA)	0	0.3 mg/kg	0.3 mg/kg	0.3 mg/kg	0.1 mg/kg
% *Ttr*編輯	C形成T	平均值	0.2%	0.1%	29.3%	56.7%	31.4%
		SD	0.0%	0.1%	5.7%	2.9%	4.9%
	C形成A/G	平均值	0.5%	0.3%	8.1%	1.8%	1.7%
		SD	0.1%	0.1%	1.3%	0.2%	0.1%
	插入/缺失	平均值	0.2%	58.2%	28.0%	5.7%	3.7%
		SD	0.0%	4.0%	5.0%	0.5%	0.1%
		SD	14.1%	6.7%	9.6%	3.5%	9.0%

5.2全總轉錄本定序

【0527】將肝臟穿孔與800 µL TRIzol試劑(Thermo Fisher Scientific，目錄號15596026)在含有陶瓷珠之溶解基質D管(MPBio，目錄號116913100)中混合。將組織在珠粒攪拌器中均勻化45秒且轉移至冰中。在4℃下以最大速度使溶解基質D管短暫離心5分鐘，且將~600 µL TRIzol (無組織碎片)與等體積之純乙醇混合。將混合物裝載於Directzol RNA小量製備管柱(Zymo Research，目錄號R2051)中且遵循製造商之方案提取RNA。經純化之RNA樣本在NanoDrop™ 8000分光光度計(Thermo Fisher Scientific)中定量且使用無核酸酶水稀釋至41.67 ng/µL。自每一實驗組隨機選擇2個樣本用於進一步總轉錄本分析。根據製造商說明書，使用NEBNext® rRNA耗竭套組(New England Biolabs，目錄號E6350L)耗竭500 ng (12 µL)經純化之總RNA之核糖體RNA (rRNA)組分。遵循製造商之方案，使用NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina® (New England Biolabs，目錄號E7765S)將耗竭rRNA之樣本轉化為雙股DNA文庫。在Qubit 4螢光計中定量擴增之文庫，且藉由毛細管電泳獲得每一文庫之平均片段大小。以4 nM之等莫耳濃度彙集文庫，且在NextSeq550定序平台(Illumina)中使用高輸出300-循環套組

(Illumina，目錄號20024908)進行雙端定序。

【0528】 用於差異基因表現分析之資料處理

【0529】 產生呈FASTQ格式之定序讀數且使用bcl2fastq程式(Illumina, v2.20)解多工。若每一索引讀數與樣本索引之間的漢明距離(Hamming, R.W. Bell Syst. Tech. J. 29, 147-160)小於或等於一，則將讀數分配至樣本。用FastQC程式(v0.11.9) (Andrews S. Babraham Inst.)檢驗定序品質。藉由用Bowtie2 (v2.3.5.1) (Langmead, B.及Salzberg, S.L. Nat. Methods 9, 357-359)將所有讀數與人類rRNA序列(GenBank U13369.1)比對來鑑別核糖體RNA讀數。使用Salmon (v0.14.1) (Patro R., 等人Nat. Methods 14, 417-419)與非核糖體RNA讀數進行總轉錄本定量。使用DESeq2 (v1.26.0) (Love, M.I., 等人Genome Biol. 15, 550)對Salmon之輸出進行差異基因表現分析。經Benjamini-Hochberg調節之P值小於0.05之基因或轉錄本經判定為差異表現。

【0530】 RNA-Seq分析顯示，與單獨用BC22n (亦即無UGI mRNA)處理之彼等動物中之223個事件及用反式Cas9及UGI mRNA處理之動物中之127個事件相比，用反式BC22n mRNA及UGI mRNA處理僅產生53個差異表現基因(圖9A至圖9C)。

實例6 -用反式UGI在T細胞中進行編輯

6.1在T細胞中編輯

【0531】 在CIITA基因座處用反式UGI及BC22n或Cas9編輯T細胞以評定編輯類型對MHC II抗原之影響。

【0532】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液

(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)及Plasmalyte A (Baxter目錄號2B2522X)之1:1調配物中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞基礎培養基中：X-VIVO 15™無血清造血細胞培養基(Lonza Bioscience)，含有5% (v/v)胎牛血清、50 μM 2-巰基乙醇、10 mM N-乙醯基-L-(+)-半胱胺酸、10 U/mL青黴素-鏈黴素，外加1X細胞介素(200 U/mL重組人類介白素-2、5 μg/mL重組人類介白素-7及5 μg/mL重組人類介白素-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec)活化T細胞。細胞在電穿孔之前在含有TransAct™之T細胞基礎培養基中擴展72小時。

T細胞之電穿孔

【0533】在無菌水中製備含有編碼Cas9 (SEQ ID NO. 11)、BC22n (SEQ ID NO: 2)或UGI (SEQ ID NO: 26)之mRNA之溶液。將50 μM CIITA sgRNA自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，如表17中所描述，將1 x 10^5個T細胞與200 ng編輯器mRNA、200 ng UGI mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式三份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL T細胞基礎培養基中靜置

10分鐘，隨後轉移至含有額外100 μL補充有2X細胞介素的T細胞基礎培養基之新平底96孔板中。所得板在37℃下培育4天。在96小時之後，將T細胞以1:3稀釋至含1X細胞介素之新鮮T細胞基礎培養基中。經電穿孔之T細胞隨後額外培養3天且如實例1中所描述收集用於流動式細胞量測術分析、NGS定序及總轉錄本學。

流動式細胞量測術及NGS定序

【0534】 在編輯後第7天，T細胞藉由流動式細胞量測術表型分型以判定MHC II類蛋白質表現。簡言之，在靶向HLA-DR、DQ、DP-PE (BioLegend®目錄號361704)及同型對照-PE (BioLegend®目錄號400234)之抗體混合液中培育T細胞。隨後洗滌細胞，在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀、活力及MHC II表現進行閘控。如實例1中所描述，對DNA樣本進行PCR及後續NGS分析。表17及圖10展示CIITA基因編輯。對於Cas9及BC22n兩種條件，總編輯接近完成，超過95%。表17及圖11展示用與Cas9或BC22n mRNA組合之UGI mRNA進行電穿孔之後的MHC II類蛋白質表現。對於G018117，用BC22n編輯導致80.50% MHC II陰性細胞，而用Cas9編輯導致51.63% MHC II抗原陰性細胞。

【0535】 表17 -以總NGS讀數之百分比呈現之T細胞中之CIITA編輯；缺少表面標記物HLA DQ/DP/DR之細胞之百分比的流動式細胞量測術評定

編輯器	導引物	% C形成T		% C形成A/G		%插入/缺失		% MHC II neg		
		平均	SD	平均	SD	平均	SD	平均	SD	N
Cas9	G018117	0.0	0.0	0.1	0.0	98.0	0.2	70.3	1.5	3
	G018118	0.0	0.0	0.1	0.1	97.5	0.5	73.7	0.5	3
	G018120	0.1	0.1	0.2	0.0	92.3	0.3	83.1	1.1	3
	G018076	0.0	0.0	0.1	0.0	98.3	0.1	62.8	1.1	3
	G018100	0.0	0.0	0.1	0.0	98.9	0.2	84.1	1.3	3
	G018091	0.0	0.0	0.0	0.0	99.4	0.2	96.2	0.4	3
	無導引物	未報導						10.5	0.0	1

BC22n	G018117	95.7	0.2	2.3	0.1	1.1	0.1	99.2	0.1	3
	G018118	95.8	0.3	2.3	0.1	1.2	0.3	99.0	0.1	3
	G018120	95.7	0.5	2.6	0.4	0.7	0.1	99.0	0.1	3
	G018076	96.5	0.4	1.2	0.2	1.1	0.3	98.5	0.2	3
	G018100	90.7	0.3	2.8	0.3	5.1	0.7	95.7	0.6	3
	G018091	95.4	0.6	2.8	0.1	1.1	0.3	98.7	0.2	3
	無導引物	未報導						10.8	0.0	1

6.2 - T細胞中之基因表現分析

全總轉錄本定序

【0536】在編輯後第7天，採集用G018117及G18078處理之T細胞且保存於-80℃下以供將來處理。遵循製造商之方案，使用Direct-zol RNA微量製備套組(Zymo Research，目錄號R2062)自TRIzol™試劑中之樣本提取總RNA。經純化之RNA樣本在NanoDrop™ 8000分光光度計(Thermo Fisher Scientific)中定量且使用無核酸酶水稀釋至41.67 ng/μL。自圖13A至圖15B中所展示之每一一式三份實驗中，隨機選擇每組樣本以用於總轉錄本分析。根據製造商說明書，使用NEBNext® rRNA耗竭套組(New England Biolabs，目錄號E6350L)耗竭500 ng (12 μL)經純化之總RNA之核糖體RNA (rRNA)組分。遵循製造商之方案，使用NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina® (New England Biolabs，目錄號E7765S)將耗竭rRNA之樣本轉化為雙股DNA文庫。在Qubit 4螢光計中定量擴增之文庫，且藉由毛細管電泳獲得每一文庫之平均片段大小。以4 nM之等莫耳濃度彙集文庫，且在NextSeq550定序平台(Illumina)中使用高輸出300-循環套組(Illumina，目錄號20024908)進行雙端定序。

用於差異基因表現分析之資料處理

【0537】產生呈FASTQ格式之定序讀數且使用bcl2fastq程式(Illumina, v2.20)解多工。若每一索引讀數與樣本索引之間的漢明距離

(Hamming, R.W. Bell Syst. Tech. J. 29, 147-160)小於或等於一，則將讀數分配至樣本。用FastQC程式(v0.11.9) (Andrews S. Babraham Inst.)檢驗定序品質。藉由用Bowtie2 (v2.3.5.1) (Langmead, B.及Salzberg, S.L. Nat. Methods 9, 357-359)將所有讀數與人類rRNA序列(GenBank U13369.1)比對來鑑別核糖體RNA讀數。使用Salmon (v0.14.1) (Patro R., 等人Nat. Methods 14, 417-419)與非核糖體RNA讀數進行總轉錄本定量。使用DESeq2 (v1.26.0) (Love, M.I., 等人Genome Biol. 15, 550)對Salmon之輸出進行差異基因表現分析。經Benjamini-Hochberg調節之p值小於0.05之基因或轉錄本經判定為差異表現。使用Metascape (Zhou, Y., 等人Nat. Comm. 10, 1523)依據基因本體來分析差異表現基因之清單。使用BioGrid、InWeb_IM及OmniPath8資料庫判定蛋白質-蛋白質相互作用(Li, T., 等人Nat. Methods 14, 61-64；Stark, C., 等人Nucleic Acids Res. 34, 535-539；Türei, D., 等人Nat. Methods 13, 966-967)。使用分子複合物偵測(MCODE)演算法鑑別密集連接之網路(Bader, G.D., 等人BMC Bioinformatics 4, 1-27)且保留依據p值之三個最佳評分項作為對應網路組件的功能描述。

【0538】與用Cas9 mRNA處理之樣本相比，用BC22n mRNA電穿孔之T細胞顯示MHC II類基因及HLA相關CD74基因之顯著較強下調(表18及表19)。觀測到對I類MHC基因之微小作用(表20及表21)。就總轉錄本範圍內之差異基因表現事件而言，當與Cas9 mRNA相比時，用BC22n mRNA處理導致較少差異表現基因(p.調節< 0.05)。在用sgRNA G018076電穿孔之T細胞中，分別觀測到Cas9及BC22n mRNA處理之總共553及65個差異基因表現事件(圖12A至圖12B)。在用sgRNA G018117電穿孔之T

細胞中觀測到類似趨勢，在分別用Cas9及BC22n mRNA處理時，其顯示303及30個差異基因表現事件(圖13A至圖13B)。當與用Cas9 mRNA處理之彼等相比時，在用BC22n mRNA處理之T細胞中差異表現基因之清單中鑑別到較少蛋白質-蛋白質相互作用網路(圖14A至圖14B及圖15A至圖15B)。

【0539】 表18 - T細胞中II類HLA基因之差異基因表現(ns =不顯著，* = p.adj.<0.05，** = p.adj.<0.01，*** = p.adj.<0.001)。關於轉錄本定量資料，參看表19。

	G018076 sgRNA				G018117 sgRNA			
	Cas9與對照		BC22n與對照		Cas9與對照		BC22n與對照	
基因	倍數變化	p. adj.	倍數變化	p. adj.	倍數變化	p. adj.	倍數變化	p. adj.
CD74	0.446	***	0.116	***	0.360	***	0.100	***
HLA-DMA	0.457	***	0.150	***	0.356	***	0.146	***
HLA-DMB	0.363	***	0.113	***	0.267	***	0.091	***
HLA-DOA	0.450	***	0.299	***	0.420	***	0.280	***
HLA-DPA1	0.474	***	0.181	***	0.385	***	0.170	***
HLA-DPB1	0.381	***	0.087	***	0.300	***	0.073	***
HLA-DQA1	0.316	***	0.017	***	0.214	***	0.009	***
HLA-DQA2	0.215	***	0.007	***	0.221	***	0.011	***
HLA-DQB1	0.383	***	0.069	***	0.290	***	0.069	***
HLA-DQB1-AS1	0.323	***	0.102	***	0.311	***	0.097	***
HLA-DRA	0.288	***	0.004	***	0.205	***	0.002	***
HLA-DRB1	0.287	***	0.029	***	0.207	***	0.027	***
HLA-DRB3	0.268	***	0.012	***	0.219	***	0.004	***
HLA-DRB4	0.282	***	0.024	***	0.224	***	0.026	***

【0540】 表19 - T細胞中II類HLA基因之表現之轉錄本定量。每一平方含有每一百萬個mRNA分子中來自給定基因之轉錄本之平均數目。關於統計顯著性，請參看表19。

導引物	無	G0188117		G018076	
mRNAs	UGI	Cas9 UGI	BC22n UGI	Cas9 UGI	BC22n UGI
CD74	385	154	38	174	45
HLA-DMA	27	11	4	12	4
HLA-DMB	11	3	1	4	1
HLA-DOA	3	2	1	2	1

導引物	無	G0188117		G018076	
mRNAs	UGI	Cas9 UGI	BC22n UGI	Cas9 UGI	BC22n UGI
HLA-DPA1	70	30	12	34	13
HLA-DPB1	16	5	1	6	1
HLA-DQA1	12	3	0	4	0
HLA-DQA2	3	1	0	1	0
HLA-DQB1	60	19	4	23	4
HLA-DQB1-AS1	9	3	1	3	1
HLA-DRA	120	27	0	35	1
HLA-DRB1	117	27	3	34	3
HLA-DRB3	17	4	0	5	0
HLA-DRB4	13	3	0	4	0

【0541】 **表20** -用不同mRNA組合及CIITA靶向sgRNA處理後7天採集之T細胞中I類HLA基因之差異基因表現(ns =不顯著，* = p.adj.<0.05，** = p.adj.<0.01，*** = p.adj.<0.001)。關於轉錄本定量資料，參看表21。

	G018076 sgRNA				G018117 sgRNA			
	Cas9與對照		BC22n與對照		Cas9與對照		BC22n與對照	
基因	倍數變化	p. adj.	倍數變化	p. adj.	倍數變化	p. adj.	倍數變化	p. adj.
HLA-A	0.995	ns	0.910	*	0.969	ns	0.926	ns
HLA-B	1.001	ns	0.881	**	1.043	ns	0.913	ns
HLA-C	1.013	ns	0.917	ns	0.995	ns	0.922	ns
HLA-E	0.925	ns	0.919	ns	0.870	***	0.949	ns
HLA-F	0.897	ns	0.812	**	0.930	ns	0.891	ns

【0542】 **表21** - T細胞中I類HLA基因之表現之轉錄本定量。每一平方含有每一百萬個mRNA分子中來自給定基因之轉錄本之平均數目。關於統計顯著性，請參看表20。

導引物	無	G0188117		G018076	
mRNAs	UGI	Cas9 UGI	BC22n UGI	Cas9 UGI	BC22n UGI
HLA-A	880	947	797	887	814
HLA-B	457	528	407	463	409
HLA-C	479	528	430	490	445
HLA-E	166	161	154	156	155
HLA-F	68	70	59	61	56

實例7 - APOBEC3A熱點處之編輯評定

【0543】 T細胞製備

【0544】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)及Plasmalyte A (Baxter目錄號2B2522X)之1:1調配物中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞基礎培養基中：X-VIVO 15™無血清造血細胞培養基(Lonza Bioscience)，含有5% (v/v)胎牛血清、50 μM 2-巰基乙醇、10 mM N-乙醯基-L-(+)-半胱胺酸、10 U/mL青黴素-鏈黴素，外加1X細胞介素(200 U/mL重組人類介白素-2、5 μg/mL重組人類介白素-7及5 μg/mL重組人類介白素-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec)活化T細胞。細胞在電穿孔之前在含有TransAct™之T細胞基礎培養基中擴展72小時。

【0545】 **T細胞之mRNA及sgRNA電穿孔**

【0546】 在無菌水中製備含有編碼Cas9 (SEQ ID NO: 11)、BC22n (SEQ ID NO: 2)或UGI (SEQ ID NO: 26)之mRNA之溶液。將50 μM靶向sgRNA (G016017)之TRAC自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng每一mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。T細胞混合物一式三份轉移至

96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL T細胞基礎培養基中靜置10分鐘，隨後轉移至含有額外100 μL補充有2X細胞介素的T細胞基礎培養基之新平底96孔板中。所得板在37℃下培育4天。在96小時之後，將T細胞以1:3稀釋至含1X細胞介素之新鮮T細胞基礎培養基中。經電穿孔之T細胞隨後額外培養3天且收集用於NGS定序。

【0547】 **NGS定序**

【0548】 在編輯後第7天，對DNA樣本進行PCR及後續NGS分析，如實例1中所描述。此研究表徵除先前描述為對APOBEC酶呈陽性之腫瘤樣本中之突變熱點的10個基因體基因座外的靶上TRAC基因座(Buisson等人，2019)。此等位點之染色體位置列出於表22上。

【0549】 表23、24及25展示靶上基因座中之C形成T、C形成A/G及插入/缺失編輯水準及所有樣本群組之所預測的APOBEC熱點位點。此等結果之圖形表示展示於圖16A至圖16C中。與用Cas9 mRNA處理之對照樣本相比，除UGI mRNA及sgRNA G016017兩者以外，用BC22n mRNA、UGI mRNA或BC22n mRNA電穿孔之T細胞不顯示先前報導為對APOBEC酶呈陽性之腫瘤樣本中之突變熱點的10個基因體基因座之編輯型態的任何顯著變化(Buisson R., 等人(2019). Science 364, 1-8.,)。在用BC22n mRNA、UGI mRNA及sgRNA G016017處理之樣本中觀測到靶上TRAC基因座處之高水準去胺作用，但在用單獨的BC22n mRNA、單獨的Cas9 mRNA或單獨的UGI mRNA處理之樣本中不存在。

【0550】 表22 -在此研究中評估之突變熱點之清單、其Entrez基因ID及基因體位置。

基因符號	Entrez基因ID	染色體	基因體位置	股
FAM83G	644815	17	18,907,093	-
PCNT	5116	21	47,783,764	-
CUEDC2	79004	10	104,184,490	-
PANX2	56666	22	50,615,649	-
GSE1	23199	16	85,691,140	-
ZNF672	79894	1	249,142,293	+
NLRP1	22861	17	5,461,801	+
MLLT4/AFDN	4301	6	168,352,586	+
OR5A1	219982	11	59,211,279	+
KIAA1522	57648	1	33,237,497	+

【0551】 表23 -除人類基因體中10個先前所描述之APOBEC熱點以外，靶上TRAC基因座中C形成T鹼基轉化之水準。SD =標準差；ND =未測定。

	C形成**T編輯**							
	Cas9 mRNA		**BC22n mRNA**		**UGI mRNA**		**BC22n mRNA + UGI mRNA + G016017**	
基因	平均	SD	平均	SD	平均	SD	平均	SD
TRAC (靶上)	0.14%	0.02%	0.13%	0.01%	0.19%	0.02%	96.26%	0.25%
FAM83G	0.23%	0.05%	0.22%	0.03%	0.22%	0.04%	0.28%	0.05%
PCNT	2.02%	ND	1.97%	0.09%	1.92%	0.04%	1.99%	0.00%
CUEDC2	0.32%	0.12%	0.36%	0.04%	0.27%	0.01%	0.28%	0.00%
PANX2	0.16%	0.01%	0.19%	0.00%	0.21%	ND	0.26%	0.01%
GSE1	0.20%	0.03%	0.11%	ND	0.15%	ND	0.12%	0.02%
ZNF672	0.15%	0.02%	0.19%	0.03%	0.20%	0.01%	0.18%	0.02%
NLRP1	0.14%	0.00%	0.15%	0.01%	0.15%	0.00%	0.16%	0.02%
MLLT4	0.12%	0.01%	0.13%	0.03%	0.13%	0.01%	0.14%	0.00%
OR5A1	0.12%	0.03%	0.13%	0.01%	0.13%	0.02%	0.14%	0.04%
KIAA1522	0.24%	0.03%	0.29%	0.08%	0.25%	0.02%	0.24%	0.01%

【0552】 表24 -除人類基因體中10個先前所描述之APOBEC熱點以外，靶上TRAC基因座中C形成A/G置換之水準。SD =標準差；ND =未測定。

	C形成**A/G編輯**							
	Cas9 mRNA		**BC22n mRNA**		**UGI mRNA**		**BC22n mRNA + UGI mRNA + G016017**	
基因	平均	SD	平均	SD	平均	SD	平均	SD
TRAC (靶上)	0.29%	0.03%	0.30%	0.03%	2.73%	0.69%	2.38%	0.20%
FAM83G	4.22%	0.11%	4.11%	0.22%	4.66%	0.03%	4.13%	0.06%
PCNT	0.45%	ND	0.53%	0.01%	0.52%	0.13%	0.53%	0.04%
CUEDC2	1.28%	0.01%	1.34%	0.11%	1.27%	0.20%	1.36%	0.01%

PANX2	2.18%	0.15%	2.32%	0.24%	2.48%	ND	2.37%	0.27%
GSE1	0.72%	0.06%	0.58%	ND	0.70%	ND	0.66%	0.03%
ZNF672	0.39%	0.03%	0.42%	0.02%	0.36%	0.04%	0.39%	0.02%
NLRP1	0.62%	0.06%	0.62%	0.01%	0.60%	0.02%	0.57%	0.08%
MLLT4	1.27%	0.09%	1.21%	0.01%	1.26%	0.03%	1.32%	0.03%
OR5A1	0.72%	0.02%	0.75%	0.06%	0.70%	0.04%	0.73%	0.03%
KIAA1522	0.72%	0.08%	0.70%	0.07%	0.76%	0.04%	0.74%	0.04%

【0553】 表25 -除人類基因體中10個先前所描述之APOBEC熱點以外，靶上TRAC基因座中插入及缺失(插入/缺失)之水準。SD =標準差；ND =未測定。

	插入/缺失							
	Cas9 mRNA		**BC22n mRNA**		**UGI mRNA**		**BC22n mRNA + UGI mRNA + G016017**	
基因	平均	SD	平均	SD	平均	SD	平均	SD
TRAC (靶上)	0.08%	0.00%	0.11%	0.01%	0.11%	0.02%	0.95%	0.26%
FAM83G	3.78%	0.10%	3.63%	0.11%	3.90%	0.13%	3.67%	0.50%
PCNT	0.11%	ND	0.23%	0.00%	0.18%	0.02%	0.21%	0.02%
CUEDC2	0.09%	0.05%	0.14%	0.03%	0.13%	0.03%	0.14%	0.02%
PANX2	0.47%	0.01%	0.54%	0.10%	0.26%	ND	0.52%	0.02%
GSE1	0.23%	0.06%	0.13%	ND	0.15%	ND	0.36%	0.05%
ZNF672	0.71%	0.06%	0.80%	0.08%	0.72%	0.01%	0.78%	0.15%
NLRP1	0.07%	0.03%	0.07%	0.03%	0.08%	0.01%	0.07%	0.01%
MLLT4	0.26%	0.00%	0.25%	0.01%	0.25%	0.02%	0.27%	0.01%
OR5A1	0.07%	0.02%	0.08%	0.01%	0.08%	0.01%	0.07%	0.01%
KIAA1522	0.38%	0.01%	0.46%	0.02%	0.42%	0.02%	0.41%	0.00%

實例8 - BC22n:UGI之比率固定之T細胞中之LNP滴定

【0554】 使用遞送至活化人類T細胞之LNP，用Cas9或BC22n評定單目標及多目標編輯之效力。

8.1 T細胞製備

【0555】 健康人類供體血球分離術可自商品取得(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至

小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)及Plasmalyte A (Baxter目錄號2B2522X)之1:1調配物中，以供將來使用。解凍時，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞基礎培養基中：X-VIVO 15™無血清造血細胞培養基(Lonza Bioscience)，含有5% (v/v)胎牛血清、50 μM 2-巰基乙醇、10 mM N-乙醯基-L-(+)-半胱胺酸、10 U/mL青黴素-鏈黴素，外加1X細胞介素(200 U/mL重組人類介白素-2、5 μg/mL重組人類介白素-7及5 μg/mL重組人類介白素-15)。用TransAct™ (稀釋1:100，Miltenyi Biotec)活化T細胞。細胞在LNP轉染之前在T細胞基礎培養基中擴展72小時。

8.2 T細胞編輯

【0556】 如實例1中所描述，每一RNA物種，亦即UGI mRNA、sgRNA或編輯器mRNA分別在LNP中調配。編輯器mRNA編碼BC22n (SEQ ID NO: 5)或Cas9 (SEQ ID NO: 23)。靶向B2M (G015995)、TRAC (G016017)、TRBC1/2 (G016206)及CIITA (G018117及G016086)之導引物係單獨或組合使用。在實驗之Cas9及BC22n兩組中均遞送編碼UGI之信使RNA (SEQ ID NO: 26)，以校正脂質量。先前實驗已確立，UGI mRNA在與Cas9 mRNA一起使用時不影響總編輯或編輯型態。如表26中所描述，將LNP與編輯器mRNA、導引RNA及UGI mRNA依分別6:3:2之固定總RNA重量比混合。在表27中所描述之4-導引物實驗中，LNP與個別導引物之劑量降低4倍，以維持總體6:3編輯器mRNA:導引物重量比及允許與基於總脂質遞送之個別導引物效力進行比較。將LNP混合物在37℃下在改用6%食蟹獼猴血清(Bioreclamation IVT，目錄號CYN220760)替代胎牛血清之T細胞基礎培養基中培育5分鐘。

【0557】 活化後七十二小時，T細胞經洗滌且懸浮於基礎T細胞培養基中。將預培育LNP混合物以1x10e5個T細胞/孔添加至每一孔中。在實驗期間，在37℃下將T細胞與5% C02一起培育。在活化之後6天及8天及活化後第十天更換T細胞培養基，採集細胞以藉由NGS及流動式細胞量測術進行分析。如實例1中所描述進行NGS分析。

【0558】 表26及圖17A至圖17E描述當個別導引物用於編輯時T細胞之編輯型態。在所有測試之導引物中，總編輯及C形成T編輯展示與BC22n mRNA、UGI mRNA及導引物之量增加的直接、劑量反應性關係。插入/缺失及C轉化為A或G與劑量逆相關，其中較低劑量導致較高百分比之此等突變。在用Cas9編輯之樣本中，總編輯及插入/缺失活性隨總RNA劑量而增加。

【0559】 表26 編輯作為總讀數之百分比-單導引物遞送

導引物	編輯器	總 RNA (ng)	% C形成T		% C形成 A/G		%插入/缺失		N
			平均	SD	平均	SD	平均	SD	
G015995 B2M	BC22n	0.0	0.3	0.0	1.5	0.1	0.2	0.0	2
		8.6	49.5	3.5	7.7	0.6	6.0	0.4	2
		17.2	68.5	1.7	6.7	1.3	4.3	0.1	2
		34.4	79.0	0.9	5.7	0.3	3.8	0.0	2
		68.8	88.2	0.8	4.6	0.0	2.5	0.2	2
		137.5	90.6	1.8	4.1	0.4	2.2	0.5	2
		275.0	92.6	0.8	3.7	0.3	2.2	0.3	2
		550.0	95.2	0.4	2.8	0.0	1.6	0.2	2
	Cas9	0.0	0.3	0.0	1.5	0.2	0.2	0.0	2
		8.6	0.3	0.0	1.2	0.1	23.7	2.1	2
		17.2	0.3	0.0	0.9	0.1	41.1	0.2	2
		34.4	0.3	0.0	0.6	0.0	59.4	0.6	2
		68.8	0.2	0.1	0.4	0.0	76.8	1.2	2
		137.5	0.1	0.1	0.2	0.0	88.2	2.0	2
		275.0	0.1	0.0	0.1	0.1	95.1	0.5	2
		550.0	0.1	0.0	0.1	0.0	97.5	0.3	2
G016017 TRAC	BC22n	0.0	0.2	0.0	2.2	0.1	0.2	0.1	2
		8.6	34.6	1.1	5.6	0.8	6.6	0.2	2
		17.2	51.3	0.8	5.7	0.1	6.7	1.0	2
		34.4	66.9	2.6	5.4	0.2	4.7	0.4	2
		68.8	79.0	0.6	4.4	0.7	4.5	0.9	2

導引物	編輯器	總 RNA (ng)	% C形成T		% C形成 A/G		%插入/缺失		N
			平均	SD	平均	SD	平均	SD	
		137.5	89.2	0.4	3.6	0.9	2.5	0.2	2
		275.0	92.8	0.9	2.9	0.0	2.3	0.0	2
		550.0	94.5	1.3	3.4	1.0	1.6	0.2	2
	Cas9	0.0	0.2	0.0	2.3	0.1	0.1	0.0	2
		8.6	0.2	0.0	2.1	0.2	20.7	0.5	2
		17.2	0.1	0.0	1.4	0.0	34.6	0.7	2
		34.4	0.1	0.0	1.5	0.4	49.8	0.4	2
		68.8	0.1	0.0	1.0	0.0	62.3	0.1	2
		137.5	0.1	0.0	0.6	0.1	77.0	0.1	2
		275.0	0.0	0.0	0.3	0.0	87.8	0.2	2
		550.0	0.0	0.0	0.2	0.0	93.8	0.6	2
G016206 TRBC1/2	BC22n	0.0	0.4	0.1	0.6	0.1	0.1	0.1	2
		8.6	23.7	1.3	6.1	0.0	6.1	0.8	2
		17.2	42.4	2.2	6.8	0.1	6.8	0.3	2
		34.4	60.1	2.2	5.7	0.3	5.9	0.7	2
		68.8	73.2	4.2	4.3	0.1	4.7	1.1	2
		137.5	81.7	0.8	3.6	0.2	3.7	0.4	2
		275.0	91.0	1.7	2.3	0.1	2.8	0.8	2
		550.0	93.6	1.9	2.0	0.2	1.7	0.6	2
	Cas9	0.0	0.3	0.0	0.5	0.0	0.1	0.0	1
		8.6	0.3	0.2	0.5	0.1	8.1	0.2	2
		17.2	0.3	0.1	0.7	0.1	14.9	0.6	2
		34.4	0.2	0.0	0.8	0.0	24.1	0.0	1
		68.8	0.2	0.0	0.4	0.0	35.9	0.0	1
		137.5	0.2	0.0	0.5	0.0	48.6	2.1	2
		275.0	0.1	0.0	0.4	0.0	63.8	0.0	1
		550.0	未测定						
G018117 CIITA	BC22n	0.0	0.3	0.0	2.7	0.1	0.3	0.0	2
		8.6	14.5	1.5	3.8	0.3	3.5	0.3	2
		17.2	28.1	0.6	3.5	0.3	3.9	1.0	2
		34.4	45.9	0.4	3.3	0.4	3.6	0.0	2
		68.8	62.8	5.3	3.6	0.1	3.7	1.2	2
		137.5	78.9	1.3	2.7	0.1	2.7	0.7	2
		275.0	86.3	1.8	2.6	0.1	2.0	0.1	2
		550.0	92.3	1.2	2.6	0.2	1.1	0.2	2
	Cas9	0.0	0.2	0.0	2.8	0.1	0.3	0.0	2
		8.6	0.3	0.0	2.5	0.0	6.0	0.2	2
		17.2	0.2	0.0	2.4	0.1	11.2	1.6	2
		34.4	0.2	0.0	2.1	0.0	20.8	0.3	2
		68.8	0.2	0.0	1.9	0.1	33.2	0.4	2
		137.5	0.1	0.0	1.3	0.1	51.2	0.0	2
		275.0	0.1	0.0	0.9	0.2	64.5	0.9	2
		550.0	0.1	0.0	0.6	0.0	78.4	1.1	2
G016086 CIITA	BC22n	0.0	0.2	0.0	1.0	0.1	0.1	0.0	2
		8.6	23.5	1.8	3.2	0.1	3.7	0.1	2
		17.2	40.9	1.1	4.4	0.7	4.6	1.0	2

導引物	編輯器	總 RNA (ng)	% C形成T		% C形成 A/G		%插入/缺失		N
			平均	SD	平均	SD	平均	SD	
		34.4	58.0	0.5	4.6	0.3	3.8	0.6	2
		68.8	73.5	0.7	3.7	0.0	2.8	0.5	2
		137.5	83.8	1.1	3.7	0.5	2.0	0.7	2
		275.0	90.1	2.4	3.1	0.1	1.9	0.8	2
		550.0	93.4	0.9	3.0	0.2	1.2	0.3	2
	Cas9	0.0	0.2	0.0	1.0	0.1	0.1	0.0	2
		8.6	0.2	0.0	1.1	0.2	7.4	0.7	2
		17.2	0.2	0.0	1.1	0.3	17.7	1.0	2
		34.4	0.2	0.0	0.8	0.1	32.1	0.1	2
		68.8	0.2	0.0	0.7	0.2	51.5	0.8	2
		137.5	0.2	0.0	0.4	0.0	69.3	0.1	2
		275.0	0.3	0.1	0.3	0.1	84.2	0.1	2
		550.0	0.3	0.0	0.1	0.1	90.0	0.7	2

【0560】 表27及圖18A至圖18D以總讀數之百分比描述了當同時使用四種導引物進行編輯時，T細胞之編輯型態。在此組實驗中，每一導引物以與單導引物編輯實驗相比25%之濃度使用。總共，T細胞同時暴露於6種不同LNP (編輯器mRNA、UGI mRNA、4種導引物)。與用Cas9編輯相比，用BC22n及反式UGI編輯使得每一基因座之最大總編輯百分比更高。

【0561】 表27-編輯作為總讀數之百分比-多導引物遞送

測定之基因座	編輯器	總RNA (ng)	% C形成T		% C形成 A/G		% 插入/缺失		N
			平均	SD	平均	SD	平均	SD	
G015995 B2M	BC22n	0.0	0.3	0.0	1.5	0.2	0.2	0.0	2
		8.6	27.3	0.2	3.8	0.1	2.6	0.1	2
		17.2	47.2	2.2	4.1	0.4	3.0	0.1	2
		34.4	61.2	3.0	3.9	0.1	2.6	0.3	2
		68.8	81.4	0.1	2.9	0.1	1.4	0.1	2
		137.5	90.0	1.1	2.6	0.3	1.3	0.5	2
		275.0	94.7	0.1	2.2	0.1	0.8	0.0	2
		550.0	95.9	0.9	2.9	1.0	0.4	0.3	2
	Cas9	0.0	0.3	0.0	1.4	0.1	0.2	0.0	2
		8.6	0.3	0.0	1.4	0.0	5.0	0.1	2
		17.2	0.3	0.0	1.3	0.0	10.5	0.4	2
		34.4	0.3	0.0	1.1	0.0	19.3	0.6	2
		68.8	0.3	0.0	0.9	0.0	34.4	0.1	2
		137.5	0.2	0.0	0.7	0.0	51.1	1.3	2
		275.0	0.2	0.1	0.5	0.0	68.0	0.1	2
		550.0	0.3	0.1	0.4	0.1	76.7	2.0	2
G016017	BC22n	0.0	0.1	0.1	1.9	0.6	0.2	0.0	2

測定之基因座	編輯器	總RNA (ng)	% C形成T		% C形成A/G		% 插入/缺失		N
			平均	SD	平均	SD	平均	SD	
TRAC		8.6	12.1	1.3	4.3	0.2	2.4	0.2	2
		17.2	25.7	2.2	4.2	0.5	3.8	0.7	2
		34.4	44.7	1.4	4.7	1.0	3.0	0.3	2
		68.8	64.2	1.9	4.4	0.6	2.5	0.1	2
		137.5	79.3	1.1	3.6	0.4	2.1	0.1	2
		275.0	90.7	0.0	3.0	0.1	1.5	0.0	2
		550.0	93.3	0.6	2.4	0.1	0.9	0.4	2
	Cas9	0.0	0.1	0.1	2.1	0.2	0.1	0.0	2
		8.6	0.2	0.1	2.3	0.2	6.1	0.2	2
		17.2	0.1	0.0	1.8	0.2	11.5	0.5	2
		34.4	0.1	0.0	2.0	0.4	21.0	0.4	2
		68.8	0.1	0.0	1.4	0.0	33.5	0.1	2
		137.5	0.1	0.0	1.2	0.1	47.5	0.5	2
		275.0	0.1	0.0	0.9	0.1	64.8	0.2	2
		550.0	0.1	0.0	0.6	0.1	76.1	1.3	2
G016206 TRBC1/2	BC22n	0.0	無資料						
		8.6	11.6	0.3	2.6	0.2	2.8	0.3	2
		17.2	23.4	0.4	3.6	0.3	2.6	0.5	2
		34.4	38.5	1.4	3.7	0.2	2.9	0.7	2
		68.8	55.6	1.7	2.3	0.4	2.4	0.0	2
		137.5	72.4	1.2	1.8	0.5	1.7	0.5	2
		275.0	85.1	1.0	1.9	0.5	1.7	0.6	2
		550.0	89.8	2.8	2.2	0.1	0.9	0.3	2
	Cas9	0.0	0.2	0.0	0.6	0.0	0.1	0.0	1
		8.6	0.2	0.1	0.7	0.1	2.3	0.3	2
		17.2	0.3	0.0	0.7	0.3	4.2	0.4	2
		34.4	0.1	0.0	0.5	0.1	6.6	0.5	2
		68.8	0.4	0.0	0.5	0.0	12.3	0.0	1
		137.5	0.2	0.0	0.5	0.0	17.8	0.0	1
		275.0	0.1	0.0	0.5	0.0	33.0	0.0	1
		550.0	0.3	0.2	0.3	0.0	43.3	1.7	2
G018117 CIITA	BC22n	0.0	0.2	0.0	2.6	0.1	0.3	0.0	2
		8.6	4.6	0.9	3.1	0.2	0.8	0.2	2
		17.2	10.5	0.2	2.9	0.1	1.1	0.2	2
		34.4	18.8	0.3	2.9	0.2	1.6	0.2	2
		68.8	35.1	0.6	2.7	0.2	1.6	0.7	2
		137.5	52.9	0.2	2.9	0.3	1.5	0.0	2
		275.0	71.9	2.4	2.5	0.3	1.3	0.1	2
		550.0	81.1	1.9	2.6	0.1	1.1	0.6	2
	Cas9	0.0	0.3	0.0	2.7	0.1	0.3	0.0	2
		8.6	0.2	0.0	2.6	0.2	1.4	0.0	2
		17.2	0.2	0.0	2.5	0.0	2.1	0.3	2
		34.4	0.3	0.0	2.5	0.0	3.9	0.1	2
		68.8	0.2	0.0	2.5	0.2	7.7	0.6	2
		137.5	0.2	0.0	2.2	0.1	13.3	0.2	2
		275.0	0.1	0.0	1.9	0.0	26.7	1.3	2

測定之基因座	編輯器	總RNA (ng)	% C形成T		% C形成A/G		% 插入/缺失		N
			平均	SD	平均	SD	平均	SD	
		550.0	0.1	0.0	1.7	0.1	42.3	0.3	2

【0562】 在活化後第10天，T細胞藉由流動式細胞量測術進行表型分型以判定編輯是否導致細胞表面蛋白損失。簡言之，在以下抗體之混合物中培育T細胞：B2M-FITC (BioLegend，目錄號316304)、CD3-AF700 (BioLegend，目錄號317322)、HLA DR DQ DP-PE (BioLegend，目錄號361704)及DAPI (BioLegend，目錄號422801)。將一子組未編輯之細胞與同型對照-PE (BioLegend®目錄號400234)一起培育。隨後洗滌細胞，在Cytoflex儀器(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀、活力及抗原表現進行閘控。

【0563】 表28及圖19A至圖19I將表型分型結果報導為對於抗體結合呈陰性之細胞的百分比。BC22n及Cas9樣本兩者之抗原陰性細胞的百分比隨著總RNA增加而以劑量反應性方式增加。對於所有測試之導引物，與用Cas9編輯之細胞相比，用BC22n編輯之細胞展示類似或更高的蛋白質敲除。在多編輯細胞中，與Cas9與反式UGI相比，BC22n與反式UGI展示實質上更高百分比之抗原陰性細胞。舉例而言，在550 ng之最高總RNA劑量下之BC22n編輯樣本展示84.2%之缺少所有三種抗原之細胞，而Cas9編輯僅產生46.8%之此類三敲除細胞。對於僅用一種導引物處理之樣本，DNA編輯與抗原減少之間的相關性為穩定的。當將C形成T轉化與抗原敲除進行比較時，BC22n之R平方量測值為0.93。當將插入/缺失與抗原敲除進行比較時，Cas9之R平方量測值為0.95。

【0564】 表28 -流動式細胞量測術資料-對於抗原呈陰性之細胞百分比(n=2)

導引物	表現型	總RNA (ng)	BC22n		Cas9	
			平均%	SD	平均%	SD
G015995 B2M	B2M neg	550.0	95.7	0.1	91.3	0.6
		275.0	94.4	0.4	89.3	0.1
		137.5	91.2	0.1	82.1	3.3
		68.8	83.9	0.4	68.7	3.3
		34.4	75.7	1.4	53.4	0.2
		17.2	60.8	2.0	30.7	1.3
		8.6	44.0	2.3	13.9	2.0
		0.0	14.1	4.1	9.9	1.9
G015995 G016017 G016206 G018117	B2M neg	550.0	94.4	0.1	74.2	0.4
		275.0	91.3	0.1	65.2	0.1
		137.5	84.3	0.2	45.4	1.9
		68.8	72.7	0.4	24.5	0.8
		34.4	56.2	1.2	14.1	2.3
		17.2	38.5	0.2	9.9	0.8
		8.6	20.6	0.7	7.6	2.4
		0.0	14.1	4.1	9.9	1.9
G016017 TRAC	CD3 neg	550.0	97.3	0.3	94.8	0.4
		275.0	96.0	0.2	87.0	4.9
		137.5	91.9	0.2	72.7	0.9
		68.8	85.7	0.5	65.6	0.1
		34.4	76.6	0.8	51.7	3.0
		17.2	61.8	1.7	35.7	1.1
		8.6	42.1	0.7	20.1	1.5
		0.0	1.0	0.1	0.9	0.1
G016206 TRBC1/2	CD3 neg	550.0	97.9	0.1	86.6	0.3
		275.0	96.0	0.1	77.3	0.1
		137.5	90.4	0.8	59.4	0.4
		68.8	82.9	0.1	40.6	1.2
		34.4	71.9	1.5	27.0	1.6
		17.2	53.4	0.3	16.1	0.1
		8.6	32.6	0.6	7.9	0.4
		0.0	0.8	0.0	0.9	0.4
G015995 G016017 G016206 G018117	CD3 neg	550.0	98.3	0.2	84.2	0.1
		275.0	96.3	0.1	74.6	0.5
		137.5	90.4	0.3	57.4	1.0
		68.8	81.3	0.3	39.4	0.1
		34.4	66.3	1.6	25.6	0.8
		17.2	48.2	1.0	15.3	0.5
		8.6	27.3	0.7	8.6	0.5
		0.0	0.9	0.1	0.9	0.2
G018117 CIITA	MHC II neg	550.0	95.7	0.4	72.0	0.1
		275.0	92.5	1.1	65.6	0.4
		137.5	85.2	0.6	55.5	0.6
		68.8	74.5	1.1	48.9	0.0
		34.4	65.8	3.7	40.7	0.6
		17.2	49.9	0.1	36.2	0.6
		8.6	41.6	0.8	34.2	1.3

		0.0	30.1	1.6	35.2	0.4
G015995 G016017 G016206 G018117	MHC II neg	550.0	88.0	0.2	52.8	1.1
		275.0	81.2	0.2	46.4	0.4
		137.5	70.4	1.3	39.9	1.8
		68.8	60.0	0.4	39.1	3.3
		34.4	48.8	0.6	37.7	2.9
		17.2	43.0	4.2	37.5	0.6
		8.6	37.8	2.1	35.0	0.0
		0.0	33.0	1.9	37.3	2.1
G015995 G016017 G016206 G018117	B2M neg CD3 neg MHC II neg	550.0	84.2	0.0	46.8	1.1
		275.0	76.2	0.0	37.8	0.2
		137.5	63.0	1.3	23.4	2.4
		68.8	48.2	0.2	10.8	0.9
		34.4	31.5	1.1	3.6	0.9
		17.2	17.8	1.7	1.1	0.2
		8.6	6.4	0.0	0.4	0.1
		0.0	0.1	0.0	0.1	0.0
G016086 CIITA	HLA DR DP DQ neg	550.0	96.0	0.1	90.9	0.7
		275.0	93.7	0.1	87.4	0.3
		137.5	88.4	0.5	76.3	0.6
		68.8	80.0	0.7	66.1	1.8
		34.4	69.2	1.5	53.4	1.1
		17.2	56.4	0.4	41.9	0.8
		8.6	45.2	2.9	37.3	0.1
		0.0	30.1	0.9	36.8	0.4

實例9 - 用反式UGI滴定在T細胞中進行編輯

【0565】 評定編輯型態以判定在具有不同編輯構築體之T細胞中達成高純度C形成T編輯所必需的UGI mRNA濃度。使用飽和劑量之編輯器mRNA及sgRNA及不同量之UGI mRNA來量測C形成T編輯純度(僅含有C形成T轉化之經編輯讀數的%)。編輯器mRNA包括編碼BC22n之mRNA (SEQ ID NO: 5)、用總共2個融合UGI部分編碼BC22之mRNA (SEQ ID NO: 29)及編碼包括2個融合UGI部分之BE4Max之mRNA (SEQ ID NO: 32) (Koblan LW, Doman JL, Wilson C, 等人 *Nat Biotechnol.* 2018;36(9):843-846.)。

【0566】 在無菌水中製備含有如表29中所列出之編輯器mRNA或UGI mRNA (SEQ ID NO: 26)的溶液。將50 μM靶向sgRNA G015995之

B2M自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng編輯器mRNA、20 pmols sgRNA及在0.8 ng至600.0 ng (0.8 nM至597.0 nM)範圍內之不同濃度之UGI mRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此mRNA + sgRNA + T細胞混合物一式三份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之CTS™ OpTmizer™ T細胞擴增無血清培養基(SFM) (ThermoFisher目錄號A1048501)中靜置10分鐘，隨後轉移至含有額外100 μL具有2X濃度之細胞介素的相同培養基之新平底96孔板中。所得板在37℃下培育9天，在此期間將細胞分裂且培養基再新兩次。如實例1中所描述，收集且處理T細胞以進行NGS定序。

【0567】 表29及圖20A至圖20C展示每一編輯類型之讀數的百分比。反式UGI mRNA之含量之增加減少所有三個編輯器構築體的插入/缺失。在199 nM UGI mRNA或更高之情況下，插入/缺失減少至小於所測試之每一編輯器構築體之總讀數之2%。在低濃度之反式UGI mRNA下，編碼UGI之編輯器構築體展示比缺少經編碼UGI之BC22n構築體更多的C形成T轉化。表30及圖21將表29及圖20A至圖20C中所擷取之資料表示為C形成T轉化之總編輯之百分比，亦稱為C形成T純度。對於所有構築體，增加反式UGI mRNA增加C形成T總編輯且增加C形成T純度。所有三個構築體在199 nM UGI mRNA下展示超過95% C形成T編輯純度，其對應於約7:1之UGI mRNA與編輯器mRNA之莫耳比。

【0568】 表29 -編輯類型作為隨著UGI mRNA增加之總讀數之百分

比

		% C形成T		% C形成A/G		% 插入/缺失	
編輯器	nM UGI mRNA	平均	SD	平均	SD	平均	SD
BC22n	無UGI	19.9	1.1	31.8	1.4	47.4	0.4
	0.82	23.2	0.6	29.7	1.6	45.9	2.8
	2.46	32.0	0.2	24.5	2.3	42.6	3.3
	7.37	45.0	1.1	23.6	1.6	30.4	2.1
	22.11	59.8	1.0	18.1	0.1	20.6	0.4
	66.33	82.7	2.6	9.3	1.7	7.2	1.2
	199	93.8	1.4	3.2	0.4	1.5	0.3
	597	95.7	0.1	1.9	0.2	1.3	0.4
BC22-2xUGI	無UGI	54.2	0.4	19.2	2.3	21.0	2.1
	0.82	58.6	0.1	18.1	1.9	21.0	2.3
	2.46	61.7	2.0	18.0	2.9	17.5	1.8
	7.37	68.5	0.1	14.5	1.1	15.1	0.8
	22.11	75.7	1.1	12.1	2.3	10.1	2.1
	66.33	88.4	1.2	5.4	0.6	4.7	1.1
	199	94.6	0.1	2.1	0.1	1.5	0.1
	597	96.9	0.6	1.4	0.1	0.6	0.1
BE4Max	無UGI	54.7	1.3	17.2	0.3	9.1	0.1
	0.82	60.3	0.5	15.8	0.5	7.3	0.7
	2.46	62.4	0.1	16.2	0.2	6.7	0.6
	7.37	65.2	0.6	15.1	2.0	5.8	0.4
	22.11	71.8	0.4	10.0	0.2	4.2	0.6
	66.33	78.6	0.6	4.9	1.1	2.1	0.4
	199	83.8	1.0	2.3	0.8	0.5	0.1
	597	85.9	1.6	1.2	0.1	0.4	0.1

【0569】 表30 - C形成T純度：僅含有C形成T轉化、無插入/缺失、無C形成A/G轉化之經編輯定序讀數之百分比(n=2)

nM UGI mRNA	BC22n		BC22-2XUGI		BE4Max	
	平均	SD	平均	SD	平均	SD
597	**96.8**	**0.7**	**98.0**	**0.1**	**98.2**	**0.1**
199	**95.3**	**0.7**	**96.4**	**0.1**	**96.8**	**1.1**
66.33	**83.4**	**2.9**	**89.8**	**1.6**	**91.9**	**0.9**
22.11	**60.8**	**0.6**	**77.4**	**0.4**	**83.6**	**0.8**
7.37	**45.4**	**0.8**	**69.9**	**0.2**	**75.8**	**1.6**
2.46	**32.3**	**0.5**	**63.5**	**1.4**	**73.2**	**0.7**
0.82	**23.5**	**0.8**	**60.0**	**0.1**	**72.4**	**0.1**
0	**19.1**	**0.4**	**57.4**	**0.1**	**67.5**	**0.8**

實例10.篩選CIITA導引RNA

【0570】 藉由使用Cas9及BC22兩者評定MHC II類細胞表面表現之

阻斷來篩選CIITA gRNA在T細胞中之功效。在用RNP進行電穿孔進行CIITA編輯之後，測定對於MHC II類蛋白呈陰性之T細胞的百分比。

10.1.T細胞之RNP電穿孔

【0571】使用Cas9核糖核蛋白(RNP)之電穿孔來評定Cas9編輯活性。在解凍之後，將Pan CD3+ T細胞(StemCell, HLA-A*02.01/ A*03.01)以0.5 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞RPMI培養基中：RPMI 1640 (Invitrogen，目錄號22400-089)，含有5% (v/v)胎牛血清、1x Gluatmax (Gibco，目錄號35050-061)、50 μM 2-巯基乙醇、100 uM非必需胺基酸(Invitrogen，目錄號11140-050)、1 mM丙酮酸鈉、10 mM HEPES緩衝液、1%之青黴素-鏈黴素及100 U/mL重組人類介白素-2(Peprotech，目錄號200-02)。用TransAct™ (1:100稀釋，Miltenyi Biotec)活化T細胞。細胞在RNP轉染之前在T細胞RPMI培養基中擴展72小時。

【0572】將靶向sgRNA之CIITA自其儲存板移除，且在95℃下變性2分鐘，隨後在室溫下冷卻10分鐘。製備20 uM sgRNA及10 uM重組Cas9-NLS蛋白質(SEQ ID No. 36)之RNP混合物且在25℃下培育10分鐘。將五μL RNP混合物與20 μL P3電穿孔緩衝液(Lonza)中之100,000個細胞組合。將22 μL RNP/細胞混合物轉移至Lonza shuttle 96孔電穿孔板之相應孔中。用製造商之脈衝碼對細胞重複兩次電穿孔。電穿孔後立即將T細胞RPMI培養基添加至細胞中。隨後在編輯後2天如實例1中所描述培養且收集經電穿孔之T細胞用於NGS定序。

10.2流動式細胞量測術

【0573】在編輯後第10天，T細胞藉由流動式細胞量測術表型分型

以判定HLA II類蛋白質表現。簡言之，在靶向HLA-DR、DQ、DP-PE (BioLegend®目錄號361704)及同型對照-AF647 (BioLegend®目錄號400234)之抗體之混合液中培育T細胞。隨後洗滌細胞，在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀、活力及MHC II表現進行閘控。如實例1中所描述，對DNA樣本進行PCR及後續NGS分析。

10.3.T細胞之mRNA電穿孔

【0574】在CIITA編輯之後，藉由用mRNA及導引物電穿孔來測定BC22編輯活性。在解凍之後，將自商業上獲得之白血球去除產物(StemCell)分離之Pan CD3+ T細胞以0.5 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞R10培養基中：RPMI 1640 (Invitrogen，目錄號22400-089)，含有10% (v/v)胎牛血清、2 mM Gluatmax (Gibco，目錄號35050-061)、22 μM 2-巰基乙醇、100 uM非必需胺基酸(Invitrogen，目錄號11140-050)、1 mM丙酮酸鈉、10 mM HEPES緩衝液、1%之青黴素-鏈黴素外加100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)。用Dynabeads®人類T-活化劑CD3/CD28 (ThermoFisher)活化T細胞。細胞在mRNA轉染之前在T細胞中擴展72小時。

【0575】將CIITA sgRNA自其儲存板移除，且在95℃下變性2分鐘，隨後在室溫下冷卻10分鐘。用P3緩衝液(Lonza)中之100,00個T細胞及10 ng/uL編碼UGI之mRNA (SEQ ID NO: 26)、10 ng/uL編碼BC22之mRNA (SEQ ID NO: 20)及2 uM sgRNA來製備五十微升電穿孔混合物。將此混合物轉移至Lonza shuttle 96孔電穿孔板之對應孔中。使用Lonza shuttle 96w程式用製造商之脈衝碼在重複孔中對細胞進行電穿孔。電穿孔

之後立即將具有IL-2之R10培養基添加至細胞中。隨後在編輯後10天培養且收集經電穿孔之T細胞用於NGS定序及流動式細胞量測術。如上文針對Cas9 RNP處理之細胞所描述進行流動式細胞量測術。如實例1中所描述，對DNA樣本進行PCR及後續NGS分析。

【0576】 表31及圖22展示使用Cas9及BC22之對於MHC II類蛋白質HLA-DR、DQ、DP之細胞表面表現呈陰性的T細胞之平均百分比與自切割位點至剪接位點邊界核苷酸之距離之關係。對於每一導引物，展示具有SpCas9之切割位點之基因體座標以及受體剪接位點邊界核苷酸或供體剪接位點邊界核苷酸與切割位點之間的距離(核苷酸之#)。正數值展示在剪接位點邊界核苷酸與切割位點之間的5'方向上之核苷酸之數目，而負數值展示在剪接位點邊界核苷酸與切割位點之間的3'方向上之核苷酸之數目。

【0577】 **表31：導引物位置與蛋白質阻斷效率**

導引物	距切割位點之距離(bp)	BC22		Cas9	
		平均% MHC II 陰性	SD	平均% MHC II 陰性	SD
G018075	11	88.3	1.56	54.7	3.54
G018076	10	88.45	0.64	51.45	6.29
G018077	9	69.15	2.48	55.9	0.14
G018078	4	71.35	4.17	83.65	3.04
G018081	0	37.9	1.27	91.1	0.42
G018082	-1	36.75	1.91	93.6	2.26
G018084	-7	45.25	3.75	44	3.39
G018085	-8	45.75	2.19	32.95	0.92

實例11 -用BC22n及Cas9篩選HLA-A導引物

【0578】 藉由評定HLA-A細胞表面表現之損失來篩選HLA-A導引RNA在T細胞中之功效。在藉由mRNA遞送進行HLA-A編輯之後，藉由流動式細胞量測術測定HLA-A2背景中對於HLA-A蛋白質呈陰性的T細胞之百分比(「% HLA-A2-」)。

11.1.T細胞之mRNA電穿孔

【0579】使用編碼Cas9之mRNA (SEQ ID NO: 11)、編碼BC22n之mRNA (SEQ ID NO: 2)或編碼UGI之mRNA (SEQ ID NO: 26)之電穿孔來評定Cas9及BC22n編輯活性。在解凍之後，將Pan CD3+ T細胞(StemCell, HLA-A*02.01/ A*02.01)以1x 10^6個細胞/mL之密度接種於由以下各者構成之TCGM中：CTS OpTmizer T細胞擴展SFM (Thermofisher，目錄號A3705001)，補充有5%人類AB血清(Gemini，目錄號100-512)、1X GlutaMAX (Thermofisher，目錄號35050061)、10 mM HEPES (Thermofisher，目錄號15630080)、1x青黴素-鏈黴素，進一步補充有200 U/mL IL-2 (Peprotech，目錄號200-02)、10 ng/ml IL-7 (Peprotech，目錄號200-07)、10 ng/ml IL-15 (Peprotech，目錄號200-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec)活化T細胞。細胞在mRNA電穿孔之前在37℃下在T細胞RPMI培養基中擴展72小時。

【0580】將HLA-A sgRNA自其儲存板移除，且在95℃下變性2分鐘，隨後在室溫下培育5分鐘。用P3緩衝液(Lonza)中之100,000個T細胞、200 ng編碼UGI之mRNA、200 ng編碼BC22n之mRNA及20 pmoles sgRNA來製備BC22n電穿孔混合物。用P3緩衝液(Lonza)中之100,000個T細胞、200 ng編碼UGI之mRNA、200 ng編碼Cas9之mRNA及20 pmoles sgRNA來製備Cas9電穿孔混合物。將每一混合物轉移至Lonza shuttle 96孔電穿孔板之對應孔中。使用Lonza shuttle 96w，使用製造商之脈衝碼對細胞重複兩次電穿孔。電穿孔後立即在無細胞介素之預溫熱TCGM中回收細胞且在37℃下培育15分鐘。經電穿孔之T細胞隨後在進一步補充有200 U/mL IL-2 (Peprotech，目錄號200-02)、10 ng/ml IL-7 (Peprotech，目錄號200-07)、10 ng/ml IL-15 (Peprotech，目錄號200-15)之TCGM中培養

且在編輯後8天收集用於流動式細胞量測術。

11.2.流動式細胞量測術

【0581】 編輯後第8天，T細胞藉由流動式細胞量測術表型分型以判定HLA-A蛋白質表現。簡言之，將T細胞與靶向HLA-A2之抗體(eBioscience目錄號17-9876-42)一起培育。隨後洗滌細胞，在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀、活力及HLA-A2表現進行閘控。**表32**展示在用BC22n或Cas9對*HLA-A*進行基因體編輯之後對於HLA-A表面蛋白質呈陰性之細胞的百分比。

【0582】 表32 -在用BC22n或Cas9對*HLA-A*進行基因體編輯之後對於HLA-A表面蛋白質呈陰性之細胞的百分比。

	BC22n		Cas9	
導引ID	**平均%A2-**	**SD % A2-**	**平均%A2-**	**SD % A2-**
G018932	20.15	2.76	43.30	1.70
G018933	10.35	1.20	74.00	0.57
G018934	0.50	0.14	15.30	1.56
G018935	0.00	0.00	69.30	0.28
G018936	0.10	0.00	29.65	2.62
G018937	0.15	0.07	50.50	0.71
G018938	0.00	0.00	0.00	0.00
G018939	0.00	0.00	44.90	1.27
G018940	0.00	0.00	12.00	0.42
G018941	0.00	0.00	2.65	0.35
G018942	0.10	0.00	2.15	0.07
G018943	0.00	0.00	16.20	0.42
G018944	0.00	0.00	3.00	0.28
G018945	0.05	0.07	3.20	0.42
G018946	0.00	0.00	2.30	0.14
G018947	0.00	0.00	1.55	0.49
G018949	0.00	0.00	47.10	0.57
G018950	0.00	0.00	0.30	0.00
G018951	0.00	0.00	13.30	0.28
G018952	0.00	0.00	0.50	0.00
G018953	0.00	0.00	3.65	0.64
G018955	0.20	0.14	5.20	0.28
G018958	0.00	0.00	1.30	0.28
G018959	0.00	0.00	3.70	0.14

	BC22n		Cas9	
導引ID	平均%A2-	SD % A2-	平均%A2-	SD % A2-
G018960	0.00	0.00	0.35	0.07
G018961	0.00	0.00	0.40	0.00
G018962	0.00	0.00	2.90	0.42
G018963	0.00	0.00	12.50	0.14
G018964	0.00	0.00	6.45	0.64
G018965	0.00	0.00	0.90	0.00
G018966	0.00	0.00	1.30	0.14
G018968	0.10	0.00	0.10	0.00
G018969	0.00	0.00	0.80	0.14
G018970	0.00	0.00	0.95	0.07
G018971	0.00	0.00	0.10	0.00
G018972	0.05	0.07	3.40	0.28
G018973	0.00	0.00	1.35	0.07
G018974	0.00	0.00	0.45	0.07
G018976	0.05	0.07	2.45	0.07
G018977	0.00	0.00	12.45	1.06
G018978	0.00	0.00	1.75	0.07
G018979	0.05	0.07	37.40	0.71
G018980	0.05	0.07	32.40	2.40
G018981	0.00	0.00	17.45	0.35
G018982	0.00	0.00	26.35	0.92
G018983	0.00	0.00	0.25	0.07
G018984	0.00	0.00	0.65	0.07
G018986	0.00	0.00	1.85	0.21
G018987	0.00	0.00	2.25	0.07
G018988	0.00	0.00	0.15	0.07
G018989	0.00	0.00	1.85	0.07
G018990	0.25	0.07	17.45	1.06
G018991	0.20	0.00	23.15	0.92
G018992	0.20	0.14	38.15	0.07
G018993	0.15	0.07	12.15	1.34
G018994	4.35	0.35	23.75	0.49
G018995	0.55	0.07	94.27	0.30
G018996	0.85	0.07	92.39	0.83
G018997	97.80	0.08	95.03	1.87
G018998	74.75	7.71	93.33	0.18
G018999	98.26	0.30	96.05	2.27
G019000	9.05	0.35	94.67	0.74
G019001	0.05	0.07	4.05	0.64
G019002	0.00	0.00	0.05	0.07
G019003	0.00	0.00	11.10	0.00
G019004	0.00	0.00	30.70	0.00
G019005	0.00	0.00	1.65	0.35
G019006	0.00	0.00	4.75	0.49
G019007	0.00	0.00	5.35	0.78
G019008	0.00	0.00	55.20	3.54
G019009	0.00	0.00	19.55	2.19

	BC22n		Cas9	
導引ID	**平均%A2-**	**SD % A2-**	**平均%A2-**	**SD % A2-**
G019010	0.05	0.07	5.40	0.14
G019011	0.00	0.00	4.40	0.85
G019012	0.05	0.07	22.90	2.55
G019013	0.00	0.00	30.60	2.40
G019014	0.05	0.07	14.65	0.49
G019015	0.00	0.00	44.70	1.70
G019016	0.00	0.00	13.95	0.35
G019017	0.00	0.00	2.35	0.35
G019018	0.00	0.00	19.90	0.00
G019019	0.00	0.00	3.20	0.14
G021205	0.00	0.00	0.00	0.00
G021206	0.00	0.00	4.10	0.28
G021207	0.00	0.00	2.80	0.28
G021208	84.75	2.05	58.50	0.28
G021209	97.96	0.16	83.35	1.77
G021210	71.45	2.90	75.20	1.70
G021211	0.10	0.00	67.80	1.70

實例12 - 用Cas9及BC22進行T細胞編輯、CIITA導引RNA

12.1 T細胞製備

【0583】 在CIITA基因座處用反式UGI及BC22或Cas9編輯T細胞以評定編輯類型對MHC II類抗原之影響。

【0584】 遵循製造商方案，使用EasySep人類T細胞分離套組(Stem Cell Technology，目錄號17951)自白血球去除產物製備T細胞。將T細胞冷凍保存於Cryostor CS10冷凍培養基(目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞R10培養基中：RPMI 1640 (Corning，目錄號10-040-CV)，含有10% (v/v)胎牛血清、2 mM Glutamax (Gibco，目錄號35050-061)、22 μM 2-巰基乙醇、100 uM非必需胺基酸(Corning，目錄號25-025-Cl)、1 mM丙酮酸鈉、10 mM HEPES緩衝液、1%青黴素-鏈黴素外加100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)。用Dynabeads®人類T-活化劑CD3/CD28 (Gibco，目錄號11141D)活化T細胞。細胞在mRNA轉染

之前在T細胞培養基中擴展72小時。

12.2用RNA電穿孔進行T細胞編輯

【0585】 在無菌水中製備含有編碼Cas9蛋白質(SEQ ID NO: 8)、BC22 (SEQ ID NO: 20)或UGI (SEQ ID NO: 26)之mRNA的溶液。將50 μM靶向sgRNA之CIITA自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，如**表33**中所描述，將1 x 10^5個T細胞與200 ng編輯器mRNA、200 ng UGI mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式兩份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞在180 ul R10培養基外加100 U/mL重組人類介白素-2中靜置，隨後轉移至新平底96孔板中。所得板在37℃下培育4天。在編輯後第10天，收集細胞用於流動式細胞量測術分析及NGS定序。

12.3流動式細胞量測術及NGS定序

【0586】 在編輯後第10天，T細胞藉由流動式細胞量測術表型分型以使用靶向HLA-DR、DQ、DP-PE之抗體(BioLegend®目錄號361704)及同型對照-PE (BioLegend®目錄號400234)判定如**實例6**中所描述之MHC II類蛋白質表現。如實例1中所描述，對DNA樣本進行PCR及後續NGS分析。**表33**展示用BC22編輯之細胞的CIITA基因編輯及MHC II類陰性結果。**表34**展示用Cas9編輯之細胞的CIITA基因編輯及MHC II類陰性結果。

【0587】 表33 -用BC22進行*CIITA*編輯之後的編輯百分比及MHC-II

陰性細胞之百分比

	% C形成T			% A至G			%插入/缺失			% MHC II類陰性		
導引物	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	n
G016030	40.2	14.2	2	3.5	1.1	2	2.4	1.1	2	39.7	5.6	2
G016031	58.8	0.0	1	3.4	3.2	2	0.6	0.8	2	41.5	3.0	2
G016032	1.8	0.6	2	18.2	1.3	2	75.2	0.6	2	45.9	4.2	2
G016033	1.6	0.1	2	30.7	2.2	2	18.0	5.2	2	38.5	1.5	2
G016034	52.8	14.8	2	1.5	0.5	2	2.0	0.3	2	41.8	2.2	2
G016035	50.3	14.5	2	1.6	0.6	2	1.4	0.4	2	40.8	2.5	2
G016036	14.2	4.9	2	2.2	0.3	2	2.4	0.3	2	40.1	2.4	2
G016037	10.1	4.5	2	1.3	0.4	2	0.3	0.1	2	38.2	0.8	2
G016038	71.3	6.5	2	3.2	0.1	2	3.0	0.6	2	45.6	2.6	2
G016039	66.0	5.9	2	5.0	0.1	2	10.5	2.9	2	38.6	0.5	2
G016040	無資料			0.0	0.0	1	0.0	0.0	1	38.4	0.7	2
G016041	無資料			3.1	4.3	2	3.3	1.2	2	40.4	2.1	2
G016042	21.5	7.9	2	3.2	0.1	2	1.6	0.9	2	44.4	3.7	2
G016043	44.7	11.5	2	2.3	0.1	2	3.2	0.5	2	40.5	1.6	2
G016044	93.4	2.3	2	1.8	0.4	2	4.9	0.7	2	39.9	0.9	2
G016045	7.1	3.0	2	1.2	0.1	2	2.2	0.2	2	39.8	0.7	2
G016046	63.7	11.5	2	2.9	0.1	2	3.3	0.1	2	46.4	1.4	2
G016047	72.7	3.0	2	2.9	0.2	2	4.6	0.9	2	45.4	2.0	2
G016048	6.2	2.4	2	2.4	0.1	2	0.2	0.1	2	38.4	0.5	2
G016049	66.8	9.0	2	5.4	0.1	2	2.8	0.1	2	42.4	2.5	2
G016050	45.4	9.0	2	2.3	0.3	2	3.0	0.6	2	39.1	2.8	2
G016051	86.2	5.9	2	3.7	0.1	2	1.3	0.3	2	39.5	0.6	2
G016052	53.7	13.7	2	4.2	0.9	2	7.4	0.4	2	42.1	1.8	2
G016053	38.6	18.7	2	1.3	0.3	2	3.1	0.8	2	40.4	1.7	2
G016054	42.0	10.7	2	1.9	0.1	2	2.1	0.4	2	42.1	4.2	2
G016055	36.6	13.1	2	3.5	0.9	2	8.2	2.3	2	41.3	1.5	2
G016056	78.0	9.1	2	3.4	0.1	2	2.0	0.1	2	39.8	3.4	2
G016057	73.3	9.1	2	3.4	0.6	2	5.3	0.0	2	39.7	1.3	2
G016058	75.0	9.1	2	1.7	0.1	2	4.2	0.0	2	46.0	2.3	2
G016059	66.5	12.0	2	4.3	0.2	2	4.7	0.7	2	41.0	0.8	2
G016060	55.6	5.2	2	3.5	0.4	2	10.7	1.0	2	44.2	1.6	2
G016061	65.5	9.3	2	2.5	0.4	2	1.2	0.0	2	38.6	2.0	2
G016062	65.8	9.1	2	3.0	0.2	2	4.3	0.3	2	39.8	0.1	2
G016063	10.2	4.2	2	0.9	0.2	2	0.3	0.1	2	39.9	2.5	2
G016064	66.8	12.2	2	3.5	0.0	2	4.4	1.1	2	59.2	2.2	2
G016065	13.5	5.5	2	0.6	0.2	2	1.1	0.4	2	40.4	2.5	2
G016066	0.1	0.0	2	0.7	0.1	2	0.3	0.0	2	35.4	1.5	2
G016067	82.7	6.4	2	2.6	0.6	2	4.6	0.2	2	59.8	1.2	2
G016068	60.1	8.9	2	2.5	0.8	2	1.1	0.1	2	54.0	0.7	2
G016069	55.8	11.6	2	2.6	0.6	2	2.6	1.1	2	34.3	4.0	2
G016070	76.5	9.6	2	3.5	1.0	2	4.4	0.3	2	53.3	1.7	2
G016071	54.3	6.8	2	4.1	0.5	2	1.4	0.6	2	45.8	0.1	2
G016072	82.0	0.0	1	4.1	0.0	1	5.1	0.0	1	25.1	1.1	2
G016073	63.4	11.1	2	3.5	0.5	2	0.9	0.0	2	38.7	1.3	2
G016074	62.7	13.0	2	3.9	0.2	2	4.2	0.7	2	53.3	2.0	2

	% C形成T			% A至G			%插入/缺失			% MHC II類陰性		
導引物	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	n
G016075	41.2	17.2	2	1.0	0.4	2	8.0	1.7	2	48.1	0.7	2
G016076	42.8	14.3	2	0.9	0.1	2	10.2	2.8	2	55.6	2.9	2
G016077	65.1	10.6	2	5.4	0.2	2	2.4	0.1	2	46.0	0.2	2
G016078	44.1	15.1	2	2.0	0.6	2	6.6	2.0	2	41.6	0.1	2
G016079	79.8	4.9	2	5.6	0.5	2	4.6	0.9	2	53.4	2.8	2
G016080	39.0	12.2	2	4.3	0.6	2	13.1	3.1	2	49.5	3.1	2
G016081	9.6	4.9	2	0.5	0.3	2	2.5	0.8	2	39.0	0.3	2
G016082	20.3	8.6	2	2.0	0.3	2	7.0	3.3	2	40.1	4.1	2
G016083	74.5	9.8	2	3.6	0.1	2	8.0	0.6	2	48.6	2.3	2
G016084	46.0	8.5	2	3.9	0.0	2	23.5	3.2	2	54.5	0.7	2
G016085	35.6	6.7	2	1.4	0.1	2	1.6	0.1	2	41.9	3.0	2
G016086	75.0	10.3	2	3.9	0.4	2	3.5	0.2	2	63.1	1.3	2
G016087	45.3	9.9	2	1.2	0.1	2	3.4	0.5	2	40.3	3.7	2
G016088	67.8	10.5	2	5.6	1.4	2	6.9	1.4	2	44.1	3.3	2
G016089	64.4	10.5	2	4.5	0.1	2	1.5	0.3	2	38.3	1.8	2
G016090	67.1	7.1	2	1.7	0.1	2	16.9	2.2	2	61.3	2.3	2
G016091	47.4	12.0	2	2.1	0.9	2	2.9	2.2	2	54.0	3.9	2
G016092	71.4	11.5	2	3.3	0.1	2	6.5	0.5	2	54.9	0.9	2
G016093	76.6	8.3	2	3.3	0.2	2	3.7	0.1	2	52.2	2.5	2
G016094	75.5	7.5	2	3.6	0.4	2	1.7	0.2	2	44.0	2.5	2
G016095	76.1	7.2	2	7.6	0.4	2	2.8	0.4	2	44.1	0.4	2
G016096	77.6	8.5	2	2.1	0.2	2	4.6	0.4	2	41.2	3.0	2
G016097	44.7	15.0	2	2.2	0.1	2	0.7	0.1	2	38.6	3.2	2
G016098	28.9	8.8	2	1.6	0.4	2	1.6	0.2	2	40.1	4.7	2
G016099	68.8	11.9	2	2.2	0.1	2	3.9	0.7	2	44.8	1.0	2
G016100	85.4	6.9	2	2.4	0.6	2	3.3	0.4	2	43.5	1.9	2
G016101	4.8	1.1	2	0.8	0.1	2	0.2	0.0	2	38.0	3.3	2
G016102	57.5	14.4	2	1.9	0.1	2	2.3	0.4	2	42.6	3.3	2
G016103	69.4	12.8	2	2.4	0.0	2	5.6	0.5	2	39.1	2.7	2
G016104	66.5	12.2	2	1.6	0.7	2	11.1	0.4	2	49.0	3.3	2
G016105	58.4	14.3	2	4.4	0.6	2	8.3	0.7	2	38.4	3.0	2
G016106	74.8	5.7	2	3.3	0.3	2	7.3	0.3	2	51.8	0.1	2
G016107	45.2	12.2	2	5.8	1.1	2	5.4	0.8	2	39.6	1.0	2
G016108	15.3	3.5	2	1.2	0.1	2	1.2	0.4	2	41.5	0.1	2
G016109	77.5	3.7	2	4.5	0.4	2	3.4	0.6	2	48.3	2.5	2
G016110	43.1	15.3	2	1.7	0.2	2	6.9	1.6	2	45.4	0.6	2
G016111	89.2	1.3	2	4.2	0.1	2	5.6	0.8	2	40.6	4.4	2
G016112	68.8	13.2	2	3.8	0.4	2	1.4	0.1	2	43.4	2.7	2
G016113	65.2	9.8	2	3.6	0.2	2	6.9	1.1	2	58.3	2.5	2
G016114	75.5	11.5	2	2.7	0.1	2	5.1	0.6	2	38.9	4.0	2
G016115	72.1	8.6	2	1.2	0.1	2	7.9	0.3	2	60.2	0.9	2
G016116	36.3	7.5	2	2.3	0.8	2	3.0	0.4	2	41.1	0.4	2
G016117	75.4	7.7	2	3.5	0.4	2	5.9	0.4	2	37.1	2.8	2

【0588】 表34 -用Cas9進行CIITA編輯之後的編輯百分比及MHC-II陰性細胞之百分比

	% C形成T			% A至G			%插入/缺失			% MHC II類陰性		
導引物	平均	SD	n	平均	SD	N	平均	SD	n	平均	SD	n
G016030	0.0	0.0	2	0.4	0.0	2	30.1	8.3	2	42.7	0.4	2
G016031	0.0	0.0	1	0.1	0.0	1	79.5	0.0	1	45.9	1.0	2
G016032	0.1	0.1	2	14.8	2.6	2	77.7	4.8	2	43.6	0.1	2
G016033	0.1	0.1	2	16.1	2.4	2	61.5	5.3	2	44.1	1.8	2
G016034	0.0	0.0	2	0.1	0.0	2	49.7	6.2	2	46.1	2.7	2
G016035	0.0	0.0	2	0.1	0.0	2	44.7	6.4	2	46.2	0.6	2
G016036	0.0	0.0	2	1.8	0.3	2	5.6	0.1	2	38.3	1.8	2
G016037	0.1	0.1	2	1.2	0.1	2	3.4	0.4	2	35.9	1.1	2
G016038	0.0	0.0	2	0.6	0.1	2	88.3	3.5	2	65.7	2.9	2
G016039	0.0	0.0	2	0.1	0.0	2	91.9	2.6	2	62.9	2.5	2
G016040	無資料									63.2	0.6	2
G016041	無資料									62.3	0.6	2
G016042	0.0	0.0	2	1.5	0.3	2	40.6	10.8	2	43.9	0.6	2
G016043	0.0	0.0	2	1.3	0.1	2	26.7	4.9	2	42.9	0.4	2
G016044	無資料			0.2	0.0	1	74.4	0.0	1	54.9	0.8	2
G016045	0.1	0.1	2	0.8	0.0	2	13.9	4.3	2	40.6	0.8	2
G016046	0.0	0.0	2	0.2	0.1	2	92.8	2.4	2	62.5	0.6	2
G016047	0.1	0.1	2	0.2	0.0	2	80.0	2.0	2	59.8	0.9	2
G016048	0.0	0.0	2	2.1	0.0	2	9.3	2.5	2	41.0	0.8	2
G016049	0.0	0.0	2	0.1	0.0	2	85.8	3.0	2	56.9	0.3	2
G016050	0.1	0.1	2	0.6	0.1	2	38.4	1.6	2	45.0	0.4	2
G016051	0.0	0.0	2	0.4	0.0	2	82.6	3.6	2	58.8	1.4	2
G016052	0.1	0.1	2	0.6	0.1	2	69.8	7.0	2	53.8	0.4	2
G016053	無資料									43.4	1.2	2
G016054	0.0	0.0	2	1.1	0.1	2	28.1	7.0	2	44.9	3.2	2
G016055	0.0	0.0	2	0.6	0.1	2	37.1	7.7	2	47.5	0.4	2
G016056	0.0	0.0	2	0.1	0.0	2	89.5	5.3	2	63.8	0.6	2
G016057	0.0	0.0	2	0.1	0.0	2	84.7	4.0	2	61.6	3.1	2
G016058	0.0	0.0	2	0.2	0.1	2	82.3	5.9	2	60.4	2.2	2
G016059	0.0	0.0	2	0.1	0.0	2	75.1	3.7	2	56.6	1.6	2
G016060	0.0	0.0	2	0.2	0.0	2	84.3	3.8	2	61.5	1.8	2
G016061	0.0	0.0	2	0.1	0.0	2	55.2	2.9	2	47.4	0.6	2
G016062	0.0	0.0	2	0.5	0.1	2	71.1	5.9	2	46.4	0.7	2
G016063	0.0	0.0	2	0.6	0.0	2	5.1	1.4	2	36.1	1.4	2
G016064	0.0	0.0	2	1.3	0.1	2	42.7	5.7	2	49.1	0.7	2
G016065	0.0	0.0	2	0.1	0.0	2	11.0	2.0	2	40.0	0.9	2
G016066	0.0	0.0	2	0.6	0.0	2	0.4	0.1	2	36.8	0.6	2
G016067	0.1	0.0	2	0.1	0.0	2	85.4	3.3	2	59.7	3.3	2
G016068	0.0	0.0	2	0.1	0.0	2	59.2	6.9	2	54.0	0.2	2
G016069	0.0	0.0	2	0.4	0.0	2	39.5	3.7	2	40.7	0.0	2
G016070	0.1	0.1	2	0.1	0.1	2	92.3	2.3	2	66.4	3.1	2
G016071	0.0	0.0	2	0.2	0.0	2	73.1	2.2	2	55.6	3.0	2
G016072	0.0	0.0	2	0.1	0.1	2	91.1	1.4	2	51.6	1.1	2
G016073	0.0	0.0	2	1.5	0.1	2	38.3	4.2	2	43.5	0.8	2
G016074	0.2	0.1	2	0.6	0.0	2	72.4	7.5	2	56.1	1.4	2
G016075	0.1	0.1	2	0.3	0.1	2	72.9	10.3	2	57.8	4.4	2
G016076	0.0	0.0	2	0.3	0.1	2	66.7	13.4	2	58.4	4.6	2

	% C形成T			% A至G			%插入/缺失			% MHC II類陰性		
導引物	平均	SD	n	平均	SD	N	平均	SD	n	平均	SD	n
G016077	0.0	0.0	2	0.5	0.1	2	80.0	5.2	2	62.5	1.5	2
G016078	0.1	0.1	2	0.3	0.2	2	59.3	10.5	2	51.6	4.5	2
G016079	0.0	0.0	2	0.7	0.1	2	81.9	4.0	2	58.4	1.0	2
G016080	0.0	0.0	2	0.5	0.1	2	71.8	6.2	2	44.9	1.4	2
G016081	0.0	0.0	2	0.4	0.0	2	8.1	1.3	2	39.1	0.7	2
G016082	0.1	0.1	2	2.1	0.0	2	10.0	2.5	2	39.0	0.8	2
G016083	0.1	0.1	2	0.2	0.1	2	92.2	1.5	2	63.6	0.7	2
G016084	0.0	0.0	2	0.4	0.0	2	70.7	6.4	2	56.1	2.6	2
G016085	0.0	0.0	2	0.3	0.1	2	17.5	0.7	2	42.3	0.4	2
G016086	0.1	0.1	2	0.2	0.1	2	85.8	6.1	2	62.2	3.0	2
G016087	0.0	0.0	2	0.2	0.0	2	89.5	2.1	2	56.1	0.1	2
G016088	0.8	0.0	2	0.3	0.1	2	76.8	4.6	2	58.1	0.5	2
G016089	0.1	0.1	2	0.3	0.1	2	73.3	6.4	2	54.2	0.0	2
G016090	0.2	0.0	2	0.3	0.0	2	88.3	5.1	2	61.2	2.3	2
G016091	0.0	0.0	1	0.7	0.0	1	42.0	0.0	1	49.5	3.8	2
G016092	0.1	0.1	2	0.5	0.1	2	60.9	10.0	2	52.0	2.9	2
G016093	0.0	0.0	2	0.5	0.1	2	68.8	8.1	2	50.6	2.5	2
G016094	0.1	0.1	2	0.1	0.0	2	71.3	6.5	2	50.5	3.3	2
G016095	0.0	0.0	2	0.6	0.1	2	70.5	5.4	2	51.6	5.0	2
G016096	0.2	0.1	2	0.1	0.0	2	94.9	2.0	2	51.2	0.1	2
G016097	0.1	0.1	2	0.3	0.0	2	39.7	12.4	2	50.9	4.5	2
G016098	0.1	0.1	2	0.2	0.0	2	23.4	7.5	2	47.2	0.5	2
G016099	0.1	0.0	2	0.2	0.0	2	84.7	5.8	2	63.2	2.5	2
G016100	0.0	0.0	2	0.3	0.1	2	79.8	7.1	2	60.3	0.6	2
G016101	0.1	0.1	2	0.6	0.1	2	2.3	0.8	2	38.8	1.5	2
G016102	0.0	0.0	2	0.4	0.1	2	75.7	8.9	2	59.9	7.1	2
G016103	0.2	0.1	2	0.6	0.1	2	76.8	4.7	2	46.9	3.4	2
G016104	1.4	0.0	1	1.1	0.0	1	66.8	0.0	1	56.1	3.1	2
G016105	0.1	0.1	2	0.7	0.3	2	90.7	5.1	2	58.0	3.0	2
G016106	0.0	0.0	2	0.2	0.0	2	95.1	2.1	2	62.2	3.0	2
G016107	0.1	0.1	2	0.2	0.0	2	84.9	2.6	2	59.5	1.1	2
G016108	0.0	0.0	2	0.6	0.1	2	19.1	4.8	2	43.3	0.8	2
G016109	0.0	0.0	2	0.1	0.0	2	86.5	3.3	2	62.9	3.5	2
G016110	0.0	0.0	2	0.6	0.1	2	34.9	10.0	2	48.0	4.2	2
G016111	65.6*	3.7	2	1.4	0.1	2	32.9	3.7	2	44.5	1.3	2
G016112	0.0	0.0	2	0.8	0.1	2	60.7	6.7	2	54.1	5.3	2
G016113	1.1	0.4	2	0.2	0.0	2	84.2	6.7	2	60.5	5.2	2
G016114	0.1	0.1	2	0.4	0.0	2	87.6	3.5	2	50.2	2.5	2
G016115	0.0	0.0	2	0.3	0.1	2	69.3	7.4	2	52.8	4.8	2
G016116	0.0	0.0	2	0.4	0.0	2	16.6	5.0	2	38.7	0.4	2
G016117	0.0	0.0	2	0.4	0.1	2	85.6	4.9	2	49.0	3.0	2

*G016111目標序列存在天然存在之C/T單核苷酸多型性。

實例13 -劑量反應及多重編輯

【0589】 來自**表33**之三種導引物G016086、G016092及G016067進

一步表徵為隨著導引物之量增加及與靶向TRAC (G013009、G016016或G016017)及B2M (G015991、G015995或G015996)之導引物組合的編輯功效。

【0590】 如**實例6**中所描述，藉由以下偏差進行細胞製備、活化及電穿孔。使用兩種分別編碼BC22 (SEQ ID NO: 20)及UGI (SEQ ID NO:26)之mRNA物種進行編輯。在多種濃度之sgRNA下評定編輯，如**表35**及**表36**中所指示。當在單一反應中使用多種導引物時，每一導引物表示總導引物濃度之四分之一。

【0591】 在編輯後第10天，T細胞藉由流動式細胞量測術表型分型以判定MHC II類蛋白質表現，如**實例6**中所描述。另外，藉由B2M-FITC抗體(BioLegend，目錄號316304)進行B2M偵測且使用CD3-BV605抗體(BioLegend，目錄號317322)測定CD3表現。如**實例1**中所描述，對DNA樣本進行PCR及後續NGS分析。**表35**提供用BC22及靶向CIITA之個別導引物編輯之細胞的MHC II類陰性流動式細胞量測術結果及NGS編輯，其中**圖24A**繪製C形成T轉化百分比且**圖24B**繪製MHC II類陰性百分比。**表36**展示用CIITA、B2M及TRAC導引物同時編輯之細胞的MHC II類陰性結果。

【0592】 表35 -*CIITA*編輯之後MHC-II陰性細胞百分比及NGS結果(n=2)

導引物濃度		**2 uM**		**1 uM**		**0.5 uM**		**0.25 uM**	
測定	**導引物**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**
MHC-II neg	G016086	80.2	12.0	72.2	19.7	60.5	14.3	49.7	16.1
	G016092	64.5	11.4	59.3	11.8	49.0	5.7	42.6	15.1
	G016067	77.3	4.4	76.8	2.1	64.5	6.3		
C形成T	G016086	75.4	12.7	66.1	25.0	53.9	20.1	38.3	28.3
	G016092	71.5	18.5	62.5	25.5	45.2	13.0	36.0	28.1
	G016067	83.1	6.8	82.9	5.7	66.9	8.8	50.1	28.1
	G016086	1.8	0.1	1.6	0.1	1.7	0.1	1.1	0.6

C形成A/G	G016092	1.6	0.1	1.3	0.2	1.2	0.0	1.2	0.5
	G016067	1.0	0.3	1.2	0.1	1.5	0.5	0.9	0.5
插入/缺失	G016086	2.5	1.4	1.4	0.5	1.5	0.3	1.2	0.5
	G016092	2.9	0.3	3.0	0.6	3.1	0.5	2.5	1.7
	G016067	3.3	0.1	2.4	0.0	3.4	1.4	2.1	1.2

【0593】 表36 - CIITA、TRAC及B2M編輯之後抗原陰性細胞百分比

	每導引物之濃度：	**0.5 uM**		**0.25 uM**		**0.125 uM**	
測定	**導引物**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**
三Neg	G015995 G016086 G016017	62.1	9.3	51.9	9.4	26.1	13.6
	G015991 G016092 G016016	43.8	15.6	20.2	7.4	8.2	7.6
	G015996 G016067 G013009	35.3	17.7	15.4	12.3	6.8	7.3
MHC II類Neg	G015995 G016086 G016017	67.0	8.0	57.6	7.8	38.6	5.4
	G015991 G016092 G016016	57.2	8.2	45.2	3.2	36.8	5.3
	G015996 G016067 G013009	53.1	7.9	69.1	43.1	41.3	7.1
CD3 Neg	G015995 G016086 G016017	92.5	2.3	90.5	3.2	77.3	15.1
	G015991 G016092 G016016	88.1	6.2	87.6	3.2	74.2	14.0
	G015996 G016067 G013009	92.8	2.0	89.5	4.8	79.3	14.4
B2M Neg	G015995 G016086 G016017	94.9	2.5	90.0	6.4	63.2	28.0
	G015991 G016092 G016016	73.4	19.2	29.1	13.1	14.3	15.2
	G015996 G016067 G013009	60.8	25.7	29.1	21.4	14.3	15.0

實例14.篩選TRAC導引RNA

【0594】 藉由使用含反式UGI之Cas9及含反式UGI之BC22來評定CD3表面表現之阻斷來篩選TRAC gRNA在T細胞中之功效。在藉由用mRNA及gRNA進行電穿孔進行TRAC編輯之後，測定對於CD3蛋白質呈陰性之T細胞的百分比及在TRAC基因座處編輯之百分比。

實例14.1. T細胞製備

【0595】 遵循製造商方案，使用EasySep人類T細胞分離套組(Stem Cell Technology，目錄號17951)自白血球去除產物製備T細胞。將T細胞冷凍保存於Cryostor CS10冷凍培養基(目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞R10培養基中：RPMI 1640 (Corning，目錄號10-040-CV)，含有10% (v/v)胎牛血清、2 mM Glutamax (Gibco，目錄號35050-061)、22

μM 2-巰基乙醇、100 uM非必需胺基酸(Corning，目錄號25-025-Cl)、1 mM丙酮酸鈉、10 mM HEPES緩衝液、1%青黴素-鏈黴素外加100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)。用Dynabeads®人類T-活化劑CD3/CD28 (Gibco，目錄號11141D)活化T細胞。細胞在mRNA轉染之前在T細胞培養基中擴展72小時。

實例14.2.用RNA電穿孔進行T細胞編輯

【0596】 在無菌水中製備含有編碼Cas9蛋白質(SEQ ID NO: 8)、BC22 (SEQ ID NO: 20)或UGI (SEQ ID NO: 26)之mRNA的溶液。將50 μM靶向sgRNA之TRAC自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，如**表37**中所描述，將1 x 10^5個T細胞與200 ng編輯器mRNA、200 ng UGI mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式三份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞在180 ul R10培養基外加100 U/mL重組人類介白素-2中靜置，隨後轉移至新平底96孔板中。所得板在37℃下培育6天。在編輯後第9天，收集細胞用於流動式細胞量測術分析及NGS定序。

實例14.3.流動式細胞量測術及NGS定序

【0597】 在編輯後第9天，T細胞藉由流動式細胞量測術表型分型以使用靶向CD3之抗體(BioLegend®目錄號317322)及同型對照-PE (BioLegend®目錄號400269)判定如**實例6**中所描述之CD3蛋白質表現。如**實例1**中所描述，對DNA樣本進行PCR及後續NGS分析。TRAC基因座處

之每一編輯類型之平均百分比及用BC22及UGI編輯之後的CD3陰性細胞之平均數目展示於**表37**中；用Cas9及UGI編輯之後的結果展示於**表38**中。C形成T編輯純度計算為僅含有C形成T轉化之經編輯讀數之百分比。

表37 -用BC22及UGI進行*TRAC*編輯之後的編輯百分比及CD3陰性細胞之百分比

	% C形成T		% A至G		%插入/缺失		% C形成T純度		n	% CD3陰性		
導引物	平均	SD	平均	SD	平均	SD	平均	SD		平均	SD	n
G012086	95.21	0.42	2.46	0.16	1.24	0.04	96.26	0.12	3	1.22	0.55	3
G013004	74.7	14.43	1.6	0.32	3.25	1.05	93.97	0.52	3	17.17	7.69	3
G013005	89.47	0.6	3.24	0.11	4.04	0.49	92.48	0.53	3	8.52	1.59	3
G013006	90.56	3.87	2.82	0.23	1.74	0.15	95.21	0.16	3	2.77	0.34	3
G013007	90.96	3.68	3.05	0.37	1.51	0.35	95.21	0.37	3	3.07	1.2	3
G013008	67.48	24.46	2.15	0.67	1.07	0.51	95.45	0.64	3	1.2	0.38	3
G013009	90.05	4.17	2.29	0.27	2.09	0.17	95.36	0.36	3	87.87	5.02	3
G014831	92.48	1.55	2.26	0.22	2.93	0.25	94.68	0.54	3	50.5	3.25	3
G015997	86.72	9.45	1.34	0.09	1.18	0.21	97.14	0.50	3	2.45	0.75	3
G015998	79.5	15.18	2.12	0.63	0.98	0.12	96.25	0.13	3	2.8	1.35	3
G015999	87.16	1.81	3.57	0.03	5.8	0.77	90.30	0.57	3	14.16	6.97	3
G016000	74.27	15.17	2.79	0.16	1.6	0.16	94.24	1.47	3	6.64	0.97	3
G016001	96.49	1.69	0.88	0.14	0.42	0.06	98.67	0.22	3	15.93	3.4	3
G016002	96.11	0.65	1.18	0.1	0.87	0.07	97.90	0.09	3	4.18	2.8	3
G016003	84.79	6.22	1.04	0.06	7.1	1.92	91.24	1.99	3	2.17	1.04	3
G016004	91.78	3.75	2.16	0.18	0.95	0.23	96.72	0.36	3	1.53	0.28	3
G016005	91.02	3.02	2.16	0.08	3.06	0.13	94.58	0.11	3	15.37	2.72	3
G016006	92.18	1.4	1.91	0.09	2.97	0.05	94.98	0.09	3	22.03	0.9	3
G016007	96.71	0.32	1.14	0.12	1.05	0.2	97.78	0.22	3	5.78	0.2	3
G016008	95.81	0.94	1.29	0.07	1.33	0.2	97.34	0.16	3	36.67	0.45	3
G016009	38.69	13.44	2.08	0.22	0.4	0.17	93.73	1.11	3	0.79	0.2	3
G016010	91.39	0.55	2.22	0.06	5.02	0.43	92.67	0.47	3	9.21	0.44	3
G016011	94.67	0.78	2.26	0.11	1.04	0.1	96.63	0.16	3	0.32	0.06	3
G016012	87.92	1.23	2	0.17	7.99	1.51	89.80	1.36	3	10.11	0.54	3
G016013	91.68	3.86	1.77	0.06	2.45	0.28	95.59	0.43	3	59.4	4.51	3
G016014	90.7	6.53	1.6	0.02	1.44	0.26	96.75	0.30	3	6.21	2.09	3
G016015	93.07	2.04	2.84	0.16	1.2	0.23	95.83	0.41	3	0.88	0.67	3
G016016	94.2	0.99	2.11	0.11	0.96	0.18	96.84	0.28	3	90.8	1.59	3
G016017	95.51	0.63	1.86	0.1	1.04	0.17	97.05	0.25	3	91.1	1.35	3
G016018	94.5	1.03	1.48	0.16	1.61	0.24	96.83	0.34	3	6.02	1.95	3
G016019	71.54	5.93	4.69	0.23	3.03	0.53	90.27	0.14	2	78.13	9.8	3
G016020	29.14	9.23	1.64	0.35	0.44	0.18	93.23	0.87	3	1.56	0.8	3
G016021	32.46	10.32	2.07	0.54	1.42	0.21	90.09	0.99	3	0.65	0.13	3
G016022	89.76	4.52	1.98	0.03	2.74	0.16	95.00	0.11	3	15.97	6.07	3
G016023	47.93	14.11	2.17	0.64	1.72	0.39	92.48	0.21	2	5.12	2.45	3
G016024	91.23	3.82	1.77	0.27	2.48	0.28	95.55	0.37	3	3.56	2.12	3

導引物	% C形成T		% A至G		%插入/缺失		% C形成T純度		n	% CD3陰性		
	平均	SD	平均	SD	平均	SD	平均	SD		平均	SD	n
G016025	59.93	18.15	1.18	0.3	0.71	0.06	96.86	0.40	3	1.86	0.37	3
G016026	93.52	3.27	1.45	0.29	0.8	0.09	97.65	0.29	3	82.27	3.13	3
G016027	92.7	1.71	1.67	0.04	3.09	0.19	95.12	0.16	3	5.05	4.02	3
G016028	84.88	9.36	1.29	0.11	0.88	0.05	97.49	0.29	3	2.01	1.07	3
G016029	51.08	14.8	1.57	0.37	0.8	0.08	95.48	0.50	3	1.29	1.14	3

表38 -用Cas9進行*TRAC*編輯之後的編輯百分比及CD3陰性細胞之百分比

導引物	% C形成T			% A至G			%插入/缺失			% CD3陰性		
	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	n
G012086	0.01	0.01	3	0.10	0.02	3	98.18	0.28	3	94.87	0.25	3
G013004	0.05	0.01	3	0.17	0.08	3	64.90	20.08	3	61.17	19.91	3
G013005	0.03	0.00	3	0.05	0.01	3	94.14	1.85	3	83.43	2.05	3
G013006	0.04	0.03	3	0.11	0.07	3	96.29	2.22	3	92.90	1.32	3
G013007	0.05	0.01	3	0.11	0.02	3	96.13	1.88	3	92.93	1.69	3
G013008	0.04	0.01	3	0.23	0.11	3	83.46	9.24	3	79.53	7.89	3
G013009	0.19	0.05	3	0.20	0.02	3	94.74	2.23	3	80.87	1.65	3
G014831	0.02	0.02	3	0.07	0.02	3	99.13	0.19	3	94.87	0.21	3
G015997	0.19	0.07	3	0.16	0.01	3	90.71	4.41	3	88.77	3.65	3
G015998	0.22	0.06	3	0.15	0.04	3	93.52	4.46	3	80.93	1.07	3
G015999	0.02	0.02	3	0.01	0.01	3	98.15	0.89	3	87.00	0.78	3
G016000	0.05	0.03	3	0.08	0.01	3	97.63	0.90	3	92.87	0.93	3
G016001	0.01	0.01	3	0.01	0.01	3	95.81	1.95	3	83.63	1.05	3
G016002	0.02	0.02	3	0.08	0.07	3	97.47	0.51	3	32.97	3.19	3
G016003	0.17	0.08	3	0.08	0.03	3	95.15	3.25	3	70.80	2.09	3
G016004	0.06	0.06	3	0.13	0.07	3	97.56	0.99	3	93.83	0.81	3
G016005	0.22	0.07	3	0.21	0.07	3	98.75	0.01	3	87.40	1.47	3
G016006	0.03	0.03	3	0.14	0.06	3	97.76	0.66	3	94.93	0.47	3
G016007	0.09	0.04	3	0.06	0.03	3	98.40	0.46	3	94.73	0.40	3
G016008	0.00	0.01	3	0.01	0.01	3	98.92	0.35	3	94.67	0.55	3
G016009	0.19	0.05	3	0.77	0.11	3	13.55	3.43	3	68.13	3.92	3
G016010	0.02	0.00	3	0.19	0.04	3	98.20	0.40	3	93.63	0.21	3
G016011	0.06	0.02	3	0.18	0.03	3	97.57	0.73	3	93.03	63.50	3
G016012	0.04	0.02	3	0.12	0.05	3	97.37	0.15	3	93.87	0.76	3
G016013	0.03	0.04	3	0.05	0.00	3	97.49	1.15	3	82.40	2.11	3
G016014	0.00	0.00	3	0.04	0.06	3	98.15	1.00	3	92.43	0.90	3
G016015	0.07	0.05	3	0.19	0.03	3	98.09	0.20	3	94.03	0.29	3
G016016	0.01	0.01	3	0.05	0.01	3	97.03	0.81	3	84.17	0.29	3
G016017	0.03	0.03	3	0.05	0.01	3	97.64	0.43	3	77.80	4.97	3
G016018	0.05	0.03	3	0.03	0.01	3	98.44	0.32	3	61.57	6.82	3
G016019	0.01	0.00	3	0.06	0.02	3	88.15	5.31	3	31.43	5.54	3
G016020	0.03	0.02	3	0.10	0.03	3	79.18	7.16	3	93.30	1.28	3
G016021	0.03	0.01	3	0.23	0.04	3	42.54	6.06	3	70.13	8.45	3
G016022	0.00	0.00	3	0.01	0.01	3	98.01	1.02	3	94.23	0.72	3
G016023	0.07	0.03	3	0.54	0.10	3	88.15	7.96	3	51.13	15.47	3
G016024	0.02	0.02	3	0.24	0.13	3	98.29	0.54	3	76.57	2.92	3
G016025	0.15	0.02	3	0.24	0.04	3	58.36	15.14	3	62.27	3.41	3

導引物	% C形成T			% A至G			%插入/缺失			% CD3陰性		
	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	n
G016026	0.00	0.01	3	0.03	0.01	3	95.34	1.69	3	65.37	10.10	3
G016027	0.08	0.01	3	0.27	0.14	3	92.27	3.82	3	15.07	5.42	3
G016028	0.07	0.06	3	0.16	0.05	3	73.05	9.53	3	90.10	0.28	2
G016029	0.09	0.01	3	0.51	0.04	3	19.24	5.53	3	95.00	0.28	2

實例15.篩選TRBC導引RNA

【0598】 藉由使用含反式UGI之Cas9及含反式UGI之BC22來評定CD3表面表現之阻斷來篩選TRBC gRNA在T細胞中之功效。在藉由用mRNA及gRNA進行電穿孔進行TRBC編輯之後，測定對於CD3蛋白質呈陰性之T細胞的百分比及在TRBC1基因座處之每一類型之編輯的百分比。

實例15.1.T細胞製備

【0599】 遵循製造商方案，使用EasySep人類T細胞分離套組(Stem Cell Technology，目錄號17951)自白血球去除產物製備T細胞。將T細胞冷凍保存於Cryostor CS10冷凍培養基(目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞R10培養基中：RPMI 1640 (Corning，目錄號10-040-CV)，含有10% (v/v)胎牛血清、2 mM Glutamax (Gibco，目錄號35050-061)、22 μM 2-巰基乙醇、100 uM非必需胺基酸(Corning，目錄號25-025-Cl)、1 mM丙酮酸鈉、10 mM HEPES緩衝液、1%青黴素-鏈黴素外加100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)。用Dynabeads®人類T-活化劑CD3/CD28 (Gibco，目錄號11141D)活化T細胞。細胞在mRNA轉染之前在T細胞培養基中擴展72小時。

實例15.2.用RNA電穿孔進行T細胞編輯

【0600】 在無菌水中製備含有編碼Cas9蛋白質(SEQ ID NO: 8)、BC22 (SEQ ID NO: 20)或UGI (SEQ ID NO: 26)之mRNA的溶液。將50

μM靶向sgRNA之TRBC自其儲存板移除，且在95℃下變性2分鐘，隨後在冰上冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，如**表39**中所描述，將1 x 10^5個T細胞與200 ng編輯器mRNA、200 ng UGI mRNA及20 pmols sgRNA在最終體積為20 uL之P3電穿孔緩衝液中混合。此混合物一式三份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞在180 ul R10培養基外加100 U/mL重組人類介白素-2中靜置，隨後轉移至新平底96孔板中。所得板在37℃下培育6天。在編輯後第9天，收集細胞用於流動式細胞量測術分析及NGS定序。

實例15.3.流動式細胞量測術及NGS定序

【0601】 在編輯後第9天，T細胞藉由流動式細胞量測術表型分型以使用靶向CD3之抗體(BioLegend® 目錄號317322)及同型對照-PE(BioLegend®目錄號400269)判定如**實例6**中所描述之CD3蛋白質表現。如**實例1**中所描述，對DNA樣本進行PCR及後續NGS分析。TRAC基因座處之每一編輯類型之平均百分比及用BC22及UGI編輯之後的CD3陰性細胞之平均數目展示於**表39**中；用Cas9及UGI編輯之後的結果展示於**表40**中。C形成T編輯純度計算為僅含有C形成T轉化之經編輯讀數之百分比。

表39 -用BC22進行*TRBC*編輯之後的編輯百分比及CD3陰性細胞之百分比

	% C形成T		% A形成G		%插入/缺失		% C形成T純度			% CD3陰性		
導引物	平均	SD	平均	SD	平均	SD	平均	SD	n	平均	SD	N
G013015	93.67	0.06	3.16	0.19	2.46	0.19	94.34	0.00	2	32.55	1.77	2
G014832	90.99	0.09	3.08	0.24	3.66	0.49	93.10	0.23	2	13.80	0.85	2
G016167	88.56	0.62	5.06	0.26	5.76	0.47	89.11	0.72	2	30.25	7.28	2
G016168	93.21	0.42	2.12	0.09	4.19	0.09	93.67	0.20	2	35.75	0.07	2
G016171	92.69	0.50	3.59	0.15	3.09	0.33	93.28	0.48	2	57.90	0.28	2
G016172	81.81	1.17	5.54	0.28	10.17	1.74	83.90	1.93	2	50.70	2.83	2

導引物	% C形成T		% A形成G		%插入/缺失		% C形成T純度		n	% CD3陰性		
	平均	SD	平均	SD	平均	SD	平均	SD		平均	SD	N
G016174	92.42	1.66	0.99	0.09	4.74	0.19	94.17	0.20	2	92.75	0.78	2
G016177	96.72	0.07	0.91	0.05	1.64	0.18	97.43	0.13	2	21.10	4.67	2
G016179	82.05	1.68	6.67	0.28	9.58	0.83	83.46	1.22	2	40.00	2.12	2
G016180	94.32	0.31	1.46	0.22	1.06	0.23	97.39	0.01	2	91.70	0.71	2
G016181	92.19	0.51	3.77	0.30	2.04	0.14	94.07	0.18	2	19.20	1.27	2
G016183	92.38	0.73	2.99	0.31	3.42	0.43	93.51	0.75	2	24.60	0.85	2
G016187	92.08	2.19	3.14	0.33	1.88	0.47	94.82	0.90	2	13.90	0.85	2
G016188	79.29	2.46	2.78	0.00	3.06	0.15	93.14	0.03	2	90.00	0.57	2
G016189	93.26	0.49	2.79	0.19	2.76	0.45	94.38	0.64	2	92.05	0.64	2
G016190	87.95	0.88	2.56	0.19	3.41	0.14	93.64	0.11	2	5.44	0.35	2
G016191	51.28	4.28	2.37	0.21	2.65	0.05	91.06	0.41	2	3.88	0.59	2
G016192	90.50	1.28	3.62	0.10	5.08	1.13	91.23	1.24	2	14.10	2.26	2
G016193	88.60	0.69	3.61	0.10	4.95	0.05	91.19	0.11	2	8.06	0.46	2
G016194	88.95	0.62	0.67	0.02	4.55	0.47	94.45	0.49	2	19.70	4.81	2
G016195	91.17	0.74	2.57	0.15	3.19	0.23	94.05	0.04	2	13.65	1.91	2
G016196	91.58	0.80	2.16	0.32	5.05	0.11	92.70	0.46	2	18.25	0.78	2
G016197	89.55	0.90	2.72	0.17	6.99	0.68	90.22	0.87	2	16.25	7.71	2
G016199	91.01	1.34	4.05	0.15	3.10	0.53	92.71	0.75	2	93.75	0.21	2
G016200	94.68	0.86	2.09	0.34	2.68	0.60	95.20	0.95	2	93.95	0.07	2
G016201	89.27	0.55	5.04	0.63	4.80	0.14	90.07	0.76	2	19.40	2.97	2
G016203	79.59	1.09	3.78	0.55	9.40	0.25	85.80	0.57	2	12.95	0.49	2
G016204	93.89	0.26	3.36	0.07	2.06	0.08	94.54	0.01	2	42.85	1.06	2
G016205	67.12	3.18	3.84	0.00	5.66	0.09	87.59	0.62	2	41.35	1.48	2
G016206	92.29	0.93	2.63	0.42	1.65	0.12	95.56	0.34	2	93.00	0.28	2
G016207	85.70	2.33	5.16	0.32	8.56	2.71	86.20	2.39	2	44.60	0.71	2
G016211	84.04	2.44	1.20	0.09	2.92	0.02	95.32	0.06	2	67.50	3.96	2
G016212	95.39	0.87	0.78	0.11	2.11	0.44	97.05	0.58	2	48.30	0.00	2
G016214	88.50	3.77	2.03	0.05	1.53	0.38	96.12	0.51	2	83.75	3.75	2
G016216	91.37	0.45	3.67	0.40	4.65	0.84	91.65	0.44	2	60.65	0.92	2
G016217	90.89	0.05	3.59	0.01	5.13	0.04	91.25	0.05	2	35.75	3.46	2
G016219	89.15	1.07	3.93	0.16	5.59	0.64	90.35	0.83	2	47.85	2.33	2
G016222	82.02	0.15	4.25	0.09	12.30	0.07	83.21	0.05	2	22.55	0.35	2
G016227	67.64	0.78	4.66	0.28	14.36	0.70	78.05	0.57	2	38.20	1.27	2
G016228	93.12	1.35	4.09	0.32	1.11	0.13	94.71	0.11	2	14.30	0.99	2
G016230	88.34	1.74	3.06	0.11	5.98	1.48	90.71	1.45	2	13.25	2.76	2
G016232	71.60	n/a	6.32	n/a	21.40	n/a	72.09	n/a	1	39.80	0.71	2
G016233	87.08	1.67	2.87	0.18	8.87	2.03	88.13	1.86	2	22.20	8.91	2
G016238	90.49	1.00	2.74	0.20	4.68	0.22	92.41	0.10	2	25.10	6.79	2
G016239	87.37	0.96	5.11	0.06	7.02	1.07	87.81	1.01	2	29.95	1.63	2
G016240	76.58	1.58	3.86	0.23	16.03	0.07	79.39	0.21	2	55.55	3.32	2
G016241	69.44	1.35	3.89	0.04	24.19	1.07	71.21	1.21	2	61.50	1.84	2
G016242	91.60	0.84	2.92	0.06	4.83	0.56	92.20	0.64	2	3.37	0.28	2
G016243	93.32	2.21	2.74	0.02	1.69	0.36	95.46	0.48	2	33.75	5.16	2
G016245	81.87	0.70	6.03	0.31	8.96	0.11	84.52	0.28	2	40.00	2.40	2
G016248	81.23	2.35	1.14	0.04	2.95	0.34	95.21	0.20	2	5.33	0.21	2
G016249	無資料									6.87	2.02	2

導引物	% C形成T		% A形成G		%插入/缺失		% C形成T純度		n	% CD3陰性		
	平均	SD	平均	SD	平均	SD	平均	SD		平均	SD	N
G016250	無資料									12.50	2.12	2
G016251	92.57	0.21	2.66	0.37	4.40	0.21	92.91	0.16	2	31.45	1.48	2
G016252	84.54	0.88	1.23	0.06	1.93	0.03	96.40	0.14	2	2.47	0.17	2
G016253	93.22	0.40	1.19	0.00	2.83	0.38	95.86	0.35	2	28.55	0.21	2
G016254	92.52	0.86	2.96	0.16	3.53	0.57	93.45	0.75	2	2.02	0.44	2
G016255	75.91	0.26	3.64	0.06	18.80	0.10	77.19	0.06	2	21.70	0.42	2
G016256	69.87	5.75	3.53	0.29	1.87	0.48	92.82	0.31	2	6.39	2.44	2
G016257	90.90	0.20	2.36	0.05	5.81	0.08	91.75	0.05	2	5.01	0.46	2
G016258	69.09	1.72	3.05	0.31	24.53	0.99	71.46	1.01	2	26.90	0.71	2
G016259	88.91	1.19	1.99	0.29	5.58	0.45	92.15	0.81	2	8.44	0.88	2
G016260	92.85	1.13	1.82	0.27	2.58	0.11	95.48	0.42	2	4.30	0.07	2
G016261	92.78	1.36	0.94	0.43	4.51	0.44	94.45	0.91	2	16.55	1.34	2
G016262	95.60	0.22	1.36	0.03	2.59	0.37	96.03	0.34	2	4.29	0.81	2
G016263	無資料									78.40	0.14	2
G016264	87.24	0.43	1.60	0.02	5.83	0.44	92.15	0.49	2	21.90	0.42	2
G016265	48.92	6.40	2.49	0.13	1.49	0.07	92.41	0.81	2	2.53	0.22	2
G016266	72.19	0.15	6.56	0.20	20.76	0.17	72.55	0.02	2	18.90	3.68	2
G016267	92.15	0.40	4.24	0.38	2.94	0.26	92.78	0.14	2	16.65	8.70	2
G016268	93.60	0.39	3.72	0.25	2.43	0.04	93.83	0.29	2	3.03	0.24	2
G016269	48.11	0.16	4.00	0.55	2.93	0.20	87.42	1.23	2	17.05	1.63	2
G016270	87.48	0.28	2.81	0.16	9.04	0.32	88.06	0.46	2	66.90	0.57	2
G016271	91.19	1.41	4.00	0.08	3.94	1.08	91.99	1.19	2	14.50	10.33	2
G016272	93.90	0.09	1.39	0.12	4.07	0.23	94.50	0.11	2	27.20	1.56	2
G016273	87.75	0.20	5.66	0.09	5.36	0.36	88.84	0.26	2	31.50	3.25	2
G016274	83.68	1.26	4.02	0.19	7.12	0.27	88.24	0.59	2	17.50	6.93	2
G016275	93.35	0.24	3.14	0.20	2.52	0.19	94.28	0.00	2	14.65	9.26	2
G016276	94.95	0.27	1.98	0.04	2.65	0.21	95.35	0.26	2	30.35	1.48	2
G016277	90.15	1.29	5.09	0.18	1.82	0.65	92.89	0.54	2	16.13	13.68	2
G016278	83.20	3.62	5.41	0.96	2.92	0.11	90.88	1.20	2	8.88	1.59	2
G016279	90.24	0.72	4.88	0.45	3.23	0.08	91.76	0.40	2	13.70	5.23	2
G016280	91.06	1.61	2.95	0.43	2.76	0.45	94.09	0.95	2	13.81	7.06	2
G016281	94.85	0.41	1.28	0.01	3.31	0.47	95.38	0.46	2	13.85	5.45	2
G016282	93.39	0.27	3.06	0.05	3.13	0.18	93.78	0.24	2	16.95	7.00	2
G016283	77.09	n/a	5.72	n/a	16.13	n/a	77.92	n/a	1	20.40	3.25	2
G016284	87.29	1.73	2.01	1.11	9.08	0.55	89.29	2.50	2	8.38	1.51	2
G016285	60.72	3.51	8.71	0.53	13.95	2.51	72.80	2.87	2	15.70	2.12	2

表40 -用Cas9進行*TRBC*編輯之後的編輯百分比及CD3陰性細胞百分比

導引物	% C形成T			% A形成G			%插入/缺失			% CD3陰性		
	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	N
G013015	0.03	0.04	2	0.09	0.01	2	99.43	0.14	2	93.60	0.28	2
G014832	0.07	0.02	2	0.10	0.00	2	98.24	0.65	2	84.95	0.07	2
G016167	0.01	0.00	2	0.00	0.00	2	99.36	0.26	2	90.10	0.28	2
G016168	0.02	0.01	2	0.18	0.14	2	98.29	0.07	2	95.00	0.28	2
G016171	0.03	0.04	2	0.03	0.02	2	99.11	0.34	2	91.80	0.71	2
G016172	0.01	0.00	2	1.29	0.45	2	96.54	1.15	2	93.60	0.42	2

	% C形成T			% A形成G			%插入/缺失			% CD3陰性		
導引物	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	N
G016174	0.05	0.05	2	0.14	0.05	2	98.65	0.68	2	94.10	0.42	2
G016177	0.10	0.03	2	0.08	0.03	2	99.02	0.28	2	94.05	0.35	2
G016179	0.09	0.02	2	0.21	0.04	2	97.55	0.18	2	93.20	0.42	2
G016180	0.01	0.00	2	0.19	0.07	2	95.64	0.93	2	91.25	1.20	2
G016181	0.25		1	0.03		1	94.84		1	92.00	0.28	2
G016183	0.04	0.04	2	0.01	0.01	2	98.56	0.53	2	92.90	0.00	2
G016187	0.18	0.00	2	0.05	0.07	2	99.07	0.07	2	93.95	0.64	2
G016188	0.07	0.03	2	0.30	0.07	2	94.24	0.69	2	85.95	0.35	2
G016189	0.12	0.03	2	0.64	0.21	2	97.19	0.73	2	89.75	0.49	2
G016190	6.51	6.05	2	0.15	0.21	2	77.21	4.03	2	70.55	0.35	2
G016191	3.67	0.17	2	0.58	0.13	2	57.71	0.58	2	63.95	0.21	2
G016192	0.11	0.08	2	0.24	0.09	2	98.50	0.20	2	89.50	0.28	2
G016193	0.05	0.02	2	0.15	0.04	2	98.54	0.99	2	92.45	0.35	2
G016194	4.24	0.49	2	0.06	0.01	2	85.43	0.76	2	68.00	0.14	2
G016195	0.03	0.04	2	0.00	0.00	2	99.51	0.20	2	93.55	0.35	2
G016196	0.06	0.01	2	0.15	0.05	2	80.55	2.75	2	82.15	1.34	2
G016197	0.00	0.01	2	0.01	0.00	2	99.64	0.02	2	75.20	0.42	2
G016199	0.15	0.01	2	0.22	0.01	2	98.25	0.19	2	91.70	0.57	2
G016200	0.01	0.01	2	0.06	0.02	2	99.45	0.16	2	93.65	0.64	2
G016201	0.05	0.05	2	0.15	0.00	2	93.38	0.20	2	85.10	0.71	2
G016203	0.05	n/a	1	0.09	n/a	1	98.61	n/a	1	92.20	0.28	2
G016204	0.08	0.02	2	0.02	0.01	2	99.31	0.23	2	92.50	0.57	2
G016205	0.05	0.04	2	0.75	0.02	2	77.14	2.06	2	76.20	2.69	2
G016206	0.24	0.09	2	0.24	0.05	2	96.55	0.05	2	91.85	0.07	2
G016207	0.06	0.03	2	0.07	0.01	2	99.25	0.02	2	93.80	0.42	2
G016211	0.04	0.02	2	0.09	0.01	2	84.26	0.46	2	87.75	1.34	2
G016212	0.09	0.00	2	0.10	0.08	2	91.57	1.87	2	90.90	0.42	2
G016214	0.07	0.05	2	0.16	0.02	2	88.68	0.74	2	87.10	0.85	2
G016216	0.08	0.06	2	0.83	0.28	2	98.49	0.46	2	88.50	0.85	2
G016217	0.17	0.06	2	0.08	0.01	2	98.85	0.25	2	93.70	0.85	2
G016219	0.15	0.21	2	0.08	0.04	2	97.51	0.98	2	89.95	0.92	2
G016222	0.03	0.02	2	0.08	0.03	2	98.09	0.23	2	93.35	0.35	2
G016227	0.02	n/a	1	0.12	n/a	1	98.97	n/a	1	84.30	0.71	2
G016228	0.12	0.17	2	0.10	0.08	2	99.05	0.21	2	92.65	0.21	2
G016230	0.10	0.00	2	0.04	0.02	2	98.96	0.30	2	77.90	0.42	2
G016232	0.13	0.04	1	0.02	0.01	1	99.07	0.51	1	94.45	0.21	2
G016233	0.07	0.01	2	0.07	0.04	2	99.00	0.45	2	71.00	1.27	2
G016238	0.09	0.08	2	0.14	0.02	2	93.50	0.81	2	90.90	0.00	2
G016239	0.08	0.08	2	0.09	0.05	2	98.74	0.30	2	85.70	0.71	2
G016240	0.00	n/a	1	0.05	n/a	1	98.91	n/a	1	84.50	0.28	2
G016241	0.00	0.00	2	0.00	0.00	2	99.56	0.05	2	86.05	0.35	2
G016242	0.00	0.00	2	0.03	0.03	2	98.50	0.02	2	87.55	0.64	2
G016243	0.00	0.00	2	0.07	0.01	2	98.44	0.49	2	93.55	0.78	2
G016245	0.45	0.51	2	2.10	0.20	2	95.23	1.04	2	92.70	0.14	2
G016248	2.51	0.44	2	0.09	0.03	2	85.91	2.49	2	78.90	1.13	2
G016249	0.00	0.00	0	0.01	0.00	0	98.87	0.42	0	93.05	0.07	2
G016250	0.00	0.00	0	0.01	0.00	0	99.11	0.30	0	93.35	1.06	2

	% C形成T			% A形成G			%插入/缺失			% CD3陰性		
導引物	平均	SD	n	平均	SD	n	平均	SD	n	平均	SD	N
G016251	0.01	0.02	2	0.04	0.02	2	97.64	1.98	2	93.40	0.42	2
G016252	0.01	0.01	2	0.05	0.01	2	76.81	1.22	2	28.95	3.75	2
G016253	0.11	0.08	2	0.06	0.05	2	95.66	0.25	2	67.70	0.71	2
G016254	0.05	0.02	2	0.07	0.01	2	98.21	0.25	2	25.65	0.92	2
G016255	0.01	0.01	2	1.08	1.33	2	97.81	0.73	2	62.75	0.07	2
G016256	0.06	0.01	2	0.46	0.07	2	80.84	1.58	2	21.05	8.41	2
G016257	0.03	0.02	2	0.01	0.00	2	97.59	0.32	2	85.70	0.00	2
G016258	0.10	0.13	2	0.23	0.04	2	78.74	3.06	2	47.45	1.20	2
G016259	0.00	0.00	2	0.21	0.04	2	97.82	0.31	2	47.00	2.12	2
G016260	1.16	0.20	2	0.15	0.15	2	94.72	0.27	2	28.30	0.28	2
G016261	0.03	0.04	2	0.03	0.04	2	95.13	0.46	2	90.95	0.07	2
G016262	1.17	0.31	2	0.07	0.05	2	98.39	0.31	2	26.85	0.49	2
G016263	0.05	0.06	0	0.08	0.07	0	97.11	2.82	0	93.50	0.28	2
G016264	0.09	0.01	2	0.14	0.04	2	75.23	0.49	2	48.70	1.70	2
G016265	0.08	0.01	2	0.29	0.01	2	47.59	0.92	2	15.60	1.13	2
G016266	0.02	0.00	2	16.72	0.36	2	82.14	0.85	2	25.25	2.76	2
G016267	0.09	0.01	2	0.15	0.06	2	97.50	0.21	2	34.20	1.56	2
G016268	0.01	0.00	2	0.07	0.00	2	98.95	0.20	2	40.30	1.41	2
G016269	0.14	0.06	2	0.65	0.01	2	38.34	4.64	2	15.35	0.64	2
G016270	0.12	0.07	2	0.32	0.13	2	99.10	0.33	2	93.60	0.85	2
G016271	0.16	0.04	2	0.10	0.01	2	98.21	0.27	2	35.55	5.16	2
G016272	0.09	0.05	2	0.19	0.04	2	94.63	1.28	2	93.45	0.78	2
G016273	0.00	0.00	2	0.01	0.00	2	97.97	0.37	2	92.85	1.20	2
G016274	0.06	0.02	2	0.23	0.12	2	87.53	0.83	2	71.30	1.84	2
G016275	0.24	0.22	2	0.03	0.00	2	98.58	0.13	2	31.50	2.97	2
G016276	0.02	0.01	2	0.34	0.04	2	98.56	0.14	2	24.35	4.03	2
G016277	0.52	0.04	2	0.32	0.04	2	97.86	0.06	2	31.75	4.31	2
G016278	0.30	0.01	2	0.27	0.04	2	98.12	0.07	2	32.10	0.28	2
G016279	0.59	0.15	2	0.14	0.00	2	98.69	0.12	2	30.20	5.37	2
G016280	0.24	0.10	2	0.24	0.01	2	90.41	0.60	2	28.55	3.46	2
G016281	0.65	0.88	2	0.03	0.04	2	98.14	0.28	2	92.90	0.42	2
G016282	0.04	0.02	2	0.01	0.00	2	98.57	0.05	2	93.45	0.21	2
G016283	0.01	n/a	1	0.01	n/a	1	93.16	n/a	1	87.35	2.47	2
G016284	0.02	0.02	2	0.01	0.00	2	97.97	0.35	2	42.05	0.64	2
G016285	0.06	0.08	2	0.01	0.01	2	97.89	0.86	2	89.80	0.14	2

實例16.在B2M編輯之後剖析RNA偏離目標

實例16.1.T細胞製備

【0602】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及

CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者組成之T細胞生長(TCG)培養基中：CTS OpTmizer T細胞擴展無血清培養基(Thermofisher，目錄號A3705001)，補充有5%人類AB血清(Gemini，目錄號100-512)、1X GlutaMAX (Thermofisher，目錄號35050061)、10 mM HEPES (Thermofisher，目錄號15630080)及1x青黴素-鏈黴素，進一步補充有200 U/mL IL-2 (Peprotech，目錄號200-02)、10 ng/ml IL-7 (Peprotech，目錄號200-07)、10 ng/ml IL-15 (Peprotech，目錄號200-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec，目錄號130-111-160)活化T細胞。細胞在mRNA電穿孔之前在37℃下擴展72小時。

實例16.2.T細胞之mRNA及sgRNA電穿孔

【0603】在無菌水中製備含有編碼Cas9 (SEQ ID NO: 11)、BC22n (SEQ ID NO: 2)、UGI (SEQ ID NO: 26)或BE4MAX (SEQ ID NO: 32)之mRNA之溶液。將50 μM靶向sgRNA (G015995)之B2M自其儲存板移除，且在95℃下變性2分鐘，隨後在室溫下冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng mRNA及20 pmols sgRNA在最終體積為20 uL之P3電穿孔緩衝液中混合。T細胞混合物以5個複製品轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL TCG培養基中靜置15分鐘，隨後轉移至含有額外100 μL補充有章節16.1中所引用

之2X細胞介素的TCG培養基之新平底96孔板中。

【0604】 為了評估BC22n之表現量達到峰值時的RNA偏離目標，在電穿孔後24小時收集一部分經編輯之T細胞。此部分進一步分成2個板，對其中之一者進行細胞溶解、PCR擴增及NGS分析，而另一部分用於RNA提取及總轉錄本定序。在電穿孔後第3天，收集剩餘T細胞用於細胞溶解及NGS定序，此使得能夠在編輯正常完成之時間點確認此等樣本中之最大B2M編輯。

實例16.3.NGS定序

【0605】 在電穿孔後24及72小時，對T細胞進行溶解、B2M基因座之PCR擴增及後續NGS分析，如實例1中所描述。**表41**及**圖25**展示在B2M編輯之後在兩個時間點處收集之T細胞中的B2M編輯水準。

表41.編輯之後B2M基因座處之平均編輯百分比

			% C形成T		% C形成A/G		%插入/缺失	
時間(h)	**mRNA**	**sgRNA**	**平均**	**SD**	**平均**	**SD**	**平均**	**SD**
24	無	無	0.58	0.06	0.60	0.05	0.22	0.01
	Cas9	G015995	0.48	0.27	0.35	0.05	49.97	9.52
	Cas9, UGI	G015995	0.35	0.09	0.36	0.05	59.44	11.46
	BC22n, UGI	G015995	66.57	5.39	1.27	0.64	1.52	0.61
	BE4MAX, UGI	G015995	36.83	4.89	0.70	0.10	0.38	0.19
72	無	無	0.60	0.09	0.61	0.06	0.23	0.06
	Cas9	G015995	0.33	0.31	0.28	0.16	89.74	1.38
	Cas9, UGI	G015995	0.30	0.24	0.25	0.21	90.02	3.54
	BC22n, UGI	G015995	91.19	1.80	1.84	0.64	1.19	0.37
	BE4MAX, UGI	G015995	67.62	2.38	0.84	0.20	0.49	0.19

實例16.4.全總轉錄本定序

【0606】 在電穿孔後24小時，將T細胞離心，且將細胞集結粒再懸浮於200 uL TRIzol™試劑(Thermo Fisher Scientific，目錄號15596026)中，其在-80℃下冷凍以供將來處理。遵循製造商之方案，使用Direct-zol RNA微量製備套組(Zymo Research，目錄號R2062)自TRIzol™試劑中之

樣本提取總RNA。經純化之RNA樣本在NanoDrop™ 8000分光光度計(Thermo Fisher Scientific)中定量且使用無核酸酶水稀釋至18.18 ng/uL。自**圖25**中所展示之每一實驗組中，隨機選擇3個樣本以用於總轉錄本分析。根據製造商說明書，使用NEBNext® rRNA耗竭套組(New England Biolabs，目錄號E6350L)自每一樣本耗竭100 ng (5.5 uL)經純化之總RNA之核糖體RNA (rRNA)組分。遵循製造商之方案，使用NEBNext® Ultra™ II directional RNA library prep kit for Illumina® (New England Biolabs，目錄號E7765S)將耗竭rRNA之樣本轉化為雙股DNA文庫。在Qubit 4螢光計(Thermo Fisher Scientific)中定量擴增之文庫，且藉由毛細管電泳獲得每一文庫之平均片段大小。以等莫耳濃度彙集文庫，且在Illumina NextSeq550平台中使用高輸出300-循環套組(Illumina，目錄號20024908)進行定序。

實例16.5.用於單核苷酸變異體(SNV)分析之資料處理

【0607】用STAR v2.7.1a將雙端讀數與人類基因體GRCh38比對(Dobin等人，2013)。用Picard MarkDuplicates v2.19.0移除PCR重複(BroadInstitute, 2019)。連續地部署GATK工具SplitNCigarReads、BaseRecalibrator、ApplyBQSR v4.1.8.1以預處理比對。用GATK HaplotypeCaller調用變異體(Auwera等人，2013；DePristo等人，2011；McKenna 等人，2010)。使用bcftools v1.8將自相同樣本之複製品發現之變異體合併(Li, 2011)。藉由使用vcflib v1.0.0排除對照物中發現之變異體來檢索樣本特異性變異體(Garrison, 2016)。藉由將C形成U變異體之數目除以每一樣本之SNV之總數目來計算相對C形成U頻率。使用不成對t檢驗比較處理組，且使用Holm-Sidak方法判定統計顯著性，其中α為0.05，而

不假定標準差一致。

【0608】與用Cas9 mRNA處理之樣本相比，用Cas9及UGI mRNA、BC22n及UGI mRNA或BE4MAX及UGI mRNA電穿孔之T細胞未展示C形成U轉換之頻率之統計學上顯著($p < 0.05$)增加，從而表明在此等樣本之總轉錄本中不存在可偵測之同源非依賴性胞嘧啶去胺作用事件(**表42**及**圖26**)。

表42 - 作為C形成U轉化之RNA轉錄本中SNV之平均百分比

		% C形成U SNV			
mRNA(s)	**sgRNA**	**平均**	**SD**	**P值 (相對於Cas9)**	**P值 (相對於Cas9, UGI)**
Cas9	G015995	10.84	0.25	NA	0.42
Cas9, UGI	G015995	11.07	0.35	0.42	NA
BC22n, UGI	G015995	10.59	0.12	0.19	0.09
BE4MAX, UGI	G015995	10.80	0.29	0.88	0.37

實例17.B2M編輯之後經擴增之T細胞基因體之全基因體定序

實例17.1.T細胞製備

【0609】健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec目錄號130-030-401/130-030-801)，使用CliniMACS® Plus及CliniMACS® LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者組成之T細胞生長(TCG)培養基中：CTS OpTmizer T細胞擴展無血清培養基(Thermofisher，目錄號A3705001)，補充有5%人類AB血清(Gemini，目錄號100-512)、1X GlutaMAX (Thermofisher，目

錄號35050061)、10 mM HEPES (Thermofisher，目錄號15630080)及1x青黴素-鏈黴素，進一步補充有200 U/mL IL-2 (Peprotech，目錄號200-02)、10 ng/ml IL-7 (Peprotech，目錄號200-07)、10 ng/ml IL-15 (Peprotech，目錄號200-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec，目錄號130-111-160)活化T細胞。細胞在mRNA電穿孔之前在37℃下擴展72小時。

實例17.2.T細胞之mRNA及sgRNA電穿孔

【0610】在無菌水中製備含有編碼Cas9 (SEQ ID NO: 11)、BC22n (SEQ ID NO: 2)或UGI (SEQ ID NO: 26)之mRNA之溶液。將50 μM靶向sgRNA (G015995)之B2M自其儲存板移除，且在95℃下變性2分鐘，隨後在室溫下冷卻。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng mRNA及20 pmols sgRNA在最終體積為20 uL之P3電穿孔緩衝液中混合。T細胞混合物以8個複製品轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL TCG培養基中靜置15分鐘，隨後轉移至含有額外100 μL補充有2X細胞介素的TCG培養基之新平底96孔板中。

【0611】為了促進擴展，使用含1X細胞介素之新鮮TCG培養基，在電穿孔後第3天及第6天分別以1:4及1:3之比率分離T細胞。在電穿孔後第7天，收集一部分細胞用於流動式細胞量測術及NGS定序，而將剩餘細胞冷凍用於後續單細胞全基因體擴增及定序。

實例17.3.流動式細胞量測術及NGS定序

【0612】在電穿孔後第7天，T細胞藉由流動式細胞量測術表型分型

以評估用sgRNA G015995編輯之後B2M表現量之損失。簡言之，在4℃下將T細胞與抗CD3 (BioLegend®目錄號317340)、CD4 (BioLegend®目錄號300537)、CD8 (BioLegend®目錄號344706)及B2M (BioLegend®目錄號316314)之抗體之混合物一起培育30分鐘，以1:200稀釋於細胞染色緩衝液(BioLegend®目錄號420201)中。隨後洗滌細胞，在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀及B2M表現進行閘控。**表43**及**圖27**展示在經編輯T細胞中表現B2M之細胞的百分比。

表43 - 藉由對用不同mRNA組合及B2M sgRNA G015995處理後7天採集之T細胞之流動式細胞量測術分析評定B2M表現之損失(缺少表面標記物之細胞的%) (SD =標準差)。

			% B2M KO	
組	sgRNA	mRNA(s)	平均	SD
1	無	無	0.36	0.32
2	G015995	Cas9	95.27	0.59
3	G015995	Cas9, UGI	95.45	0.44
4	G015995	BC22n, UGI	99.37	0.21

【0613】 在電穿孔後第7天，對T細胞進行溶解、B2M基因座之PCR擴增及後續NGS分析，如實例1中所描述。**表44**及**圖28**展示B2M編輯之後32個樣本(每組8個複製品)中之B2M編輯水準。

表44 - 用不同mRNA組合及B2M sgRNA G015995處理後7天採集之T細胞之B2M編輯百分比(Indels =插入或缺失)。

組	樣本	%C形成 T	%C形成 A/G	%插入/缺失
1 -僅電穿孔	1	0.35	1.47	0.17
	2	0.31	1.35	0.14
	3	0.29	1.49	0.14
	4	0.29	1.48	0.18
	5	0.30	1.52	0.20
	6	0.27	1.51	0.21
	7	0.31	1.55	0.21
	8	0.31	1.57	0.21

組	樣本	%C形成 T	%C形成 A/G	%插入/缺失
2 - Cas9 + G015995	9	0.08	0.10	96.96
	10	0.18	0.07	96.47
	11	0.18	0.08	97.57
	12	0.16	0.04	97.59
	13	0.16	0.06	97.53
	14	0.10	0.05	97.73
	15	0.43	0.11	96.12
	16	0.15	0.09	97.36
3 - Cas9 + UGI + G015995	17	0.09	0.08	97.05
	18	0.42	0.17	96.70
	19	0.23	0.16	96.70
	20	0.28	0.04	97.20
	21	0.20	0.03	97.60
	22	0.06	0.09	97.14
	23	0.32	0.06	97.38
	24	0.16	0.05	97.36
4 - BC22n + UGI + G015995	25	94.29	2.68	0.99
	26	93.74	3.25	1.19
	27	93.61	3.14	0.84
	28	93.94	2.93	1.01
	29	94.47	2.86	1.17
	30	94.55	2.53	1.45
	31	94.63	2.40	0.79
	32	94.14	2.79	0.78

實例17.4.單一T細胞分離、溶解、全基因體擴增及定序

【0614】自每一組8個複製品中隨機選擇一個樣本用於單一細胞分離、全基因體擴增及定序。將來自樣本12、21及30 (**表44**)之冷凍細胞轉移至合同研究組織(Singulomics Corporation, Inc.)中，其中自每一樣本分離10個單一T細胞。此等單一T細胞經溶解，且其基因體根據先前公開之方法使用多重置換擴增(MDA)進行擴增(Dong等人，Nat Methods, 2017)。如實例1中所描述，對經擴增之基因體進行B2M基因座之PCR擴增及後續NGS分析，旨在確認單一T細胞中之經編輯基因型。遵循製造商之方案，自每一組10個單一細胞，使用KAPA HyperPlus套組(Roche，目錄號07962410001)將6個DNA樣本轉化成全基因體定序文庫。在Illumina NovaSeq 6000平台中使用S4試劑套組v1.5 (Illumina，目錄號20028312)

對所得18個文庫進行定序。

實例17.5.用於單核苷酸變異體(SNV)分析之資料處理

【0615】 用BWA-MEM v0.7.17將雙端讀數與人類基因體GRCh38比對(Li, 2013)。用Picard MarkDuplicates v2.19.0移除PCR重複(Broad Institute, 2019)。隨後，使用GATK BaseRecalibrator及ApplyBQSR v4.1.8.1校正鹼基評分(Auwera等人，2013；DePristo等人，2011；McKenna等人，2010)。使用DeepVariant v1.0.0調用變異體(Poplin等人，2018)。藉由將C形成T變異體之總數目除以每一樣本之SNV之總數目來計算相對C形成T頻率。使用不成對t檢驗比較處理組，且使用Holm-Sidak方法判定統計顯著性，其中α為0.05，而不假定標準差一致。

【0616】 與用Cas9 mRNA處理之樣本相比，用Cas9及UGI mRNA電穿孔之T細胞或用BC22n及UGI mRNA處理之彼等未展示在經擴增基因體DNA中C形成T轉換之頻率之統計學上顯著($p < 0.05$)增加，從而表明在此等樣本中不存在可偵測之同源非依賴性胞嘧啶去胺作用事件(**表45**及**圖29**)。

表45.用不同mRNA組合及靶向sgRNA G015995之B2M在電穿孔後7天採集之來自單一T細胞之經擴增基因體DNA中所有單核苷酸變異體(SNV)之C形成T轉換百分比(SD =標準差；NA =不適用)。

		% C形成T SNV			
sgRNA	**mRNA(s)**	**平均**	**SD**	**P值 (相對於Cas9)**	**P值 (相對於Cas9, UGI)**
G015995	**Cas9**	**16.32**	**0.13**	**NA**	**0.21**
G015995	**Cas9, UGI**	**16.46**	**0.21**	**0.21**	**NA**
G015995	**BC22n, UGI**	**16.47**	**0.15**	**0.11**	**0.96**

實例18.B2M編輯之後純系地擴展之eHap1細胞之全基因體定序

實例18.1.eHap1細胞培養

【0617】 完全單倍體、經工程改造之Hap1 (eHap1)細胞為商業獲得的(Horizon Discovery目錄號C669)，且細胞在由補充有10% (v/v)胎牛血清(Thermofisher目錄號A3840001)及1x青黴素-鏈黴素(Thermofisher目錄號 15140122) 之 Iscove 改 良 Dulbecco 培 養 基 (Thermofisher 目 錄 號 12440053)構成之IMDM生長培養基中培養。在解凍之後，將eHap1細胞在37℃下培養48小時且在LNP處理之前24小時以6 x 10^5個細胞/孔之密度接種於6孔板中，其在37℃下培育直至處理。

實例18.2.eHap1編輯

【0618】 B2M靶向sgRNA G015991及編碼Cas9 (SEQ ID NO: 11)、BC22n (SEQ ID NO: 2)、UGI (SEQ ID NO: 26)或BE4MAX (SEQ ID NO: 32)之mRNA調配為如實例1中所描述之LNP中之個別RNA物種。將LNP以與以下總RNA濃度之不同組合施用至T細胞：0.104 μg/mL編輯器mRNA；0.55 μg/mL UGI mRNA；0.4175 μg/mL sgRNA。將不同LNP組合(**表46**)預混合於補充有10 μg/mL重組人類ApoE3 (Peprotech目錄號350-02)之IMDM生長培養基中，且在37℃下培育15分鐘。移除eHap1細胞之培養基且每一孔接受3 mL LNP混合物。未處理之對照接受3 mL補充有10 μg/mL ApoE3而不含LNP之IMDM生長培養基。細胞在37℃下培育24小時且移除培養基且用IMDM生長培養基替換。

【0619】 在處理之後三天及五天，將eHap1細胞分離，以較低密度重新接種，且返回至37℃培育箱。在5天時間點，用抗B2M抗體(BioLegend目錄號316304)染色一部分細胞以藉由流動式細胞量測術評估B2M表現之損失。將此等細胞在4℃下與在細胞染色緩衝液(BioLegend®目錄號420201)中以1:200稀釋之抗B2M抗體一起培育30分鐘。隨後洗滌

細胞，在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。eHap1細胞基於大小、形狀及B2M表現進行閘控。**表46**及**圖30**展示經編輯之eHap1細胞中B2M蛋白質表現量。

表46 - 在B2M處用不同mRNA組合編輯之後B2M陰性eHap1細胞的平均百分比。

		% B2M KO	
sgRNA	**mRNA(s)**	平均	**SD**
無	無	0.30	0.00
G015991	Cas9	71.93	1.93
G015991	Cas9, UGI	75.20	0.46
G015991	BC22n	74.87	0.67
G015991	BC22n, UGI	91.63	1.39
G015991	BE4MAX	44.00	2.54
G015991	BE4MAX, UGI	55.70	1.66

【0620】 在處理之後七天，將eHap1細胞分離，彙集每一處理組之複製品且離心所得細胞懸浮液。如實例1中所描述，收集來自每一池之一小部分細胞用於批量NGS定序。**表47**及**圖31**展示此等樣本中之B2M編輯水準。將剩餘eHap1細胞與抗B2M (BioLegend目錄號316304)之抗體混合，以1:200 (v/v)稀釋於細胞染色緩衝液(BioLegend®目錄號420201)中且在4℃下培育30分鐘。隨後在MA900螢光活化細胞分選(FACS)儀器(Sony Biotechnology)中洗滌及處理細胞。對於B2M表現呈陰性之單一細胞個別地接種於96孔板中。對於未處理之對照，實情為接種具有B2M表現之陽性訊號的單一細胞。單一細胞在37℃下培育10天以允許建立及擴展單一細胞純系。

表47 - 用不同mRNA組合及B2M sgRNA G015991處理之後eHap1細胞之B2M編輯結果(NGS定序) (Indels =插入或缺失)。

		NGS定序		
sgRNA	**mRNA(s)**	**%C形成 T**	**%C形成 A/G**	**%插入/缺失**
無	無	0.19	0.24	0.27
G015991	Cas9	0.18	0.35	89.90
G015991	Cas9, UGI	0.22	0.23	93.71
G015991	BC22n	12.78	40.92	35.39
G015991	BC22n, UGI	93.08	0.55	1.24
G015991	BE4MAX	25.51	15.65	16.17
G015991	BE4MAX, UGI	63.57	0.28	0.75

實例18.3.純系擴展、基因體DNA之提取及全基因體定序

【0621】 在培養10天之後，在倒置螢光顯微鏡下目測檢驗純系。將來自每一處理組之十二個純系轉移至6孔板，以使得能夠進一步擴展。如實例1中所描述收集來自每一純系之一小部分細胞用於NGS定序，同時將剩餘細胞接種於6板中且在37℃下培養直至達至會合。基於其靶上編輯結果，選擇每組之5個純系進行全基因體定序。除eHap1細胞之一個非純系樣本以外，將來自所有純系群體之細胞溶解，且遵循製造商之方案，使用DNeasy血液及組織套組(Qiagen目錄號69504)提取其基因體DNA。遵循製造商說明書，使用KAPA HyperPlus套組(Roche，目錄號07962410001)將DNA樣本轉化成全基因體定序文庫。在Illumina NovaSeq 6000平台中使用S4試劑套組v1.5 (Illumina，目錄號20028312)對所得36個文庫進行定序。

實例18.4.用於單核苷酸變異體(SNV)分析之資料處理

【0622】 首先用bwa (v0.7.17)將來自每一樣本之讀數與人類基因體構築hg38比對(Li, 2013；Li and Durbin, 2010)。用samtools (v1.11)模組fixmate、sort及markdup連續處理比對(Kumaran等人，2019；Li等人，

2009)。使用DeepVariant (v1.0.0)自經處理之比對調用變異體(Poplin等人，2018)。接著使用GLnexus (v1.3.1)合併來自每一樣本之變異體(Lin等人，2018；Yun等人，2021)。自所有純系樣本排除eHap1細胞之非純系樣本中出現的變異體。亦忽略讀數深度低於10或基因型品質評分低於15之變異體。藉由將C形成T變異體之總數目除以每一樣本之SNV之總數目來計算相對C形成T頻率。使用不成對t檢驗比較處理組，且使用Holm-Sidak方法判定統計顯著性，其中α為0.05，假定標準差一致。

與未處理之對照相比，在UGI mRNA不存在或存在之情況下，用Cas9、BC22n或BE4MAX mRNA處理之eHap1細胞並未展示在基因體中C形成T轉換之頻率之統計學上顯著($p < 0.05$)增加，從而表明在此等樣本中不存在可偵測之同源非依賴性胞嘧啶去胺作用事件(**表48**及**圖32**)。

表48 - 在B2M處用不同mRNA組合編輯之後純系地擴展之eHap1細胞中所有單核苷酸變異體(SNV)中C形成T轉換的百分比(NA =不適用)。

		% C形成**T SNV**			
sgRNA	**mRNA(s)**	**平均**	**SD**	**P值 (相對於第1組)**	**顯著？ (p<0.05？)**
無	無	12.52	0.43	NA	NA
G015991	Cas9	12.16	0.09	0.105	否
G015991	Cas9, UGI	12.04	0.42	0.112	否
G015991	BC22n	12.44	0.53	0.820	否
G015991	BC22n, UGI	12.08	0.84	0.336	否
G015991	BE4MAX	12.19	0.48	0.284	否
G015991	BE4MAX, UGI	12.59	0.48	0.789	否

實例19.在經由電穿孔或LNP遞送之後，在T細胞中用BC22n或Cas9進行同時四重編輯

【0623】 為評定與遞送條件及藉由Cas9或鹼基編輯器編輯相關之結構基因體變化的量，將T細胞用電穿孔處理以遞送RNP或用脂質奈米粒子(LNP)處理以遞送四種導引物，且分析Cas9或BC22n之細胞活力、DNA雙

股斷裂、編輯、表面蛋白質表現及染色體結構。

實例19.1.T細胞製備

【0624】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中。使用EasySep™人類T細胞分離套組(Stemcell目錄號17951)經由陰性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor® CS10 (StemCell Technologies目錄號07930)及Plasmalyte A (Baxter目錄號2B2522X)之1:1調配物中以供將來使用。

【0625】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於基於OpTmizer之培養基中，該培養基含有CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中用TransAct™ (1:100稀釋，Miltenyi Biotec)活化72小時，此時將其洗滌且一式四份接種以用於藉由電穿孔或脂質奈米粒子編輯。

實例19.2.用脂質奈米粒子進行單一gRNA及4 gRNA T細胞編輯

【0626】 LNP一般如同實例1用單一RNA物種負荷調配。負荷係選自編碼BC22n之mRNA、編碼Cas9之mRNA、編碼UGI之mRNA、靶向B2M之sgRNA G015995、靶向TRAC之sgRNA G016017、靶向TRBC之sgRNA G016200或靶向CIITA之sgRNA G016086。每一LNP在37℃下在基於OpTmizer之培養基中培育15分鐘，該培養基具有如上文所描述之細胞介素，補充有20 ug/ml重組人類ApoE3 (Peprotech，目錄號350-02)。

活化後七十二小時，T細胞經洗滌且懸浮於具有細胞介素而無人類血清之OpTmizer培養基中。對於單一sgRNA編輯條件，將預培育之LNP混合物添加至100,000個細胞之每一孔中，以產生2.3 ug/ml編輯器mRNA (BC22n或Cas9)、1.1 ug/mL UGI及4.6 ug/uL G016017之最終濃度。對於四重sgRNA編輯，將LNP混合物添加至100,000個細胞之每一孔中，以產生2.3 ug/ml編輯器mRNA (BC22n或Cas9)、1.1 ug/mL UGI、1.15 ug/uL G015995、1.15 ug/uL G016017、1.15 ug/uL G016200及1.15 ug/uL G016086之最終濃度。亦包括對照組，其包括未經編輯之T細胞(無LNP)。在遞送後16小時，使用一子組細胞來量測細胞活力，且處理另一子組細胞以用於γH2AX病灶成像。剩餘T細胞在培養物中繼續擴展。在活化之後5天及8天及活化後第十一天更換培養基，採集細胞以藉由NGS、流動式細胞量測術及UnIT進行分析。如同實例1進行NGS。

實例19.3.用mRNA電穿孔進行單一gRNA及4 gRNA T細胞編輯

【0627】在活化後72小時進行電穿孔。靶向B2M之sgRNA G015995 (SEQ ID NO: 182)、靶向TRAC之sgRNA G016017 (SEQ ID NO: 184)、靶向TRBC之sgRNA G016200 (SEQ ID NO:801)及sgRNA G016086 (SEQ ID NO: 586)在95℃下變性2分鐘，隨後在室溫下冷卻10分鐘。採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於單一sgRNA編輯條件，將1 x 10^5個T細胞與40 ng/uL編輯器mRNA (BC22n或Cas9)、10 ng/uL UGI mRNA及80 pmols sgRNA在最終體積為20 uL之P3電穿孔緩衝液中混合。對於四重sgRNA編輯條件，將1 x 10^5個T細胞與40 ng/uL編輯器mRNA (BC22n或Cas9)、10 ng/uL UGI mRNA及20 pmols四種個別sgRNA在最終體積為20 uL之P3電穿孔緩衝液中混合。此混合物一式四份轉移至96孔

Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞在80 ul具有細胞介素之基於OpTmizer之培養基中靜置，隨後轉移至新平底96孔板中。亦包括對照組，其包括未經編輯之T細胞(無EP)。在遞送後16小時，使用一子組細胞來量測細胞活力，且處理另一子組細胞以用於γH2AX病灶成像。

實例19.4.經由Cell Titer Glo之相對活力

【0628】 電穿孔或脂質奈米粒子遞送後十六小時，自原始板移除20 uL對照或編輯細胞且添加至具有黑色壁之新平底96孔板(Corning目錄號3904)。添加CellTiter-Glo® 2.0 (Promega目錄號G9241)且根據製造商之方案處理樣本。相對發光單元(RLU)由CLARIstar plus (BMG Labtech)板讀取器讀出，其中增益設定為3600。如**表49**及**圖33**中所展示之相對活力係藉由將所有樣本RLU除以未處理之對照RLU之平均值來計算。所有電穿孔條件之活力均相比於未處理之對照水準下降了大於5倍，而LNP處理即使在同時對4種導引物進行編輯時亦維持接近未處理之對照樣本之細胞活力。

表49 - 用各種編輯及遞送條件處理之後16小時的相對細胞活力

		EP		LNP	
編輯器	**導引物**	**平均**	**SD**	**平均**	**SD**
無編輯器	無導引物	100.00	2.52	100.00	5.90
無編輯器	G016017	13.88	1.05	89.48	1.77
Cas9	G016017	13.25	1.18	96.43	9.82
BC22n	G016017	14.78	1.37	91.20	4.67
Cas9	4種導引物	13.45	0.65	98.30	4.80
BC22n	4種導引物	14.38	1.49	103.40	2.75

實例19.5.γH2AX病灶之染色、成像及定量

【0629】 電穿孔或脂質奈米粒子遞送後16小時，使用Cytospin 4 (Thermo Fisher)將T細胞細胞離心至載玻片上。在冰上在PBS/0.5% Trion X-100中預提取5分鐘之後，將細胞固定在4%多聚甲醛中10分鐘。接著，

細胞在PBS中洗滌若干次且在PBS/0.1% TX-100/1% BSA中阻斷30分鐘。將初級抗體(小鼠抗磷酸-組蛋白H2A.X (Ser139) (Millipore目錄號05-636)在4℃下在阻斷緩衝液中培育隔夜。在PBS/0.05% Tween-20中洗滌三次之後，將二級抗體(山羊抗小鼠IgG Alexa 568 (Thermo Fisher目錄號A31556)在室溫下在阻斷緩衝液中培育30分鐘。細胞在PBS/0.05% Tween-20中洗滌，且細胞核用Hoechst 33342進行對比染色。藉由共焦成像用Leica SP8產生影像。經由常規方案在Thermo Scientific HCS Studio Cell Analysis Software Spot Detector模組上進行影像分析。**表50**及**圖34**展示在用所述編輯及遞送條件處理之後，每個細胞核之總γH2AX光點強度。與LNP Cas9-4導引物之樣本相比，EP Cas9與4種導引物樣本展示每個細胞核之gH2AX病灶顯著增加。

表50 - 用各種編輯及遞送條件處理之後，每個細胞核之平均總γH2AX光點強度

	無編輯器			Cas9，4種導引物			BC22n，4種導引物		
遞送	**平均**	**SD**	**N**	**平均**	**SD**	**N**	**平均**	**SD**	**N**
未處理	134.33	95.78	5						
EP				21386.62	4336.69	3	未完成		
LNP				2550.88	562.77	3	1770.11	291.97	5

實例19.6.流動式細胞量測術及NGS定序

【0630】 在編輯後第8天，T細胞藉由流動式細胞量測術表型分型以使用靶向B2M-APC/Fire™ 750 (BioLegend®目錄號316314)、CD3-BV605 (BioLegend®目錄號316314)及HLA II- DR、DP、DQ-PE (BioLegend®目錄號361716)之抗體判定如**實例6**中所描述之B2M、CD3及HLA II- DR、DP、DQ蛋白質表現。如**實例1**中所描述，對DNA樣本進行PCR及後續NGS分析。**表51**及**圖35**展示在用LNP處理之後，所關注基因座之編輯百分比。在由LNP遞送4種導引物之情況下，BC22n之每一基因

座處之編輯百分比高於Cas9。**表52**及**圖36**展示LNP處理之後的所關注表面蛋白表現。相比於用Cas9編輯，用BC22n編輯產生更大百分比之三敲除細胞。

表51 - 在藉由LNP遞送用所述編輯方案處理之後的**平均編輯百分比**。

編輯器	導引物	讀出基因座	C形成T %			C形成A/G %			插入/缺失%		
			平均	SD	N	平均	SD	N	平均	SD	N
無編輯器	無導引物	B2M	0.20	0.00	2	0.41	0.01	2	0.13	0.01	2
		TRAC	0.05	0.07	2	0.53	0.01	2	0.09	0.01	2
		TRBC1	0.25	0.07	2	0.86	0.09	2	0.24	0.02	2
		TRBC2	0.30	0.14	2	0.85	0.04	2	0.27	0.01	2
		CIITA	0.15	0.07	2	0.26	0.03	2	0.06	0.00	2
Cas9	G016017	TRAC	0.00	0.00	2	0.05	0.00	2	96.59	0.52	2
	4種導引物	B2M	0.30	0.14	2	0.37	0.21	2	83.61	2.72	2
		TRAC	0.00	0.00	2	0.06	0.04	2	89.45	0.25	2
		TRBC1	0.00	0.00	2	0.35	0.01	2	75.98	2.09	2
		TRBC2	0.00	0.00	2	0.38	0.03	2	78.07	1.51	2
		CIITA	0.20	0.14	2	0.38	0.04	2	55.23	0.92	2
BC22n	G016017	TRAC	93.90	0.57	2	2.29	0.29	2	2.34	0.08	2
	4種導引物	B2M	95.65	0.07	2	1.42	0.23	2	1.07	0.16	2
		TRAC	95.00	0.57	2	1.65	0.07	2	1.44	0.43	2
		TRBC1	92.40	0.00	2	1.55	0.18	2	1.91	0.10	2
		TRBC2	92.50	0.00	2	1.62	0.02	2	1.87	0.33	2
		CIITA	91.35	0.35	2	0.93	0.04	2	0.64	0.04	2

表52 - 在藉由LNP遞送用所述編輯方案處理之後表現表面之細胞的平均百分比。

編輯器	導引物	表面蛋白質	平均	SD	N
無編輯器	無導引物	CD3-	2.30	2.12	2
		B2M-	4.00	2.26	2
		HLA DP DQ DR-	60.40	1.70	2
Cas9	G016017	CD3-	97.05	0.16	2
	4種導引物	B2M-	77.90	4.67	2
		CD3-	94.54	1.34	2
		HLA DP DQ DR-	70.10	4.81	2
		CD3- B2M- HLA DP DQ DR-	61.58	5.42	2
BC22n	G016017	CD3-	96.20	0.13	2
	4種導引物	B2M-	97.35	0.37	2
		CD3-	97.34	0.08	2
		HLA DP DQ DR-	93.46	0.89	2
		CD3- B2M- HLA DP DQ DR-	90.63	0.89	2

實例19.7.藉由UnIT量測結構變異及易位

【0631】 在編輯後第8天，收集來自未處理之LNP-Cas9-4導引物及LNP-BC22n-4導引物樣本之一子組T細胞，短暫離心且再懸浮於100 uL PBS中。使用DNeasy血液及組織套組(Qiagen目錄號69504)自細胞分離gDNA。將UnIT結構變異表徵測定應用於此等gDNA樣本。高分子量基因體DNA用Tn5轉座酶及具有部分Illumina P5序列及12 bp獨特分子標識符(UMI)之轉接子同時進行片段化及序列標記(『片段化標記(tagmented)』)。使用P5引子及半嵌套基因特異性引子(GSP)之兩個連續PCR將P7序列賦予Illumina，以產生每個樣本兩個Illumina相容性NGS文庫。用兩個文庫對CRISPR/Cas9靶向切割位點之兩個方向進行定序允許推斷及定量基因體編輯之後DNA修復結果中的結構變異。若兩個片段與不同染色體比對，則將SV歸類為「染色體間易位」。結構變異結果表明，當藉由BC22n進行多重編輯時，染色體間易位降至背景水準，而Cas9多重編輯使得結構變異顯著增加，如**表53**及**圖37**中所展示。

表53 - 在藉由LNP遞送用所述編輯方案處理之後總獨特分子標識符中之染色體間易位的平均百分比。

編輯	基因座	平均	SD	N
未處理	B2M	0.16	0.09	2
	TRAC	0.21	0.13	2
	CIITA	0.10	0.04	2
Cas9，4種導引物	B2M	2.71	0.52	2
	TRAC	1.55	0.24	2
	CIITA	0.92	0.37	2
BC22n，4種導引物	B2M	0.14	0.06	2
	TRAC	0.21	0.08	2
	CIITA	0.14	0.08	2

實例20 - 用Cas9及BC22n在T細胞中進行CD38導引RNA篩選

實例20.1 T細胞製備

【0632】 在CD38基因座處用Cas9或BC22n及UGI mRNA編輯T細胞

以評定編輯結果及CD38表現之對應損失。

【0633】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞在LOVO裝置上經洗滌且再懸浮於CliniMACS PBS/EDTA緩衝液(Miltenyi Biotec，目錄號130-070-525)中。使用CD4及CD8磁珠(Miltenyi Biotec，目錄號130- 030-401/130-030-801)使用CliniMACS Plus及CliniMACS LS一次性套組，經由陽性選擇分離T細胞。將T細胞等分至小瓶中且冷凍保存於Cryostor CS10 (StemCell Technologies，目錄號07930)中以供將來使用。在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞X-VIVO 15擴展培養基中：X-VIVO 15 (Lonza，目錄號BE02-06Q)，含有5% (v/v)胎牛血清(ThermoFisher，目錄號A3160902)、50 μM (1X) 2-巰基乙醇(ThermoFisher，目錄號31350010)、1%青黴素-鏈黴素(ThermoFisher，目錄號15140122)、1 M N-乙醯基L-胱胺酸(Fisher，目錄號ICN19460325)，稀釋於磷酸鹽緩衝鹽水(PBS)中且正規化至pH 7，補充有100 U/mL重組人類介白素-2(Peprotech，目錄號200-02)、5 ng/mL 重組人類介白素-7 (Peprotech，目錄號200-07)及5 ng/mL重組人類介白素-15 (Peprotech，目錄號200-15)。用TransAct™ (1:100稀釋，Miltenyi Biotec，目錄號130-111-160)活化T細胞。細胞在mRNA電穿孔之前在37℃下擴展72小時。

實例20.2 用RNA電穿孔進行T細胞編輯

【0634】 在無菌水中製備含有編碼Cas9蛋白質、BC22n或UGI之mRNA的溶液。將50 μM靶向sgRNA之CD38自其儲存板移除，且在95℃下變性2分鐘，且在室溫下培育5分鐘。活化後七十二小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液

(Lonza)中。如實例1中所描述製備信使RNA。對於待電穿孔之每一孔，如表54中所描述，將1 x 10^5個T細胞與200 ng Cas9或BC22n mRNA、200 ng UGI mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式兩份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL X-VIVO 15培養基中靜置15分鐘，隨後轉移至含有額外90 μL補充有2X細胞介素的X-VIVO 15培養基之新平底96孔板中。所得板在37℃下培育10天。為了促進擴展，使用含1X細胞介素之新鮮X-VIVO 15培養基，在電穿孔後第3天及第6天分別以1:4及1:3之比率分離T細胞。在電穿孔後第9天，將細胞以1:2分成2個U形底板，且收集一個板用於NGS定序，而另一板在第10天用於流動式細胞量測術。

實例20.3 流動式細胞量測術及NGS定序

【0635】 編輯後第10天，T細胞藉由流動式細胞量測術表型分型以判定CD38受體表現。簡言之，在4℃下將T細胞與抗CD3 (BioLegend，目錄號317340)、CD4 (BioLegend，目錄號300537)、以1:200稀釋之CD8 (BioLegend，目錄號344706)及CD38 (BioLegend，目錄號303546)之抗體之混合物一起培育30分鐘，以1:100稀釋於細胞染色緩衝液(BioLegend，目錄號420201)中。隨後洗滌細胞且用以1:10,000稀釋於細胞染色緩衝液中之活力抗體DAPI (BioLegend，目錄號422801)染色。接著細胞在Cytoflex流式細胞儀(Beckman Coulter)上處理且使用FlowJo套裝軟體進行分析。T細胞基於大小、形狀、活力及CD38表現進行閘控。

【0636】 在第9天，對DNA樣本進行PCR及後續NGS分析，如實例1中所描述。**表54**展示用BC22n或Cas9編輯之細胞的CD38基因編輯及

CD38陽性結果。

表54 - 用Cas9或BC22n鹼基編輯器進行CD38編輯之後的編輯百分比及CD38陽性細胞之百分比

	Cas9 %插入/缺失			Cas9 %CD38+			BC22n %C形成T			BC22 %CD38+		
導引ID	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
G019761	94.82	0.97	2	22.35	0.49	2	87.21	1.57	2	56.45	2.05	2
G019762	98.19	0.63	2	15.45	1.06	2	85.04	0.42	2	58.55	0.07	2
G019763	91.42	1.77	2	8.17	2.38	2	87.01	0.51	2	2.53	0.21	2
G019764	87.78	1.04	2	11.80	0.71	2	87.00	2.33	2	41.40	2.12	2
G019765	96.43	0.40	2	13.15	2.33	2	81.51	5.02	2	60.40	1.27	2
G019766	97.61	0.06	2	5.31	1.15	2	80.51	2.67	2	61.80	0.85	2
G019767	97.54	0.08	2	17.45	0.21	2	81.92	0.46	2	62.55	3.46	2
G019768	96.65	0.96	2	2.19	1.06	2	89.45	0.78	2	2.49	1.18	2
G019769	95.63	2.44	2	2.58	0.35	2	69.93	5.38	2	14.40	4.81	2
G019770	97.74	1.26	2	1.15	0.59	2	85.06	5.81	2	38.80	3.54	2
G019771	96.90	0.54	2	1.18	0.18	2	87.34	0.16	2	1.39	0.26	2
G019772	96.38	0.05	2	14.50	1.98	2	88.86	0.71	2	70.25	1.63	2
G019773	95.38	2.21	2	6.70	0.57	2	79.83	0.15	2	64.15	4.45	2
G019774	97.12	0.07	2	14.55	0.92	2	71.14	2.52	2	68.60	2.83	2
G019775	95.33	3.04	2	16.75	1.63	2	92.02	0.11	2	74.90	0.28	2
G019776	98.87	0.45	2	1.95	1.04	2	84.25	0.57	2	11.45	1.63	2
G019777	97.87	0.54	2	14.00	1.27	2	86.76	1.32	2	71.75	2.62	2
G019778	95.81	1.24	2	13.75	1.48	2	86.96	1.81	2	62.30	2.26	2
G019779	97.78	0.26	2	10.87	2.17	2	88.77	0.53	2	74.35	0.07	2
G019780	95.75	1.84	2	14.00	2.55	2	89.81	0.30	2	69.05	3.18	2
G019781	93.81	2.35	2	15.90	0.85	2	86.84	4.62	2	68.30	0.71	2
G019782	93.10	4.65	2	10.21	2.82	2	82.19	1.92	2	63.15	0.49	2
G019783	97.88	0.30	2	2.58	0.40	2	77.26	4.30	2	64.10	0.14	2
G019784	97.61	0.86	2	16.80	2.69	2	76.82	0.81	2	69.00	0.71	2
G019785	98.30	0.27	2	1.58	0.66	2	80.95	1.14	2	33.90	5.80	2
G019786	86.22	3.34	2	28.10	4.67	2	88.42	2.78	2	72.35	5.02	2
G019787	98.76	0.45	2	2.06	0.86	2	80.23	2.14	2	1.89	0.83	2
G019788	96.34	1.98	2	11.05	0.92	2	90.88	0.06	2	1.88	0.21	2
G019789	97.68	1.33	2	15.80	1.27	2	67.12	n.a.	1	52.85	1.34	2
G019790	94.58	1.87	2	12.15	0.07	2	89.81	0.22	2	77.10	2.69	2
G019791	97.79	0.90	2	3.25	0.86	2	79.56	3.97	2	9.51	0.62	2
G019792	96.99	0.13	2	9.19	0.11	2	85.20	4.14	2	64.65	0.35	2
G019793	96.13	0.29	2	19.95	2.33	2	85.55	2.40	2	71.40	2.69	2
G019794	98.30	0.28	2	12.75	0.07	2	76.28	0.67	2	31.40	0.85	2
G019795	97.56	0.59	2	2.52	0.56	2	91.40	2.37	2	1.22	0.34	2
G019796	97.70	1.27	2	7.60	2.87	2	92.29	0.28	2	6.52	0.16	2
G019797	97.04	0.26	2	9.80	2.26	2	87.45	0.46	2	3.07	0.84	2
G019798	97.56	1.17	2	4.92	0.93	2	89.68	0.89	2	59.05	1.34	2
G019799	97.65	0.22	2	8.83	1.46	2	87.59	0.90	2	66.85	0.49	2
G019800	76.71	3.24	2	25.45	4.88	2	74.46	2.84	2	16.00	3.54	2

導引ID	Cas9 %插入/缺失			Cas9 %CD38+			BC22n %C形成T			BC22 %CD38+		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
G019801	92.76	3.74	2	6.10	2.28	2	82.69	0.52	2	33.65	4.03	2
G019802	64.21	7.62	2	33.70	5.52	2	69.14	0.45	2	73.00	0.42	2
G019803	50.46	6.67	2	43.50	5.23	2	45.01	1.82	2	55.40	1.98	2
G019804	89.70	3.71	2	7.05	3.23	2	21.88	0.42	2	67.25	2.76	2
G019805	52.39	2.21	2	40.30	0.14	2	78.69	4.52	2	9.15	1.77	2
G019806	93.47	0.40	2	4.64	0.82	2	72.68	1.54	2	21.30	4.95	2
G019807	86.45	2.17	2	12.70	1.84	2	63.32	3.90	2	65.85	0.21	2
G019808	97.15	0.70	2	2.23	1.37	2	32.87	6.70	2	64.10	1.84	2
G019809	41.04	6.38	2	56.35	4.31	2	68.30	3.73	2	27.50	5.94	2
G019810	46.14	4.29	2	52.05	5.16	2	78.63	2.98	2	10.40	2.97	2
G019811	95.15	0.67	2	14.05	1.06	2	83.21	2.11	2	4.42	2.68	2
G019812	93.95	1.06	2	4.46	2.11	2	84.23	5.13	2	24.90	2.55	2
G019813	96.79	1.07	2	2.51	0.60	2	75.68	3.13	2	5.51	1.97	2
G019814	87.26	0.64	2	11.56	2.75	2	72.31	1.65	2	13.80	2.83	2
G019815	77.53	7.29	2	18.65	3.89	2	86.69	0.87	2	8.47	0.74	2
G019816	76.89	1.37	2	38.25	6.86	2	87.17	2.00	2	8.82	2.94	2
G019817	90.53	1.09	2	5.95	1.39	2	72.59	1.92	2	33.85	1.34	2
G019818	97.71	0.21	2	1.69	0.57	2	77.99	3.46	2	14.15	3.75	2
G019819	94.33	1.87	2	3.70	2.29	2	84.14	3.95	2	2.47	0.45	2
G019820	82.74	4.09	2	21.00	3.39	2	81.28	0.66	2	14.80	2.12	2
G019821	70.98	8.64	2	26.80	8.49	2	73.39	3.46	2	11.09	3.27	2
G019822	46.59	2.28	2	50.80	5.09	2	58.43	2.69	2	73.55	0.21	2
G019823	93.48	2.48	2	4.04	1.94	2	79.65	0.80	2	24.45	6.01	2
G019824	95.90	0.76	2	6.32	1.92	2	89.11	1.03	2	74.75	3.18	2
G019825	29.68	7.06	2	56.10	0.57	2	39.49	6.14	2	66.20	3.54	2
G019826	92.62	1.03	2	3.74	1.05	2	69.37	5.37	2	61.70	0.42	2
G019827	39.32	4.26	2	54.80	2.55	2	48.52	0.86	2	38.15	1.20	2
G019828	87.90	3.26	2	9.98	1.16	2	80.25	0.57	2	7.40	2.33	2
G019829	31.95	2.81	2	63.40	1.98	2	76.10	2.57	2	14.50	2.69	2
G019830	81.01	6.21	2	16.45	3.32	2	83.57	1.78	2	4.29	1.12	2
G019831	98.29	0.30	2	0.91	0.25	2	71.43	0.65	2	2.05	0.84	2
G019832	62.85	1.73	2	34.70	3.54	2	90.87	2.45	2	71.05	6.01	2
G019833	92.66	0.94	2	4.28	0.82	2	75.96	0.45	2	18.40	2.26	2
G019834	94.43	0.37	2	2.75	0.76	2	76.23	0.91	2	69.00	2.83	2
G019835	42.83	n.a.	1	49.95	5.73	2	51.27	8.38	2	43.95	6.72	2
G019836	無資料			46.05	5.02	2	31.44	6.72	2	75.10	0.00	2
G019837	43.86	6.82	2	49.85	5.44	2	63.03	1.17	2	51.50	1.70	2
G019838	75.85	0.40	2	24.25	0.64	2	74.87	1.14	2	19.05	2.62	2
G019839	97.44	n.a..	1	1.82	0.21	2	69.11	4.60	2	40.55	2.05	2
G019840	59.58	4.30	2	37.90	0.85	2	47.06	4.04	2	73.05	1.06	2
G019841	96.14	n.a.	1	3.60	1.68	2	69.28	2.55	2	27.15	2.33	2
G019842	33.72	6.77	2	58.65	2.05	2	29.32	2.31	2	71.50	3.82	2
G019843	6.02	0.04	2	73.15	0.49	2	20.85	1.36	2	70.75	0.35	2
G019844	85.26	12.45	2	6.30	0.47	2	76.89	3.63	2	39.45	3.75	2
G019845	36.76	2.44	2	55.25	3.18	2	62.90	1.02	2	60.15	2.62	2
G019846	25.85	4.33	2	64.80	2.69	2	57.55	1.80	2	63.95	4.88	2

導引ID	Cas9 %插入/缺失			Cas9 %CD38+			BC22n %C形成T			BC22 %CD38+		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
G019847	58.00	5.06	2	37.85	2.19	2	71.58	0.74	2	42.55	5.16	2
G019848	47.39	6.18	2	46.90	5.09	2	71.78	4.09	2	67.15	3.32	2

無資料意謂樣本在所有複製品中均具有技術故障。N.A.在僅一個複製品為可用的且因此其不適用於計算標準差時使用。

實例21.用Nme2Cas9鹼基編輯器及HepG2細胞中經化學修飾之sgRNA進行鹼基編輯

【0637】用HepG2細胞中之各種導引設計測試包含融合至Nme2Cas9 D16A切口酶之APOBEC3A去胺酶結構域的鹼基編輯器構築體的鹼基轉化效率。

【0638】HepG2細胞組成性過度表現溶質載劑家族10成員1(SLC10A1) (HepG2-NTCP, Seeger等人Mol Ther Nucleic Acids. 2014 Dec; 3(12): e216)經解凍且再懸浮於補充有10%胎牛血清(FBS)之Dulbecco改良Eagle培養基(DMEM) (培養基Y)中，隨後離心。丟棄上澄液且將細胞再懸浮於培養基Y中，且以25,000個細胞/孔之密度將96孔膠原蛋白塗佈之板(Corning，目錄號354407)接種於100 uL培養基Y中。

【0639】Nme2Cas9鹼基編輯器mRNA基本上如實例1中所描述自編碼SEQ ID No: 304 (2XNLS N末端，1xC末端NLS Nme2Cas9鹼基編輯器)、SEQ ID No: 310 (2XNLS N末端，NLS Nme2Cas9鹼基編輯器)及SEQ ID No: 301 (1X C末端NLS Nme2Cas9鹼基編輯器)之質體藉由活體外轉錄製備。使用相同方法自質體轉錄SpyCas9 mRNA及尿嘧啶醣苷酶抑制劑(UGI) mRNA (SEQ ID No: 34)。

【0640】使用常規方法合成具有不同PAM序列(G020927、G020928)或VEGF(G020073)之靶向NTCP之經化學修飾的NmeCas9

sgRNA及靶向NTCP之SpyCas9 sgRNA (G020929)。

【0641】 靶向NTCP之經測試NmeCas9 sgRNA包括24個核苷酸導引序列（如由N表示）及如下之導引骨架：mN*mNNNNNNNNmNNNmNNNNNNNNNNNNNNmGUUGmUmAmGmCUCCCmUmGmAmAmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmCmGmAmAmAmGmAmUGUGCmCGCmAmAmCmGCUCUmGmCCmUmUmCmUGmGCmAmUC*mG*mU*mU (SEQ ID NO: 522)，除非另外指示，否則其中A、C、G、U及N分別為腺嘌呤、胞嘧啶、鳥嘌呤、尿嘧啶及任何核糖核苷酸。m指示2'O-甲基修飾，且*指示核苷酸之間的硫代磷酸酯鍵。導引物之未經修飾及經修飾之版本提供於表5C中。將導引RNA、編輯器mRNA及UGI mRNA以1:1:1重量比與含有分別為50:38:9:3莫耳比之脂質A、膽固醇、DSPC及PEG2k-DMG之預混合轉染試劑混合。試劑以約6.0之脂質胺與RNA磷酸(N:P)莫耳比組合。RNA-脂質混合物與10% FBS培養基近似1:1混合且培育10分鐘。培育後，自400 ng總編輯器RNA/孔開始，以8點、2倍連續稀釋用RNA-脂質混合物處理細胞。

【0642】 處理後72小時，溶解細胞以進行NGS分析，如實例1中所提供。

【0643】 編輯效率對導引濃度之劑量反應一式三份進行。**表55**展示所計算之平均編輯百分比在每一導引濃度下及經計算之EC50值。VEGFA中之目標位點由於高GC含量而易於形成插入/缺失。所有編輯器mRNA達成相同的最大C形成T編輯。EC50存在輕微差異，其中SEQ ID No: 310 mRNA勝過SEQ ID No: 304及SEQ ID No: 301。

表55.VEGFA基因座(G020073)及Nme2Cas9鹼基編輯器處HepG2-NTCP

細胞中之平均編輯百分比

mRNA	Nme-鹼基編輯器(ng)	C形成T %				C形成A/G %			插入/缺失%		
		平均	SD	n	EC50	平均	SD	n	平均	SD	n
SEQ ID No: 304	0	0.20	0.14	2	6.86	0.80	0.00	2	0.70	0.14	2
	6.25	36.05	1.63	2		2.30	0.28	2	14.25	0.21	2
	12.5	49.70	1.13	2		2.95	0.49	2	16.35	1.06	2
	25	57.60	0.42	2		2.75	0.07	2	17.45	0.21	2
	50	67.15	1.34	2		2.65	0.07	2	17.90	0.14	2
	100	70.50	0.99	2		2.65	0.07	2	18.80	0.28	2
	200	72.75	0.49	2		2.90	0.57	2	18.75	0.49	2
	400	72.00	0.14	2		3.10	0.14	2	20.40	0.99	2
SEQ ID No: 310	0	0.50	0.00	1	3.86	1.00	0.00	1	0.60	0.00	1
	6.25	49.60	3.25	2		2.10	0.14	2	14.05	0.21	2
	12.5	57.05	0.78	2		2.50	0.42	2	16.50	0.14	2
	25	66.95	0.49	2		2.40	0.00	2	16.25	0.21	2
	50	71.45	0.35	2		2.40	0.00	2	17.25	0.07	2
	100	71.60	0.85	2		2.55	0.35	2	17.90	0.14	2
	200	73.70	0.28	2		2.65	0.07	2	19.00	0.28	2
	400	73.80	0.14	2		3.05	0.35	2	18.70	0.42	2
SEQ ID No: 301	0	0.55	0.49	2	4.84	1.05	0.21	2	0.55	0.07	2
	6.25	45.55	0.21	2		2.60	0.28	2	17.15	0.64	2
	12.5	56.40	1.84	2		2.80	0.00	2	19.40	0.14	2
	25	64.95	1.06	2		3.15	0.35	2	19.40	1.70	2
	50	70.70	0.28	2		3.25	0.21	2	20.00	0.71	2
	100	72.20	2.83	2		2.75	0.21	2	19.80	1.56	2
	200	70.90	0.99	2		3.15	0.35	2	19.70	0.85	2
	400	71.80	0.14	2		3.45	0.21	2	20.95	0.35	2

實例22.用PMH中經化學修飾之sgRNA進行鹼基編輯

【0644】 用原代小鼠肝細胞(PMH)中之各種導引設計測試包含融合至Nme2Cas9切口酶之APOBEC3A去胺酶結構域的鹼基編輯器構築體的鹼基轉化效率。

【0645】 PMH (In Vitro ADMET Laboratories, cat# MC148)經解凍且再懸浮於50 mL經冷凍保存之Hepatocyte Recovery Media (CHRM) (Invitrogen, CM7000)中，隨後離心。細胞藉由接種補充劑再懸浮於肝細胞培養基中：具有FBS含量之Williams' E Medium Plating Supplements (Gibco，目錄號A13450)。細胞藉由離心成球粒，再懸浮於培養基中，且

以20,000個細胞/孔之密度接種於經Bio-coat膠原蛋白I塗佈之96孔板(Corning # 354407)上。使接種之細胞在37℃及5% CO2氛圍下在組織培養恆溫箱中靜置且黏附4-6小時。在培育之後，檢查細胞之單層形成且洗滌一次，且用100 uL肝細胞維持培養基接種：Williams' E Medium (Gibco，目錄號A12176-01)外加補充劑包(Gibco，目錄號CM3000)。

【0646】 Nme2Cas9鹼基編輯器mRNA、SEQ ID No: 304、SEQ ID No: 310及SEQ ID No: 301；及尿嘧啶醣苷酶抑制劑(UGI) mRNA (SEQ ID No: 34)如實例1中所描述來製備且與靶向小鼠TTR之一系列經化學修飾之sgRNA成對且以128 ng鹼基編輯器mRNA之單次劑量篩選。處理後72小時，溶解細胞以進行NGS分析，如實例1中所提供。代表性導引物之平均編輯(編輯類型之比)展示於表56中。

表56 - 使用靶向TTR基因座之經修飾gRNA及Nme2Cas9鹼基編輯器之PMH細胞中之平均編輯百分比。當報導僅1個複製品時，「n/a」意謂SD不適用。

mRNA	導引物	C形成T %			C形成A/G %			插入/缺失%		
		平均	SD	N	平均	SD	N	平均	SD	N
SEQ ID No: 304	G021237	69.00	5.94	2	3.65	1.63	2	9.00	3.39	2
	G021249	47.15	2.33	2	1.20	0.14	2	1.45	1.34	2
	G021321	7.25	0.92	2	0.25	0.21	2	91.25	0.92	2
SEQ ID No: 310	G021237	76.75	1.34	2	4.35	1.48	2	7.95	1.34	2
	G021249	54.05	4.17	2	1.20	0.28	2	1.60	0.42	2
	G021321	0.50	n/a	1	0.10	n/a	1	99.00	n/a	1
SEQ ID No: 301	G021237	73.55	5.44	2	5.15	2.47	2	12.50	1.70	2
	G021249	53.30	5.52	2	1.05	0.21	2	2.15	1.63	2
	G021321	7.05	1.20	2	0.55	0.21	2	90.40	2.97	2

實例23.用gRNA進行活體內鹼基編輯

【0647】 在小鼠模型中用Nme2Cas9鹼基編輯器構築體測試具有不同mRNA之經修飾之gRNA的編輯效率。

【0648】 LNP一般如同實例1用單一RNA物種作為負荷製備。用分

別為50:38:9:3莫耳比之脂質A、膽固醇、DSPC及PEG2k-DMG製備所使用LNP。用約6之脂質胺與RNA磷酸酯(N:P)莫耳比來調配LNP。LNP如實例1中所描述調配，不同之處在於每一組分、導引RNA或mRNA個別地調配於LNP中，且LNP在投與之前混合，如表57中所描述。對於Nme2Cas9及Nme2Cas9鹼基編輯器樣本，LNP以按gRNA與編輯器mRNA負荷之重量計2:1之比率混合。對於SpyCas9鹼基編輯器樣本，LNP以按gRNA與編輯器mRNA負荷之重量計1:2之比率混合。如表57及圖38中所指示之劑量基於gRNA與編輯器mRNA之組合RNA重量計算。用額外0.03 mpk UGI mRNA處理鹼基編輯器樣本。用於LNP製備之運輸及儲存溶液(TSS)在實驗中作為僅媒劑陰性對照給藥。

【0649】 包括連接子之測試NmeCas9 gRNA (G021844)具有$(N)_{24}$之以下修飾模式：GUUGmUmAmGmCUCCCmUmUmC(L1)mGmAmCmCGUUmGmCUAmCAAU*AAGmGmCCmGmUmC(L1)mGmAmUGUGCmCGmCAAmCGCUCUmGmCC(L1)GGCAUCG*mU*mU (SEQ ID NO: 519)，除非另外指示，否則其中A、C、G、U及N分別為腺嘌呤、胞嘧啶、鳥嘌呤、尿嘧啶及任何核糖核苷酸。m指示2'O-甲基修飾，且*指示核苷酸之間的硫代磷酸酯鍵。導引物之未經修飾及經修飾版本提供於表5C (序列表)中。

【0650】 將6至10週齡範圍內之CD-1雌性小鼠用於涉及小鼠之每一研究中(除了TSS對照n = 4之外，n = 5/組)。根據表57中所列出之劑量，經由尾部靜脈注射靜脈內投與調配物。在給藥後至少24小時，定期觀測動物之不良反應。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集肝臟組織用於下游分析。收集重量在5與15 mg之間的肝臟穿孔

以分離基因體DNA及總RNA。使用DNA分離套組(ZymoResearch, D3010)提取基因體DNA且用NGS定序分析樣本，如實例1中所描述。含有所指示gRNA之LNP之編輯效率展示於表57中且說明於圖38中。

表57 - 小鼠肝臟中之平均編輯百分比。

樣本	劑量 (mg/kg)	C形成T %			C形成A/G %			插入/缺失%		
		平均	SD	n	平均	SD	n	平均	SD	n
TSS	0	0.00	0.00	4	0.10	0.00	4	0.08	0.05	4
SEQ ID NO: 340+ G021844 (Nme2Cas9 +pgRNA)	0.03	0.00	0.00	5	0.08	0.04	5	40.88	14.16	5
	0.1	0.00	0.00	5	0.02	0.04	5	66.02	5.01	5
SEQ ID No: 310 + SEQ ID No: 34 + G021844 (Nme2Cas9鹼基編輯器+ UGI + pgRNA)	0.03	25.60	5.28	5	3.50	0.76	5	11.14	2.18	5
	0.1	46.34	1.53	5	5.74	0.33	5	13.52	0.90	5
SEQ ID No: 1 + SEQ ID No: 34 + G000502 (SpyBC22n + UGI + sgRNA)	0.03	9.28	2.82	5	0.94	0.54	5	7.34	1.61	5
	0.1	30.72	8.51	5	2.86	0.23	5	15.60	2.58	5

實例24.C形成**T**去胺酶鹼基編輯篩選

【0651】根據C形成T轉化活性之效率評估候選去胺酶-Cas9融合構築體。將所有實驗去胺酶C形成T轉化活性與編碼BE3之構築體BC27對照比較(Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016;533(7603):420-424)。總計，如表58中所提及之56種去胺酶-Cas9融合構築體各自在單一實驗中針對sg005883一式三份地評估。設計構築體且進行如實例1A中所描述之方法。

表59及圖39展示所有測試之鹼基編輯器構築體中含有至少1個胞嘧啶至胸苷轉化之全部讀數之百分比。

表58 - 在鹼基編輯器活性篩選中測試之去胺酶

鹼基編輯器構築體ID	去胺酶結構域之UniProt	去胺酶基因名稱	去胺酶物種	胺基酸序列(SEQ ID NO)
BC01	A0A0N4SVL6	Apobec1	小家鼠(*M. musculus*)	960
BC02	A0A0N4SW85	Apobec1	小家鼠	961
BC03	A0QT11	cdd	包皮垢分枝桿菌(*M. smegmatis*)	962
BC04	Q3JJN0	cdd	假性鼻疽菌(*B. pseudomallei*)	963
BC05	B2HDU6	cdd	海棲分枝桿菌(*M. marinum*)	964
BC06	Q81LT6	cdd2	炭疽芽孢桿菌(*B. anthracis*)	965
BC07	P9WPH3	cdd	結核分枝桿菌(*M. tuberculosis*)	966
BC08	A0A0H3MRL9	cdd	麻瘋分枝桿菌(*M. leprae*)	967
BC09	P19079	cdd	枯草芽孢桿菌(*B. subtilis*)	968
BC10	Q06549	CDD1	釀酒酵母	969
BC11	Q81Y61	GBAA	炭疽芽孢桿菌	970
BC12	P56389	Cda Cdd	小家鼠	971
BC13	P32320	CDA	智人	972
BC14	Q12178	FCY1	釀酒酵母	973
BC15	Q22922	cdd	秀麗隱桿線蟲(*C. elegans*)	974
BC16	Q20628	cdd	秀麗隱桿線蟲	975
BC17	Q9NRW3	APOBEC3C	智人	976
BC18	A0A087WX48	Apobec3DE	智人	977
BC19	Q82Y41	NE0047	亞硝酸單胞菌(*N. europaea*)	978
BC20	Q9GZX7	AICDA AID	智人	979
BC21	Q9WVE0	Aicda Aid	小家鼠	980
BC22	P31941	APOBEC3A	智人	40
BC23	Q6NTF7	APOBEC3H	智人	981
BC24	Q9Y235	APOBEC2	智人	982
BC25	Q9WV35	Apobec2	小家鼠	983
BC26	P51908	Apobec1	小家鼠	984
BC27	P38483	Apobec1	褐家鼠	41
BC28	Q9TUI7	APOBEC1	家蠅(*M. domestica*)	985
BC29	P41238	APOBEC1	智人	986
BC30	P47855	APOBEC1	穴兔(*O. cuniculus*)	987
BC31	Q8TWU6	MK0935	甲烷嗜熱菌(*M.*	988

鹼基編輯器構築體ID	去胺酶結構域之UniProt	去胺酶基因名稱	去胺酶物種	胺基酸序列(SEQ ID NO)
			kandleri)	
BC32	P0ABF6	cdd	大腸桿菌	989
BC33	Q9KSM5	cdd	霍亂弧菌(*V. cholera*)	990
BC34	Q3TI69	Apobec3	小家鼠	991
BC35	O65896	CDA1	殘青葉蜂屬(*A.thalia*)	992
BC36	Q7YR23	APOBEC3G	恆河猴(*M. mulatta*)	993
BC37	Q8IUX4	APOBEC3F	智人	994
BC38	Q7YR25	APOBEC3G	草原猴(*C. aethiops*)	995
BC39	Q9UH17	APOBEC3B	智人	996
BC40	M1GSK9	APOBEC3G	恆河猴	997
BC41	Q9HC16	APOBEC3G	智人	998
BC42	Q7YR24	APOBEC3G	黑猩猩(*P. troglodytes*)	999
BC43	Q96AK3	APOBEC3D	智人	1000
BC44	H3BJQ3	Apobec3	小家鼠	1001
BC45	H3BKE5	Apobec3	小家鼠	1002
BC46	E9QMH1	Apobec3	小家鼠	1003
BC47	Q99J72	Apobec3	小家鼠	1004
BC48	H3BJ44	Apobec3	小家鼠	1005
BC49	H3BJL0	Apobec3	小家鼠	1006
BC50	G3UW39	Cdadc1	小家鼠	1007
BC51	P25524	codA	大腸桿菌	1008
BC52	Q19Q52	APOBEC3H	恆河猴	1009
BC53	Q97MB6	CA_C0282	丙酮丁醇桿菌(*C.acetobutylicum*)	1010
BC54	A0A0E1CHI1	KPNJ1	肺炎克雷伯氏菌(*K. pneumoniae*)	1011
BC55	P46087	NOP2	智人	1012
BC56	Q08J23	NSUN2	智人	1013

表59對於sg005883含有至少1種胞嘧啶至胸苷轉化之總讀數之百分比。

(n=3)

構築體	平均	SD	構築體	平均	SD	構築體	平均	SD
1XNLS Cas9	0.0	0.1	BC18	6.0	1.0	BC38	26.8	1.5
3XNLS Cas9	0.0	0.0	BC19	2.3	0.3	BC39	50.0	7.4
BC01	1.5	0.3	BC20	17.9	3.5	BC40	31.9	3.3
BC02	1.3	0.6	BC21	27.8	5.3	BC41	35.0	9.1
BC03	1.4	0.5	BC22	46.0	7.7	BC42	49.0	6.9
BC04	1.2	0.5	BC23	2.5	0.7	BC43	9.8	2.3
BC05	1.9	0.2	BC24	1.7	0.2	BC44	12.8	4.8

構築體	平均	SD	構築體	平均	SD	構築體	平均	SD
BC06	1.0	0.4	BC25	1.5	0.5	BC45	22.7	5.2
BC07	1.7	0.3	BC26	42.1	1.5	BC46	14.6	6.0
BC08	1.8	0.3	BC27	40.8	5.2	BC47	14.8	4.6
BC09	1.8	0.5	BC28	42.9	5.0	BC48	31.5	4.2
BC10	2.2	0.8	BC29	20.3	1.0	BC49	13.0	4.3
BC11	1.8	0.4	BC30	23.7	5.2	BC50	1.7	0.3
BC12	2.0	0.5	BC31	1.9	0.2	BC51	1.1	0.2
BC13	1.0	0.2	BC32	1.9	0.4	BC52	8.0	0.5
BC14	2.1	0.6	BC33	2.2	0.6	BC53	1.1	0.2
BC15	0.9	0.2	BC34	2.5	0.7	BC54	1.7	0.5
BC16	1.6	0.3	BC35	1.4	0.5	BC55	2.5	0.9
BC17	10.7	1.5	BC36	53.2	5.1	BC56	1.7	0.6
BC18	6.0	1.0	BC37	14.7	3.2	GFP	0.2	0.1

實例25.當在U-2OS細胞中由質體表現時，藉由具有各種連接子之構築體進行鹼基編輯

【0652】將表60中所列出之涵蓋各種長度及可撓性之一組六十八個胺基酸連接子編碼於如實例1A中所提及之表現質體BC27之N末端胞嘧啶去胺酶與C末端Cas9切口酶之間的區中。表58中所描述之所選鹼基編輯器構築體藉由用來自**表60**之連接子取代胞嘧啶去胺酶結構域與Spy Cas9切口酶結構域之間的XTEN連接子而重新設計。使用具有目標序列UCCCUGGCUGAGGAUCCCCA (SEQ ID NO: 157)之sg001373進行BC27連接子篩選。使用具有目標序列CCCCCCGCCGUGUUUGUGGG (SEQ ID NO: 159)之sg005883進行另一10個去胺酶結構域連接子篩選。

表60.在連接子活性篩選中測試之六十八個胺基酸連接子。

連接子ID	**連接子胺基酸序列**
L001 (XTEN對照)	SGSETPGTSESATPES (SEQ ID NO: 46)
L002	GGS (SEQ ID NO: 211)
L003	GGGGS (SEQ ID NO: 212)
L004	EAAAK (SEQ ID NO: 213)
L005	SEGSA (SEQ ID NO: 214)
L006	SEGSAGTST (SEQ ID NO: 215)
L007	GGGGSGGGGS (SEQ ID NO: 216)
L008	GGGGSEAAAK (SEQ ID NO: 217)

連接子 ID	連接子胺基酸序列
L009	EAAAKGGGGS (SEQ ID NO: 218)
L010	EAAAKEAAAK (SEQ ID NO: 219)
L011	SEGSAGTSTESEGSA (SEQ ID NO: 220)
L012	GGGGSGGGGSGGGGS(SEQ ID NO: 221)
L013	GGGGSGGGGSEAAAK(SEQ ID NO: 222)
L014	GGGGSEAAAKGGGGS(SEQ ID NO: 223)
L015	GGGGSEAAAKEAAAK(SEQ ID NO: 49)
L016	EAAAKGGGGSGGGGS(SEQ ID NO: 50)
L017	EAAAKGGGGSEAAAK(SEQ ID NO: 224)
L018	EAAAKEAAAKGGGGS(SEQ ID NO: 225)
L019	EAAAKEAAAKEAAAK (SEQ ID NO: 51)
L020	SEGSAGTSTESEGSAGTSTE (SEQ ID NO: 226)
L021	GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 52)
L022	GGGGSGGGGSGGGGSEAAAK (SEQ ID NO: 227)
L023	GGGGSGGGGSEAAAKGGGGS (SEQ ID NO: 228)
L024	GGGGSGGGGSEAAAKEAAAK (SEQ ID NO: 53)
L025	GGGGSEAAAKGGGGSGGGGS (SEQ ID NO: 54)
L026	GGGGSEAAAKGGGGSEAAAK (SEQ ID NO: 229)
L027	GGGGSEAAAKEAAAKGGGGS (SEQ ID NO: 230)
L028	GGGGSEAAAKEAAAKEAAAK (SEQ ID NO: 231)
L029	EAAAKGGGGSGGGGSGGGGS (SEQ ID NO: 232)
L030	EAAAKGGGGSGGGGSEAAAK (SEQ ID NO: 233)
L031	EAAAKGGGGSEAAAKGGGGS (SEQ ID NO: 234)
L032	EAAAKGGGGSEAAAKEAAAK (SEQ ID NO: 235)
L033	EAAAKEAAAKGGGGSGGGGS (SEQ ID NO: 236)
L034	EAAAKEAAAKGGGGSEAAAK (SEQ ID NO: 237)
L035	EAAAKEAAAKEAAAKGGGGS (SEQ ID NO: 238)
L036	EAAAKEAAAKEAAAKEAAAK (SEQ ID NO: 56)
L037	SEGSAGTSTESEGSAGTSTESEGSA (SEQ ID NO: 239)
L038	GGGGSGGGGSGGGGSGGGGSGGGGS(SEQ ID NO: 240)
L039	GGGGSGGGGSGGGGSGGGGSEAAAK (SEQ ID NO: 241)
L040	GGGGSGGGGSGGGGSEAAAKGGGGS (SEQ ID NO: 242)
L041	GGGGSGGGGSGGGGSEAAAKEAAAK (SEQ ID NO: 243)
L042	GGGGSGGGGSEAAAKGGGGSGGGGS (SEQ ID NO: 244)
L043	GGGGSGGGGSEAAAKGGGGSEAAAK (SEQ ID NO: 245)
L044	GGGGSGGGGSEAAAKEAAAKGGGGS (SEQ ID NO: 246)
L045	GGGGSGGGGSEAAAKEAAAKEAAAK (SEQ ID NO: 247)
L046	GGGGSEAAAKGGGGSGGGGSGGGGS (SEQ ID NO: 248)
L047	GGGGSEAAAKGGGGSGGGGSEAAAK (SEQ ID NO: 249)
L048	GGGGSEAAAKGGGGSEAAAKGGGGS (SEQ ID NO: 250)
L049	GGGGSEAAAKGGGGSEAAAKEAAAK (SEQ ID NO: 251)
L050	GGGGSEAAAKEAAAKGGGGSGGGGS (SEQ ID NO: 252)
L051	GGGGSEAAAKEAAAKGGGGSEAAAK (SEQ ID NO: 57)
L052	GGGGSEAAAKEAAAKEAAAKGGGGS (SEQ ID NO: 253)
L053	GGGGSEAAAKEAAAKEAAAKEAAAK (SEQ ID NO: 254)
L054	EAAAKGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 255)

連接子ID	連接子胺基酸序列
L055	EAAAKGGGGSGGGGSGGGGSEAAAK (SEQ ID NO: 256)
L056	EAAAKGGGGSGGGGSEAAAKGGGGS (SEQ ID NO: 257)
L057	EAAAKGGGGSGGGGSEAAAKEAAAK (SEQ ID NO: 258)
L058	EAAAKGGGGSEAAAKGGGGSGGGGS (SEQ ID NO: 259)
L059	EAAAKGGGGSEAAAKGGGGSEAAAK (SEQ ID NO: 260)
L060	EAAAKGGGGSEAAAKEAAAKGGGGS (SEQ ID NO: 261)
L061	EAAAKGGGGSEAAAKEAAAKEAAAK (SEQ ID NO: 262)
L062	EAAAKEAAAKGGGGSGGGGSGGGGS (SEQ ID NO: 58)
L063	EAAAKEAAAKGGGGSGGGGSEAAAK (SEQ ID NO: 59)
L064	EAAAKEAAAKGGGGSEAAAKGGGGS (SEQ ID NO: 263)
L065	EAAAKEAAAKGGGGSEAAAKEAAAK (SEQ ID NO: 264)
L066	EAAAKEAAAKEAAAKGGGGSGGGGS (SEQ ID NO: 55)
L067	EAAAKEAAAKEAAAKGGGGSEAAAK (SEQ ID NO: 265)
L068	EAAAKEAAAKEAAAKEAAAKGGGGS (SEQ ID NO: 266)
L069	EAAAKEAAAKEAAAKEAAAKEAAAK (SEQ ID NO: 267)

【0653】 使用pUC19主鏈(GenBank®登錄號U47119)之質體A表現來自U6啟動子之化膿性鏈球菌單導引RNA (sgRNA)。稱為pCI之質體B表現來自CMV啟動子之鹼基編輯器構築體，其由藉由實驗連接子融合至化膿性鏈球菌-D10A-Cas9之候選去胺酶構成，該實驗連接子隨後融合至UGI之一個複本及SV40 NLS之一個複本。使用Mirus TransIT-X2®，用質體A及質體B各100 ng對在96孔板中在補充有10%胎牛血清(FBS)之Dulbecco改良Eagle培養基(DMEM)中生長之U-2OS細胞進行轉染。在初始轉染之後24小時添加100 uL新鮮培養基。在額外48小時之後，移除培養基且用QuickExtract™ DNA提取溶液(Lucigen，目錄號QE09050)溶解細胞。表61A及61B列出所有測試之去胺酶結構域中含有至少1種胞嘧啶至胸苷轉化之全部讀數之百分比且代表性資料展示於圖40A至圖40K中。

表61A.含有至少1種胞嘧啶至胸苷轉化之總讀數之百分比(% C形成T)

連接子	BC18			BC22			BC27			BC28			BC29			BC30		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L001 (XTEN 對照)	2.07	0.90	3	50.50	2.36	3	13.47	2.42	3	43.15	8.56	2	9.70	3.97	3	12.50	2.94	3
L002	0.53	0.19	3	57.43	9.03	3	5.70	1.31	3	19.30	0.42	2	5.03	2.14	3	7.25	1.10	3
L003	1.10	0.57	3	54.37	12.74	3	6.87	2.15	3	6.80	2.12	2	4.20	1.51	3	3.30	0.87	3
L004	0.40	0.08	3	30.97	0.65	3	6.07	0.64	3	34.65	9.40	2	3.93	1.43	3	11.55	1.18	3
L005	0.93	0.54	3	29.30	2.41	3	8.07	1.10	3	17.50	3.25	2	3.60	1.47	3	10.45	2.14	3
L006	1.50	0.96	3	57.70	6.70	3	8.03	3.06	3	28.20	9.90	2	9.10	1.74	3	4.20	1.73	3
L007	1.00	0.54	3	57.10	4.87	3	5.40	1.40	3	23.50	0.42	2	7.23	2.31	3	11.05	2.36	3
L008	1.87	1.04	3	46.07	0.74	3	6.23	1.86	3	22.85	6.01	2	11.00	2.42	3	9.55	1.34	3
L009	1.50	1.20	3	58.83	5.76	3	12.73	1.93	3	22.95	7.71	2	5.87	1.27	3	2.45	0.95	3
L010	0.70	0.41	3	60.83	6.66	3	10.03	1.63	3	22.60	10.18	2	5.97	1.80	3	5.00	1.47	3
L011	1.23	0.78	3	53.87	1.56	3	10.70	2.61	3	40.70	3.82	2	12.37	4.82	3	3.15	0.85	3
L012	0.73	0.25	3	49.30	4.60	3	7.97	0.84	3	41.85	1.34	2	6.87	2.48	3	7.45	1.75	3
L013	1.53	1.11	3	53.50	4.95	3	8.40	1.85	3	32.70	9.62	2	13.63	7.80	3	2.95	0.45	3
L014	1.60	1.06	3	61.13	2.70	3	6.83	1.99	3	35.85	6.72	2	10.80	2.43	3	7.65	1.18	3
L015	0.60	0.28	3	57.80	3.47	3	6.23	1.17	3	37.30	1.27	2	14.40	1.82	3	6.70	2.08	3
L016	2.03	1.30	3	59.23	4.37	3	9.97	0.81	3	30.95	7.14	2	4.00	1.15	3	7.85	1.97	3
L017	1.23	0.49	3	52.60	3.40	3	9.83	0.59	3	37.15	1.77	2	15.23	1.79	3	8.75	2.68	3
L018	2.77	1.58	3	53.93	3.61	3	4.90	0.82	3	32.65	2.62	2	12.70	5.78	3	11.80	2.86	3
L019	0.73	0.05	3	58.03	2.42	3	9.33	1.61	3	36.35	6.72	2	13.93	5.31	3	15.65	1.59	3
L020	2.23	1.41	3	56.40	3.21	3	10.33	0.25	3	26.95	11.10	2	14.77	1.90	3	8.80	1.78	3
L021	0.83	0.09	3	54.17	10.11	3	8.50	2.01	3	25.45	8.13	2	9.10	1.15	3	7.95	2.65	3
L022	1.80	0.78	3	53.87	4.14	3	6.43	4.02	3	22.20	8.91	2	10.43	2.23	3	7.85	1.60	3
L023	1.50	1.07	3	42.73	5.58	3	6.27	1.36	3	33.75	1.63	2	13.00	4.80	3	3.45	1.42	3
L024	3.07	1.52	3	57.00	2.35	3	9.83	3.35	3	38.30	2.26	2	14.60	1.99	3	7.10	2.48	3
L025	2.03	1.24	3	54.70	1.92	3	4.90	0.82	3	39.45	0.21	2	2.87	1.70	3	3.75	1.70	3

連接子	BC18			BC22			BC27			BC28			BC29			BC30		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L026	1.00	0.83	3	51.07	2.79	3	5.67	2.28	3	32.95	2.19	2	8.07	4.16	3	3.35	0.32	3
L027	2.00	1.44	3	58.23	5.15	3	9.07	0.31	3	37.80	4.81	2	6.53	4.43	3	6.80	0.74	3
L028	2.60	1.70	3	24.20	5.10	3	7.90	1.41	3	19.25	4.60	2	11.53	0.90	3	2.30	1.31	3
L029	1.93	0.95	3	59.35	3.82	3	8.57	0.80	3	18.90	1.41	2	12.47	2.51	3	9.15	1.84	3
L030	2.67	0.39	3	52.50	6.90	3	8.77	1.15	3	35.30	0.57	2	18.23	2.30	3	9.80	1.50	3
L031	0.67	0.29	3	56.57	2.35	3	10.47	0.59	3	23.65	0.64	2	8.03	1.91	3	3.40	1.25	3
L032	1.40	0.78	3	27.07	6.12	3	8.90	1.22	3	15.75	2.90	2	19.57	3.56	3	10.80	1.88	3
L033	0.63	0.26	3	57.75	4.76	3	8.93	2.55	3	13.15	5.87	2	12.40	5.44	3	3.55	1.23	3
L034	0.23	0.12	3	50.70	6.94	3	11.70	4.20	3	22.45	3.46	2	0.80	0.26	3	6.50	1.22	3
L035	2.00	1.13	3	55.00	4.45	3	8.80	3.99	3	44.80	7.21	2	10.77	8.43	3	10.60	-	1
L036	2.17	0.50	3	51.90	9.44	3	11.47	2.01	3	27.75	25.95	2	12.60	4.39	3	11.50	0.10	3
L037	1.17	0.45	3	53.30	2.92	3	10.23	1.65	3	34.70	8.06	2	9.20	4.12	3	7.90	0.83	3
L038	0.83	0.54	3	23.97	2.82	3	8.23	1.38	3	37.30	2.26	2	6.80	2.01	3	1.50	0.23	3
L039	1.07	0.69	3	58.70	6.50	3	10.67	2.49	3	15.40	0.99	2	11.40	3.21	3	6.35	0.71	3
L040	1.80	1.14	3	54.37	3.81	3	7.20	1.83	3	13.35	1.63	2	4.50	3.22	3	4.95	2.54	3
L041	0.33	0.21	3	47.27	9.92	3	11.57	3.50	3	33.15	2.19	2	15.67	1.39	3	10.70	0.10	3
L042	0.60	0.08	3	43.97	2.45	3	7.60	0.95	3	19.60	8.91	2	6.83	3.21	3	11.00	1.99	3
L043	1.17	0.42	3	45.07	1.69	3	2.93	0.81	3	31.55	8.56	2	11.37	8.06	3	6.95	2.52	3
L044	1.00	0.64	3	66.35	4.26	3	8.00	0.52	3	25.95	9.12	2	10.37	2.06	3	2.60	0.42	3
L045	0.73	0.45	3	64.20	3.24	3	10.27	2.05	3	34.60	6.22	2	12.30	2.90	3	5.95	1.36	3
L046	1.77	1.11	3	47.70	11.53	3	6.70	1.97	3	20.05	2.33	2	8.60	4.10	3	6.40	0.78	3
L047	2.00	0.57	3	45.37	12.50	3	9.43	1.02	3	40.15	4.60	2	11.33	7.96	3	1.65	0.75	3
L048	0.67	0.41	3	50.53	11.07	3	6.37	1.37	3	42.25	3.32	2	13.30	6.26	3	2.70	0.45	3
L049	1.47	0.50	3	22.23	0.48	3	6.57	0.95	3	18.05	1.91	2	14.97	4.96	3	5.35	0.98	3
L050	1.47	1.07	3	43.87	5.89	3	4.80	0.40	3	22.65	10.68	2	13.23	2.67	3	4.10	0.70	3
L051	1.20	0.59	3	57.13	3.24	3	7.53	2.51	3	30.80	8.63	2	10.97	8.58	3	8.85	2.08	3
L052	2.00	1.28	3	49.30	1.31	3	10.80	3.12	3	43.40	0.14	2	11.27	1.78	3	3.95	2.18	3
L053	2.00	1.35	3	42.30	3.48	3	9.27	1.05	3	37.05	6.86	2	10.13	6.62	3	13.80	1.23	3
L054	1.60	0.99	3	56.00	1.80	3	6.23	3.70	3	32.10	7.07	2	12.03	6.46	3	7.05	1.00	3

連接子	BC18			BC22			BC27			BC28			BC29			BC30		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L055	0.50	0.22	3	55.37	1.92	3	4.43	0.78	3	14.85	5.59	2	12.77	6.56	3	6.80	2.86	3
L056	2.47	1.40	3	56.43	2.27	3	8.67	5.59	3	29.00	5.37	2	3.30	1.73	3	6.20	0.99	3
L057	3.17	0.97	3	53.63	6.42	3	9.57	2.49	3	27.65	6.86	2	15.07	8.36	3	3.00	0.50	3
L058	1.03	0.42	3	52.20	9.24	3	4.67	0.76	3	23.05	5.59	2	9.90	2.18	3	1.15	1.27	3
L059	1.47	0.52	3	41.27	17.48	3	11.10	3.01	3	44.20	4.67	2	8.80	4.41	3	5.95	1.59	3
L060	2.03	1.25	3	42.53	1.09	3	8.33	0.55	3	26.80	6.08	2	13.00	6.80	3	1.60	0.92	3
L061	1.53	0.87	3	33.53	4.62	3	11.10	1.65	3	34.35	9.83	2	15.10	11.23	3	3.20	0.12	3
L062	2.33	0.94	3	56.47	5.91	3	12.63	5.36	3	42.20	8.20	2	13.10	7.41	3	9.00	1.93	3
L063	2.17	1.25	3	60.77	3.09	3	11.03	0.91	3	32.20	8.34	2	8.77	4.32	3	9.00	1.45	3
L064	1.97	1.14	3	55.70	10.99	3	10.40	1.00	3	26.35	3.04	2	9.50	3.74	3	8.40	2.60	3
L065	2.10	1.31	3	61.57	4.12	3	7.93	2.32	3	41.55	1.77	2	9.27	4.77	3	4.95	2.04	3
L066	1.47	0.94	3	35.83	3.98	3	8.40	2.82	3	26.45	7.14	2	9.67	5.69	3	10.75	3.61	3
L067	1.70	1.15	3	52.07	3.77	3	10.13	2.87	3	30.20	1.27	2	13.90	6.69	3	12.00	3.89	3
L068	1.57	0.62	3	54.97	0.16	3	13.40	1.71	3	45.60	0.99	2	8.43	1.76	3	11.30	2.78	3
L069	1.50	0.45	3	45.43	0.45	3	12.10	5.22	3	34.25	0.49	2	8.00	3.39	3	7.55	2.70	3
無處理	0.30	0.22	3	0.40	0.22	3	0.23	0.06	3	0.05	0.07	2	0.40	0.10	3	0.00	0.00	3
1XNLS Cas9	0.07	0.09	3	0.50	4.77	3	0.07	0.06	0	0.00	0.00	2	0.10	0.00	3	0.00	0.06	3
GFP	0.13	0.12	3			3	0.30	0.20	1	0.10	0.14	2	0.13	0.12	3	0.10	0.10	3

表61B.含有至少1種胞嘧啶至胸苷轉化之總讀數之平均百分比(% C形成T)

連接子	BC36			BC38			BC39			BC41			BC42		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L001 (XTEN對照)	33.95	15.20	2	22.90	0.42	2	29.47	3.11	3	0.33	0.09	3	55.80	4.60	3
L002	26.15	6.72	2	1.70	0.42	2	40.03	3.27	3	22.60	1.63	3	57.15	3.55	3
L003	34.35	7.28	2	2.05	0.07	2	39.30	5.48	3	27.73	2.58	3	39.90	8.40	3
L004	38.85	3.18	2	5.35	2.05	2	36.73	3.75	3	30.97	2.17	3	47.45	0.85	3
L005	28.70	6.08	2	6.45	4.60	2	42.53	3.93	3	17.90	3.16	3	41.15	2.85	3
L006	33.50	5.94	2	20.20	1.13	2	43.60	2.02	3	17.17	0.88	3	39.80	2.20	3
L007	38.35	1.63	2	5.75	2.62	2	23.37	2.80	3	20.03	2.01	3	32.55	8.15	3
L008	19.30	1.84	2	12.30	2.26	2	37.15	4.88	3	17.70	0.71	3	30.95	14.55	3
L009	26.70	5.23	2	6.70	0.85	2	25.40	0.96	3	15.27	4.74	3	40.85	3.95	3
L010	24.70	2.12	2	12.10	6.08	2	29.85	1.06	3	12.20	2.13	3	39.05	10.55	3
L011	22.40	1.13	2	8.00	0.00	2	33.67	5.40	3	13.07	4.90	3	52.95	0.95	3
L012	31.75	5.59	2	14.00	15.41	2	39.67	2.90	3	14.00	4.01	3	28.40	4.90	3
L013	53.15	4.60	2	10.20	1.41	2	38.80	5.02	3	12.40	2.57	3	43.25	3.55	3
L014	48.25	4.31	2	13.80	3.39	2	41.50	5.51	3	10.60	4.83	3	42.65	3.85	3
L015	46.45	5.87	2	15.05	1.77	2	41.23	2.85	3	11.97	3.06	3	37.25	6.45	3
L016	48.15	3.61	2	4.60	0.85	2	45.47	2.84	3	9.57	2.47	3	38.70	2.90	3
L017	49.50	10.47	2	9.00	0.42	2	40.40	2.10	3	20.07	1.80	3	47.10	3.90	3
L018	50.75	9.12	2	6.45	2.62	2	42.60	5.54	3	17.50	3.15	3	41.80	12.30	3
L019	44.05	0.07	2	26.45	4.17	2	43.20	5.78	3	8.13	1.72	3	47.35	0.75	3
L020	39.40	5.09	2	14.40	6.08	2	41.90	3.65	3	9.63	3.84	3	39.95	3.55	3
L021	51.10	2.83	2	16.80	2.69	2	38.83	1.74	3	10.30	3.89	3	26.40	6.20	3
L022	35.20	2.12	2	3.30	1.27	2	29.05	1.63	3	16.77	2.65	3	34.10	3.10	3
L023	48.70	10.18	2	5.40	3.82	2	35.23	4.81	3	8.23	3.21	3	56.10	1.50	3
L024	45.80	0.42	2	15.45	5.59	2	33.87	2.02	3	14.87	3.20	3	22.10	7.20	3
L025	57.40	7.21	2	18.35	4.03	2	38.27	3.41	3	24.83	2.50	3	45.90	1.10	3
L026	51.50	11.74	2	10.70	0.42	2	43.47	3.01	3	13.80	5.37	3	35.30	0.60	3
L027	51.00	2.69	2	18.00	4.95	2	41.73	3.43	3	10.90	3.24	3	49.90	0.10	3

連接子	BC36			BC38			BC39			BC41			BC42		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L028	50.25	2.90	2	20.40	2.69	2	41.53	3.00	3	15.67	5.03	3	40.90	6.70	3
L029	33.80	1.56	2	16.85	1.06	2	37.70	3.80	3	23.47	2.16	3	25.75	9.15	3
L030	25.80	3.68	2	19.10	3.54	2	43.77	3.59	3	15.10	7.97	3	46.80	3.60	3
L031	53.35	5.02	2	7.60	2.12	2	40.80	4.72	3	9.73	5.61	3	47.75	1.65	3
L032	61.65	8.98	2	11.35	3.04	2	23.70	4.80	3	29.97	3.97	3	30.70	4.60	3
L033	19.90	3.68	2	11.75	0.49	2	32.37	1.42	3	12.37	3.82	3	49.95	1.65	3
L034	48.00	0.85	2	7.55	3.32	2	19.60	0.99	3	14.63	2.67	3	32.05	1.25	3
L035	40.85	0.64	2	5.75	1.48	2	27.43	4.48	3	9.87	4.11	3	42.10	1.30	3
L036	30.50	5.23	2	9.80	4.10	2	27.27	3.21	3	16.03	2.52	3	41.60	1.30	3
L037	41.80	11.17	2	27.50	3.39	2	26.73	3.25	3	12.90	7.05	3	39.75	2.65	3
L038	41.20	1.98	2	4.55	0.78	2	42.27	0.76	3	10.07	2.83	3	41.85	0.95	3
L039	39.20	0.99	2	12.85	7.85	2	32.83	3.56	3	16.00	7.47	3	29.30	3.70	3
L040	58.90	3.54	2	7.20	2.55	2	41.53	5.04	3	15.37	4.58	3	30.25	3.85	3
L041	25.00	1.84	2	10.30	4.10	2	31.27	4.11	3	15.80	6.83	3	46.85	1.65	3
L042	59.35	9.26	2	14.80	0.28	2	27.70	2.63	3	17.97	4.63	3	37.35	8.25	3
L043	34.45	6.58	2	0.20	0.28	2	25.53	5.01	3	8.53	2.82	3	39.95	6.45	3
L044	50.70	4.10	2	13.20	1.27	2	34.77	3.35	3	16.63	4.64	3	24.85	4.15	3
L045	36.40	6.36	2	7.45	3.75	2	36.67	2.66	3	18.67	2.53	3	43.45	1.65	3
L046	49.05	5.16	2	9.35	0.64	2	26.90	0.28	3	14.33	1.87	3	40.00	0.10	3
L047	49.05	8.84	2	10.50	1.13	2	33.10	5.60	3	15.03	2.81	3	48.10	8.50	3
L048	56.50	0.14	2	7.45	3.46	2	40.77	2.81	3	17.60	2.84	3	46.95	5.45	3
L049	29.50	3.82	2	13.35	0.78	2	38.67	2.25	3	11.30	4.30	3	19.50	5.00	3
L050	36.70	0.28	2	13.30	2.26	2	29.10	2.08	3	9.80	6.38	3	39.85	5.15	3
L051	31.30	0.99	2	24.45	7.14	2	34.07	3.72	3	11.33	3.11	3	30.50	3.20	3
L052	50.55	5.30	2	19.45	0.21	2	33.63	3.65	3	13.07	5.70	3	48.20	2.60	3
L053	44.35	4.60	2	6.55	3.75	2	35.83	2.54	3	12.83	4.09	3	49.65	2.25	3
L054	33.65	4.31	2	25.50	2.69	2	39.97	7.47	3	21.33	8.77	3	53.95	2.15	3
L055	47.80	2.40	2	7.95	0.78	2	28.17	2.50	3	12.17	7.25	3	49.60	2.50	3
L056	31.10	3.39	2	9.55	0.92	2	45.03	6.52	3	12.37	3.70	3	51.35	2.25	3
L057	52.45	7.85	2	12.90	9.90	2	26.93	1.20	3	14.63	5.10	3	47.65	4.55	3

連接子	BC36			BC38			BC39			BC41			BC42		
	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N	平均	SD	N
L058	44.95	3.61	2	7.90	0.42	2	26.85	2.05	3	11.17	0.57	3	38.80	3.50	3
L059	54.65	7.57	2	8.45	4.31	2	33.60	4.75	3	11.03	4.98	3	44.90	7.60	3
L060	60.95	1.34	2	16.25	2.62	2	31.47	1.54	3	11.63	5.54	3	1.35	0.75	3
L061	38.25	3.75	2	8.25	2.33	2	42.17	1.14	3	18.40	5.80	3	30.95	5.15	3
L062	30.95	3.18	2	10.40	5.52	2	33.70	6.12	3	22.27	7.07	3	31.60	10.50	3
L063	41.15	1.20	2	24.15	4.45	2	38.67	4.02	3	14.50	3.11	3	32.35	3.05	3
L064	60.90	3.11	2	22.20	2.83	2	40.80	2.30	3	17.30	3.49	3	43.90	0.90	3
L065	55.45	6.01	2	18.75	2.19	2	34.97	4.17	3	21.40	1.28	3	36.45	11.15	3
L066	34.10	3.82	2	25.05	3.32	2	24.77	1.02	3	18.30	2.55	3	40.95	5.95	3
L067	28.15	0.78	2	8.60	6.65	2	38.77	0.93	3	22.00	9.53	3	37.25	5.45	3
L068	16.55	1.77	2	26.75	2.62	2	35.30	1.87	3	5.00	1.80	3	42.00	8.00	3
L069	51.70	3.25	2	20.40	2.40	2	40.30	2.82	3	9.93	3.16	3	36.30	10.40	3
無處理	0.15	0.07	2	0.15	0.07	2	1.27	1.36	3	0.17	0.09	3	0.20	0.00	3
1XNLS Cas9	0.15	0.21	2	0.00	0.00	2	0.00	0.00	3	0.03	0.05	3	0.10	0.10	3
GFP	0.40	0.28	2	0.00	0.00	2	0.33	0.12	3	0.23	0.05	3	0.25	0.05	3

實例26.藉由在Huh-7細胞中具有各種連接子之構築體進行鹼基編輯

【0654】 使用mRNA及gRNA之脂染胺轉染測定衍生自BC22但具有經取代於胞嘧啶去胺酶與Cas9切口酶之間的來自表60之連接子的選擇鹼基編輯器構築體的C形成T鹼基編輯活性。測試之鹼基編輯器mRNA包括SEQ ID NOs: 19及347-357。構築體在150 ng至1.17 ng範圍內之Huh-7細胞中之鹼基編輯器mRNA的稀釋系列中經篩選，在100 uL培養基中與20至0.15 nM範圍內之SERPINA1 sgRNA (G000255)及25至0.20 ng之劑量之UGI mRNA (SEQ ID No: 25)之稀釋系列共遞送。將每一構築體之C形成T鹼基編輯與BC22 (SEQ ID No: 19)進行比較。

實例26.1.細胞製備及轉染

【0655】 在100 uL培養基中以150 ng鹼基編輯器mRNA、25 ng UGI mRNA及20 nM sgRNA之最大劑量開始，使用Lipofectamine® RNAiMAX，以8點、兩倍稀釋系列轉染96孔板中補充有10%胎牛血清(FBS)之Dulbecco改良Eagle培養基(DMEM)中生長的Huh-7細胞。

實例26.2.藉由NGS評估C形成T編輯純度

【0656】 轉染後七十二小時，對Huh-7細胞進行溶解、SERPINA1基因座之PCR擴增及後續NGS分析，如實例1中所描述。表62及圖41展示用2.3或75 ng不同鹼基編輯器mRNA及對應量之經稀釋UGI mRNA及G000255 (SERPINA1)處理之樣本中的SERPINA1編輯水準及C形成T編輯純度。具有不同連接子之鹼基編輯器mRNA的C形成T轉化平均百分比展示於表63A至表63B中。表64及圖42展示在9.7至23.1 ng範圍內之EC90(編輯90%之最大C形成T編輯所需的鹼基編輯器mRNA之質量)。所有經測試之鹼基編輯器mRNA在高劑量下具有類似水準之最大編輯。

表62 - Huh-7中SERPINA1處之編輯百分比，Indels =插入或缺失。

鹼基編輯器 mRNA (ng)	連接子	C形成T (%)		C形成A/G (%)		插入/缺失(%)	
		平均	SD	平均	SD	平均	SD
2.3	L001 (XTEN對照)	49.6	3.0	3.0	0.4	10.7	0.6
	L015	43.7	0.8	2.7	0.1	9.0	1.6
	L016	43.4	2.8	3.0	0.4	10.7	0.5
	L019	50.2	5.7	3.3	0.4	11.3	0.6
	L021	45.3	7.5	3.1	0.6	10.5	0.1
	L024	46.3	2.2	3.3	0.0	10.7	0.1
	L025	33.2	14.3	2.4	0.7	9.9	0.9
	L036	46.5	1.4	3.0	0.6	8.0	1.2
	L051	38.4	6.2	2.5	0.1	7.2	0.4
	L062	40.8	7.7	1.2	1.7	10.0	2.6
	L063	37.8	1.8	2.0	0.5	6.9	0.3
	L066	33.4	9.2	2.7	0.4	7.2	1.6
75	L001 (XTEN對照)	89.8	0.8	2.3	0.4	4.4	0.2
	L015	83.6	0.8	2.9	0.8	5.3	0.1
	L016	87.9	1.1	2.9	0.0	5.2	0.3
	L019	89.6	0.8	2.7	0.2	4.3	0.5
	L021	91.1	0.3	2.0	0.3	3.3	0.3
	L024	89.9	2.1	3.0	0.5	3.8	0.9
	L025	89.8	0.8	3.4	0.1	3.5	0.3
	L036	90.4	1.0	2.8	0.0	3.4	0.1
	L051	91.3	0.9	2.0	0.1	3.3	0.4
	L062	91.1	0.4	2.6	0.2	2.7	0.2
	L063	87.2	3.5	2.6	0.2	3.6	0.4
	L066	91.9	0.4	2.4	0.1	3.1	0.1

表63A - Huh-7細胞中SERPINA1處之C形成T編輯的平均百分比。

鹼基編輯器 mRNA (ng)	L001 (XTEN對照)		L015		L016		L019		L021		L024	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
150.00	83.4	0.9	81.3	0.4	79.9	0.3	80.4	1.0	81.6	3.4	84.4	-
75.00	89.8	0.8	83.6	0.8	87.9	1.1	89.6	0.8	91.1	0.3	89.9	2.1
37.50	87.9	1.0	84.2	6.2	88.6	0.7	88.1	0.6	87.9	0.5	88.7	1.3
18.75	85.6	1.5	74.7	4.7	83.8	1.0	85.4	2.3	83.6	1.9	84.9	1.6
9.38	73.2	0.1	68.7	0.1	74.5	3.6	72.2	4.5	71.6	5.3	76.5	1.8
4.69	66.1	0.3	54.7	4.0	61.0	3.7	66.9	1.9	62.3	1.2	58.2	2.0
2.34	49.6	3.0	43.7	0.8	43.4	2.8	50.2	5.7	45.3	7.5	46.3	2.2
1.17	29.0	0.2	25.8	0.8	25.0	0.9	28.3	3.7	24.9	3.0	25.1	2.6

表63B - Huh-7細胞中SERPINA1處之C形成T編輯的平均百分比。

鹼基編輯器mRNA (ng)	L025		L036		L051		L062		L063		L066	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
150.00	81.5	3.4	82.2	3.7	84.0	0.5	84.3	1.6	78.7	2.4	78.8	3.5
75.00	89.8	0.8	90.4	1.0	91.3	0.9	91.1	0.4	87.2	3.5	91.9	0.4
37.50	85.4	4.0	90.0	2.2	89.6	2.6	89.1	1.8	81.7	1.6	89.5	0.7
18.75	83.1	1.0	87.0	1.3	84.1	2.9	86.2	1.0	74.9	1.8	84.8	0.6
9.38	71.7	0.3	78.9	0.5	76.8	0.7	73.9	7.4	67.2	2.5	67.9	1.0
4.69	59.3	2.1	68.3	2.2	58.7	5.1	62.7	4.1	48.6	2.0	55.7	8.5
2.34	33.2	14.3	46.5	1.4	38.4	6.2	40.8	7.7	37.8	1.8	33.4	9.2
1.17	23.1	0.7	30.8	1.4	25.1	1.1	26.8	1.2	23.5	3.6	28.1	2.8

表64 - 在SERPINA1處產生90%之最大C形成T編輯之BC22 mRNA的質量。亦展示每一EC90值之95%信賴區間。

連接子	EC90 (ng)	95%信賴區間	
		最大(ng)	最小(ng)
L001 (XTEN對照)	11.23	16.33	8.199
L015	18.84	32.71	12.28
L016	11.57	16.91	8.421
L019	9.974	17.4	6.444
L021	13.07	22.77	8.449
L024	14.67	21.5	10.700
L025	13.99	25.53	8.893
L036	9.744	13.98	7.213
L051	14.25	21.44	10.21
L062	13.84	22.82	9.324
L063	23.14	41.8	14.77
L066	19.38	48.34	10.54

實例27.在原代人類肝細胞(PHH)中藉由具有各種連接子之構築體進行鹼基編輯

【0657】 在PHH中測定衍生自BC22n但具有經取代於胞嘧啶去胺酶與Cas9切口酶之間的來自**表65**之連接子的選擇鹼基編輯器構築體的C形成T鹼基編輯活性。構築體(SEQ ID NOs: 341-346)在PHH細胞中之鹼基編輯器mRNA之12點稀釋系列中經篩選，與固定質量之ANAPC5 sgRNA (G019427)及UGI mRNA (SEQ ID NO: 34)共遞送。將每一基於測試之編輯器構築體之C形成T編輯效率與BC22n(SEQ ID NO: 1)進行比較。

表65 - 額外連接子肽。

連接子ID	連接子胺基酸序列
L001 (XTEN對照)	SGSETPGTSESATPES (SEQ ID NO: 46)
L070	GTKDSTKDIPETPSKD (SEQ ID NO: 268)
L071	GRDVRQPEVKEEKPES (SEQ ID NO: 269)
L072	EGKSSGSGSESKSTAG (SEQ ID NO: 270)
L073	TPGSPAGSPTSTEEGT (SEQ ID NO: 271)
L074	GSEPATSGSETPGTST (SEQ ID NO: 272)
L019	EAAAKEAAAKEAAAK (SEQ ID NO: 51)

實例27.1.細胞製備及轉染

【0658】 將PHH細胞解凍且在CHRM培養基(Gibco, cat#CM7000)中回收。接著將其再懸浮於原代肝細胞接種培養基(由William's E培養基(Gibco, Cat#A1217601)及原代肝細胞接種補充劑(Gibco, Cat#CM3000)組成))中以33,000個細胞/孔之密度接種於經膠原蛋白塗佈之96孔板中二十四小時。在二十四小時後，洗滌細胞，且在細胞上添加新鮮原代肝細胞維持培養基。細胞接著與個別地與UGI mRNA(SEQ ID No: 34)、ANAPC5 sgRNA G019427或鹼基編輯器mRNA一起形成之單獨脂複合體同時轉染。

【0659】 脂質體轉染試劑製備為50/9/38/3脂質A、DSPC、膽固醇及PEG2k-DMG之比率的脂質混合物，如實例1中所描述。藉由分別與每一RNA物種批量混合來組合脂質體轉染試劑：鹼基編輯器mRNA、UGI mRNA或gRNA G019427。物質以約6之脂質胺與RNA磷酸(N:P)莫耳比組合。所得批量混合脂複合體材料(脂質套組)在添加至肝細胞之前與10% FBS (Gibco; A3160501)一起在原代肝細胞維持培養基(由William's E培養基(Gibco, Cat#A1217601)及原代肝細胞維持補充劑(Gibco, Cat#CM4000)組成)中預培育15分鐘。

【0660】 每一孔接受最終體積為100 uL之三種組分：在400 ng至0

ng mRNA範圍內之鹼基編輯器mRNA、30 ng UGI mRNA及5 pmols G019427 (ANAPC5)。

實例27.2藉由下一代定序(NGS)評估C形成T編輯純度

【0661】 轉染後七十二小時，對PHH細胞進行溶解、ANAPC5基因座之PCR擴增及後續NGS分析，如實例1中所描述。**表66**及**圖43**展示除30 ng UGI mRNA (SEQ ID No: 34)及5 pmols G019427 (ANAPC5)以外，用400或6.25 ng不同鹼基編輯器mRNA處理之樣本中的ANAPC5總編輯水準及C形成T編輯純度。

【0662】 一系列鹼基編輯器mRNA劑量之C形成T鹼基編輯展示於**表67**中。如**表68**及**圖44**中所展示計算EC95 (編輯95%之最大C形成T編輯所需之BC22n mRNA的質量)。所有鹼基編輯器mRNA能夠在高劑量下達成類似水準之最大編輯。

表66 - 使用設計有各種肽連接子之鹼基編輯構築體在PHH細胞中ANAPC5處的平均編輯百分比。Indels =插入或缺失。

鹼基編輯器mRNA (ng)	連接子	C形成T (%)		C形成A/G (%)		插入/缺失(%)	
		平均	SD	平均	SD	平均	SD
6.25	L001 (XTEN對照)	74.9	1.6	0.6	0.1	0.6	0.2
	L070	58.0	3.4	0.5	0.0	0.5	0.1
	L071	57.8	2.0	0.6	0.1	0.9	0.2
	L072	63.7	2.8	0.4	0.1	0.7	0.6
	L073	59.7	1.3	0.5	0.1	0.6	0.1
	L074	53.1	2.5	0.5	0.3	0.7	0.6
	L019	59.9	3.5	0.4	0.1	0.8	0.2
400	L001 (XTEN對照)	86.3	0.1	0.6	0.4	1.2	0.4
	L070	84.3	3.3	0.6	0.2	0.7	0.1
	L071	87.7	2.4	0.7	0.2	0.5	0.4
	L072	86.0	0.1	0.9	0.4	0.7	0.4
	L073	87.9	1.8	0.9	0.0	0.8	0.3
	L074	86.6	1.8	0.6	0.1	0.7	0.0
	L019	86.7	4.9	0.9	0.0	1.2	0.1

表67 - 設計有各種肽連接子之鹼基編輯構築體在PHH中之ANAPC5基因

座處的C形成T編輯平均百分比。

mRNA (ng)	L001		L070		L071		L072		L073		L074		L019	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
400.00	86.3	0.1	84.3	3.3	87.7	2.4	86.0	0.1	87.9	1.8	86.6	1.8	86.7	4.9
200.00	87.8	2.4	83.9	1.1	88.1	0.5	86.9	5.4	87.6	1.8	86.6	2.5	87.4	3.2
100.00	91.1	0.2	84.7	2.3	84.6	4.5	87.0	2.5	83.6	0.1	85.1	4.7	85.9	2.5
50.00	89.0	1.8	78.0	5.4	82.4	5.0	85.8	0.6	83.9	1.8	84.3	0.8	85.0	3.7
25.00	86.9	1.8	79.1	0.2	78.6	4.6	81.3	3.3	79.4	2.3	79.4	0.5	82.7	1.1
12.50	83.2	0.8	71.3	2.5	69.3	6.0	71.8	1.6	72.6	4.4	69.2	0.9	72.8	2.5
6.25	74.9	1.6	58.0	3.4	57.8	2.0	63.7	2.8	59.7	1.3	53.1	2.5	59.9	3.5
3.13	64.3	2.9	40.5	3.0	42.8	2.9	47.8	1.4	42.4	0.6	37.7	2.1	45.6	1.6
1.56	50.8	2.7	24.6	6.6	30.8	0.2	28.3	0.7	27.8	0.7	27.1	0.7	31.6	1.1
0.78	35.7	2.3	18.8	0.0	20.1	0.0	20.8	0.7	17.4	0.8	16.0	0.8	22.8	3.7
0.39	23.6	3.9	12.1	1.7	12.1	0.7	13.2	0.6	12.5	1.1	10.0	0.6	14.6	0.8
0.00	0.4	0.2	0.6	0.1	0.5	0.0	0.6	0.2	0.4	0.1	0.4	0.3	0.6	0.1

表68 - 導致95%之最大C形成T編輯的鹼基編輯器mRNA的質量。亦展示每一EC95值之95%信賴區間。

連接子	EC95 (ng)	95%信賴區間	
		最大(ng)	最小(ng)
L001 (XTEN對照)	22.73	31.91	16.75
L070	48.99	84.83	30.52
L071	83.46	134.60	54.97
L072	45.72	67.33	32.28
L073	53.62	73.54	40.17
L074	69.89	98.83	51.13
L019	62.06	98.67	41.39

實例28.藉由在T細胞中具有各種連接子之構築體進行鹼基編輯

【0663】 測定衍生自BC22n但具有經取代於胞嘧啶去胺酶與Cas9切口酶之間的來自表65之連接子的選擇鹼基編輯器構築體的C形成T鹼基編輯活性。構築體(SEQ ID Nos: 341-346)在健康人類T細胞中之鹼基編輯器mRNA之12點稀釋系列中經篩選，與固定量之TRAC sgRNA (G016017)及UGI mRNA (SEQ ID NO: 34)共遞送。將每一鹼基編輯器mRNA構築體之

C形成T編輯效率與BC22n (SEQ ID NO: 1)進行比較。

實例28.1.T細胞製備

【0664】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌，再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8 MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0665】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在用於篩選實驗之前活化48小時。

實例28.2.T細胞電穿孔及擴展

【0666】 使靶向TRAC之sgRNA (G016017)在95℃下變性2分鐘，在室溫下培育5分鐘且儲存於冰上。活化後48小時，採集T細胞，在500 g下離心5分鐘，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液

(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與減少量之在400 ng至0 ng之範圍內的鹼基編輯器mRNA、200 ng UGI mRNA及40 pmols G016017在最終體積為20 uL之P3電穿孔緩衝液中混合。

所得混合物一式兩份轉移至96孔Nucleofector™板(Lonza)且使用製造商之脈衝碼電穿孔。緊接在電穿孔之後，T細胞接受80 μL TCGM且將板在37℃下培育15分鐘。在培育之後，將80 μL轉移至含有80 μL TCGM之新平底96孔板中。將T細胞在37℃下培育4天，此時將其混合，用新鮮TCGM以1:4分裂，且在藉由流動式細胞量測術進行表型評定之前再培育3天。

實例28.3.藉由下一代定序(NGS)評估C形成T編輯純度

【0667】 電穿孔後四天，對T細胞進行溶解、TRAC基因座之PCR擴增及後續NGS分析，如實例1中所描述。表69及圖45展示除200 ng UGI mRNA (SEQ ID No: 34)及40 pmols G016017 (TRAC)以外，用400或6.25 ng不同鹼基編輯器mRNA處理之樣本中的TRAC編輯水準及C形成T編輯純度。

【0668】 在N末端胞嘧啶去胺酶與C末端Cas9切口酶之間測試的連接子皆不限制胞嘧啶鹼基編輯之功效或影響C形成T編輯純度的水準。

表69 - 用設計有各種連接子肽之鹼基編輯器構築體處理之T細胞中TRAC基因座處的平均編輯百分比。Indels =插入或缺失。

鹼基編輯器mRNA (ng)	連接子	C形成T (%)		C形成A/G (%)		插入/缺失(%)	
		平均	SD	平均	SD	平均	SD
6.25	L001 (XTEN對照)	78.9	4.9	0.3	0.1	0.3	0.3
	L070	68.2	1.8	0.3	0.2	0.2	0.1
	L071	62.3	8.5	0.2	0.1	0.4	0.0
	L072	62.0	4.7	0.1	0.2	0.2	0.1
	L073	57.4	3.4	0.4	0.4	0.3	0.1
	L074	64.8	2.1	0.1	0.0	0.3	0.0
	L019	67.3	7.0	0.3	0.0	0.2	0.0

400	L001 (XTEN對照)	97.0	0.9	0.3	0.1	0.7	0.3
	L070	98.1	0.1	0.2	0.1	0.4	0.2
	L071	97.7	0.5	0.3	0.1	0.5	0.1
	L072	97.6	0.6	0.2	0.1	0.3	0.0
	L073	97.5	0.7	0.4	0.0	0.6	0.0
	L074	96.9	0.5	0.4	0.3	0.6	0.1
	L019	97.4	0.3	0.3	0.2	0.2	0.2

實例28.4.藉由流動式細胞量測術評估受體敲除

【0669】 電穿孔後七天，藉由流動式細胞量測術測定T細胞以評估CD3表現之損失。將T細胞與可固定活力染料(Beckman Coulter，目錄號C36628)及靶向以下分子之抗體混合液一起培育：CD3 (Biolegend，目錄號317336)、CD4 (Biolegend，目錄號317434)及CD8 (Biolegend，目錄號301046)。隨後洗滌細胞，在Cytoflex LX儀器(Beckman Coulter)上使用FlowJo套裝軟體進行分析。在判定任何標記物表現之前，T細胞以大小、活力及CD8陽性進行閘控。所得資料繪製在GraphPad Prism v. 9.0.2上且使用可變斜率(四個參數)非線性回歸進行分析。

【0670】 如表70中所展示，用>100 ng所測試之鹼基編輯器mRNA中之任一者處理產生>95%之缺少CD3表現之CD8+ T細胞。用每一非線性回歸之95%信賴區間測試之鹼基編輯器mRNA之EC90 (亦即，產生90%缺少CD3之CD8+ T細胞之mRNA的質量)展示於表71及圖46中。

表70 - 在用設計有各種連接子肽之鹼基編輯器構築體處理之後對於CD3表面表現呈陰性的CD8+ T細胞之平均百分比。

鹼基編輯器mRNA (ng)	L001 (XTEN對照)		L070		L071		L072		L073		L074		L019	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
400.00	96.5	0.3	97.2	0.5	96.1	0.3	96.1	0.4	96.2	0.2	96.2	0.4	95.6	0.4
200.00	96.8	0.8	96.4	1.8	96.7	0.8	96.8	0.9	96.1	1.0	95.7	0.9	96.2	1.0
100.00	97.1	0.1	96.2	1.6	97.0	0.2	95.0	1.4	96.0	0.7	96.4	0.7	95.3	0.3
50.00	96.3	0.7	96.	0.	95.	1.	95.	1.	94.	2.	94.	1.	95.	1.

			0	6	2	2	2	6	6	3	5	2	8	3
25.00	94.9	1.5	92.8	3.4	92.1	3.7	90.7	2.4	90.7	0.3	91.5	1.2	91.7	1.1
12.50	91.5	1.6	85.7	5.1	82.8	5.9	83.6	4.2	82.5	2.3	79.9	0.6	85.0	1.8
6.25	76.1	7.9	69.0	5.4	61.8	8.6	63.8	3.6	61.8	3.1	65.7	4.1	67.1	5.6
3.13	56.5	6.2	49.0	5.5	42.6	6.3	42.2	5.7	43.0	6.7	43.7	3.2	47.7	5.5
1.56	37.8	2.2	29.0	4.9	26.9	2.8	24.1	5.4	24.4	3.2	25.1	2.7	29.0	3.5
0.78	23.5	3.7	17.6	3.7	14.0	0.1	13.8	2.1	14.0	3.1	13.5	1.8	16.3	2.1
0.39	13.2	2.9	9.0	2.3	7.6	0.8	7.7	0.5	7.0	0.3	6.5	0.7	9.0	0.9
0.00	1.9	0.5	1.5	0.1	1.4	0.7	2.1	1.3	1.3	0.4	1.6	0.7	2.1	0.5

表71 - 導致90%之最大CD3阻斷的鹼基編輯器mRNA的質量。亦展示每一EC90值之95%信賴區間。

連接子	**EC90 (ng)**	**95%信賴區間**	
		最小(ng)	**最大(ng)**
L001 (XTEN對照)	13.4	10.6	17.5
L070	17.1	13.6	21.9
L071	21.5	16.6	28.7
L072	18.9	15.5	23.5
L073	20.7	17.1	25.5
L074	19.7	17.2	22.6
L019	17.6	14.6	21.5

實例29.藉由在T細胞中具有各種連接子之構築體進行多重鹼基編輯

【0671】 經由蛋白質阻斷測定衍生自BC22n但具有經取代於胞嘧啶去胺酶與Cas9切口酶之間的來自表65之連接子的選擇鹼基編輯器構築體的多個同時鹼基編輯功效。構築體在健康人類T細胞中之鹼基編輯器mRNA之12點稀釋系列中經篩選，與固定質量之UGI mRNA (SEQ ID NO: 34)及4種不同的91聚體sgRNA共遞送。將每一mRNA構築體之效力與BC22n mRNA (SEQ ID NO: 1)進行比較以評估每一連接子在表型受體敲除方面之作用。

實例29.1.T細胞製備

【0672】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌，再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8 MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0673】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在用於篩選實驗之前活化48小時。

實例29.2.T細胞電穿孔及擴展

【0674】 使靶向TRAC (G023520)、TRBC1/2 (G023524)、CIITA (G023521)及HLA-A (G023523)之四個91聚體sgRNA在95℃下變性2分鐘，在室溫培育5分鐘且儲存在冰上。活化後48小時，採集T細胞，在500 g下離心5分鐘，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與400 ng至

0 ng之鹼基編輯器mRNA (SEQ ID NOs: 1及321-326)、200 ng UGI mRNA (SEQ ID NO: 34)、3.6 pmols G023520 (TRAC)、6.96 pmols G023524 (TRBC1/2)、17.12 pmols G023521 (CIITA)及52.24 pmols G023523 (HLA-A)之稀釋系列在最終體積為20 uL之P3電穿孔緩衝液中混合。

【0675】 所得混合物一式兩份轉移至96孔Nucleofector™板(Lonza)且使用製造商之脈衝碼電穿孔。緊接在電穿孔之後，T細胞接受80 µL TCGM且將板在37℃下培育15分鐘。在培育之後，將80 µL轉移至含有80 µL TCGM之新平底96孔板中。將T細胞在37℃下培育4天，此時其藉由新鮮TCGM以1:4分裂，且在藉由流動式細胞量測術進行表型評定之前再培育3天。

實例29.3.藉由流動式細胞量測術評估受體敲除

【0676】 電穿孔後七天，藉由流動式細胞量測術測定T細胞以評估CD3、HLA-A3及/或HLA-DR、DP、DQ之損失。將T細胞與可固定活力染料(Beckman Coulter，目錄號C36628)及靶向以下分子之抗體混合液一起培育：CD3 (Biolegend，目錄號317336)、CD4 (Biolegend，目錄號317434)、CD8 (Biolegend，目錄號301046)、HLA-A3 (ThermoFisher，目錄號12-5754-42)及HLA-DP、DQ、 DR (Biolegend，目錄號361714)。隨後洗滌細胞，在Cytoflex LX儀器(Beckman Coulter)上使用FlowJo套裝軟體進行分析。在判定任何標記物表現之前，T細胞以大小、活力及CD8陽性進行閘控。所得資料繪製在GraphPad Prism v. 9.0.2上且使用可變斜率(四個參數)非線性回歸進行分析。

【0677】 如表72中所展示，用>100 ng所測試之BC22n mRNA中之任一者處理產生>97%之缺少CD3、HLA-A3及HLA-DR、DP、DQ表現之

CD8+ T細胞。用每一非線性回歸之95%信賴區間測試之鹼基編輯器mRNA之EC90 (亦即，產生90%缺少CD3之CD8+ T細胞之mRNA的質量)展示於表73及圖47中。

表72 - 在用鹼基編輯器mRNA處理之後對於CD3、HLA-A3及HLA-DR、DP、DQ表面表現呈陰性的CD8+ T細胞之平均百分比。

mRNA (ng)	L001 (XTEN對照)		L070		L071		L072		L073		L074		L019	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
400.00	97.4	0.5	98.3	ND	98.4	0.3	98.7	0.1	97.8	0.7	98.1	0.5	98.6	0.4
200.00	98.4	0.1	98.6	0.2	98.2	0.2	98.3	0.4	98.1	0.7	98.7	0.1	98.9	0.1
100.00	97.1	0.8	97.5	1.1	97.0	2.1	97.7	0.5	97.4	0.5	98.5	0.5	98.7	0.1
50.00	95.7	0.1	96.6	0.2	95.4	0.9	95.6	0.8	95.1	2.8	97.4	0.7	97.1	0.3
25.00	90.8	0.1	88.5	4.0	89.7	3.3	89.1	2.8	87.6	3.2	91.5	2.6	93.6	1.9
12.50	75.5	3.2	77.8	3.7	75.6	4.8	71.6	6.6	69.1	3.2	77.9	4.7	82.6	3.3
6.25	54.9	4.2	54.0	1.1	54.8	6.2	53.3	5.5	46.2	5.9	55.6	7.8	60.0	5.1
3.13	32.9	2.1	32.7	1.9	31.5	3.2	30.5	2.6	27.6	2.5	32.9	3.6	35.7	2.5
1.56	17.1	0.5	16.6	1.6	16.3	2.4	16.1	1.6	15.5	3.1	18.4	2.5	21.0	2.1
0.78	10.0	1.3	9.4	1.2	9.5	0.3	7.5	0.4	7.3	0.5	9.6	2.9	11.7	0.3
0.39	5.1	0.4	4.5	0.6	4.7	0.4	4.5	0.8	4.4	1.2	5.2	0.0	6.8	1.4
0.00	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.3	0.2	0.2	0.2	0.2	0.1

表73 - 導致90%之CD3、HLA-A3及HLA-DR、DP、DQ (EC90)之最大阻斷的鹼基編輯器mRNA之質量。亦展示每一EC90值之95%信賴區間。

連接子	EC90 (ng)	95%信賴區間	
		最小(ng)	最大(ng)
L001 (XTEN對照)	26.3	22.9	30.4
L070	26.5	22.8	31.1
L071	26.4	22.0	32.1
L072	30.3	25.1	37.3
L073	34.3	28.3	42.4
L074	25.0	20.4	31.2
L019	4.709	4.314	5.130

實例30 用BC22n、UGI及91聚體sgRNA編輯人類T細胞

【0678】 將藉由NGS及/或受體敲除評定之91聚體sgRNA之鹼基編輯功效與具有相同導引序列之100聚體sgRNA對照之鹼基編輯功效進行比較。

【0679】 經測試之91聚體sgRNA包括20個核苷酸導引序列(如由N表示)及如下之導引骨架：mN*mN*mN*NNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU (SEQ ID NO: 520)，除非另外指示，否則其中A、C、G、U及N分別為腺嘌呤、胞嘧啶、鳥嘌呤、尿嘧啶及任何核糖核苷酸。m指示2'O-甲基修飾，且*指示核苷酸之間的硫代磷酸酯鍵。導引物之未經修飾及經修飾版本提供於表5C (序列表)中。

實例30.1.T細胞製備

【0680】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌，再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8

MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0681】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在LNP處理之前活化48小時。

實例30.2.T細胞LNP處理及擴展

【0682】 活化後四十八小時，採集T細胞，在500 g下離心5分鐘，且以1 x 10^6個T細胞/mL之濃度再懸浮於T細胞接種培養基(TCPM)中：無血清版本TCGM，含有400 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、10 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及10 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。在平底96孔板中每孔添加50 µL TCPM中之T細胞(5 x 10^4個T細胞)以進行處理。

【0683】 如實例1中所描述以35/47.5/15/2.5 (脂質A/膽固醇/DSPC/PEG2k-DMG)之比率製備LNP。用約6之脂質胺與RNA磷酸酯(N:P)莫耳比來調配LNP。LNP囊封單一RNA物種，即如表74中所描述之

sgRNA、BC22n mRNA (SEQ ID No: 1)或UGI mRNA (SEQ ID No. 34)。

表74 - 100聚體及91聚體sgRNA。

基因目標	100聚體	91聚體
TRAC	G016017	G023520
TRBC1/2	G016200	G023524
CIITA	G016086	G023521
B2M	G015991	G023519
CD38	G019771	G023522
HLA-A	G021209	G023523

【0684】 在T細胞處理之前，囊封sgRNA之LNP在T細胞處理培養基(TCTM)中稀釋至6.64 μg/mL：含有20 ug/mL rhApoE3，不存在介白素2、5或7的TCGM版本。此等LNP在37℃下培育15分鐘且使用TCTM以1:4連續稀釋，此產生6.64 μg/mL至零範圍內之8點稀釋系列。類似地，將具有BC22n mRNA (SEQ ID NO: 1)或UGI mRNA (SEQ ID NO: 34)之單負荷LNP在TCTM中分別稀釋至3.32及1.67 μg/mL，在37℃下培育15分鐘，且以1:1之體積與先前步驟中連續稀釋之sgRNA LNP混合。最後，將來自所得混合物之50 μL以1:1體積比添加至96孔板中之T細胞中。將T細胞在37℃下培育24小時，此時收集其，在500 g下離心5分鐘，再懸浮於200 μL TCGM中，且返回至培育箱。

實例30.3.藉由下一代定序(NGS)評估編輯結果

【0685】 LNP處理後四天，對T細胞進行溶解、每一靶向基因座之PCR擴增及後續NGS分析，如實例1中所描述。表75至80及圖48、50A、50B、51展示用減少質量之靶向TRAC、TRBC1、TRBC2、CIITA、B2M或CD38之100聚體或91聚體sgRNA處理之T細胞中之編輯水準及C形成T編輯純度。

【0686】 當與其100聚體版本相比時，91聚體sgRNA在相同濃度下遞送時產生較高編輯頻率。對於藉由NGS測定之所有5個不同組之sgRNA

觀測到此結果，該等sgRNA靶向6個不同基因體基因座。在100聚體與91聚體sgRNA之間未觀測到C形成T編輯純度之差異。藉由流動式細胞量測術而非NGS評估靶向HLA-A基因之該組sgRNA，此係由於HLA-A基因座之超多態性質。

表75 - 用100聚體(G016017)或91聚體格式(G023520)中之sgRNA處理之T細胞中之TRAC基因座處的平均編輯百分比。

sgRNA (ng)	TRAC											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	96.7	0.4	1.0	0.2	1.5	0.3	94.9	0.0	2.2	0.2	2.5	0.3
41.50	98.0	0.5	0.4	0.1	0.5	0.4	97.5	0.1	0.8	0.0	1.2	0.1
10.38	98.4	0.4	0.2	0.1	0.5	0.1	98.4	0.1	0.4	0.1	0.7	0.1
2.59	97.2	0.1	0.3	0.1	0.4	0.1	98.2	0.2	0.3	0.1	0.5	0.0
0.65	78.3	0.9	0.3	0.1	0.5	0.0	92.0	0.5	0.3	0.1	0.4	0.1
0.16	37.4	0.9	0.1	0.0	0.2	0.1	55.3	0.7	0.2	0.0	0.3	0.1
0.04	11.6	0.9	0.2	0.1	0.1	0.1	19.4	0.9	0.2	0.1	0.2	0.1
0.00	0.9	0.2	0.1	0.1	0.1	0.0	0.8	0.1	0.2	0.0	0.1	0.0

表76 - 用100聚體(G016200)或91聚體格式(G023524)中之sgRNA處理之T細胞中之TRBC1基因座處的平均編輯百分比。

sgRNA (ng)	TRBC1											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	95.1	0.5	1.3	0.2	1.9	0.2	91.6	1.0	3.4	0.1	4.0	0.8
41.50	96.2	0.8	0.6	0.1	1.3	0.3	95.3	0.6	1.5	0.2	2.1	0.3
10.38	94.6	0.6	0.4	0.1	1.0	0.2	96.0	0.4	0.8	0.2	1.1	0.1
2.59	83.5	0.7	0.5	0.1	0.7	0.3	92.1	0.6	0.6	0.1	0.9	0.5
0.65	48.1	2.0	0.4	0.1	0.3	0.1	69.8	0.1	0.4	0.2	0.4	0.2
0.16	17.3	0.7	0.3	0.1	0.3	0.4	34.0	0.5	0.4	0.0	0.3	0.1
0.04	6.2	1.2	0.3	0.1	0.2	0.1	10.9	0.7	0.5	0.1	0.1	0.1
0.00	1.3	0.1	0.4	0.1	0.2	0.1	1.2	0.4	0.3	0.2	0.1	0.1

表77 - 用100聚體(G016200)或91聚體格式(G023524)中之sgRNA處理之T細胞中之TRBC2基因座處的平均編輯百分比。

sgRNA (ng)	TRBC2											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	96.5	0.1	1.2	0.3	1.3	0.3	92.4	0.4	3.2	0.1	3.7	0.3
41.50	97.3	0.5	0.7	0.0	0.9	0.0	96.1	0.3	1.3	0.1	1.7	0.5
10.38	95.3	0.9	0.6	0.2	1.0	0.1	97.1	0.1	0.6	0.1	1.2	0.2
2.59	78.3	1.4	0.6	0.0	0.6	0.1	92.8	0.8	0.7	0.1	0.7	0.2
0.65	41.1	1.1	0.3	0.0	0.4	0.1	66.5	2.0	0.4	0.3	0.5	0.2
0.16	13.9	1.5	0.3	0.1	0.2	0.0	29.7	2.5	0.3	0.2	0.3	0.2
0.04	5.1	0.7	0.3	0.0	0.3	0.1	10.3	0.5	0.4	0.1	0.3	0.1
0.00	1.5	0.4	0.4	0.1	0.2	0.1	1.8	0.3	0.4	0.1	0.2	0.1

表78 - 用100聚體(G016086)或91聚體格式(G023521)中之sgRNA處理之T細胞中之CIITA基因座處的平均編輯百分比。

sgRNA (ng)	CIITA											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	98.1	0.2	0.7	0.1	0.6	0.1	96.9	0.3	1.3	0.0	1.4	0.2
41.50	97.3	0.2	0.4	0.1	0.3	0.1	98.1	0.2	0.6	0.1	0.8	0.1
10.38	82.9	0.3	0.3	0.0	0.2	0.1	97.5	0.4	0.5	0.2	0.4	0.1
2.59	43.3	0.5	0.3	0.1	0.2	0.1	88.0	1.1	0.4	0.1	0.3	0.1
0.65	14.5	0.9	0.3	0.1	0.1	0.1	50.4	1.9	0.3	0.1	0.1	0.1
0.16	4.3	0.2	0.2	0.1	0.0	0.0	17.7	0.5	0.3	0.0	0.1	0.1
0.04	1.8	0.2	0.3	0.1	0.1	0.0	5.7	0.1	0.2	0.1	0.1	0.0
0.00	0.6	0.1	0.2	0.1	0.1	0.0	0.8	0.0	0.2	0.1	0.1	0.0

表79 - 用100聚體(G015991)或91聚體格式(G023519)中之sgRNA處理之T細胞中之B2M基因座處的平均編輯百分比。

sgRNA (ng)	B2M											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	92.5	0.3	4.2	0.2	2.8	0.4	89.0	0.9	6.9	0.5	3.8	0.3
41.50	97.2	0.2	1.3	0.2	1.1	0.1	96.1	0.4	2.1	0.1	1.5	0.4
10.38	97.6	0.4	0.6	0.1	0.9	0.1	97.7	0.1	0.8	0.0	1.0	0.1
2.59	96.8	0.1	0.5	0.0	0.7	0.1	97.9	0.1	0.6	0.0	0.6	0.1
0.65	79.5	0.9	0.3	0.0	0.3	0.0	90.3	0.3	0.4	0.0	0.5	0.1
0.16	39.8	0.3	0.3	0.0	0.2	0.1	54.1	0.4	0.3	0.1	0.2	0.0
0.04	13.9	0.3	0.3	0.1	0.1	0.0	20.8	0.8	0.3	0.0	0.1	0.1
0.00	2.1	0.2	0.3	0.0	0.1	0.0	2.0	0.4	0.3	0.0	0.1	0.0

表80 - 用100聚體(G019771)或91聚體格式(G023522)中之sgRNA處理之T細胞中之CD38基因座處的平均編輯百分比。

sgRNA (ng)	CD38											
	100聚體						91聚體					
	C形成T		C形成A/G		插入/缺失		C形成T		C形成A/G		插入/缺失	
	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
166.00	92.7	0.6	1.6	0.2	5.4	0.4	91.0	0.6	2.5	0.2	6.1	0.5
41.50	93.9	0.4	0.7	0.1	5.1	0.3	93.4	0.5	1.0	0.0	5.2	0.5
10.38	93.7	0.1	0.7	0.1	4.8	0.2	94.0	0.4	0.6	0.1	4.6	0.2
2.59	88.4	0.9	0.5	0.1	3.3	0.3	92.4	0.7	0.6	0.1	3.8	0.3
0.65	54.8	1.6	0.4	0.0	1.9	0.3	67.3	0.3	0.4	0.1	2.3	0.0
0.16	19.7	0.4	0.5	0.1	0.7	0.1	27.8	0.4	0.5	0.1	1.0	0.2
0.04	5.9	0.5	0.5	0.0	0.3	0.1	9.1	0.6	0.4	0.1	0.4	0.1
0.00	0.4	0.0	0.4	0.1	0.1	0.0	0.5	0.1	0.4	0.0	0.0	0.0

實例30.4.藉由流動式細胞量測術評估受體敲除

【0687】 LNP處理後七天，藉由流動式細胞量測術測定T細胞以評估受體敲除。將T細胞與可固定活力染料(Beckman Coulter，目錄號C36628)及靶向以下分子之抗體混合液一起培育：CD3 (Biolegend，目錄號317336)、CD4 (Biolegend，目錄號317434)及CD8 (Biolegend，目錄號301046)、B2M (Biolegend，目錄號316306)、CD38 (Biolegend，目錄號303516)、HLA-A2 (Biolegend，目錄號343304)及HLA-DR、DP、DQ (Biolegend，目錄號361714)。隨後洗滌細胞，在Cytoflex LX儀器(Beckman Coulter)上使用FlowJo套裝軟體進行分析。在判定任何標記物表現之前，T細胞以大小、活力及CD8陽性進行閘控。所得資料繪製在GraphPad Prism v. 9.0.2上且使用可變斜率(四個參數)非線性回歸進行分析。

【0688】 如表81至表83及圖52、圖53A至圖55B，所有測試之91聚體sgRNA勝過其100聚體版本。如**表84**中所展示，此效能增加為可變的，其中CIITA觀測到4.6倍增加且B2M觀測到1.14倍增加。在所測試之6個目

標中，在100聚體格式(CIITA及HLA-A)中具有較低效力(亦即，較高EC50)之彼等似乎最受益於使用91聚體sgRNA。

表81 -在以100聚體或91聚體格式靶向TRAC或TRBC1/2之sgRNA之後對於CD3表面受體呈陰性之CD8+ T細胞之平均百分比。

sgRA (ng)	TRAC (CD3-)				sgRNA (ng)	TRBC1/2 (CD3-)			
	100聚體		91聚體			100聚體		91聚體	
	平均	SD	平均	SD		平均	SD	平均	SD
166.00	98.4	0.3	98.2	0.3	166.00	99.6	0.3	99.1	0.3
41.50	98.1	0.1	98.5	0.5	41.50	99.8	0.1	99.6	0.1
10.38	97.7	0.2	98.0	0.4	10.38	98.8	0.4	99.9	0.1
2.59	95.2	0.4	97.4	0.6	2.59	84.9	1.1	97.4	0.6
0.65	74.7	1.0	88.0	0.8	0.65	45.7	1.6	73.5	2.8
0.16	33.5	2.4	51.0	1.0	0.16	16.4	0.9	31.6	0.8
0.04	11.0	0.7	18.3	0.8	0.04	5.5	0.4	10.2	0.5
0.00	1.1	0.2	1.3	0.2	0.00	1.2	0.2	1.2	0.1

表82 - 分別以100聚體或91聚體格式處理靶向CIITA或HLA-A之sgRNA之後對於HLA-DR、DP、DQ或HLA-A2表面受體呈陰性之CD8+ T細胞之平均百分比。

sgRA (ng)	CIITA (HLA-DR、DP、DQ-)				sgRNA (ng)	HLA-A (HLA-A2-)			
	100聚體		91聚體			100聚體		91聚體	
	平均	SD	平均	SD		平均	SD	平均	SD
166.00	98.3	0.2	98.7	0.2	166.00	98.8	0.1	99.6	0.2
41.50	96.9	0.7	98.4	0.3	41.50	93.6	0.8	99.2	0.4
10.38	85.2	0.7	97.7	0.3	10.38	70.2	1.0	93.8	1.4
2.59	58.7	0.2	89.4	1.3	2.59	34.0	2.1	63.2	3.0
0.65	44.8	1.1	63.4	0.5	0.65	12.1	1.3	28.5	1.2
0.16	38.2	1.6	45.2	2.6	0.16	3.3	0.2	8.3	0.6
0.04	37.8	1.0	38.2	0.5	0.04	0.9	0.3	2.6	0.5
0.00	35.1	2.5	37.6	1.7	0.00	0.1	0.0	0.3	0.2

表83 - 分別以100聚體或91聚體格式用靶向B2M或CD38之sgRNA處理之後對於B2M或CD38表面受體呈陰性之CD8+ T細胞之平均百分比。

sgRNA (ng)	B2M (B2M-)				sgRNA (ng)	CD38 (CD38-)			
	100聚體		91聚體			100聚體		91聚體	
	平均	SD	平均	SD		平均	SD	平均	SD
166.00	98.0	0.4	98.3	0.2	166.00	99.8	0.2	99.8	0.1
41.50	98.2	0.0	98.4	0.4	41.50	99.6	0.1	99.9	0.1
10.38	94.5	0.7	97.2	0.3	10.38	98.4	0.3	99.5	0.1
2.59	68.3	3.2	81.4	3.4	2.59	87.4	1.9	94.3	0.9
0.65	8.4	6.8	11.4	2.6	0.65	47.0	4.3	60.0	1.9

sgRNA (ng)	B2M (B2M-)				sgRNA (ng)	CD38 (CD38-)			
	100聚體		91聚體			100聚體		91聚體	
	平均	SD	平均	SD		平均	SD	平均	SD
0.16	0.4	0.3	0.5	0.1	0.16	20.5	4.9	23.8	1.6
0.04	0.4	0.6	0.2	0.1	0.04	16.5	10.1	12.5	0.6
0.00	0.9	0.7	1.6	0.9	0.00	17.2	4.1	13.7	0.7

表84 - 導致CD8+ T細胞表面中受體表現之50%損失之sgRNA的量(pmol) (EC50)。最右行展示當與具有相同導引序列之其100聚體相比時，由91聚體sgRNA達成之效力之倍數增加。

基因目標	100聚體		91聚體		EC50移位 (100聚體/91聚體)
	sgRNA ID	EC50 (pmols)	sgRNA ID	EC50 (pmols)	
TRAC	G016017	0.008	G023520	0.005	1.63
TRBC1/2	G016200	0.023	G023524	0.010	2.22
CIITA	G016086	0.123	G023521	0.027	4.60
B2M	G015991	0.055	G023519	0.048	1.14
CD38	G019771	0.027	G023522	0.020	1.41
HLA-A	G021209	0.150	G023523	0.053	2.81

實例31 UGI mRNA劑量對活體內編輯之鹼基編輯影響

【0689】 使用固定劑量之BC22n (**SEQ ID No: 1**)及靶向ANAPC5 (G019427)以及連續稀釋之UGI mRNA (**SEQ ID No: 34**)的導引RNA來評估活體內肝臟編輯型態。

實例31.1如藉由NGS測定之活體內編輯

【0690】 在此研究中使用6-10週齡範圍內之十五隻可商購CD-1雌性小鼠(n=3/組)。給藥前對動物稱重以進行給藥計算。在LNP中分別調配每一RNA物種。LNP一般如實例1中所描述調配。LNP含有分別為50:38:9:3莫耳比之可離子化脂質A、膽固醇、DSPC及PEG2k-DMG。脂質核酸組裝體用約6之脂質胺與RNA磷酸酯(N:P)莫耳比調配。LNP囊封單一RNA物種，G019427、BC22n mRNA (SEQ ID No: 1)或UGI mRNA (SEQ ID No. 34)。

【0691】 將囊封鹼基編輯器mRNA之LNP與囊封sgRNA之LNP分別

以按重量計0.2 mpk及0.1 mpk RNA之固定劑量(編輯器mRNA及sgRNA)以及按重量計0.0、0.03、0.1及0.3 mpk RNA之UGI mRNA劑量同時混合及投與。陰性對照組僅用TSS緩衝液給藥。根據**表85**中所列出之劑量，經由尾部靜脈注射靜脈內投與調配物。

表85 - 動物組及各別LNP

樣本	LNP負荷	編輯器mRNA (mg/kg)	sgRNA (mg/kg)	UGI mRNA (mg/kg)
TSS	無	0	0	0
0.0 MPK UGI	BC22n mRNA	0.2 mg/kg	0.1 mg/kg	n/a
0.03 MPK UGI	UGI mRNA			0.03 mg/kg
0.1 MPK UGI	G019427			0.1 mg/kg
0.3 MPK UGI				0.3 mg/kg

【0692】 在給藥後至少24小時，定期觀測動物之不良反應。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集肝臟組織用於下游分析。收集重量在5與15 mg之間的肝臟穿孔以分離基因體DNA。用NGS定序分析基因體DNA樣本，如實例1中所描述。編輯資料及C形成T純度百分比展示於**表86及圖56至圖57**中。

表86 - 在UGI mRNA之量增加下小鼠肝臟中之ANAPC5基因座處之平均編輯百分比。

UGI mRNA (mpK)	% C形成T		% C形成A/G		插入/缺失		%C形成T純度	
	平均	SD	平均	SD	平均	SD	平均	SD
TSS	0.10	0.00	0.71	0.03	0.11	0.10	11.01	0.38
0	25.77	4.18	21.64	1.52	24.29	26.51	34.80	4.90
0.03	68.20	2.38	2.30	0.54	4.11	4.02	91.50	1.27
0.1	67.47	0.55	2.04	0.25	3.92	3.71	92.15	0.39
0.3	66.67	0.67	2.17	0.14	3.88	3.63	91.99	0.66

實例32.活體外判定BC22n與UGI比率

【0693】 蛋白質表現量使用蛋白質之經HiBiT標記版本判定。為判定針對具有高C形成T純度之有效鹼基編輯所表現的鹼基編輯器蛋白質及UGI蛋白質之相對量，進行並行編輯實驗，其中之一者使用編碼經HiBiT

標記之鹼基編輯器的mRNA且其中之另一者使用編碼經HiBiT標記之UGI的mRNA。

【0694】 如實例9中進行細胞製備、工程改造及編輯測定。實驗之一個組(經標記編輯器)用編碼經HiBiT標記之BC22n (SEQ ID No. 4)及mRNA UGI (SEQ ID No: 34)之mRNA轉染。實驗之另一組(經標記UGI)用編碼鹼基編輯器(SEQ ID No: 1)之mRNA及編碼經Hibit標記之UGI之mRNA轉染。

【0695】 在轉染之後二十四小時，使用細胞titer-glo測定(Promega目錄號G7571)判定每樣本之活T細胞的數目且使用Nano-Glo® HiBiT溶解偵測測定(Promega目錄號N3040)量測經HiBiT標記之蛋白質的數目。在轉染後96小時進行NGS定序以評定總編輯及C形成T純度水準。針對總編輯水準繪製BC22n及UGI蛋白質水準以判定達成飽和編輯水準及C形成T純度所需之每一蛋白質細胞之最小數目。

【0696】 BC22n與UGI蛋白質之最佳比率係藉由將達成飽和編輯水準所需之每個細胞之BC22蛋白質的最小數目除以達成最大C形成T純度所需之每個細胞之UGI蛋白質的最小數目來計算。

【0697】 可使用類似方法計算使用不同細胞類型、不同導引物或不同轉染方法之鹼基編輯器與UGI蛋白質之比率。

實例33.以較低劑量進行活體內UGI滴定

【0698】 在小鼠中進行鹼基編輯以評定總體編輯效率及較低水準之UGI mRNA之C形成T純度。實驗細節如**實例30**中所描述，但有以下例外。囊封BC22n mRNA之LNP及囊封sgRNA之LNP分別以0.2 mg/kg及0.1 mg/kg RNA負荷的固定劑量混合，且與0.0、0.0001、0.001、0.003、

0.01 、0.03、0.1及0.3 mg/kg之UGI mRNA劑量組合。陰性對照組為經TSS處理之動物。經由尾部靜脈注射靜脈內投與調配物。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集肝臟組織用於下游分析。收集重量在5與15 mg之間的肝臟穿孔以分離基因體DNA及總RNA。用如實例1中所描述之NGS定序分析基因體DNA樣本以判定小鼠肝臟中最大C形成T編輯純度所需之最小UGI mRNA劑量。

實例34.經工程改造之T細胞之細胞毒性敏感性

【0699】 當藉由自然殺手(NK)細胞靶向時，測定經工程改造之T細胞之細胞毒性敏感性。

【0700】 NK細胞(Stemcell Technologies)經解凍且以1x10^6個細胞/ml之細胞濃度再懸浮於由OpTmizer TCGM構成且進一步補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml IL-7 (Peprotech，目錄號200-07)、5 ng/ml IL-15 (Peprotech，目錄號200-15)之T細胞生長培養基(TCGM)中。細胞在37℃下培育24小時。

【0701】 解凍後二十四小時，NK細胞用0.5 μM Cell Trace Violet標記如下：將一小瓶Cell Trace Violet (CellTrace™ Violet Cell Proliferation Kit, for flow cytometry, 目錄號C34571)在來自套組之DMSO中重構以得到5 mM儲備濃度。用18 μL磷酸鹽緩衝鹽水(Corning，目錄號21-040-CV)稀釋兩μL CTV儲備液以獲得0.5 mM之濃度。NK細胞在500xg下離心5分鐘，抽吸培養基，且將細胞以1x10^6個細胞/mL之濃度再懸浮於磷酸鹽緩衝鹽水(PBS)中，使得CTV染料之最終濃度為0.5 μM。將細胞與Cell Trace Violet (CTV)染料溶液混合，在37℃下培育20分鐘。藉由添加TCGM來淬滅未結合染料且培育5分鐘。將細胞以500xg離心5分

鐘。細胞以2x10^6個細胞/mL之濃度再懸浮於補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml IL-7 (Peprotech，目錄號200-07)、5 ng/ml IL-15 (Peprotech，目錄號200-15)之TCGM中。為測試效應子:目標(E:T)比率範圍，將經CTV標記之NK細胞等分至100 ul培養基中，6點、2倍連續稀釋，最高數目之細胞為2 x 10^5個細胞，包括僅培養基樣本作為陰性對照。

【0702】 使用如**實例14**中所描述之BC22n及UGI mRNA使用靶向HLA-A之G023523或靶向B2M之G015991工程改造T細胞。亦包括未編輯之(WT) T細胞、未染色之LD熱殺死型及7-AAD FMO (2x10^4未經標記之NK細胞及2x10^4 WT T細胞)及CTV+ (2 x 10^5 CTV標記之NK細胞)作為對照。T細胞以TCGM之2x10^5個細胞之密度再懸浮，該TCGM由OpTmizer TCGM構成且進一步補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml IL-7 (Peprotech，目錄號200-07)、5 ng/ml IL-15 (Peprotech，目錄號200-15)。將兩萬個T細胞添加至NK細胞及培養基對照之每一孔中。細胞在37℃下培育24小時。

【0703】 在二十四小時時，將來自LD熱殺死孔之一半體積之細胞熱殺死且轉移回至測定板中的相同孔。將細胞離心且再懸浮於80 μL之7-AAD (BD Biosciences，目錄號559925)於FACS緩衝液(PBS + 2% FBS (Gibco，目錄號A31605-02) + 2mM EDTA (Invitrogen，目錄號15-575-020))之1:200 v/v溶液中。藉由流動式細胞量測術使用Cytoflex LX儀器(Beckman Coulter)獲取T細胞之比溶胞率之資料且使用FlowJo套裝軟體進行分析。首先在CTV陰性群體上抽取閘極以清除NK細胞，接著在單重態上閘控，其後在7-AAD陰性群體上抽取閘極以閘控活T細胞。藉由自100

減去活細胞百分比來計算T細胞之溶解百分比。

實例35.此段落有意留白。

實例36.原代人類肝細胞中之鹼基編輯器及UGI之蛋白質表現

【0704】 用編碼原代人類肝細胞中具有融合HiBiT標籤之蛋白質的mRNA進行鹼基編輯以判定適合於具有高C形成T純度之高效率編輯之鹼基編輯器及UGI蛋白質酶單元的相對量。

【0705】 將編碼具有C末端HiBiT標籤之BC22n (BC22n-HiBIT, SEQ ID NO: 4)、具有C末端HiBiT標籤之BC22-2XUGI (順式UGI之2個串聯複本) (BC22-2XUGI-HibIT, SEQ ID NO: 314)及具有C末端HiBiT標籤之UGI (UGI-HiBiT, SEQ ID NO: 316)的信使RNA在劑量反應中以固定濃度之靶向B2M之導引RNA (G015991; SEQ ID NO: 179)轉染至原代人類肝細胞(PHH)中以判定細胞內鹼基編輯器及UGI蛋白質複本之最小數目以進行具有高活性(總編輯% = 2X EC90)及高C形成T純度(C形成T純度% = 2X EC90)的鹼基編輯。BC22n-HiBiT在固定濃度之B2M導引及UGI (SEQ ID NO: 34)上滴定，UGI-HiBiT在固定濃度之B2M導引及BC22n (SEQ ID NO: 1)上滴定，且BC22-2XUGI-HiBiT在固定濃度之B2M導引上滴定，而無任何額外反式UGI mRNA。轉染後二十小時進行HiBiT溶解測定(Promega目錄號N3040)以判定早期時間點處之細胞內蛋白質水準。接著將彼等蛋白質水準與轉染後九十六小時衍生自NGS資料之B2M基因座處之端點編輯相關。

實例36.1細胞製備及轉染

【0706】 將PHH細胞(ThermoFisher，批次HU8284)解凍且在CHRM培養基(Gibco, cat#CM7000)中回收。將細胞再懸浮於原代肝細胞接種培養基(由William's E培養基(Gibco，目錄號A1217601)及原代肝細

胞接種補充劑(Gibco，目錄號CM3000)組成)中，隨後以30,000個細胞/孔之密度接種於經膠原蛋白塗佈之96孔板中二十四小時。洗滌細胞，且添加新鮮原代肝細胞維持培養基。

【0707】 如實例1中所描述製備脂質體轉染試劑，其中脂質A、DSPC、膽固醇及PEG2k-DMG莫耳比分別為50/9/38/3。每一RNA物種(鹼基編輯器mRNA、UGI mRNA或gRNA G015991 (SEQ ID NO: 179))以約6之脂質胺與RNA磷酸酯(N:P)莫耳比個別地與脂質體轉染試劑批量混合。所得批量混合脂複合體材料在添加至肝細胞之前與10% FBS (Gibco，目錄號A3160501)一起在原代肝細胞維持培養基(由William's E培養基(Gibco，目錄號A1217601)及原代肝細胞維持補充劑(Gibco，目錄號CM4000)組成)中預培育15分鐘。

【0708】 對於BC22n-HiBiT滴定，每一孔接受最終體積為100 uL之三種組分：在100 ng至0 ng範圍內之BC22n-HiBiT mRNA、11 ng UGI mRNA及2 pmols G015991 (B2M)，如**表87**中所描述。對於UGI-HiBiT滴定，每一孔接受最終體積為100 uL之三種組分：在100 ng至0 ng範圍內之UGI-HiBiT mRNA、33 ng BC22n mRNA及2 pmols G015991 (B2M)，如**表88**中所描述。對於BC22-2XUGI-HiBiT滴定，每一孔接受最終體積為100 uL之三種組分：在100 ng至0 ng範圍內之BC22-2XUGI-HiBiT mRNA、11 ng UGI mRNA及2 pmols G015991 (B2M)，如**表89**中所描述。

【0709】 轉染後九十六小時，將對已與HiBiT板同時轉染之單獨PHH複製板進行溶解、B2M基因座之PCR擴增及後續NGS分析，如實例1中所描述。所有實驗均以生物一式三份進行。藉由計算一組未處理孔之平均背景速率自所有孔減去背景C形成T、C形成A/G及插入/缺失編輯(均<

2%)。不同BC22n-HiBiT mRNA濃度之編輯結果展示於**表87**中，且不同BC22n-HiBiT mRNA濃度下之總編輯展示於**圖58A**中。不同UGI-HiBiT mRNA濃度之編輯結果展示於**表88**中且不同UGI-HiBiT mRNA濃度下之C形成T純度展示於**圖58B**中。不同BC22-2XUGI-HiBiT mRNA濃度之編輯結果展示於**表89**中。不同BC22-2XUGI-HiBiT mRNA濃度之總編輯及C形成T純度分別展示於**圖58C**及**圖58D**中。

【0710】 為促進不同大小之mRNA之間的比較，所有圖式在莫耳濃度方面顯示mRNA劑量。出於此等目的，BC22n mRNA之分子量被視為1,724.25 kDa，BC22-2X-UGI mRNA為1915.12 kDa，UGI mRNA為287.58 kDa且sgRNA為29.66 kDa。將HiBiT標籤添加至任何mRNA使其分子量增加18.24 kDa。

表87 - 具有增加劑量之BC22n-HiBiT mRNA的PHH中之平均編輯。

劑量 (ng)	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
100.00	0.2857	3	84.87	1.37	0.95	0.28	0.80	0.61	86.74	1.83	97.99	0.93
33.00	0.0952	3	78.63	0.70	0.73	0.19	0.93	0.29	80.08	0.94	97.93	0.50
11.00	0.0317	3	66.33	3.72	0.46	0.24	0.72	0.39	67.19	3.67	98.27	0.39
3.70	0.0106	3	45.33	1.25	0.19	0.21	0.40	0.21	46.43	1.70	98.72	0.25
1.23	0.0035	3	26.57	0.99	0.32	0.29	0.90	0.58	26.92	1.29	95.69	2.67
0.41	0.0012	3	11.77	0.61	0.12	0.21	0.03	0.05	11.96	0.72	98.75	1.55
0.14	0.0004	3	5.43	0.85	0.00	0.00	0.08	0.14	5.47	0.82	98.58	2.45
0.00	0.0000	3	0.09	0.13	0.07	0.13	0.03	0.03	1.25	0.55	NA	NA

表88 - 具有增加劑量之UGI-Hibit mRNA的PHH中之平均編輯。

劑量(ng)	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
100.00	1.6400	3	81.10	3.33	0.80	0.13	1.09	0.42	83.32	3.34	97.74	0.52
25.00	0.4100	1	80.73	2.17	0.52	0.32	1.43	0.11	82.40	1.81	97.64	0.49
6.25	0.1025	3	77.10	3.71	0.64	0.55	1.15	0.61	79.19	4.40	97.74	0.39
1.56	0.0256	3	78.63	2.72	1.92	0.22	1.45	0.53	83.53	3.42	95.91	0.61
0.39	0.0064	3	74.87	1.88	3.15	0.04	2.98	0.71	82.23	1.91	92.45	0.70
0.10	0.0016	3	73.60	2.70	5.62	1.25	4.21	0.53	85.06	2.51	88.22	2.18
0.02	0.0004	3	67.33	0.46	7.30	1.64	5.84	0.61	80.15	1.21	83.67	1.18
0.00	0.0000	3	71.47	2.72	6.99	1.28	5.51	0.63	79.80	3.99	85.15	1.16

表89 - 具有增加劑量之BC22-2XUGI-Hibit mRNA的PHH中之平均編輯。

劑量(ng)	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
100.00	0.2575	3	81.90	2.37	1.47	0.87	1.34	0.20	84.29	1.23	96.67	0.85
33.00	0.0858	3	79.70	0.49	1.41	0.81	0.92	0.37	82.58	1.13	97.17	1.15
11.00	0.0286	3	65.93	0.75	1.70	0.30	1.47	0.19	68.52	0.96	95.41	0.20
3.70	0.0095	3	47.90	1.01	1.45	0.72	0.89	0.29	50.21	0.91	95.34	1.32
1.23	0.0032	3	27.77	2.64	1.45	0.74	0.86	0.60	29.52	2.34	92.39	3.92
0.41	0.0011	3	14.90	3.07	0.79	0.35	0.30	0.35	15.71	3.41	93.63	2.84
0.14	0.0004	3	7.30	0.74	0.19	0.15	0.02	0.02	7.51	0.86	97.33	1.89
0.00	0.0000	3	0.09	0.13	0.06	0.10	0.02	0.03	0.15	0.10	NA	NA

實例36.2評估細胞內蛋白質水準

【0711】轉染後二十小時，根據製造商之方案，使用Nano-Glo® HiBiT溶解偵測系統(Promega目錄號N3040)偵測蛋白質水準。Promega #N3010，具有HiBiT標籤之一可商購對照蛋白質(已知濃度及已知分子量)在PBS中連續稀釋(1:5)且摻加至含有尚未轉染之PHH之孔中為參考對照。將一百μL經重構之HiBiT溶解試劑添加至標準孔及所有其他實驗孔。將溶解物移動至白壁板，且藉由CLARIstar plus (BMG Labtech)板讀取器讀出相對發光單元(RLU)，其中增益設定為3,600。自所有孔減去背景訊號，且使用藉由HiBiT標準推導之線性回歸方程計算每一樣本之每孔蛋白質複本數目。HiBiT定量呈現於**表90**中且正規化為3.7 ng BC22-2XUGI-HiBiT mRNA樣本之表現量。

表90 - 經Hibit標記之蛋白質之平均蛋白質表現(任意單位)。

Hibit mRNA	劑量(ng)	劑量(nM)	平均	SD
BC22n-HiBiT	100.00	0.2857	22.59	2.05
	33.00	0.0952	10.07	1.04
	11.00	0.0317	4.12	0.59
	3.70	0.0106	1.09	0.02
UGI-HiBiT	100.00	1.6400	4063.15	532.85
	25.00	0.4100	993.10	76.48
	6.25	0.1025	254.04	26.29
	1.56	0.0256	67.16	7.73
	0.39	0.0064	21.66	1.83
BC22-2XUGI-HiBiT	100.00	0.2575	25.82	2.08
	33.00	0.0858	9.13	1.15
	11.00	0.0286	2.87	0.72
	3.70	0.0095	1.00	0.27

【0712】 **表90**中之資料用於產生雙曲線曲線且內插在為達成飽和編輯或C形成T純度水準所需之最小劑量下表現的蛋白質單元。作為飽和水準之最低劑量在此處定義為EC90之兩倍(2X EC90)，對於每一所測試之mRNA分別達成90%總編輯或C或T純度所需的濃度。**表91**展示在此實驗中測試之mRNA的2X EC90劑量(以ng及nM為單位)及BC22及UGI肽單元及其在此等劑量下之比率。對於鹼基編輯器及UGI-HiBiT，蛋白質單元等於肽單元。BC22-2XUGI之UGI肽單元係藉由將BC22-2XUGI蛋白質單元乘以因數2來計算。對於用表現為單獨的未融合蛋白質之BC22n及UGI編輯之樣本，在總編輯2x EC90下之BC22n肽單元與在C形成T純度2X EC90下之UGI肽單元的比率為大約1:10。對於用BC22-2XUGI編輯之樣本，在總編輯2x EC90下之鹼基編輯器肽單元與在C形成T純度2X EC90下之UGI肽單元的比率為大約1:5。

表91 - 相關編輯讀出下mRNA及蛋白質之2X EC90。

mRNA	**編輯讀出**	**mRNA (ng)**	**mRNA (nM)**	**肽單元**
BC22n-HiBiT	總編輯	53.97	0.16	14.94
UGI-HiBiT	C形成T純度	3.85	0.06	156.38
BC22-2XUGI-HiBiT	總編輯(鹼基編輯器)	49.89	0.13	13.39
	C形成T純度(UGI)	139.23	0.36	70.14

實例37.T細胞中鹼基編輯器及UGI之蛋白質表現

【0713】 用編碼經分離人類T細胞中具有融合HiBiT標籤之蛋白質的mRNA進行鹼基編輯以判定適合於具有高C形成T純度之高效率編輯之鹼基編輯及UGI蛋白質酶單元的相對量。

實例37.1.T細胞製備

【0714】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌，再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目

錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8 MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0715】在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。在此培養基中24小時之後。用以1:100體積比添加之T細胞TransAct™，人類試劑(Miltenyi，目錄號130-111-160)活化T細胞。

實例37.2.T細胞LNP處理及擴展

【0716】活化後四十八小時，採集T細胞，在500 g下離心5分鐘，且以1 x 10^6個T細胞/mL之濃度再懸浮於T細胞接種培養基(TCPM)中：無血清版本TCGM，含有400 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、10 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及10 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。在平底96孔板中每孔添加50 ul TCPM中之五萬個T細胞以進行處理。

【0717】如實例1中所描述以35/47.5/15/2.5 (脂質A/膽固醇/DSPC/PEG2k-DMG)之莫耳比產生LNP。在T細胞處理之前，在T細胞處

理培養基(TCTM)中製備兩種單獨的LNP混合物(下文稱為混合物「A」及「B」)：含有20 ug/mL rhApoE3(Peprotech，目錄號350-02)，不存在介白素2、5或7之TCGM版本。

【0718】 為判定使總編輯飽和所需之BC22n-HiBiT mRNA之最小水準，混合物「A」由具有稀釋至6.68 μg/mL (3.83 nM)之BC22n-HiBiT mRNA(SEQ ID NO: 4)的LNP組成，而混合物「B」由具有稀釋至1.67 μg/mL (5.8 nM)之UGI mRNA (SEQ ID NO: 34)的LNP及含有稀釋至6.68 μg/mL (225.19 nM)之比率為4.5/8.7/21.4/65.4之sgRNA G023520 (TRAC)、G023524 (TRBC1/2)、G023521 (CIITA)及G023523 (HLA-A)之多負荷LNP組成。在37℃下將LNP混合物「A」及「B」個別地培育15分鐘。混合物「A」在TCTM中以1:4連續稀釋，且按體積計與混合物「B」 1:1混合。以1:1體積比(50 μL/孔)將所得溶液添加至96孔板中之T細胞中。

【0719】 為判定使C形成T純度飽和所需之UGI-HiBiT mRNA之最小水準，混合物「A」由具有稀釋至6.68 μg/mL (21.84 nM)之UGI-HiBiT mRNA(SEQ ID NO: 316)的LNP組成，而混合物「B」由具有稀釋至3.34 μg/mL (1.94 nM)之BC22n mRNA (SEQ ID NO: 1)的LNP及含有稀釋至6.68 μg/mL (225.19 nM)之比率為4.5/8.7/21.4/65.4之sgRNA G023520 (TRAC)、G023524 (TRBC1/2)、G023521 (CIITA)及G023523 (HLA-A)之多負荷LNP組成。在37℃下將LNP混合物「A」及「B」個別地培育15分鐘。混合物「A」在TCTM中以1:4連續稀釋，且按體積計與混合物「B」 1:1混合。以1:1體積比(50 μL/孔)將所得溶液添加至96孔板中之T細胞中。

【0720】 為判定使總編輯及C形成T純度飽和所需之BC22-2XUGI-HiBiT mRNA之最小水準，混合物「A」由具有稀釋至6.68 μg/mL (3.46 nM)之BC22-2XUGI-HiBiT mRNA(SEQ ID NO: 314)的LNP組成，而混合物「B」由含有稀釋至6.68 μg/mL (225.19 nM)之比率為4.5/8.7/21.4/65.4之sgRNA G023520 (TRAC)、G023524 (TRBC1/2)、G023521 (CIITA)及G023523 (HLA-A)之多負荷LNP組成。在37℃下將LNP混合物「A」及「B」個別地培育15分鐘。混合物「A」在TCTM中以1:4連續稀釋，且按體積計與混合物「B」 1:1混合。以1:1體積比(50 μL/孔)將所得溶液添加至96孔板中之T細胞中。

【0721】 在添加LNP之後，將T細胞在37℃下培育24小時，此時採集一半細胞用於細胞活力及蛋白質表現測定，且將剩餘細胞在500 g下離心5分鐘，再懸浮於200 μL TCGM中，且返回至培育箱。

實例37.3.藉由下一代定序(NGS)評估編輯結果

【0722】 在LNP處理後第4天，將T細胞在500 g下離心5分鐘，進行每一靶向基因座之溶解、PCR擴增及後續NGS分析，如實例1中所描述。具有不同濃度之HiBiT mRNA之TRAC、TRBC1、TRBC2及CIITA基因座下之編輯結果分別展示於表92至表95中。圖59A展示在不同BC22n-HiBiT mRNA濃度下之總編輯。圖59B展示在不同UGI-HiBiT mRNA濃度下之C形成T純度。不同BC22-2XUGI-HiBiT mRNA濃度之總編輯及C形成T純度分別展示於圖59C及圖59D中。

【0723】 表92至表95展示4種不同基因體基因座(TRAC、TRBC1、TRBC2及CIITA)之編輯資料。

表92.T細胞中TRAC基因座處之平均編輯。

mRNA	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
BC22n-HiBiT	0.9584	3	97.29	0.35	0.84	0.29	0.60	0.36	98.72	0.16	98.55	0.22
	0.2396	3	97.82	0.31	0.58	0.27	0.67	0.20	99.07	0.32	98.74	0.07
	0.0599	3	96.50	0.50	0.79	0.22	0.68	0.15	97.97	0.31	98.50	0.36
	0.0150	3	87.53	0.41	0.68	0.09	0.45	0.31	88.66	0.14	98.72	0.39
	0.0037	3	50.82	2.39	0.57	0.13	0.32	0.15	51.71	2.22	98.27	0.49
	0.0009	3	17.33	1.00	0.46	0.17	0.17	0.13	17.97	1.18	96.50	1.09
	0.0002	3	5.31	0.28	0.37	0.10	0.19	0.07	5.88	0.21	90.36	1.67
	0.0000	3	0.67	0.08	0.44	0.13	0.13	0.04	1.24	0.18	NA	NA
UGI-HiBiT	5.4608	3	97.00	0.65	0.81	0.37	0.37	0.23	98.18	0.38	98.80	0.29
	1.3652	1	97.22	ND	0.28	ND	1.39	ND	98.89	ND	98.31	ND
	0.3413	3	95.90	0.49	1.43	0.16	1.01	0.21	98.35	0.58	97.51	0.18
	0.0853	3	82.34	3.24	7.45	2.31	8.06	0.86	97.85	0.15	84.15	3.22
	0.0213	3	55.53	1.88	17.35	3.45	23.98	2.08	96.86	0.39	57.34	2.17
	0.0053	3	32.80	2.32	24.36	3.54	38.14	1.67	95.30	1.10	34.44	2.78
	0.0013	3	26.28	0.77	28.61	2.18	41.47	1.09	96.36	0.43	27.28	0.91
	0.0000	3	22.46	1.08	28.38	3.67	44.56	2.27	95.40	0.37	23.55	1.22
BC22-2XUGI-HiBiT	0.8638	3	81.31	2.75	2.41	0.03	2.10	0.85	85.82	1.90	94.73	1.12
	0.2159	3	67.03	1.79	5.49	1.44	5.52	0.11	78.03	1.36	85.90	1.92
	0.0540	3	28.40	1.39	9.46	0.96	14.74	0.45	52.60	1.77	53.99	1.31
	0.0135	3	12.89	1.33	6.69	0.29	11.11	0.84	30.69	1.91	41.93	2.10
	0.0034	3	4.87	0.42	2.68	0.10	5.99	0.61	13.54	0.80	35.97	1.75
	0.0008	3	1.86	0.23	0.85	0.19	1.51	0.30	4.22	0.47	44.33	6.34
	0.0002	3	0.82	0.21	0.48	0.01	0.77	0.18	2.07	0.04	39.42	9.51
	0.0000	3	0.63	0.05	0.37	0.08	0.13	0.09	1.13	0.13	NA	NA

表93.T細胞中TRBC1基因座處之平均編輯。

mRNA	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
BC22n-HiBiT	0.9584	3	94.22	1.08	1.41	0.30	1.71	0.25	97.33	0.57	96.80	0.56
	0.2396	3	93.82	0.51	1.35	0.28	1.25	0.12	96.41	0.22	97.31	0.31
	0.0599	3	94.12	0.66	1.24	0.15	1.43	0.38	96.80	0.53	97.24	0.24
	0.0150	3	88.80	1.47	1.30	0.28	0.86	0.19	90.96	1.38	97.62	0.14
	0.0037	3	61.60	1.71	1.13	0.21	0.75	0.32	63.48	2.11	97.05	0.55
	0.0009	3	24.05	2.20	1.08	0.09	0.34	0.20	25.47	2.36	94.43	0.19
	0.0002	3	8.54	0.72	1.11	0.08	0.30	0.05	9.95	0.71	85.79	1.62
	0.0000	3	2.52	0.08	1.09	0.09	0.30	0.05	3.92	0.07	NA	NA
UGI-HiBiT	5.4608	3	93.60	1.03	1.45	0.08	1.38	0.26	96.44	0.90	97.06	0.26
	1.3652	3	93.90	0.77	1.59	0.16	1.57	0.49	97.05	0.33	96.75	0.47
	0.3413	3	89.15	1.94	4.27	1.30	2.99	0.98	96.41	0.34	92.48	2.33
	0.0853	3	72.64	2.56	12.64	0.23	11.89	3.35	97.16	0.88	74.78	3.31
	0.0213	3	40.67	3.56	24.32	0.89	31.25	2.94	96.25	1.16	42.23	3.22
	0.0053	3	17.56	3.20	32.38	1.05	42.82	2.69	92.76	1.49	18.90	3.14
	0.0013	3	11.59	2.11	34.92	3.79	48.02	5.70	94.53	1.67	12.27	2.31
	0.0000	3	8.51	1.36	33.48	1.78	51.60	2.15	93.60	1.31	9.08	1.34
BC22-	0.8638	3	83.49	0.86	4.26	0.27	3.64	0.71	91.39	1.58	91.36	0.93

mRNA	劑量 (nM)	n	C形成T 平均	C形成T SD	C形成A/G 平均	C形成A/G SD	插入/缺失 平均	插入/缺失 SD	總編輯 平均	總編輯 SD	C形成T純度 平均	C形成T純度 SD
2XUGI-HiBiT	0.2159	3	68.57	2.32	10.23	1.51	7.39	1.54	86.19	1.60	79.54	1.23
	0.0540	3	35.21	1.71	20.43	1.18	20.76	0.94	76.41	2.69	46.07	0.61
	0.0135	3	20.21	1.22	18.44	1.47	18.28	1.63	56.92	2.62	35.56	2.76
	0.0034	3	10.88	0.49	9.98	1.82	8.13	3.43	28.99	5.28	38.36	6.83
	0.0008	3	4.48	1.11	2.35	0.47	3.64	1.34	10.46	2.87	43.01	2.64
	0.0002	3	3.39	0.37	1.71	0.23	0.97	0.69	6.07	0.83	56.10	4.73
	0.0000	3	2.81	0.22	1.15	0.09	0.34	0.07	4.30	0.26	NA	NA

表94.T細胞中TRBC2基因座處之平均編輯

mRNA	劑量 (nM)	n	C形成T 平均	C形成T SD	C形成A/G 平均	C形成A/G SD	插入/缺失 平均	插入/缺失 SD	總編輯 平均	總編輯 SD	C形成T純度 平均	C形成T純度 SD
BC22n-HiBiT	0.9584	3	94.58	0.49	1.89	0.43	1.90	0.15	98.37	0.20	96.14	0.31
	0.2396	3	95.25	0.63	1.68	0.04	1.20	0.26	98.13	0.42	97.06	0.26
	0.0599	3	94.01	0.63	1.36	0.09	1.63	0.44	97.00	0.58	96.92	0.37
	0.0150	3	88.99	0.35	1.39	0.27	1.04	0.19	91.41	0.08	97.35	0.45
	0.0037	3	56.12	2.38	1.29	0.12	0.74	0.30	58.15	2.64	96.51	0.61
	0.0009	3	20.90	0.73	1.20	0.25	0.40	0.09	22.50	0.59	92.85	1.31
	0.0002	3	8.08	1.04	1.11	0.15	0.32	0.09	9.51	0.94	84.81	3.36
	0.0000	3	2.97	0.24	1.08	0.10	0.49	0.24	4.55	0.51	NA	NA
UGI-HiBiT	5.4608	3	94.87	0.14	1.43	0.21	1.06	0.20	97.35	0.12	97.45	0.02
	1.3652	1	94.76	0.11	1.67	0.13	1.51	0.09	97.94	0.14	96.76	0.20
	0.3413	3	91.81	0.45	3.34	0.40	3.16	0.47	98.31	0.20	93.39	0.27
	0.0853	3	73.09	0.73	12.14	0.96	12.56	0.15	97.79	0.41	74.74	0.95
	0.0213	3	39.77	0.07	23.73	1.69	32.65	1.19	96.15	1.22	41.37	0.53
	0.0053	3	19.66	0.29	29.74	0.81	46.54	0.63	95.93	0.45	20.49	0.20
	0.0013	3	11.79	1.55	31.00	1.01	52.42	3.12	95.21	0.94	12.40	1.73
	0.0000	3	9.04	1.42	32.73	1.37	53.94	1.88	95.71	1.35	9.45	1.57
BC22-2XUGI-HiBiT	0.8638	3	85.85	2.78	4.34	0.88	3.57	0.69	93.76	1.23	91.55	1.76
	0.2159	3	68.48	2.35	10.64	0.47	8.73	0.23	87.85	1.95	77.93	0.95
	0.0540	3	34.87	2.26	19.85	1.23	22.41	1.15	77.12	0.42	45.21	2.75
	0.0135	3	17.86	0.57	16.46	0.44	18.42	1.68	52.74	2.57	33.89	0.95
	0.0034	3	9.52	1.12	8.01	0.14	8.16	0.27	25.69	1.10	37.01	2.90
	0.0008	3	5.17	0.59	3.15	0.38	3.19	0.19	11.50	0.65	44.83	3.28
	0.0002	3	3.06	0.16	1.38	0.14	1.26	0.35	5.71	0.54	53.91	3.87
	0.0000	3	2.79	0.05	1.11	0.22	0.35	0.12	4.25	0.28	NA	NA

表95.T細胞中CIITA基因座處之平均編輯

mRNA	劑量 (nM)	n	C形成T 平均	C形成T SD	C形成A/G 平均	C形成A/G SD	插入/缺失 平均	插入/缺失 SD	總編輯 平均	總編輯 SD	C形成T純度 平均	C形成T純度 SD
BC22n-HiBiT	0.9584	3	96.75	0.28	1.68	0.18	0.57	0.07	99.00	0.05	97.72	0.23
	0.2396	3	96.80	0.15	1.51	0.25	0.53	0.11	98.83	0.24	97.94	0.14
	0.0599	3	96.31	0.64	1.39	0.17	0.42	0.17	98.12	0.43	98.15	0.31
	0.0150	3	89.04	1.09	1.19	0.07	0.41	0.07	90.63	0.99	98.24	0.16
	0.0037	3	56.77	1.94	1.24	0.18	0.18	0.02	58.18	1.79	97.56	0.38
	0.0009	3	22.38	0.53	1.29	0.07	0.12	0.07	23.78	0.60	94.09	0.13
	0.0002	3	7.16	0.27	1.19	0.14	0.16	0.05	8.52	0.35	84.06	1.27

mRNA	劑量 (nM)	n	C形成T		C形成A/G		插入/缺失		總編輯		C形成T純度	
			平均	SD	平均	SD	平均	SD	平均	SD	平均	SD
	0.0000	3	0.88	0.06	1.16	0.27	0.05	0.02	2.09	0.22	NA	NA
UGI-HiBiT	5.4608	3	96.10	0.31	1.49	0.20	0.45	0.29	98.04	0.13	98.02	0.37
	1.3652	1	96.09	0.59	1.69	0.25	0.92	0.25	98.69	0.13	97.36	0.51
	0.3413	3	94.04	0.58	3.10	0.29	1.70	0.58	98.83	0.12	95.15	0.65
	0.0853	3	80.13	1.16	8.99	0.79	9.57	0.60	98.69	0.06	81.20	1.17
	0.0213	3	51.75	1.05	20.78	0.75	25.48	0.97	98.02	0.40	52.80	1.28
	0.0053	3	32.69	1.17	27.04	1.89	37.48	0.98	97.21	0.34	33.63	1.14
	0.0013	3	26.59	0.34	26.78	1.72	43.51	1.10	96.88	1.06	27.45	0.37
	0.0000	3	25.47	1.76	27.78	1.86	43.47	3.32	96.72	0.63	26.33	1.72
BC22-2XUGI-HiBiT	0.8638	3	86.31	2.68	3.78	1.26	2.13	0.51	92.22	1.69	93.59	1.81
	0.2159	3	67.79	6.14	9.39	1.85	9.25	3.55	86.43	1.80	78.37	5.68
	0.0540	3	41.54	1.66	17.05	0.26	21.16	1.07	79.75	2.54	52.08	0.85
	0.0135	3	26.63	0.45	14.36	1.00	19.33	2.27	60.32	3.17	44.23	2.37
	0.0034	3	12.13	1.48	6.22	1.17	9.19	0.82	27.54	2.50	44.09	4.45
	0.0008	3	3.99	0.46	2.94	0.39	2.94	0.45	9.87	1.00	40.47	3.90
	0.0002	3	1.40	0.38	1.56	0.34	0.83	0.23	3.79	0.51	36.41	5.18
	0.0000	3	0.67	0.10	1.10	0.16	0.09	0.08	1.86	0.17	NA	NA

實例37.4.評估細胞內蛋白質水準

【0724】在LNP處理後二十四小時，充分混合所有樣本且將25 µL之兩種等分試樣轉移至含有75 µL TCGM之白壁96孔板中。一個板進行CellTiter-Glo® 2.0細胞活力測定(Promega目錄號G9242)且另一板進行Nano-Glo® HiBiT溶解偵測測定(Promega目錄號N3040)。遵循製造商之方案進行兩種測定。使用已知數目之供體匹配T細胞或具有HiBiT標籤(Promega目錄號N3010)之可商購蛋白質製備標準曲線。HiBiT定量呈現於**表96**中，正規化為0.0037 nM BC22n-HiBiT mRNA樣本之表現量。

表96.經HiBiT標記之蛋白質之平均蛋白質表現(任意單位)。

mRNA	劑量 (nM)	n	平均值	SD
BC22n-HiBiT	0.9584	3	51.93	2.20
	0.2396	3	33.39	4.42
	0.0599	3	15.40	1.34
	0.0150	3	4.05	0.07
	0.0037	3	1.00	0.05
UGI-HiBiT	5.4608	3	1499.52	106.66
	1.3652	3	583.54	53.95
	0.3413	3	180.50	16.40
	0.0853	3	55.38	3.55
	0.0213	3	16.05	1.26
	0.0053	3	4.32	0.32
BC22-2XUGI-HiBiT	0.8638	3	80.23	4.45
	0.2159	3	43.95	10.80
	0.0540	3	14.74	1.31
	0.0135	3	4.17	0.66
	0.0034	3	1.32	0.15

【0725】 來自表96之資料用於產生雙曲線曲線且內插在為達成飽和編輯或C形成T純度水準所需之最小劑量下表現的蛋白質單元。作為飽和水準之最低劑量在此處定義為EC90之兩倍(2X EC90)，對於每一所測試之mRNA分別達成90%總編輯或C或T純度所需的濃度。

【0726】 表97展示在此實驗中測試之mRNA的2X EC90劑量及BC22及UGI肽單元及其在此等劑量下之比率。對於鹼基編輯器及UGI-HiBiT，蛋白質單元等於肽單元。BC22-2XUGI之UGI肽單元係藉由將BC22-2XUGI蛋白質單元乘以因數2來計算。表98展示在總編輯2x EC90下之鹼基編輯器肽單元與在C形成T純度2X EC90下之UGI肽單元的比率。

表97.相關編輯讀出下mRNA及蛋白質之2X EC90。

HiBiT mRNA	編輯讀出	基因座	nM	肽單元
BC22n-HiBiT	總編輯	TRAC	0.038	10.07
		TRBC1	0.031	8.41
		TRBC2	0.033	8.86
		CIITA	0.035	9.32
		平均值	0.034	9.16
		SD	0.003	0.71
UGI-HiBiT	C形成T純度	TRAC	0.354	177.22
		TRBC1	0.560	271.33
		TRBC2	0.557	269.91
		CIITA	0.461	227.02
		平均值	0.483	236.37
		SD	0.098	44.48
BC22-2XUGI-HiBiT	總編輯	TRAC	1.979	95.56
		TRBC1	0.480	65.60
		TRBC2	0.434	62.84
		CIITA	0.334	55.54
		平均值	0.807	69.88
		SD	0.784	17.63
	C形成T純度	TRAC	0.859	160.35
		TRBC1	1.024	168.00
		TRBC2	1.103	171.04
		CIITA	1.660	185.66
		平均值	1.161	171.26
		SD	0.348	10.60

表98.鹼基編輯器與UGI酶比率。

構築體	基因座	鹼基編輯器與UGI酶比率
BC22n-HiBiT / UGI-HiBiT	TRAC	1 to 18
	TRBC1	1 to 32
	TRBC2	1 to 30
	CIITA	1 to 24
	平均值	1 to 26
	SD	7
BC22-2XUGI-HiBiT	TRAC	1 to 1.7
	TRBC1	1 to 2.6
	TRBC2	1 to 2.7
	CIITA	1 to 3.3
	平均值	1 to 2.5
	SD	0.6

實例38.用反式UGI進行活體內編輯

【0727】 當將UGI反式(作為單獨的mRNA)遞送時，將含有去胺酶之構築體之活體內編輯型態與Cas9進行比較。所使用之構築體編碼包括

D10A SpyCas9與去胺酶之融合蛋白質。

【0728】 在此研究中使用6-10週齡範圍內之二十四隻可商購CD-1雌性小鼠(n=3/組)。給藥前對動物稱重以進行給藥計算。在LNP中分別調配每一RNA物種。含有編輯器mRNA、UGI mRNA及G019427 sgRNA之調配物以RNA負荷之w/w比率混合。第2組之調配物混合物僅含有編輯器mRNA及sgRNA且此等以2:1 (編輯器mRNA:sgRNA)之w/w比率混合。第3-8組含有以2:1之w/w比率之mRNA:sgRNA及以1:3、1:10、1:30、1:100、1: 300及1:3000之w/w比率(編輯器mRNA+sgRNA:UGI mRNA)混合之UGI mRNA。除僅用TSS緩衝液給藥之陰性對照組之外，所有組在用G019427靶向之ANACP5基因座處產生編輯。根據表99中所列出之劑量，經由尾部靜脈注射靜脈內投與調配物。在給藥後至少24小時，定期觀測動物之不良反應。處理之後六天，在異氟醚麻醉下藉由心臟穿刺將動物安樂死；收集肝臟組織用於下游分析。收集重量在5與15 mg之間的肝臟穿孔以分離基因體DNA。用NGS定序分析基因體DNA樣本，如實例1中所描述。編輯資料展示於表100及圖60中。圖60展示C形成T純度。

表99 - 每一實驗組之RNA物種的劑量

組	樣本	LNP負荷	編輯器mRNA (mg/kg)	sgRNA劑量 (mg/kg)	UGI mRNA (mg/kg)
1	TSS	無	0	0	0
2	0.0 MPK UGI	BC22n (SEQ ID NO: 2)	0.2	0.1	0.0
3	0.1 MPK UGI	BC22n (SEQ ID NO: 2) G019427 UGI (SEQ ID NO: 26)			0.1
4	0.03 MPK UGI				0.03
5	0.01 MPK UGI				0.01
6	0.003 MPK UGI				0.003
7	0.001 MPK UGI				0.001
8	0.0001 MPK UGI				0.0001

表100 - 小鼠肝臟中之平均編輯

組	C形成T		C形成A/G		插入/缺失		C形成T純度	
	平均	SD	平均	SD	平均	SD	平均	SD
1	0.13	0.06	1.42	0.07	0.09	0.02	7.99	2.88
2	27.30	1.40	21.13	1.99	29.55	1.16	35.00	1.39
3	67.47	0.35	2.99	0.31	5.19	1.05	89.21	1.57
4	65.50	0.87	3.56	0.40	5.17	1.01	88.25	1.68
5	64.73	1.37	4.54	0.49	6.65	0.64	85.25	1.39
6	59.53	1.50	7.07	0.52	9.79	0.84	77.93	1.24
7	53.20	4.94	10.27	1.99	14.08	4.01	68.67	7.23
8	33.90	2.88	18.37	1.82	25.81	2.21	43.44	3.90

實例39.經工程改造之T細胞之細胞毒性敏感性

【0729】 當藉由自然殺手(NK)細胞靶向時，測定經工程改造之T細胞之細胞毒性敏感性。

【0730】 NK細胞(Stemcell Technologies)經解凍且以1x10^6個細胞/ml之細胞濃度再懸浮於由OpTmizer TCGM構成且進一步補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/mL IL-7 (Peprotech，目錄號200-07)、5 ng/mL IL-15 (Peprotech，目錄號200-15)之T細胞生長培養基(TCGM)中。將細胞在37℃下培育24小時。

【0731】 解凍後二十四小時，NK細胞用0.5 μM Cell Trace Violet (CTV)標記如下：將一小瓶CTV (CellTrace™ Violet Cell Proliferation Kit, for flow cytometry, 目錄號C34571)在來自套組之DMSO中重構以得到5 mM儲備濃度。用18 μL磷酸鹽緩衝鹽水(PBS) (Corning，目錄號21-040-CV)稀釋兩μL CTV儲備液以獲得0.5 mM之濃度。NK細胞在500 x g下離心5分鐘，抽吸培養基，且將細胞以1x10^6個細胞/mL之濃度再懸浮於PBS中，使得CTV染料之最終濃度為0.5 μM。將細胞與CTV染料溶液混合，在37℃下培育20分鐘。藉由添加TCGM來淬滅未結合染料且培育5分鐘。將細胞以500 x g離心5分鐘。細胞以2 x 10^6個細胞/mL之濃度再懸浮

於補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/mL IL-7 (Peprotech，目錄號200-07)、5 ng/mL IL-15 (Peprotech，目錄號200-15)中。為測試效應子:目標(E:T)比率範圍，將經CTV標記之NK細胞等分至100 μL培養基中，6點、2倍連續稀釋，最高數目之細胞為2 x 10^5個細胞。包括僅培養基樣本作為陰性對照。

【0732】 使用如實例14中所描述之BC22n及UGI mRNA，使用靶向HLA-A之G023523 (SEQ ID NO: 501)作為測試樣本且用靶向B2M之G023519 (SEQ ID NO: 498)作為NK殺死之陽性對照來工程改造T細胞。測定未編輯之T細胞作為NK殺死之陰性對照。流動式細胞量測術之其他對照包括無T細胞之經CTV標記的NK細胞；組合未經標記之NK細胞與T細胞之「未染色」樣本；及用7AAD染色之未經標記之熱殺死及非熱殺死NK細胞與T細胞之1:1混合物。T細胞以2 x10^5個細胞之密度再懸浮由OpTmizer TCGM構成且進一步補充有100 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/mL IL-7 (Peprotech，目錄號200-07)、5 ng/mL IL-15 (Peprotech，目錄號200-15)之TCGM中。將兩萬個T細胞添加至NK細胞及培養基對照之每一孔中。將細胞在37℃下培育24小時。

【0733】 在24小時時，將來自LD熱殺死孔之一半體積之細胞熱殺死且轉移回至測定板中的相同孔。將細胞離心且再懸浮於80 μL之7-AAD (BD Biosciences，目錄號559925)於FACS緩衝液(PBS + 2% FBS (Gibco，目錄號A31605-02) + 2mM EDTA (Invitrogen，目錄號15-575-020))之1:200 v/v溶液中。藉由流動式細胞量測術使用Cytoflex LX儀器(Beckman Coulter)獲取T細胞之比溶胞率之資料且使用FlowJo套裝軟體進

行分析。首先在CTV陰性群體上抽取閘極以清除NK細胞，接著在單重態上閘控，其後在7-AAD陰性群體上抽取閘極以閘控活T細胞。藉由自100減去活細胞百分比來計算T細胞之溶解百分比。使用BC22n及HLA-A導引G023523 (SEQ ID NO: 501)編輯之T細胞受到保護，免受NK細胞介導之細胞毒性，如表101及圖62中所展示。

表101 - 暴露於HLA-B及C匹配NK細胞之經工程改造之T細胞的平均溶解百分比

E:T	未編輯			G023519 B2M			G023523 HLA-A		
	平均	SD	n	平均	SD	n	平均	SD	n
10	19.65	2.33	2	69.60	4.81	2	22.23	1.10	3
5	18.80	1.59	3	61.10	0.85	2	21.35	0.49	2
2.5	22.27	6.62	3	47.95	0.49	2	22.10	1.27	2
1.25	18.47	1.27	3	39.20	2.98	3	21.00	0.81	3
0.63	19.30	0.66	3	30.20	NA	1	19.75	0.35	2
0.31	20.70	5.02	3	40.60	NA	1	20.27	1.67	3
0	19.77	2.01	3	26.57	2.73	3	18.30	1.41	3

實例40 - 用於SpyCas9及Nme2Cas9鹼基編輯器之編輯視窗

【0734】 藉由在導引區中具有胞嘧啶殘基之一組目標位點上逐個位置地評估C形成T轉化功效來測定可用於藉由設計有Nme2Cas9切口酶或SPyCas9切口酶及APOBEC3a之鹼基編輯器去胺作用的導引位置範圍。

實例40.1 T細胞製備

【0735】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8 MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0736】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTmizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/ml重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在電穿孔之前活化48小時。

實例40.2用RNA電穿孔進行T細胞編輯

【0737】 在P3緩衝液中製備含有編碼Spy BC22n (SEQ ID NO: 1)或Nme2 BC22n (SEQ ID NO: 315)及UGI (SEQ ID NO: 34)之mRNA的溶液。自儲存移除靶向SCAP、LINC01588、LSP1、SEC61B、VEGFA、FancF、AAVS1或ARHGEF9基因座之導引RNA，且在95℃下變性2分鐘且在室溫下培育5分鐘。

【0738】 活化後四十八小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於待電穿孔之每一孔，將1 x 10^5個T細胞與200 ng BC22n或Nme2鹼基編輯器mRNA、200 ng UGI mRNA及4 μM sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式兩份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL CTS最佳化器T細胞生長培養基中靜置15分鐘，隨後轉移至含有額外80 μL補

充有2X細胞介素之CTS OpTmizer T細胞生長培養基的新平底96孔板中。將所得板在37℃下培育4天。在電穿孔後第4天，採集100 μL細胞用於DNA提取。對DNA樣本進行PCR及藉由兩個單獨引子組(技術複製品)之後續NGS分析，如實例1中所描述。

實例40.3鹼基編輯器編輯視窗分析

【0739】 位置值係分配給原型間隔區及其5'及3'相鄰核苷酸內之每一DNA鹼基。對於SpyCas9，位置1至20表示SpyCas9導引物所結合之20個鹼基，其中位置1為PAM遠端鹼基且位置20為PAM近端鹼基。對於Nme2Cas9，位置1至24表示Nme2Cas9導引物所結合之24個鹼基，其中位置1為PAM遠端鹼基且位置24為PAM近端鹼基。原型間隔區外部之5'及3'端分別經分配為負及正位置；相對於位置1。

【0740】 **定義轉化頻率：**導引物可經設計以靶向基因之參考股(股+)或反向互補股(股-)。對於股+導引物，記錄目標區中之每一野生型胞嘧啶位置且將該位置處之轉化頻率(胞嘧啶至胸腺嘧啶)計算為在該位置處具有胸腺嘧啶之定序讀數與在該位置處具有胞嘧啶或胸腺嘧啶之讀數之比率；對於股-導引物，記錄目標區中之每一野生型鳥嘌呤位置且將該位置處之轉化頻率(鳥嘌呤至腺嘌呤)計算為在該位置處具有腺嘌呤之定序讀數與在該位置處具有腺嘌呤及鳥嘌呤之讀數之比率。

【0741】 **對導引活性進行分類：**量測每一導引物之四個複製品：兩個生物複製品中之每一者的兩個技術複製品。僅將進一步分析具有>500個定序讀數之複製品中之位置。對於每一導引物，位置之平均轉化頻率為複製品之平均值，且導引物之所有位置之最高平均轉化頻率用於對此導引物之轉化活性進行分類：低、中及高活性導引物分別具有<50%、50%及

<70%、>70%之最高平均轉化頻率。選擇BC22n (n=38)及Nme2鹼基編輯器(n=14)之高活性導引物以用於如表102中所展示之進一步視窗分析。

表102 - 包括於編輯視窗分析中之高活性導引序列

導引物	編輯器物種	導引物	編輯器物種	導引物	編輯器物種
G021514	Nme2	G009272	Spy	G021549	Spy
G021519	Nme2	G009295	Spy	G021573	Spy
G021524	Nme2	G009303	Spy	G021574	Spy
G021529	Nme2	G009330	Spy	G021575	Spy
G021550	Nme2	G009333	Spy	G021576	Spy
G021551	Nme2	G012243	Spy	G021577	Spy
G021552	Nme2	G013549	Spy	G021578	Spy
G021553	Nme2	G013578	Spy	G021579	Spy
G021554	Nme2	G021537	Spy	G021582	Spy
G021555	Nme2	G021538	Spy	G021584	Spy
G021556	Nme2	G021540	Spy	G021585	Spy
G021560	Nme2	G021541	Spy	G021586	Spy
G021562	Nme2	G021542	Spy	G021587	Spy
G021570	Nme2	G021543	Spy	G021588	Spy
G009252	Spy	G021544	Spy	G021589	Spy
G009255	Spy	G021545	Spy	G021591	Spy
G009260	Spy	G021548	Spy	G021593	Spy
G009269	Spy				

【0742】 **定義所有導引物上每一位置之轉化率**：若導引物具有所記錄位置，則其複製品中之每一者在該位置具有>500個定序讀數被視為「案例」。針對所有導引物之每一位置對總案例求和且充當轉化率計算之分母。在每一案例中，若轉化頻率大於50%，則其被視為高轉化「事件」，且總事件為所有導引物及複製品上之每一位置之高轉化事件的總和。「事件」充當轉化率計算之分子。位置之轉化率等於在所有案例中針對每一位置之高轉化事件的百分比。

【0743】 表103顯示spyBC22n C形成T編輯視窗之位置、案例、事件及轉化率。圖63展示按位置BC22n之轉化率。圖64展示用於Nme2鹼基編輯器之按位置之轉化率。用於spyBC22n之位置1至11及用於Nme2BC22之位置4至20展示超過25%之轉化率。

表103 - 針對Spy鹼基編輯器及Nme2鹼基編輯器構築體之轉化率。

編輯器	Pos.	事件	案例	轉化率	編輯器	Pos.	事件	案例	轉化率
Nme2	-20	0	14	0.0%	Spy	-20	0	48	0.0%
Nme2	-19	0	9	0.0%	Spy	-19	0	29	0.0%
Nme2	-18	0	24	0.0%	Spy	-18	0	26	0.0%
Nme2	-17	0	24	0.0%	Spy	-17	0	32	0.0%
Nme2	-16	0	24	0.0%	Spy	-16	0	30	0.0%
Nme2	-15	0	14	0.0%	Spy	-15	0	43	0.0%
Nme2	-14	0	15	0.0%	Spy	-14	0	39	0.0%
Nme2	-13	0	9	0.0%	Spy	-13	0	54	0.0%
Nme2	-12	0	17	0.0%	Spy	-12	0	60	0.0%
Nme2	-11	0	17	0.0%	Spy	-11	0	35	0.0%
Nme2	-10	0	10	0.0%	Spy	-10	4	47	8.5%
Nme2	-9	0	24	0.0%	Spy	-9	0	38	0.0%
Nme2	-8	0	12	0.0%	Spy	-8	0	33	0.0%
Nme2	-7	0	14	0.0%	Spy	-7	0	24	0.0%
Nme2	-6	0	30	0.0%	Spy	-6	4	41	9.8%
Nme2	-5	0	19	0.0%	Spy	-5	4	37	10.8%
Nme2	-4	0	12	0.0%	Spy	-4	0	25	0.0%
Nme2	-3	0	4	0.0%	Spy	-3	0	42	0.0%
Nme2	-2	0	24	0.0%	Spy	-2	0	38	0.0%
Nme2	-1	0	18	0.0%	Spy	-1	11	56	19.6%
Nme2	1	0	14	0.0%	Spy	1	26	43	60.5%
Nme2	2	1	17	5.9%	Spy	2	31	51	60.8%
Nme2	3	3	17	17.6%	Spy	3	34	38	89.5%
Nme2	4	6	24	25.0%	Spy	4	41	41	100.0%
Nme2	5	8	14	57.1%	Spy	5	52	52	100.0%
Nme2	6	8	14	57.1%	Spy	6	39	39	100.0%
Nme2	7	8	18	44.4%	Spy	7	37	37	100.0%
Nme2	8	5	18	27.8%	Spy	8	42	42	100.0%
Nme2	9	7	28	25.0%	Spy	9	38	38	100.0%
Nme2	10	14	17	82.4%	Spy	10	33	45	73.3%
Nme2	11	15	21	71.4%	Spy	11	28	48	58.3%
Nme2	12	12	16	75.0%	Spy	12	8	57	14.0%
Nme2	13	6	10	60.0%	Spy	13	0	63	0.0%
Nme2	14	11	11	100.0%	Spy	14	1	55	1.8%
Nme2	15	21	23	91.3%	Spy	15	0	45	0.0%
Nme2	16	17	19	89.5%	Spy	16	0	50	0.0%
Nme2	17	11	16	68.8%	Spy	17	0	42	0.0%
Nme2	18	2	16	12.5%	Spy	18	0	59	0.0%
Nme2	19	2	12	16.7%	Spy	19	0	62	0.0%
Nme2	20	6	16	37.5%	Spy	20	0	54	0.0%
Nme2	21	4	20	20.0%	Spy	21	n/a	0	n/a
Nme2	22	0	19	0.0%	Spy	22	n/a	0	n/a
Nme2	23	0	16	0.0%	Spy	23	0	23	0.0%
Nme2	24	0	20	0.0%	Spy	24	0	46	0.0%
Nme2	25	n/a	0	n/a	Spy	25	0	123	0.0%
Nme2	26	n/a	0	n/a	Spy	26	0	127	0.0%

編輯器	Pos.	事件	案例	轉化率	編輯器	Pos.	事件	案例	轉化率
Nme2	27	0	10	0.0%	Spy	27	0	47	0.0%
Nme2	28	0	8	0.0%	Spy	28	0	38	0.0%
Nme2	29	0	45	0.0%	Spy	29	0	37	0.0%
Nme2	30	0	45	0.0%	Spy	30	0	51	0.0%
Nme2	31	0	9	0.0%	Spy	31	0	44	0.0%
Nme2	32	0	12	0.0%	Spy	32	0	42	0.0%
Nme2	33	0	22	0.0%	Spy	33	0	34	0.0%
Nme2	34	0	24	0.0%	Spy	34	0	39	0.0%
Nme2	35	0	18	0.0%	Spy	35	0	43	0.0%
Nme2	36	0	13	0.0%	Spy	36	0	37	0.0%
Nme2	37	0	13	0.0%	Spy	37	0	32	0.0%
Nme2	38	0	9	0.0%	Spy	38	0	33	0.0%
Nme2	39	0	16	0.0%	Spy	39	0	50	0.0%
Nme2	40	0	6	0.0%	Spy	40	0	33	0.0%

實例41 - 用BC22n在T細胞中進行CIITA導引RNA篩選

【0744】 使用C形成T鹼基編輯篩選不同sgRNA在人類T細胞中剔除CIITA基因之效力。在用mRNA及不同sgRNA電穿孔之後進行CIITA編輯之後，測定對於MHC II類及/或CD74蛋白質表現呈陰性之T細胞的百分比。

實例41.1 T細胞製備

【0745】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌且再懸浮於CliniMACS® PBS/EDTA緩衝液(Miltenyi Biotec目錄號130-070-525)中且在MultiMACS™ Cell 24 Separator Plus裝置(Miltenyi Biotec)中進行處理。使用Straight from Leukopak® CD4/CD8 MicroBead套組，人類(Miltenyi Biotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor® CS10 (StemCell Technologies目錄號07930)中冷凍保存以供將來使用。

【0746】 在解凍之後，將T細胞以1.0 x 10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTS OpTimizer T細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類

AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1X Glutamax、10 mM HEPES、200 U/mL重組人類介白素-2 (Peprotech，目錄號200-02)、5 ng/mL重組人類介白素7 (Peprotech，目錄號200-07)及5 ng/ml重組人類介白素15 (Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在電穿孔之前活化48小時。

實例41.2用RNA電穿孔進行T細胞編輯

【0747】 在P3緩衝液中製備含有編碼BC22n (SEQ ID NO: 1)及UGI (SEQ ID NO: 34)之mRNA的溶液。將一百μM CIITA靶向sgRNA自其儲存板移除，且在95℃下變性2分鐘，且在室溫下培育5分鐘。活化後四十八小時，採集T細胞，離心，且以12.5 x 10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。對於電穿孔，如表1中所描述，將1 x 10^5個T細胞與20 ng/μL BC22n mRNA、20 ng/μL UGI mRNA及20 pmols sgRNA在最終體積為20 μL之P3電穿孔緩衝液中混合。此混合物一式兩份轉移至96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80 μL CTS最佳化器T細胞生長培養基中靜置15分鐘，隨後轉移至含有額外80 μL補充有2X細胞介素之CTS最佳化器T細胞生長培養基的新平底96孔板中。將所得板在37℃下培育10天。在電穿孔後第4天，細胞在2個U形底板中以1:2分裂。收集一個板用於NGS定序，而另一板補充有含1X細胞介素之CTS最佳化器新鮮培養基。此板在第7天用於流動式細胞量測術。

實例41.3流動式細胞量測術及NGS定序

【0748】 編輯後第7天，藉由流動式細胞量測術測定T細胞以判定CD74及HLA-DR、DP、DQ之表面表現。簡言之，將T細胞與在細胞染色緩衝液(BioLegend，目錄號420201)中稀釋之抗體的混合物一起在4℃下培育30分鐘。抗CD3 (BioLegend，目錄號317336)、CD4 (BioLegend，目錄號317434)、CD8 (BioLegend，目錄號301046)及Viakrome (Beckman Coulter，目錄號C36628)之抗體以1:100稀釋，且抗HLA II-DR (BioLegend，目錄號327018)、HLA II-DP (BD Biosciences，目錄號750872)、HLA II-DQ (BioLegend，目錄號561504)及CD74 (BioLegend，目錄號326808)之抗體以1:50稀釋。隨後洗滌細胞，再懸浮於100 μL細胞染色緩衝液中且在Cytoflex流式細胞儀(Beckman Coulter)上進行處理。使用FlowJo套裝軟體分析流動式細胞量測術資料。T細胞基於大小、形狀、活力、CD8、HLA II-DP、HLA II-DQ、HLA II-DR及CD74表現進行閘控。

表104.用BC22n對*CIITA*進行基因體編輯之後對於表面蛋白質呈陰性之細胞的百分比。(n=2)

導引ID	%HLA II-DP-		%HLA II-DQ-		%HLA II-DR-		%CD74-	
	平均	SD	平均	SD	平均	SD	平均	SD
G000502	68.70	3.54	76.30	4.24	76.70	3.96	66.25	5.87
G016788	62.95	1.91	73.40	3.11	73.50	4.38	61.35	4.60
G016053	70.25	6.72	71.50	4.95	73.90	4.10	60.20	6.08
G016103	63.05	6.29	73.95	1.20	75.30	0.71	63.25	1.63
G016114	65.80	1.98	74.70	4.38	75.85	5.30	65.25	5.87
G016117	63.70	0.57	74.60	3.25	76.00	3.11	63.45	5.30
G016034	85.55	2.19	86.30	1.13	87.95	0.07	80.30	0.14
G016035	85.35	3.75	83.55	1.06	84.05	0.35	75.25	1.20
G016039	74.95	0.35	78.20	0.71	78.50	0.28	68.90	1.27
G016040	61.90	0.85	76.30	2.26	77.80	1.56	64.10	2.55
G016041	68.60	1.84	77.30	0.85	76.75	0.35	64.20	0.00
G016043	79.95	1.48	82.55	0.35	82.50	0.71	73.80	0.00
G016044	87.84	3.17	87.80	1.56	88.65	1.34	83.75	1.91
G016045	82.25	2.90	88.70	0.99	88.35	0.78	83.40	0.99
G016047	76.85	0.21	85.40	0.28	85.05	0.21	79.20	0.00
G016050	59.05	1.91	86.80	0.71	83.40	0.57	79.00	0.99

導引ID	%HLA II-DP-		%HLA II-DQ-		%HLA II-DR-		%CD74-	
	平均	SD	平均	SD	平均	SD	平均	SD
G016052	76.85	0.21	79.25	0.78	80.55	0.92	70.85	1.34
G016054	70.30	1.70	79.85	1.20	79.30	0.42	70.35	0.35
G016055	73.35	1.34	82.15	2.19	82.15	1.77	73.10	1.56
G016056	75.80	1.41	86.05	1.20	86.35	1.34	79.05	1.91
G016057	77.90	0.71	83.95	0.35	84.45	0.21	75.30	0.99
G016058	83.65	2.19	87.25	1.06	88.20	0.99	81.20	1.41
G016060	72.55	0.78	82.70	1.84	83.05	2.47	73.55	2.76
G016061	73.15	6.29	83.10	0.57	82.55	0.21	74.50	0.42
G016063	74.60	7.35	83.75	0.64	83.50	0.71	75.45	0.35
G016064	97.98	0.17	97.80	0.18	96.83	0.13	98.58	0.04
G016065	77.80	0.28	77.70	1.98	80.00	1.56	69.35	3.18
G016068	97.73	0.26	98.07	0.81	97.59	0.66	98.55	0.66
G016071	87.05	4.31	88.55	0.49	89.45	0.49	84.80	0.85
G016074	96.88	0.19	96.34	0.04	95.85	0.57	96.56	0.23
G016075	86.05	0.92	88.20	0.85	88.50	0.14	83.50	1.27
G016076	96.69	0.64	96.67	0.01	96.38	0.02	96.34	0.18
G016077	92.27	2.50	91.20	1.22	91.40	1.44	89.39	1.68
G016078	71.20	0.28	79.55	1.48	80.65	1.48	70.40	0.85
G016079	89.31	1.57	91.24	0.55	90.24	0.00	88.40	0.14
G016081	74.35	0.07	83.05	1.06	83.00	0.42	73.20	1.41
G016082	82.30	5.09	87.50	0.71	88.80	0.14	82.25	0.07
G016083	74.95	4.88	82.90	0.57	83.95	0.21	74.65	1.06
G016085	79.90	2.97	85.40	0.71	87.45	0.07	79.45	0.49
G016086	97.71	0.33	98.06	0.44	96.63	0.08	98.89	0.18
G016087	70.25	9.12	78.55	3.61	78.30	3.39	69.30	4.24
G016088	82.25	5.16	87.40	0.57	88.30	0.42	81.75	1.06
G016089	69.00	1.27	76.65	1.34	79.00	1.70	67.35	1.06
G016091	95.35	0.95	96.81	0.24	96.64	0.25	97.15	0.28
G016092	94.89	0.61	94.87	0.45	95.35	0.83	94.65	0.37
G016093	91.33	0.31	92.35	0.26	93.94	0.23	90.51	0.37
G016094	79.70	4.24	84.85	2.05	85.70	2.69	78.75	2.90
G016095	83.00	2.12	90.55	0.23	90.54	0.24	85.25	0.49
G016097	71.85	6.86	82.80	1.56	82.40	1.27	73.00	1.70
G016098	74.40	5.66	82.35	3.32	83.50	2.69	74.55	4.45
G016099	86.30	2.69	89.71	1.00	90.57	0.35	86.25	1.06
G016100	76.65	1.34	83.90	2.69	86.25	2.19	77.25	3.04
G016101	69.30	0.71	77.55	1.48	78.55	1.77	68.65	1.77
G016102	71.00	1.84	80.70	0.99	80.60	1.56	70.10	0.99
G016106	82.00	1.27	87.55	0.64	88.80	0.71	81.30	1.41
G016108	88.24	3.73	91.49	0.02	91.42	0.66	87.00	0.85
G016109	88.05	0.92	90.20	1.27	90.41	1.85	86.85	2.05
G016110	88.50	3.25	91.12	0.99	90.14	1.05	87.35	1.20
G016111	78.15	0.92	84.45	0.78	85.80	0.85	78.45	1.20
G016112	72.20	3.82	79.85	2.33	81.70	2.26	73.05	2.47
G016115	95.58	1.10	98.36	0.73	97.69	0.48	98.54	0.40
G016116	88.95	0.35	91.15	2.47	92.29	1.79	88.08	2.94
G016066	68.90	0.57	73.20	1.70	74.20	0.99	62.25	2.76

導引ID	%HLA II-DP-		%HLA II-DQ-		%HLA II-DR-		%CD74-	
	平均	SD	平均	SD	平均	SD	平均	SD
G016113	93.60	1.15	93.02	0.98	93.75	0.66	92.13	1.20
G016084	96.42	0.83	98.38	0.33	97.32	0.69	98.77	0.17
G016104	84.95	1.77	89.69	1.53	91.20	0.97	86.00	1.41
G016070	90.52	0.16	92.10	0.50	92.49	0.64	89.75	0.91
G016090	96.41	1.27	98.06	0.08	97.43	0.15	98.66	0.10
G016048	76.80	1.56	80.60	0.99	81.70	1.41	72.25	2.19
G016051	65.85	20.44	83.15	1.63	84.45	1.34	75.20	2.40
G016073	82.00	1.98	82.65	1.20	83.15	2.76	75.90	0.14
G016037	80.55	1.91	78.05	0.35	80.15	0.07	70.20	0.57
G016038	85.45	0.49	82.45	0.35	84.90	0.28	76.10	1.13
G016046	90.10	0.05	90.75	0.47	91.09	0.86	87.45	0.78
G016049	84.50	0.00	84.90	0.42	86.75	0.07	78.75	0.21
G016036	85.05	1.06	83.15	1.48	85.00	0.99	76.45	2.47
G016080	91.13	2.02	92.11	1.07	92.99	0.97	89.72	1.16
G016096	75.00	4.38	82.90	3.82	83.45	3.61	75.65	4.31
G016032	97.50	0.09	97.42	0.65	96.30	0.33	98.19	0.36
G016033	91.32	0.88	87.75	0.49	88.20	0.28	84.10	0.14
G016030	93.42	0.08	88.10	0.71	88.40	0.42	85.10	0.28
G016067	96.69	0.25	95.82	0.69	95.14	0.64	96.30	0.48
G016031	80.45	1.20	82.10	0.99	83.95	0.07	74.80	0.57
G016062	74.80	11.17	86.60	0.28	86.75	0.35	80.15	0.35
G016059	77.05	3.75	83.05	0.92	83.85	0.92	75.00	1.41
G016105	66.55	5.87	74.90	3.68	76.50	3.68	65.25	3.75
G016107	71.80	4.10	80.70	0.28	80.75	0.49	71.00	0.57
G016042	95.06	0.02	95.90	0.30	94.17	0.35	94.89	1.02
G016069	52.65	3.18	76.35	0.21	75.90	0.28	62.35	0.21
G016072	46.45	4.45	73.50	0.57	71.35	0.92	56.55	0.64
G018021	76.60	0.99	84.00	0.57	84.65	0.49	76.85	0.07
G018022	60.00	3.39	72.20	1.13	73.25	1.34	60.35	2.62
G018023	64.80	2.97	74.35	0.07	75.85	0.35	63.85	2.33
G018024	64.10	1.70	74.80	1.84	74.90	1.98	63.75	4.03
G018025	63.85	6.15	73.50	6.08	74.90	6.36	63.75	6.72
G018026	72.15	4.17	81.35	0.92	82.55	1.48	73.00	0.71
G018027	82.40	0.99	81.45	1.91	82.40	2.26	72.35	3.32
G018028	78.25	0.49	78.40	0.00	80.05	0.49	67.90	2.40
G018029	75.60	3.11	74.80	0.14	76.95	0.07	64.15	2.05
G018030	76.70	1.56	76.35	3.46	77.80	3.54	66.65	5.44
G018031	81.40	3.96	84.00	1.13	82.40	0.42	75.55	0.49
G018032	77.00	2.97	79.70	0.14	79.30	0.42	70.35	0.92
G018033	81.15	3.04	82.05	0.35	81.60	0.57	73.20	1.27
G018034	96.87	0.43	93.49	0.88	92.67	0.99	92.96	1.63
G018035	94.39	0.64	88.20	1.13	88.64	2.03	83.70	2.97
G018036	73.80	0.28	76.45	2.19	77.55	2.90	65.30	3.82
G018037	71.80	0.14	72.25	5.16	73.85	5.73	61.40	7.64
G018038	70.25	7.85	74.95	1.06	75.65	2.05	63.65	2.62
G018039	94.72	0.49	91.67	0.05	91.17	0.51	89.20	0.99
G018040	77.30	1.13	81.70	0.42	81.60	0.57	72.35	0.64

導引ID	%HLA II-DP-		%HLA II-DQ-		%HLA II-DR-		%CD74-	
	平均	SD	平均	SD	平均	SD	平均	SD
G018041	75.10	1.70	80.15	0.35	80.15	0.21	70.50	0.85
G018042	89.35	0.49	86.60	0.14	87.90	0.14	80.50	0.00
G018043	85.50	1.13	84.00	1.56	84.95	0.35	77.55	0.64
G018044	88.20	0.99	89.01	1.57	89.25	0.78	83.95	2.19
G018045	76.15	1.34	82.35	2.33	81.60	2.26	72.50	3.25
G018046	87.20	0.42	88.65	0.21	89.00	0.57	82.80	1.27
G018047	79.95	1.63	84.60	2.12	84.25	2.76	76.25	3.61
G018048	88.50	2.12	88.00	1.13	89.50	0.42	81.60	0.14
G018049	81.40	3.25	81.40	4.24	82.60	5.23	74.00	5.66
G018050	77.75	0.49	78.60	0.85	80.85	0.07	70.25	0.35
G018051	81.20	1.56	81.95	1.48	84.20	1.13	73.55	3.04
G018052	76.30	1.56	81.70	1.27	81.10	1.56	70.90	2.69
G018053	77.25	1.06	81.40	0.85	82.35	1.06	71.55	1.63
G018054	90.23	0.14	89.00	0.99	89.25	0.64	84.50	0.28
G018055	73.80	3.39	79.20	0.99	79.85	1.06	67.80	1.41
G018056	73.40	2.97	83.15	0.35	83.15	0.78	73.15	0.78
G018057	73.95	1.63	81.40	2.97	81.45	1.91	71.30	3.11
G018058	73.40	3.25	80.90	0.99	81.05	0.07	69.15	0.35
G018059	75.15	4.17	81.70	0.14	81.55	0.07	71.10	1.13
G018060	75.90	2.69	81.30	0.28	81.55	0.78	72.05	1.91
G018061	71.65	2.05	81.60	1.41	80.65	1.06	72.00	1.41
G018062	70.75	2.33	75.05	0.64	76.30	1.56	64.65	2.33
G018063	78.45	0.92	80.95	0.92	82.20	0.85	72.50	0.14
G018064	76.15	0.78	82.50	0.00	82.90	0.28	73.90	0.28
G018065	77.65	0.21	82.60	0.42	83.85	0.35	74.05	0.07
G018066	72.60	0.00	82.30	0.28	83.05	0.64	73.60	0.14
G018067	97.57	0.81	98.24	0.19	97.73	0.28	98.83	0.04
G018068	89.05	0.64	90.79	0.52	90.81	1.02	87.20	1.27
G018069	75.90	2.55	81.55	0.92	82.15	0.35	71.85	1.20
G018070	75.30	1.27	82.05	1.20	82.15	0.64	71.20	0.42
G018071	77.40	3.39	83.35	1.77	84.75	1.91	74.65	0.92
G018072	72.05	1.63	81.45	0.78	81.95	1.91	71.95	2.62
G018073	72.35	0.07	79.30	1.13	79.25	2.19	69.40	2.26
G018074	67.25	2.05	75.25	0.49	76.40	0.57	64.35	0.35
G018075	96.86	1.46	97.33	0.14	96.08	0.31	98.35	0.04
G018076	94.26	4.87	97.96	0.21	97.57	0.15	98.55	0.06
G018077	74.75	2.76	81.65	0.35	82.25	0.21	72.25	1.34
G018078	94.30	0.48	94.87	0.31	95.03	0.06	93.43	0.24
G018079	86.00	1.56	89.55	0.35	89.80	0.28	84.25	0.78
G018080	80.50	3.96	85.50	1.70	85.45	1.63	78.35	0.78
G018081	79.85	1.06	86.05	1.20	86.00	0.85	78.70	0.57
G018082	80.10	0.14	83.10	0.42	84.05	1.20	75.65	1.91
G018083	86.75	1.34	89.50	0.28	89.35	0.21	84.55	0.21
G018084	84.60	3.25	87.35	1.34	87.95	0.92	82.00	1.27
G018085	86.95	2.76	90.35	2.05	90.03	1.03	86.30	2.26
G018086	68.15	1.34	78.60	0.42	75.95	0.07	66.25	0.92
G018087	61.40	2.26	74.35	2.33	72.65	2.62	61.85	1.63

導引ID	%HLA II-DP-		%HLA II-DQ-		%HLA II-DR-		%CD74-	
	平均	SD	平均	SD	平均	SD	平均	SD
G018088	88.80	0.85	91.11	0.28	91.88	0.11	87.60	1.41
G018089	81.75	4.17	89.00	1.83	89.28	1.53	83.75	1.77
G018090	81.65	1.20	90.11	0.29	89.98	0.25	85.35	1.34
G018091	97.02	0.49	98.63	0.03	98.15	0.12	98.98	0.08
G018092	71.40	5.23	81.90	0.71	82.40	0.85	73.45	0.92
G018093	94.15	1.20	96.36	0.21	96.36	0.02	95.70	0.18
G018094	77.50	2.12	84.55	1.63	85.25	1.48	76.50	0.14
G018095	69.50	0.00	83.05	0.07	82.70	0.14	73.90	0.99
G018096	69.25	0.21	83.50	0.99	83.45	1.06	75.25	2.05
G018097	68.55	4.74	81.60	2.83	82.20	1.84	73.25	3.75
G018098	66.65	0.21	78.85	0.21	79.75	0.21	68.75	1.20
G018099	65.05	3.18	73.70	4.95	74.55	4.31	62.40	4.53
G018100	95.51	0.40	95.99	0.19	95.62	0.92	96.21	0.18
G018101	93.00	0.33	93.70	0.01	94.03	0.25	93.11	0.28
G018102	96.55	0.33	96.31	0.64	96.34	0.08	96.58	0.08
G018103	96.92	1.46	97.58	0.02	97.53	0.08	98.36	0.40
G018104	72.00	0.99	82.45	2.19	82.70	1.84	73.40	2.12
G018105	71.60	1.98	82.20	0.71	81.80	0.28	73.30	0.00
G018106	92.49	1.33	98.62	0.06	97.03	0.43	98.96	0.04
G018107	96.55	1.25	98.14	0.56	97.53	0.70	98.98	0.08
G018108	85.50	0.42	88.00	0.71	89.35	0.92	83.40	1.56
G018109	84.10	1.56	84.55	2.19	86.90	1.27	79.75	3.32
G018110	67.65	3.04	75.15	0.49	77.50	0.99	65.35	1.48
G018111	96.49	0.35	96.85	1.05	95.24	1.32	97.03	0.52
G018112	68.60	5.09	76.65	4.88	77.30	4.53	66.60	4.38
G018113	72.75	3.89	79.60	3.54	80.15	2.76	70.30	3.96
G018114	70.80	2.26	80.05	2.47	81.25	1.77	71.65	2.62
G018115	62.40	1.41	77.40	0.57	76.90	1.27	67.00	1.56
G018116	96.05	0.89	98.01	0.39	96.99	0.42	98.32	0.21
G018117	96.93	1.27	97.63	0.52	97.19	0.87	98.96	0.25
G018118	97.25	0.51	97.71	0.25	96.94	0.44	98.91	0.26
G018119	94.78	1.02	96.29	1.11	95.57	1.05	97.00	1.20
G018120	96.04	1.87	97.61	0.06	97.42	0.56	98.94	0.07
G018121	95.26	0.62	97.12	0.41	96.44	0.23	97.85	0.45

【0749】 在編輯後第4天，對DNA樣本進行PCR及後續NGS分析，如實例1中所描述。表105展示用BC22n編輯之T細胞中之CIITA編輯結果。

表105 - 在CIITA基因座處用BC22n之平均編輯百分比。(n=2)

導引ID	%C形成T		%C形成A/G		%插入/缺失	
	平均	SD	平均	SD	平均	SD
G000502	84.63	2.39	0.82	0.19	1.26	0.37
G016788	95.63	0.06	0.99	0.39	0.72	0.15
G016053	94.77	1.07	1.66	0.43	0.71	0.02
G016103	95.60	0.97	0.63	0.23	0.75	0.29
G016114	96.42	0.23	0.66	0.59	0.65	0.09
G016117	96.23	0.70	0.82	0.28	0.90	0.17
G016034	93.11	1.07	0.61	0.21	1.49	0.52
G016035	95.41	0.59	0.52	0.31	0.62	0.24
G016039	88.20	1.33	1.51	0.42	7.99	1.32
G016043	88.51	2.91	1.27	0.11	2.23	0.46
G016044	0.13	0.03	90.04	0.38	9.83	0.41
G016045	61.66	0.51	1.73	0.90	7.12	0.22
G016047	92.74	0.48	0.80	0.06	3.00	0.13
G016050	90.63	0.04	1.35	0.38	1.87	0.56
G016052	92.68	1.74	0.83	0.44	3.26	1.66
G016054	90.82	2.94	1.03	0.89	4.38	4.28
G016055	83.61	1.98	0.46	0.21	10.63	1.04
G016056	96.69	0.65	0.30	0.03	0.64	0.35
G016057	93.83	0.35	0.98	0.18	0.99	0.47
G016058	95.49	0.06	0.35	0.14	0.41	0.31
G016060	85.95	0.54	0.49	0.16	7.63	1.63
G016061	92.81	2.51	0.59	0.34	0.75	0.19
G016063	70.60	1.87	0.31	0.15	0.25	0.07
G016064	94.14	2.28	0.81	0.41	0.97	0.33
G016065	57.50	1.68	0.61	0.37	1.15	0.32
G016068	94.26	0.97	0.34	0.16	0.52	0.21
G016071	93.78	0.73	0.84	0.14	2.17	0.40
G016074	93.88	1.20	0.92	0.19	2.41	0.28
G016075	91.72	0.73	0.58	0.15	2.89	0.52
G016076	91.24	1.10	0.28	0.20	3.02	1.02
G016077	94.94	1.07	1.08	0.53	1.50	0.46
G016078	93.52	1.78	0.41	0.15	3.30	1.54
G016079	96.29	0.05	0.51	0.08	0.81	0.13
G016081	75.32	7.28	1.33	1.44	7.61	7.04
G016082	31.35	5.20	0.07	0.14	34.39	6.24
G016083	0.24	0.08	99.63	0.11	0.08	0.06
G016085	80.16	3.07	0.74	0.37	0.36	0.12
G016086	96.02	1.68	1.45	0.46	0.84	0.38
G016087	90.30	1.43	0.32	0.20	5.11	0.54
G016088	92.14	0.51	1.05	0.33	2.24	0.86
G016089	94.49	0.39	0.61	0.30	1.14	0.30
G016091	95.93	0.99	1.03	0.23	0.37	0.09
G016092	95.62	0.79	1.17	0.40	0.71	0.28
G016093	95.74	0.81	0.94	0.43	0.43	0.18
G016094	95.85	1.03	0.58	0.39	0.99	0.48

導引ID	%C形成T		%C形成A/G		%插入/缺失	
	平均	SD	平均	SD	平均	SD
G016095	94.77	0.52	1.32	0.31	0.72	0.37
G016097	94.90	1.64	0.55	0.19	1.40	0.51
G016098	91.71	1.11	0.48	0.18	0.50	0.36
G016099	93.42	1.55	0.56	0.05	3.64	1.06
G016100	96.54	0.93	0.46	0.22	0.46	0.36
G016101	41.21	1.15	0.77	0.07	0.22	0.04
G016102	96.06	1.23	0.46	0.05	0.69	0.25
G016106	90.41	1.16	3.33	0.54	2.66	0.49
G016108	76.19	0.74	0.42	0.28	0.69	0.38
G016109	94.93	0.35	0.46	0.21	1.86	0.59
G016110	87.64	1.01	0.55	0.20	7.63	0.72
G016111	92.93	1.09	1.17	0.58	2.11	1.08
G016112	1.56	0.46	1.79	0.90	0.03	0.05
G016115	89.86	1.01	0.67	0.29	7.30	0.50
G016116	91.37	0.33	0.54	0.27	0.59	0.09
G016066	1.02	0.16	0.32	0.07	0.40	0.21
G016113	93.23	0.98	1.10	0.16	2.40	0.57
G016084	74.10	1.35	0.87	0.16	21.41	0.94
G016104	0.00	0.00	0.00	0.00	0.00	0.00
G016070	94.80	0.30	0.54	0.04	1.66	0.17
G016090	84.09	0.00	0.51	0.00	12.29	0.00
G016048	48.81	1.82	0.78	0.07	0.54	0.18
G016051	95.69	0.45	1.06	0.09	0.91	0.25
G016073	94.11	0.83	0.76	0.18	1.37	0.29
G016037	64.35	3.31	1.61	0.81	3.46	4.94
G016038	94.99	2.01	1.80	0.64	1.25	0.88
G016046	82.29	2.89	0.88	0.54	14.28	2.86
G016049	95.33	0.15	1.41	0.87	0.46	0.66
G016036	71.71	3.82	0.63	0.14	1.94	0.40
G016080	81.09	1.58	1.33	0.47	5.64	0.94
G016096	94.79	0.33	0.45	0.10	1.81	0.37
G016032	90.27	1.53	2.25	2.37	2.97	0.38
G016033	83.90	0.89	1.79	1.63	5.03	0.94
G016030	96.66	1.35	0.65	0.39	0.31	0.14
G016067	95.79	0.26	0.61	0.17	1.37	0.26
G016031	94.51	0.24	0.75	0.07	2.35	0.68
G016062	93.37	0.45	1.17	0.13	1.91	0.33
G016059	90.26	0.93	0.80	0.30	5.62	0.33
G016105	95.81	1.17	0.53	0.24	0.47	0.45
G016107	91.94	2.74	0.66	0.36	3.18	2.72
G016042	90.07	0.00	0.97	0.00	2.51	0.00
G016069	93.31	0.96	0.96	0.31	1.03	0.33
G016072	84.94	7.39	0.39	0.08	11.91	8.00
G018021	91.14	2.38	2.45	0.52	3.22	2.60
G018022	93.68	3.27	1.83	0.33	1.46	0.10
G018023	92.37	1.73	2.25	0.07	2.31	0.52
G018024	96.06	1.54	0.41	0.37	0.97	0.07

導引ID	%C形成T		%C形成A/G		%插入/缺失	
	平均	SD	平均	SD	平均	SD
G018025	96.88	0.78	0.63	0.12	0.43	0.06
G018026	89.15	1.37	1.66	0.04	7.20	1.31
G018027	88.89	3.13	1.02	0.04	5.37	2.62
G018028	91.28	2.09	0.59	0.24	2.96	2.02
G018029	22.86	0.72	0.43	0.07	0.17	0.02
G018030	79.89	2.66	0.36	0.51	0.18	0.25
G018031	90.43	1.35	0.47	0.38	1.52	0.07
G018032	64.78	2.64	1.39	0.69	1.06	0.50
G018033	88.94	0.84	1.98	0.29	1.97	0.44
G018034	89.00	1.56	1.09	0.11	6.23	0.88
G018035	95.10	1.59	0.50	0.25	0.66	0.17
G018036	83.69	0.01	1.91	0.30	0.53	0.20
G018037	94.50	0.54	1.64	0.03	1.18	0.23
G018038	90.91	0.00	1.11	0.00	3.74	0.00
G018039	94.88	0.00	0.60	0.00	0.41	0.00
G018040	44.77	1.52	0.33	0.14	0.50	0.03
G018041	66.56	2.05	0.60	0.30	0.27	0.20
G018042	90.79	1.10	1.28	0.47	1.64	0.35
G018043	94.94	0.55	0.57	0.03	0.40	0.06
G018044	91.71	1.61	0.89	0.40	1.25	0.20
G018045	90.26	1.59	1.46	0.54	3.91	1.89
G018046	94.59	1.33	0.76	0.05	2.03	0.64
G018047	93.84	1.32	0.46	0.08	2.03	0.64
G018048	95.20	2.58	0.54	0.52	0.62	0.30
G018049	89.68	2.09	0.17	0.23	0.45	0.30
G018050	95.74	0.65	0.31	0.22	0.84	0.39
G018051	92.47	0.90	0.54	0.76	0.73	0.31
G018052	93.14	0.85	1.39	0.91	0.85	0.78
G018053	78.88	3.77	0.74	0.13	0.52	0.34
G018054	92.69	1.11	0.79	0.10	2.55	0.46
G018055	89.68	1.52	0.48	0.57	1.05	0.36
G018056	94.00	1.10	0.45	0.14	1.85	0.99
G018057	89.87	0.49	0.72	0.04	1.31	0.31
G018058	91.04	0.77	0.59	0.12	1.46	0.28
G018059	49.64	3.56	0.46	0.19	1.56	0.43
G018060	97.65	0.65	1.22	0.17	1.13	0.47
G018061	92.52	0.29	0.89	0.33	2.76	0.52
G018062	88.19	0.72	0.84	0.18	6.65	0.41
G018063	92.94	0.63	1.54	0.20	0.94	0.38
G018064	94.14	1.12	1.38	0.31	0.97	0.09
G018065	93.20	1.50	1.32	0.57	0.91	0.23
G018066	91.62	0.45	1.69	0.06	0.45	0.17
G018067	92.72	1.43	3.06	0.48	0.42	0.15
G018068	93.33	0.49	0.62	0.08	0.27	0.06
G018069	93.83	0.77	0.94	0.33	0.99	0.07
G018070	94.61	0.57	0.59	0.08	1.33	0.35
G018071	87.61	0.46	0.26	0.22	1.10	0.29

導引ID	%C形成T		%C形成A/G		%插入/缺失	
	平均	SD	平均	SD	平均	SD
G018072	92.86	0.84	1.76	0.04	0.34	0.06
G018073	87.03	0.52	1.48	0.33	0.40	0.15
G018074	80.06	11.41	0.42	0.13	0.46	0.24
G018075	92.85	0.27	0.59	0.37	0.61	0.08
G018076	95.88	1.59	0.56	0.38	0.61	0.30
G018077	0.23	0.12	0.55	0.26	0.13	0.08
G018078	94.97	1.42	0.48	0.16	0.44	0.22
G018079	89.45	1.79	0.38	0.26	0.81	0.47
G018080	80.86	3.14	0.22	0.15	0.58	0.35
G018081	93.61	0.63	0.17	0.14	0.91	0.44
G018082	93.15	1.21	0.16	0.07	1.80	0.50
G018083	78.69	0.88	0.29	0.13	2.73	0.50
G018084	81.88	0.70	0.43	0.19	1.39	0.60
G018085	93.17	1.26	0.44	0.16	2.62	0.43
G018086	95.03	1.07	0.61	0.20	1.39	0.44
G018087	94.37	1.49	1.07	0.79	1.41	0.21
G018088	91.62	1.31	1.01	0.43	1.91	0.99
G018089	94.41	1.17	0.75	0.41	3.04	1.52
G018090	93.66	0.82	0.54	0.28	3.12	0.96
G018091	96.82	0.00	0.60	0.00	0.77	0.00
G018092	90.55	1.58	0.74	0.27	2.02	0.34
G018093	94.46	0.49	1.13	0.13	0.96	0.28
G018094	82.55	5.17	0.55	0.11	12.35	6.02
G018095	94.60	0.85	1.94	0.68	0.75	0.21
G018096	54.68	0.62	1.99	0.16	0.38	0.12
G018097	91.89	2.73	0.96	0.89	1.01	0.80
G018098	70.42	0.00	0.35	0.00	0.00	0.00
G018099	96.84	0.16	0.43	0.10	0.64	0.16
G018100	93.24	1.08	0.77	0.20	3.07	0.06
G018101	92.34	0.51	2.16	0.73	3.06	0.06
G018102	91.87	0.99	0.42	0.34	0.61	0.16
G018103	94.50	1.22	0.59	0.22	1.25	0.53
G018104	94.14	0.76	0.31	0.14	1.09	0.65
G018105	95.51	0.98	0.42	0.14	0.82	0.21
G018106	94.77	0.90	1.12	0.18	2.15	0.28
G018107	94.66	0.57	0.80	0.03	2.09	0.04
G018108	94.77	1.14	1.23	0.70	1.55	0.96
G018109	94.40	1.37	1.06	0.91	1.80	0.67
G018110	92.19	1.30	1.86	0.34	4.04	0.77
G018111	91.96	3.12	0.72	0.17	5.54	3.11
G018112	91.54	1.34	0.80	0.15	5.69	0.44
G018113	96.42	0.45	0.43	0.22	1.40	0.35
G018114	95.95	0.89	0.79	0.32	0.27	0.20
G018115	92.89	1.00	0.59	0.16	1.10	0.40
G018116	91.94	0.57	0.99	0.54	0.61	0.24
G018117	95.48	1.10	0.62	0.31	0.55	0.31
G018118	96.20	0.38	0.43	0.31	0.46	0.17

導引ID	%C形成T		%C形成A/G		%插入/缺失	
	平均	SD	平均	SD	平均	SD
G018119	83.25	1.31	0.43	0.08	0.44	0.25
G018120	97.00	0.72	0.42	0.26	0.38	0.20
G018121	95.42	0.58	0.50	0.13	0.42	0.15

實例42 - 在T細胞中篩選與BC22n呈劑量-反應之CIITAsgRNA

【0750】 進一步測定實例41中鑑別之高效CIITAsgRNA在T細胞中在多個導引物濃度下之鹼基編輯功效。藉由NGS或藉由流動式細胞量測術破壞HLA-DR、DP、DQ之表面蛋白質表現測定每一者之效力之基因體編輯功效。

實例42.1T細胞製備

【0751】 健康人類供體血球分離術為商業獲得的(Hemacare)，且細胞經洗滌且再懸浮於CliniMACS®PBS/EDTA緩衝液(MiltenyiBiotec目錄號 130-070-525) 中且在 MultiMACS™Cell24SeparatorPlus 裝置(MiltenyiBiotec) 中進行處理。使用 StraightfromLeukopak®CD4/CD8MicroBead套組，人類(MiltenyiBiotec目錄號130-122-352)經由陽性選擇分離T細胞。將T細胞等分且在Cryostor®CS10(StemCellTechnologies目錄號07930)中冷凍保存以供將來使用。

【0752】 在解凍之後，將T細胞以1.0x10^6個細胞/mL之密度接種於由以下各者構成之T細胞生長培養基(TCGM)中：CTSOpTmizerT細胞擴展SFM及T細胞擴展補充物(ThermoFisher目錄號A1048501)、5%人類AB血清(GeminiBio，目錄號100-512)、1X青黴素-鏈黴素、1XGlutamax、10mMHEPES、200U/mL重組人類介白素-2(Peprotech，目錄號200-02)、5ng/mL重組人類介白素7(Peprotech，目錄號200-07)及5ng/mL重組人類介白素15(Peprotech，目錄號200-15)。T細胞在此培養基中靜置24小

時，此時其經以1:100體積比添加之T細胞TransAct™人類試劑(Miltenyi，目錄號130-111-160)活化。T細胞在電穿孔之前活化48小時。

實例42.2用RNA電穿孔進行T細胞編輯

【0753】在P3緩衝液中製備含有編碼BC22n(SEQ ID NO:1)及UGI(SEQ ID NO:34)之mRNA的溶液。將100μM靶向sgRNA之CIITA自其儲存板移除，且在95℃下變性2分鐘，且在室溫下培育5分鐘。活化後四十八小時，採集T細胞，離心，且以12.5x10^6個T細胞/mL之濃度再懸浮於P3電穿孔緩衝液(Lonza)中。在96孔PCR板中自60pmols開始，一式兩份地在P3電穿孔緩衝液中以1:2之比率連續稀釋每一sgRNA。稀釋之後，將1x10^5個T細胞、20ng/μLBC22nmRNA及20ng/μLUGImRNA與sgRNA板混合以製備最終體積為20μL之P3電穿孔緩衝液。此混合物轉移至4個對應96孔Nucleofector™板中且使用製造商之脈衝碼電穿孔。經電穿孔之T細胞緊接著在不含細胞介素之80μLCTS最佳化器T細胞生長培養基中靜置15分鐘，隨後轉移至含有額外80μL補充有2X細胞介素之CTSOpTmizerT細胞生長培養基的新平底96孔板中。將所得板在37℃下培育7天。在電穿孔後第4天，細胞在2個U形底板中以1:2分裂，且收集一個板用於NGS定序，而將另一板補充有含有1X細胞介素之CTS最佳化器新鮮培養基。此板在第7天用於流動式細胞量測術。

實例42.3流動式細胞量測術及NGS定序

【0754】編輯後第7天，藉由流動式細胞量測術測定T細胞以判定HLA-DR、DP、DQ之表面表現。簡言之，將T細胞與在細胞染色緩衝液(BioLegend，目錄號420201)中稀釋之抗體的混合物一起在4℃下培育30分鐘。抗CD3(BioLegend，目錄號317336)、CD4(BioLegend，目錄號

317434)、CD8(BioLegend，目錄號301046)及Viakrome(BeckmanCoulter，目錄號C36628)之抗體以1:100稀釋，且抗HLAII-DR、DP、DQ(BioLegend，目錄號361714)之抗體以1:50稀釋。隨後洗滌細胞，再懸浮於100μL細胞染色緩衝液中且在Cytoflex流式細胞儀(BeckmanCoulter)上進行處理。使用FlowJo套裝軟體分析流動式細胞量測術資料。T細胞基於大小、形狀、活力、CD8及HLA-DR、DP、DQ進行閘控。

【0755】 表106展示CIITA編輯結果及在用BC22n進行鹼基編輯之後T細胞中對於HLA-DR、DP、DQ呈陰性之T細胞的百分比。

表106-編輯百分比及在用BC22n鹼基編輯器進行CIITA編輯之後的HLAII-DP、DQ、DR陰性細胞的百分比

		C>T			%HLAII-DR,DP,DQ			%CD74		
	sgRNA(pmols)	Ave	SD	N	Ave	SD	N	Ave	SD	N
G016064	60	96.20%	0.69%	2	99.65	0.07	2	96.2	0.14	2
	30	94.85%	0.69%	2	99.15	0.35	2	92.65	0.21	2
	15	90.26%	0.03%	2	96.70	0.28	2	90.15	2.19	2
	7.5	72.95%	1.76%	2	87.45	1.20	2	80.95	3.32	2
	3.75	49.55%	2.09%	2	73.05	0.64	2	66.35	4.31	2
	1.88	28.63%	1.34%	2	59.40	1.70	2	55.2	5.8	2
	0.94	14.98%	0.01%	2	54.60	2.40	2	46.9	1.84	2
	0	0.26%	0.02%	2	46.70	5.52	2	45.15	0.49	2
G016068	60	97.40%	0.87%	2	99.70	0.00	2	94.25	1.2	2
	30	90.31%	0.83%	2	93.15	0.07	2	85.15	1.2	2
	15	75.08%	0.17%	2	82.45	0.21	2	74.65	1.48	2
	7.5	49.64%	2.08%	2	68.65	1.91	2	57	1.27	2
	3.75	28.95%	1.51%	2	57.85	1.63	2	43.9	1.27	2
	1.88	14.90%	0.58%	2	51.10	2.26	2	35.85	3.75	2
	0.94	7.11%	0.22%	2	49.50	4.67	2	38.2	4.1	2
	0	0.21%	0.02%	2	51.50	1.13	2	44.8	1.56	2
G016074	60	96.62%		2	96.95	0.21	2	90.6	0.28	2
	30	94.89%	0.58%	2	93.50	1.27	2	85.45	1.06	2
	15	89.79%	3.18%	2	88.50	0.28	2	80.35	0.64	2
	7.5	72.00%	1.61%	2	77.75	0.35	2	68.35	1.77	2
	3.75	47.99%	0.39%	2	65.30	1.84	2	53.05	1.91	2
	1.88	27.92%	0.44%	2	57.60	0.14	2	45	0.42	2

	0.94	13.11%	1.79%	2	54.30	0.71	2	37.9	0	2
	0	0.41%	0.13%	2	49.15	2.05	2	44.05	1.91	2
G016076	60	96.03%	0.07%	2	94.30	0.14	2	90	0.71	2
	30	93.29%	ND	2	89.10	0.99	2	81.65	1.48	2
	15	80.74%	0.41%	2	83.55	0.35	2	74.1	0.85	2
	7.5	51.33%	1.82%	2	69.05	1.91	2	57.7	2.97	2
	3.75	28.40%	2.41%	2	58.90	2.26	2	43.15	0.64	2
	1.88	15.12%	1.91%	2	56.05	0.78	2	38.45	1.77	2
	0.94	7.23%	0.26%	2	52.80	0.71	2	38.2	0.28	2
	0	0.27%	0.00%	2	47.70	1.70	2	43.5	3.68	2
G016086	60	97.81%	0.16%	2	99.25	0.35	2	94.35	0.92	2
	30	ND	ND	2	98.65	0.07	2	90.25	1.2	2
	15	ND	ND	2	98.20	0.28	2	88.8	1.98	2
	7.5	97.19%	1.91%	2	95.85	0.07	2	87.5	0.14	2
	3.75	ND	ND	2	87.10	0.28	2	74.95	2.47	2
	1.88	ND	ND	2	72.45	0.07	2	60.75	2.76	2
	0.94	ND	ND	2	59.10	0.85	2	48.05	3.89	2
	0	ND	ND	2	50.65	2.76	2	46.15	2.19	2
G016091	60	ND	ND	2	98.05	0.07	2	89.85	0.21	2
	30	ND	ND	2	96.95	0.07	2	87.9	0.85	2
	15	ND	ND	2	91.40	1.84	2	83.65	2.76	2
	7.5	ND	ND	2	82.00	1.27	2	74	3.11	2
	3.75	ND	ND	2	69.70	0.99	2	62.75	2.33	2
	1.88	ND	ND	2	59.40	1.41	2	54.4	3.54	2
	0.94	ND	ND	2	54.25	2.05	2	46.3	5.09	2
	0	ND	ND	2	46.30	2.26	2	48.3	4.67	2
G016115	60	93.33%	0.70%	2	96.80	0.14	2	92.55	0.07	2
	30	94.46%	0.23%	2	92.70	1.41	2	87.8	1.98	2
	15	93.51%	0.70%	2	89.85	0.35	2	82.75	3.75	2
	7.5	90.13%	0.37%	2	83.35	0.35	2	78.35	2.47	2
	3.75	75.18%	1.51%	2	71.40	1.27	2	65.5	2.4	2
	1.88	51.65%	1.64%	2	64.20	4.95	2	56.1	1.84	2
	0.94	30.19%	2.14%	2	55.25	3.04	2	49.15	4.88	2
	0	0.26%	0.03%	2	46.85	7.57	2	47.1	3.25	2
G016084	60	73.43%	0.13%	2	97.00	0.14	2	91.35	1.06	2
	30	73.70%	0.38%	2	94.80	0.42	2	84.9	0.42	2
	15	67.30%	1.19%	2	91.60	0.71	2	80.6	0.57	2
	7.5	48.91%	0.27%	2	80.20	0.00	2	67.5	0.42	2
	3.75	28.24%	0.35%	2	67.50	0.57	2	51.85	3.18	2
	1.88	16.89%	0.30%	2	59.05	2.76	2	42.7	0.14	2
	0.94	7.42%	0.06%	2	54.65	0.92	2	40.05	0.78	2
	0	1.06%	0.06%	2	49.25	2.47	2	46.9	1.98	2
G016090	60	87.05%	2.52%	2	98.70	1.27	2	93.25	2.19	2
	30	88.93%	0.06%	2	98.90	0.14	2	91	0.99	2
	15	89.51%	0.24%	2	98.70	0.28	2	90.45	0.21	2

	7.5	83.78%	0.02%	2	93.80	0.57	2	85.05	0.07	2
	3.75	66.23%	0.40%	2	83.35	1.06	2	72.35	0.35	2
	1.88	44.49%	0.27%	2	69.50	0.57	2	57.75	1.34	2
	0.94	22.90%	1.49%	2	57.25	1.77	2	45.15	2.47	2
	0	0.61%	0.14%	2	49.55	1.63	2	47.5	4.1	2
G016032	60	91.66%	0.76%	2	99.35	0.07	2	93.65	2.05	2
	30	86.77%	2.13%	2	94.25	1.06	2	87.45	1.63	2
	15	75.23%	1.22%	2	86.10	2.26	2	74.65	0.78	2
	7.5	54.08%	0.63%	2	74.10	0.85	2	60.65	1.34	2
	3.75	33.34%	2.39%	2	63.20	3.82	2	45.95	3.75	2
	1.88	16.30%	1.21%	2	57.20	0.57	2	39.7	0.28	2
	0.94	7.33%	0.38%	2	53.10	0.85	2	37.6	1.13	2
	0	0.33%	0.00%	2	52.65	4.31	2	47.75	2.62	2
G016067	60	97.37%	0.56%	2	93.10	0.14	2	85.95	2.19	2
	30	97.47%	0.36%	2	93.00	0.28	2	81.8	3.54	2
	15	95.78%	0.13%	2	89.30	1.41	2	79.45	0.49	2
	7.5	86.53%	0.24%	2	81.05	2.19	2	71	2.26	2
	3.75	68.12%	1.27%	2	69.35	1.20	2	58.3	2.4	2
	1.88	43.82%	0.48%	2	57.70	1.98	2	48.2	0.99	2
	0.94	22.80%	1.26%	2	54.95	0.35	2	42.55	1.34	2
	0	0.14%	0.06%	2	49.55	1.63	2	43.7	1.98	2
G018067	60	95.58%	0.35%	2	99.40	0.00	2	91.45	1.34	2
	30	94.13%	0.08%	2	98.90	0.42	2	91.75	1.63	2
	15	91.49%	0.05%	2	95.95	0.21	2	89.45	0.07	2
	7.5	77.17%	1.50%	2	83.95	0.92	2	76.6	0.57	2
	3.75	56.15%	1.07%	2	71.00	0.71	2	63.65	4.03	2
	1.88	32.76%	0.32%	2	57.65	3.46	2	50.6	3.39	2
	0.94	17.47%	0.95%	2	50.85	3.04	2	46.1	3.82	2
	0	0.41%	0.01%	2	49.45	5.16	2	47.85	1.91	2
G018075	60	96.12%	1.35%	2	98.25	0.07	2	92	1.27	2
	30	94.07%	3.53%	2	97.45	1.06	2	88.65	2.76	2
	15	92.08%	0.90%	2	97.10	0.14	2	87.25	2.05	2
	7.5	83.76%	3.28%	2	90.65	0.21	2	80.1	2.69	2
	3.75	67.35%	2.13%	2	78.85	0.21	2	67.1	2.97	2
	1.88	42.66%	2.51%	2	63.65	0.07	2	52.55	2.33	2
	0.94	25.54%	0.32%	2	56.55	3.75	2	43.1	3.25	2
	0	0.23%	0.02%	2	48.70	1.84	2	42.1	0.42	2
G018091	60	97.80%	ND	2	99.65	0.21	2	92.2	0.57	2
	30	96.32%	0.91%	2	97.50	0.28	2	88.7	1.7	2
	15	84.48%	2.73%	2	91.90	0.71	2	82.1	0.71	2
	7.5	76.56%	0.49%	2	78.05	1.63	2	64.15	0.35	2
	3.75	52.08%	1.50%	2	67.00	1.56	2	46.8	1.84	2
	1.88	30.00%	2.36%	2	58.80	2.55	2	40.7	2.4	2
	0.94	15.01%	1.12%	2	50.70	2.26	2	33	2.83	2
	0	0.00%	0.00%	2	47.90	1.70	2	39	0	2

G018100	60	95.55%	0.47%	2	94.30	0.57	2	85.3	2.69	2
	30	95.22%	1.02%	2	91.75	0.78	2	79.1	0.85	2
	15	93.33%	0.49%	2	90.80	0.99	2	77.1	0.28	2
	7.5	88.77%	0.15%	2	84.40	0.85	2	69.9	1.56	2
	3.75	71.03%	4.26%	2	75.20	2.40	2	54.4	0.57	2
	1.88	46.87%	1.95%	2	63.80	0.28	2	45.7	0.28	2
	0.94	27.20%	0.21%	2	54.80	1.56	2	36.5	2.4	2
	0	0.17%	0.04%	2	52.25	1.63	2	42.8	0	2
G018102	60	93.32%	0.10%	2	93.00	0.14	2	84.65	0.64	2
	30	77.08%	2.22%	2	80.40	1.84	2	68.7	2.55	2
	15	52.42%	1.28%	2	70.50	0.28	2	55.4	0.85	2
	7.5	31.87%	0.20%	2	58.80	4.53	2	39.4	4.38	2
	3.75	16.76%	0.26%	2	56.85	1.63	2	33.65	0.07	2
	1.88	8.18%	0.06%	2	54.15	0.21	2	30.35	0.92	2
	0.94	4.12%	0.66%	2	52.25	3.32	2	32.2	0.57	2
	0	0.28%	0.12%	2	50.00	3.68	2	42.45	4.17	2
G018103	60	96.34%	0.21%	2	98.85	0.07	2	89.2	2.12	2
	30	90.93%	0.17%	2	95.15	0.92	2	84.95	0.07	2
	15	80.01%	0.34%	2	87.95	1.63	2	76.7	0.14	2
	7.5	59.92%	0.48%	2	70.90	2.97	2	56.45	3.18	2
	3.75	36.07%	1.23%	2	62.05	2.33	2	44.65	0.49	2
	1.88	19.59%	2.15%	2	58.65	2.76	2	38.2	1.41	2
	0.94	7.98%	0.08%	2	52.75	0.07	2	33.25	2.62	2
	0	0.22%	0.03%	2	50.95	0.64	2	43.1	2.69	2
G018107	60	ND	ND	2	99.50	0.14	2	89.05	0.07	2
	30	ND	ND	2	99.05	0.07	2	91.1	0.85	2
	15	ND	ND	2	97.05	0.64	2	90	3.25	2
	7.5	ND	ND	2	90.45	0.07	2	83.25	2.76	2
	3.75	ND	ND	2	79.60	0.99	2	72.3	2.4	2
	1.88	ND	ND	2	66.20	2.26	2	58.7	4.81	2
	0.94	ND	ND	2	53.40	1.41	2	45.55	3.89	2
	0	ND	ND	2	51.65	2.05	2	47.35	4.03	2
G018111	60	96.87%	0.26%	2	95.65	0.49	2	92.45	0.35	2
	30	95.44%	0.07%	2	89.40	0.71	2	86.5	0.42	2
	15	89.11%	0.91%	2	81.35	0.07	2	75.75	2.62	2
	7.5	71.93%	0.55%	2	70.05	3.32	2	61.15	0.21	2
	3.75	47.48%	0.33%	2	56.45	5.02	2	48.5	0.14	2
	1.88	25.72%	1.46%	2	59.00	3.11	2	44.95	0.07	2
	0.94	12.27%	0.79%	2	51.30	3.39	2	42.3	0.99	2
	0	0.15%	0.01%	2	51.00	3.25	2	45.1	1.41	2
G018116	60	86.65%	0.01%	2	92.95	0.35	2	87.7	0.42	2
	30	62.59%	0.13%	2	79.90	1.84	2	69.75	2.9	2
	15	40.44%	1.09%	2	69.90	0.71	2	60.15	1.34	2
	7.5	23.19%	2.46%	2	60.35	4.74	2	45.45	0.92	2
	3.75	10.65%	0.83%	2	55.45	1.91	2	40.2	1.41	2

	1.88	5.63%	0.47%	2	56.85	1.06	2	40.75	0.64	2
	0.94	1.93%	0.33%	2	57.80	3.96	2	40	0.14	2
	0	0.19%	0.10%	2	50.55	0.21	2	47	1.41	2
G018117	60	98.01%	0.17%	2	99.65	0.07	2	93.65	0.49	2
	30	97.14%	0.69%	2	99.20	0.14	2	92.35	0.07	2
	15	93.65%	0.39%	2	97.75	0.64	2	91.55	0.21	2
	7.5	81.77%	0.50%	2	91.60	0.42	2	81.85	0.35	2
	3.75	56.56%	2.70%	2	80.55	3.46	2	69.25	3.32	2
	1.88	33.70%	3.00%	2	69.30	1.13	2	56.8	2.69	2
	0.94	17.14%	0.83%	2	60.40	1.84	2	48.25	1.34	2
	0	0.18%	0.01%	2	51.95	2.76	2	46.5	1.13	2
G018118	60	98.36%	0.27%	2	99.65	0.07	2	94.35	0.49	2
	30	97.70%	0.19%	2	99.45	0.21	2	88.35	8.13	2
	15	94.59%	1.64%	2	98.30	0.14	2	90.45	0.21	2
	7.5	83.77%	2.47%	2	92.80	1.13	2	81.2	0.57	2
	3.75	64.07%	0.54%	2	81.25	1.06	2	71.5	1.56	2
	1.88	40.72%	2.16%	2	70.65	2.90	2	61.15	3.18	2
	0.94	22.33%	3.64%	2	63.90	0.85	2	51.05	2.76	2
	0	0.14%	0.02%	2	52.95	1.48	2	47.85	1.77	2
G018120	60	98.22%	0.32%	2	99.10	0.14	2	91.65	0.78	2
	30	96.96%	0.43%	2	99.15	0.07	2	89.1	0.57	2
	15	93.71%	0.19%	2	97.05	0.21	2	88.15	0.64	2
	7.5	82.19%	1.50%	2	90.25	0.78	2	80	0.99	2
	3.75	61.25%	1.50%	2	80.30	1.56	2	66.45	1.77	2
	1.88	37.98%	1.29%	2	68.85	0.78	2	52.75	3.04	2
	0.94	18.96%	0.67%	2	59.85	0.64	2	47.25	2.19	2
	0	0.17%	0.02%	2	49.60	0.57	2	46.1	0.99	2
G018121	60	97.55%	0.01%	2	97.25	0.35	2	87.45	0.35	2
	30	92.24%	0.98%	2	92.50	0.71	2	83.6	3.96	2
	15	78.58%	0.52%	2	84.90	0.28	2	76.85	2.9	2
	7.5	57.37%	0.50%	2	73.75	3.04	2	64.5	3.25	2
	3.75	35.06%	0.53%	2	60.70	0.00	2	50.5	3.25	2
	1.88	18.80%	2.81%	2	61.00	1.41	2	45.95	4.31	2
	0.94	9.25%	0.17%	2	56.95	4.31	2	42.8	1.7	2
	0	0.21%	0.00%	2	47.45	3.04	2	44.55	1.34	2

實例43.額外實施例

【0756】 以下經編號實施例提供對本文中之實施例之額外支援及描述。

實施例A1. 一種mRNA，其包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框，其中多肽不包含尿嘧啶醣苷酶抑

制劑(UGI)。

實施例A2. 一種組合物，其包含：第一mRNA，其包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA，視情況其中組合物包含脂質奈米粒子。

實施例A3. 如實施例A2之組合物，其中第一多肽不包含UGI。

實施例A4. 如實施例A2或A3之組合物，其中第二mRNA與第一mRNA之莫耳比為1:1至30:1。

實施例A5. 一種修飾目標基因之方法，其包含向細胞遞送：第一mRNA，其包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之第一多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA；及至少一種導引RNA(gRNA)。

實施例A6. 如實施例A2至A5中任一例之組合物或方法，其中第二mRNA與第一mRNA之莫耳比為1:1至30:1。

實施例A7. 如實施例A4至A6中任一例之組合物或方法，其中莫耳比為2:1至30:1。

實施例A8. 如實施例A4至A6中任一例之組合物或方法，其中莫耳比為7:1至22:1。

實施例A9. 一種細胞，其包含含有以下之組合物：第一mRNA，該第一mRNA包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，該第二mRNA包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA。

實施例A10. 一種經工程改造之細胞，其包含至少一種鹼基編輯及/或插入/缺失，其中鹼基編輯及/或插入/缺失藉由使細胞與組合物接觸而形成，該組合物包含含有編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框之第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中第二mRNA不同於第一mRNA。

實施例A11. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少87%一致性之胺基酸序列。

實施例A12. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少90%一致性之胺基酸序列。

實施例A13. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少95%一致性之胺基酸序列。

實施例A14. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少98%一致性之胺基酸序列。

實施例A15. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少99%一致性之胺基酸序列。

實施例A16. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含SEQ ID NO:40之胺基酸序列。

實施例A17. 如前述實施例中任一例之mRNA、組合物、方法、細胞

或經工程改造之細胞，其中A3A為人類A3A。

實施例A18. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A為野生型A3A。

實施例A19. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少80%一致性之胺基酸序列。

實施例A20. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少90%一致性之胺基酸序列。

實施例A21. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少95%一致性之胺基酸序列。

實施例A22. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少98%一致性之胺基酸序列。

實施例A23. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少99%一致性之胺基酸序列。

實施例A24. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含SEQ ID NO:27之胺基酸序列。

實施例A25. 如前述實施例中任一例之組合物、方法或細胞，其進一步包含至少一種導引RNA(gRNA)。

實施例A26. 如前述實施例中任一例之組合物、方法、細胞或經工程

改造之細胞，其包含gRNA，其中gRNA為sgRNA。

實施例A27. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中gRNA為dgRNA。

實施例A28. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中gRNA為包含含有髮夾區之sgRNA之保守部分的較短單導引RNA(短sgRNA)，其中髮夾區缺少至少5至10個核苷酸，且其中短sgRNA包含5'端修飾及/或3'端修飾。

實施例A29. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為Cas切口酶。

實施例A30. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為2類Cas切口酶。

實施例A31. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為Cas9切口酶。

實施例A32. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為化膿性鏈球菌Cas9切口酶。

實施例A33. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為D10 ASpyCas9切口酶。

實施例A34. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為腦膜炎雙球菌Cas9切口酶。

實施例A35. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為D16A Nme2Cas9切口

酶。

實施例A36. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶包含與SEQ ID NO:70、73或76中之任一者具有至少80%、90%、95%、98%或99%一致性的胺基酸序列。

實施例A37. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶包含SEQ ID NO:70、73或76中之任一者的胺基酸序列。

實施例A38. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含與SEQ ID NO:72、75或78中的任一者之核苷酸序列具有至少80%、90%、95%、98%或99%一致性之核苷酸序列。

實施例A39. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含與SEQ ID NO:72、75或78中的任一者之核苷酸序列具有至少90%一致性之核苷酸序列。

實施例A40. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含與SEQ ID NO:72、75或78中的任一者之核苷酸序列具有至少95%一致性之核苷酸序列。

實施例A41. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含與SEQ ID NO:72、75或78中的任一者之核苷酸序列具有至少98%一致性之核苷酸序

列。

實施例A42. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含與SEQ ID NO:72、75或78中的任一者之核苷酸序列具有至少99%一致性之核苷酸序列。

實施例A43. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶之序列包含SEQ ID NO:71、72、74、75或77至90中之任一者的核苷酸序列。

實施例A44. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含與SEQ ID NO:91至98中之任一者具有至少90%一致性之5'UTR。

實施例A45. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含與SEQ ID NO:99至106中之任一者具有至少90%一致性之3'UTR。

實施例A46. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含來自同一源之5'UTR及3'UTR。

實施例A47. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含選自Cap0、Cap1及Cap2之5'端帽。

實施例A48. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框包含最小腺嘌呤密碼子及/或最小尿苷密碼子。

實施例A49. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框包含最小腺嘌呤密碼子。

實施例A50. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框具有增加哺乳動物中之mRNA轉譯的密碼子。

實施例A51. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框具有增加哺乳動物中之mRNA轉譯的密碼子，其中哺乳動物為人類。

實施例A52. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A位於多肽中之RNA導引之切口酶的N末端。

實施例A53. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)。

實施例A54. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中NLS處於RNA導引之切口酶之C末端。

實施例A55. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號

(NLS)，且其中NLS處於RNA導引之切口酶之N末端，或其中NLS融合至RNA導引之切口酶之N末端及C末端兩者。

實施例A56. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中連接子存在於RNA導引之切口酶之N末端與NLS之間，視情況其中連接子為肽連接子。

實施例A57. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中NLS包含與SEQ ID NO:63及110至122中之任一者具有至少80%、85%、90%或95%一致性之序列。

實施例A58. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中NLS包含SEQ ID NO:63及110至122中之任一者之序列。

實施例A59. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中NLS由與SEQ ID NO:123至135中之任一者之序列具有至少80%、85%、90%、95%、98%或100%一致性的序列編碼。

實施例A60. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中A3A位於多肽中之NLS之N末端。

實施例A61. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中RNA導引之切口酶位於多肽中之NLS的N末端。

實施例A62. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框包含與SEQ ID NO:1之序列具有至少80%、85%、90%、95%、98%或100%一致性的序列。

實施例A63. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的開讀框包含與序列SEQ ID NO:4具有至少80%、85%、90%、95%、98%或100%一致性之序列。

實施例A64. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA中至少10%之尿苷由經修飾之尿苷取代。

實施例A65. 如實施例A64之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷、假尿苷、5-甲氧基尿苷或5-碘尿苷中之一或多者。

實施例A66. 如實施例A64或A65之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷或5-甲氧基尿苷中之一者或兩者。

實施例A67. 如實施例A64至A66中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷。

實施例A68. 如實施例A64至A66中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為5-甲氧基尿苷。

實施例A69. 如實施例A64至A68中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中15%至45%之尿苷由經修飾之尿苷取

代。

實施例A70. 如實施例A64至A69中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中至少20%或至少30%之尿苷由經修飾之尿苷取代。

實施例A71. 如實施例A64至A70中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中至少80%或至少90%之尿苷由經修飾之尿苷取代。

實施例A72. 如實施例A64至A71中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中100%之尿苷由經修飾之尿苷取代。

實施例A73. 如前述實施例中任一例之mRNA、組合物、方法或細胞，其進一步編碼A3A與RNA導引之切口酶之間的肽連接子，視情況其中肽連接子為XTEN。

實施例A74. 如前述實施例中任一例之mRNA、組合物、方法或細胞，其進一步編碼A3A與RNA導引之切口酶之間的肽連接子，其中肽連接子包含至少1個、至少2個、至少3個、至少4個、至少5個、至少6個、至少7個、至少8個、至少9個、至少10個、至少15個、至少20個、至少25個、至少30個、至少40個、至少50個或更多個胺基酸。

實施例A75. 如前述實施例中任一例之mRNA、組合物、方法或細胞，其進一步編碼A3A與RNA導引之切口酶之間的肽連接子，其中肽連接子包含選自SEQ ID NO:46至59及211至267之一或多個序列。

實施例A76. 一種多肽，其由如前述實施例A中任一例之mRNA編碼。

實施例A77. 一種載體，其包含如前述實施例A中任一例之mRNA。

實施例A78. 一種表現構築體，其包含可操作地連接於編碼如前述實施例A中任一例之mRNA之序列的啟動子。

實施例A79. 一種質體，其包含實施例A78之表現構築體。

實施例A80. 一種宿主細胞，其包含如實施例A77之載體、如實施例A78之表現構築體或如實施例A79之質體。

實施例A81. 如前述實施例中任一例之mRNA或組合物，其中mRNA或組合物調配為脂質核酸組裝組合物，視情況為脂質奈米粒子。

實施例A82. 一種如前述實施例中任一例之mRNA或組合物的用途，其用於修飾細胞中之目標基因。

實施例A83. 一種如前述實施例中任一例之mRNA或組合物的用途，其用於製造用於修飾細胞中之目標基因的藥劑。

實施例A84. 一種修飾細胞中之目標基因的方法，其包含向該細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，該一或多種脂質核酸組裝組合物包含：

(a) 第一mRNA，其包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框；

(b) 第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c) 一或多種導引RNA。

實施例A85. 如實施例A84之方法，其中部分(a)及(b)在單獨的脂質核酸組裝組合物中。

實施例A86. 如實施例A84之方法，其中部分(a)及(b)在同一脂質核酸組裝組合物中。

實施例A87. 如實施例A84之方法，其中部分(a)及(c)在單獨的脂質核酸組裝組合物中。

實施例A88. 如實施例A84之方法，其中部分(a)及(c)在同一脂質核酸組裝組合物中。

實施例A89. 如實施例A84之方法，其中部分(b)及(c)在單獨的脂質核酸組裝組合物中。

實施例A90. 如實施例A84之方法，其中部分(a)及(c)在同一脂質核酸組裝組合物中，且部分(b)在單獨的脂質核酸組裝組合物中。

實施例A91. 如實施例A84之方法，其中部件(a)、(b)及(c)各自在單獨的脂質核酸組裝組合物中。

實施例A92. 如實施例A84之方法，其中部件(a)、(b)及(c)在同一脂質核酸組裝組合物中。

實施例A93. 如實施例A84至A88、A90及A92中任一例之方法，其中一或多種導引RNA各自在單獨的脂質核酸組裝組合物中。

實施例A94. 如實施例A84至A93中任一例之方法，其包含向細胞遞送脂質核酸組裝組合物，該脂質核酸組裝組合物包含在同一脂質核酸組裝組合物中的包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶的多肽之第一開讀框的第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。

實施例A95. 如實施例A84至A93中任一例之方法，其包含向細胞遞送：第一脂質核酸組裝組合物，其包含含有編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框的第一mRNA；及第二脂質核酸組裝組合物，其包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開

讀框的第二mRNA。

實施例A96. 如實施例A84至A95中任一例之方法，其進一步包含遞送一或多種脂質核酸組裝組合物中之一或多種導引RNA，該一或多種脂質核酸組裝組合物與包含A3A及UGI之脂質核酸組裝組合物分離。

實施例A97. 如實施例A84至A96中任一例之方法，其中向細胞遞送至少2、3、4、5、6、7、8、9或10種脂質核酸組裝組合物。

實施例A98. 如實施例A84至A97中任一例之方法，其中至少一種脂質核酸組裝組合物包含脂質奈米粒子(LNP)，視情況其中所有脂質核酸組裝組合物包含LNP。

實施例A99. 如實施例A84至A98中任一例之方法，其中至少一種脂質核酸組裝組合物為脂質複合物組合物。

實施例A100. 如實施例A84至A99中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質。

實施例A101. 如實施例A84至A100中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質，且其中可離子化脂質包含可生物降解之可離子化脂質。

實施例A102. 如實施例A84至A101中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質，且其中可離子化脂質之PK值在約5.1至約7.4之範圍內之pKa的範圍內，該pKa在諸如約5.5至約6.6、約5.6至約6.4、約5.8至約6.2或約5.8至約6.5之範圍內。

實施例A103. 如實施例A84至A102中任一例之方法，其中脂質核酸組裝組合物包含胺脂質。

實施例A104. 如實施例A84至A103中任一例之方法，其中脂質核酸

組裝組合物包含脂質A。

實施例A105.如實施例A84至A104中任一例之方法，其中脂質核酸組裝組合物包含輔助脂質。

實施例A106.如實施例A84至A105中任一例之方法，其中脂質核酸組裝組合物包含輔助脂質，其中輔助脂質為膽固醇。

實施例A107.如實施例A84至A106中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質。

實施例A108.如實施例A84至A107中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質，其中隱形脂質為PEG2k-DMG。

實施例A109.如實施例A84至A108中任一例之方法，其中脂質核酸組裝組合物包含中性脂質。

實施例A110.如實施例A84至A109中任一例之方法，其中脂質核酸組裝組合物包含中性脂質，其中中性脂質為DSPC。

實施例A111.如實施例A84至A110中任一例之方法，其中脂質核酸組裝組合物包含中性脂質，其中中性脂質以約9mol%存在。

實施例A112.如實施例A84至A111中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質，其中隱形脂質以約3mol%存在。

實施例A113.如實施例A84至A112中任一例之方法，其中脂質核酸組裝組合物包含輔助脂質，其中輔助脂質以約38mol%存在。

實施例A114.如實施例A84至A113中任一例之方法，其中脂質核酸組裝組合物之N/P比約為6。

實施例A115.如實施例A84至A114中任一例之方法，其中脂質核酸組裝組合物包含約50mol%胺脂質，諸如脂質A；約9mol%中性脂質，諸

如DSPC；約3mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中N/P比約為6。

實施例A116.如實施例A84至A115中任一例之方法，其包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，及/或靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA，及/或靶向降低或消除內源性TCR表現之基因的一種gRNA。

實施例A117.如實施例A84至A115中任一例之方法，其包含選自以下之至少兩種gRNA：靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA、靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

實施例A118.如實施例A84至A115中任一例之方法，其包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA、靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之一種gRNA。

實施例A119.如實施例A84至A115中任一例之方法，其包含選自靶向TRAC、TRBC、B2M、HLA-A或CIITA之gRNA的一種gRNA。

實施例A120.如實施例A84至A116及A119中任一例之方法，其中gRNA靶向TRBC，其中gRNA包含選自以下之導引序列：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序

列。

實施例A121.如實施例A84至A116及A119中任一例之方法，其中gRNA靶向TRBC，其中gRNA包含選自以下之導引序列：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。

實施例A122.如實施例A84至A115中任一例之方法，其包含選自靶向TRAC、TRBC或B2M之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。

實施例A123.如實施例A84至A115中任一例之方法，其包含選自靶向TRAC、TRBC或HLA-A之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。

實施例A124.如實施例A84至A115中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA。

實施例A125.如實施例A84至A115中任一例之方法，其包含靶向B2M之一種導引RNA及靶向CIITA之一種gRNA。

實施例A126.如實施例A84至A115中任一例之方法，其包含靶向HLA-A之一種導引RNA及靶向CIITA之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例A127.如實施例A84至A115中任一例之方法，其包含靶向

TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向B2M之一種gRNA。

實施例A128.如實施例A84至A115中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向HLA-A之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例A129.如實施例A84至A115中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向B2M之一種gRNA及靶向CIITA之一種gRNA。

實施例A130.如實施例A84至A115中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向HLA-A之一種gRNA及靶向CIITA之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例A131.如前述實施例中任一例之方法，其中該方法產生目標序列內之胞嘧啶(C)至胸腺嘧啶(T)轉化。

實施例A132.如前述實施例中任一例之方法，其中相對於目標序列中之總編輯，該方法引起至少60%C形成T轉化。

實施例A133.如前述實施例中任一例之方法，其中相對於目標序列中之總編輯，該方法引起至少65%、70%、75%、80%、85%、90%、95%、98%或99%的C形成T轉化。

實施例A134.如前述實施例中任一例之方法，其中C形成T轉化與非預期編輯之比大於1:1。

實施例A135.如前述實施例中任一例之方法，其中C形成T轉化與非

預期編輯之比為2:1至99:1。

實施例A136.如前述實施例中任一例之方法，其中C形成T轉化與非預期編輯之比為2:1、3:1、4:1、5:1、6:1、7:1或8:1。

實施例A137.如前述實施例中任一例之方法，其中該方法使A3A進行對應於相對於導引序列之5'端的位置-1至位置10中之任一者的鹼基編輯。

實施例A138.如前述實施例中任一例之方法，其中方法使A3A在距導引序列之5'端的1、2、3、4、5、6、7、8、9或10個核苷酸位置處進行鹼基編輯。

實施例A139.如前述實施例中任一例之方法，其中第一mRNA、第二mRNA及導引RNA(若存在)以約6:2:3(w:w:w)之比遞送。

實施例A140.如前述實施例中任一例之方法，其中mRNA、組合物或LNP以5至600ng之總RNA量投與。

實施例A141.如前述實施例中任一例之方法，其中總RNA量為8至550ng。

實施例A142.如前述實施例中任一例之方法，其中總RNA量為35至550ng。

實施例A143.如前述實施例中任一例之方法，其中總RNA量為70至550ng。

實施例A144.如前述實施例中任一例之方法，其中總RNA量為138至550ng。

實施例A145.如前述實施例中任一例之方法，其中總RNA量為275至550ng。

實施例A146.如前述實施例中任一例之方法、細胞或經工程改造之細

胞，其中細胞為淋巴細胞。

實施例A147. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為B淋巴細胞。

實施例A148. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為T淋巴細胞。

實施例A149. 如前述實施例中任一例之方法或用途，其中目標基因之修飾係在活體內進行。

實施例A150. 如前述實施例中任一例之方法或用途，其中目標基因之修飾係在活體外進行。

實施例A151. 如前述實施例中任一例之方法或用途，其中目標基因之修飾降低或消除目標基因之表現。

實施例A152. 如前述實施例中任一例之方法或用途，其中目標基因之基因體編輯或修飾使目標基因之表現降低至少50%、55%、60%、65%、70%、75%、80%、85%、90%、或95%。

實施例A153. 如前述實施例中任一例之方法或用途，其中目標基因之基因體編輯或修飾在基因中產生誤義突變。

實施例A154. 一種多肽，其包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶，其中多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

實施例A155. 一種組合物，其包含：第一多肽，其包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶；及第二多肽，其包含UGI，其中第二多肽不同於第一多肽。

實施例A156. 如實施例A152或A153之多肽，其中A3A經由肽連接子，視情況XTEN融合至RNA導引之切口酶。

實施例A157.如實施例A152或A153之多肽，其中A3A連接至包含有機分子、聚合物或化學部分之連接子。

實施例A158.一種藥物組合物，其包含如前述實施例A中任一例之mRNA、組合物或多肽，及醫藥學上可接受之載劑。

實施例A159.一種套組，其包含如前述實施例A中任一例之mRNA、組合物或多肽。

實施例A160.如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶的多肽以胺基至羧基末端順序包括：A3A、連接子及RNA導引之切口酶。

實施例A161.一種改變TRAC基因內之DNA序列的方法，其包含向細胞遞送：

(a)　包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b)　編碼(a.)之gRNA的核酸。

實施例A162.一種降低TRAC基因之表現的方法，其包含向細胞遞送：

(a)　包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷

酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b) 編碼(a.)之gRNA的核酸。

實施例A163.一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之基因修飾：

chr14:22547596-22547616；chr14:22550570-22550590；chr14:22547763-22547783；chr14:22550596-22550616；chr14:22550566-22550586；chr14:22547753-22547773；chr14:22550601-22550621；chr14:22550599-22550619；chr14:22547583-22547603；chr14:22547671-22547691；chr14:22547770-22547790；chr14:22547676-22547696；chr14:22547772-22547792；chr14:22547771-22547791；chr14:22547733-22547753；chr14:22547776-22547796；或

其中該細胞係藉由向該細胞遞送以下而經工程改造：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；

或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b) 編碼(a.)之gRNA的核酸。

實施例A164.如實施例A161至A163中任一例之方法，其中導引序列包含SEQ ID NO:706至709中之任一者。

實施例A165.如實施例A161至A164中任一例之方法，其中導引序列包含SEQ ID NO:706至708中之任一者。

實施例A166.如實施例A161至A165中任一例之方法，其中導引序列包含SEQ ID NO:706。

實施例A167.如實施例A161至A165中任一例之方法，其中導引序列包含SEQ ID NO:707。

實施例A168.如實施例A161至A165中任一例之方法，其中導引序列包含SEQ ID NO:708。

實施例A169.一種改變TRBC1及/或TRBC2基因內之DNA序列的方法，其包含向細胞遞送組合物，其中該組合物包含：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b) 編碼(a.)之導引RNA的核酸。

實施例A170.一種降低TRBC1及/或TRBC2基因之表現的方法，其包含向細胞遞送組合物，其中該組合物包含：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b) 編碼(a.)之導引RNA的核酸。

實施例A171.一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之修飾：chr7:142791757-142791777；chr7:142801104-142801124；chr7:142791811-142791831；chr7:142801158-142801178；chr7:142792728-142792748；chr7:142791719-142791739；chr7:142791766-142791786；chr7:142801113-142801133；chr7:142791928-142791948；chr7:142801275-142801295；chr7:142792062-142792082；chr7:142801409-142801429；chr7:142792713-142792733；chr7:142802126-142802146；chr7:142791808-142791828；chr7:142801155-142801175；chr7:142792003-142792023；chr7:142801350-142801370；chr7:142791760-142791780；chr7:142791715-142791735；chr7:142792781-142792801；chr7:142792040-142792060；chr7:142801387-142801407；chr7:142791862-142791882；chr7:142791716-142791736；chr7:142791787-142791807；

chr7:142791759-142791779 ; chr7:142801106-142801126 ;

chr7:142791807-142791827 ; chr7:142801154-142801174 ;

chr7:142791879-142791899 ; chr7:142801226-142801246 ;

chr7:142791805-142791825 ; chr7:142791700-142791720 ;

chr7:142791765-142791785 ; chr7:142801112-142801132 ;

chr7:142791820-142791840 ; chr7:142791872-142791892 ;

chr7:142801219-142801239 ; chr7:142791700-142791720 ;

chr7:142791806-142791826 ; chr7:142801153-142801173 ;

chr7:142792035-142792055 ; chr7:142792724-142792744 ;

chr7:142792754-142792774 ; chr7:142791804-142791824 ;

chr7:142792684-142792704 ; chr7:142791823-142791843 ;

chr7:142792728-142792748 ; chr7:142792721-142792741 ;

chr7:142792749-142792769 ; chr7:142792685-142792705 ;

chr7:142791816-142791836 ; chr7:142801163-142801183 ;

chr7:142792686-142792706 ; chr7:142791793-142791813 ;

chr7:142793110-142793130 ; chr7:142791815-142791835 ;

chr7:142801162-142801182 ; chr7:142792770-142792790 ;

chr7:142792047-142792067 ; chr7:142801394-142801414 ;

chr7:142791871-142791891 ; chr7:142801218-142801238 ;

chr7:142791894-142791914 ; chr7:142792723-142792743 ;

chr7:142792724-142792744 ; chr7:142791897-142791917 ;

chr7:142801244-142801264 ; chr7:142792757-142792777 ;

chr7:142792740-142792760；chr7:142792758-142792778；或

其中該細胞係藉由向細胞遞送以下而經工程改造：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

(b) 編碼(a.)之導引RNA的核酸。

實施例A172. 如實施例A169至A171中任一例之方法，其中導引序列包含SEQ ID NO:618至627中之任一者。

實施例A173. 如實施例A169至A172中任一例之方法，其中導引序列包含SEQ ID NO:618至621中之任一者。

實施例A174. 如實施例A169至A173中任一例之方法，其中導引序列包含SEQ ID NO:618。

實施例A175. 如實施例A169至A173中任一例之方法，其中導引序列包含SEQ ID NO:619。

實施例A176. 如實施例A169至A173中任一例之方法，其中導引序列包含SEQ ID NO:620。

實施例A177. 如實施例A169至A173中任一例之方法,其中導引序列包含SEQ ID NO:621。

實施例A178. 如實施例A161至A177中任一例之方法,其中組合物進一步包含如實施例A1至A76中任一例之mRNA或組合物。

實施例A179. 一種組合物，其包含：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

(b) 如實施例A1至A76中任一例之mRNA或組合物。

實施例A180.如實施例A179之組合物，其中導引序列包含SEQ ID NO:706至709中之任一者。

實施例A181.如實施例A179或A180之組合物，其用於改變細胞中之TRAC基因內的DNA序列。

實施例A182.如實施例A179至A181中任一例之組合物，其用於降低細胞中之TRAC基因之表現。

實施例A183.如實施例A179至A182中任一例之組合物，其用於個體之免疫療法中。

實施例A184.一種組合物，其包含：

(a) 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

(b) 如實施例A11至A75中任一例之mRNA或組合物。

實施例A185.如實施例A184之組合物，其中導引序列包含SEQ ID NO:618至621中之任一者。

實施例A186.如實施例A184或A185之組合物，其用於改變細胞中之TRBC1及/或TRBC2基因內的DNA序列。

實施例A187.如實施例A184至A186中任一例之組合物，其用於降低細胞中之TRBC1及/或TRBC2基因之表現。

實施例A188.如實施例A184至A187中任一例之組合物，其用於個體之免疫療法中。

實施例A189.一種細胞，其藉由如實施例A120至A121及A161至A178中任一例之方法改變。

實施例A190.如實施例A189之細胞，其中細胞在活體外改變。

實施例A191.如實施例A189或A190之細胞，其中細胞為T細胞。

實施例A192.如實施例A189至A191中任一例之細胞，其中細胞為$CD4^+$或$CD8^+$ T細胞。

實施例A193.如實施例A189至A192中任一例之細胞，其中細胞為哺乳動物細胞、靈長類動物細胞或人類細胞。

實施例A194.如實施例A189至A193中任一例之細胞，其用於個體之免疫療法中。

實施例A195.一種已降低或消除TRAC之表面表現的經工程改造之細胞，其包含人類TRAC基因中之基因修飾，其中該基因修飾包含選自以下之基因體座標內的至少一個核苷酸之修飾：

chr14:22547596-22547616 ; chr14:22550570-22550590 ; chr14:22547763-22547783 ; chr14:22550596-22550616 ;

chr14:22550566-22550586 ; chr14:22547753-22547773 ;

chr14:22550601-22550621 ; chr14:22550599-22550619 ;

chr14:22547583-22547603 ; chr14:22547671-22547691 ;

chr14:22547770-22547790 ; chr14:22547676-22547696 ;

chr14:22547772-22547792 ; chr14:22547771-22547791 ;

chr14:22547733-22547753；chr14:22547776-22547796。

實施例A196.一種已降低或消除TRBC1/2之表面表現的經工程改造之細胞，其包含人類TRBC1/2基因中之基因修飾，其中該基因修飾包含選自以下之基因體座標內的至少一個核苷酸之修飾：

chr7:142791757-142791777 ; chr7:142801104-142801124 ;

chr7:142791811-142791831 ; chr7:142801158-142801178 ;

chr7:142792728-142792748 ; chr7:142791719-142791739 ;

chr7:142791766-142791786 ; chr7:142801113-142801133 ;

chr7:142791928-142791948 ; chr7:142801275-142801295 ;

chr7:142792062-142792082 ; chr7:142801409-142801429 ;

chr7:142792713-142792733 ; chr7:142802126-142802146 ;

chr7:142791808-142791828 ; chr7:142801155-142801175 ;

chr7:142792003-142792023 ; chr7:142801350-142801370 ;

chr7:142791760-142791780 ; chr7:142791715-142791735 ;

chr7:142792781-142792801 ; chr7:142792040-142792060 ;

chr7:142801387-142801407 ; chr7:142791862-142791882 ;

chr7:142791716-142791736 ; chr7:142791787-142791807 ;

chr7:142791759-142791779 ; chr7:142801106-142801126 ;

chr7:142791807-142791827 ; chr7:142801154-142801174 ;

chr7:142791879-142791899 ; chr7:142801226-142801246 ;

chr7:142791805-142791825 ; chr7:142791700-142791720 ;

chr7:142791765-142791785 ; chr7:142801112-142801132 ;

chr7:142791820-142791840 ; chr7:142791872-142791892 ;

chr7:142801219-142801239 ; chr7:142791700-142791720 ;

chr7:142791806-142791826 ; chr7:142801153-142801173 ;

chr7:142792035-142792055 ; chr7:142792724-142792744 ;

chr7:142792754-142792774 ; chr7:142791804-142791824 ;

chr7:142792684-142792704 ; chr7:142791823-142791843 ;

chr7:142792728-142792748 ; chr7:142792721-142792741 ;

chr7:142792749-142792769 ; chr7:142792685-142792705 ;

chr7:142791816-142791836 ; chr7:142801163-142801183 ;

chr7:142792686-142792706 ; chr7:142791793-142791813 ;

chr7:142793110-142793130 ; chr7:142791815-142791835 ;

chr7:142801162-142801182 ; chr7:142792770-142792790 ;

chr7:142792047-142792067 ; chr7:142801394-142801414 ;

chr7:142791871-142791891 ; chr7:142801218-142801238 ;

chr7:142791894-142791914 ; chr7:142792723-142792743 ;

chr7:142792724-142792744 ; chr7:142791897-142791917 ;

chr7:142801244-142801264 ; chr7:142792757-142792777 ;

chr7:142792740-142792760；chr7:142792758-142792778。

實施例A197.一或多種脂質核酸組裝組合物，視情況脂質奈米粒子，

其包含：

(a)　第一mRNA，其包含編碼包含APOBEC3A去胺酶(A3A)及RNA導引之切口酶之多肽的第一開讀框；

(b)　第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)　一或多種導引RNA。

實施例A198. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為免疫細胞。

實施例A199. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為淋巴細胞。

實施例A200. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為T細胞。

【0757】 以下經編號實施例提供對本文中之實施例之額外支援及描述。

實施例B1.　一種mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框，其中該多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

實施例B2.　一種組合物，其包含：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA，視情況其中組合物包含脂質奈米粒子。

實施例B3.　如實施例B2之組合物，其中第一開讀框不包含編碼UGI之序列。

實施例B4. 如實施例B2或B3之組合物，其中第二mRNA與第一mRNA之莫耳比為1:1至30:1。

實施例B5. 如實施例B2至B4中任一例之組合物，其中組合物包含第一組合物及第二組合物，其中第一組合物包含含有編碼包含胞苷去胺酶及RNA導引之切口酶且不包含尿嘧啶醣苷酶抑制劑(UGI)之多肽的第一開讀框之第一mRNA，且第二組合物包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中第二mRNA不同於第一mRNA，視情況其中組合物包含脂質奈米粒子。

實施例B6. 如實施例B2至B5中任一例之組合物，其中第一mRNA及第二mRNA在同一或單獨小瓶中。

實施例B7. 一種修飾目標基因之方法，其包含向細胞遞送：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之第一多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA；及至少一種導引RNA(gRNA)，其中若切口酶為SpyCas9切口酶，則gRNA為SpyCas9 gRNA，且若切口酶為NmeCas9切口酶，則gRNA為Nme gRNA。

實施例B8. 如實施例B2至B7中任一例之組合物或方法，其中第二mRNA與第一mRNA之莫耳比為1:1至30:1。

實施例B9. 如實施例B2至B7中任一例之組合物或方法，其中莫耳比為2:1至30:1。

實施例B10. 如實施例B2至B7中任一例之組合物或方法，其中莫耳比為7:1至22:1。

實施例B11. 一種細胞，其包含含有以下之組合物：第一mRNA，其

包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；及第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中第二mRNA不同於第一mRNA。

實施例B12. 一種經工程改造之細胞，其包含至少一種鹼基編輯及/或插入/缺失，其中鹼基編輯及/或插入/缺失藉由使細胞與組合物接觸而形成，組合物包含含有編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框之第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中第二mRNA不同於第一mRNA。

實施例B13.如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶為

(i)APOBEC家族之酶，視情況為APOBEC3子群之酶；

(ii)包含與SEQ ID NO:40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iii)包含與SEQ ID NO:40、41及960至1013中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iv)包含與SEQ ID NO:40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；或

(v)包含與SEQ ID NO:40、976、981、984、986及1014至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶。

實施例B14. 如實施例B13之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶包含與SEQ ID NO:40、41及960至1023具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基

酸序列。

實施例B15. 如實施例B13之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶包含與SEQ ID NO:40、41及960至1013具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

實施例B16. 如實施例B13之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶包含與SEQ ID NO:40、41、976、977、979、980、984至987、993至1006及1009具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

實施例B17. 如實施例B13之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶包含與SEQ ID NO:40、976、981、984、986、1014至1023具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

實施例B18. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶為APOBEC3A去胺酶(A3A)。

實施例B19. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少87%一致性之胺基酸序列。

實施例B20. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少90%一致性之胺基酸序列。

實施例B21. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少95%一致性之胺基

酸序列。

實施例B22. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少98%一致性之胺基酸序列。

實施例B23. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:40具有至少99%一致性之胺基酸序列。

實施例B24. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含SEQ ID NO:40之胺基酸序列。

實施例B25. 如實施例B18至B24中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A為人類A3A。

實施例B26. 如實施例B18至B24中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A為野生型A3A。

實施例B27. 如實施例B18之mRNA、組合物、方法、細胞或經工程改造之細胞，其中A3A包含與SEQ ID NO:976、977、993至1006及1009具有至少87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

實施例B28. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少80%一致性之胺基酸序列。

實施例B29. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少90%一致性之胺基酸序列。

實施例B30. 如前述實施例中任一例之組合物、方法、細胞或經工程

改造之細胞，其中UGI包含與SEQ ID NO:27具有至少95%一致性之胺基酸序列。

實施例B31. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少98%一致性之胺基酸序列。

實施例B32. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含與SEQ ID NO:27具有至少99%一致性之胺基酸序列。

實施例B33. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其中UGI包含SEQ ID NO:27之胺基酸序列。

實施例B34. 如前述實施例中任一例之組合物、方法或細胞，其進一步包含至少一種導引RNA(gRNA)。

實施例B35. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中gRNA為sgRNA。

實施例B36. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中gRNA為dgRNA。

實施例B37. 如前述實施例中任一例之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中gRNA為包含含有髮夾區之sgRNA之保守部分的短單導引RNA(短sgRNA)，其中髮夾區缺少至少5至10個核苷酸且其中短sgRNA包含5'端修飾或3'端修飾或兩者。

實施例B38. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為Cas切口酶。

實施例B39. 如前述實施例中任一例之mRNA、組合物、方法、細胞

或經工程改造之細胞，其中RNA導引之切口酶為2類Cas切口酶。

實施例B40. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為Cas9切口酶。

實施例B41. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引切口酶為化膿性鏈球菌(Spy)Cas9切口酶。

實施例B42. 如實施例B41之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為D10A SpyCas9切口酶。

實施例B43. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶包含與SEQ ID NO:70、73或76中之任一者具有至少80%、90%、95%、98%或99%一致性的胺基酸序列。

實施例B44. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶包含SEQ ID NO:70、73或76中之任一者的胺基酸序列。

實施例B45. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少80%、90%、95%、98%或99%一致性的核苷酸序列。

實施例B46. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少90%一致性的核苷酸序列。

實施例B47. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少95%一致性的核苷酸序列。

實施例B48. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少98%一致性的核苷酸序列。

實施例B49. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少99%一致性的核苷酸序列。

實施例B50. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼RNA導引之切口酶的序列包含SEQ ID NO:71、72、74、75或77至90中之任一者之核苷酸序列。

實施例B51. 如實施例B1至B37中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為腦膜炎雙球菌(Nme)Cas9切口酶。

實施例B52. 如實施例B51之mRNA、組合物、方法、細胞或經工程改造之細胞，其中RNA導引之切口酶為D16A NmeCas9切口酶，視情況為D16A Nme2Cas9。

實施例B53. 如實施例B1至B37、B51或B52中任一例之mRNA、組合物、方法、細胞，經工程改造之細胞，其中編碼RNA導引之切口酶的

序列包含SEQ ID NO:380及387中之任一者之核苷酸序列。

實施例B54. 如前述實施例中任一例之mRNA、組合物、方法、細胞，經工程改造之細胞，其中mRNA包含與SEQ ID NO:91至98中之任一者具有至少90%一致性之5'UTR。

實施例B55. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含與SEQ ID NO:99至106中之任一者具有至少90%一致性之3'UTR。

實施例B56. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含來自同一源之5'UTR及3'UTR。

實施例B57. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA包含選自Cap0、Cap1及Cap2之5'端帽。

實施例B58. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框包含最小腺嘌呤密碼子及/或最小尿苷密碼子。

實施例B59. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框包含最小腺嘌呤密碼子。

實施例B60. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框具有增加哺乳

動物中之mRNA轉譯的密碼子。

實施例B61. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之開讀框具有增加哺乳動物中之mRNA轉譯的密碼子，其中哺乳動物為人類。

實施例B62. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中胞苷去胺酶位於多肽中之RNA導引之切口酶的N末端。

實施例B63.如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)。

實施例B64. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中NLS處於RNA導引之切口酶之C末端。

實施例B65. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA之導引切口酶包含核定位訊號(NLS)，且其中NLS處於RNA導引之切口酶之N末端，或其中NLS融合至RNA導引之切口酶的N末端及C末端兩者。

實施例B66. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中連接子存在於RNA導引之切口酶之N末端與NLS之間，視情況其中連接子為肽連接子。

實施例B67. 如前述實施例中任一例之mRNA、組合物、方法、細胞

或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS包含與SEQ ID NO:63及110至122具有至少80%、85%、90%或95%一致性之序列。

實施例B68. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS包含SEQ ID NO:63及110至122中之任一者之序列。

實施例B69. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS由與SEQ ID NO:123至135中之任一者之序列具有至少80%、85%、90%、95%、98%或100%一致性的序列編碼。

實施例B70. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中胞苷去胺酶位於多肽中之NLS的N末端。

實施例B71. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中RNA導引之切口酶位於多肽中之NLS的N末端。

實施例B72. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框包含與SEQ ID NO:1之序列具有至少80%、85%、90%、95%、98%或100%一致性之序列。

實施例B73. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之

多肽的開讀框包含與SEQ ID NO:4之序列具有至少80%、85%、90%、95%、98%或100%一致性之序列。

實施例B74. 如前述實施例中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中mRNA中至少10%之尿苷由經修飾之尿苷取代。

實施例B75. 如實施例B64之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷、假尿苷、5-甲氧基尿苷或5-碘尿苷中之一或多者。

實施例B76. 如實施例B64或B65之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷或5-甲氧基尿苷中之一者或兩者。

實施例B77. 如實施例B74至B76中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為N1-甲基-假尿苷。

實施例B78. 如實施例B74至B76中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中經修飾之尿苷為5-甲氧基尿苷。

實施例B79. 如實施例B74至B78中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中15%至45%之尿苷由經修飾之尿苷取代。

實施例B80. 如實施例B74至B79中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中至少20%或至少30%之尿苷由經修飾之尿苷取代。

實施例B81. 如實施例B74至B80中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中至少80%或至少90%之尿苷由經修飾

之尿苷取代。

實施例B82. 如實施例B74至B81中任一例之mRNA、組合物、方法、細胞或經工程改造之細胞，其中100%之尿苷由經修飾之尿苷取代。

實施例B83. 如前述實施例中任一例之mRNA、組合物、方法或細胞， 其進一步編碼胞苷去胺酶與RNA導引之切口酶之間的肽連接子，視情況其中肽連接子為XTEN。

實施例B84. 如前述實施例中任一例之mRNA、組合物、方法或細胞，其進一步編碼胞苷去胺酶與RNA導引之切口酶之間的肽連接子，其中肽連接子包含至少1個、至少2個、至少3個、至少4個、至少5個、至少6個、至少7個、至少8個、至少9個、至少10個、至少15個、至少20個、至少25個、至少30個、至少40個、至少50個或更多個胺基酸。

實施例B85. 如前述實施例中任一例之mRNA、組合物、方法或細胞，其進一步編碼胞苷去胺酶與RNA導引之切口酶之間的肽連接子，其中肽連接子包含選自SEQ ID NO:46至59、61及211至272之一或多個序列。

實施例B86. 一種多肽，其由如前述實施例中任一例之mRNA編碼。

實施例B87. 一種核糖核蛋白複合物(RNP)，其包含(i)由如前述實施例中任一例之mRNA中之任一者編碼的多肽；及(ii)導引RNA。

實施例B88. 一種載體，其包含如前述實施例中任一例之mRNA。

實施例B89. 一種表現構築體，其包含可操作地連接於編碼如前述實施例中任一例之mRNA之序列的啟動子。

實施例B90. 一種質體，其包含如實施例B89之表現構築體。

實施例B91. 一種宿主細胞，其包含如實施例B88之載體、如實施例

B89之表現構築體或如實施例B90之質體。

實施例B92. 如前述實施例中任一例之mRNA或組合物，其中mRNA或組合物經調配為脂質核酸組裝組合物，視情況為脂質奈米粒子。

實施例B93. 一種如前述實施例中任一例之mRNA或組合物之用途，其用於修飾細胞中之目標基因。

實施例B94. 一種如前述實施例中任一例之mRNA或組合物之用途，其用於製造用於修飾細胞中之目標基因的藥劑。

實施例B95. 一種修飾細胞中之目標基因之方法，其包含向該細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，該一或多種脂質核酸組裝組合物包含：

(a)第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；

(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)一或多種導引RNA。

實施例B96. 如實施例B95之方法，其中部分(a)及(b)在單獨的脂質核酸組裝組合物中。

實施例B97. 如實施例B95之方法，其中部分(a)及(b)在同一脂質核酸組裝組合物中。

實施例B98. 如實施例B95之方法，其中部分(a)及(c)在單獨的脂質核酸組裝組合物中。

實施例B99. 如實施例B95之方法，其中部分(a)及(c)在同一脂質核酸組裝組合物中。

實施例B100. 如實施例B95之方法，其中部分(b)及(c)在單獨的脂質核酸組裝組合物中。

實施例B101. 如實施例B95之方法，其中部分(a)及(c)在同一脂質核酸組裝組合物中，且部分(b)在單獨的脂質核酸組裝組合物中。

實施例B102. 如實施例B95之方法，其中部件(a)、(b)及(c)各自在單獨的脂質核酸組裝組合物中。

實施例B103. 如實施例B95之方法，其中部件(a)、(b)及(c)在同一脂質核酸組裝組合物中。

實施例B104. 如實施例B95及B98至B103中任一例之方法，其中一或多種導引RNA各自在單獨的脂質核酸組裝組合物中。

實施例B105. 如實施例B95至B104中任一例之方法，其包含向細胞遞送脂質核酸組裝組合物，該脂質核酸組裝組合物包含在同一脂質核酸組裝組合物中的包含編碼包含胞苷去胺酶及RNA導引之切口酶的多肽之第一開讀框的第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。

實施例B106. 如實施例B95至B104中任一例之方法，其包含向細胞遞送：第一脂質核酸組裝組合物，其包含含有編碼包含胞苷去胺酶及RNA導引之切口酶的多肽之第一開讀框的第一mRNA；及第二脂質核酸組裝組合物，其包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。

實施例B107. 如實施例B95至B104中任一例之方法，其進一步包含遞送一或多種脂質核酸組裝組合物中之一或多種導引RNA，該一或多種脂質核酸組裝組合物與包含胞苷去胺酶及UGI之脂質核酸組裝組合物分離。

實施例B108. 如實施例B95至B107中任一例之方法，其中向細胞遞送至少2、3、4、5、6、7、8、9或10種脂質核酸組裝組合物。

實施例B109. 如實施例B95至B108中任一例之方法，其中至少一種脂質核酸組裝組合物包含脂質奈米粒子(LNP)，視情況其中所有脂質核酸組裝組合物包含LNP。

實施例B110. 如實施例B95至B109中任一例之方法，其中至少一種脂質核酸組裝組合物為脂質複合物組合物。

實施例B111. 如實施例B95至B110中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質。

實施例B112. 如實施例B95至B111中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質，且其中可離子化脂質包含可生物降解可離子化脂質。

實施例B113. 如實施例B95至B112中任一例之方法，其中脂質核酸組裝組合物包含可離子化脂質，且其中可離子化脂質之PK值在約5.1至約7.4之範圍內之pKa的範圍內，該pKa在諸如約5.5至約6.6、約5.6至約6.4、約5.8至約6.2或約5.8至約6.5之範圍內。

實施例B114. 如實施例B95至B113中任一例之方法，其中脂質核酸組裝組合物包含胺脂質。

實施例B115. 如實施例B95至B114中任一例之方法，其中脂質核酸組裝組合物包含脂質A。

實施例B116. 如實施例B95至B115中任一例之方法，其中脂質核酸組裝組合物包含輔助脂質。

實施例B117. 如實施例B95至B116中任一例之方法，其中脂質核酸組

裝組合物包含輔助脂質，其中輔助脂質為膽固醇。

實施例B118. 如實施例B95至B117中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質。

實施例B119. 如實施例B95至B118中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質，其中隱形脂質為PEG2k-DMG。

實施例B120. 如實施例B95至B119中任一例之方法，其中脂質核酸組裝組合物包含中性脂質。

實施例B121. 如實施例B95至B120中任一例之方法，其中脂質核酸組裝組合物包含中性脂質，其中中性脂質為DSPC。

實施例B122. 如實施例B95至B121中任一例之方法，其中脂質核酸組裝組合物包含中性脂質，其中中性脂質以約9mol%存在。

實施例B123. 如實施例B95至B122中任一例之方法，其中脂質核酸組裝組合物包含隱形脂質，其中隱形脂質以約3mol%存在。

實施例B124. 如實施例B95至B123中任一例之方法，其中脂質核酸組裝組合物包含輔助脂質，其中輔助脂質以約38mol%存在。

實施例B125. 如實施例B95至B124中任一例之方法，其中脂質核酸組裝組合物之N/P比約為6。

實施例B126. 如實施例B95至B125中任一例之方法，其中脂質核酸組裝組合物包含約50mol%胺脂質，諸如脂質A；約9mol%中性脂質，諸如DSPC；約3mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中N/P比約為6。

實施例B127. 如實施例B95至B126中任一例之方法，其包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，及/或靶向降低或

消除細胞表面上之MHC II類表現之基因的一種gRNA，及/或靶向降低或消除內源性TCR表現之基因的一種gRNA。

實施例B128. 如實施例B95至B127中任一例之方法，其包含選自以下之至少兩種gRNA：靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA、靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

實施例B129. 如實施例B95至B128中任一例之方法，其包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA，靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA，及靶向降低或消除內源性TCR表現之基因的一種gRNA。

實施例B130. 如實施例B95至129中任一例之方法，其包含選自靶向TRAC、TRBC、B2M、HLA-A或CIITA之gRNA的一種gRNA。

實施例B131. 如實施例B95至B130中任一例之方法,其中gRNA靶向TRBC，其中gRNA包含選自以下之導引序列：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。

實施例B132. 如實施例B95至B130中任一例之方法，其中gRNA靶向TRBC，其中gRNA包含選自以下之導引序列：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的

導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。

實施例B133. 如實施例B95至B130中任一例之方法，其包含選自靶向TRAC、TRBC或B2M之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。

實施例B134. 如實施例B95至B130中任一例之方法，其包含選自靶向TRAC、TRBC或HLA-A之gRNA的至少兩種gRNA，其中兩種導引RNA不靶向相同基因。

實施例B135. 如實施例B95至B130中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA。

實施例B136. 如實施例B95至B130中任一例之方法，其包含靶向B2M之一種導引RNA及靶向CIITA之一種gRNA。

實施例B137. 如實施例B95至B130中任一例之方法，其包含靶向HLA-A之一種導引RNA及靶向CIITA之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例B138. 如實施例B95至B130中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向B2M之一種gRNA。

實施例B139. 如實施例B95至B130中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向HLA-A之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例B140. 如實施例B95至B130中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向B2M之一種gRNA及靶向CIITA之一種gRNA。

實施例B141. 如實施例B95至B130中任一例之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向HLA-A之一種gRNA及靶向CIITA之一種gRNA，視情況其中細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

實施例B142. 如前述實施例中任一例之方法，其中該方法產生目標序列內之胞嘧啶(C)至胸腺嘧啶(T)轉化。

實施例B143. 如前述實施例中任一例之方法，其中相對於目標序列中之總編輯，該方法引起至少60%的C形成T轉化。

實施例B144. 如前述實施例中任一例之方法，其中相對於目標序列中之總編輯，該方法引起至少65%、70%、75%、80%、85%、90%、95%、98%或99%的C形成T轉化。

實施例B145. 如前述實施例中任一例之方法，其中C形成T轉化與非預期編輯之比大於1:1。

實施例B146. 如前述實施例中任一例之方法，其中C形成T轉化與非預期編輯之比為2:1至99:1。

實施例B147. 如前述實施例中任一例之方法，其中C形成T轉化與非預期編輯之比為2:1、3:1、4:1、5:1、6:1、7:1或8:1。

實施例B148. 如前述實施例中任一例之方法，其中該方法使胞苷去胺酶進行對應於相對於導引序列之5'端的位置-1至位置10中之任一者的鹼基編輯。

實施例B149. 如前述實施例中任一例之方法，其中該方法使胞苷去胺酶在距導引序列之5'端的1、2、3、4、5、6、7、8、9或10個核苷酸的位置處進行鹼基編輯。

實施例B150. 如前述實施例中任一例之方法，其中第一mRNA、第二mRNA及導引RNA(若存在)以約6:2:3(w:w:w)之比遞送。

實施例B151. 如前述實施例中任一例之方法，其中mRNA、組合物或LNP以5至600ng之總RNA量投與。

實施例B152. 如前述實施例中任一例之方法，其中總RNA量為8至550ng。

實施例B153. 如前述實施例中任一例之方法，其中總RNA量為35至550ng。

實施例B154. 如前述實施例中任一例之方法，其中總RNA量為70至550ng。

實施例B155. 如前述實施例中任一例之方法，其中總RNA量為138至550ng。

實施例B156. 如前述實施例中任一例之方法，其中總RNA量為275至550ng。

實施例B157. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為淋巴細胞。

實施例B158. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為B淋巴細胞。

實施例B159. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為T淋巴細胞。

實施例B160. 如前述實施例中任一例之方法或用途，其中目標基因之修飾在活體內進行。

實施例B161. 如前述實施例中任一例之方法或用途，其中目標基因之修飾在活體外進行。

實施例B162. 如前述實施例中任一例之方法或用途，其中目標基因之修飾降低或消除目標基因之表現。

實施例B163. 如前述實施例中任一例之方法或用途，其中目標基因之基因體編輯或修飾使目標基因之表現降低至少50%、55%、60%、65%、70%、75%、80%、85%、90%、或95%。

實施例B164. 如前述實施例中任一例之方法或用途，其中目標基因之基因體編輯或修飾在基因中產生誤義突變。

實施例B165. 一種多肽，其包含胞苷去胺酶及RNA導引之切口酶，其中多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

實施例B166. 一種核糖核蛋白複合物(RNP)，其包含如實施例B165之多肽及導引RNA，其中若RNP包含SpyCas9切口酶，則導引RNA為Spy導引RNA，且其中若RNP包含NmeCas切口酶，則導引RNA為Nme導引RNA。

實施例B167. 一種組合物，其包含：第一多肽，其包含胞苷去胺酶及RNA導引之切口酶，其中第一多肽不包含尿嘧啶醣苷酶抑制劑(UGI)；及第二多肽，其包含UGI，其中第二多肽不同於第一多肽。

實施例B168. 如實施例B165至B167中任一例之多肽、RNP或組合物，其中胞苷去胺酶經由肽連接子，視情況XTEN融合至RNA導引之切口酶。

實施例B169. 如實施例B165至B167中任一例之多肽、RNP或組合物，其中胞苷去胺酶連接至包含有機分子、聚合物或化學部分之連接子。

實施例B170. 一種藥物組合物，其包含如前述實施例中任一例之mRNA、RNP、組合物或多肽，及醫藥學上可接受之載劑。

實施例B171. 一種套組，其包含如前述實施例中任一例之mRNA、RNP、組合物或多肽。

實施例B172. 如前述實施例中任一例之mRNA、RNP、組合物、方法、細胞或經工程改造之細胞，其中包含胞苷去胺酶及RNA導引之切口酶之多肽以胺基至羧基末端順序包括：胞苷去胺酶、連接子及RNA導引之切口酶。

實施例B173. 一種改變TRAC基因內之DNA序列的方法，其包含向細胞遞送：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

實施例B174. 一種降低TRAC基因之表現的方法，其包含向細胞遞送：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；

iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

實施例B175. 一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之基因修飾：

chr14:22547596-22547616；chr14:22550570-22550590；chr14:22547763-22547783；chr14:22550596-22550616；chr14:22550566-22550586；chr14:22547753-22547773；chr14:22550601-22550621；chr14:22550599-22550619；chr14:22547583-22547603；chr14:22547671-22547691；chr14:22547770-22547790；chr14:22547676-22547696；chr14:22547772-22547792；chr14:22547771-22547791；chr14:22547733-22547753；chr14:22547776-22547796；或

其中該細胞係藉由向該細胞遞送以下而經工程改造：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)

與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

實施例B176. 如實施例B173至B175中任一例之方法,其中導引序列包含SEQ ID NO:706至709中之任一者。

實施例B177. 如實施例B173至B175中任一例之方法,其中導引序列包含SEQ ID NO:706至708中之任一者。

實施例B178. 如實施例B173至B175中任一例之方法,其中導引序列包含SEQ ID NO:706。

實施例B179. 如實施例B173至B175中任一例之方法，其中導引序列包含SEQ ID NO:707。

實施例B180. 如實施例B173至B175中任一例之方法，其中導引序列包含SEQ ID NO:708。

實施例B181. 一種改變TRBC1及/或TRBC2基因內之DNA序列的方法，其包含向細胞遞送組合物，其中組合物包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

實施例B182. 一種降低TRBC1及/或TRBC2基因之表現的方法，其包含向細胞遞送組合物，其中組合物包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

實施例B183. 一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之修飾：chr7:142791757-142791777；chr7:142801104-142801124；chr7:142791811-142791831；chr7:142801158-142801178；chr7:142792728-142792748；chr7:142791719-142791739；chr7:142791766-142791786；chr7:142801113-142801133；chr7:142791928-142791948；chr7:142801275-142801295；chr7:142792062-142792082；chr7:142801409-142801429；chr7:142792713-142792733；chr7:142802126-142802146；chr7:142791808-142791828；chr7:142801155-142801175；chr7:142792003-142792023；chr7:142801350-142801370；chr7:142791760-142791780；chr7:142791715-142791735；chr7:142792781-142792801；chr7:142792040-142792060；chr7:142801387-142801407；chr7:142791862-142791882；chr7:142791716-142791736；chr7:142791787-142791807；

chr7:142791759-142791779 ; chr7:142801106-142801126 ;

chr7:142791807-142791827 ; chr7:142801154-142801174 ;

chr7:142791879-142791899 ; chr7:142801226-142801246 ;

chr7:142791805-142791825 ; chr7:142791700-142791720 ;

chr7:142791765-142791785 ; chr7:142801112-142801132 ;

chr7:142791820-142791840 ; chr7:142791872-142791892 ;

chr7:142801219-142801239 ; chr7:142791700-142791720 ;

chr7:142791806-142791826 ; chr7:142801153-142801173 ;

chr7:142792035-142792055 ; chr7:142792724-142792744 ;

chr7:142792754-142792774 ; chr7:142791804-142791824 ;

chr7:142792684-142792704 ; chr7:142791823-142791843 ;

chr7:142792728-142792748 ; chr7:142792721-142792741 ;

chr7:142792749-142792769 ; chr7:142792685-142792705 ;

chr7:142791816-142791836 ; chr7:142801163-142801183 ;

chr7:142792686-142792706 ; chr7:142791793-142791813 ;

chr7:142793110-142793130 ; chr7:142791815-142791835 ;

chr7:142801162-142801182 ; chr7:142792770-142792790 ;

chr7:142792047-142792067 ; chr7:142801394-142801414 ;

chr7:142791871-142791891 ; chr7:142801218-142801238 ;

chr7:142791894-142791914 ; chr7:142792723-142792743 ;

chr7:142792724-142792744 ; chr7:142791897-142791917 ;

chr7:142801244-142801264 ; chr7:142792757-142792777 ;

chr7:142792740-142792760；chr7:142792758-142792778；或

其中該細胞係藉由向細胞遞送以下而經工程改造：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

實施例B184. 如實施例B181至B183中任一例之方法，其中導引序列包含SEQ ID NO:618至627中之任一者。

實施例B185. 如實施例B181至B184中任一例之方法，其中導引序列包含SEQ ID NO:618至621中之任一者。

實施例B186. 如實施例B181至B185中任一例之方法，其中導引序列包含SEQ ID NO:618。

實施例B187. 如實施例B181至B185中任一例之方法，其中導引序列包含SEQ ID NO:619。

實施例B188. 如實施例B181至B185中任一例之方法，其中導引序列包含SEQ ID NO:620。

實施例B189. 如實施例B181至B185中任一例之方法，其中導引序列包含SEQ ID NO:621。

實施例B190. 如實施例B173至B189中任一例之方法，其中組合物進一步包含如前述實施例中任一例之與mRNA或組合物相關之mRNA或組合物。

實施例B191. 一種組合物，其包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

b. 如前述實施例中任一例之與mRNA或組合物相關之mRNA或組合物。

實施例B192. 如實施例B191之組合物，其中導引序列包含SEQ ID NO:706至709中之任一者。

實施例B193. 如實施例B191或B192之組合物，其用於改變細胞中之TRAC基因內的DNA序列。

實施例B194. 如實施例B191至B193中任一例之組合物，其用於降低細胞中之TRAC基因之表現。

實施例B195. 如實施例B191至B194中任一例之組合物，其用於個體之免疫療法中。

實施例B196. 一種組合物，其包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)

與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

b.如前述實施例中任一例之與mRNA或組合物相關之mRNA或組合物。

實施例B197.如實施例B196之組合物，其中導引序列包含SEQ ID NO:618至621中之任一者。

實施例B198.如實施例B196或B197之組合物，其用於改變細胞中之TRBC1及/或TRBC2基因內之DNA序列。

實施例B199.如實施例B196至B198中任一例之組合物，其用於降低細胞中之TRBC1及/或TRBC2基因之表現。

實施例B200.如實施例B196至B199中任一例之組合物，其用於個體之免疫療法中。

實施例B201.一種細胞，其藉由如實施例B120至B121及161至178中任一例之方法改變。

實施例B202.如實施例B201之細胞，其中細胞在活體外改變。

實施例B203.如實施例B201或B202之細胞，其中細胞為T細胞。

實施例B204.如實施例B201至B203中任一例之細胞，其中細胞為$CD4^+$或$CD8^+$ T細胞。

實施例B205.如實施例B201至B204中任一例之細胞，其中細胞為哺乳動物細胞、靈長類動物細胞或人類細胞。

實施例B206.如實施例B201至B205中任一例之細胞，其用於個體之免疫療法中。

實施例B207.一種已降低或消除TRAC之表面表現的經工程改造之細胞，其包含人類TRAC基因中之基因修飾，其中該基因修飾包含選自以下

之基因體座標內的至少一個核苷酸之修飾：

chr14:22547596-22547616 ； chr14:22550570-22550590 ；
chr14:22547763-22547783 ； chr14:22550596-22550616 ；
chr14:22550566-22550586 ； chr14:22547753-22547773 ；
chr14:22550601-22550621 ； chr14:22550599-22550619 ；
chr14:22547583-22547603 ； chr14:22547671-22547691 ；
chr14:22547770-22547790 ； chr14:22547676-22547696 ；
chr14:22547772-22547792 ； chr14:22547771-22547791 ；
chr14:22547733-22547753；

chr14:22547776-22547796。

實施例B208. 一種已降低或消除TRBC1/2之表面表現的經工程改造之細胞，其包含人類TRBC1/2基因中之基因修飾，其中基因修飾包含選自以下之基因體座標內的至少一個核苷酸之修飾：

chr7:142791757-142791777 ； chr7:142801104-142801124 ；
chr7:142791811-142791831 ； chr7:142801158-142801178 ；
chr7:142792728-142792748 ； chr7:142791719-142791739 ；
chr7:142791766-142791786 ； chr7:142801113-142801133 ；
chr7:142791928-142791948 ； chr7:142801275-142801295 ；
chr7:142792062-142792082 ； chr7:142801409-142801429 ；
chr7:142792713-142792733 ； chr7:142802126-142802146 ；
chr7:142791808-142791828 ； chr7:142801155-142801175 ；
chr7:142792003-142792023 ； chr7:142801350-142801370 ；
chr7:142791760-142791780 ； chr7:142791715-142791735 ；

chr7:142792781-142792801	;	chr7:142792040-142792060	;
chr7:142801387-142801407	;	chr7:142791862-142791882	;
chr7:142791716-142791736	;	chr7:142791787-142791807	;
chr7:142791759-142791779	;	chr7:142801106-142801126	;
chr7:142791807-142791827	;	chr7:142801154-142801174	;
chr7:142791879-142791899	;	chr7:142801226-142801246	;
chr7:142791805-142791825	;	chr7:142791700-142791720	;
chr7:142791765-142791785	;	chr7:142801112-142801132	;
chr7:142791820-142791840	;	chr7:142791872-142791892	;
chr7:142801219-142801239	;	chr7:142791700-142791720	;
chr7:142791806-142791826	;	chr7:142801153-142801173	;
chr7:142792035-142792055	;	chr7:142792724-142792744	;
chr7:142792754-142792774	;	chr7:142791804-142791824	;
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chr7:142791816-142791836	;	chr7:142801163-142801183	;
chr7:142792686-142792706	;	chr7:142791793-142791813	;
chr7:142793110-142793130	;	chr7:142791815-142791835	;
chr7:142801162-142801182	;	chr7:142792770-142792790	;
chr7:142792047-142792067	;	chr7:142801394-142801414	;
chr7:142791871-142791891	;	chr7:142801218-142801238	;
chr7:142791894-142791914	;	chr7:142792723-142792743	;

chr7:142792724-142792744 ； chr7:142791897-142791917 ；chr7:142801244-142801264 ； chr7:142792757-142792777 ；chr7:142792740-142792760；chr7:142792758-142792778。

實施例B209. 一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：

(a)第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；

(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)一或多種導引RNA。

實施例B210. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為免疫細胞。

實施例B211. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為淋巴細胞。

實施例B212. 如前述實施例中任一例之方法、細胞或經工程改造之細胞，其中細胞為T細胞。

【序列表】

<110> 美商英特利亞醫療公司(INTELLIA THERAPEUTICS, INC.)

<120> 用於涉及去胺作用之基因體編輯之多核苷酸、組合物及方法

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His Ile  Val Pro Gln Ser Phe  Leu Lys Asp Asp Ser  Ile Asp Asn
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Lys Val  Leu Thr Arg Ser Asp  Lys Asn Arg Gly Lys  Ser Asp Asn
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His Val  Ala Gln Ile Leu Asp  Ser Arg Met Asn Thr  Lys Tyr Asp
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Glu Asn  Asp Lys Leu Ile Arg  Glu Val Lys Val Ile  Thr Leu Lys
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Ser Lys  Leu Val Ser Asp Phe  Arg Lys Asp Phe Gln  Phe Tyr Lys
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Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
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Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
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Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
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Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
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Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
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Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
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Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

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Glu Ser Ala Thr Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
210 215 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225 230 235 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
245 250 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
260 265 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
275 280 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
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Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
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Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
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Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
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Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
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Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
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Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
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Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
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Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
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Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
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Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
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Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
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Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175
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Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
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Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
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Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
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Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
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Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
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Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
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Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
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Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
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Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
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Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
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Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
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Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
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Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
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Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
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His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
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Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
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Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
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Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
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Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
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Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
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Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
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Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
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Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
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Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
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Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
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Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
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Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
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Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
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Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

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Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
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Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
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Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
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Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
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Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
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Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
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His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
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Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
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Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
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Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
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Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
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Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
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Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
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Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
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Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
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His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
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His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
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Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
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Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
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Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
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Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
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Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
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Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
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Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
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Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
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Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
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Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
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Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
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Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
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Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
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Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
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Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
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Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
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Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
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Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
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Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
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Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
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Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
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Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
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Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
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Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
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Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
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Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
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Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
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Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
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Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
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Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
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Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
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His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
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Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
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Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
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Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

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His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
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Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
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Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
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Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
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Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
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Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
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Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
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Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
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Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
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Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
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Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
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Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
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Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
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Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
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Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
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Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
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Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
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Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
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Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
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His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
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Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
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Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
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Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
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Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
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Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
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Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
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Ala Thr Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly
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Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys
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Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys
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Lys Val Met Gly Arg His Lys Pro  Glu Asn Ile Val Ile  Glu Met Ala
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160
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Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
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Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

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195 200 205

Glu Ser Ala Thr Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
210 215 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225 230 235 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
245 250 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
260 265 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
275 280 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
290 295 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305 310 315 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
325 330 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
340 345 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
355 360 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
370 375 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
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Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
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Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
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Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
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Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
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Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
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Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
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Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
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Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
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Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
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Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
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Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
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Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
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Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705 710 715 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
725 730 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
740 745 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
755 760 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
770 775 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785 790 795 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
805 810 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
820 825 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
835 840 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
850 855 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865 870 875 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
885 890 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
900 905 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
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Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
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Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
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His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
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Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
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Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
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Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
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Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
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His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
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Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
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Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
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Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
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Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
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Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
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Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
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Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
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Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
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Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
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Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
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Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
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Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
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Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
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Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
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Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
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Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
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Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
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Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
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Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
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Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
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Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
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Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
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Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
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Leu Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile
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Glu Lys Glu Thr Gly Lys Gln Leu Val Ile Gln Glu Ser Ile Leu
1595 1600 1605

Met Leu Pro Glu Glu Val Glu Glu Val Ile Gly Asn Lys Pro Glu
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Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu Ser Thr Asp Glu
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Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp
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Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
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Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175
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Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
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Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
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Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
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Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
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370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
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Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
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Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
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Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
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Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
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Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
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Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
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Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
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Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

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610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
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645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
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Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
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Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
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gcugacaucg gacgcaccgg aauacaagcc gugggcacug gucauccagg acucgaacgg 360

agaaaacaag aucaagaugc ugugauaguc uagacaucac auuuaaaagc aucucagccu 420

accaugagaa uaagagaaag aaaaugaaga ucaauagcuu auucaucucu uuuucuuuuu 480

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20 25 30

Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp
35 40 45

Glu Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
50 55 60

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys
65 70 75 80

Ile Lys Met Leu Ser Gly Gly Ser Lys Arg Thr Ala Asp Gly Ser Glu
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Phe Glu Ser Pro Lys Lys Lys Arg Lys Val Glu
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Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
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Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
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Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
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Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
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Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
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Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
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Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
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Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
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Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
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Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
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Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
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Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
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Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
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cggcugaagc ggaccgcccg gcggcgguac acccggcgga agaaccggau cugcuaccug 1080

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guggacgagg uggccuacca cgagaaguac cccaccaucu accaccugcg gaagaagcug 1260

guggacucca ccgacaaggc cgaccugcgg cugaucuacc uggcccuggc ccacaugauc 1320

aaguuccggg gccacuuccu gaucgagggc gaccugaacc ccgacaacuc cgacguggac 1380

aagcuguuca uccagcuggu gcagaccuac aaccagcugu ucgaggagaa ccccaucaac 1440

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aagcugcagc uguccaagga caccuacgac gacgaccugg acaaccugcu ggcccagauc 1680

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aucgacggcg gcgccuccca ggaggaguuc uacaaguuca ucaagcccau ccuggagaag 1980

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cugcggcggc aggaggacuu cuaccccuuc cugaaggaca accgggagaa gaucgagaag 2160

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gccuggauga cccggaaguc cgaggagacc aucacccccu ggaacuucga ggagguggug 2280

gacaagggcg ccuccgccca guccuucauc gagcggauga ccaacuucga caagaaccug 2340

cccaacgaga aggugcugcc caagcacucc cugcuguacg aguacuucac cguguacaac 2400

gagcugacca aggugaagua cgugaccgag ggcaugcgga agcccgccuu ccuguccggc 2460

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cggaucgagg agggcaucaa ggagcugggc ucccagaucc ugaaggagca ccccguggag 3240

aacacccagc ugcagaacga gaagcuguac cuguacuacc ugcagaacgg ccgggacaug 3300

uacguggacc aggagcugga caucaaccgg cuguccgacu acgacgugga ccacaucgug 3360

ccccaguccu uccugaagga cgacuccauc gacaacaagg ugcugacccg guccgacaag 3420

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guguccgacu uccggaagga cuuccaguuc uacaaggugc gggagaucaa caacuaccac 3780

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gccaaguccg agcaggagau cggcaaggcc accgccaagu acuucuucua cuccaacauc 3960

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aagaaggacu gggaccccaa gaaguacggc ggcuucgacu cccccaccgu ggccuacucc 4260

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gaggccaagg gcuacaagga ggugaagaag gaccugauca ucaagcugcc caaguacucc 4440

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aagcacuacc uggacgagau caucgagcag aucuccgagu ucuccaagcg ggugauccug 4680

gccgacgcca accuggacaa ggugcugucc gccuacaaca agcaccggga caagcccauc 4740

cgggagcagg ccgagaacau cauccaccug uucacccuga ccaaccuggg cgcccccgcc 4800

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cccgaggagg uggaggaggu gaucggcaac aagcccgagu ccgacauccu ggugcacacc 5100

gccuacgacg aguccaccga cgagaacgug augcugcuga ccuccgacgc ccccgaguac 5160

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aucggcaaca agcccgaguc cgacauccug gugcacaccg ccuacgacga guccaccgac 5400

gagaacguga ugcugcugac cuccgacgcc cccgaguaca agcccugggc ccuggugauc 5460

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gacggcuccg aguucgagcc caagaagaag cggaaggugu gauag 5565

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Arg Arg Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg
35 40 45

Glu Leu Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly
50 55 60

Arg His Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val
65 70 75 80

Glu Val Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro
85 90 95

Asn Thr Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly
100 105 110

Glu Cys Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val
115 120 125

Thr Leu Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg
130 135 140

Asn Arg Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln
145 150 155 160

Ile Met Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn
165 170 175

Tyr Ser Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp
180 185 190

Val Arg Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro
195 200 205

Pro Cys Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe
210 215 220

Thr Ile Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile
225 230 235 240

Leu Trp Ala Thr Gly Leu Lys Ser Gly Gly Ser Ser Gly Gly Ser Ser
245 250 255

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Ser
260 265 270

Gly Gly Ser Ser Gly Gly Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
275 280 285

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
290 295 300

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
305 310 315 320

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
325 330 335

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
340 345 350

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
355 360 365

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
370 375 380

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
385 390 395 400

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
405 410 415

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile

420 425 430

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
435 440 445

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
450 455 460

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
465 470 475 480

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
485 490 495

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
500 505 510

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
515 520 525

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
530 535 540

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
545 550 555 560

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
565 570 575

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
580 585 590

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
595 600 605

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
610 615 620

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
625 630 635 640

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
645 650 655

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
660 665 670

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
675 680 685

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
690 695 700

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
705 710 715 720

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
725 730 735

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
740 745 750

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
755 760 765

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
770 775 780

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
785 790 795 800

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
805 810 815

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys

820 825 830

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
835 840 845

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
850 855 860

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
865 870 875 880

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
885 890 895

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
900 905 910

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
915 920 925

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
930 935 940

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
945 950 955 960

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
965 970 975

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
980 985 990

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
995 1000 1005

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp
1010 1015 1020

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Glu Leu  Val Lys Val Met Gly  Arg His Lys Pro Glu  Asn Ile Val
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Ile Glu  Met Ala Arg Glu Asn  Gln Thr Thr Gln Lys  Gly Gln Lys
    1040                1045                1050

Asn Ser  Arg Glu Arg Met Lys  Arg Ile Glu Glu Gly  Ile Lys Glu
    1055                1060                1065

Leu Gly  Ser Gln Ile Leu Lys  Glu His Pro Val Glu  Asn Thr Gln
    1070                1075                1080

Leu Gln  Asn Glu Lys Leu Tyr  Leu Tyr Tyr Leu Gln  Asn Gly Arg
    1085                1090                1095

Asp Met  Tyr Val Asp Gln Glu  Leu Asp Ile Asn Arg  Leu Ser Asp
    1100                1105                1110

Tyr Asp  Val Asp His Ile Val  Pro Gln Ser Phe Leu  Lys Asp Asp
    1115                1120                1125

Ser Ile  Asp Asn Lys Val Leu  Thr Arg Ser Asp Lys  Asn Arg Gly
    1130                1135                1140

Lys Ser  Asp Asn Val Pro Ser  Glu Glu Val Val Lys  Lys Met Lys
    1145                1150                1155

Asn Tyr  Trp Arg Gln Leu Leu  Asn Ala Lys Leu Ile  Thr Gln Arg
    1160                1165                1170

Lys Phe  Asp Asn Leu Thr Lys  Ala Glu Arg Gly Gly  Leu Ser Glu
    1175                1180                1185

Leu Asp  Lys Ala Gly Phe Ile  Lys Arg Gln Leu Val  Glu Thr Arg
    1190                1195                1200

Gln Ile  Thr Lys His Val Ala  Gln Ile Leu Asp Ser  Arg Met Asn
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1205 1210 1215

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val
1220 1225 1230

Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe
1235 1240 1245

Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala His
1250 1255 1260

Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
1265 1270 1275

Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
1280 1285 1290

Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1295 1300 1305

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
1310 1315 1320

Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg
1325 1330 1335

Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp
1340 1345 1350

Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1355 1360 1365

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1370 1375 1380

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1385 1390 1395

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1400 1405 1410

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1415 1420 1425

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1430 1435 1440

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1445 1450 1455

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1460 1465 1470

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1475 1480 1485

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1490 1495 1500

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1505 1510 1515

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1520 1525 1530

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1535 1540 1545

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1550 1555 1560

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1565 1570 1575

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu

1580 1585 1590

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1595 1600 1605

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1610 1615 1620

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1625 1630 1635

Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly Gly Ser Gly Gly Ser
1640 1645 1650

Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly
1655 1660 1665

Lys Gln Leu Val Ile Gln Glu Ser Ile Leu Met Leu Pro Glu Glu
1670 1675 1680

Val Glu Glu Val Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val
1685 1690 1695

His Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn Val Met Leu Leu
1700 1705 1710

Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala Leu Val Ile Gln
1715 1720 1725

Asp Ser Asn Gly Glu Asn Lys Ile Lys Met Leu Ser Gly Gly Ser
1730 1735 1740

Gly Gly Ser Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu Lys
1745 1750 1755

Glu Thr Gly Lys Gln Leu Val Ile Gln Glu Ser Ile Leu Met Leu
1760 1765 1770

Pro Glu Glu Val Glu Glu Val Ile Gly Asn Lys Pro Glu Ser Asp
1775 1780 1785

Ile Leu Val His Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn Val
1790 1795 1800

Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala Leu
1805 1810 1815

Val Ile Gln Asp Ser Asn Gly Glu Asn Lys Ile Lys Met Leu Ser
1820 1825 1830

Gly Gly Ser Lys Arg Thr Ala Asp Gly Ser Glu Phe Glu Pro Lys
1835 1840 1845

Lys Lys Arg Lys Val
1850

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ccgaggaggu ggaggaggug aucggcaaca agcccgaguc cgacauccug gugcacaccg 180

ccuacgacga guccaccgac gagaacguga ugcugcugac cuccgacgcc cccgaguaca 240

agcccugggc ccuggugauc caggacucca acggcgagaa caagaucaag augcuguccg 300

gcggcuccaa gcggaccgcc gacggcuccg aguucgaguc ccccaagaag aagcggaagg 360

uggagugaua gcuagcacca gccucaagaa cacccgaaug gagucucuaa gcuacauaau 420

accaacuuac acuuuacaaa auguugcccc ccaaaaugua gccauucgua ucugcuccua 480

auaaaaagaa aguuucuuca cauucucucg agaaaaaaaa aaaauggaaa aaaaaaaaac 540

ggaaaaaaaa aaaagguaaa aaaaaaaaau auaaaaaaaa aaaacauaaa aaaaaaaaac 600

gaaaaaaaaa aaacguaaaa aaaaaaaacu caaaaaaaaa aaagauaaaa aaaaaaaacc 660

uaaaaaaaaa aaauguaaaa aaaaaaaagg gaaaaaaaaa aaacgcaaaa aaaaaaaaca 720

caaaaaaaaa aaaugcaaaa aaaaaaaauc gaaaaaaaaa aaaucuaaaa aaaaaaaacg 780

aaaaaaaaaa aacccaaaaa aaaaaaagac aaaaaaaaaa aauagaaaaa aaaaaaaguu 840

aaaaaaaaaa aacugaaaaa aaaaaaauuu aaaaaaaaaa aaucuag 887

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auccuggugc acaccgccua cgacgagucc accgacgaga acgugaugcu gcugaccucc 180

gacgcccccg aguacaagcc cugggcccug gugauccagg acuccaacgg cgagaacaag 240

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aagaagaagc ggaaggugga guga 324

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<212> PRT
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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
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Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn

210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

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<210> 38

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<210> 39

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1 5 10 15

Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
20 25 30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg

115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn
195

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<213> 褐家鼠(R.norvegicus)

<400> 41

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
35 40 45

Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val Glu Val
50 55 60

Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro Asn Thr
65 70 75 80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
85 90 95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
100 105 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
115 120 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
130 135 140

Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn Tyr Ser
145 150 155 160

Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp Val Arg
165 170 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
180 185 190

Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
195 200 205

Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
210 215 220

Ala Thr Gly Leu Lys
225

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<213> 人工序列

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ctcgtgcaca ccgcctacga cgagagcacc gacgagaatg tcatgcttct gactagcgac 180

gcccctgaat acaagccttg ggctctggtc atacaggata gcaacggtga gaacaagatt 240

aagatgctc 249

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<211> 83
<212> PRT
<213> 人工序列

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<223> 合成

<400> 43

Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu Val
1 5 10 15

Ile Gln Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val Ile
20 25 30

Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu
35 40 45

Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr
50 55 60

Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys Ile
65 70 75 80

Lys Met Leu

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<212> DNA
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<210> 45
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<213> 人工序列

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<400> 45
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<210> 46
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<213> 人工序列

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<400> 46

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
1 5 10 15

<210> 47
<211> 12
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<400> 47

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
1 5 10

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<211> 21
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<213> 人工序列

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<223> 合成

<400> 48

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Gly
1 5 10 15

Gly Ser Gly Gly Ser
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<210> 49
<211> 15
<212> PRT
<213> 人工序列

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<400> 49

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10 15

<210> 50
<211> 15
<212> PRT
<213> 人工序列

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<400> 50

Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 51
<211> 15
<212> PRT
<213> 人工序列

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<400> 51

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10 15

<210> 52
<211> 20
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<400> 52

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 53
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<212> PRT
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<400> 53

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys
20

<210> 54
<211> 20
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<400> 54

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

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<213> 人工序列

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<400> 55

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 56
<211> 20
<212> PRT
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<400> 56

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys
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<211> 25
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<220>
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<400> 57

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly
1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
20 25

<210> 58
<211> 25
<212> PRT
<213> 人工序列

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<400> 58

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 59
<211> 25
<212> PRT
<213> 人工序列

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<400> 59

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
20 25

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<211> 12
<212> DNA
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<400> 60
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<400> 61

Ser Gly Gly Ser
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<400> 62
cccaagaaga agaggaaagt c 21

<210> 63
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<400> 63

Pro Lys Lys Lys Arg Lys Val
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gtcattagtt catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc 240

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agtaacgcca atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc 360

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cggtaaatgg cccgcctggc attatgccca gtacatgacc ttacgggact ttcctacttg 480

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caatgggagt ttgttttggc accaaaatca acgggacttt ccaaaatgtc gtaacaactg 660

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attaattgtt gccgggaagc tagagtaagt agttcgccag ttaatagttt gcgcaacgtt 240

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tttcttgggt agtttgcagt tttaaaatta tgttttaaaa tggactatca tatgcttacc 180

gtaacttgaa agtatttcga tttcttggct ttatatatct tgtggaaagg acg 233

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<211> 588
<212> DNA
<213> 人工序列

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aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc aatgggtgga 180

gtatttacgg taaactgccc acttggcagt acatcaagtg tatcatatgc caagtccgcc 240

ccctattgac gtcaatgacg gtaaatggcc cgcctggcat tatgcccagt acatgacctt 300

acgggacttt cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtgat 360

gcggttttgg cagtacacca atgggcgtgg atagcggttt gactcacggg gatttccaag 420

tctccacccc attgacgtca atgggagttt gttttggcac caaaatcaac gggactttcc 480

aaaatgtcgt aacaactgcg atcgcccgcc ccgttgacgc aaatgggcgg taggcgtgta 540

cggtgggagg tctatataag cagagctcgt ttagtgaacc gtcagatc 588

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<212> RNA
<213> 人工序列

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uagcuuauuc aucucuuuuu cuuuuucguu gguguaaagc caacacccug ucuaaaaaac 120

auaaauuucu uuaaucauuu ugccucuuuu cucugugcuu caauuaauaa aaaauggaaa 180

gaa 183

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<212> PRT
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<400> 70

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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
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Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

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Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405                 410                 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420                 425                 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435                 440                 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450                 455                 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480
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Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
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Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
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Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

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cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240

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aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag 420

aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480

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Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

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Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145                 150                 155                 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255
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Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
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Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

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Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
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Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485                 490                 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500                 505                 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515                 520                 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530                 535                 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545                 550                 555                 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
                565                 570                 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580                 585                 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655
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Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

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Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                1045                1050
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Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
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Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
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Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
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Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
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Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
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Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
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Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
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Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
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Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
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Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
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His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
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Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
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Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
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Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

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Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile
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Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr
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Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn
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aagaaccggg gcaagagcga caacgtgccc agcgaggagg tggtgaagaa gatgaagaac 2640

tactggcggc agctgctgaa cgccaagctg atcacccagc ggaagttcga caacctgacc 2700

aaggccgagc ggggcggcct gagcgagctg gacaaggccg gcttcatcaa gcggcagctg 2760

gtggagaccc ggcagatcac caagcacgtg gcccagatcc tggacagccg gatgaacacc 2820

aagtacgacg agaacgacaa gctgatccgg gaggtgaagg tgatcaccct gaagagcaag 2880

ctggtgagcg acttccggaa ggacttccag ttctacaagg tgcgggagat caacaactac 2940

caccacgccc acgacgccta cctgaacgcc gtggtgggca ccgccctgat caagaagtac 3000

cccaagctgg agagcgagtt cgtgtacggc gactacaagg tgtacgacgt gcggaagatg 3060

atcgccaaga gcgagcagga gatcggcaag gccaccgcca agtacttctt ctacagcaac 3120

atcatgaact tcttcaagac cgagatcacc ctggccaacg gcgagatccg gaagcggccc 3180

ctgatcgaga ccaacggcga gaccggcgag atcgtgtggg acaagggccg ggacttcgcc 3240

accgtgcgga aggtgctgag catgccccag gtgaacatcg tgaagaagac cgaggtgcag 3300

accggcggct tcagcaagga gagcatcctg cccaagcgga acagcgacaa gctgatcgcc 3360

cggaagaagg actgggaccc caagaagtac ggcggcttcg acagccccac cgtggcctac 3420

agcgtgctgg tggtggccaa ggtggagaag ggcaagagca agaagctgaa gagcgtgaag 3480

gagctgctgg gcatcaccat catggagcgg agcagcttcg agaagaaccc catcgacttc 3540

ctggaggcca agggctacaa ggaggtgaag aaggacctga tcatcaagct gcccaagtac 3600

agcctgttcg agctggagaa cggccggaag cggatgctgg ccagcgccgg cgagctgcag 3660

aagggcaacg agctggccct gcccagcaag tacgtgaact tcctgtacct ggccagccac 3720

tacgagaagc tgaagggcag ccccgaggac aacgagcaga agcagctgtt cgtggagcag 3780

cacaagcact acctggacga gatcatcgag cagatcagcg agttcagcaa gcgggtgatc 3840

ctggccgacg ccaacctgga caaggtgctg agcgcctaca acaagcaccg ggacaagccc 3900

atccgggagc aggccgagaa catcatccac ctgttcaccc tgaccaacct gggcgccccc 3960

gccgccttca agtacttcga caccaccatc gaccggaagc ggtacaccag caccaaggag 4020

gtgctggacg ccaccctgat ccaccagagc atcaccggcc tgtacgagac ccggatcgac 4080

ctgagccagc tgggcggcga c 4101

<210> 91
<211> 50
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 91
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<210> 92
<211> 66
<212> DNA
<213> 人工序列

<220>

<223> 合成

<400> 92
cataaaccct ggcgcgctcg cggcccggca ctcttctggt ccccacagac tcagagagaa 60

cccacc 66

<210> 93
<211> 29
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 93
aagctcagaa taaacgctca actttggcc 29

<210> 94
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 94
cagggtcctg tggacagctc accagct 27

<210> 95
<211> 61
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 95
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c 61

<210> 96
<211> 42
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 96
cagatcgcct ggagacgcca tccacgctgt tttgacctcc at 42

<210> 97
<211> 42
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 97
agaagacacc gggaccgatc cagcctccgc ggccgggaac gg 42

<210> 98
<211> 42
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 98
tgcattggaa cgcggattcc ccgtgccaag agtgactcac cg 42

<210> 99
<211> 132
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 99
gctcgctttc ttgctgtcca atttctatta aaggttcctt tgttccctaa gtccaactac 60

taaactgggg gatattatga agggccttga gcatctggat tctgcctaat aaaaaacatt 120

tattttcatt gc 132

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<211> 110

<212> DNA
<213> 人工序列

<220>
<223> 合成

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ttcctgcacc cgtacccccg tggtctttga ataaagtctg agtgggcggc 110

<210> 101
<211> 130
<212> DNA
<213> 人工序列

<220>
<223> 合成

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caaaatgttg tcccccaaaa tgtagccatt cgtatctgct cctaataaaa agaaagtttc 120

ttcacattct 130

<210> 102
<211> 102
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 102
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tcccactgtc ctttcctaat aaaatgagga attgcatcg ca 102

<210> 103
<211> 93
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 103
gctgccttct gcggggcttg ccttctggcc atgcccttct tctctccctt gcacctgtac 60

ctcttggtct ttgaataaag cctgagtagg aag 93

<210> 104
<211> 278
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 104
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ccccgacctc gggtcccagg tatgctccca cctccacctg ccccactcac cacctctgct 120

agttccagac acctcccaag cacgcagcaa tgcagctcaa aacgcttagc ctagccacac 180

ccccacggga aacagcagtg attaaccttt agcaataaac gaaagtttaa ctaagctata 240

ctaaccccag ggttggtcaa tttcgtgcca gccacacc 278

<210> 105
<211> 278
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 105
caagcacgca gcaatgcagc tcaaaacgct tagcctagcc acacccccac gggaaacagc 60

agtgattaac ctttagcaat aaacgaaagt ttaactaagc tatactaacc ccagggttgg 120

tcaatttcgt gccagccaca ccctggtact gcatgcacgc aatgctagct gccccttcc 180

cgtcctgggt accccgagtc tcccccgacc tcgggtccca ggtatgctcc cacctccacc 240

tgccccactc accacctctg ctagttccag acacctcc 278

<210> 106
<211> 260
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 106
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caaaatgttg tcccccaaaa tgtagccatt cgtatctgct cctaataaaa agaaagtttc 120

ttcacattct accagcctca agaacacccg aatggagtct ctaagctaca taataccaac 180

ttacacttta caaaatgttg tcccccaaaa tgtagccatt cgtatctgct cctaataaaa 240

agaaagtttc ttcacattct 260

<210> 107
<211> 10
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 107
gccrccaugg 10

<210> 108
<211> 13
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 108
gccgccrcca ugg 13

<210> 109
<211> 105
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 109
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa gcgaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaccgaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 105

<210> 110
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 110

Leu Ala Ala Lys Arg Ser Arg Thr Thr
1 5

<210> 111
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 111

Gln Ala Ala Lys Arg Ser Arg Thr Thr
1 5

<210> 112
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 112

Pro Ala Pro Ala Lys Arg Glu Arg Thr Thr
1 5 10

<210> 113
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 113

Gln Ala Ala Lys Arg Pro Arg Thr Thr
1 5

<210> 114
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 114

Arg Ala Ala Lys Arg Pro Arg Thr Thr
1 5

<210> 115
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 115

Ala Ala Ala Lys Arg Ser Trp Ser Met Ala Ala
1 5 10

<210> 116
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 116

Ala Ala Ala Lys Arg Val Trp Ser Met Ala Phe
1 5 10

<210> 117
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 117

Ala Ala Ala Lys Arg Ser Trp Ser Met Ala Phe
1 5 10

<210> 118
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 118

Ala Ala Ala Lys Arg Lys Tyr Phe Ala Ala
1 5 10

<210> 119
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 119

Arg Ala Ala Lys Arg Lys Ala Phe Ala Ala
1 5 10

<210> 120
<211> 10
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 120

Arg Ala Ala Lys Arg Lys Tyr Phe Ala Val
1 5 10

<210> 121
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 121

Pro Lys Lys Lys Arg Arg Val
1 5

<210> 122
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 122

Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys
1 5 10 15

<210> 123
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 123
ccgaagaaga agagaaaggt c 21

<210> 124
<211> 27

<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 124
ctggcagcaa agagaagcag aacaaca 27

<210> 125
<211> 27
<212> DNA
<213> 人工序列

<220>
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<400> 125
caggcagcaa agagaagcag aacaaca 27

<210> 126
<211> 30
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 126
ccggcaccgg caaagagaga aagaacaaca 30

<210> 127
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 127
caggcagcaa agagaccgag aacaaca 27

<210> 128
<211> 27
<212> DNA
<213> 人工序列

<220>
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<400> 128
agagcagcaa agagaccgag aacaaca 27

<210> 129
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 129
gcagcagcaa agagaagctg gagcatggca gca 33

<210> 130
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 130
gcagcagcaa agagagtctg gagcatggca ttc 33

<210> 131
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 131
gcagcagcaa agagaagctg gagcatggca ttc 33

<210> 132
<211> 30
<212> DNA
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<220>

<223> 合成

<400> 132
gcagcagcaa agagaaagta cttcgcagca 30

<210> 133
<211> 30
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 133
agagcagcaa agagaaaggc attcgcagca 30

<210> 134
<211> 30
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 134
agagcagcaa agagaaagta cttcgcagtc 30

<210> 135
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成

<400> 135
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<210> 136

<400> 136
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<210> 137

<400> 137

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<210> 138

<400> 138
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<210> 139
<211> 22
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 139
guuuuagagc uaugcuguuu ug 22

<210> 140
<211> 76
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 140
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu 60

ggcaccgagu cggugc 76

<210> 141
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(20)
<223> n爲a、c、g或u

<400> 141
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 142
<211> 80
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 142
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu 60

ggcaccgagu cggugcuuuu 80

<210> 143
<211> 84
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(4)
<223> n爲a、c、g或u

<400> 143
nnnnguuuua gagcuagaaa uagcaaguua aaauaaggcu aguccguuau caacuugaaa 60

aaguggcacc gagucggugc uuuu 84

<210> 144
<211> 81
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(1)
<223> n爲a、c、g或u

<400> 144
nguuuuagag cuagaaauag caaguuaaaa uaaggcuagu ccguuaucaa cuugaaaaag 60

uggcaccgag ucggugcuuu u 81

<210> 145
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(20)
<223> n爲a、c、g或u

<400> 145
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 146
<211> 80

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
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ggcaccgagu cggugcuuuu 80

<210> 147

<400> 147
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<210> 148

<400> 148
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<400> 149
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<210> 150

<400> 150
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<210> 151
<211> 20
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 151
uaaggccagu ggaaagaauu 20

<210> 152
<211> 20
<212> RNA
<213> 人工序列

<220>

<223> 合成

<400> 152
uuaccccacu uaacuaucuu 20

<210> 153
<211> 20
<212> RNA
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<220>
<223> 合成

<400> 153
uuacagccac gucuacagca 20

<210> 154
<211> 20
<212> RNA
<213> 人工序列

<220>
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<400> 154
uucaaaaccu gucagugauu 20

<210> 155
<211> 20
<212> RNA
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<220>
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<400> 155
cgcugucaag uccaguucua 20

<210> 156
<211> 20
<212> RNA
<213> 人工序列

<220>
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<400> 156
ccuuccgaaa gaggcccccc 20

<210> 157
<211> 20
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<213> 人工序列

<220>
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<400> 157
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<210> 158
<211> 20
<212> RNA
<213> 人工序列

<220>
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<400> 158
acucacgaug aaauccugga 20

<210> 159
<211> 20
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<213> 人工序列

<220>
<223> 合成

<400> 159
ccccccgccg uguuuguggg 20

<210> 160
<211> 20
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<213> 人工序列

<220>
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<400> 160
gagccccca cuguggugac 20

<210> 161
<211> 20
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<213> 人工序列

<220>
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<400> 161
accggcucug caaaggccag 20

<210> 162
<211> 20
<212> RNA
<213> 人工序列

<220>
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<400> 162
caccggcucu gcaaaggcca 20

<210> 163
<211> 20
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<213> 人工序列

<220>
<223> 合成

<400> 163
ccaccggcuc ugcaaaggcc 20

<210> 164
<211> 20
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<220>
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<400> 164
cugcuccacc ggcucugcaa 20

<210> 165
<211> 20
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<220>
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<400> 165
cugugucacc cguuucaggu 20

<210> 166
<211> 20
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<213> 人工序列

<220>
<223> 合成

<400> 166
ugugucaccc guuucaggug 20

<210> 167
<211> 20
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<220>
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<400> 167
acccguuuca ggugggguga 20

<210> 168
<211> 20
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<220>
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<400> 168
cccguuucag gugggugag 20

<210> 169
<211> 20

<212> RNA
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<220>
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<400> 169
ugugcagacu cagaggugag 20

<210> 170
<211> 20
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<220>
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<400> 170
cagcgcaucc aggcugcagg 20

<210> 171
<211> 20
<212> RNA
<213> 人工序列

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<400> 171
gcguccacau ccugcaaggg 20

<210> 172
<211> 20
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 172
ggcguccaca uccugcaagg 20

<210> 173
<211> 20
<212> RNA
<213> 人工序列

<220>
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<400> 173
ugggcgucca cauccugcaa 20

<210> 174

<400> 174
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<210> 175

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<210> 177
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<220>
<223> 合成

<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 177
uaggcagaca gacuugucac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 178
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<212> RNA
<213> 人工序列

<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 178
uuucaaaacc ugucagugau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 179
<211> 100
<212> RNA
<213> 人工序列

<220>
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<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 179
acucacgcug gauagccucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 180
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 180
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Ser Glu Gly Ser Ala Gly Thr Ser Thr Glu Ser Glu Gly Ser Ala Gly
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<400> 227

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Ala Ala Ala Lys
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Gly Gly Gly Ser
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Ala Ala Ala Lys
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Gly Gly Gly Ser
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Ala Ala Ala Lys
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1 5 10 15

Gly Gly Gly Ser
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Gly Gly Gly Ser
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Ala Ala Ala Lys
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Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
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1 5 10 15

Ala Ala Ala Lys
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1 5 10 15

Gly Gly Gly Ser
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1 5 10 15

Thr Ser Thr Glu Ser Glu Gly Ser Ala
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1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
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<400> 242

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

<210> 243
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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25

<210> 244
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<400> 244

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser

20 25

<210> 245
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<400> 245

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly
1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
20 25

<210> 246
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<400> 246

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

<210> 247
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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu

1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25

<210> 248
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Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 249
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<400> 249

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
20 25

<210> 250
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Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Glu
1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

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Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Glu
1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25

<210> 252
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<400> 252

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 253
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Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

<210> 254
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<400> 254

Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25

<210> 255
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<400> 255

Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 256
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<400> 256

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1 5 10 15

Gly Gly Gly Ser Glu Ala Ala Ala Lys
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<210> 257
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Ala Ala Ala Lys Gly Gly Gly Gly Ser
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<400> 258

Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
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Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

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Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

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Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25

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<400> 263

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1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
20 25

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<400> 264

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1 5 10 15

Ala Ala Ala Lys Glu Ala Ala Ala Lys
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Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly
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Gly Gly Gly Ser Glu Ala Ala Ala Lys
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<400> 266

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
1 5 10 15

Ala Ala Ala Lys Gly Gly Gly Gly Ser
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Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
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Ala Ala Ala Lys Glu Ala Ala Ala Lys
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Gly Thr Lys Asp Ser Thr Lys Asp Ile Pro Glu Thr Pro Ser Lys Asp
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Gly Arg Asp Val Arg Gln Pro Glu Val Lys Glu Glu Lys Pro Glu Ser
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Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Ala Gly
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Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
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ucggccggca caagaccuac cugugcuacg agguggagcg gcuggacaac ggcaccuccg 180

ugaagaugga ccagcaccgg ggcuuccugc acaaccaggc caagaaccug cugugcggcu 240

ucuacggccg gcacgccgag cugcgguucc uggaccuggu gcccucccug cagcuggacc 300

ccgcccagau cuaccgggug accugguuca ucuccugguc ccccugcuuc uccuggggcu 360

gcgccggcga ggugcgggcc uuccugcagg agaacaccca cgugcggcug cggaucuucg 420

ccgcccggau cuacgacuac gacccccugu acaaggaggc ccugcagaug cugcgggacg 480

ccggcgccca gguguccauc augaccuacg acgaguucaa gcacugcugg gacaccuucg 540

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gcaccuccga guccgccacc cccgaguccg cagcguucaa accaaauccc aucaacuaca 720

uccugggccu ggccaucggc aucgccuccg uggggcuggg caugguggag aucgacgagg 780

aggagaaccc cauccggcug aucgaccugg gcgugcgggu guucgagcgg gccgaggugc 840

ccaagaccgg cgacucccug gccauggccc ggcggcuggc ccgguccgug cggcggcuga 900

cccggcggcg ggcccaccgg cugcugcggg cccggcggcu gcugaagcgg gagggcgugc 960

ugcaggccgc cgacuucgac gagaacggcc ugaucaaguc ccugcccaac acccccuggc 1020

agcugcgggc cgccgcccug gaccggaagc ugaccccccu ggaguggucc gccgugcugc 1080

ugcaccugau caagcaccgg ggcuaccugu cccagcggaa gaacgagggc gagaccgccg 1140

acaaggagcu gggcgcccug cugaagggcg uggccaacaa cgcccacgcc cugcagaccg 1200

gcgacuuccg gacccccgcc gagcuggccc ugaacaaguu cgagaaggag uccggccaca 1260

uccggaacca gcgggggcgac uacucccaca ccuucucccg gaaggaccug caggccgagc 1320

ugauccugcu guucgagaag cagaaggagu ucggcaaccc ccacgugucc ggcggccuga 1380

aggagggcau cgagacccug cugaugaccc agcggcccgc ccuguccggc gacgccgugc 1440

agaagaugcu gggccacugc accuucgagc ccgccgagcc caaggccgcc aagaacaccu 1500

acaccgccga gcgguucauc uggcugacca agcugaacaa ccugcggauc cuggagcagg 1560

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ucaagggccu gcgguacggc aaggacaacg ccgaggccuc cacccugaug gagaugaagg 1740

ccuaccacgc caucucccgg gcccuggaga aggagggccu gaaggacaag aaguccccc 1800

ugaaccuguc cuccgagcug caggacgaga ucggcaccgc cuucucccug uucaagaccg 1860

acgaggacau caccggccgg cugaaggacc gggugcagcc cgagauccug gaggcccugc 1920

ugaagcacau cuccuucgac aaguucgugc agaucucccu gaaggcccug cggcggaucg 1980

ugccccugau ggagcagggc aagcgguacg acgaggccug cgccgagauc uacggcgacc 2040

acuacggcaa gaagaacacc gaggagaaga ucuaccugcc ccccaucccc gccgacgaga 2100

uccggaaccc cguggugcug cgggcccugu cccaggcccg gaaggugauc aacggcgugg 2160

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ccuucaagga ccggaaggag aucgagaagc ggcaggagga gaaccggaag gaccgggaga 2280

aggccgccgc caaguuccgg gaguacuucc ccaacuucgu gggcgagccc aaguccaagg 2340

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agaucaaccu ggugcggcug aacgagaagg gcuacgugga gaucgaccac gcccugcccu 2460

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ucccccagcc cugggaguuc uucgcccagg aggugaugau ccggguguuc ggcaagcccg 3060

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ccaucuacgc cuggcaggug gccgagaaca uccugcccga caucgacugc aagggcuacc 3660

ggaucgacga cuccuacacc uucugcuucu cccugcacaa guacgaccug aucgccuucc 3720

agaaggacga gaaguccaag guggaguucg ccuacuacau caacugcgac uccuccaacg 3780

gccgguucua ccuggccugg cacgacaagg gcuccaagga gcagcaguuc cggaucucca 3840

cccagaaccu ggugcugauc cagaaguacc aggugaacga gcugggcaag gagauccggc 3900

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cacccgaaug gagucucuaa gcuacauaau accaacuuac acuuuacaaa auguuguccc 4080

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<212> RNA
<213> 人工序列

<220>
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gacaacggca ccuccgugaa gauggaccag caccggggcu uccugcacaa ccaggccaag 180

aaccugcugu gcggcuucua cggccggcac gccgagcugc gguuccugga ccuggugccc 240

ucccugcagc uggaccccgc ccagaucuac cgggugaccu gguucaucuc cuggucccccc 300

ugcuucuccu ggggcugcgc cggcgaggug cgggccuucc ugcaggagaa cacccacgug 360

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cagaugcugc gggacgccgg cgcccaggug uccaucauga ccuacgacga guucaagcac 480

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gagcacuccc aggcccuguc cggccggcug cgggccaucc ugcagaacca gggcaacucc 600

ggcuccgaga ccccccggcac cuccgagucc gccacccccg aguccgcagc guucaaacca 660

aaucccauca acuacauccu gggccuggcc aucggcaucg ccuccguggg cuggggccaug 720

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<211> 1317
<212> PRT
<213> 人工序列

<220>
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<400> 303

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Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
20 25 30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Ser Gly Ser Glu Thr Pro Gly Thr Ser
195 200 205

Glu Ser Ala Thr Pro Glu Ser Ala Ala Phe Lys Pro Asn Pro Ile Asn
210 215 220

Tyr Ile Leu Gly Leu Ala Ile Gly Ile Ala Ser Val Gly Trp Ala Met
225 230 235 240

Val Glu Ile Asp Glu Glu Glu Asn Pro Ile Arg Leu Ile Asp Leu Gly
245 250 255

Val Arg Val Phe Glu Arg Ala Glu Val Pro Lys Thr Gly Asp Ser Leu
260 265 270

Ala Met Ala Arg Arg Leu Ala Arg Ser Val Arg Arg Leu Thr Arg Arg
275 280 285

Arg Ala His Arg Leu Leu Arg Ala Arg Arg Leu Leu Lys Arg Glu Gly

290 295 300

Val Leu Gln Ala Ala Asp Phe Asp Glu Asn Gly Leu Ile Lys Ser Leu
305 310 315 320

Pro Asn Thr Pro Trp Gln Leu Arg Ala Ala Ala Leu Asp Arg Lys Leu
325 330 335

Thr Pro Leu Glu Trp Ser Ala Val Leu Leu His Leu Ile Lys His Arg
340 345 350

Gly Tyr Leu Ser Gln Arg Lys Asn Glu Gly Glu Thr Ala Asp Lys Glu
355 360 365

Leu Gly Ala Leu Leu Lys Gly Val Ala Asn Asn Ala His Ala Leu Gln
370 375 380

Thr Gly Asp Phe Arg Thr Pro Ala Glu Leu Ala Leu Asn Lys Phe Glu
385 390 395 400

Lys Glu Ser Gly His Ile Arg Asn Gln Arg Gly Asp Tyr Ser His Thr
405 410 415

Phe Ser Arg Lys Asp Leu Gln Ala Glu Leu Ile Leu Leu Phe Glu Lys
420 425 430

Gln Lys Glu Phe Gly Asn Pro His Val Ser Gly Gly Leu Lys Glu Gly
435 440 445

Ile Glu Thr Leu Leu Met Thr Gln Arg Pro Ala Leu Ser Gly Asp Ala
450 455 460

Val Gln Lys Met Leu Gly His Cys Thr Phe Glu Pro Ala Glu Pro Lys
465 470 475 480

Ala Ala Lys Asn Thr Tyr Thr Ala Glu Arg Phe Ile Trp Leu Thr Lys
485 490 495

Leu Asn Asn Leu Arg Ile Leu Glu Gln Gly Ser Glu Arg Pro Leu Thr
500 505 510

Asp Thr Glu Arg Ala Thr Leu Met Asp Glu Pro Tyr Arg Lys Ser Lys
515 520 525

Leu Thr Tyr Ala Gln Ala Arg Lys Leu Leu Gly Leu Glu Asp Thr Ala
530 535 540

Phe Phe Lys Gly Leu Arg Tyr Gly Lys Asp Asn Ala Glu Ala Ser Thr
545 550 555 560

Leu Met Glu Met Lys Ala Tyr His Ala Ile Ser Arg Ala Leu Glu Lys
565 570 575

Glu Gly Leu Lys Asp Lys Lys Ser Pro Leu Asn Leu Ser Ser Glu Leu
580 585 590

Gln Asp Glu Ile Gly Thr Ala Phe Ser Leu Phe Lys Thr Asp Glu Asp
595 600 605

Ile Thr Gly Arg Leu Lys Asp Arg Val Gln Pro Glu Ile Leu Glu Ala
610 615 620

Leu Leu Lys His Ile Ser Phe Asp Lys Phe Val Gln Ile Ser Leu Lys
625 630 635 640

Ala Leu Arg Arg Ile Val Pro Leu Met Glu Gln Gly Lys Arg Tyr Asp
645 650 655

Glu Ala Cys Ala Glu Ile Tyr Gly Asp His Tyr Gly Lys Lys Asn Thr
660 665 670

Glu Glu Lys Ile Tyr Leu Pro Pro Ile Pro Ala Asp Glu Ile Arg Asn
675 680 685

Pro Val Val Leu Arg Ala Leu Ser Gln Ala Arg Lys Val Ile Asn Gly

690 695 700

Val Val Arg Arg Tyr Gly Ser Pro Ala Arg Ile His Ile Glu Thr Ala
705 710 715 720

Arg Glu Val Gly Lys Ser Phe Lys Asp Arg Lys Glu Ile Glu Lys Arg
725 730 735

Gln Glu Glu Asn Arg Lys Asp Arg Glu Lys Ala Ala Ala Lys Phe Arg
740 745 750

Glu Tyr Phe Pro Asn Phe Val Gly Glu Pro Lys Ser Lys Asp Ile Leu
755 760 765

Lys Leu Arg Leu Tyr Glu Gln Gln His Gly Lys Cys Leu Tyr Ser Gly
770 775 780

Lys Glu Ile Asn Leu Val Arg Leu Asn Glu Lys Gly Tyr Val Glu Ile
785 790 795 800

Asp His Ala Leu Pro Phe Ser Arg Thr Trp Asp Asp Ser Phe Asn Asn
805 810 815

Lys Val Leu Val Leu Gly Ser Glu Asn Gln Asn Lys Gly Asn Gln Thr
820 825 830

Pro Tyr Glu Tyr Phe Asn Gly Lys Asp Asn Ser Arg Glu Trp Gln Glu
835 840 845

Phe Lys Ala Arg Val Glu Thr Ser Arg Phe Pro Arg Ser Lys Lys Gln
850 855 860

Arg Ile Leu Leu Gln Lys Phe Asp Glu Asp Gly Phe Lys Glu Cys Asn
865 870 875 880

Leu Asn Asp Thr Arg Tyr Val Asn Arg Phe Leu Cys Gln Phe Val Ala
885 890 895

Asp His Ile Leu Leu Thr Gly Lys Gly Lys Arg Arg Val Phe Ala Ser
900 905 910

Asn Gly Gln Ile Thr Asn Leu Leu Arg Gly Phe Trp Gly Leu Arg Lys
915 920 925

Val Arg Ala Glu Asn Asp Arg His His Ala Leu Asp Ala Val Val Val
930 935 940

Ala Cys Ser Thr Val Ala Met Gln Gln Lys Ile Thr Arg Phe Val Arg
945 950 955 960

Tyr Lys Glu Met Asn Ala Phe Asp Gly Lys Thr Ile Asp Lys Glu Thr
965 970 975

Gly Lys Val Leu His Gln Lys Thr His Phe Pro Gln Pro Trp Glu Phe
980 985 990

Phe Ala Gln Glu Val Met Ile Arg Val Phe Gly Lys Pro Asp Gly Lys
995 1000 1005

Pro Glu Phe Glu Glu Ala Asp Thr Pro Glu Lys Leu Arg Thr Leu
1010 1015 1020

Leu Ala Glu Lys Leu Ser Ser Arg Pro Glu Ala Val His Glu Tyr
1025 1030 1035

Val Thr Pro Leu Phe Val Ser Arg Ala Pro Asn Arg Lys Met Ser
1040 1045 1050

Gly Ala His Lys Asp Thr Leu Arg Ser Ala Lys Arg Phe Val Lys
1055 1060 1065

His Asn Glu Lys Ile Ser Val Lys Arg Val Trp Leu Thr Glu Ile
1070 1075 1080

Lys Leu Ala Asp Leu Glu Asn Met Val Asn Tyr Lys Asn Gly Arg

1085 1090 1095

Glu Ile Glu Leu Tyr Glu Ala Leu Lys Ala Arg Leu Glu Ala Tyr
1100 1105 1110

Gly Gly Asn Ala Lys Gln Ala Phe Asp Pro Lys Asp Asn Pro Phe
1115 1120 1125

Tyr Lys Lys Gly Gly Gln Leu Val Lys Ala Val Arg Val Glu Lys
1130 1135 1140

Thr Gln Glu Ser Gly Val Leu Leu Asn Lys Lys Asn Ala Tyr Thr
1145 1150 1155

Ile Ala Asp Asn Gly Asp Met Val Arg Val Asp Val Phe Cys Lys
1160 1165 1170

Val Asp Lys Lys Gly Lys Asn Gln Tyr Phe Ile Val Pro Ile Tyr
1175 1180 1185

Ala Trp Gln Val Ala Glu Asn Ile Leu Pro Asp Ile Asp Cys Lys
1190 1195 1200

Gly Tyr Arg Ile Asp Asp Ser Tyr Thr Phe Cys Phe Ser Leu His
1205 1210 1215

Lys Tyr Asp Leu Ile Ala Phe Gln Lys Asp Glu Lys Ser Lys Val
1220 1225 1230

Glu Phe Ala Tyr Tyr Ile Asn Cys Asp Ser Ser Asn Gly Arg Phe
1235 1240 1245

Tyr Leu Ala Trp His Asp Lys Gly Ser Lys Glu Gln Gln Phe Arg
1250 1255 1260

Ile Ser Thr Gln Asn Leu Val Leu Ile Gln Lys Tyr Gln Val Asn
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Glu Leu Gly Lys Glu Ile Arg Pro Cys Arg Leu Lys Lys Arg Pro
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His Leu Met Asp Pro His Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile
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Gly Arg His Lys Thr Tyr Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn
65 70 75 80

Gly Thr Ser Val Lys Met Asp Gln His Arg Gly Phe Leu His Asn Gln
85 90 95

Ala Lys Asn Leu Leu Cys Gly Phe Tyr Gly Arg His Ala Glu Leu Arg
100 105 110

Phe Leu Asp Leu Val Pro Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr

115 120 125

Arg Val Thr Trp Phe Ile Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys
130 135 140

Ala Gly Glu Val Arg Ala Phe Leu Gln Glu Asn Thr His Val Arg Leu
145 150 155 160

Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu
165 170 175

Ala Leu Gln Met Leu Arg Asp Ala Gly Ala Gln Val Ser Ile Met Thr
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Tyr Asp Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp His Gln Gly
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Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln Ala Leu
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Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn Ser Gly Ser
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Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Ala Ala Phe
245 250 255

Lys Pro Asn Pro Ile Asn Tyr Ile Leu Gly Leu Ala Ile Gly Ile Ala
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Ser Val Gly Trp Ala Met Val Glu Ile Asp Glu Glu Glu Asn Pro Ile
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Arg Leu Ile Asp Leu Gly Val Arg Val Phe Glu Arg Ala Glu Val Pro
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Lys Thr Gly Asp Ser Leu Ala Met Ala Arg Arg Leu Ala Arg Ser Val
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Arg Arg Leu Thr Arg Arg Arg Ala His Arg Leu Leu Arg Ala Arg Arg
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Leu Leu Lys Arg Glu Gly Val Leu Gln Ala Ala Asp Phe Asp Glu Asn
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Gly Leu Ile Lys Ser Leu Pro Asn Thr Pro Trp Gln Leu Arg Ala Ala
355 360 365

Ala Leu Asp Arg Lys Leu Thr Pro Leu Glu Trp Ser Ala Val Leu Leu
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His Leu Ile Lys His Arg Gly Tyr Leu Ser Gln Arg Lys Asn Glu Gly
385 390 395 400

Glu Thr Ala Asp Lys Glu Leu Gly Ala Leu Leu Lys Gly Val Ala Asn
405 410 415

Asn Ala His Ala Leu Gln Thr Gly Asp Phe Arg Thr Pro Ala Glu Leu
420 425 430

Ala Leu Asn Lys Phe Glu Lys Glu Ser Gly His Ile Arg Asn Gln Arg
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Gly Asp Tyr Ser His Thr Phe Ser Arg Lys Asp Leu Gln Ala Glu Leu
450 455 460

Ile Leu Leu Phe Glu Lys Gln Lys Glu Phe Gly Asn Pro His Val Ser
465 470 475 480

Gly Gly Leu Lys Glu Gly Ile Glu Thr Leu Leu Met Thr Gln Arg Pro
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Ala Leu Ser Gly Asp Ala Val Gln Lys Met Leu Gly His Cys Thr Phe
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Glu Pro Ala Glu Pro Lys Ala Ala Lys Asn Thr Tyr Thr Ala Glu Arg

515 520 525

Phe Ile Trp Leu Thr Lys Leu Asn Asn Leu Arg Ile Leu Glu Gln Gly
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Ser Glu Arg Pro Leu Thr Asp Thr Glu Arg Ala Thr Leu Met Asp Glu
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Pro Tyr Arg Lys Ser Lys Leu Thr Tyr Ala Gln Ala Arg Lys Leu Leu
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Gly Leu Glu Asp Thr Ala Phe Phe Lys Gly Leu Arg Tyr Gly Lys Asp
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Ser Arg Ala Leu Glu Lys Glu Gly Leu Lys Asp Lys Lys Ser Pro Leu
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Phe Lys Thr Asp Glu Asp Ile Thr Gly Arg Leu Lys Asp Arg Val Gln
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Pro Glu Ile Leu Glu Ala Leu Leu Lys His Ile Ser Phe Asp Lys Phe
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Val Gln Ile Ser Leu Lys Ala Leu Arg Arg Ile Val Pro Leu Met Glu
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Gln Gly Lys Arg Tyr Asp Glu Ala Cys Ala Glu Ile Tyr Gly Asp His
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Tyr Gly Lys Lys Asn Thr Glu Glu Lys Ile Tyr Leu Pro Pro Ile Pro
705 710 715 720

Ala Asp Glu Ile Arg Asn Pro Val Val Leu Arg Ala Leu Ser Gln Ala
725 730 735

Arg Lys Val Ile Asn Gly Val Val Arg Arg Tyr Gly Ser Pro Ala Arg
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Ile His Ile Glu Thr Ala Arg Glu Val Gly Lys Ser Phe Lys Asp Arg
755 760 765

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Lys Cys Leu Tyr Ser Gly Lys Glu Ile Asn Leu Val Arg Leu Asn Glu
820 825 830

Lys Gly Tyr Val Glu Ile Asp His Ala Leu Pro Phe Ser Arg Thr Trp
835 840 845

Asp Asp Ser Phe Asn Asn Lys Val Leu Val Leu Gly Ser Glu Asn Gln
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Asn Lys Gly Asn Gln Thr Pro Tyr Glu Tyr Phe Asn Gly Lys Asp Asn
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Ser Arg Glu Trp Gln Glu Phe Lys Ala Arg Val Glu Thr Ser Arg Phe
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Pro Arg Ser Lys Lys Gln Arg Ile Leu Leu Gln Lys Phe Asp Glu Asp
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Gly Phe Lys Glu Cys Asn Leu Asn Asp Thr Arg Tyr Val Asn Arg Phe

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Thr Ile Asp Lys Glu Thr Gly Lys Val Leu His Gln Lys Thr His
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Cys Asp Ser Ser Asn Gly Arg Phe Tyr Leu Ala Trp His Asp Lys
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Leu Ile Gln Lys Tyr Gln Val Asn Glu Leu Gly Lys Glu Ile Arg
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Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu
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Ala Leu Gln Met Leu Arg Asp Ala Gly Ala Gln Val Ser Ile Met Thr
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Tyr Asp Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp His Gln Gly
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Gly Arg His Lys Thr Tyr Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn
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Ala Lys Asn Leu Leu Cys Gly Phe Tyr Gly Arg His Ala Glu Leu Arg
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Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu
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Tyr Asp Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp His Gln Gly
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Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln Ala Leu
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Asn Ala His Ala Leu Gln Thr Gly Asp Phe Arg Thr Pro Ala Glu Leu

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Gly Asp Tyr Ser His Thr Phe Ser Arg Lys Asp Leu Gln Ala Glu Leu
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Pro Glu Ile Leu Glu Ala Leu Leu Lys His Ile Ser Phe Asp Lys Phe
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Val Gln Ile Ser Leu Lys Ala Leu Arg Arg Ile Val Pro Leu Met Glu
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Gln Gly Lys Arg Tyr Asp Glu Ala Cys Ala Glu Ile Tyr Gly Asp His
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Tyr Gly Lys Lys Asn Thr Glu Glu Lys Ile Tyr Leu Pro Pro Ile Pro
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Thr Ile Asp Lys Glu Thr Gly Lys Val Leu His Gln Lys Thr His
1010 1015 1020

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Thr Pro  Glu Lys Leu Arg Thr  Leu Leu Ala Glu Lys  Leu Ser Ser
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Arg Pro  Glu Ala Val His Glu  Tyr Val Thr Pro Leu  Phe Val Ser
    1070                1075                1080

Arg Ala  Pro Asn Arg Lys Met  Ser Gly Ala His Lys  Asp Thr Leu
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Arg Ser  Ala Lys Arg Phe Val  Lys His Asn Glu Lys  Ile Ser Val
    1100                1105                1110

Lys Arg  Val Trp Leu Thr Glu  Ile Lys Leu Ala Asp  Leu Glu Asn
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Met Val  Asn Tyr Lys Asn Gly  Arg Glu Ile Glu Leu  Tyr Glu Ala
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Phe Asp  Pro Lys Asp Asn Pro  Phe Tyr Lys Lys Gly  Gly Gln Leu
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Val Lys  Ala Val Arg Val Glu  Lys Thr Gln Glu Ser  Gly Val Leu
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Leu Asn  Lys Lys Asn Ala Tyr  Thr Ile Ala Asp Asn  Gly Asp Met
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Val Arg  Val Asp Val Phe Cys  Lys Val Asp Lys Lys  Gly Lys Asn
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Tyr Thr Phe Cys Phe Ser Leu His Lys Tyr Asp Leu Ile Ala Phe
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Gln Lys Asp Glu Lys Ser Lys Val Glu Phe Ala Tyr Tyr Ile Asn
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Cys Asp Ser Ser Asn Gly Arg Phe Tyr Leu Ala Trp His Asp Lys
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Gly Ser Lys Glu Gln Gln Phe Arg Ile Ser Thr Gln Asn Leu Val
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35 40 45

Tyr Ile Leu Gly Leu Asp Ile Gly Ile Ala Ser Val Gly Trp Ala Met
50 55 60

Val Glu Ile Asp Glu Glu Glu Asn Pro Ile Arg Leu Ile Asp Leu Gly
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Val Arg Val Phe Glu Arg Ala Glu Val Pro Lys Thr Gly Asp Ser Leu
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Pro Asn Thr Pro Trp Gln Leu Arg Ala Ala Ala Leu Asp Arg Lys Leu
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Thr Pro Leu Glu Trp Ser Ala Val Leu Leu His Leu Ile Lys His Arg
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Gly Tyr Leu Ser Gln Arg Lys Asn Glu Gly Glu Thr Ala Asp Lys Glu
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Leu Gly Ala Leu Leu Lys Gly Val Ala Asn Asn Ala His Ala Leu Gln
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Lys Glu Ser Gly His Ile Arg Asn Gln Arg Gly Asp Tyr Ser His Thr
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Phe Ser Arg Lys Asp Leu Gln Ala Glu Leu Ile Leu Leu Phe Glu Lys
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Gln Lys Glu Phe Gly Asn Pro His Val Ser Gly Gly Leu Lys Glu Gly
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Ile Glu Thr Leu Leu Met Thr Gln Arg Pro Ala Leu Ser Gly Asp Ala
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Val Gln Lys Met Leu Gly His Cys Thr Phe Glu Pro Ala Glu Pro Lys
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Phe Phe Lys Gly Leu Arg Tyr Gly Lys Asp Asn Ala Glu Ala Ser Thr
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Leu Met Glu Met Lys Ala Tyr His Ala Ile Ser Arg Ala Leu Glu Lys
385 390 395 400

Glu Gly Leu Lys Asp Lys Lys Ser Pro Leu Asn Leu Ser Ser Glu Leu
405 410 415

Gln Asp Glu Ile Gly Thr Ala Phe Ser Leu Phe Lys Thr Asp Glu Asp
420 425 430

Ile Thr Gly Arg Leu Lys Asp Arg Val Gln Pro Glu Ile Leu Glu Ala
435 440 445

Leu Leu Lys His Ile Ser Phe Asp Lys Phe Val Gln Ile Ser Leu Lys
450 455 460

Ala Leu Arg Arg Ile Val Pro Leu Met Glu Gln Gly Lys Arg Tyr Asp
465 470 475 480

Glu Ala Cys Ala Glu Ile Tyr Gly Asp His Tyr Gly Lys Lys Asn Thr
485 490 495

Glu Glu Lys Ile Tyr Leu Pro Pro Ile Pro Ala Asp Glu Ile Arg Asn
500 505 510

Pro Val Val Leu Arg Ala Leu Ser Gln Ala Arg Lys Val Ile Asn Gly
515 520 525

Val Val Arg Arg Tyr Gly Ser Pro Ala Arg Ile His Ile Glu Thr Ala
530 535 540

Arg Glu Val Gly Lys Ser Phe Lys Asp Arg Lys Glu Ile Glu Lys Arg
545 550 555 560

Gln Glu Glu Asn Arg Lys Asp Arg Glu Lys Ala Ala Ala Lys Phe Arg
565 570 575

Glu Tyr Phe Pro Asn Phe Val Gly Glu Pro Lys Ser Lys Asp Ile Leu
580 585 590

Lys Leu Arg Leu Tyr Glu Gln Gln His Gly Lys Cys Leu Tyr Ser Gly
595 600 605

Lys Glu Ile Asn Leu Val Arg Leu Asn Glu Lys Gly Tyr Val Glu Ile
610 615 620

Asp His Ala Leu Pro Phe Ser Arg Thr Trp Asp Asp Ser Phe Asn Asn
625 630 635 640

Lys Val Leu Val Leu Gly Ser Glu Asn Gln Asn Lys Gly Asn Gln Thr
645 650 655

Pro Tyr Glu Tyr Phe Asn Gly Lys Asp Asn Ser Arg Glu Trp Gln Glu
660 665 670

Phe Lys Ala Arg Val Glu Thr Ser Arg Phe Pro Arg Ser Lys Lys Gln
675 680 685

Arg Ile Leu Leu Gln Lys Phe Asp Glu Asp Gly Phe Lys Glu Cys Asn
690 695 700

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Leu Asn Asp Thr Arg Tyr Val Asn Arg Phe Leu Cys Gln Phe Val Ala
705                 710                 715                 720

Asp His Ile Leu Leu Thr Gly Lys Gly Lys Arg Arg Val Phe Ala Ser
                725                 730                 735

Asn Gly Gln Ile Thr Asn Leu Leu Arg Gly Phe Trp Gly Leu Arg Lys
            740                 745                 750

Val Arg Ala Glu Asn Asp Arg His His Ala Leu Asp Ala Val Val Val
        755                 760                 765

Ala Cys Ser Thr Val Ala Met Gln Gln Lys Ile Thr Arg Phe Val Arg
    770                 775                 780

Tyr Lys Glu Met Asn Ala Phe Asp Gly Lys Thr Ile Asp Lys Glu Thr
785                 790                 795                 800

Gly Lys Val Leu His Gln Lys Thr His Phe Pro Gln Pro Trp Glu Phe
                805                 810                 815

Phe Ala Gln Glu Val Met Ile Arg Val Phe Gly Lys Pro Asp Gly Lys
            820                 825                 830

Pro Glu Phe Glu Glu Ala Asp Thr Pro Glu Lys Leu Arg Thr Leu Leu
        835                 840                 845

Ala Glu Lys Leu Ser Ser Arg Pro Glu Ala Val His Glu Tyr Val Thr
    850                 855                 860

Pro Leu Phe Val Ser Arg Ala Pro Asn Arg Lys Met Ser Gly Ala His
865                 870                 875                 880

Lys Asp Thr Leu Arg Ser Ala Lys Arg Phe Val Lys His Asn Glu Lys
                885                 890                 895
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Ile Ser Val Lys Arg Val Trp Leu Thr Glu Ile Lys Leu Ala Asp Leu
900 905 910

Glu Asn Met Val Asn Tyr Lys Asn Gly Arg Glu Ile Glu Leu Tyr Glu
915 920 925

Ala Leu Lys Ala Arg Leu Glu Ala Tyr Gly Gly Asn Ala Lys Gln Ala
930 935 940

Phe Asp Pro Lys Asp Asn Pro Phe Tyr Lys Lys Gly Gly Gln Leu Val
945 950 955 960

Lys Ala Val Arg Val Glu Lys Thr Gln Glu Ser Gly Val Leu Leu Asn
965 970 975

Lys Lys Asn Ala Tyr Thr Ile Ala Asp Asn Gly Asp Met Val Arg Val
980 985 990

Asp Val Phe Cys Lys Val Asp Lys Lys Gly Lys Asn Gln Tyr Phe Ile
995 1000 1005

Val Pro Ile Tyr Ala Trp Gln Val Ala Glu Asn Ile Leu Pro Asp
1010 1015 1020

Ile Asp Cys Lys Gly Tyr Arg Ile Asp Asp Ser Tyr Thr Phe Cys
1025 1030 1035

Phe Ser Leu His Lys Tyr Asp Leu Ile Ala Phe Gln Lys Asp Glu
1040 1045 1050

Lys Ser Lys Val Glu Phe Ala Tyr Tyr Ile Asn Cys Asp Ser Ser
1055 1060 1065

Asn Gly Arg Phe Tyr Leu Ala Trp His Asp Lys Gly Ser Lys Glu
1070 1075 1080

Gln Gln Phe Arg Ile Ser Thr Gln Asn Leu Val Leu Ile Gln Lys
1085 1090 1095

Tyr Gln Val Asn Glu Leu Gly Lys Glu Ile Arg Pro Cys Arg Leu
1100 1105 1110

Lys Lys Arg Pro Pro Val Arg
1115 1120

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Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Gly Thr Lys Asp Ser Thr Lys Asp Ile
195 200 205

Pro Glu Thr Pro Ser Lys Asp Asp Lys Lys Tyr Ser Ile Gly Leu Ala
210 215 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225 230 235 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
245 250 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
260 265 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
275 280 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
290 295 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305 310 315 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
325 330 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
340 345 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
355 360 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
370 375 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
405 410 415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
420 425 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
435 440 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
450 455 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465 470 475 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
485 490 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
500 505 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
515 520 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
530 535 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545 550 555 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
595 600 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
610 615 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625 630 635 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
645 650 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
660 665 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705 710 715 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
725 730 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
740 745 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
755 760 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
770 775 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785 790 795 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
805 810 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
820 825 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
835 840 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
850 855 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865 870 875 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
885 890 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
900 905 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
1010 1015 1020

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
1565 1570 1575

Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

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Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Gly Arg Asp Val Arg Gln Pro Glu Val
        195                 200                 205

Lys Glu Glu Lys Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
    210                 215                 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225                 230                 235                 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
                245                 250                 255
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Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
260 265 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
275 280 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
290 295 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305 310 315 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
325 330 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
340 345 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
355 360 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
370 375 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
405 410 415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
420 425 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
435 440 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
450 455 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465 470 475 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
485 490 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
500 505 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
515 520 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
530 535 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545 550 555 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
595 600 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
610 615 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625 630 635 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
645 650 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
660 665 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705 710 715 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
725 730 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
740 745 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
755 760 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
770 775 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785 790 795 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
805 810 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
820 825 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
835 840 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
850 855 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865 870 875 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
885 890 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
900 905 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
1010 1015 1020

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
1565 1570 1575

Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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            20                  25                  30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175
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Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Glu Gly Lys Ser Ser Gly Ser Gly Ser
        195                 200                 205

Glu Ser Lys Ser Thr Ala Gly Asp Lys Lys Tyr Ser Ile Gly Leu Ala
    210                 215                 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225                 230                 235                 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
                245                 250                 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
            260                 265                 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
        275                 280                 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
    290                 295                 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305                 310                 315                 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
                325                 330                 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
            340                 345                 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
        355                 360                 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
    370                 375                 380
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Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
405 410 415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
420 425 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
435 440 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
450 455 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465 470 475 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
485 490 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
500 505 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
515 520 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
530 535 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545 550 555 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
595 600 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
610 615 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625 630 635 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
645 650 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
660 665 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705 710 715 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
725 730 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
740 745 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
755 760 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
770 775 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785 790 795 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
805 810 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
820 825 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
835 840 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
850 855 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865 870 875 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
885 890 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
900 905 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
1010 1015 1020

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
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Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

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Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Thr Pro Gly Ser Pro Ala Gly Ser Pro
        195                 200                 205

Thr Ser Thr Glu Glu Gly Thr Asp Lys Lys Tyr Ser Ile Gly Leu Ala
    210                 215                 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225                 230                 235                 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
                245                 250                 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
            260                 265                 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
        275                 280                 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
    290                 295                 300
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Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305 310 315 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
325 330 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
340 345 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
355 360 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
370 375 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
405 410 415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
420 425 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
435 440 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
450 455 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465 470 475 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
485 490 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
500 505 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
515 520 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
530 535 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545 550 555 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
595 600 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
610 615 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625 630 635 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
645 650 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
660 665 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

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Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705                 710                 715                 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
                725                 730                 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
            740                 745                 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
        755                 760                 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
    770                 775                 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785                 790                 795                 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
                805                 810                 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
            820                 825                 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
        835                 840                 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
    850                 855                 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865                 870                 875                 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
                885                 890                 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
            900                 905                 910
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Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
1010 1015 1020

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
1565 1570 1575

Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Gly Ser Glu Pro Ala Thr Ser Gly Ser
195 200 205

Glu Thr Pro Gly Thr Ser Thr Asp Lys Lys Tyr Ser Ile Gly Leu Ala
210 215 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225 230 235 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
245 250 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
260 265 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
275 280 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
290 295 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305 310 315 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
325 330 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
340 345 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
355 360 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
370 375 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385 390 395 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
405 410 415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
420 425 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
435 440 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
450 455 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465 470 475 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
485 490 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
500 505 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
515 520 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
530 535 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545 550 555 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
565 570 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
580 585 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
595 600 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
610 615 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625 630 635 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
645 650 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
660 665 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
675 680 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
690 695 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705 710 715 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
725 730 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
740 745 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
755 760 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
770 775 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785 790 795 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
805 810 815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
820 825 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
835 840 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
850 855 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865 870 875 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
885 890 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
900 905 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
915 920 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
930 935 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945 950 955 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
965 970 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
980 985 990

Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln
995 1000 1005

Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu
1010 1015 1020

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
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Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
195 200 205

Lys Glu Ala Ala Ala Lys Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile
210 215 220

Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val
225 230 235 240

Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile
245 250 255

Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala
260 265 270

Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg
275 280 285

Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala
290 295 300

Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val
305 310 315 320

Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val
325 330 335

Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg
340 345 350

Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr
355 360 365

Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu
370 375 380

Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln
385 390 395 400

Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala
405 410 415

Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser
420 425 430

Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn
435 440 445

Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn
450 455 460

Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser
465 470 475 480

Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly
485 490 495

Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala
500 505 510

Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala
515 520 525

Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp
530 535 540

Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr
545 550 555 560

Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile
565 570 575

Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile
580 585 590

Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg
595 600 605

Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro
610 615 620

His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu
625 630 635 640

Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile
645 650 655

Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn
660 665 670

Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro
675 680 685

Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe
690 695 700

Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val
705 710 715 720

Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu
725 730 735

Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe
740 745 750

Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr
755 760 765

Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys
770 775 780

Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe
785 790 795 800

Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp
805 810 815

Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile
820 825 830

Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg
835 840 845

Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu
850 855 860

Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile
865 870 875 880

Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu
885 890 895

Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp
900 905 910

Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly
915 920 925

Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro
930 935 940

Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu
945 950 955 960

Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met
965 970 975

Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu
980 985 990

Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile
995 1000 1005

Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys
1010 1015 1020

Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp
1025 1030 1035

Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
1040 1045 1050

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys
1055 1060 1065

Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val
1070 1075 1080

Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln
1085 1090 1095

Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu
1100 1105 1110

Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
1115 1120 1125

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His
1130 1135 1140

Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu
1145 1150 1155

Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
1160 1165 1170

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val
1175 1180 1185

Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn
1190 1195 1200

Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu
1205 1210 1215

Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys
1220 1225 1230

Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys
1235 1240 1245

Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile
1250 1255 1260

Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr
1265 1270 1275

Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe
1280 1285 1290

Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val
1295 1300 1305

Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile
1310 1315 1320

Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp
1325 1330 1335

Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala
1340 1345 1350

Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys
1355 1360 1365

Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu
1370 1375 1380

Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys
1385 1390 1395

Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys
1400 1405 1410

Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala
1415 1420 1425

Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser
1430 1435 1440

Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu
1445 1450 1455

Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu
1460 1465 1470

Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu
1475 1480 1485

Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val
1490 1495 1500

Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln
1505 1510 1515

Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala
1520 1525 1530

Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg
1535 1540 1545

Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln
1550 1555 1560

Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu
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Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Gly Gly Gly Gly Ser Glu Ala Ala Ala
195 200 205

Lys Glu Ala Ala Ala Lys Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile
210 215 220

Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val
225 230 235 240

Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile
245 250 255

Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala
260 265 270

Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg
275 280 285

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Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala
    290                 295                 300

Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val
305                 310                 315                 320

Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val
                325                 330                 335

Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg
            340                 345                 350

Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr
        355                 360                 365

Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu
    370                 375                 380

Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln
385                 390                 395                 400

Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala
                405                 410                 415

Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser
            420                 425                 430

Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn
        435                 440                 445

Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn
    450                 455                 460

Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser
465                 470                 475                 480

Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly
                485                 490                 495
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Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala
500 505 510

Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala
515 520 525

Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp
530 535 540

Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr
545 550 555 560

Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile
565 570 575

Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile
580 585 590

Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg
595 600 605

Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro
610 615 620

His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu
625 630 635 640

Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile
645 650 655

Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn
660 665 670

Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro
675 680 685

Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe
690 695 700

Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val
705 710 715 720

Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu
725 730 735

Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe
740 745 750

Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr
755 760 765

Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys
770 775 780

Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe
785 790 795 800

Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp
805 810 815

Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile
820 825 830

Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg
835 840 845

Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu
850 855 860

Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile
865 870 875 880

Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu
885 890 895

Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp
900 905 910

Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly
915 920 925

Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro
930 935 940

Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu
945 950 955 960

Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met
965 970 975

Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu
980 985 990

Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile
995 1000 1005

Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys
1010 1015 1020

Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp
1025 1030 1035

Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
1040 1045 1050

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys
1055 1060 1065

Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val
1070 1075 1080

Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln
1085 1090 1095

Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu
1100 1105 1110

Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
1115 1120 1125

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His
1130 1135 1140

Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu
1145 1150 1155

Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
1160 1165 1170

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val
1175 1180 1185

Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn
1190 1195 1200

Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu
1205 1210 1215

Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys
1220 1225 1230

Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys
1235 1240 1245

Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile
1250 1255 1260

Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr
1265 1270 1275

Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe
1280 1285 1290

Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val
1295 1300 1305

Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile
1310 1315 1320

Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp
1325 1330 1335

Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala
1340 1345 1350

Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys
1355 1360 1365

Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu
1370 1375 1380

Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys
1385 1390 1395

Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys
1400 1405 1410

Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala
1415 1420 1425

Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser
1430 1435 1440

Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu
1445 1450 1455

Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu
1460 1465 1470

Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu
1475 1480 1485

Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val
1490 1495 1500

Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln
1505 1510 1515

Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala
1520 1525 1530

Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg
1535 1540 1545

Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln
1550 1555 1560

Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu
1565 1570 1575

Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu
1580 1585 1590

Lys Glu Thr Gly Lys Gln Leu Val Ile Gln Glu Ser Ile Leu Met
1595 1600 1605

Leu Pro Glu Glu Val Glu Glu Val Ile Gly Asn Lys Pro Glu Ser
1610 1615 1620

Asp Ile Leu Val His Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn
1625 1630 1635

Val Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala
1640 1645 1650

Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys Ile Lys Met Leu
1655 1660 1665

Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1670 1675

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Met Glu Ala Ser Pro Ala Ser Gly Pro Arg His Leu Met Asp Pro His
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Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Gly Gly Gly Gly
195 200 205

Ser Gly Gly Gly Gly Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile
210 215 220

Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val
225 230 235 240

Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile
245 250 255

Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala
260 265 270

Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg
275 280 285

Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala
290 295 300

Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val
305 310 315 320

Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val
325 330 335

Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg
340 345 350

Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr
355 360 365

Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu
370 375 380

Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln
385 390 395 400

Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala
405 410 415

Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser
420 425 430

Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn
435 440 445

Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn
450 455 460

Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser
465 470 475 480

Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly
485 490 495

Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala
500 505 510

Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala
515 520 525

Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp
530 535 540

Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr
545 550 555 560

Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile
565 570 575

Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile
580 585 590

Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg
595 600 605

Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro
610 615 620

His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu
625 630 635 640

Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile
645 650 655

Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn
660 665 670

Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro
675 680 685

Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe
690 695 700

Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val
705 710 715 720

Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu
725 730 735

Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe
740 745 750

Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr
755 760 765

Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys
770 775 780

Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe
785 790 795 800

Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp
805 810 815

Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile
820 825 830

Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg
835 840 845

Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu
850 855 860

Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile
865 870 875 880

Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu
885 890 895

Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp
900 905 910

Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly
915 920 925

Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro
930 935 940

Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu
945 950 955 960

Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met
965 970 975

Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu
980 985 990

Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile
995 1000 1005

Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys
1010 1015 1020

Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp
1025 1030 1035

Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
1040 1045 1050

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys
1055 1060 1065

Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val
1070 1075 1080

Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln
1085 1090 1095

Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu
1100 1105 1110

Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
1115 1120 1125

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His
1130 1135 1140

Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu
1145 1150 1155

Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
1160 1165 1170

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val
1175 1180 1185

Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn
1190 1195 1200

Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu
1205 1210 1215

Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys
1220 1225 1230

Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys
1235 1240 1245

Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile
1250 1255 1260

Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr
1265 1270 1275

Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe
1280 1285 1290

Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val
1295 1300 1305

Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile
1310 1315 1320

Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp
1325 1330 1335

Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala
1340 1345 1350

Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys
1355 1360 1365

Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu
1370 1375 1380

Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys
1385 1390 1395

Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys
1400 1405 1410

Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala
1415 1420 1425

Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser
1430 1435 1440

Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu
1445 1450 1455

Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu
1460 1465 1470

Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu
1475 1480 1485

Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val
1490 1495 1500

Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln
1505 1510 1515

Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala
1520 1525 1530

Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg
1535 1540 1545

Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln
1550 1555 1560

Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu
1565 1570 1575

Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu
1580 1585 1590

Lys Glu Thr Gly Lys Gln Leu Val Ile Gln Glu Ser Ile Leu Met
1595 1600 1605

Leu Pro Glu Glu Val Glu Glu Val Ile Gly Asn Lys Pro Glu Ser
1610 1615 1620

Asp Ile Leu Val His Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn
1625 1630 1635

Val Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala
1640 1645 1650

Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys Ile Lys Met Leu
1655 1660 1665

Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1670 1675

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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
195 200 205

Lys Glu Ala Ala Ala Lys Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile
210 215 220

Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val
225 230 235 240

Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile
245 250 255

Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala
260 265 270

Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg
275 280 285

Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala
290 295 300

Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val
305 310 315 320

Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val
325 330 335

Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg
340 345 350

Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr
355 360 365

Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu
370 375 380

Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln
385 390 395 400

Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala
405 410 415

Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser
420 425 430

Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn
435 440 445

Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn
450 455 460

Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser
465 470 475 480

Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly
485 490 495

Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala
500 505 510

Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala
515 520 525

Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp
530 535 540

Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr
545 550 555 560

Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile
565 570 575

Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile
580 585 590

Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg
595 600 605

Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro
610 615 620

His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu
625 630 635 640

Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile
645 650 655

Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn
660 665 670

Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro
675 680 685

Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe
690 695 700

Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val
705 710 715 720

Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu
725 730 735

Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe
740 745 750

Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr
755 760 765

Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys
770 775 780

Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe
785 790 795 800

Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp
805 810 815

Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile
820 825 830

Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg
835 840 845

Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu
850 855 860

Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile
865 870 875 880

Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu
885 890 895

Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp
900 905 910

Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly
915 920 925

Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro
930 935 940

Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu
945 950 955 960

Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met
965 970 975

Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu
980 985 990

Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile
995 1000 1005

Leu Lys Glu His Pro Val Glu Asn Thr Gln Leu Gln Asn Glu Lys
1010 1015 1020

Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val Asp
1025 1030 1035

Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp His
1040 1045 1050

Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys
1055 1060 1065

Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn Val
1070 1075 1080

Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg Gln
1085 1090 1095

Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu
1100 1105 1110

Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
1115 1120 1125

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His
1130 1135 1140

Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu
1145 1150 1155

Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
1160 1165 1170

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val
1175 1180 1185

Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn
1190 1195 1200

Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu
1205 1210 1215

Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys
1220 1225 1230

Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys
1235 1240 1245

Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile
1250 1255 1260

Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr
1265 1270 1275

Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe
1280 1285 1290

Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val
1295 1300 1305

Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile
1310 1315 1320

Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp
1325 1330 1335

Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala
1340 1345 1350

Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys
1355 1360 1365

Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu
1370 1375 1380

Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys
1385 1390 1395

Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys
1400 1405 1410

Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala
1415 1420 1425

Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser
1430 1435 1440

Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu
1445 1450 1455

Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu
1460 1465 1470

Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu
1475 1480 1485

Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val
1490 1495 1500

Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln
1505 1510 1515

Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala
1520 1525 1530

Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg
1535 1540 1545

Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln
1550 1555 1560

Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu
1565 1570 1575

Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu
1580 1585 1590

Lys Glu Thr Gly Lys Gln Leu Val Ile Gln Glu Ser Ile Leu Met
1595 1600 1605

Leu Pro Glu Glu Val Glu Glu Val Ile Gly Asn Lys Pro Glu Ser
1610 1615 1620

Asp Ile Leu Val His Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn
1625 1630 1635

Val Met Leu Leu Thr Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala
1640 1645 1650

Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys Ile Lys Met Leu
1655 1660 1665

Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
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            20                  25                  30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190
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Ile Leu Gln Asn Gln Gly Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly
195 200 205

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Lys Tyr Ser
210 215 220

Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr
225 230 235 240

Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr
245 250 255

Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp
260 265 270

Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg
275 280 285

Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe
290 295 300

Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu
305 310 315 320

Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile
325 330 335

Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr
340 345 350

Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp
355 360 365

Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly
370 375 380

His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp
385 390 395 400

Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu
405 410 415

Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala
420 425 430

Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro
435 440 445

Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu
450 455 460

Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala
465 470 475 480

Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu
485 490 495

Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys
500 505 510

Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr
515 520 525

Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp
530 535 540

Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln
545 550 555 560

Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly
565 570 575

Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys
580 585 590

Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu
595 600 605

Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp
610 615 620

Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile
625 630 635 640

Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu
645 650 655

Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro
660 665 670

Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu
675 680 685

Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala
690 695 700

Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu
705 710 715 720

Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe
725 730 735

Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met
740 745 750

Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp
755 760 765

Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu
770 775 780

Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly
785 790 795 800

Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu
805 810 815

Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp
820 825 830

Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu
835 840 845

Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys
850 855 860

Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu
865 870 875 880

Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr
885 890 895

Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met
900 905 910

Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys
915 920 925

Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn
930 935 940

Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys
945 950 955 960

Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn
965 970 975

Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln
980 985 990

Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu
995 1000 1005

Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln
1010 1015 1020

Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg
1025 1030 1035

Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
1040 1045 1050

Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp
1055 1060 1065

Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly
1070 1075 1080

Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
1085 1090 1095

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg
1100 1105 1110

Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu
1115 1120 1125

Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg
1130 1135 1140

Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
1145 1150 1155

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val
1160 1165 1170

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Ile Thr  Leu Lys Ser Lys Leu  Val Ser Asp Phe Arg  Lys Asp Phe
    1175                1180                1185

Gln Phe  Tyr Lys Val Arg Glu  Ile Asn Asn Tyr His  His Ala His
    1190                1195                1200

Asp Ala  Tyr Leu Asn Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys
    1205                1210                1215

Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val
    1220                1225                1230

Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly
    1235                1240                1245

Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe
    1250                1255                1260

Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg
    1265                1270                1275

Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp
    1280                1285                1290

Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys Val Leu  Ser Met Pro
    1295                1300                1305

Gln Val  Asn Ile Val Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe
    1310                1315                1320

Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile
    1325                1330                1335

Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp
    1340                1345                1350

Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val Val Ala  Lys Val Glu
    1355                1360                1365
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Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1370 1375 1380

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1385 1390 1395

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1400 1405 1410

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1415 1420 1425

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1430 1435 1440

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1445 1450 1455

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1460 1465 1470

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1475 1480 1485

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1490 1495 1500

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1505 1510 1515

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1520 1525 1530

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1535 1540 1545

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1550 1555 1560

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1565 1570 1575

Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu
1580 1585 1590

Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu Val Ile Gln
1595 1600 1605

Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val Ile Gly
1610 1615 1620

Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu
1625 1630 1635

Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
1640 1645 1650

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn
1655 1660 1665

Lys Ile Lys Met Leu Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys
1670 1675 1680

Val

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Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
            20                  25                  30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly
        195                 200                 205
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Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Asp Lys Lys Tyr Ser
210 215 220

Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr
225 230 235 240

Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr
245 250 255

Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp
260 265 270

Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg
275 280 285

Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe
290 295 300

Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu
305 310 315 320

Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile
325 330 335

Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr
340 345 350

Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp
355 360 365

Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly
370 375 380

His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp
385 390 395 400

Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu
405 410 415

Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala
420 425 430

Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro
435 440 445

Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu
450 455 460

Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala
465 470 475 480

Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu
485 490 495

Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys
500 505 510

Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr
515 520 525

Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp
530 535 540

Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln
545 550 555 560

Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly
565 570 575

Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys
580 585 590

Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu
595 600 605

Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp
610 615 620

Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile
625 630 635 640

Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu
645 650 655

Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro
660 665 670

Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu
675 680 685

Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala
690 695 700

Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu
705 710 715 720

Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe
725 730 735

Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met
740 745 750

Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp
755 760 765

Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu
770 775 780

Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly
785 790 795 800

Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu
805 810 815

Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp
820 825 830

Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu
835 840 845

Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys
850 855 860

Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu
865 870 875 880

Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr
885 890 895

Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met
900 905 910

Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys
915 920 925

Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn
930 935 940

Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys
945 950 955 960

Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn
965 970 975

Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln
980 985 990

Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu
995 1000 1005

Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln
1010 1015 1020

Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg
1025 1030 1035

Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
1040 1045 1050

Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp
1055 1060 1065

Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly
1070 1075 1080

Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
1085 1090 1095

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg
1100 1105 1110

Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu
1115 1120 1125

Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg
1130 1135 1140

Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
1145 1150 1155

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val
1160 1165 1170

Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe
1175 1180 1185

Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala His
1190 1195 1200

Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
1205 1210 1215

Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
1220 1225 1230

Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1235 1240 1245

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
1250 1255 1260

Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg
1265 1270 1275

Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp
1280 1285 1290

Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1295 1300 1305

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1310 1315 1320

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1325 1330 1335

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1340 1345 1350

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1355 1360 1365

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1370 1375 1380

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1385 1390 1395

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1400 1405 1410

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1415 1420 1425

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1430 1435 1440

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1445 1450 1455

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1460 1465 1470

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1475 1480 1485

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1490 1495 1500

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1505 1510 1515

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1520 1525 1530

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1535 1540 1545

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1550 1555 1560

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1565 1570 1575

Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu
1580 1585 1590

Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu Val Ile Gln
1595 1600 1605

Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val Ile Gly
1610 1615 1620

Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu
1625 1630 1635

Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
1640 1645 1650

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn
1655 1660 1665

Lys Ile Lys Met Leu Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys
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Met Glu Ala Ser Pro Ala Ser Gly Pro Arg His Leu Met Asp Pro His
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Gly Gly Gly Gly Ser Glu Ala Ala Ala
        195                 200                 205

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Lys Tyr Ser
    210                 215                 220
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Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr
225 230 235 240

Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr
245 250 255

Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp
260 265 270

Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg
275 280 285

Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe
290 295 300

Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu
305 310 315 320

Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile
325 330 335

Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr
340 345 350

Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp
355 360 365

Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly
370 375 380

His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp
385 390 395 400

Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu
405 410 415

Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala
420 425 430

Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro
435 440 445

Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu
450 455 460

Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala
465 470 475 480

Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu
485 490 495

Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys
500 505 510

Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr
515 520 525

Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp
530 535 540

Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln
545 550 555 560

Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly
565 570 575

Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys
580 585 590

Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu
595 600 605

Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp
610 615 620

Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile
625 630 635 640

Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu
645 650 655

Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro
660 665 670

Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu
675 680 685

Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala
690 695 700

Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu
705 710 715 720

Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe
725 730 735

Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met
740 745 750

Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp
755 760 765

Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu
770 775 780

Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly
785 790 795 800

Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu
805 810 815

Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp
820 825 830

Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu
835 840 845

Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys
850 855 860

Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu
865 870 875 880

Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr
885 890 895

Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met
900 905 910

Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys
915 920 925

Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn
930 935 940

Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys
945 950 955 960

Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn
965 970 975

Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln
980 985 990

Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu
995 1000 1005

Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln
1010 1015 1020

Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg
1025 1030 1035

Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
1040 1045 1050

Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp
1055 1060 1065

Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly
1070 1075 1080

Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
1085 1090 1095

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg
1100 1105 1110

Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu
1115 1120 1125

Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg
1130 1135 1140

Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
1145 1150 1155

Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val
1160 1165 1170

Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe
1175 1180 1185

Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala His
1190 1195 1200

Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
1205 1210 1215

Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
1220 1225 1230

Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1235 1240 1245

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
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Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg
1265 1270 1275

Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp
1280 1285 1290

Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1295 1300 1305

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1310 1315 1320

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1325 1330 1335

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1340 1345 1350

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1355 1360 1365

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1370 1375 1380

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1385 1390 1395

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1400 1405 1410

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
1415 1420 1425

Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
1430 1435 1440

Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1445 1450 1455

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1460 1465 1470

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1475 1480 1485

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1490 1495 1500

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
1505 1510 1515

Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
1520 1525 1530

Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1535 1540 1545

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
1550 1555 1560

Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
1565 1570 1575

Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu
1580 1585 1590

Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu Val Ile Gln
1595 1600 1605

Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val Ile Gly
1610 1615 1620

Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu
1625 1630 1635

Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
1640 1645 1650

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn
1655 1660 1665

Lys Ile Lys Met Leu Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys
1670 1675 1680

Val

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        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
        195                 200                 205

Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Asp Lys Lys Tyr Ser
    210                 215                 220

Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr
225                 230                 235                 240
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Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr
245 250 255

Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp
260 265 270

Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg
275 280 285

Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe
290 295 300

Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu
305 310 315 320

Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile
325 330 335

Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr
340 345 350

Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp
355 360 365

Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly
370 375 380

His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp
385 390 395 400

Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu
405 410 415

Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala
420 425 430

Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro
435 440 445

Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu
450 455 460

Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala
465 470 475 480

Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu
485 490 495

Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys
500 505 510

Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr
515 520 525

Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp
530 535 540

Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln
545 550 555 560

Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly
565 570 575

Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys
580 585 590

Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu
595 600 605

Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp
610 615 620

Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile
625 630 635 640

Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu
645 650 655

Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro
660 665 670

Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu
675 680 685

Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala
690 695 700

Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu
705 710 715 720

Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe
725 730 735

Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met
740 745 750

Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp
755 760 765

Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu
770 775 780

Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly
785 790 795 800

Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu
805 810 815

Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp
820 825 830

Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu
835 840 845

Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys
850 855 860

Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu
865 870 875 880

Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr
885 890 895

Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met
900 905 910

Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys
915 920 925

Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn
930 935 940

Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys
945 950 955 960

Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn
965 970 975

Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln
980 985 990

Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly Ile Lys Glu
995 1000 1005

Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn Thr Gln
1010 1015 1020

Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg
1025 1030 1035

Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
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Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp
1055 1060 1065

Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly
1070 1075 1080

Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
1085 1090 1095

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg
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Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu
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Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg
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Gln Ile Thr Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn
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Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val
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Ile Thr Leu Lys Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe
1175 1180 1185

Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn Tyr His His Ala His
1190 1195 1200

Asp Ala Tyr Leu Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys
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Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val
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Tyr Asp Val Arg Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly
1235 1240 1245

Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe
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Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg
1265 1270 1275

Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp
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Lys Gly Arg Asp Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro
1295 1300 1305

Gln Val Asn Ile Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe
1310 1315 1320

Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile
1325 1330 1335

Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp
1340 1345 1350

Ser Pro Thr Val Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu
1355 1360 1365

Lys Gly Lys Ser Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly
1370 1375 1380

Ile Thr Ile Met Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp
1385 1390 1395

Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile
1400 1405 1410

Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg
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Lys Arg Met Leu Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu
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Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser
1445 1450 1455

His Tyr Glu Lys Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys
1460 1465 1470

Gln Leu Phe Val Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile
1475 1480 1485

Glu Gln Ile Ser Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala
1490 1495 1500

Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys
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Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu
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Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr
1535 1540 1545

Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala
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Thr Leu Ile His Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile
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Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly Gly Ser Thr Asn Leu
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Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu Val Ile Gln
1595 1600 1605

Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val Ile Gly
1610 1615 1620

Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp Glu
1625 1630 1635

Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
1640 1645 1650

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn
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Lys Ile Lys Met Leu Ser Gly Gly Ser Pro Lys Lys Lys Arg Lys
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Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
35 40 45

```
Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Gly Gly Gly Gly Ser Glu Ala Ala Ala
        195                 200                 205

Lys Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys
    210                 215                 220

Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly
225                 230                 235                 240

Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys
                245                 250                 255
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Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly
260 265 270

Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys
275 280 285

Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr
290 295 300

Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe
305 310 315 320

Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His
325 330 335

Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His
340 345 350

Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser
355 360 365

Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met
370 375 380

Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp
385 390 395 400

Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn
405 410 415

Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys
420 425 430

Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu
435 440 445

Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu
450 455 460

Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp
465 470 475 480

Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp
485 490 495

Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu
500 505 510

Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile
515 520 525

Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met
530 535 540

Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala
545 550 555 560

Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp
565 570 575

Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln
580 585 590

Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly
595 600 605

Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys
610 615 620

Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly
625 630 635 640

Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu
645 650 655

Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro
660 665 670

Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met
675 680 685

Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val
690 695 700

Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn
705 710 715 720

Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu
725 730 735

Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr
740 745 750

Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys
755 760 765

Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val
770 775 780

Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser
785 790 795 800

Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr
805 810 815

Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn
820 825 830

Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu
835 840 845

Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His
850 855 860

Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr
865 870 875 880

Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys
885 890 895

Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala
900 905 910

Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys
915 920 925

Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His
930 935 940

Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile
945 950 955 960

Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg
965 970 975

His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr
980 985 990

Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu
995 1000 1005

Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
1010 1015 1020

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr
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Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile
1040 1045 1050

Asn Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser
1055 1060 1065

Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser
1070 1075 1080

Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val
1085 1090 1095

Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys
1100 1105 1110

Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg
1115 1120 1125

Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
1130 1135 1140

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu
1145 1150 1155

Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile
1160 1165 1170

Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp
1175 1180 1185

Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn
1190 1195 1200

Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val Val Gly Thr
1205 1210 1215

Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr
1220 1225 1230

Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala Lys Ser
1235 1240 1245

Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser
1250 1255 1260

Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly
1265 1270 1275

Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly
1280 1285 1290

Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val Arg Lys
1295 1300 1305

Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr Glu Val
1310 1315 1320

Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn
1325 1330 1335

Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys
1340 1345 1350

Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val Leu Val
1355 1360 1365

Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys Ser Val
1370 1375 1380

Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser Phe Glu
1385 1390 1395

Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val
1400 1405 1410

Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu
1415 1420 1425

Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly Glu Leu
1430 1435 1440

Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe
1445 1450 1455

Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser Pro Glu
1460 1465 1470

Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys His Tyr
1475 1480 1485

Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys Arg Val
1490 1495 1500

Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn
1505 1510 1515

Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile
1520 1525 1530

His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys
1535 1540 1545

Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys
1550 1555 1560

Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr Gly Leu
1565 1570 1575

Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly
1580 1585 1590

Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys
1595 1600 1605

Gln Leu Val Ile Gln Glu Ser Ile Leu Met Leu Pro Glu Glu Val
1610 1615 1620

Glu Glu Val Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His
1625 1630 1635

Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn Val Met Leu Leu Thr
1640 1645 1650

Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp
1655 1660 1665

Ser Asn Gly Glu Asn Lys Ile Lys Met Leu Ser Gly Gly Ser Pro
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Lys Lys Lys Arg Lys Val
1685

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35 40 45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
50 55 60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65 70 75 80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
85 90 95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
100 105 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
195 200 205

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
210 215 220

Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly
225 230 235 240

Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys
245 250 255

Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly
260 265 270

Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys
275 280 285

Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr
290 295 300

Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe
305 310 315 320

Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His
325 330 335

Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His
340 345 350

Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser
355 360 365

Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met
370 375 380

Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp
385 390 395 400

Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn
405 410 415

Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys
420 425 430

Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu
435 440 445

Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu
450 455 460

Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp
465 470 475 480

Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp
485 490 495

Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu
500 505 510

Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile
515 520 525

Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met
530 535 540

Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala
545 550 555 560

Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp
565 570 575

Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln
580 585 590

Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly
595 600 605

Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys
610 615 620

Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly
625 630 635 640

Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu
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Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro
660 665 670

Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met
675 680 685

Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val
690 695 700

Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn
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Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu
725 730 735

Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr
740 745 750

Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys
755 760 765

Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val
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Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser
785 790 795 800

Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr
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Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn
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Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu
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Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His
850 855 860

Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr
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Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys
885 890 895

Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala
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Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys
915 920 925

Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His
930 935 940

Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile
945 950 955 960

Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg
965 970 975

His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr
980 985 990

Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu
995 1000 1005

Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
1010 1015 1020

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr
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Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile
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Asn Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser
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Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser
1070 1075 1080

Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val
1085 1090 1095

Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys
1100 1105 1110

Leu Ile Thr Gln Arg Lys Phe Asp Asn Leu Thr Lys Ala Glu Arg
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Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
1130 1135 1140

Leu Val Glu Thr Arg Gln Ile Thr Lys His Val Ala Gln Ile Leu
1145 1150 1155

Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp Lys Leu Ile
1160 1165 1170

Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp
1175 1180 1185

Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn
1190 1195 1200

Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val Val Gly Thr
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Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr
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Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala Lys Ser
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Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser
1250 1255 1260

Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala Asn Gly
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Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu Thr Gly
1280 1285 1290

Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val Arg Lys
1295 1300 1305

Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr Glu Val
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Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys Arg Asn
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Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys
1340 1345 1350

Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val Leu Val
1355 1360 1365

Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys Ser Val
1370 1375 1380

Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser Phe Glu
1385 1390 1395

Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys Glu Val
1400 1405 1410

Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu Phe Glu
1415 1420 1425

Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly Glu Leu
1430 1435 1440

Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val Asn Phe
1445 1450 1455

Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser Pro Glu
1460 1465 1470

Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys His Tyr
1475 1480 1485

Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys Arg Val
1490 1495 1500

Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn
1505 1510 1515

Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile
1520 1525 1530

His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys
1535 1540 1545

Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys
1550 1555 1560

Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr Gly Leu
1565 1570 1575

Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly
1580 1585 1590

Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys
1595 1600 1605

Gln Leu Val Ile Gln Glu Ser Ile Leu Met Leu Pro Glu Glu Val
1610 1615 1620

Glu Glu Val Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His
1625 1630 1635

Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn Val Met Leu Leu Thr
1640 1645 1650

Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp
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Lys Lys Lys Arg Lys Val
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Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
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Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
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Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
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Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
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Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
115 120 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
130 135 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
195 200 205

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ala Ala Ala Lys
210 215 220

Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly
225 230 235 240

Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys
245 250 255

Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly
260 265 270

Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys
275 280 285

Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr
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Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe
305 310 315 320

Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His
325 330 335

Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His
340 345 350

Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser
355 360 365

Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met
370 375 380

Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp
385 390 395 400

Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn
405 410 415

Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys
420 425 430

Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu
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Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu
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Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp
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Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp
485 490 495

Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu
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Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile
515 520 525

Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met
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Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp
565 570 575

Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln
580 585 590

Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly
595 600 605

Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys
610 615 620

Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly
625 630 635 640

Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu
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Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro
660 665 670

Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met
675 680 685

Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val
690 695 700

Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn
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Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu
725 730 735

Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr
740 745 750

Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys
755 760 765

Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val
770 775 780

Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser
785 790 795 800

Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr
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Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn
820 825 830

Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu
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Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His
850 855 860

Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr
865 870 875 880

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885 890 895

Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala
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Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys
915 920 925

Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His
930 935 940

Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile
945 950 955 960

Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg
965 970 975

His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr
980 985 990

Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu
995 1000 1005

Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
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Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr
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Leu Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile
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Asn Arg Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser
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Phe Leu Lys Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser
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Asp Lys Asn Arg Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val
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Val Lys Lys Met Lys Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys
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Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly Phe Ile Lys Arg Gln
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Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp
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Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg Glu Ile Asn Asn
1190 1195 1200

Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val Val Gly Thr
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Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr
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Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala Lys Ser
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Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe Tyr Ser
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Glu Ile  Val Trp Asp Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys
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Val Leu  Ser Met Pro Gln Val  Asn Ile Val Lys Lys  Thr Glu Val
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Gln Thr  Gly Gly Phe Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn
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Ser Asp  Lys Leu Ile Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys
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Tyr Gly  Gly Phe Asp Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val
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Val Ala  Lys Val Glu Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val
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Lys Glu  Leu Leu Gly Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu
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Lys Asn  Pro Ile Asp Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val
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Lys Lys  Asp Leu Ile Ile Lys  Leu Pro Lys Tyr Ser  Leu Phe Glu
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Leu Glu  Asn Gly Arg Lys Arg  Met Leu Ala Ser Ala  Gly Glu Leu
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Gln Lys  Gly Asn Glu Leu Ala  Leu Pro Ser Lys Tyr  Val Asn Phe
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Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser Pro Glu
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Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys His Tyr
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Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala Tyr Asn
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Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile
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His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala Phe Lys
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Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys
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Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr Gly Leu
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Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp Ser Gly
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Gly Ser Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys
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Glu Glu Val Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His
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Thr Ala Tyr Asp Glu Ser Thr Asp Glu Asn Val Met Leu Leu Thr
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Ser Asp Ala Pro Glu Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp
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Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
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Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
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Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
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Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
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Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145 150 155 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
165 170 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
180 185 190

Ile Leu Gln Asn Gln Gly Asn Glu Ala Ala Ala Lys Glu Ala Ala Ala
195 200 205

Lys Glu Ala Ala Ala Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
210 215 220

Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly
225 230 235 240

Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys
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Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly
260 265 270

Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys
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Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr
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Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe
305 310 315 320

Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His
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Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His
340 345 350

Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser
355 360 365

Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met
370 375 380

Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp
385 390 395 400

Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn
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Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys
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Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu
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Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln
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Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly
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Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu
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Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro
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Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met
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Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val
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Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn
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Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr
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Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys
755 760 765

Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val
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Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser
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Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr
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Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn
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Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu
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Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His
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Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile
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Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg
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His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr
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Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu
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Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
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Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr
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Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val Ser Asp
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Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe Val Tyr
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Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro Lys Lys
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Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys Arg Val
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Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn Ile Ile
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Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser Thr Lys
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

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<400> 407
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<400> 427
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<400> 438
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<400> 455
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 501
gcugcagcgc acggguacca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucacg aaagggcacc gagucggugc u 91

<210> 502
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 502
ccacacccaa aaggccacac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucacg aaagggcacc gagucggugc u 91

<210> 503
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 503
gugugucccu cuccccaccc guccguugua gcucccugaa accguugcua caauaaggcc 60

gucgaaagau gugccgcaac gcucugccuu cuggcaucgu u 101

<210> 504
<211> 100
<212> RNA
<213> 人工序列

<220>
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<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 504
aucugccuuu auagggcacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 505
<211> 99
<212> RNA
<213> 人工序列

<220>
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 505
agucacgaug ccuuuauagg uuuuagagcu agaaauagca aguuaaaaua aggcuagucc 60

guuaucaacu ugaaaaagug gcaccgaguc ggugcuuuu 99

<210> 506
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<212> RNA
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<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 506
gguugcaagg aaugagaacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 507
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<400> 507
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gucgaaagau gugccgcaac gcucugccuu cuggcaucgu u 101

<210> 508
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<400> 508
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gucgaaagau gugccgcaac gcucugccuu cuggcaucgu u 101

<210> 509
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<400> 509
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gucgaaagau gugccgcaac gcucugccuu cuggcaucgu u 101

<210> 510
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<400> 510
ccaagugucu uccaguacga uuugguugua gcucccuucg accguugcua caauaaggcc 60

gucgaugugc cgcaacgcuc ugccggcauc guu 93

<210> 511
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<400> 511
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 512
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<222> (1)..(24)
<223> n爲a、c、g或u

<220>
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<222> (21)..(25)
<223> n可能存在或可能不存在

<400> 512
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gaaccguugc uacaauaagg ccgucugaaa agaugugccg caacgcucug ccccuuaaag 120

cuucugcuuu aaggggcauc guuua 145

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<212> RNA
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<220>
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<220>
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<223> n爲a、c、g或u

<220>
<221> misc_feature
<222> (21)..(25)
<223> n可能存在或可能不存在

<400> 513
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cgucgaaaga ugugccgcaa cgcucugccu ucuggcaucg uu 102

<210> 514
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<212> RNA
<213> 人工序列

<220>
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<223> n爲a、c、g或u

<220>
<221> misc_feature
<222> (21)..(25)
<223> n可能存在或可能不存在

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cgucgaaaga ugugccgcaa cgcucugccu ucuggcaucg uuuauu 106

<210> 515
<211> 108
<212> RNA
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<220>
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<223> n爲a、c、g或u

<220>
<221> misc_feature
<222> (21)..(25)
<223> n可能存在或可能不存在

<400> 515
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gccgucgaaa gaugugccgc aacgcucugc cuucuggcau cguuuauu 108

<210> 516
<211> 77
<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 516
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ugccuucugg caucguu 77

<210> 517

<211> 77
<212> RNA
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<220>
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 517
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ugccuucugg caucguu 77

<210> 518
<211> 94
<212> RNA
<213> 人工序列

<220>
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<220>
<221> misc_feature
<223> 含有內部連接子L1；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(25)
<223> n爲a、c、g或u

<220>
<221> misc_feature
<222> (21)..(25)
<223> n可能存在或可能不存在

<400> 518
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cgucgaugug ccgcaacgcu cugccggcau cguu 94

<210> 519
<211> 93

<212> RNA
<213> 人工序列

<220>
<223> 合成

<220>
<221> misc_feature
<223> 含有2'-O-Me及PS修飾以及內部連接子L1；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(24)
<223> n爲a、c、g或u

<400> 519
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gucgaugugc cgcaacgcuc ugccggcauc guu 93

<210> 520
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
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<222> (1)..(20)
<223> n爲a、c、g或u

<400> 520
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<210> 521
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<220>
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<223> n爲a、c、g或u

<400> 521
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cguuaucacg aaagggcacc gagucggugc u 91

<210> 522
<211> 101
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(24)
<223> n爲a、c、g或u

<400> 522
nnnnnnnnnn nnnnnnnnnn nnnnguugua gcucccugaa accguugcua caauaaggcc 60

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<210> 523
<211> 80
<212> RNA
<213> 人工序列

<220>
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<220>
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<223> 含有2'-O-ME及PS修飾以及內部連接子L1及L2；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 523
acgcaaauau caguccagcg guuuuagagc uauagcaagu uaaaauaagg cguccguuau 60

cacgggcacc gagucggugc 80

<210> 524
<211> 93
<212> RNA
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<220>
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<220>
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<223> 含有內部連接子L1；關於取代及優選實施例之詳細描述，參見所提交之說明書

<220>
<221> misc_feature
<222> (1)..(20)
<223> n爲a、c、g或u

<400> 524
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aucaacuuaa guggcaccga gucggugcuu uuu 93

<210> 525

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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 529
uucccggccu uuuuaccuug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 530
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<220>
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<400> 530
ucaacugcga ccaguucagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 531
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 531
agcgcaggca guggcaggca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 532
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 533
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<400> 534
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 535
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 536
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 537
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<400> 537
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 539
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 540
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 549
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<400> 550
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<400> 571
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<213> 人工序列

<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 812
caaacacagc gaccucgggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 813
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 813
uaccauggcc aucaacacaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 814
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<400> 814
gcgcugacga ucugggugac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 815

<211> 100
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<220>
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<400> 815
cacggacccg cagccccuca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 816
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 816
ucaaacacag cgaccucggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 817
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 817
cagggaagaa gccuguggcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 818
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<400> 818
caguguggcc uuuugggugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 819
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<400> 819
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 820
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<212> RNA
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<400> 820
gagggcgggc ugcuccuuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 821
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<400> 821
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 822
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 822
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 823
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 823
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 824
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 824
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 825
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 825
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 826
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 826
cgggugggaa caccuuguuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 827
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<400> 827
cagcucagcu ccacgugguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 828
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 829
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<400> 829
uagcaggauc ucauagagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 830
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 831
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<400> 831
cugaccacgu ggagcugagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 832
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<400> 832
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 833
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<400> 833
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 834
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<400> 834
cuaugagauc cugcuaggga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 835
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<400> 835
caggaucuca uagaggaugg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 836
ggccacccug uaugcugugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 837
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<400> 837
caacaguguc cuaccagcaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 838
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<400> 838
agcugagcug gugggugaau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 839
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<400> 839
aacagugucc uaccagcaag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 840
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<400> 840
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 841
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<400> 841
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 842
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 842
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 843
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<400> 843
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 844
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<400> 844
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 845
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<400> 845
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 846
<211> 100
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 846
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 847
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<400> 847

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 848
<211> 100
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<400> 848
uccucuauga gauccugcua guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 849
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<400> 849
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 850
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<400> 850
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 851
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<400> 851
acaggguggc cuucccuagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 852
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<400> 852
cgcugaccag cacagcauac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 853
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<400> 853
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 854
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<400> 854
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 855
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 855
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 856
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<400> 856
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 857
<211> 100
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 857
cugacagguu uugaaaguuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 858
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 858
cuggggaaga aggugucuuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 859
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 859
uccuccuccu gaaaguggcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 860
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<400> 860
ccacuuucag gaggaggauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 861
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 861
auuuguuuga gaaucaaaau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 862
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 862
cuucaagagc aacagugcug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 863
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<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 863
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 864
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<220>
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<400> 864
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 865
<211> 100
<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 865
aaagcugccc uuaccugggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 866
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 866
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 867
<211> 100
<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 867
uggaauaaug cuguuguuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 868
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 868
caccaaagcu gcccuuaccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 869
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 869
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 870
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 870
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 871
<211> 100
<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 871
gcaucgcgcc aggacggucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 872
<211> 100
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<400> 872
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 873
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<220>
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<400> 873
caccgggcug aacucgcagu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 874
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<220>
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<400> 874
ucgcgguggu cgucccgagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 875
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 875
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 876
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<400> 876
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 877
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<400> 877
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 878
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<400> 878
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 879
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<400> 879
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 880
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<400> 880
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 881
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 882
aggguuuguc cccggacacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 883
gcgaguucag cccggugucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 884
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<400> 884
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 885
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 886
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<400> 886
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 887
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<400> 887
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 888
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<400> 888
cgagcaccac gacgaggauc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 889
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 890
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 891
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 892
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 893
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 894
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 895
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 896
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<400> 896
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 897
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 898
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 899
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 900
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 900
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 901
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<400> 901
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 902
<211> 100
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<400> 902
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<210> 903

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 903
gcgccagcag uggagcgguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 904
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 904
uccacugcug gcgccaccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 905
<211> 100
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<213> 人工序列

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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 905
aggagagccc aacucugucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 906
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 906
acugacgcca agacagaguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 907
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<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 907
aacccugcug ccggcucucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 908
<211> 100

<212> RNA
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<220>
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 908
uaucagccac uaaugaaguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 909
<211> 100
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 909
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 910
<211> 100
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<400> 910
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<211> 100
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 911
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 912
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 912
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 913
<211> 100

<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 913
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 914
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 914
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 915
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 916
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<400> 916
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 917
<211> 100
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 917
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 918
<211> 100
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<400> 918
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 919
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<400> 919
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 920
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<400> 920
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 921
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 922
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<400> 922
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 923
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 924
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<400> 924
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 925
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<400> 925
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 926
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 927
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 928
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<400> 928
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 929
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 930
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<400> 930
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<210> 931
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<400> 931
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 932
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<400> 932
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 933
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<400> 933
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 934

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<210> 935

<400> 935
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<210> 936

<400> 936
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<210> 937
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<400> 937
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 938
<211> 100
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<400> 938
gggauccauu gagcaucaca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 939
<211> 100
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<400> 939
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 940
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<400> 940
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 941
<211> 100
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<400> 941
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 942
<211> 100
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<400> 942
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 943
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<400> 943
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 944
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<400> 944
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 945
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<400> 945
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 946
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 947
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<400> 947
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 948
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 949

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<400> 949
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 950
<211> 100
<212> RNA
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<220>
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<400> 950
cuucccaga gacuuaugcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 951
<211> 100
<212> RNA
<213> 人工序列

<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 951
uuaccuguag auauucuugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 952
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<212> RNA
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<400> 952
gcucuuuuau ggugggaucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 953
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<400> 953
ggaucccacc auaaaagagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 954
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<400> 954
cgauuccagc ucuuuuaugg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 955
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 955
gauuccagcu cuuuuauggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 956
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 956
aaucgauucc agcucuuuua guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 957

<400> 957
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<210> 959

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<210> 960
<211> 113
<212> PRT
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<220>
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<400> 960

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
35 40 45

Ser Val Trp Arg His Thr Ser Gln Asn Thr Ser Asn His Val Glu Val
50 55 60

Asn Phe Leu Glu Lys Phe Thr Thr Glu Arg Tyr Phe Arg Pro Asn Thr
65 70 75 80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
85 90 95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg His Pro Tyr Val Thr Leu
100 105 110

Phe

<210> 961
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 961

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
35 40 45

Ser Val Trp Arg His Thr Ser Gln Asn Thr Ser Asn His Val Glu Val
50 55 60

Asn Phe Leu Glu Lys Phe Thr Thr Glu Arg Tyr Phe Arg Pro Asn Thr
65 70 75 80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
85 90 95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg His Pro Tyr Val Thr Leu
100 105 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His
115 120

<210> 962
<211> 128
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 962

Met Asn Trp Asn Ala Leu Arg Ser Lys Ala Ile Glu Val Ser Arg His
1 5 10 15

Ala Tyr Ala Pro Tyr Ser Gly Phe Pro Val Gly Ala Ala Ala Leu Val
20 25 30

Asp Asp Gly Arg Thr Val Thr Gly Cys Asn Val Glu Asn Val Ser Tyr
35 40 45

Gly Leu Gly Leu Cys Ala Glu Cys Ala Val Val Cys Ala Leu His Ser
50 55 60

Gly Gly Gly Gly Arg Leu Val Ala Leu Ser Cys Val Gly Pro Asp Gly
65 70 75 80

Gly Val Leu Met Pro Cys Gly Arg Cys Arg Gln Val Leu Leu Glu His
85 90 95

Gly Gly Pro Glu Leu Leu Ile Asp His Ala His Gly Pro Arg Pro Leu
100 105 110

Arg Glu Leu Leu Pro Asp Ala Phe Gly Pro Asp Asp Leu Gly Arg Arg
115 120 125

<210> 963
<211> 130
<212> PRT
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<220>
<223> 合成

<400> 963

Met Thr His His Ala Leu Ile Glu Ala Ala Lys Ala Ala Arg Glu Lys
1 5 10 15

Ala Tyr Ala Pro Tyr Ser Asn Phe Lys Val Gly Ala Ala Leu Val Thr
20 25 30

Asn Asp Gly Lys Val Phe His Gly Cys Asn Val Glu Asn Ala Ser Tyr
35 40 45

Gly Leu Cys Asn Cys Ala Glu Arg Thr Ala Leu Phe Ser Ala Leu Ala
50 55 60

Ala Gly Tyr Arg Pro Gly Glu Phe Ala Ala Ile Ala Val Val Gly Glu
65 70 75 80

Thr His Gly Pro Ile Ala Pro Cys Gly Ala Cys Arg Gln Val Met Ile
85 90 95

Glu Leu Gly Lys Pro Thr Leu Glu Val Val Leu Thr Asn Met Gln Gly
100 105 110

Asp Val Arg Val Thr Ser Ala Gly Asp Leu Leu Pro Asp Ala Phe Tyr
115 120 125

Leu Ala
130

<210> 964
<211> 132
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 964

Met Pro Asp Ile Asp Trp Lys Gln Leu Arg Asp Lys Ala Thr Gln Val
1 5 10 15

Ala Ala Gly Ala Tyr Ala Pro Tyr Ser Arg Phe Pro Val Gly Ala Ala
20 25 30

Ala Leu Val Asp Asp Gly Arg Val Val Thr Gly Cys Asn Val Glu Asn
35 40 45

Val Ser Tyr Gly Leu Ala Leu Cys Ala Glu Cys Gly Val Val Cys Ala
50 55 60

Leu His Ala Thr Gly Gly Gly Arg Leu Val Ala Leu Ala Cys Val Asp
65 70 75 80

Gly Arg Gly Ala Pro Leu Met Pro Cys Gly Arg Cys Arg Gln Leu Leu
85 90 95

Phe Glu His Gly Gly Pro Glu Leu Leu Val Asp His Leu Ala Gly Pro
100 105 110

Arg Arg Leu Gly Asp Leu Leu Pro Glu Pro Phe His Ala Asp Leu Thr
115 120 125

Gly Glu Pro Thr
130

<210> 965
<211> 132
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 965

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Met Asn Ser Lys Gln Leu Ile Gln Glu Ala Ile Glu Ala Arg Lys Gln
1               5                  10                  15

Ala Tyr Val Pro Tyr Ser Lys Phe Gln Val Gly Ala Ala Leu Leu Thr
            20                  25                  30

Gln Asp Gly Lys Val Tyr Arg Gly Cys Asn Val Glu Asn Ala Ser Tyr
        35                  40                  45

Gly Leu Cys Asn Cys Ala Glu Arg Thr Ala Leu Phe Lys Ala Val Ser
    50                  55                  60

Glu Gly Asp Lys Glu Phe Val Ala Ile Ala Ile Val Ala Asp Thr Lys
65                  70                  75                  80

Arg Pro Val Pro Pro Cys Gly Ala Cys Arg Gln Val Met Val Glu Leu
                85                  90                  95

Cys Lys Gln Asp Thr Lys Val Tyr Leu Ser Asn Leu His Gly Asp Val
            100                 105                 110

Gln Glu Thr Thr Val Gly Glu Leu Leu Pro Gly Ala Phe Leu Ala Glu
        115                 120                 125

Asp Leu His Glu
    130
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<210> 966
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 966

Met Pro Asp Val Asp Trp Asn Met Leu Arg Gly Asn Ala Thr Gln Ala
1 5 10 15

Ala Ala Gly Ala Tyr Val Pro Tyr Ser Arg Phe Ala Val Gly Ala Ala
20 25 30

Ala Leu Val Asp Asp Gly Arg Val Val Thr Gly Cys Asn Val Glu Asn
35 40 45

Val Ser Tyr Gly Leu Thr Leu Cys Ala Glu Cys Ala Val Val Cys Ala
50 55 60

Leu His Ser Thr Gly Gly Gly Arg Leu Leu Ala Leu Ala Cys Val Asp
65 70 75 80

Gly His Gly Ser Val Leu Met Pro Cys Gly Arg Cys Arg Gln Val Leu
85 90 95

Leu Glu His Gly Gly Ser Glu Leu Leu Ile Asp His Pro Val Arg Pro
100 105 110

Arg Arg Leu Gly Asp Leu Leu Pro Asp Ala Phe Gly Leu Asp Asp Leu
115 120 125

Pro Arg Glu Arg Arg
130

<210> 967
<211> 134
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 967

Met Gly Asp Val Asn Trp Asp Thr Leu Gln Lys Ala Ala Val Ala Ala
1 5 10 15

Arg Ala Asn Ser Tyr Ala Pro Tyr Ser Asn Phe Pro Val Gly Val Ala
20 25 30

Gly Phe Val Asn Asp Gly Arg Leu Ile Thr Gly Val Asn Val Glu Asn
35 40 45

Ala Ser Tyr Gly Leu Ala Leu Cys Ala Glu Cys Ser Met Ile Ser Ala
50 55 60

Leu Tyr Ala Thr Gly Gly Gly Arg Leu Val Ala Val Tyr Cys Val Asp
65 70 75 80

Gly Asn Gly Asp Ser Leu Met Pro Cys Gly Arg Cys Arg Gln Leu Leu
85 90 95

Tyr Glu His Gly Gly Pro Glu Leu Lys Ile Met Thr Pro Lys Gly Val
100 105 110

Gln Thr Met Ala Gln Leu Leu Pro Gln Ala Phe Asn Pro Gln Glu Arg
115 120 125

Ile Phe Gly Asn Asp Glu
130

<210> 968
<211> 136
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 968

Met Asn Arg Gln Glu Leu Ile Thr Glu Ala Leu Lys Ala Arg Asp Met
1 5 10 15

Ala Tyr Ala Pro Tyr Ser Lys Phe Gln Val Gly Ala Ala Leu Leu Thr
20 25 30

Lys Asp Gly Lys Val Tyr Arg Gly Cys Asn Ile Glu Asn Ala Ala Tyr
35 40 45

Ser Met Cys Asn Cys Ala Glu Arg Thr Ala Leu Phe Lys Ala Val Ser
50 55 60

Glu Gly Asp Thr Glu Phe Gln Met Leu Ala Val Ala Ala Asp Thr Pro
65 70 75 80

Gly Pro Val Ser Pro Cys Gly Ala Cys Arg Gln Val Ile Ser Glu Leu
85 90 95

Cys Thr Lys Asp Val Ile Val Val Leu Thr Asn Leu Gln Gly Gln Ile
100 105 110

Lys Glu Met Thr Val Glu Glu Leu Leu Pro Gly Ala Phe Ser Ser Glu
115 120 125

Asp Leu His Asp Glu Arg Lys Leu
130 135

<210> 969
<211> 142
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 969

Met Lys Val Gly Gly Ile Glu Asp Arg Gln Leu Glu Ala Leu Lys Arg
1 5 10 15

Ala Ala Leu Lys Ala Cys Glu Leu Ser Tyr Ser Pro Tyr Ser His Phe
20 25 30

Arg Val Gly Cys Ser Ile Leu Thr Asn Asn Asp Val Ile Phe Thr Gly
35 40 45

Ala Asn Val Glu Asn Ala Ser Tyr Ser Asn Cys Ile Cys Ala Glu Arg
50 55 60

Ser Ala Met Ile Gln Val Leu Met Ala Gly His Arg Ser Gly Trp Lys
65 70 75 80

Cys Met Val Ile Cys Gly Asp Ser Glu Asp Gln Cys Val Ser Pro Cys
85 90 95

Gly Val Cys Arg Gln Phe Ile Asn Glu Phe Val Val Lys Asp Phe Pro
100 105 110

Ile Val Met Leu Asn Ser Thr Gly Ser Arg Ser Lys Val Met Thr Met
115 120 125

Gly Glu Leu Leu Pro Met Ala Phe Gly Pro Ser His Leu Asn
130 135 140

<210> 970
<211> 142
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 970

Met Asn Ile Glu Gln Gln Leu Tyr Asp Val Val Lys Gln Leu Ile Glu
1 5 10 15

Gln Arg Tyr Pro Asn Asp Trp Gly Gly Ala Ala Ala Ile Arg Val Glu
20 25 30

Asp Gly Thr Ile Tyr Thr Ser Val Ala Pro Asp Val Ile Asn Ala Ser
35 40 45

Thr Glu Leu Cys Met Glu Thr Gly Ala Ile Leu Glu Ala His Lys Phe
50 55 60

Gln Lys Lys Val Thr His Ser Ile Cys Leu Ala Arg Glu Asn Glu His
65 70 75 80

Ser Glu Leu Lys Val Leu Ser Pro Cys Gly Val Cys Gln Glu Arg Leu
85 90 95

Phe Tyr Trp Gly Pro Glu Val Gln Cys Ala Ile Thr Asn Ala Lys Gln
100 105 110

Asp Ile Ile Phe Lys Pro Leu Lys Glu Leu Gln Pro Tyr His Trp Thr
115 120 125

Glu Ala Tyr His Asp Glu Met Val Lys Glu Trp Ser Thr Arg
130 135 140

<210> 971
<211> 146
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 971

Met Ala Gln Glu Arg Pro Ser Cys Ala Val Glu Pro Glu His Val Gln
1 5 10 15

Arg Leu Leu Leu Ser Ser Arg Glu Ala Lys Lys Ser Ala Tyr Cys Pro
20 25 30

Tyr Ser Arg Phe Pro Val Gly Ala Ala Leu Leu Thr Gly Asp Gly Arg
35 40 45

Ile Phe Ser Gly Cys Asn Ile Glu Asn Ala Cys Tyr Pro Leu Gly Val
50 55 60

Cys Ala Glu Arg Thr Ala Ile Gln Lys Ala Ile Ser Glu Gly Tyr Lys
65 70 75 80

Asp Phe Arg Ala Ile Ala Ile Ser Ser Asp Leu Gln Glu Glu Phe Ile
85 90 95

Ser Pro Cys Gly Ala Cys Arg Gln Val Met Arg Glu Phe Gly Thr Asp
100 105 110

Trp Ala Val Tyr Met Thr Lys Pro Asp Gly Thr Phe Val Val Arg Thr
115 120 125

Val Gln Glu Leu Leu Pro Ala Ser Phe Gly Pro Glu Asp Leu Gln Lys
130 135 140

Ile Gln
145

<210> 972
<211> 146
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 972

Met Ala Gln Lys Arg Pro Ala Cys Thr Leu Lys Pro Glu Cys Val Gln
1 5 10 15

Gln Leu Leu Val Cys Ser Gln Glu Ala Lys Lys Ser Ala Tyr Cys Pro
20 25 30

Tyr Ser His Phe Pro Val Gly Ala Ala Leu Leu Thr Gln Glu Gly Arg
35 40 45

Ile Phe Lys Gly Cys Asn Ile Glu Asn Ala Cys Tyr Pro Leu Gly Ile
50 55 60

Cys Ala Glu Arg Thr Ala Ile Gln Lys Ala Val Ser Glu Gly Tyr Lys
65 70 75 80

Asp Phe Arg Ala Ile Ala Ile Ala Ser Asp Met Gln Asp Asp Phe Ile
85 90 95

Ser Pro Cys Gly Ala Cys Arg Gln Val Met Arg Glu Phe Gly Thr Asn
100 105 110

Trp Pro Val Tyr Met Thr Lys Pro Asp Gly Thr Tyr Ile Val Met Thr
115 120 125

Val Gln Glu Leu Leu Pro Ser Ser Phe Gly Pro Glu Asp Leu Gln Lys
130 135 140

Thr Gln
145

<210> 973
<211> 158
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 973

Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
1 5 10 15

Ile Ala Tyr Glu Glu Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro
20 25 30

Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
35 40 45

Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
50 55 60

Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
65 70 75 80

Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
85 90 95

Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val
100 105 110

Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
115 120 125

Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe
130 135 140

Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155

<210> 974
<211> 158
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 974

Met Thr Thr Thr Lys Ala Asn Leu Thr Glu Phe Glu Gln Gln Leu Val
1 5 10 15

Asp Lys Ala Ile Gly Ala Met Glu Asn Ala Tyr Cys Lys Tyr Ser Asn
20 25 30

Phe Lys Val Gly Ala Ala Leu Val Cys Asp Asp Gly Glu Ile Ile Ile
35 40 45

Gly Ala Asn His Glu Asn Ala Ser Tyr Gly Ala Thr Ile Cys Ala Glu
50 55 60

Arg Ser Ala Ile Val Thr Ala Leu Thr Lys Gly His Arg Lys Phe Lys
65 70 75 80

Tyr Ile Val Val Ala Thr Glu Leu Glu Ala Pro Cys Ser Pro Cys Gly
85 90 95

Val Cys Arg Gln Val Leu Ile Glu Phe Gly Asp Tyr Lys Val Ile Leu
100 105 110

Gly Ser Ser Thr Ser Asp Gln Ile Ile Glu Thr Thr Thr Tyr Glu Leu
115 120 125

Leu Pro Tyr Ala Phe Thr Pro Lys Ser Leu Asp Asp His Glu Lys Glu
130 135 140

Thr Glu Glu Arg Lys His His Asn Asp His Asn Asn Lys Glu
145 150 155

<210> 975
<211> 166
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 975

Met Ala Ala Asn Ser Leu Pro Gln Asp Ile Ser Asp Val Glu Leu Val
1 5 10 15

His Leu Ala Arg Ala Ala Met Lys Arg Ala His Cys Pro Tyr Ser Lys
20 25 30

Phe Pro Val Gly Ala Ala Leu Leu Thr Glu Ser Gly Glu Ile Val Gln
35 40 45

Gly Cys Asn Val Glu Asn Ala Ser Tyr Gly Gly Thr Ile Cys Ala Glu
50 55 60

Arg Ser Ala Ile Val Ser Ala Val Ser Gln Gly Tyr Thr Lys Phe Arg
65 70 75 80

Ala Ile Ala Val Val Thr Glu Leu Ser Glu Pro Ala Ser Pro Cys Gly
85 90 95

Leu Cys Arg Gln Phe Leu Val Glu Phe Gly Asp Tyr Lys Val Val Val
100 105 110

Gly Thr Ala Ser Asn Asn Lys Ile Leu Ile Thr Ser Thr Arg Ala Leu
115 120 125

Leu Pro Phe Ala Phe Thr Pro Glu Ser Leu Asp Thr Phe Glu Gln Glu
130 135 140

Lys Ala Ser Glu Ala Lys Gly Leu Lys Gln Asp Asp Ala Thr Glu His
145 150 155 160

Asn Val Thr Val Val Ser
165

<210> 976
<211> 190
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 976

Met Asn Pro Gln Ile Arg Asn Pro Met Lys Ala Met Tyr Pro Gly Thr
1 5 10 15

Phe Tyr Phe Gln Phe Lys Asn Leu Trp Glu Ala Asn Asp Arg Asn Glu
20 25 30

Thr Trp Leu Cys Phe Thr Val Glu Gly Ile Lys Arg Arg Ser Val Val
35 40 45

Ser Trp Lys Thr Gly Val Phe Arg Asn Gln Val Asp Ser Glu Thr His
50 55 60

Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys Asp Asp Ile Leu
65 70 75 80

Ser Pro Asn Thr Lys Tyr Gln Val Thr Trp Tyr Thr Ser Trp Ser Pro
85 90 95

Cys Pro Asp Cys Ala Gly Glu Val Ala Glu Phe Leu Ala Arg His Ser
100 105 110

Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Tyr Tyr Phe Gln Tyr
115 120 125

Pro Cys Tyr Gln Glu Gly Leu Arg Ser Leu Ser Gln Glu Gly Val Ala
130 135 140

Val Glu Ile Met Asp Tyr Glu Asp Phe Lys Tyr Cys Trp Glu Asn Phe
145 150 155 160

Val Tyr Asn Asp Asn Glu Pro Phe Lys Pro Trp Lys Gly Leu Lys Thr
165 170 175

Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ser Leu Gln
180 185 190

<210> 977
<211> 190
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 977

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Ala Met Tyr Pro His Ile
1 5 10 15

Phe Tyr Phe His Phe Lys Asn Leu Leu Lys Ala Cys Gly Arg Asn Glu
20 25 30

Ser Trp Leu Cys Phe Thr Met Glu Val Thr Lys His His Ser Ala Val
35 40 45

Phe Arg Lys Arg Gly Val Phe Arg Asn Gln Val Asp Pro Glu Thr His
50 55 60

Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys Asp Asp Ile Leu
65 70 75 80

Ser Pro Asn Thr Asn Tyr Glu Val Thr Trp Tyr Thr Ser Trp Ser Pro
85 90 95

Cys Pro Glu Cys Ala Gly Glu Val Ala Glu Phe Leu Ala Arg His Ser
100 105 110

Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Cys Tyr Phe Trp Asp
115 120 125

Thr Asp Tyr Gln Glu Gly Leu Cys Ser Leu Ser Gln Glu Gly Ala Ser
130 135 140

Val Lys Ile Met Gly Tyr Lys Asp Phe Val Ser Cys Trp Lys Asn Phe
145 150 155 160

Val Tyr Ser Asp Asp Glu Pro Phe Lys Pro Trp Lys Gly Leu Gln Thr
165 170 175

Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ile Leu Gln
180 185 190

<210> 978
<211> 193
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 978

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Met Asn Asp Ala Leu His Ile Gly Leu Pro Pro Phe Leu Val Gln Ala
1               5                  10                  15

Asn Asn Glu Pro Arg Val Leu Ala Ala Pro Glu Ala Arg Met Gly Tyr
            20                  25                  30

Val Leu Glu Leu Val Arg Ala Asn Ile Ala Ala Asp Gly Gly Pro Phe
        35                  40                  45

Ala Ala Ala Val Phe Glu Arg Asp Ser Gly Leu Leu Ile Ala Ala Gly
    50                  55                  60

Thr Asn Arg Val Val Pro Gly Arg Cys Ser Ala Ala His Ala Glu Ile
65                  70                  75                  80

Leu Ala Leu Ser Leu Ala Gln Ala Lys Leu Asp Thr His Asp Leu Ser
                85                  90                  95

Ala Asp Gly Leu Pro Ala Cys Glu Leu Val Thr Ser Ala Glu Pro Cys
            100                 105                 110

Val Met Cys Phe Gly Ala Val Ile Trp Ser Gly Val Arg Ser Leu Val
        115                 120                 125

Cys Ala Ala Arg Ser Asp Asp Val Glu Ala Ile Gly Phe Asp Glu Gly
    130                 135                 140

Pro Arg Pro Glu Asn Trp Met Gly Gly Leu Glu Ala Arg Gly Ile Thr
145                 150                 155                 160

Val Thr Thr Gly Leu Leu Arg Asp Ala Ala Cys Ala Leu Leu Arg Glu
                165                 170                 175
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Tyr Asn Ala Cys Asn Gly Val Ile Tyr Asn Ala Arg Cys Gly Val His
180 185 190

Lys

<210> 979
<211> 198
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 979

Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1 5 10 15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Tyr Val
20 25 30

Val Lys Arg Arg Asp Ser Ala Thr Ser Phe Ser Leu Asp Phe Gly Tyr
35 40 45

Leu Arg Asn Lys Asn Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
50 55 60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65 70 75 80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Asp
85 90 95

Phe Leu Arg Gly Asn Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
100 105 110

Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
115 120 125

Leu His Arg Ala Gly Val Gln Ile Ala Ile Met Thr Phe Lys Asp Tyr
130 135 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn His Glu Arg Thr Phe Lys
145 150 155 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln Leu
165 170 175

Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp Ala
180 185 190

Phe Arg Thr Leu Gly Leu
195

<210> 980
<211> 198
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 980

Met Asp Ser Leu Leu Met Lys Gln Lys Lys Phe Leu Tyr His Phe Lys
1 5 10 15

Asn Val Arg Trp Ala Lys Gly Arg His Glu Thr Tyr Leu Cys Tyr Val
20 25 30

Val Lys Arg Arg Asp Ser Ala Thr Ser Cys Ser Leu Asp Phe Gly His
35 40 45

Leu Arg Asn Lys Ser Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
50 55 60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65 70 75 80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Glu
85 90 95

Phe Leu Arg Trp Asn Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
100 105 110

Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
115 120 125

Leu His Arg Ala Gly Val Gln Ile Gly Ile Met Thr Phe Lys Asp Tyr
130 135 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn Arg Glu Arg Thr Phe Lys
145 150 155 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Thr Arg Gln Leu
165 170 175

Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp Ala
180 185 190

Phe Arg Met Leu Gly Phe
195

<210> 981
<211> 200
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 981

Met Ala Leu Leu Thr Ala Glu Thr Phe Arg Leu Gln Phe Asn Asn Lys
1 5 10 15

Arg Arg Leu Arg Arg Pro Tyr Tyr Pro Arg Lys Ala Leu Leu Cys Tyr
20 25 30

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Gln Leu Thr Pro Gln Asn Gly Ser Thr Pro Thr Arg Gly Tyr Phe Glu
        35                  40                  45

Asn Lys Lys Lys Cys His Ala Glu Ile Cys Phe Ile Asn Glu Ile Lys
    50                  55                  60

Ser Met Gly Leu Asp Glu Thr Gln Cys Tyr Gln Val Thr Cys Tyr Leu
65                  70                  75                  80

Thr Trp Ser Pro Cys Ser Ser Cys Ala Trp Glu Leu Val Asp Phe Ile
                85                  90                  95

Lys Ala His Asp His Leu Asn Leu Gly Ile Phe Ala Ser Arg Leu Tyr
            100                 105                 110

Tyr His Trp Cys Lys Pro Gln Gln Lys Gly Leu Arg Leu Leu Cys Gly
        115                 120                 125

Ser Gln Val Pro Val Glu Val Met Gly Phe Pro Lys Phe Ala Asp Cys
    130                 135                 140

Trp Glu Asn Phe Val Asp His Glu Lys Pro Leu Ser Phe Asn Pro Tyr
145                 150                 155                 160

Lys Met Leu Glu Glu Leu Asp Lys Asn Ser Arg Ala Ile Lys Arg Arg
                165                 170                 175

Leu Glu Arg Ile Lys Ile Pro Gly Val Arg Ala Gln Gly Arg Tyr Met
            180                 185                 190

Asp Ile Leu Cys Asp Ala Glu Val
        195                 200
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<210> 982
<211> 224
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 982

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Met Ala Gln Lys Glu Glu Ala Ala Val Ala Thr Glu Ala Ala Ser Gln
1               5                  10                  15

Asn Gly Glu Asp Leu Glu Asn Leu Asp Asp Pro Glu Lys Leu Lys Glu
            20                  25                  30

Leu Ile Glu Leu Pro Pro Phe Glu Ile Val Thr Gly Glu Arg Leu Pro
        35                  40                  45

Ala Asn Phe Phe Lys Phe Gln Phe Arg Asn Val Glu Tyr Ser Ser Gly
    50                  55                  60

Arg Asn Lys Thr Phe Leu Cys Tyr Val Val Glu Ala Gln Gly Lys Gly
65                  70                  75                  80

Gly Gln Val Gln Ala Ser Arg Gly Tyr Leu Glu Asp Glu His Ala Ala
                85                  90                  95

Ala His Ala Glu Glu Ala Phe Phe Asn Thr Ile Leu Pro Ala Phe Asp
            100                 105                 110

Pro Ala Leu Arg Tyr Asn Val Thr Trp Tyr Val Ser Ser Ser Pro Cys
        115                 120                 125

Ala Ala Cys Ala Asp Arg Ile Ile Lys Thr Leu Ser Lys Thr Lys Asn
    130                 135                 140

Leu Arg Leu Leu Ile Leu Val Gly Arg Leu Phe Met Trp Glu Glu Pro
145                 150                 155                 160

Glu Ile Gln Ala Ala Leu Lys Lys Leu Lys Glu Ala Gly Cys Lys Leu
                165                 170                 175

Arg Ile Met Lys Pro Gln Asp Phe Glu Tyr Val Trp Gln Asn Phe Val
            180                 185                 190
```

Glu Gln Glu Glu Gly Glu Ser Lys Ala Phe Gln Pro Trp Glu Asp Ile
195 200 205

Gln Glu Asn Phe Leu Tyr Tyr Glu Glu Lys Leu Ala Asp Ile Leu Lys
210 215 220

<210> 983
<211> 224
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 983

Met Ala Gln Lys Glu Glu Ala Ala Glu Ala Ala Ala Pro Ala Ser Gln
1 5 10 15

Asn Gly Asp Asp Leu Glu Asn Leu Glu Asp Pro Glu Lys Leu Lys Glu
20 25 30

Leu Ile Asp Leu Pro Pro Phe Glu Ile Val Thr Gly Val Arg Leu Pro
35 40 45

Val Asn Phe Phe Lys Phe Gln Phe Arg Asn Val Glu Tyr Ser Ser Gly
50 55 60

Arg Asn Lys Thr Phe Leu Cys Tyr Val Val Glu Val Gln Ser Lys Gly
65 70 75 80

Gly Gln Ala Gln Ala Thr Gln Gly Tyr Leu Glu Asp Glu His Ala Gly
85 90 95

Ala His Ala Glu Glu Ala Phe Phe Asn Thr Ile Leu Pro Ala Phe Asp
100 105 110

Pro Ala Leu Lys Tyr Asn Val Thr Trp Tyr Val Ser Ser Ser Pro Cys
115 120 125

Ala Ala Cys Ala Asp Arg Ile Leu Lys Thr Leu Ser Lys Thr Lys Asn
130 135 140

Leu Arg Leu Leu Ile Leu Val Ser Arg Leu Phe Met Trp Glu Glu Pro
145 150 155 160

Glu Val Gln Ala Ala Leu Lys Lys Leu Lys Glu Ala Gly Cys Lys Leu
165 170 175

Arg Ile Met Lys Pro Gln Asp Phe Glu Tyr Ile Trp Gln Asn Phe Val
180 185 190

Glu Gln Glu Glu Gly Glu Ser Lys Ala Phe Glu Pro Trp Glu Asp Ile
195 200 205

Gln Glu Asn Phe Leu Tyr Tyr Glu Glu Lys Leu Ala Asp Ile Leu Lys
210 215 220

<210> 984
<211> 229
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 984

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
35 40 45

Ser Val Trp Arg His Thr Ser Gln Asn Thr Ser Asn His Val Glu Val
50 55 60

Asn Phe Leu Glu Lys Phe Thr Thr Glu Arg Tyr Phe Arg Pro Asn Thr
65 70 75 80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
85 90 95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg His Pro Tyr Val Thr Leu
100 105 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Thr Asp Gln Arg Asn Arg
115 120 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
130 135 140

Thr Glu Gln Glu Tyr Cys Tyr Cys Trp Arg Asn Phe Val Asn Tyr Pro
145 150 155 160

Pro Ser Asn Glu Ala Tyr Trp Pro Arg Tyr Pro His Leu Trp Val Lys
165 170 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
180 185 190

Leu Lys Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
195 200 205

Thr Leu Gln Thr Cys His Tyr Gln Arg Ile Pro Pro His Leu Leu Trp
210 215 220

Ala Thr Gly Leu Lys
225

<210> 985
<211> 235
<212> PRT
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<220>
<223> 合成

<400> 985

```
Met Asn Ser Lys Thr Gly Pro Ser Val Gly Asp Ala Thr Leu Arg Arg
1               5                  10                  15

Arg Ile Lys Pro Trp Glu Phe Val Ala Phe Phe Asn Pro Gln Glu Leu
            20                  25                  30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Lys Trp Gly Asn Gln Asn
        35                  40                  45

Ile Trp Arg His Ser Asn Gln Asn Thr Ser Gln His Ala Glu Ile Asn
    50                  55                  60

Phe Met Glu Lys Phe Thr Ala Glu Arg His Phe Asn Ser Ser Val Arg
65                  70                  75                  80

Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys Ser
                85                  90                  95

Lys Ala Ile Arg Lys Phe Leu Asp His Tyr Pro Asn Val Thr Leu Ala
            100                 105                 110

Ile Phe Ile Ser Arg Leu Tyr Trp His Met Asp Gln Gln His Arg Gln
        115                 120                 125

Gly Leu Lys Glu Leu Val His Ser Gly Val Thr Ile Gln Ile Met Ser
    130                 135                 140

Tyr Ser Glu Tyr His Tyr Cys Trp Arg Asn Phe Val Asp Tyr Pro Gln
145                 150                 155                 160

Gly Glu Glu Asp Tyr Trp Pro Lys Tyr Pro Tyr Leu Trp Ile Met Leu
                165                 170                 175
```

Tyr Val Leu Glu Leu His Cys Ile Ile Leu Gly Leu Pro Pro Cys Leu
180 185 190

Lys Ile Ser Gly Ser His Ser Asn Gln Leu Ala Leu Phe Ser Leu Asp
195 200 205

Leu Gln Asp Cys His Tyr Gln Lys Ile Pro Tyr Asn Val Leu Val Ala
210 215 220

Thr Gly Leu Val Gln Pro Phe Val Thr Trp Arg
225 230 235

<210> 986
<211> 236
<212> PRT
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<220>
<223> 合成

<400> 986

Met Thr Ser Glu Lys Gly Pro Ser Thr Gly Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro Trp Glu Phe Asp Val Phe Tyr Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Ala Cys Leu Leu Tyr Glu Ile Lys Trp Gly Met Ser Arg
35 40 45

Lys Ile Trp Arg Ser Ser Gly Lys Asn Thr Thr Asn His Val Glu Val
50 55 60

Asn Phe Ile Lys Lys Phe Thr Ser Glu Arg Asp Phe His Pro Ser Met
65 70 75 80

Ser Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys
85 90 95

Ser Gln Ala Ile Arg Glu Phe Leu Ser Arg His Pro Gly Val Thr Leu
100 105 110

Val Ile Tyr Val Ala Arg Leu Phe Trp His Met Asp Gln Gln Asn Arg
115 120 125

Gln Gly Leu Arg Asp Leu Val Asn Ser Gly Val Thr Ile Gln Ile Met
130 135 140

Arg Ala Ser Glu Tyr Tyr His Cys Trp Arg Asn Phe Val Asn Tyr Pro
145 150 155 160

Pro Gly Asp Glu Ala His Trp Pro Gln Tyr Pro Pro Leu Trp Met Met
165 170 175

Leu Tyr Ala Leu Glu Leu His Cys Ile Ile Leu Ser Leu Pro Pro Cys
180 185 190

Leu Lys Ile Ser Arg Arg Trp Gln Asn His Leu Thr Phe Phe Arg Leu
195 200 205

His Leu Gln Asn Cys His Tyr Gln Thr Ile Pro Pro His Ile Leu Leu
210 215 220

Ala Thr Gly Leu Ile His Pro Ser Val Ala Trp Arg
225 230 235

<210> 987
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 987

Met Ala Ser Glu Lys Gly Pro Ser Asn Lys Asp Tyr Thr Leu Arg Arg
1 5 10 15

```
Arg Ile Glu Pro Trp Glu Phe Glu Val Phe Phe Asp Pro Gln Glu Leu
            20                  25                  30

Arg Lys Glu Ala Cys Leu Leu Tyr Glu Ile Lys Trp Gly Ala Ser Ser
        35                  40                  45

Lys Thr Trp Arg Ser Ser Gly Lys Asn Thr Thr Asn His Val Glu Val
    50                  55                  60

Asn Phe Leu Glu Lys Leu Thr Ser Glu Gly Arg Leu Gly Pro Ser Thr
65                  70                  75                  80

Cys Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys
                85                  90                  95

Ser Met Ala Ile Arg Glu Phe Leu Ser Gln His Pro Gly Val Thr Leu
            100                 105                 110

Ile Ile Phe Val Ala Arg Leu Phe Gln His Met Asp Arg Arg Asn Arg
        115                 120                 125

Gln Gly Leu Lys Asp Leu Val Thr Ser Gly Val Thr Val Arg Val Met
    130                 135                 140

Ser Val Ser Glu Tyr Cys Tyr Cys Trp Glu Asn Phe Val Asn Tyr Pro
145                 150                 155                 160

Pro Gly Lys Ala Ala Gln Trp Pro Arg Tyr Pro Pro Arg Trp Met Leu
                165                 170                 175

Met Tyr Ala Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
            180                 185                 190

Leu Lys Ile Ser Arg Arg His Gln Lys Gln Leu Thr Phe Phe Ser Leu
        195                 200                 205

Thr Pro Gln Tyr Cys His Tyr Lys Met Ile Pro Pro Tyr Ile Leu Leu
    210                 215                 220
```

Ala Thr Gly Leu Leu Gln Pro Ser Val Pro Trp Arg
225 230 235

<210> 988
<211> 278
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 988

Met Lys Val Ser Leu Ala Gly Gln Thr Val Asp Val Lys Lys Ile Leu
1 5 10 15

Asn Glu Ile Pro Lys Arg Thr Val Thr Ala Ala Leu Leu Glu Gly Gly
20 25 30

Glu Ile Val Ala Val Glu Glu Ala Asp Asp Glu His Ala Glu Arg Lys
35 40 45

Leu Val Arg Arg His Asp Val Glu Gly Lys Val Val Phe Val Thr Ala
50 55 60

Arg Pro Cys Leu Tyr Cys Ala Arg Glu Leu Ala Glu Ala Gly Val Ala
65 70 75 80

Gly Val Val Tyr Leu Gly Arg Gly Arg Gly Leu Gly Pro Tyr Tyr Leu
85 90 95

Ala Arg Ser Gly Val Glu Val Val Glu Val His Pro Asp Glu Pro Leu
100 105 110

Gly Tyr Asp Pro Val Asp Arg Leu Asp Val Leu Leu Thr Phe Gly Gly
115 120 125

Asn Pro Tyr Leu Thr Glu Glu Asp Val Ala Ala Arg Val Tyr Cys Leu
130 135 140

Leu Thr Gly Arg Gly Phe Asp Ala Asp Ile Ala Pro Ala Pro Glu Asn
145 150 155 160

Leu Ser Gly Arg Val Glu Ile Met Val Thr Arg Gly Asp Pro Asp Glu
165 170 175

Ala Val Glu Leu Leu Lys Glu Glu Leu Pro Val Phe Arg Ile Arg Arg
180 185 190

Phe Leu Ile Ser Gly Glu Phe Asp Arg Asp Glu Leu Arg Glu Arg Ile
195 200 205

Leu Glu Asp Ile Glu Pro Arg Ile Leu Asp Pro Phe Ala Val Arg Ala
210 215 220

Arg Ile Ala Arg Ala Gly Ala Phe Ser Ser Ser Arg Glu Ala Glu Val
225 230 235 240

Phe Ile Gly Asp Val Leu Thr Ser Val Gly Arg Glu Val Asn Leu Asn
245 250 255

Asp Pro Arg Thr Val Val Thr Val Asp Val Leu Gly Pro Arg Val Ser
260 265 270

Val Gly Val Glu Lys Arg
275

<210> 989
<211> 294
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 989

Met His Pro Arg Phe Gln Thr Ala Phe Ala Gln Leu Ala Asp Asn Leu
1 5 10 15

Gln Ser Ala Leu Glu Pro Ile Leu Ala Asp Lys Tyr Phe Pro Ala Leu
20 25 30

Leu Thr Gly Glu Gln Val Ser Ser Leu Lys Ser Ala Thr Gly Leu Asp
35 40 45

Glu Asp Ala Leu Ala Phe Ala Leu Leu Pro Leu Ala Ala Ala Cys Ala
50 55 60

Arg Thr Pro Leu Ser Asn Phe Asn Val Gly Ala Ile Ala Arg Gly Val
65 70 75 80

Ser Gly Thr Trp Tyr Phe Gly Ala Asn Met Glu Phe Ile Gly Ala Thr
85 90 95

Met Gln Gln Thr Val His Ala Glu Gln Ser Ala Ile Ser His Ala Trp
100 105 110

Leu Ser Gly Glu Lys Ala Leu Ala Ala Ile Thr Val Asn Tyr Thr Pro
115 120 125

Cys Gly His Cys Arg Gln Phe Met Asn Glu Leu Asn Ser Gly Leu Asp
130 135 140

Leu Arg Ile His Leu Pro Gly Arg Glu Ala His Ala Leu Arg Asp Tyr
145 150 155 160

Leu Pro Asp Ala Phe Gly Pro Lys Asp Leu Glu Ile Lys Thr Leu Leu
165 170 175

Met Asp Glu Gln Asp His Gly Tyr Ala Leu Thr Gly Asp Ala Leu Ser
180 185 190

Gln Ala Ala Ile Ala Ala Ala Asn Arg Ser His Met Pro Tyr Ser Lys
195 200 205

Ser Pro Ser Gly Val Ala Leu Glu Cys Lys Asp Gly Arg Ile Phe Ser
210 215 220

Gly Ser Tyr Ala Glu Asn Ala Ala Phe Asn Pro Thr Leu Pro Pro Leu
225 230 235 240

Gln Gly Ala Leu Ile Leu Leu Asn Leu Lys Gly Tyr Asp Tyr Pro Asp
245 250 255

Ile Gln Arg Ala Val Leu Ala Glu Lys Ala Asp Ala Pro Leu Ile Gln
260 265 270

Trp Asp Ala Thr Ser Ala Thr Leu Lys Ala Leu Gly Cys His Ser Ile
275 280 285

Asp Arg Val Leu Leu Ala
290

<210> 990
<211> 295
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 990

Met Arg Asn Arg Ile Glu Gln Ala Leu Gln Gln Met Pro Ala Ser Phe
1 5 10 15

Ala Pro Tyr Leu Arg Glu Leu Val Leu Ala Lys Asp Phe Asp Ala Thr
20 25 30

Phe Ser Ala Glu Gln Tyr Gln Gln Leu Leu Thr Leu Ser Gly Leu Glu
35 40 45

Asp Ala Asp Leu Arg Val Ala Leu Leu Pro Ile Ala Ala Ala Tyr Ser
50 55 60

Tyr Ala Pro Ile Ser Glu Phe Tyr Val Gly Ala Ile Val Arg Gly Ile
65 70 75 80

Ser Gly Arg Leu Tyr Leu Gly Ala Asn Met Glu Phe Thr Gly Ala Gln
85 90 95

Leu Gly Gln Thr Val His Ala Glu Gln Cys Ala Ile Ser His Ala Trp
100 105 110

Met Lys Gly Glu Lys Gly Val Ala Asp Ile Thr Ile Asn Phe Ser Pro
115 120 125

Cys Gly His Cys Arg Gln Phe Met Asn Glu Leu Thr Thr Ala Ser Ser
130 135 140

Leu Lys Ile Gln Leu Pro Lys Arg Ala Ala Lys Thr Leu Gln Glu Tyr
145 150 155 160

Leu Pro Glu Ser Phe Gly Pro Ala Asp Leu Gly Ile Asp Ser Gly Leu
165 170 175

Met Ser Pro Val Asn His Gly Lys Thr Ser Asp Asp Asp Glu Glu Leu
180 185 190

Ile Gln Gln Ala Leu Arg Ala Met Asn Ile Ser His Ser Pro Tyr Thr
195 200 205

Gln Asn Phe Ser Gly Val Ala Leu Lys Met Arg Ser Gly Ala Ile Tyr
210 215 220

Leu Gly Ala Tyr Ala Glu Asn Ala Ala Phe Asn Pro Ser Leu Pro Pro
225 230 235 240

Leu Gln Val Ala Leu Ala Gln Ala Met Met Met Gly Glu Ser Phe Glu
245 250 255

Asp Ile Glu Ala Ala Ala Leu Val Glu Ser Ala Thr Gly Lys Ile Ser
260 265 270

His Leu Ala Asp Thr Gln Ala Thr Leu Glu Val Ile Asn Pro Asp Ile
275 280 285

Pro Leu Ser Tyr Leu Ser Leu
290 295

<210> 991
<211> 297
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 991

Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile Val Arg Phe
1 5 10 15

Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser Ser Arg Leu
20 25 30

Tyr Asn Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys Arg Leu Val
35 40 45

Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu Phe Lys Lys
50 55 60

Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe Arg Pro Trp
65 70 75 80

Lys Arg Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys Leu Gln Glu
85 90 95

Ile Leu Arg Arg Met Asp Pro Leu Ser Glu Glu Glu Phe Tyr Ser Gln
100 105 110

Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr His Arg Met Lys
115 120 125

Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly Gln Ala Pro Leu
130 135 140

Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His Ala Glu Ile Leu
145 150 155 160

Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln Val Thr Ile Thr
165 170 175

Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala Trp Gln Leu Ala
180 185 190

Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His Ile Tyr Thr Ser
195 200 205

Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys Gly Leu Cys Ser
210 215 220

Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp Leu Pro Gln Phe
225 230 235 240

Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg Pro Phe Trp Pro
245 250 255

Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln Arg Arg Leu Arg
260 265 270

Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val Asn Asp Phe Gly
275 280 285

Asn Leu Gln Leu Gly Pro Pro Met Ser
290 295

<210> 992
<211> 301
<212> PRT
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<223> 合成

<400> 992

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Met Asp Lys Pro Ser Phe Val Ile Gln Ser Lys Glu Ala Glu Ser Ala
1               5                  10                  15

Ala Lys Gln Leu Gly Val Ser Val Ile Gln Leu Leu Pro Ser Leu Val
            20                  25                  30

Lys Pro Ala Gln Ser Tyr Ala Arg Thr Pro Ile Ser Lys Phe Asn Val
        35                  40                  45

Ala Val Val Gly Leu Gly Ser Ser Gly Arg Ile Phe Leu Gly Val Asn
    50                  55                  60

Val Glu Phe Pro Asn Leu Pro Leu His His Ser Ile His Ala Glu Gln
65                  70                  75                  80

Phe Leu Val Thr Asn Leu Thr Leu Asn Gly Glu Arg His Leu Asn Phe
                85                  90                  95

Phe Ala Val Ser Ala Ala Pro Cys Gly His Cys Arg Gln Phe Leu Gln
            100                 105                 110

Glu Ile Arg Asp Ala Pro Glu Ile Lys Ile Leu Ile Thr Asp Pro Asn
        115                 120                 125

Asn Ser Ala Asp Ser Asp Ser Ala Ala Asp Ser Asp Gly Phe Leu Arg
    130                 135                 140

Leu Gly Ser Phe Leu Pro His Arg Phe Gly Pro Asp Asp Leu Leu Gly
145                 150                 155                 160

Lys Asp His Pro Leu Leu Leu Glu Ser His Asp Asn His Leu Lys Ile
                165                 170                 175
```

Ser Asp Leu Asp Ser Ile Cys Asn Gly Asn Thr Asp Ser Ser Ala Asp
180 185 190

Leu Lys Gln Thr Ala Leu Ala Ala Ala Asn Arg Ser Tyr Ala Pro Tyr
195 200 205

Ser Leu Cys Pro Ser Gly Val Ser Leu Val Asp Cys Asp Gly Lys Val
210 215 220

Tyr Arg Gly Trp Tyr Met Glu Ser Ala Ala Tyr Asn Pro Ser Met Gly
225 230 235 240

Pro Val Gln Ala Ala Leu Val Asp Tyr Val Ala Asn Gly Gly Gly Gly
245 250 255

Gly Tyr Glu Arg Ile Val Gly Ala Val Leu Val Glu Lys Glu Asp Ala
260 265 270

Val Val Arg Gln Glu His Thr Ala Arg Leu Leu Leu Glu Thr Ile Ser
275 280 285

Pro Lys Cys Glu Phe Lys Val Phe His Cys Tyr Glu Ala
290 295 300

<210> 993
<211> 370
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 993

Met Val Glu Pro Met Asp Pro Arg Thr Phe Val Ser Asn Phe Asn Asn
1 5 10 15

Arg Pro Ile Leu Ser Gly Leu Asn Thr Val Trp Leu Cys Cys Glu Val
20 25 30

Lys Thr Lys Asp Pro Ser Gly Pro Pro Leu Asp Ala Lys Ile Phe Gln
35 40 45

Gly Lys Val Tyr Ser Lys Ala Lys Tyr His Pro Glu Met Arg Phe Leu
50 55 60

Arg Trp Phe His Lys Trp Arg Gln Leu His His Asp Gln Glu Tyr Lys
65 70 75 80

Val Thr Trp Tyr Val Ser Trp Ser Pro Cys Thr Arg Cys Ala Asn Ser
85 90 95

Val Ala Thr Phe Leu Ala Lys Asp Pro Lys Val Thr Leu Thr Ile Phe
100 105 110

Val Ala Arg Leu Tyr Tyr Phe Trp Lys Pro Asp Tyr Gln Gln Ala Leu
115 120 125

Arg Ile Leu Cys Gln Lys Arg Gly Gly Pro His Ala Thr Met Lys Ile
130 135 140

Met Asn Tyr Asn Glu Phe Gln Asp Cys Trp Asn Lys Phe Val Asp Gly
145 150 155 160

Arg Gly Lys Pro Phe Lys Pro Arg Asn Asn Leu Pro Lys His Tyr Thr
165 170 175

Leu Leu Gln Ala Thr Leu Gly Glu Leu Leu Arg His Leu Met Asp Pro
180 185 190

Gly Thr Phe Thr Ser Asn Phe Asn Asn Lys Pro Trp Val Ser Gly Gln
195 200 205

His Glu Thr Tyr Leu Cys Tyr Lys Val Glu Arg Leu His Asn Asp Thr
210 215 220

Trp Val Pro Leu Asn Gln His Arg Gly Phe Leu Arg Asn Gln Ala Pro
225 230 235 240

Asn Ile His Gly Phe Pro Lys Gly Arg His Ala Glu Leu Cys Phe Leu
245 250 255

Asp Leu Ile Pro Phe Trp Lys Leu Asp Gly Gln Gln Tyr Arg Val Thr
260 265 270

Cys Phe Thr Ser Trp Ser Pro Cys Phe Ser Cys Ala Gln Glu Met Ala
275 280 285

Lys Phe Ile Ser Asn Asn Glu His Val Ser Leu Cys Ile Phe Ala Ala
290 295 300

Arg Ile Tyr Asp Asp Gln Gly Arg Tyr Gln Glu Gly Leu Arg Ala Leu
305 310 315 320

His Arg Asp Gly Ala Lys Ile Ala Met Met Asn Tyr Ser Glu Phe Glu
325 330 335

Tyr Cys Trp Asp Thr Phe Val Asp Arg Gln Gly Arg Pro Phe Gln Pro
340 345 350

Trp Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg
355 360 365

Ala Ile
370

<210> 994
<211> 373
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 994

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

```
Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Arg
        35                  40                  45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Gln Pro Glu His
    50                  55                  60

His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu Pro
65                  70                  75                  80

Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro Cys
                85                  90                  95

Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ala Glu His Pro Asn
            100                 105                 110

Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu Arg
        115                 120                 125

Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg Val
    130                 135                 140

Lys Ile Met Asp Asp Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe Val
145                 150                 155                 160

Tyr Ser Glu Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn
                165                 170                 175

Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met
            180                 185                 190

Glu Ala Met Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Arg
        195                 200                 205
```

```
Lys Ala Tyr Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val
    210                 215                 220

Val Lys His His Ser Pro Val Ser Trp Lys Arg Gly Val Phe Arg Asn
225                 230                 235                 240

Gln Val Asp Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser
                245                 250                 255

Trp Phe Cys Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr
            260                 265                 270

Trp Tyr Thr Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala
        275                 280                 285

Glu Phe Leu Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala
    290                 295                 300

Arg Leu Tyr Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Arg Ser
305                 310                 315                 320

Leu Ser Gln Glu Gly Ala Ser Val Glu Ile Met Gly Tyr Lys Asp Phe
                325                 330                 335

Lys Tyr Cys Trp Glu Asn Phe Val Tyr Asn Asp Asp Glu Pro Phe Lys
            340                 345                 350

Pro Trp Lys Gly Leu Lys Tyr Asn Phe Leu Phe Leu Asp Ser Lys Leu
        355                 360                 365

Gln Glu Ile Leu Glu
    370
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<210> 995
<211> 377
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 995

```
Met Asn Pro Gln Ile Arg Asn Met Val Glu Gln Met Glu Pro Asp Ile
1               5                  10                  15

Phe Val Tyr Tyr Phe Asn Asn Arg Pro Ile Leu Ser Gly Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Asp Pro Ser Gly Pro Pro
        35                  40                  45

Leu Asp Ala Asn Ile Phe Gln Gly Lys Leu Tyr Pro Glu Ala Lys Asp
    50                  55                  60

His Pro Glu Met Lys Phe Leu His Trp Phe Arg Lys Trp Arg Gln Leu
65                  70                  75                  80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Val Ser Trp Ser Pro
                85                  90                  95

Cys Thr Arg Cys Ala Asn Ser Val Ala Thr Phe Leu Ala Glu Asp Pro
            100                 105                 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Lys
        115                 120                 125

Pro Asp Tyr Gln Gln Ala Leu Arg Ile Leu Cys Gln Glu Arg Gly Gly
    130                 135                 140

Pro His Ala Thr Met Lys Ile Met Asn Tyr Asn Glu Phe Gln His Cys
145                 150                 155                 160

Trp Asn Glu Phe Val Asp Gly Gln Gly Lys Pro Phe Lys Pro Arg Lys
                165                 170                 175

Asn Leu Pro Lys His Tyr Thr Leu Leu His Ala Thr Leu Gly Glu Leu
            180                 185                 190
```

Leu Arg His Val Met Asp Pro Gly Thr Phe Thr Ser Asn Phe Asn Asn
195 200 205

Lys Pro Trp Val Ser Gly Gln Arg Glu Thr Tyr Leu Cys Tyr Lys Val
210 215 220

Glu Arg Ser His Asn Asp Thr Trp Val Leu Leu Asn Gln His Arg Gly
225 230 235 240

Phe Leu Arg Asn Gln Ala Pro Asp Arg His Gly Phe Pro Lys Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Leu Ile Pro Phe Trp Lys Leu Asp
260 265 270

Asp Gln Gln Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys Phe
275 280 285

Ser Cys Ala Gln Lys Met Ala Lys Phe Ile Ser Asn Asn Lys His Val
290 295 300

Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg Cys
305 310 315 320

Gln Glu Gly Leu Arg Thr Leu His Arg Asp Gly Ala Lys Ile Ala Val
325 330 335

Met Asn Tyr Ser Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Asp Arg
340 345 350

Gln Gly Arg Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln
355 360 365

Ala Leu Ser Gly Arg Leu Arg Ala Ile
370 375

<210> 996
<211> 382
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 996

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
20 25 30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
35 40 45

Leu Trp Asp Thr Gly Val Phe Arg Gly Gln Val Tyr Phe Lys Pro Gln
50 55 60

Tyr His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu
65 70 75 80

Pro Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro
85 90 95

Cys Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ser Glu His Pro
100 105 110

Asn Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu
115 120 125

Arg Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg
130 135 140

Val Thr Ile Met Asp Tyr Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe
145 150 155 160

Val Tyr Asn Glu Gly Gln Gln Phe Met Pro Trp Tyr Lys Phe Asp Glu
165 170 175

Asn Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Tyr Leu
180 185 190

Met Asp Pro Asp Thr Phe Thr Phe Asn Phe Asn Asn Asp Pro Leu Val
195 200 205

Leu Arg Arg Arg Gln Thr Tyr Leu Cys Tyr Glu Val Glu Arg Leu Asp
210 215 220

Asn Gly Thr Trp Val Leu Met Asp Gln His Met Gly Phe Leu Cys Asn
225 230 235 240

Glu Ala Lys Asn Leu Leu Cys Gly Phe Tyr Gly Arg His Ala Glu Leu
245 250 255

Arg Phe Leu Asp Leu Val Pro Ser Leu Gln Leu Asp Pro Ala Gln Ile
260 265 270

Tyr Arg Val Thr Trp Phe Ile Ser Trp Ser Pro Cys Phe Ser Trp Gly
275 280 285

Cys Ala Gly Glu Val Arg Ala Phe Leu Gln Glu Asn Thr His Val Arg
290 295 300

Leu Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys
305 310 315 320

Glu Ala Leu Gln Met Leu Arg Asp Ala Gly Ala Gln Val Ser Ile Met
325 330 335

Thr Tyr Asp Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Tyr Arg Gln
340 345 350

Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser Gln Ala
355 360 365

Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
370 375 380

<210> 997
<211> 383
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 997

Met Lys Pro Gln Ile Arg Asn Met Val Glu Pro Met Asp Pro Arg Thr
1 5 10 15

Phe Val Ser Asn Phe Asn Asn Arg Pro Ile Leu Ser Gly Leu Asp Thr
20 25 30

Val Trp Leu Cys Cys Glu Val Lys Thr Lys Asp Pro Ser Gly Pro Pro
35 40 45

Leu Asp Ala Lys Ile Phe Gln Gly Lys Val Tyr Pro Lys Ala Lys Tyr
50 55 60

His Pro Glu Met Arg Phe Leu Arg Trp Phe His Lys Trp Arg Gln Leu
65 70 75 80

His His Asp Gln Glu Tyr Lys Val Thr Trp Tyr Val Ser Trp Ser Pro
85 90 95

Cys Thr Arg Cys Ala Asn Ser Val Ala Thr Phe Leu Ala Lys Asp Pro
100 105 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Lys
115 120 125

Pro Asp Tyr Gln Gln Ala Leu Arg Ile Leu Cys Gln Lys Arg Asp Gly
130 135 140

Pro His Ala Thr Met Lys Ile Met Asn Tyr Asn Glu Phe Gln Asp Cys
145 150 155 160

Trp Asn Lys Phe Val Asp Gly Arg Gly Lys Pro Phe Lys Pro Trp Asn
165 170 175

Asn Leu Pro Lys His Tyr Thr Leu Leu Gln Ala Thr Leu Gly Glu Leu
180 185 190

Leu Arg His Leu Met Asp Pro Gly Thr Phe Thr Ser Asn Phe Asn Asn
195 200 205

Lys Pro Trp Val Ser Gly Gln His Glu Thr Tyr Leu Cys Tyr Lys Val
210 215 220

Glu Arg Leu His Asn Asp Thr Trp Val Pro Leu Asn Gln His Arg Gly
225 230 235 240

Phe Leu Arg Asn Gln Ala Pro Asn Ile His Gly Phe Pro Lys Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Leu Ile Pro Phe Trp Lys Leu Asp
260 265 270

Gly Gln Gln Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys Phe
275 280 285

Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Asn Asn Glu His Val
290 295 300

Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg Tyr
305 310 315 320

Gln Glu Gly Leu Arg Thr Leu His Arg Asp Gly Ala Lys Ile Ala Met
325 330 335

Met Asn Tyr Ser Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Asp Arg
340 345 350

Gln Gly Arg Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln
355 360 365

Ala Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
370 375 380

<210> 998
<211> 384
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 998

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
20 25 30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
35 40 45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Glu Leu Lys Tyr
50 55 60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65 70 75 80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
85 90 95

Cys Thr Lys Cys Thr Arg Asp Met Ala Thr Phe Leu Ala Glu Asp Pro
100 105 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
115 120 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
130 135 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145 150 155 160

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
165 170 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
180 185 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Phe Asn Phe Asn Asn
195 200 205

Glu Pro Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
210 215 220

Glu Arg Met His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225 230 235 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
260 265 270

Leu Asp Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
275 280 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Lys Asn Lys His
290 295 300

Val Ser Leu Cys Ile Phe Thr Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305 310 315 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Glu Ala Gly Ala Lys Ile Ser
325 330 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
340 345 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser
355 360 365

Gln Asp Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Glu Asn
370 375 380

<210> 999
<211> 384
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 999

Met Lys Pro His Phe Arg Asn Pro Val Glu Arg Met Tyr Gln Asp Thr
1 5 10 15

Phe Ser Asp Asn Phe Tyr Asn Arg Pro Ile Leu Ser His Arg Asn Thr
20 25 30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
35 40 45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Lys Leu Lys Tyr
50 55 60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65 70 75 80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
85 90 95

Cys Thr Lys Cys Thr Arg Asp Val Ala Thr Phe Leu Ala Glu Asp Pro
100 105 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
115 120 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
130 135 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145 150 155 160

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
165 170 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
180 185 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Ser Asn Phe Asn Asn
195 200 205

Glu Leu Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
210 215 220

Glu Arg Leu His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225 230 235 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
260 265 270

Leu His Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
275 280 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Asn Asn Lys His
290 295 300

Val Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305 310 315 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Lys Ala Gly Ala Lys Ile Ser
325 330 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
340 345 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser
355 360 365

Gln Ala Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
370 375 380

<210> 1000
<211> 386
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1000

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
20 25 30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
35 40 45

Leu Trp Asp Thr Gly Val Phe Arg Gly Pro Val Leu Pro Lys Arg Gln
50 55 60

Ser Asn His Arg Gln Glu Val Tyr Phe Arg Phe Glu Asn His Ala Glu
65 70 75 80

Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Arg Leu Pro Ala Asn Arg
85 90 95

Arg Phe Gln Ile Thr Trp Phe Val Ser Trp Asn Pro Cys Leu Pro Cys
100 105 110

Val Val Lys Val Thr Lys Phe Leu Ala Glu His Pro Asn Val Thr Leu
115 120 125

Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Arg Asp Arg Asp Trp Arg
130 135 140

Trp Val Leu Leu Arg Leu His Lys Ala Gly Ala Arg Val Lys Ile Met
145 150 155 160

Asp Tyr Glu Asp Phe Ala Tyr Cys Trp Glu Asn Phe Val Cys Asn Glu
165 170 175

Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn Tyr Ala Ser
180 185 190

Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met Glu Ala Met
195 200 205

Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Leu Lys Ala Cys
210 215 220

Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val Thr Lys His
225 230 235 240

His Ser Ala Val Phe Arg Lys Arg Gly Val Phe Arg Asn Gln Val Asp
245 250 255

Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys
260 265 270

Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr Trp Tyr Thr
275 280 285

Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala Glu Phe Leu
290 295 300

Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Cys
305 310 315 320

Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Cys Ser Leu Ser Gln
325 330 335

Glu Gly Ala Ser Val Lys Ile Met Gly Tyr Lys Asp Phe Val Ser Cys
340 345 350

Trp Lys Asn Phe Val Tyr Ser Asp Asp Glu Pro Phe Lys Pro Trp Lys
355 360 365

Gly Leu Gln Thr Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ile
370 375 380

Leu Gln
385

<210> 1001
<211> 392
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1001

Met Gln Pro Gln Arg Leu Gly Pro Arg Ala Gly Met Gly Pro Phe Cys
1 5 10 15

Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro Ile Arg Asn Leu Ile
20 25 30

Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn Leu Gly Tyr Ala Lys
35 40 45

Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val Thr Arg Lys Asp Cys
50 55 60

Asp Ser Pro Val Ser Leu His His Gly Val Phe Lys Asn Lys Asp Asn
65 70 75 80

Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe His Asp Lys Val Leu
85 90 95

Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile Thr Trp Tyr Met Ser
100 105 110

Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile Val Arg Phe Leu Ala
115 120 125

Thr His His Asn Leu Ser Leu Asp Ile Phe Ser Ser Arg Leu Tyr Asn
130 135 140

Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys Arg Leu Val Gln Glu
145 150 155 160

Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu Phe Lys Lys Cys Trp
165 170 175

Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe Arg Pro Trp Lys Arg
180 185 190

Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys Leu Gln Glu Ile Leu
195 200 205

Arg Arg Met Asp Pro Leu Ser Glu Glu Glu Phe Tyr Ser Gln Phe Tyr
210 215 220

```
Asn Gln Arg Val Lys His Leu Cys Tyr Tyr His Arg Met Lys Pro Tyr
225                 230                 235                 240

Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly Gln Ala Pro Leu Lys Gly
                245                 250                 255

Cys Leu Leu Ser Glu Lys Gly Lys Gln His Ala Glu Ile Leu Phe Leu
            260                 265                 270

Asp Lys Ile Arg Ser Met Glu Leu Ser Gln Val Thr Ile Thr Cys Tyr
        275                 280                 285

Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala Trp Gln Leu Ala Ala Phe
    290                 295                 300

Lys Arg Asp Arg Pro Asp Leu Ile Leu His Ile Tyr Thr Ser Arg Leu
305                 310                 315                 320

Tyr Phe His Trp Lys Arg Pro Phe Gln Lys Gly Leu Cys Ser Leu Trp
                325                 330                 335

Gln Ser Gly Ile Leu Val Asp Val Met Asp Leu Pro Gln Phe Thr Asp
            340                 345                 350

Cys Trp Thr Asn Phe Val Asn Pro Lys Arg Pro Phe Trp Pro Trp Lys
        355                 360                 365

Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln Arg Arg Leu Arg Arg Ile
    370                 375                 380

Lys Glu Ser Arg Ser His Ala Ser
385                 390
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<210> 1002
<211> 407
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 1002

Met Gln Pro Gln Arg Leu Gly Pro Arg Ala Gly Met Gly Pro Phe Cys
1 5 10 15

Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro Ile Arg Asn Leu Ile
20 25 30

Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn Leu Gly Tyr Ala Lys
35 40 45

Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val Thr Arg Lys Asp Cys
50 55 60

Asp Ser Pro Val Ser Leu His His Gly Val Phe Lys Asn Lys Asp Asn
65 70 75 80

Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe His Asp Lys Val Leu
85 90 95

Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile Thr Trp Tyr Met Ser
100 105 110

Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile Val Arg Phe Leu Ala
115 120 125

Thr His His Asn Leu Ser Leu Asp Ile Phe Ser Ser Arg Leu Tyr Asn
130 135 140

Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys Arg Leu Val Gln Glu
145 150 155 160

Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu Phe Lys Lys Cys Trp
165 170 175

Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe Arg Pro Trp Lys Arg
180 185 190

Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys Leu Gln Glu Ile Leu
195 200 205

Arg Arg Met Asp Pro Leu Ser Glu Glu Glu Phe Tyr Ser Gln Phe Tyr
210 215 220

Asn Gln Arg Val Lys His Leu Cys Tyr Tyr His Arg Met Lys Pro Tyr
225 230 235 240

Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly Gln Ala Pro Leu Lys Gly
245 250 255

Cys Leu Leu Ser Glu Lys Gly Lys Gln His Ala Glu Ile Leu Phe Leu
260 265 270

Asp Lys Ile Arg Ser Met Glu Leu Ser Gln Val Thr Ile Thr Cys Tyr
275 280 285

Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala Trp Gln Leu Ala Ala Phe
290 295 300

Lys Arg Asp Arg Pro Asp Leu Ile Leu His Ile Tyr Thr Ser Arg Leu
305 310 315 320

Tyr Phe His Trp Lys Arg Pro Phe Gln Lys Gly Leu Cys Ser Leu Trp
325 330 335

Gln Ser Gly Ile Leu Val Asp Val Met Asp Leu Pro Gln Phe Thr Asp
340 345 350

Cys Trp Thr Asn Phe Val Asn Pro Lys Arg Pro Phe Trp Pro Trp Lys
355 360 365

Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln Arg Arg Leu Arg Arg Ile
370 375 380

Lys Glu Ser Trp Gly Leu Gln Asp Leu Val Asn Asp Phe Gly Asn Leu
385 390 395 400

Gln Leu Gly Pro Pro Met Ser
405

<210> 1003
<211> 429
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1003

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1 5 10 15

Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
20 25 30

Leu Gly Tyr Ala Lys Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
35 40 45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
50 55 60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65 70 75 80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
85 90 95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile
100 105 110

Val Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
115 120 125

Ser Arg Leu Tyr Asn Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys
130 135 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145 150 155 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
165 170 175

Arg Pro Trp Lys Arg Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
180 185 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Ser Val Pro Ser Ser Ser
195 200 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
210 215 220

Arg Phe Trp Val Glu Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu
225 230 235 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
245 250 255

His Arg Met Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
260 265 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
275 280 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
290 295 300

Val Thr Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305 310 315 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
325 330 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
340 345 350

Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
355 360 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
370 375 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385 390 395 400

Arg Arg Leu Arg Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
405 410 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
420 425

<210> 1004
<211> 429
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1004

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1 5 10 15

Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
20 25 30

Leu Gly Tyr Ala Lys Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
35 40 45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
50 55 60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65 70 75 80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
85 90 95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile
100 105 110

Val Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
115 120 125

Ser Arg Leu Tyr Asn Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys
130 135 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145 150 155 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
165 170 175

Arg Pro Trp Lys Arg Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
180 185 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Pro Val Pro Ser Ser Ser
195 200 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
210 215 220

Arg Phe Cys Val Glu Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu
225 230 235 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
245 250 255

```
His Arg Met Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
            260                 265                 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
        275                 280                 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
    290                 295                 300

Val Thr Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305                 310                 315                 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
                325                 330                 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
            340                 345                 350

Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
        355                 360                 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
    370                 375                 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385                 390                 395                 400

Arg Arg Leu Arg Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
                405                 410                 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
            420                 425
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<210> 1005
<211> 430
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 1005

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Met Gln Pro Gln Arg Leu Gly Pro Arg Ala Gly Met Gly Pro Phe Cys
1               5                  10                  15

Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro Ile Arg Asn Leu Ile
            20                  25                  30

Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn Leu Gly Tyr Ala Lys
        35                  40                  45

Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val Thr Arg Lys Asp Cys
    50                  55                  60

Asp Ser Pro Val Ser Leu His His Gly Val Phe Lys Asn Lys Asp Asn
65                  70                  75                  80

Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe His Asp Lys Val Leu
                85                  90                  95

Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile Thr Trp Tyr Met Ser
            100                 105                 110

Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile Val Arg Phe Leu Ala
        115                 120                 125

Thr His His Asn Leu Ser Leu Asp Ile Phe Ser Ser Arg Leu Tyr Asn
    130                 135                 140

Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys Arg Leu Val Gln Glu
145                 150                 155                 160

Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu Phe Lys Lys Cys Trp
                165                 170                 175

Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe Arg Pro Trp Lys Arg
            180                 185                 190
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Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys Leu Gln Glu Ile Leu
        195                 200                 205

Arg Pro Cys Tyr Ile Ser Val Pro Ser Ser Ser Ser Ser Thr Leu Ser
    210                 215                 220

Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr Arg Phe Trp Val Glu
225                 230                 235                 240

Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu Phe Tyr Ser Gln Phe
                245                 250                 255

Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr His Arg Met Lys Pro
            260                 265                 270

Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly Gln Ala Pro Leu Lys
        275                 280                 285

Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His Ala Glu Ile Leu Phe
    290                 295                 300

Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln Val Thr Ile Thr Cys
305                 310                 315                 320

Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala Trp Gln Leu Ala Ala
                325                 330                 335

Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His Ile Tyr Thr Ser Arg
            340                 345                 350

Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys Gly Leu Cys Ser Leu
        355                 360                 365

Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp Leu Pro Gln Phe Thr
    370                 375                 380
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Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg Pro Phe Trp Pro Trp
385 390 395 400

Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln Arg Arg Leu Arg Arg
405 410 415

Ile Lys Glu Val Arg Thr Thr Leu Leu Gln Gly Pro Ala Ser
420 425 430

<210> 1006
<211> 440
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1006

Met Gln Pro Gln Arg Leu Gly Pro Arg Ala Gly Met Gly Pro Phe Cys
1 5 10 15

Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro Ile Arg Asn Leu Ile
20 25 30

Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn Leu Gly Tyr Ala Lys
35 40 45

Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val Thr Arg Lys Asp Cys
50 55 60

Asp Ser Pro Val Ser Leu His His Gly Val Phe Lys Asn Lys Asp Asn
65 70 75 80

Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe His Asp Lys Val Leu
85 90 95

Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile Thr Trp Tyr Met Ser
100 105 110

Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile Val Arg Phe Leu Ala
115 120 125

Thr His His Asn Leu Ser Leu Asp Ile Phe Ser Ser Arg Leu Tyr Asn
130 135 140

Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys Arg Leu Val Gln Glu
145 150 155 160

Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu Phe Lys Lys Cys Trp
165 170 175

Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe Arg Pro Trp Lys Arg
180 185 190

Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys Leu Gln Glu Ile Leu
195 200 205

Arg Pro Cys Tyr Ile Ser Val Pro Ser Ser Ser Ser Ser Thr Leu Ser
210 215 220

Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr Arg Phe Trp Val Glu
225 230 235 240

Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu Phe Tyr Ser Gln Phe
245 250 255

Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr His Arg Met Lys Pro
260 265 270

Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly Gln Ala Pro Leu Lys
275 280 285

Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His Ala Glu Ile Leu Phe
290 295 300

Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln Val Thr Ile Thr Cys
305 310 315 320

Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala Trp Gln Leu Ala Ala
325 330 335

Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His Ile Tyr Thr Ser Arg
340 345 350

Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys Gly Leu Cys Ser Leu
355 360 365

Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp Leu Pro Gln Phe Thr
370 375 380

Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg Pro Phe Trp Pro Trp
385 390 395 400

Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln Arg Arg Leu Arg Arg
405 410 415

Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val Asn Asp Phe Gly Asn
420 425 430

Leu Gln Leu Gly Pro Pro Met Ser
435 440

<210> 1007
<211> 525
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1007

Met Lys Glu Thr Asp Gln Met Gln Ser Leu Glu Gly Ser Gly Ala Glu
1 5 10 15

Arg Ser Val Gly Thr Gln Thr Gly Ser Met Thr Gly Gln Ile Pro Arg
20 25 30

Leu Ser Lys Val Asn Leu Phe Thr Leu Leu Ser Leu Trp Met Glu Leu
35 40 45

Phe Pro Gly Val Glu Ala Gln Gly Gln Lys Ser Gln Lys Thr Glu Glu
50 55 60

Glu Ser Arg Gly Pro Leu Gly Asp Asn Glu Glu Leu Thr Arg Val Ser
65 70 75 80

Thr Glu Lys Lys Gln Val Lys Lys Thr Gly Leu Val Val Val Lys Asn
85 90 95

Met Lys Ile Ile Gly Leu His Cys Ser Ser Glu Asp Leu His Thr Gly
100 105 110

Gln Ile Ala Leu Ile Lys His Gly Ser Arg Leu Lys Asn Cys Asp Leu
115 120 125

Tyr Phe Ser Arg Lys Pro Cys Ser Ala Cys Leu Lys Met Ile Val Asn
130 135 140

Ala Gly Val Asn Arg Ile Ser Tyr Trp Pro Ser Asp Pro Glu Ile Ser
145 150 155 160

Leu Leu Thr Glu Ala Ser Ser Ser Glu Asp Ala Lys Leu Asp Ala Lys
165 170 175

Ala Ala Glu Arg Leu Lys Ser Asn Ser Arg Ala His Val Cys Val Leu
180 185 190

Leu Gln Pro Leu Val Cys Tyr Met Val Gln Phe Val Glu Glu Thr Ser
195 200 205

Tyr Lys Cys Asp Phe Ile Gln Lys Thr Ala Lys Ala Leu Pro Gly Ala
210 215 220

Asp Thr Asp Phe Tyr Ser Glu Cys Lys Gln Glu Arg Ile Lys Glu Tyr
225 230 235 240

Glu Met Leu Phe Leu Val Ser Asn Glu Glu Arg His Lys Gln Ile Leu
245 250 255

Met Thr Ile Gly Leu Glu Ser Leu Cys Glu Asp Pro Tyr Phe Ser Asn
260 265 270

Leu Arg Gln Asn Met Lys Asp Leu Ile Leu Leu Leu Ala Thr Val Ala
275 280 285

Ser Ser Val Pro Asn Leu Lys His Phe Gly Phe Tyr Cys Ser Ser Pro
290 295 300

Glu Gln Ile Asn Glu Ile His Asn Gln Ser Leu Pro Gln Glu Val Ala
305 310 315 320

Arg His Cys Met Val Gln Ala Arg Leu Leu Ala Tyr Arg Thr Glu Asp
325 330 335

His Lys Thr Gly Val Gly Ala Val Ile Trp Ala Glu Ala Lys Ser Arg
340 345 350

Ser Cys Asp Gly Thr Gly Ala Met Tyr Phe Ile Gly Cys Gly Tyr Asn
355 360 365

Ala Phe Pro Val Gly Ser Glu Tyr Ala Asp Phe Pro His Met Asp Asp
370 375 380

Lys His Lys Asp Arg Glu Ile Arg Lys Phe Arg Tyr Ile Ile His Ala
385 390 395 400

Glu Gln Asn Ala Leu Thr Phe Arg Cys Gln Asp Ile Lys Pro Glu Glu
405 410 415

Arg Ser Met Ile Phe Val Thr Lys Cys Pro Cys Asp Glu Cys Val Pro
420 425 430

Leu Ile Lys Gly Ala Gly Ile Lys Gln Ile Tyr Ala Gly Asp Val Asp
435 440 445

Val Gly Lys Lys Lys Ala Asp Ile Ser Tyr Met Lys Phe Gly Glu Leu
450 455 460

Glu Gly Val Arg Lys Phe Thr Trp Gln Leu Asn Pro Ser Glu Ala Tyr
465 470 475 480

Ser Leu Asp Pro Asn Glu Pro Glu Arg Arg Glu Asn Gly Val Leu Arg
485 490 495

Arg Arg Ser Ala Lys Asp Glu Gln Arg Ser Ser Lys Arg Pro Arg Leu
500 505 510

Glu Thr Arg Ser Ala Gly Ser Ala Thr Thr Ala Cys Phe
515 520 525

<210> 1008
<211> 427
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1008

Met Ser Asn Asn Ala Leu Gln Thr Ile Ile Asn Ala Arg Leu Pro Gly
1 5 10 15

Glu Glu Gly Leu Trp Gln Ile His Leu Gln Asp Gly Lys Ile Ser Ala
20 25 30

Ile Asp Ala Gln Ser Gly Val Met Pro Ile Thr Glu Asn Ser Leu Asp
35 40 45

Ala Glu Gln Gly Leu Val Ile Pro Pro Phe Val Glu Pro His Ile His
50 55 60

```
Leu Asp Thr Thr Gln Thr Ala Gly Gln Pro Asn Trp Asn Gln Ser Gly
65                  70                  75                  80

Thr Leu Phe Glu Gly Ile Glu Arg Trp Ala Glu Arg Lys Ala Leu Leu
                85                  90                  95

Thr His Asp Asp Val Lys Gln Arg Ala Trp Gln Thr Leu Lys Trp Gln
            100                 105                 110

Ile Ala Asn Gly Ile Gln His Val Arg Thr His Val Asp Val Ser Asp
        115                 120                 125

Ala Thr Leu Thr Ala Leu Lys Ala Met Leu Glu Val Lys Gln Glu Val
    130                 135                 140

Ala Pro Trp Ile Asp Leu Gln Ile Val Ala Phe Pro Gln Glu Gly Ile
145                 150                 155                 160

Leu Ser Tyr Pro Asn Gly Glu Ala Leu Leu Glu Glu Ala Leu Arg Leu
                165                 170                 175

Gly Ala Asp Val Val Gly Ala Ile Pro His Phe Glu Phe Thr Arg Glu
            180                 185                 190

Tyr Gly Val Glu Ser Leu His Lys Thr Phe Ala Leu Ala Gln Lys Tyr
        195                 200                 205

Asp Arg Leu Ile Asp Val His Cys Asp Glu Ile Asp Asp Glu Gln Ser
    210                 215                 220

Arg Phe Val Glu Thr Val Ala Ala Leu Ala His His Glu Gly Met Gly
225                 230                 235                 240

Ala Arg Val Thr Ala Ser His Thr Thr Ala Met His Ser Tyr Asn Gly
                245                 250                 255
```

Ala Tyr Thr Ser Arg Leu Phe Arg Leu Leu Lys Met Ser Gly Ile Asn
260 265 270

Phe Val Ala Asn Pro Leu Val Asn Ile His Leu Gln Gly Arg Phe Asp
275 280 285

Thr Tyr Pro Lys Arg Arg Gly Ile Thr Arg Val Lys Glu Met Leu Glu
290 295 300

Ser Gly Ile Asn Val Cys Phe Gly His Asp Asp Val Phe Asp Pro Trp
305 310 315 320

Tyr Pro Leu Gly Thr Ala Asn Met Leu Gln Val Leu His Met Gly Leu
325 330 335

His Val Cys Gln Leu Met Gly Tyr Gly Gln Ile Asn Asp Gly Leu Asn
340 345 350

Leu Ile Thr His His Ser Ala Arg Thr Leu Asn Leu Gln Asp Tyr Gly
355 360 365

Ile Ala Ala Gly Asn Ser Ala Asn Leu Ile Ile Leu Pro Ala Glu Asn
370 375 380

Gly Phe Asp Ala Leu Arg Arg Gln Val Pro Val Arg Tyr Ser Val Arg
385 390 395 400

Gly Gly Lys Val Ile Ala Ser Thr Gln Pro Ala Gln Thr Thr Val Tyr
405 410 415

Leu Glu Gln Pro Glu Ala Ile Asp Tyr Lys Arg
420 425

<210> 1009
<211> 210
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 1009

Met Ala Leu Leu Thr Ala Lys Thr Phe Ser Leu Gln Phe Asn Asn Lys
1 5 10 15

Arg Arg Val Asn Lys Pro Tyr Tyr Pro Arg Lys Ala Leu Leu Cys Tyr
20 25 30

Gln Leu Thr Pro Gln Asn Gly Ser Thr Pro Thr Arg Gly His Leu Lys
35 40 45

Asn Lys Lys Lys Asp His Ala Glu Ile Arg Phe Ile Asn Lys Ile Lys
50 55 60

Ser Met Gly Leu Asp Glu Thr Gln Cys Tyr Gln Val Thr Cys Tyr Leu
65 70 75 80

Thr Trp Ser Pro Cys Pro Ser Cys Ala Gly Glu Leu Val Asp Phe Ile
85 90 95

Lys Ala His Arg His Leu Asn Leu Arg Ile Phe Ala Ser Arg Leu Tyr
100 105 110

Tyr His Trp Arg Pro Asn Tyr Gln Glu Gly Leu Leu Leu Leu Cys Gly
115 120 125

Ser Gln Val Pro Val Glu Val Met Gly Leu Pro Glu Phe Thr Asp Cys
130 135 140

Trp Glu Asn Phe Val Asp His Lys Glu Pro Pro Ser Phe Asn Pro Ser
145 150 155 160

Glu Lys Leu Glu Glu Leu Asp Lys Asn Ser Gln Ala Ile Lys Arg Arg
165 170 175

Leu Glu Arg Ile Lys Ser Arg Ser Val Asp Val Leu Glu Asn Gly Leu
180 185 190

Arg Ser Leu Gln Leu Gly Pro Val Thr Pro Ser Ser Ser Ile Arg Asn
195 200 205

Ser Arg
210

<210> 1010
<211> 428
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1010

Met Glu Lys Asp Ile Asn Leu Lys Ile Phe Lys Gly Asn Leu Ile Phe
1 5 10 15

Thr Lys Thr Ser Asp Lys Phe Thr Ile Met Lys Asp Ser Tyr Ile Val
20 25 30

Val Ile Asp Gly Lys Ile Ala Ser Val Ser Ser Asn Leu Pro Asp Lys
35 40 45

Tyr Lys Gly Asn Pro Ile Ile Asp Phe Arg Asn Asn Ile Ile Ile Pro
50 55 60

Gly Met Asn Asp Leu His Ala His Ala Ser Gln Tyr Lys Asn Leu Gly
65 70 75 80

Ile Gly Met Asp Lys Glu Leu Leu Pro Trp Leu Asn Asn Tyr Thr Phe
85 90 95

Pro Glu Glu Ala Lys Phe Leu Asn Val Asp Tyr Ala Lys Lys Thr Tyr
100 105 110

Gly Arg Leu Ile Lys Asp Leu Ile Lys Asn Gly Thr Thr Arg Val Ala
115 120 125

```
Leu Phe Ala Thr Leu His Lys Asp Ser Thr Ile Glu Leu Phe Asn Met
    130                 135                 140

Leu Ile Lys Ser Gly Ile Gly Ala Tyr Val Gly Lys Val Asn Met Asp
145                 150                 155                 160

Tyr Asn Cys Pro Asp Tyr Leu Thr Glu Asn Tyr Ile Thr Ser Leu Asn
                165                 170                 175

Asp Thr Glu Glu Ile Ile Leu Lys Tyr Lys Asp Lys Ser Asn Ile Val
            180                 185                 190

Lys Pro Ile Ile Thr Pro Arg Phe Val Pro Ser Cys Ser Asn Glu Leu
        195                 200                 205

Met Asp Gly Leu Gly Lys Leu Ser Tyr Lys Tyr Arg Leu Pro Val Gln
    210                 215                 220

Ser His Leu Ser Glu Asn Leu Asp Glu Ile Ala Val Val Lys Ser Leu
225                 230                 235                 240

His Lys Lys Ser Asn Phe Tyr Gly Glu Val Tyr Asp Lys Phe Gly Leu
                245                 250                 255

Phe Gly Asn Thr Pro Thr Leu Met Ala His Cys Ile His Ser Ser Lys
            260                 265                 270

Glu Glu Ile Asn Leu Ile Lys Arg Asn Asn Val Thr Ile Val His Cys
        275                 280                 285

Pro Thr Ser Asn Phe Asn Leu Gly Ser Gly Met Met Pro Val Arg Lys
    290                 295                 300

Tyr Leu Asn Leu Gly Ile Asn Val Val Leu Gly Ser Asp Ile Ser Ala
305                 310                 315                 320
```

Gly His Thr Cys Ser Leu Phe Lys Val Ile Ala Tyr Ala Ile Gln Asn
325 330 335

Ser Lys Ile Lys Trp Gln Glu Ser Gly Lys Lys Asp Met Phe Leu Ser
340 345 350

Thr Ser Glu Ala Phe Tyr Met Ala Thr Lys Lys Gly Gly Ser Phe Phe
355 360 365

Gly Lys Val Gly Ser Phe Glu Glu Gly Tyr Asp Phe Asp Ala Leu Val
370 375 380

Ile Asn Asp Ser Asn Leu Tyr Pro Glu Asp Tyr Asp Leu Thr Glu Arg
385 390 395 400

Leu Glu Arg Phe Ile Tyr Leu Gly Asp Asp Arg Asn Ile Met Lys Arg
405 410 415

Tyr Val Cys Gly Asn Glu Ile Phe Gly Pro Lys Phe
420 425

<210> 1011
<211> 412
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1011

Met Lys Ile Ile Asn Ala Arg Leu Arg Arg Gln Glu Ala Leu Phe Thr
1 5 10 15

Leu Asp Leu Gln Asp Gly Ile Ile His Arg Ile Thr Ala Gln Ala Ala
20 25 30

Met Gln Thr Ala Asp Ala Gly Ala Ile Asp Ala Gln Gly Arg Leu Ala
35 40 45

Ile Pro Pro Phe Val Glu Pro His Ile His Leu Asp Ala Thr Leu Thr
50 55 60

Ala Gly Glu Pro Glu Trp Asn Arg Ser Gly Thr Leu Phe Glu Gly Ile
65 70 75 80

Thr Arg Trp Ser Gln Arg Lys Ala Ser Ile Thr Pro Glu Asp Thr Arg
85 90 95

Gln Arg Ala Leu Lys Thr Ile Gly Met Leu Arg Asp Phe Gly Val Gln
100 105 110

His Val Arg Thr His Val Asp Val Thr Asp Pro Ser Leu Ala Ala Leu
115 120 125

Gln Ala Leu Leu Ala Val Lys Gln Glu Ala Ala Asp Leu Ile Asp Leu
130 135 140

Gln Ile Val Ala Phe Pro Gln Glu Gly Ile Glu Ser Tyr Pro Asn Gly
145 150 155 160

Arg Glu Leu Met Thr Arg Ala Ile Glu Met Gly Ala Asp Val Val Gly
165 170 175

Gly Ile Pro His Tyr Glu Asn Thr Arg Asp Lys Gly Val Ser Ser Val
180 185 190

Met Phe Leu Met Asp Leu Ala Gln Arg Tyr Gly Arg Leu Val Asp Val
195 200 205

His Cys Asp Glu Ile Asp Asp Pro Gln Ser Arg Phe Leu Glu Val Leu
210 215 220

Ala Glu Glu Ala Arg Val Arg Gly Met Gly Ala Gln Val Thr Ala Ser
225 230 235 240

His Thr Cys Ala Met Gly Ser Tyr Asp Asn Ala Tyr Cys Ser Lys Leu
245 250 255

```
Phe Arg Leu Leu Lys Ala Ser Gly Ile Asn Phe Ile Ser Cys Pro Thr
            260                 265                 270

Glu Ser Ile His Leu Gln Gly Arg Phe Asp Ser Trp Pro Lys Arg Arg
        275                 280                 285

Gly Val Thr Arg Val Ala Glu Leu Asp Arg Ala Gly Ile Asn Val Cys
    290                 295                 300

Phe Ala Gln Asp Ser Ile Gln Asp Pro Trp Tyr Pro Leu Gly Asn Gly
305                 310                 315                 320

Asn Ile Leu Arg Ile Leu Asp Ala Gly Leu His Ile Cys His Met Leu
                325                 330                 335

Gly Tyr Asp Asp Leu Gln Arg Cys Leu Asp Phe Val Thr Asp Asn Ser
            340                 345                 350

Ala Arg Ala Leu Cys Leu Gly Asp Asn Tyr Gly Leu Ala Glu Gly Arg
        355                 360                 365

Pro Ala Asn Leu Leu Ile Leu Asp Ala Glu Asn Asp Tyr Glu Ala Val
    370                 375                 380

Arg Arg Gln Ala Arg Val Leu Thr Ser Ile Arg His Gly Lys Val Ile
385                 390                 395                 400

Leu Gln Arg Glu Val Glu His Ile Arg Tyr Pro Ala
                405                 410
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<210> 1012
<211> 812
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1012

Met Gly Arg Lys Leu Asp Pro Thr Lys Glu Lys Arg Gly Pro Gly Arg
1 5 10 15

Lys Ala Arg Lys Gln Lys Gly Ala Glu Thr Glu Leu Val Arg Phe Leu
20 25 30

Pro Ala Val Ser Asp Glu Asn Ser Lys Arg Leu Ser Ser Arg Ala Arg
35 40 45

Lys Arg Ala Ala Lys Arg Arg Leu Gly Ser Val Glu Ala Pro Lys Thr
50 55 60

Asn Lys Ser Pro Glu Ala Lys Pro Leu Pro Gly Lys Leu Pro Lys Gly
65 70 75 80

Ile Ser Ala Gly Ala Val Gln Thr Ala Gly Lys Lys Gly Pro Gln Ser
85 90 95

Leu Phe Asn Ala Pro Arg Gly Lys Lys Arg Pro Ala Pro Gly Ser Asp
100 105 110

Glu Glu Glu Glu Glu Glu Asp Ser Glu Glu Asp Gly Met Val Asn His
115 120 125

Gly Asp Leu Trp Gly Ser Glu Asp Asp Ala Asp Thr Val Asp Asp Tyr
130 135 140

Gly Ala Asp Ser Asn Ser Glu Asp Glu Glu Glu Gly Glu Ala Leu Leu
145 150 155 160

Pro Ile Glu Arg Ala Ala Arg Lys Gln Lys Ala Arg Glu Ala Ala Ala
165 170 175

Gly Ile Gln Trp Ser Glu Glu Glu Thr Glu Asp Glu Glu Glu Glu Lys
180 185 190

Glu Val Thr Pro Glu Ser Gly Pro Pro Lys Val Glu Glu Ala Asp Gly
195 200 205

Gly Leu Gln Ile Asn Val Asp Glu Glu Pro Phe Val Leu Pro Pro Ala
210 215 220

Gly Glu Met Glu Gln Asp Ala Gln Ala Pro Asp Leu Gln Arg Val His
225 230 235 240

Lys Arg Ile Gln Asp Ile Val Gly Ile Leu Arg Asp Phe Gly Ala Gln
245 250 255

Arg Glu Glu Gly Arg Ser Arg Ser Glu Tyr Leu Asn Arg Leu Lys Lys
260 265 270

Asp Leu Ala Ile Tyr Tyr Ser Tyr Gly Asp Phe Leu Leu Gly Lys Leu
275 280 285

Met Asp Leu Phe Pro Leu Ser Glu Leu Val Glu Phe Leu Glu Ala Asn
290 295 300

Glu Val Pro Arg Pro Val Thr Leu Arg Thr Asn Thr Leu Lys Thr Arg
305 310 315 320

Arg Arg Asp Leu Ala Gln Ala Leu Ile Asn Arg Gly Val Asn Leu Asp
325 330 335

Pro Leu Gly Lys Trp Ser Lys Thr Gly Leu Val Val Tyr Asp Ser Ser
340 345 350

Val Pro Ile Gly Ala Thr Pro Glu Tyr Leu Ala Gly His Tyr Met Leu
355 360 365

Gln Gly Ala Ser Ser Met Leu Pro Val Met Ala Leu Ala Pro Gln Glu
370 375 380

His Glu Arg Ile Leu Asp Met Cys Cys Ala Pro Gly Gly Lys Thr Ser
385 390 395 400

Tyr Met Ala Gln Leu Met Lys Asn Thr Gly Val Ile Leu Ala Asn Asp
405 410 415

Ala Asn Ala Glu Arg Leu Lys Ser Val Val Gly Asn Leu His Arg Leu
420 425 430

Gly Val Thr Asn Thr Ile Ile Ser His Tyr Asp Gly Arg Gln Phe Pro
435 440 445

Lys Val Val Gly Gly Phe Asp Arg Val Leu Leu Asp Ala Pro Cys Ser
450 455 460

Gly Thr Gly Val Ile Ser Lys Asp Pro Ala Val Lys Thr Asn Lys Asp
465 470 475 480

Glu Lys Asp Ile Leu Arg Cys Ala His Leu Gln Lys Glu Leu Leu Leu
485 490 495

Ser Ala Ile Asp Ser Val Asn Ala Thr Ser Lys Thr Gly Gly Tyr Leu
500 505 510

Val Tyr Cys Thr Cys Ser Ile Thr Val Glu Glu Asn Glu Trp Val Val
515 520 525

Asp Tyr Ala Leu Lys Lys Arg Asn Val Arg Leu Val Pro Thr Gly Leu
530 535 540

Asp Phe Gly Gln Glu Gly Phe Thr Arg Phe Arg Glu Arg Arg Phe His
545 550 555 560

Pro Ser Leu Arg Ser Thr Arg Arg Phe Tyr Pro His Thr His Asn Met
565 570 575

Asp Gly Phe Phe Ile Ala Lys Phe Lys Lys Phe Ser Asn Ser Ile Pro
580 585 590

```
Gln Ser Gln Thr Gly Asn Ser Glu Thr Ala Thr Pro Thr Asn Val Asp
        595                 600                 605

Leu Pro Gln Val Ile Pro Lys Ser Glu Asn Ser Ser Gln Pro Ala Lys
    610                 615                 620

Lys Ala Lys Gly Ala Ala Lys Thr Lys Gln Gln Leu Gln Lys Gln Gln
625                 630                 635                 640

His Pro Lys Lys Ala Ser Phe Gln Lys Leu Asn Gly Ile Ser Lys Gly
                645                 650                 655

Ala Asp Ser Glu Leu Ser Thr Val Pro Ser Val Thr Lys Thr Gln Ala
            660                 665                 670

Ser Ser Ser Phe Gln Asp Ser Ser Gln Pro Ala Gly Lys Ala Glu Gly
        675                 680                 685

Ile Arg Glu Pro Lys Val Thr Gly Lys Leu Lys Gln Arg Ser Pro Lys
    690                 695                 700

Leu Gln Ser Ser Lys Lys Val Ala Phe Leu Arg Gln Asn Ala Pro Pro
705                 710                 715                 720

Lys Gly Thr Asp Thr Gln Thr Pro Ala Val Leu Ser Pro Ser Lys Thr
                725                 730                 735

Gln Ala Thr Leu Lys Pro Lys Asp His His Gln Pro Leu Gly Arg Ala
            740                 745                 750

Lys Gly Val Glu Lys Gln Gln Leu Pro Glu Gln Pro Phe Glu Lys Ala
        755                 760                 765

Ala Phe Gln Lys Gln Asn Asp Thr Pro Lys Gly Pro Gln Pro Pro Thr
    770                 775                 780

Val Ser Pro Ile Arg Ser Ser Arg Pro Pro Pro Ala Lys Arg Lys Lys
785                 790                 795                 800
```

Ser Gln Ser Arg Gly Asn Ser Gln Leu Leu Leu Ser
805 810

<210> 1013
<211> 767
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1013

Met Gly Arg Arg Ser Arg Gly Arg Arg Leu Gln Gln Gln Gln Arg Pro
1 5 10 15

Glu Asp Ala Glu Asp Gly Ala Glu Gly Gly Gly Lys Arg Gly Glu Ala
20 25 30

Gly Trp Glu Gly Gly Tyr Pro Glu Ile Val Lys Glu Asn Lys Leu Phe
35 40 45

Glu His Tyr Tyr Gln Glu Leu Lys Ile Val Pro Glu Gly Glu Trp Gly
50 55 60

Gln Phe Met Asp Ala Leu Arg Glu Pro Leu Pro Ala Thr Leu Arg Ile
65 70 75 80

Thr Gly Tyr Lys Ser His Ala Lys Glu Ile Leu His Cys Leu Lys Asn
85 90 95

Lys Tyr Phe Lys Glu Leu Glu Asp Leu Glu Val Asp Gly Gln Lys Val
100 105 110

Glu Val Pro Gln Pro Leu Ser Trp Tyr Pro Glu Glu Leu Ala Trp His
115 120 125

Thr Asn Leu Ser Arg Lys Ile Leu Arg Lys Ser Pro His Leu Glu Lys
130 135 140

Phe His Gln Phe Leu Val Ser Glu Thr Glu Ser Gly Asn Ile Ser Arg
145 150 155 160

Gln Glu Ala Val Ser Met Ile Pro Pro Leu Leu Leu Asn Val Arg Pro
165 170 175

His His Lys Ile Leu Asp Met Cys Ala Ala Pro Gly Ser Lys Thr Thr
180 185 190

Gln Leu Ile Glu Met Leu His Ala Asp Met Asn Val Pro Phe Pro Glu
195 200 205

Gly Phe Val Ile Ala Asn Asp Val Asp Asn Lys Arg Cys Tyr Leu Leu
210 215 220

Val His Gln Ala Lys Arg Leu Ser Ser Pro Cys Ile Met Val Val Asn
225 230 235 240

His Asp Ala Ser Ser Ile Pro Arg Leu Gln Ile Asp Val Asp Gly Arg
245 250 255

Lys Glu Ile Leu Phe Tyr Asp Arg Ile Leu Cys Asp Val Pro Cys Ser
260 265 270

Gly Asp Gly Thr Met Arg Lys Asn Ile Asp Val Trp Lys Lys Trp Thr
275 280 285

Thr Leu Asn Ser Leu Gln Leu His Gly Leu Gln Leu Arg Ile Ala Thr
290 295 300

Arg Gly Ala Glu Gln Leu Ala Glu Gly Gly Arg Met Val Tyr Ser Thr
305 310 315 320

Cys Ser Leu Asn Pro Ile Glu Asp Glu Ala Val Ile Ala Ser Leu Leu
325 330 335

Glu Lys Ser Glu Gly Ala Leu Glu Leu Ala Asp Val Ser Asn Glu Leu
340 345 350

Pro Gly Leu Lys Trp Met Pro Gly Ile Thr Gln Trp Lys Val Met Thr
355 360 365

Lys Asp Gly Gln Trp Phe Thr Asp Trp Asp Ala Val Pro His Ser Arg
370 375 380

His Thr Gln Ile Arg Pro Thr Met Phe Pro Pro Lys Asp Pro Glu Lys
385 390 395 400

Leu Gln Ala Met His Leu Glu Arg Cys Leu Arg Ile Leu Pro His His
405 410 415

Gln Asn Thr Gly Gly Phe Phe Val Ala Val Leu Val Lys Lys Ser Ser
420 425 430

Met Pro Trp Asn Lys Arg Gln Pro Lys Leu Gln Gly Lys Ser Ala Glu
435 440 445

Thr Arg Glu Ser Thr Gln Leu Ser Pro Ala Asp Leu Thr Glu Gly Lys
450 455 460

Pro Thr Asp Pro Ser Lys Leu Glu Ser Pro Ser Phe Thr Gly Thr Gly
465 470 475 480

Asp Thr Glu Ile Ala His Ala Thr Glu Asp Leu Glu Asn Asn Gly Ser
485 490 495

Lys Lys Asp Gly Val Cys Gly Pro Pro Pro Ser Lys Lys Met Lys Leu
500 505 510

Phe Gly Phe Lys Glu Asp Pro Phe Val Phe Ile Pro Glu Asp Asp Pro
515 520 525

Leu Phe Pro Pro Ile Glu Lys Phe Tyr Ala Leu Asp Pro Ser Phe Pro
530 535 540

Arg Met Asn Leu Leu Thr Arg Thr Thr Glu Gly Lys Lys Arg Gln Leu
545 550 555 560

Tyr Met Val Ser Lys Glu Leu Arg Asn Val Leu Leu Asn Asn Ser Glu
565 570 575

Lys Met Lys Val Ile Asn Thr Gly Ile Lys Val Trp Cys Arg Asn Asn
580 585 590

Ser Gly Glu Glu Phe Asp Cys Ala Phe Arg Leu Ala Gln Glu Gly Ile
595 600 605

Tyr Thr Leu Tyr Pro Phe Ile Asn Ser Arg Ile Ile Thr Val Ser Met
610 615 620

Glu Asp Val Lys Ile Leu Leu Thr Gln Glu Asn Pro Phe Phe Arg Lys
625 630 635 640

Leu Ser Ser Glu Thr Tyr Ser Gln Ala Lys Asp Leu Ala Lys Gly Ser
645 650 655

Ile Val Leu Lys Tyr Glu Pro Asp Ser Ala Asn Pro Asp Ala Leu Gln
660 665 670

Cys Pro Ile Val Leu Cys Gly Trp Arg Gly Lys Ala Ser Ile Arg Thr
675 680 685

Phe Val Pro Lys Asn Glu Arg Leu His Tyr Leu Arg Met Met Gly Leu
690 695 700

Glu Val Leu Gly Glu Lys Lys Lys Glu Gly Val Ile Leu Thr Asn Glu
705 710 715 720

Ser Ala Ala Ser Thr Gly Gln Pro Asp Asn Asp Val Thr Glu Gly Gln
725 730 735

Arg Ala Gly Glu Pro Asn Ser Pro Asp Ala Glu Glu Ala Asn Ser Pro
740 745 750

Asp Val Thr Ala Gly Cys Asp Pro Ala Gly Val His Pro Pro Arg
755 760 765

<210> 1014
<211> 429
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1014

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1 5 10 15

Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
20 25 30

Leu Gly Tyr Ala Lys Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
35 40 45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
50 55 60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65 70 75 80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
85 90 95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile
100 105 110

Val Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
115 120 125

Ser Arg Leu Tyr Asn Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys
130 135 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145 150 155 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
165 170 175

Arg Pro Trp Lys Arg Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
180 185 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Pro Val Pro Ser Ser Ser
195 200 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
210 215 220

Arg Phe Cys Val Glu Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu
225 230 235 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
245 250 255

His Arg Met Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
260 265 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
275 280 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
290 295 300

Val Thr Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305 310 315 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
325 330 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
340 345 350

Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
355 360 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
370 375 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385 390 395 400

Arg Arg Leu Arg Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
405 410 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
420 425

<210> 1015
<211> 429
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1015

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1 5 10 15

Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
20 25 30

Leu Arg Tyr Ala Ile Asp Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
35 40 45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
50 55 60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65 70 75 80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
85 90 95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Val
100 105 110

Leu Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
115 120 125

Ser Arg Leu Tyr Asn Ile Arg Asp Pro Glu Asn Gln Gln Asn Leu Cys
130 135 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145 150 155 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
165 170 175

Arg Pro Trp Lys Lys Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
180 185 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Pro Val Pro Ser Ser Ser
195 200 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
210 215 220

Arg Phe Cys Val Glu Arg Arg Arg Val His Leu Leu Ser Glu Glu Glu
225 230 235 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
245 250 255

His Gly Val Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
260 265 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
275 280 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
290 295 300

Val Ile Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305 310 315 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
325 330 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
340 345 350

Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
355 360 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
370 375 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385 390 395 400

Arg Arg Leu His Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
405 410 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
420 425

<210> 1016
<211> 370
<212> PRT
<213> 人工序列

<220>

<223> 合成

<400> 1016

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Met Val Glu Pro Met Asp Pro Arg Thr Phe Val Ser Asn Phe Asn Asn
1               5                  10                  15

Arg Pro Ile Leu Ser Gly Leu Asn Thr Val Trp Leu Cys Cys Glu Val
            20                  25                  30

Lys Thr Lys Asp Pro Ser Gly Pro Pro Leu Asp Ala Lys Ile Phe Gln
        35                  40                  45

Gly Lys Val Tyr Ser Lys Ala Lys Tyr His Pro Glu Met Arg Phe Leu
    50                  55                  60

Arg Trp Phe His Lys Trp Arg Gln Leu His His Asp Gln Glu Tyr Lys
65                  70                  75                  80

Val Thr Trp Tyr Val Ser Trp Ser Pro Cys Thr Arg Cys Ala Asn Ser
                85                  90                  95

Val Ala Thr Phe Leu Ala Lys Asp Pro Lys Val Thr Leu Thr Ile Phe
            100                 105                 110

Val Ala Arg Leu Tyr Tyr Phe Trp Lys Pro Asp Tyr Gln Gln Ala Leu
        115                 120                 125

Arg Ile Leu Cys Gln Lys Arg Gly Gly Pro His Ala Thr Met Lys Ile
    130                 135                 140

Met Asn Tyr Asn Glu Phe Gln Asp Cys Trp Asn Lys Phe Val Asp Gly
145                 150                 155                 160

Arg Gly Lys Pro Phe Lys Pro Arg Asn Asn Leu Pro Lys His Tyr Thr
                165                 170                 175

Leu Leu Gln Ala Thr Leu Gly Glu Leu Leu Arg His Leu Met Asp Pro
            180                 185                 190
```

Gly Thr Phe Thr Ser Asn Phe Asn Asn Lys Pro Trp Val Ser Gly Gln
195 200 205

His Glu Thr Tyr Leu Cys Tyr Lys Val Glu Arg Leu His Asn Asp Thr
210 215 220

Trp Val Pro Leu Asn Gln His Arg Gly Phe Leu Arg Asn Gln Ala Pro
225 230 235 240

Asn Ile His Gly Phe Pro Lys Gly Arg His Ala Glu Leu Cys Phe Leu
245 250 255

Asp Leu Ile Pro Phe Trp Lys Leu Asp Gly Gln Gln Tyr Arg Val Thr
260 265 270

Cys Phe Thr Ser Trp Ser Pro Cys Phe Ser Cys Ala Gln Glu Met Ala
275 280 285

Lys Phe Ile Ser Asn Asn Glu His Val Ser Leu Cys Ile Phe Ala Ala
290 295 300

Arg Ile Tyr Asp Asp Gln Gly Arg Tyr Gln Glu Gly Leu Arg Ala Leu
305 310 315 320

His Arg Asp Gly Ala Lys Ile Ala Met Met Asn Tyr Ser Glu Phe Glu
325 330 335

Tyr Cys Trp Asp Thr Phe Val Asp Arg Gln Gly Arg Pro Phe Gln Pro
340 345 350

Trp Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg
355 360 365

Ala Ile
370

<210> 1017
<211> 384
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1017

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Met Lys Pro His Phe Arg Asn Pro Val Glu Arg Met Tyr Gln Asp Thr
1               5                  10                  15

Phe Ser Asp Asn Phe Tyr Asn Arg Pro Ile Leu Ser His Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
        35                  40                  45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Lys Leu Lys Tyr
    50                  55                  60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65                  70                  75                  80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
                85                  90                  95

Cys Thr Lys Cys Thr Arg Asp Val Ala Thr Phe Leu Ala Glu Asp Pro
            100                 105                 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
        115                 120                 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
    130                 135                 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145                 150                 155                 160
```

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
165 170 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
180 185 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Ser Asn Phe Asn Asn
195 200 205

Glu Leu Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
210 215 220

Glu Arg Leu His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225 230 235 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
260 265 270

Leu His Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
275 280 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Asn Asn Lys His
290 295 300

Val Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305 310 315 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Lys Ala Gly Ala Lys Ile Ser
325 330 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
340 345 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser
355 360 365

Gln Ala Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
370 375 380

<210> 1018
<211> 377
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1018

Met Asn Pro Gln Ile Arg Asn Met Val Glu Gln Met Glu Pro Asp Ile
1 5 10 15

Phe Val Tyr Tyr Phe Asn Asn Arg Pro Ile Leu Ser Gly Arg Asn Thr
20 25 30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Asp Pro Ser Gly Pro Pro
35 40 45

Leu Asp Ala Asn Ile Phe Gln Gly Lys Leu Tyr Pro Glu Ala Lys Asp
50 55 60

His Pro Glu Met Lys Phe Leu His Trp Phe Arg Lys Trp Arg Gln Leu
65 70 75 80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Val Ser Trp Ser Pro
85 90 95

Cys Thr Arg Cys Ala Asn Ser Val Ala Thr Phe Leu Ala Glu Asp Pro
100 105 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Lys
115 120 125

Pro Asp Tyr Gln Gln Ala Leu Arg Ile Leu Cys Gln Glu Arg Gly Gly
130 135 140

```
Pro His Ala Thr Met Lys Ile Met Asn Tyr Asn Glu Phe Gln His Cys
145                 150                 155                 160

Trp Asn Glu Phe Val Asp Gly Gln Gly Lys Pro Phe Lys Pro Arg Lys
                165                 170                 175

Asn Leu Pro Lys His Tyr Thr Leu Leu His Ala Thr Leu Gly Glu Leu
            180                 185                 190

Leu Arg His Val Met Asp Pro Gly Thr Phe Thr Ser Asn Phe Asn Asn
        195                 200                 205

Lys Pro Trp Val Ser Gly Gln Arg Glu Thr Tyr Leu Cys Tyr Lys Val
    210                 215                 220

Glu Arg Ser His Asn Asp Thr Trp Val Leu Leu Asn Gln His Arg Gly
225                 230                 235                 240

Phe Leu Arg Asn Gln Ala Pro Asp Arg His Gly Phe Pro Lys Gly Arg
                245                 250                 255

His Ala Glu Leu Cys Phe Leu Asp Leu Ile Pro Phe Trp Lys Leu Asp
            260                 265                 270

Asp Gln Gln Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys Phe
        275                 280                 285

Ser Cys Ala Gln Lys Met Ala Lys Phe Ile Ser Asn Asn Lys His Val
    290                 295                 300

Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg Cys
305                 310                 315                 320

Gln Glu Gly Leu Arg Thr Leu His Arg Asp Gly Ala Lys Ile Ala Val
                325                 330                 335
```

Met Asn Tyr Ser Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Asp Arg
340 345 350

Gln Gly Arg Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln
355 360 365

Ala Leu Ser Gly Arg Leu Arg Ala Ile
370 375

<210> 1019
<211> 384
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1019

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
20 25 30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
35 40 45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Glu Leu Lys Tyr
50 55 60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65 70 75 80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
85 90 95

Cys Thr Lys Cys Thr Arg Asp Met Ala Thr Phe Leu Ala Glu Asp Pro
100 105 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
115 120 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
130 135 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145 150 155 160

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
165 170 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
180 185 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Phe Asn Phe Asn Asn
195 200 205

Glu Pro Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
210 215 220

Glu Arg Met His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225 230 235 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
245 250 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
260 265 270

Leu Asp Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
275 280 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Lys Asn Lys His
290 295 300

Val Ser Leu Cys Ile Phe Thr Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305 310 315 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Glu Ala Gly Ala Lys Ile Ser
325 330 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
340 345 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser
355 360 365

Gln Asp Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Glu Asn
370 375 380

<210> 1020
<211> 373
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1020

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
20 25 30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Arg
35 40 45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Gln Pro Glu His
50 55 60

His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu Pro
65 70 75 80

Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro Cys
85 90 95

```
Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ala Glu His Pro Asn
            100                 105                 110

Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu Arg
        115                 120                 125

Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg Val
    130                 135                 140

Lys Ile Met Asp Asp Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe Val
145                 150                 155                 160

Tyr Ser Glu Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn
                165                 170                 175

Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met
            180                 185                 190

Glu Ala Met Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Arg
        195                 200                 205

Lys Ala Tyr Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val
    210                 215                 220

Val Lys His His Ser Pro Val Ser Trp Lys Arg Gly Val Phe Arg Asn
225                 230                 235                 240

Gln Val Asp Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser
                245                 250                 255

Trp Phe Cys Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr
            260                 265                 270

Trp Tyr Thr Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala
        275                 280                 285
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Glu Phe Leu Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala
290 295 300

Arg Leu Tyr Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Arg Ser
305 310 315 320

Leu Ser Gln Glu Gly Ala Ser Val Glu Ile Met Gly Tyr Lys Asp Phe
325 330 335

Lys Tyr Cys Trp Glu Asn Phe Val Tyr Asn Asp Asp Glu Pro Phe Lys
340 345 350

Pro Trp Lys Gly Leu Lys Tyr Asn Phe Leu Phe Leu Asp Ser Lys Leu
355 360 365

Gln Glu Ile Leu Glu
370

<210> 1021
<211> 382
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1021

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
20 25 30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
35 40 45

Leu Trp Asp Thr Gly Val Phe Arg Gly Gln Val Tyr Phe Lys Pro Gln
50 55 60

```
Tyr His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu
65                  70                  75                  80

Pro Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro
                85                  90                  95

Cys Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ser Glu His Pro
            100                 105                 110

Asn Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu
        115                 120                 125

Arg Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg
    130                 135                 140

Val Thr Ile Met Asp Tyr Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe
145                 150                 155                 160

Val Tyr Asn Glu Gly Gln Gln Phe Met Pro Trp Tyr Lys Phe Asp Glu
                165                 170                 175

Asn Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Tyr Leu
            180                 185                 190

Met Asp Pro Asp Thr Phe Thr Phe Asn Phe Asn Asn Asp Pro Leu Val
        195                 200                 205

Leu Arg Arg Arg Gln Thr Tyr Leu Cys Tyr Glu Val Glu Arg Leu Asp
    210                 215                 220

Asn Gly Thr Trp Val Leu Met Asp Gln His Met Gly Phe Leu Cys Asn
225                 230                 235                 240

Glu Ala Lys Asn Leu Leu Cys Gly Phe Tyr Gly Arg His Ala Glu Leu
                245                 250                 255

Arg Phe Leu Asp Leu Val Pro Ser Leu Gln Leu Asp Pro Ala Gln Ile
            260                 265                 270
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Tyr Arg Val Thr Trp Phe Ile Ser Trp Ser Pro Cys Phe Ser Trp Gly
275 280 285

Cys Ala Gly Glu Val Arg Ala Phe Leu Gln Glu Asn Thr His Val Arg
290 295 300

Leu Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys
305 310 315 320

Glu Ala Leu Gln Met Leu Arg Asp Ala Gly Ala Gln Val Ser Ile Met
325 330 335

Thr Tyr Asp Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Tyr Arg Gln
340 345 350

Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser Gln Ala
355 360 365

Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
370 375 380

<210> 1022
<211> 386
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1022

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1 5 10 15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
20 25 30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
35 40 45

Leu Trp Asp Thr Gly Val Phe Arg Gly Pro Val Leu Pro Lys Arg Gln
50 55 60

Ser Asn His Arg Gln Glu Val Tyr Phe Arg Phe Glu Asn His Ala Glu
65 70 75 80

Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Arg Leu Pro Ala Asn Arg
85 90 95

Arg Phe Gln Ile Thr Trp Phe Val Ser Trp Asn Pro Cys Leu Pro Cys
100 105 110

Val Val Lys Val Thr Lys Phe Leu Ala Glu His Pro Asn Val Thr Leu
115 120 125

Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Arg Asp Arg Asp Trp Arg
130 135 140

Trp Val Leu Leu Arg Leu His Lys Ala Gly Ala Arg Val Lys Ile Met
145 150 155 160

Asp Tyr Glu Asp Phe Ala Tyr Cys Trp Glu Asn Phe Val Cys Asn Glu
165 170 175

Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn Tyr Ala Ser
180 185 190

Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met Glu Ala Met
195 200 205

Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Leu Lys Ala Cys
210 215 220

Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val Thr Lys His
225 230 235 240

His Ser Ala Val Phe Arg Lys Arg Gly Val Phe Arg Asn Gln Val Asp
245 250 255

Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys
260 265 270

Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr Trp Tyr Thr
275 280 285

Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala Glu Phe Leu
290 295 300

Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Cys
305 310 315 320

Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Cys Ser Leu Ser Gln
325 330 335

Glu Gly Ala Ser Val Lys Ile Met Gly Tyr Lys Asp Phe Val Ser Cys
340 345 350

Trp Lys Asn Phe Val Tyr Ser Asp Asp Glu Pro Phe Lys Pro Trp Lys
355 360 365

Gly Leu Gln Thr Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ile
370 375 380

Leu Gln
385

<210> 1023
<211> 229
<212> PRT
<213> 人工序列

<220>
<223> 合成

<400> 1023

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Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1               5                  10                  15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
            20                  25                  30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
        35                  40                  45

Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val Glu Val
    50                  55                  60

Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro Asn Thr
65                  70                  75                  80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
                85                  90                  95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
            100                 105                 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
        115                 120                 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
    130                 135                 140

Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn Tyr Ser
145                 150                 155                 160

Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp Val Arg
                165                 170                 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
            180                 185                 190

Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
        195                 200                 205
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Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
210 215 220

Ala Thr Gly Leu Lys
225

<210> 1024
<211> 100
<212> RNA
<213> 人工序列

<220>
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<400> 1024
ccacacccaa aaggccacac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1025
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1025
cccaccagcu cagcuccacg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1026
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1026
ucccuagcag gaucucauag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1027
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1027
ggcucaaaca cagcgaccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1028
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1028
ggcacaccag uguggccuuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1029
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1029
agguggccga gacccucagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1030
<211> 100
<212> RNA
<213> 人工序列

<220>

<223> 合成

<400> 1030
accugcucua ccccaggccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1031
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1031
cauagaggau gguggcagac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1032
<211> 100
<212> RNA
<213> 人工序列

<220>
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<400> 1032
ccacguggag cugagcuggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1033
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1033
ggagaaugac gaguggaccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1034
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1034
ccaguguggc cuuuuggggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1035
<211> 100
<212> RNA
<213> 人工序列

<220>
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<400> 1035
caaacacagc gaccucgggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1036
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1036
uaccauggcc aucaacacaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1037
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1037
gcgcugacga ucugggugac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1038
<211> 100
<212> RNA
<213> 人工序列

<220>
<223> 合成

<400> 1038
cacggacccg cagccccuca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1039
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1040
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1041
<211> 100

<212> RNA
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1042
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1043
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1044
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1045
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1046
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1047
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1048
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1049
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<220>
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1050
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1051
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1052
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1053
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1054
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<223> 合成

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1055
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1056
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1057
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1058
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1059
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<400> 1059
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1060
<211> 100
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1061
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<220>
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1062
<211> 100
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<400> 1062
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1063
<211> 100
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1064
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1065
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1066
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<212> RNA
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<220>
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1067
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1068
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1069
<211> 100
<212> RNA
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<220>
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<400> 1069
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1070
<211> 100
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1071
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1072
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<400> 1072
gcaguaucug gagucauuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1073
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<400> 1073
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1074
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1075
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1076
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1076
uccuaccugu cagagcccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1077
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1077
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1078
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1078
agccccaagg uaaaaaggcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1079
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<400> 1079
uuucccggcc uuuuuaccuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1080
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1080
cuuucccggc cuuuuuaccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1081
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<400> 1081
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1082
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1082
cacacuguga gcugccuggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1083
<211> 100
<212> RNA
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<220>
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<400> 1083
guggcacacu gugagcugcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1084
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<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1084
gagauugagc ucuacucagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1085
<211> 100
<212> RNA
<213> 人工序列

<220>
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<400> 1085
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1086
<211> 100

<212> RNA
<213> 人工序列

<220>
<223> 合成

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<400> 1086
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1087
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<212> RNA
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<400> 1087
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1088
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<212> RNA
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<221> misc_feature
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<400> 1088
uaccggaaga gaccagaggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1089
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<212> RNA
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<400> 1089
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1090
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<212> RNA
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1090
ggcuuaugcc aauaucggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1091
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<400> 1091
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1092
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<212> RNA
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<220>
<223> 合成

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1092
gacugcgcuu uuccuugucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1093
<211> 100
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<220>
<223> 合成

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1093
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1094
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1094
ccaguuccgc ugcccagaca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1095
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<212> RNA
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<400> 1095
gaccugaagc acuggaagcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1096
<211> 100
<212> RNA
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<220>
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1096
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1097
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<400> 1097
cacuggaagc caggugugca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1098
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<212> RNA
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<220>
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<400> 1098
ggaagccagg ugugcagggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1099
<211> 100
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<400> 1099
agccaggugu gcagggcagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1100
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<400> 1100
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<400> 1101
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1102

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1103
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1104
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1105
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1106
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<400> 1106
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1107
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1108
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1109
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1110
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1111
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1112
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1113
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1114
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<400> 1114
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1115
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1116
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<400> 1116
ccacucucca cccccaaugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1117

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<400> 1117
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1118
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<400> 1118
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<400> 1119
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1120
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1121
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<400> 1121
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1122
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<400> 1123
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1124
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<400> 1126
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<400> 1127
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<210> 1128
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<400> 1128
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1129
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<400> 1130
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1131
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<400> 1132
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1133
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1134
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<400> 1135
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<400> 1136
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<400> 1137
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1138
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1139
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<400> 1140
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<400> 1141
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1142
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1143
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1144
ccugagacag ggcccagccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1145
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1145
aucugauucc accugcagcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1146
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<400> 1146
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1147
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1149
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1150
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1151
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<210> 1152
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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1153
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<400> 1154
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1155
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<400> 1155
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1156
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<400> 1156
guacaagcug ucggaaacag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1157
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1158
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<400> 1158
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 1159
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<400> 1159
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<400> 1160
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> 含有2'-O-Me及PS修飾；關於取代及優選實施例之詳細描述，參見所提交之說明書

<400> 1161
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<400> 1162
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 1163
gugggcgucc acauccugca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

【發明申請專利範圍】

【請求項1】

一種組合物，其包含：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中該第二mRNA不同於該第一mRNA，視情況其中該組合物包含脂質奈米粒子。

【請求項2】

如請求項1之組合物，其中該第一開讀框不包含編碼UGI之序列。

【請求項3】

如請求項1或2之組合物，其中該組合物包含第一組合物及第二組合物，其中該第一組合物包含含有編碼包含胞苷去胺酶及RNA導引之切口酶且不包含尿嘧啶醣苷酶抑制劑(UGI)之多肽的第一開讀框之第一mRNA，且該第二組合物包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中該第二mRNA不同於該第一mRNA，視情況其中該等組合物包含脂質奈米粒子。

【請求項4】

如請求項1至3中任一項之組合物，其中該第一mRNA及該等第二mRNA在同一或單獨小瓶中。

【請求項5】

一種修飾目標基因之方法，其包含向細胞遞送：第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之第一多肽的第一開讀框；第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框，其中該第二mRNA不同於該第一mRNA；及至少一種導引RNA(gRNA)。

【請求項6】

如請求項5之方法，其中若該切口酶為SpyCas9切口酶，則該gRNA為SpyCas9gRNA，且若該切口酶為NmeCas9切口酶，則該gRNA為NmegRNA。

【請求項7】

如請求項5或6之方法，其中該第一開讀框不包含編碼UGI之序列。

【請求項8】

如請求項1至7中任一項之組合物或方法，其中該第二mRNA與該第一mRNA之莫耳比為1:1至30:1。

【請求項9】

如請求項1至7中任一項之組合物或方法，其中該莫耳比為2:1至30:1。

【請求項10】

如請求項1至7中任一項之組合物或方法，其中該莫耳比為7:1至22:1。

【請求項11】

一種mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框，其中該多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

【請求項12】

一種修飾細胞中之目標基因內之至少一個胞苷的方法，其包含在該細胞中表現以下或使該細胞與以下接觸：(i)包含胞苷去胺酶及RNA導引之切口酶的第一多肽，其中該第一多肽不包含尿嘧啶醣苷酶抑制劑(UGI)；(ii)UGI多肽；及(iii)至少一種導引RNA(gRNA)，其中該第一多

肽及gRNA與該目標基因一起形成複合物且修飾該目標基因中之至少一個胞苷。

【請求項13】

如請求項12之方法，其中若該切口酶為SpyCas9切口酶，則該gRNA為SpyCas9 gRNA，且若該切口酶為NmeCas9切口酶，則該gRNA為NmegRNA。

【請求項14】

如請求項12或13之方法，其中該UGI多肽與該第一多肽之比為10:1至50:1。

【請求項15】

一種細胞，其中如請求項1至4及8至11中任一項之mRNA或組合物已引入至該細胞中，其中該細胞在該引入之後已經修飾。

【請求項16】

一種經工程改造之細胞，其藉由如請求項5至10及12至14之方法改變。

【請求項17】

一種經工程改造之細胞，其包含至少一種鹼基編輯及/或插入/缺失，其中該鹼基編輯及/或插入/缺失係藉由使細胞與組合物接觸而形成，該組合物包含含有編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框之第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框之第二mRNA，其中該第二mRNA不同於該第一mRNA。

【請求項18】

如請求項17之經工程改造之細胞，其中該第一開讀框不包含編碼

UGI之序列。

【請求項19】

如請求項1至18中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶為

(i)APOBEC家族之酶，視情況為APOBEC3子群之酶；

(ii)包含與SEQ ID NO:40、41及960至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iii)包含與SEQ ID NO:40、41及960至1013中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；

(iv)包含與SEQ ID NO:40、41、976、977、979、980、984至987、993至1006及1009中之任一者至少80%一致之胺基酸序列的胞苷去胺酶；或

(v)包含與SEQ ID NO:40、976、981、984、986及1014至1023中之任一者至少80%一致之胺基酸序列的胞苷去胺酶。

【請求項20】

如請求項19之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶包含與SEQ ID NO:40、41及960至1023具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

【請求項21】

如請求項19之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶包含與SEQ ID NO:40、41及960至1013具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

【請求項22】

如請求項19之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶包含與SEQ ID NO:40、41、976、977、979、980、984至987、993至1006及1009至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

【請求項23】

如請求項19之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶包含與SEQ ID NO:40、976、981、984、986、1014至1023具有至少80%、85%、87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

【請求項24】

如請求項1至23中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶為APOBEC3A去胺酶(A3A)。

【請求項25】

如請求項24之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該A3A包含SEQ ID NO:40之胺基酸序列或與SEQ ID NO:40具有至少87%、至少90%、至少95%、至少98%、至少99%一致性之胺基酸序列。

【請求項26】

如請求項24至25中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該A3A為人類A3A。

【請求項27】

如請求項24至26中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該A3A為野生型A3A。

【請求項28】

如請求項24之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該A3A包含與SEQ ID NO:976、977、993至1006及1009具有至少87%、90%、95%、98%、99%或100%一致性之胺基酸序列。

【請求項29】

如請求項1至28中任一項之組合物、方法、細胞或經工程改造之細胞，其中該UGI包含SEQ ID NO:27之胺基酸序列或與SEQ ID NO:27具有至少80%、至少90%、至少95%、至少98%、至少99%一致性之胺基酸序列。

【請求項30】

如請求項1至4、8至10及15至29中任一項之組合物、方法或細胞，進一步包含至少一種導引RNA(gRNA)。

【請求項31】

如請求項1至4、8至10及15至30中任一項之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中該gRNA為sgRNA。

【請求項32】

如請求項1至4、8至10及15至31中任一項之組合物、方法、細胞或經工程改造之細胞，其包含gRNA，其中該gRNA為包含含有髮夾區之sgRNA之保守部分的短單導引RNA(短sgRNA)，其中該髮夾區缺少至少5至10個核苷酸且其中該短sgRNA包含5'端修飾或3'端修飾或兩者。

【請求項33】

如請求項1至32中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該RNA導引之切口酶為Cas9切口酶。

【請求項34】

如請求項1至33中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該RNA導引之切口酶為化膿性鏈球菌(*S. pyogenes*)(Spy)Cas9切口酶。

【請求項35】

如請求項34之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該RNA導引之切口酶為D10A SpyCas9切口酶。

【請求項36】

如請求項1至35中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該RNA導引之切口酶包含SEQ ID NO:70、73或76中之任一者的胺基酸序列或與SEQ ID NO:70、73或76中之任一者具有至少80%、90%、95%、98%或99%一致性的胺基酸序列。

【請求項37】

如請求項1至36中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼該RNA導引之切口酶之序列包含SEQ ID NO:72、75或78中之任一者的核苷酸序列或與SEQ ID NO:72、75或78中之任一者之核苷酸序列具有至少80%、90%、95%、98%或99%一致性的核苷酸序列。

【請求項38】

如請求項1至37中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼該RNA導引之切口酶之該序列包含SEQ ID NO:71、72、74、75或77至90中之任一者之核苷酸序列。

【請求項39】

如請求項1至33中任一項之mRNA、組合物、方法、細胞或經工程改

造之細胞，其中該RNA導引之切口酶為腦膜炎雙球菌(*N. meningitides*)(Nme)Cas9切口酶。

【請求項40】

如請求項39之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該RNA導引之切口酶為D16A NmeCas9切口酶，視情況為D16A Nme2Cas9。

【請求項41】

如請求項1至33、39或40中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼該RNA導引之切口酶之序列包含SEQ ID NO:380及387中之任一者之核苷酸序列。

【請求項42】

如請求項1至41中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該mRNA包含與SEQ ID NO:91至98中之任一者具有至少90%一致性的5'UTR。

【請求項43】

如請求項1至42中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該mRNA包含與SEQ ID NO:99至106中之任一者具有至少90%一致性的3'UTR。

【請求項44】

如請求項1至43中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該mRNA進一步包含選自Cap0、Cap1、Cap2之5'端帽及共轉錄或轉錄後添加之端帽，視情況其中該共轉錄添加之端帽選自抗逆端帽類似物(ARCA)、AG(m7G(5')ppp(5')(2'OMeA)pG或

GG(m7G(5')ppp(5') (2'OMeG)pG、轉錄後添加之端帽。

【請求項45】

如請求項1至44中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該mRNA進一步包含多腺苷酸化(poly-A)尾，視情況其中該poly-A尾係藉由PCR加尾或酶促加尾添加至mRNA且視情況其中該poly-A尾包含SEQ ID NO:109之序列。

【請求項46】

如請求項1至45中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的該開讀框及/或編碼尿嘧啶醣苷酶抑制劑(UGI)之該開讀框包含(i)最小腺嘌呤密碼子及/或最小尿苷密碼子；(ii)最小腺嘌呤密碼子；(iii)增加哺乳動物中該mRNA之轉譯的密碼子；或(iv)增加哺乳動物中該mRNA之轉譯的密碼子，其中該哺乳動物為人類。

【請求項47】

如請求項1至46中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該胞苷去胺酶位於該多肽中之該RNA導引之切口酶的N末端。

【請求項48】

如請求項1至47中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)。

【請求項49】

如請求項1至48中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且

其中該NLS處於該RNA導引之切口酶之C末端。

【請求項50】

如請求項1至49中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS處於該RNA導引之切口酶之N末端，或其中NLS融合至該RNA導引之切口酶之該N末端及該C末端兩者。

【請求項51】

如請求項1至50中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中連接子存在於該RNA導引之切口酶之該N末端與該NLS之間，視情況其中該連接子為肽連接子。

【請求項52】

如請求項1至51中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS包含與SEQ ID NO:63及110至122中之任一者具有至少80%、85%、90%或95%一致性之序列。

【請求項53】

如請求項1至52中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該NLS包含SEQ ID NO:63及110至122中之任一者之序列。

【請求項54】

如請求項1至53中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且

其中該NLS係由與SEQ ID NO:123至135中之任一者之序列具有至少80%、85%、90%、95%、98%或100%一致性的序列編碼。

【請求項55】

如請求項1至54中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼RNA之導引之切口酶包含核定位訊號(NLS)，且其中該胞苷去胺酶位於該多肽中之該NLS的N末端。

【請求項56】

如請求項1至55中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經編碼之RNA導引之切口酶包含核定位訊號(NLS)，且其中該RNA導引之切口酶位於該多肽中之該NLS的N末端。

【請求項57】

如請求項1至56中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的該開讀框包含與SEQ ID NO:1之序列具有至少80%、85%、90%、95%、98%或100%一致性之序列。

【請求項58】

如請求項1至57中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的該開讀框包含與SEQ ID NO:4之序列具有至少80%、85%、90%、95%、98%或100%一致性之序列。

【請求項59】

如請求項1至58中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的該開

讀框包含與SEQ ID NO:321之序列具有至少80%、85%、90%、95%98%、99%或100%一致性之序列。

【請求項60】

如請求項1至59中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的該開讀框包含與SEQ ID NO:313之序列具有至少80%、85%、90%、95%、98%、99%或100%一致性之序列。

【請求項61】

如請求項1至60中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該mRNA中至少10%之尿苷由經修飾之尿苷取代。

【請求項62】

如請求項61之mRNA、組合物、方法、細胞或經工程改造之細胞，其中該經修飾之尿苷為N1-甲基-假尿苷、假尿苷、5-甲氧基尿苷或5-碘尿苷中之一或多者。

【請求項63】

如請求項61至62中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中15%至45%之尿苷由該經修飾之尿苷取代。

【請求項64】

如請求項61至63中任一項之mRNA、組合物、方法、細胞或經工程改造之細胞，其中至少20%或至少30%、至少80%、或至少90%、或100%之尿苷由該經修飾之尿苷取代。

【請求項65】

如前述請求項61至64中任一項之mRNA、組合物、方法或細胞，其

進一步編碼該胞苷去胺酶與該RNA導引之切口酶之間的肽連接子，視情況其中該肽連接子為XTEN或該肽連接子包含GTKDSTKDIPETPSKD之序列(SEQ ID NO:268)。

【請求項66】

如請求項61至65中任一項之mRNA、組合物、方法或細胞，其進一步編碼該胞苷去胺酶與該RNA導引之切口酶之間的肽連接子，其中該肽連接子包含至少1個、至少2個、至少3個、至少4個、至少5個、至少6個、至少7個、至少8個、至少9個、至少10個、至少15個、至少20個、至少25個、至少30個、至少40個、至少50個或更多個胺基酸。

【請求項67】

如請求項61至66中任一項之mRNA、組合物、方法或細胞，其進一步編碼該胞苷去胺酶與該RNA導引之切口酶之間的肽連接子，其中該肽連接子包含選自SEQ ID NO:46至59、61及211至272之一或多個序列。

【請求項68】

一種多肽，其由如請求項1至28及33至67中任一項之mRNA中之任一者編碼。

【請求項69】

一種核糖核蛋白複合物(RNP)，其包含(i)由如請求項1至28及33至67中任一項之mRNA中之任一者編碼的多肽；及(ii)導引RNA。

【請求項70】

一種載體，其包含如請求項1至28及33至67中任一項之mRNA中之任一者。

【請求項71】

一種表現構築體，其包含可操作地連接至編碼如請求項1至28、33至60及65至67中任一項之mRNA中之任一者之序列的啟動子。

【請求項72】

一種質體，其包含如請求項71之表現構築體。

【請求項73】

一種宿主細胞，其包含如請求項70之載體、如請求項71之表現構築體或如請求項72之質體。

【請求項74】

如請求項1至4、8至11及19至67中任一項之mRNA或組合物，其中該mRNA或該組合物經調配成脂質核酸組裝組合物，視情況為脂質奈米粒子。

【請求項75】

一種如請求項1至4、8至11及19至67中任一項之mRNA或組合物的用途，其用於修飾細胞中之目標基因。

【請求項76】

一種如請求項1至4、8至11及19至67中任一項之mRNA或組合物的用途，其用於製造用於修飾細胞中之目標基因的藥劑。

【請求項77】

一種修飾細胞中之目標基因的方法，其包含向該細胞遞送一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，該一或多種脂質核酸組裝組合物包含：

(a)第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；

(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)一或多種導引RNA。

【請求項78】

如請求項77之方法，其中部件(a)、(b)及(c)各自在單獨的脂質核酸組裝組合物中。

【請求項79】

如請求項77之方法，其中部件(a)、(b)及(c)在同一脂質核酸組裝組合物中。

【請求項80】

如請求項77至79中任一項之方法，其中該一或多種導引RNA各自在單獨的脂質核酸組裝組合物中。

【請求項81】

如請求項77至80中任一項之方法，其包含向該細胞遞送脂質核酸組裝組合物，該脂質核酸組裝組合物包含在同一脂質核酸組裝組合物中的包含編碼包含胞苷去胺酶及RNA導引之切口酶的多肽之第一開讀框的第一mRNA及包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。

【請求項82】

如請求項77至81中任一項之方法，其包含向該細胞遞送：第一脂質核酸組裝組合物，其包含含有編碼包含胞苷去胺酶及RNA導引之切口酶的多肽之第一開讀框的第一mRNA；及第二脂質核酸組裝組合物，其包含含有編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框的第二mRNA。

【請求項83】

如請求項77至82中任一項之方法，其進一步包含遞送一或多種脂質核酸組裝組合物中之一或多種導引RNA，該一或多種脂質核酸組裝組合物與包含該胞苷去胺酶及該UGI之該脂質核酸組裝組合物分開。

【請求項84】

如請求項77至83中任一項之方法，其中向該細胞遞送至少2、3、4、5、6、7、8、9或10種脂質核酸組裝組合物。

【請求項85】

如請求項77至84中任一項之方法，其中至少一種脂質核酸組裝組合物包含脂質奈米粒子(LNP)，視情況其中所有脂質核酸組裝組合物包含LNP。

【請求項86】

如請求項77至85中任一項之方法，其中至少一種脂質核酸組裝組合物為脂質複合物組合物。

【請求項87】

如請求項77至86中任一項之方法，其中該脂質核酸組裝組合物包含可離子化脂質。

【請求項88】

如請求項77至87中任一項之方法，其中該脂質核酸組裝組合物包含可離子化脂質且其中該可離子化脂質之pKa在約5.1至約7.4，諸如約5.5至約6.6、約5.6至約6.4、約5.8至約6.2或約5.8至約6.5之範圍內。

【請求項89】

如請求項77至88中任一項之方法，其中該脂質核酸組裝組合物包含

(i)胺脂質；(ii)輔助脂質；(iii)隱形脂質；(iv)中性脂質；或(i)至(iv)中之一或多者之組合。

【請求項90】

如請求項89之方法，其中(i)該胺脂質為脂質A；(ii)該輔助脂質為膽固醇；(iii)該隱形脂質為PEG2k-DMG；(iv)該中性脂質為DSPC；或(i)至(iv)中之一或多者之組合。

【請求項91】

如請求項77至90中任一項之方法，其中該脂質核酸組裝組合物之N/P比為約6。

【請求項92】

如請求項77至91中任一項之方法，其中該脂質核酸組裝組合物包含約50mol%胺脂質，諸如脂質A；約9mol%中性脂質，諸如DSPC；約3mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且該脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中該脂質核酸組裝組合物之N/P比為約6。

【請求項93】

如請求項77至92中任一項之方法，其中該脂質核酸組裝組合物包含約35mol%胺脂質，諸如脂質A；約15mol%中性脂質，諸如DSPC；約2.5mol%隱形脂質，諸如PEG脂質，諸如PEG2k-DMG，且該脂質組分之其餘部分為輔助脂質，諸如膽固醇，其中該脂質核酸組裝組合物之N/P比為約6。

【請求項94】

如請求項77至93中任一項之方法，其包含靶向降低或消除細胞表面

上之MHC第I類表現之基因的一種gRNA，及/或靶向降低或消除細胞表面上之MHC第II類表現之基因的一種gRNA，及/或靶向降低或消除內源性TCR表現之基因的一種gRNA。

【請求項95】

如請求項77至94中任一項之方法，其包含選自以下之至少兩種gRNA：靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA、靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

【請求項96】

如請求項77至95中任一項之方法，其包含靶向降低或消除細胞表面上之MHC I類表現之基因的一種gRNA、靶向降低或消除細胞表面上之MHC II類表現之基因的一種gRNA及靶向降低或消除內源性TCR表現之基因的一種gRNA。

【請求項97】

如請求項77至96中任一項之方法，其包含選自靶向TRAC、TRBC、B2M、HLA-A或CIITA之gRNA的一種gRNA。

【請求項98】

如請求項77至97中任一項之方法，其中該gRNA靶向TRBC，其中該gRNA包含選自以下之導引序列：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)

之序列至少95%、90%或85%一致的導引序列。

【請求項99】

如請求項77至97中任一項之方法，其中該gRNA靶向TRBC，其中該gRNA包含選自以下之導引序列：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列。

【請求項100】

如請求項77至97中任一項之方法，其包含選自靶向TRAC、TRBC或B2M之gRNA的至少兩種gRNA，其中該兩種導引RNA不靶向相同基因。

【請求項101】

如請求項77至97中任一項之方法，其包含選自靶向TRAC、TRBC或HLA-A之gRNA的至少兩種gRNA，其中該兩種導引RNA不靶向相同基因。

【請求項102】

如請求項77至97中任一項之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA。

【請求項103】

如請求項77至97中任一項之方法，其包含靶向B2M之一種導引RNA及靶向CIITA之一種gRNA。

【請求項104】

如請求項77至97中任一項之方法，其包含靶向HLA-A之一種導引RNA及靶向CIITA之一種gRNA，視情況其中該細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

【請求項105】

如請求項77至97中任一項之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向B2M之一種gRNA。

【請求項106】

如請求項77至97中任一項之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA及靶向HLA-A之一種gRNA，視情況其中該細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

【請求項107】

如請求項77至97中任一項之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向B2M之一種gRNA及靶向CIITA之一種gRNA。

【請求項108】

如請求項77至97中任一項之方法，其包含靶向TRAC之一種導引RNA及靶向TRBC之一種gRNA、靶向HLA-A之一種gRNA及靶向CIITA之一種gRNA，視情況其中該細胞對於HLA-B為同型組合的且對於HLA-C為同型組合的。

【請求項109】

如請求項5至10、12至14、19至67及77至108中任一項之方法，其中該方法在存在於目標序列內時，會產生胞嘧啶(C)至胸腺嘧啶(T)轉化，視情況其中若該切口酶為SpyCas9切口酶，則該C形成T轉化包含1至12個C

形成T轉化，且若該切口酶為NmeCas9切口酶，則該C形成T轉化包含1至20個C形成T轉化。

【請求項110】

如請求項5至10、12至14、19至67及77至109中任一項之方法，其中相對於該目標序列中之總編輯，該方法引起至少60%的C形成T轉化。

【請求項111】

如請求項5至10、12至14、19至67及77至110中任一項之方法，其中相對於該目標序列中之總編輯，該方法引起至少65%、70%、75%、80%、85%、90%、95%、98%或99%的C形成T轉化。

【請求項112】

如請求項5至10、12至14、19至67及77至111中任一項之方法，其中C形成T轉化與非預期編輯之比大於1:1。

【請求項113】

如請求項5至10、12至14、19至67及77至112中任一項之方法，其中C形成T轉化與非預期編輯之比為2:1至99:1。

【請求項114】

如請求項5至10、12至14、19至67及77至113中任一項之方法，其中C形成T轉化與非預期編輯之比為2:1、3:1、4:1、5:1、6:1、7:1或8:1。

【請求項115】

如請求項5至10、12至14、19至67及77至114中任一項之方法，其中該方法使該胞苷去胺酶在對應於該導引序列之5'端的相對位置-1至位置10中之任一者進行鹼基編輯。

【請求項116】

如請求項5至10、12至14、19至67及77至115中任一項之方法，其中該方法使該胞苷去胺酶在距該導引序列之5'端的1、2、3、4、5、6、7、8、9或10個核苷酸的位置處存在之胞苷進行鹼基編輯。

【請求項117】

如請求項5至10、12至14、19至67及77至116中任一項之方法，其中該切口酶為SpyCas9切口酶，且該方法使該胞苷去胺酶在距該導引序列之5'端的1、2、3、4、5、6、7、8、9、10或11個核苷酸的位置處存在之胞苷進行鹼基編輯。

【請求項118】

如請求項5至10、12至14、19至67及77至116中任一項之方法，其中該切口酶為NmeCas9切口酶，且該方法使該胞苷去胺酶在距該導引序列之5'端的4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19或20個核苷酸的位置處存在之胞苷進行鹼基編輯。

【請求項119】

如請求項5至10、12至14、19至67及77至118中任一項之方法，其中該第一mRNA、該第二mRNA及該導引RNA(若存在)，以約6:2:3(w:w:w)之比遞送。

【請求項120】

如請求項5至10、12至67及77至119中任一項之方法、細胞或經工程改造之細胞，其中該細胞為淋巴細胞。

【請求項121】

如請求項5至10、12至14、19至67及75至120中任一項之方法或用途，其中該目標基因之修飾係在活體內進行。

【請求項122】

如請求項5至10、12至14、19至67及75至120中任一項之方法或用途，其中該目標基因之該修飾係在活體外進行。

【請求項123】

如請求項5至10、12至14、19至67及75至122中任一項之方法或用途，其中該目標基因之修飾降低或消除該目標基因之表現。

【請求項124】

如請求項5至10、12至14、19至67及75至123中任一項之方法或用途，其中該目標基因之基因體編輯或修飾使該目標基因之表現降低至少50%、55%、60%、65%、70%、75%、80%、85%、90%、或95%。

【請求項125】

如請求項5至10、12至14、19至67及75至124中任一項之方法或用途，其中該目標基因之基因體編輯或修飾在該基因中產生誤義突變。

【請求項126】

一種多肽，其包含胞苷去胺酶及RNA導引之切口酶，其中該多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

【請求項127】

一種核糖核蛋白複合物(RNP)，其包含如請求項126之多肽及導引RNA，其中若該RNP包含SpyCas9切口酶，則該導引RNA為Spy導引RNA，且其中若該RNP包含NmeCas切口酶，則該導引RNA為Nme導引RNA。

【請求項128】

一種組合物，其包含：第一多肽，包含胞苷去胺酶及RNA導引之切

口酶，其中該第一多肽不包含尿嘧啶醣苷酶抑制劑(UGI)；及第二多肽，其包含UGI，其中該第二多肽不同於該第一多肽。

【請求項129】

如請求項126至128中任一項之多肽、RNP或組合物，其中該胞苷去胺酶係經由肽連接子，視情況XTEN或包含GTKDSTKDIPETPSKD之序列(SEQ ID NO:268)之肽連接子融合至該RNA導引之切口酶。

【請求項130】

如請求項126至128中任一項之多肽、RNP或組合物，其中該胞苷去胺酶連接至包含有機分子、聚合物或化學部分之連接子。

【請求項131】

一種藥物組合物，其包含如請求項1至4、8至11、19至69、74及126至130之mRNA、RNP、組合物或多肽，及醫藥學上可接受之載劑。

【請求項132】

一種套組，其包含如請求項1至4、8至11、19至69、74及126至130中任一項之mRNA、RNP、組合物或多肽。

【請求項133】

如請求項1至132中任一項之mRNA、RNP、組合物、方法、用途、細胞或經工程改造之細胞，其中包含胞苷去胺酶及RNA導引之切口酶的該多肽以胺基至羧基末端順序包括：該胞苷去胺酶、連接子及該RNA導引之切口酶。

【請求項134】

一種改變TRAC基因內之DNA序列的方法，其包含向細胞遞送：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)

選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b.編碼(a.)之gRNA的核酸。

【請求項135】

一種降低TRAC基因之表現的方法，其包含向細胞遞送：

a.包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b.編碼(a.)之gRNA的核酸。

【請求項136】

一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之基因修飾：

chr14:22547596-22547616；chr14:22550570-22550590；chr14:22547763-22547783；chr14:22550596-22550616；chr14:22550566-22550586；chr14:22547753-22547773；

chr14:22550601-22550621 ; chr14:22550599-22550619 ;

chr14:22547583-22547603 ; chr14:22547671-22547691 ;

chr14:22547770-22547790 ; chr14:22547676-22547696 ;

chr14:22547772-22547792 ; chr14:22547771-22547791 ;

chr14:22547733-22547753；chr14:22547776-22547796；或

其中該細胞係藉由向該細胞遞送以下而經工程改造：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之gRNA的核酸。

【請求項137】

一種改變TRBC1及/或TRBC2基因內之DNA序列的方法，其包含向細胞遞送組合物，其中該組合物包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

【請求項138】

一種降低TRBC1及/或TRBC2基因之表現的方法，其包含向細胞遞送組合物，其中該組合物包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

【請求項139】

一種免疫療法之方法，其包含向個體投與包含經工程改造之細胞的組合物，

其中該細胞包含選自以下之基因體座標內的至少一個核苷酸之修飾：chr7:142791757-142791777；chr7:142801104-142801124；chr7:142791811-142791831；chr7:142801158-142801178；chr7:142792728-142792748；chr7:142791719-142791739；chr7:142791766-142791786；chr7:142801113-142801133；chr7:142791928-142791948；chr7:142801275-142801295；chr7:142792062-142792082；chr7:142801409-142801429；chr7:142792713-142792733；chr7:142802126-142802146；chr7:142791808-142791828；chr7:142801155-142801175；

chr7:142792003-142792023	;	chr7:142801350-142801370	;
chr7:142791760-142791780	;	chr7:142791715-142791735	;
chr7:142792781-142792801	;	chr7:142792040-142792060	;
chr7:142801387-142801407	;	chr7:142791862-142791882	;
chr7:142791716-142791736	;	chr7:142791787-142791807	;
chr7:142791759-142791779	;	chr7:142801106-142801126	;
chr7:142791807-142791827	;	chr7:142801154-142801174	;
chr7:142791879-142791899	;	chr7:142801226-142801246	;
chr7:142791805-142791825	;	chr7:142791700-142791720	;
chr7:142791765-142791785	;	chr7:142801112-142801132	;
chr7:142791820-142791840	;	chr7:142791872-142791892	;
chr7:142801219-142801239	;	chr7:142791700-142791720	;
chr7:142791806-142791826	;	chr7:142801153-142801173	;
chr7:142792035-142792055	;	chr7:142792724-142792744	;
chr7:142792754-142792774	;	chr7:142791804-142791824	;
chr7:142792684-142792704	;	chr7:142791823-142791843	;
chr7:142792728-142792748	;	chr7:142792721-142792741	;
chr7:142792749-142792769	;	chr7:142792685-142792705	;
chr7:142791816-142791836	;	chr7:142801163-142801183	;
chr7:142792686-142792706	;	chr7:142791793-142791813	;
chr7:142793110-142793130	;	chr7:142791815-142791835	;
chr7:142801162-142801182	;	chr7:142792770-142792790	;
chr7:142792047-142792067	;	chr7:142801394-142801414	;

chr7:142791871-142791891 ; chr7:142801218-142801238 ;

chr7:142791894-142791914 ; chr7:142792723-142792743 ;

chr7:142792724-142792744 ; chr7:142791897-142791917 ;

chr7:142801244-142801264 ; chr7:142792757-142792777 ;

chr7:142792740-142792760；chr7:142792758-142792778；或

其中該細胞係藉由向細胞遞送以下而經工程改造：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；或

b. 編碼(a.)之導引RNA的核酸。

【請求項140】

一種組合物，其包含：

a.包含選自以下之導引序列的gRNA：i)SEQ ID NO:706至721；ii)選自SEQ ID NO:706至721之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:706至721之序列至少95%、90%或85%一致的導引序列；iv)包含表5A中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

b.如前述請求項中任一項之與mRNA或組合物相關之mRNA或組合

物。

【請求項141】

一種組合物，其包含：

a. 包含選自以下之導引序列的gRNA：i)SEQ ID NO:618至669；ii)選自SEQ ID NO:618至669之序列之至少17、18、19或20個連續核苷酸；iii)與選自SEQ ID NO:618至669之序列至少95%、90%或85%一致的導引序列；iv)包含表5B中所列出之基因體座標之10個連續核苷酸±10個核苷酸的序列；v)來自(iv)之序列之至少17、18、19或20個連續核苷酸；或vi)與選自(v)之序列至少95%、90%或85%一致的導引序列；及視情況

b. 如前述請求項中任一項之與mRNA或組合物相關之mRNA或組合物。

【請求項142】

一種已降低或消除TRAC之表面表現的經工程改造之細胞，其包含人類TRAC基因中之基因修飾，其中該基因修飾包含選自以下之基因體座標內的至少一個核苷酸之修飾：

chr14:22547596-22547616；chr14:22550570-22550590；chr14:22547763-22547783；chr14:22550596-22550616；chr14:22550566-22550586；chr14:22547753-22547773；chr14:22550601-22550621；chr14:22550599-22550619；chr14:22547583-22547603；chr14:22547671-22547691；chr14:22547770-22547790；chr14:22547676-22547696；chr14:22547772-22547792；chr14:22547771-22547791；chr14:22547733-22547753；chr14:22547776-22547796。

【請求項143】

一種已降低或消除TRBC1/2之表面表現的經工程改造之細胞，其包含人類TRBC1/2基因中之基因修飾，其中該基因修飾包含選自以下之基因體座標內的至少一個核苷酸之修飾：

chr7:142791757-142791777 ; chr7:142801104-142801124 ;
chr7:142791811-142791831 ; chr7:142801158-142801178 ;
chr7:142792728-142792748 ; chr7:142791719-142791739 ;
chr7:142791766-142791786 ; chr7:142801113-142801133 ;
chr7:142791928-142791948 ; chr7:142801275-142801295 ;
chr7:142792062-142792082 ; chr7:142801409-142801429 ;
chr7:142792713-142792733 ; chr7:142802126-142802146 ;
chr7:142791808-142791828 ; chr7:142801155-142801175 ;
chr7:142792003-142792023 ; chr7:142801350-142801370 ;
chr7:142791760-142791780 ; chr7:142791715-142791735 ;
chr7:142792781-142792801 ; chr7:142792040-142792060 ;
chr7:142801387-142801407 ; chr7:142791862-142791882 ;
chr7:142791716-142791736 ; chr7:142791787-142791807 ;
chr7:142791759-142791779 ; chr7:142801106-142801126 ;
chr7:142791807-142791827 ; chr7:142801154-142801174 ;
chr7:142791879-142791899 ; chr7:142801226-142801246 ;
chr7:142791805-142791825 ; chr7:142791700-142791720 ;
chr7:142791765-142791785 ; chr7:142801112-142801132 ;
chr7:142791820-142791840 ; chr7:142791872-142791892 ;

chr7:142801219-142801239 ; chr7:142791700-142791720 ;
chr7:142791806-142791826 ; chr7:142801153-142801173 ;
chr7:142792035-142792055 ; chr7:142792724-142792744 ;
chr7:142792754-142792774 ; chr7:142791804-142791824 ;
chr7:142792684-142792704 ; chr7:142791823-142791843 ;
chr7:142792728-142792748 ; chr7:142792721-142792741 ;
chr7:142792749-142792769 ; chr7:142792685-142792705 ;
chr7:142791816-142791836 ; chr7:142801163-142801183 ;
chr7:142792686-142792706 ; chr7:142791793-142791813 ;
chr7:142793110-142793130 ; chr7:142791815-142791835 ;
chr7:142801162-142801182 ; chr7:142792770-142792790 ;
chr7:142792047-142792067 ; chr7:142801394-142801414 ;
chr7:142791871-142791891 ; chr7:142801218-142801238 ;
chr7:142791894-142791914 ; chr7:142792723-142792743 ;
chr7:142792724-142792744 ; chr7:142791897-142791917 ;
chr7:142801244-142801264 ; chr7:142792757-142792777 ;
chr7:142792740-142792760；chr7:142792758-142792778。

【請求項144】

一種脂質核酸組裝組合物，其包含mRNA，該mRNA包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的開讀框，其中該多肽不包含尿嘧啶醣苷酶抑制劑(UGI)。

【請求項145】

一或多種脂質核酸組裝組合物，視情況為脂質奈米粒子，其包含：

(a)第一mRNA，其包含編碼包含胞苷去胺酶及RNA導引之切口酶之多肽的第一開讀框；

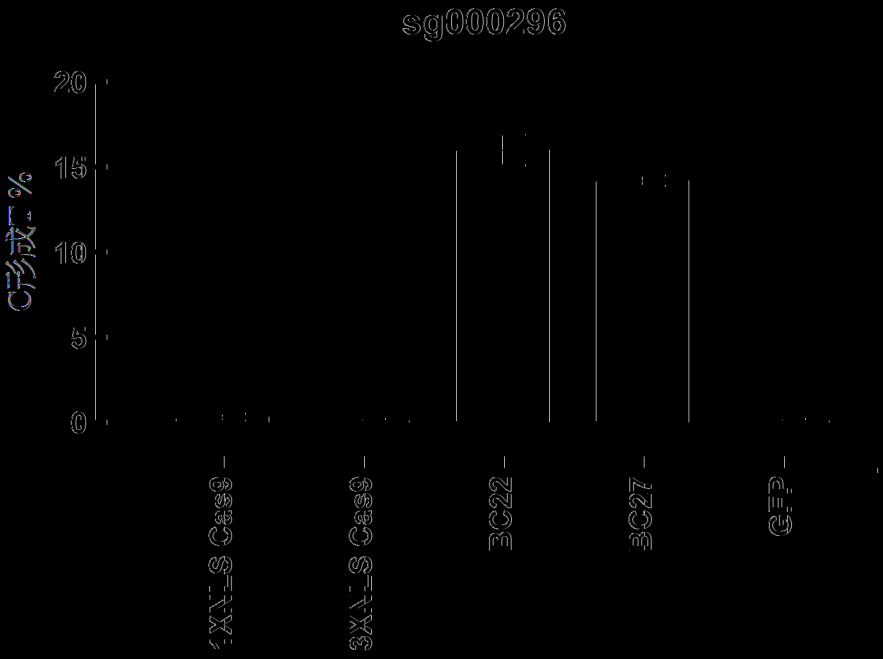
(b)第二mRNA，其包含編碼尿嘧啶醣苷酶抑制劑(UGI)之第二開讀框；及

(c)一或多種導引RNA。

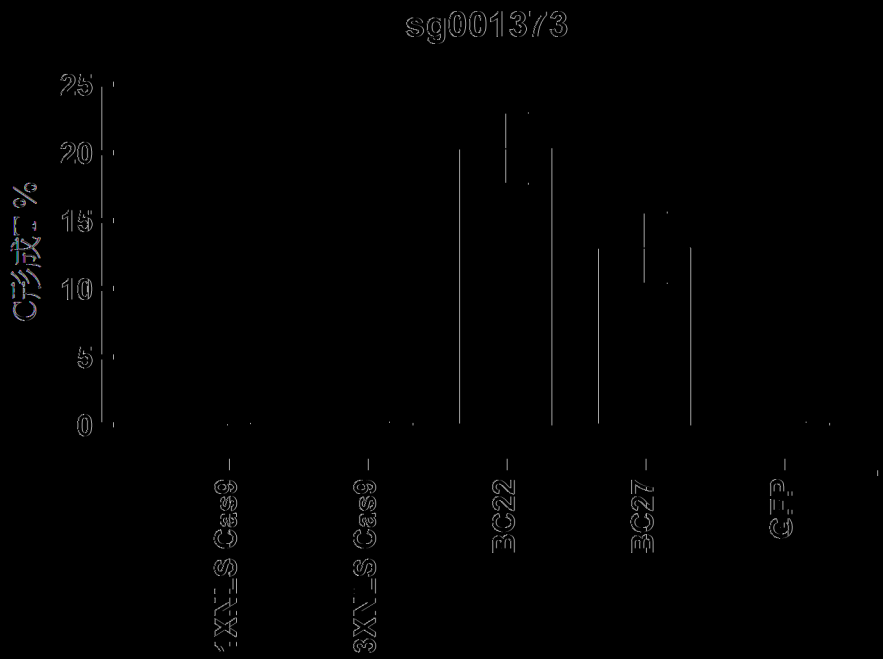
【請求項146】

如請求項134至143中任一項之方法、細胞或經工程改造之細胞，其中該細胞為免疫細胞、淋巴細胞或T細胞。

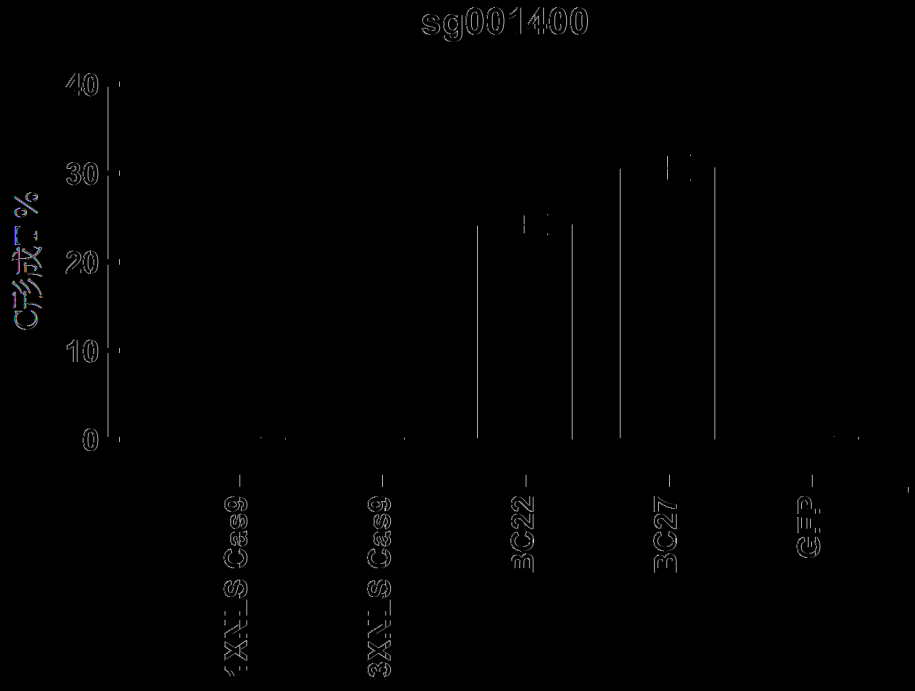
【發明圖式】


sg000296
20
15
10
5
0
C形成工%
1XNLS Cas9
3XNLS Cas9
BC22
BC27
GFP

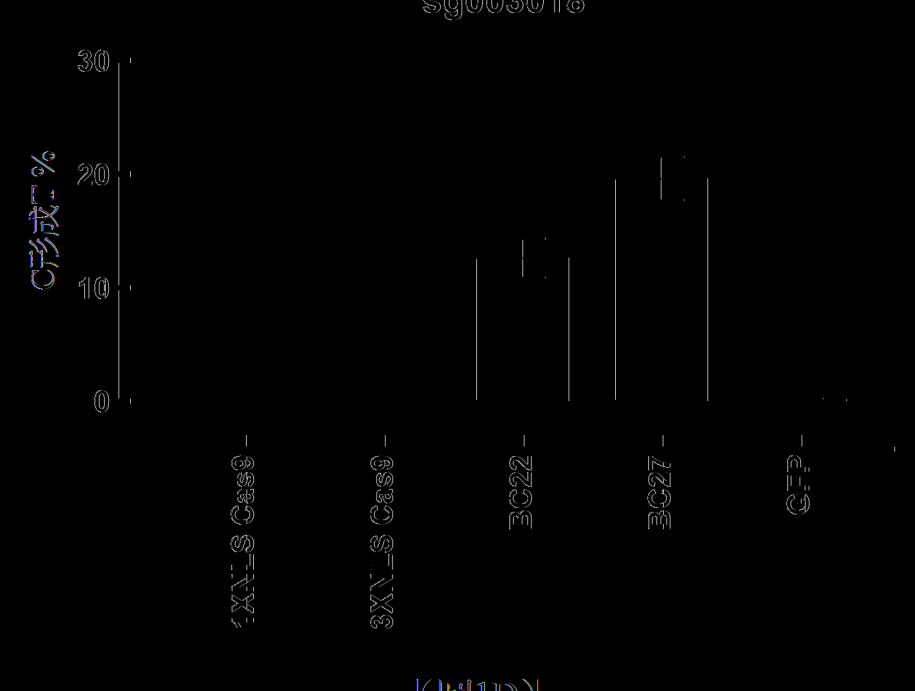
【圖1A】


sg001373
25
20
15
10
5
0
C形成工%
1XNLS Cas9
3XNLS Cas9
BC22
BC27
GFP

【圖1B】


sg001400
40
30
20
10
0
C形成工%
1XNLS Cas9
3XNLS Cas9
BC22
BC27
GFP

|(圖1C)|


sg003018
30
20
10
0
C形成工%
1XNLS Cas9
3XNLS Cas9
BC22
BC27
GFP

|(圖1D)|

|(圖10)|

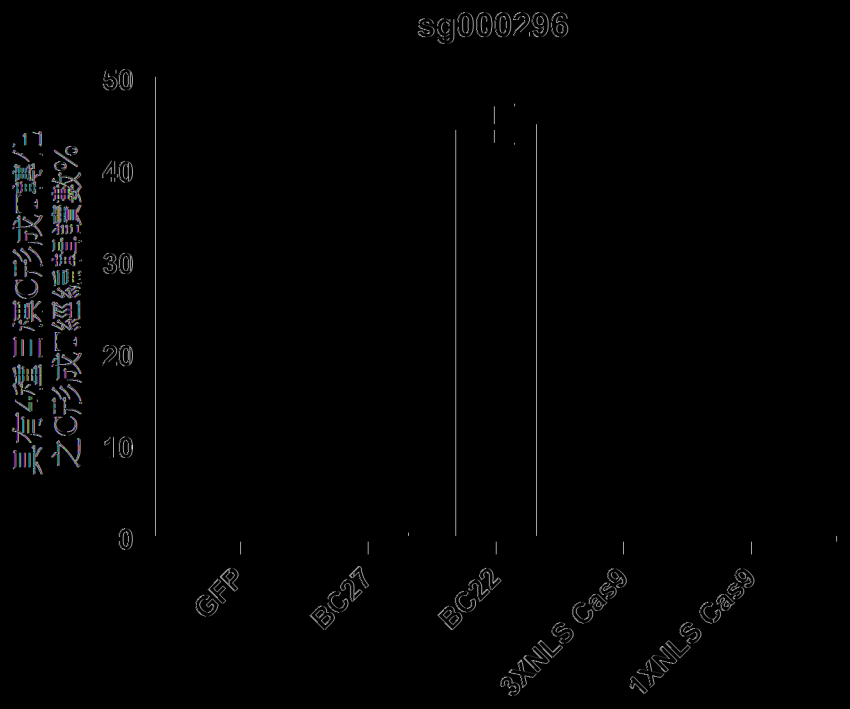

sg000296
50
40
30
20
10
0
GFP
BC27
BC22
3XNLS Cas9
1XNLS Cas9

圖2A

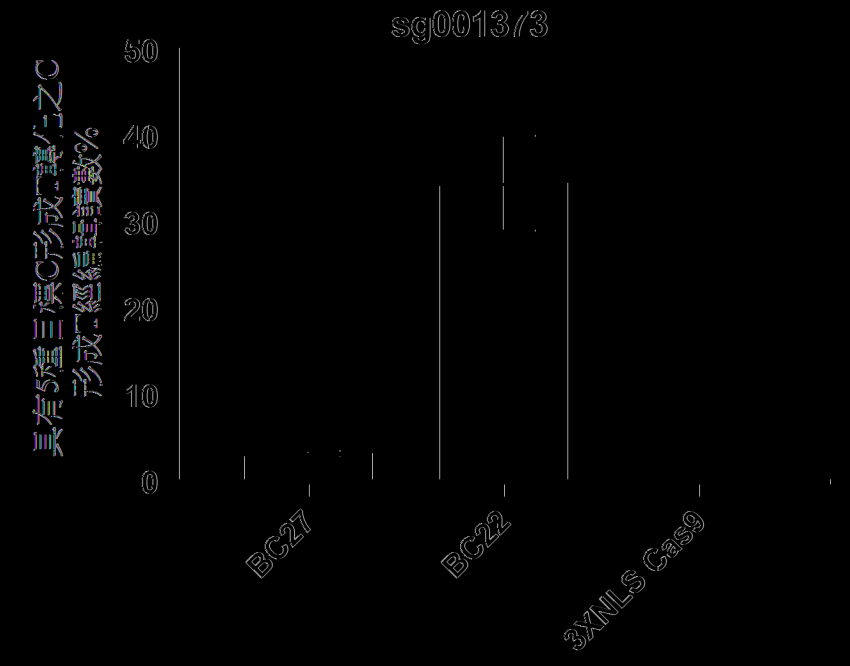

sg00013/3
50
40
30
20
10
0
BC27
BC22
3XNLS Cas9

圖2B

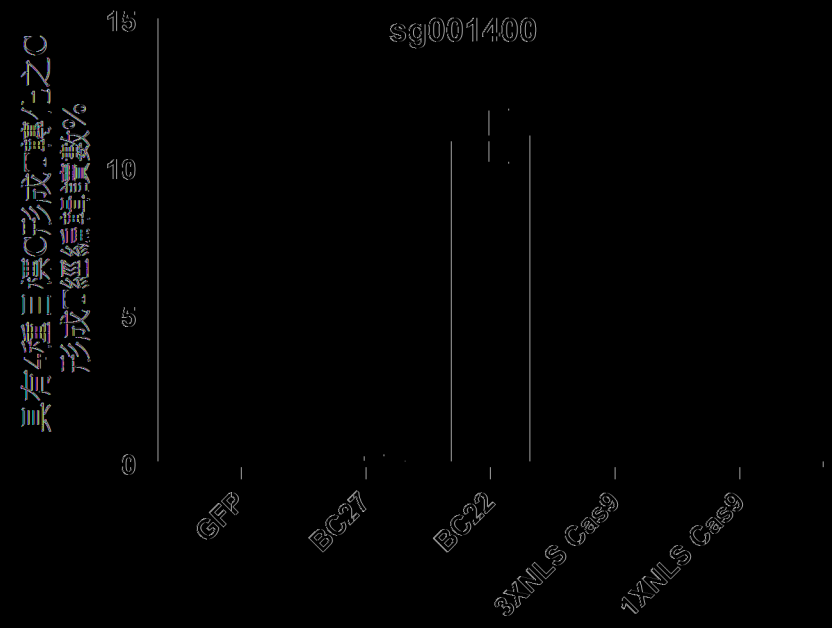

sg001400
15
10
5
0
GFP
BC27
BC22
3XNLS Cas9
1XNLS Cas9

圖2C

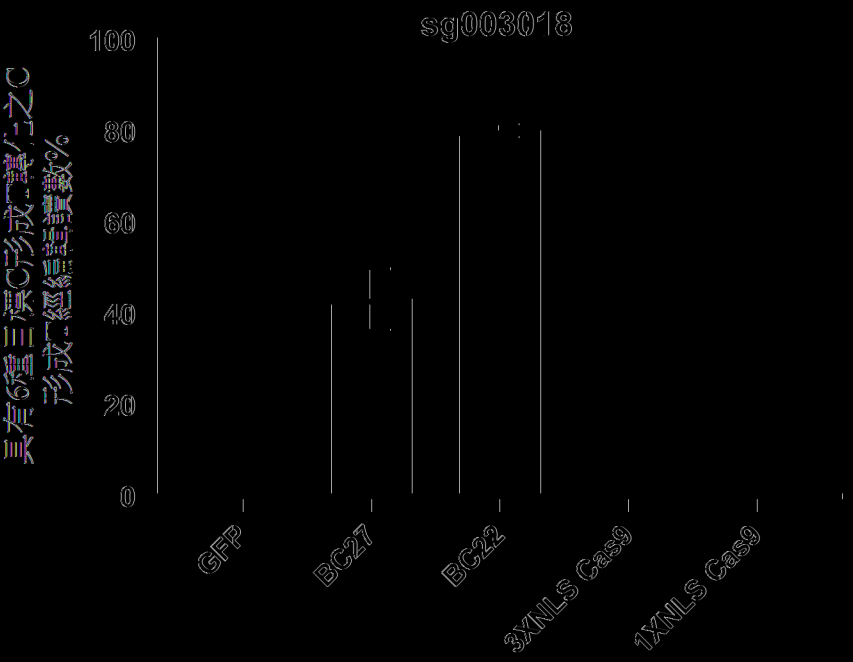
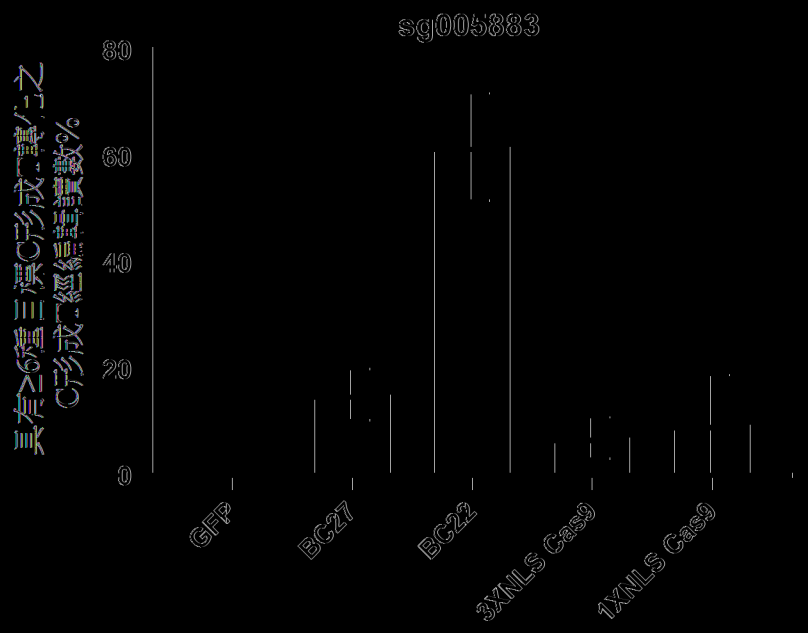

sg003018
100
80
60
40
20
0
GFP
BC27
BC22
3XNLS Cas9
1XNLS Cas9

圖2D


sg005883
80
60
40
20
0
具有≥6種三碟C形成二轉化之C形成二經編輯讀數%
GFP
BC27
BC22
3XNLS Cas9
1XNLS Cas9

|(圖2E)|

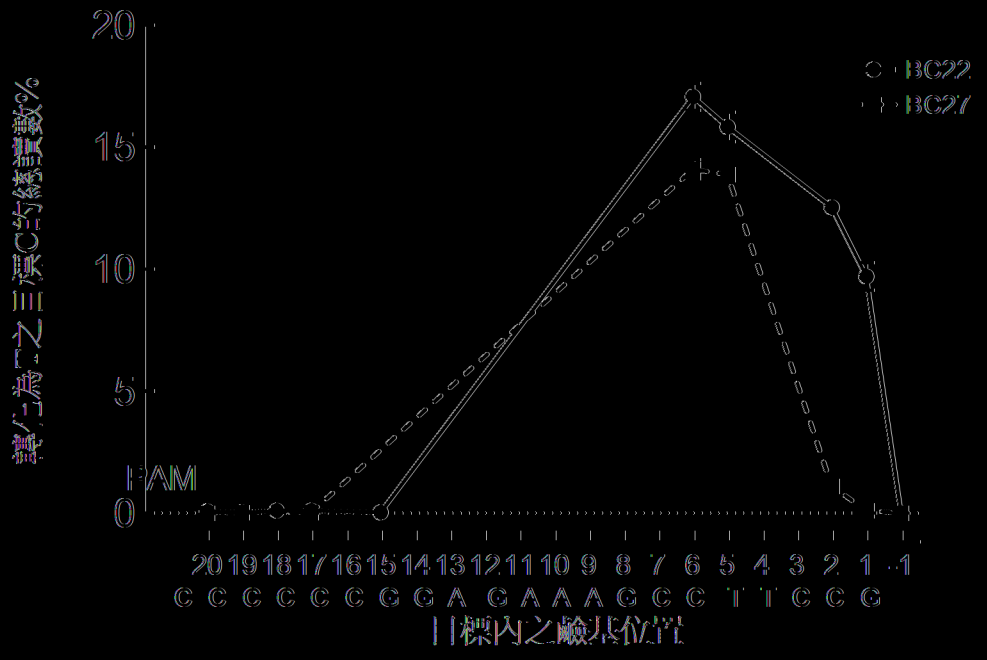

20
15
10
5
0
FAM
BC22
BC27
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 -1
C C C C C C C G G A G A A A G C C T T C C G

圖3A

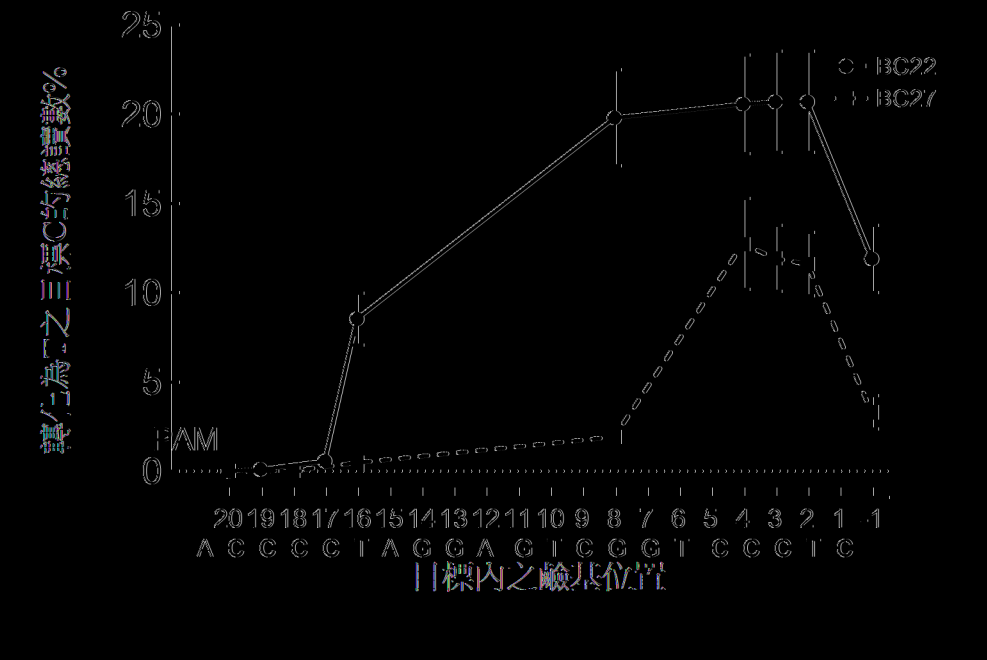
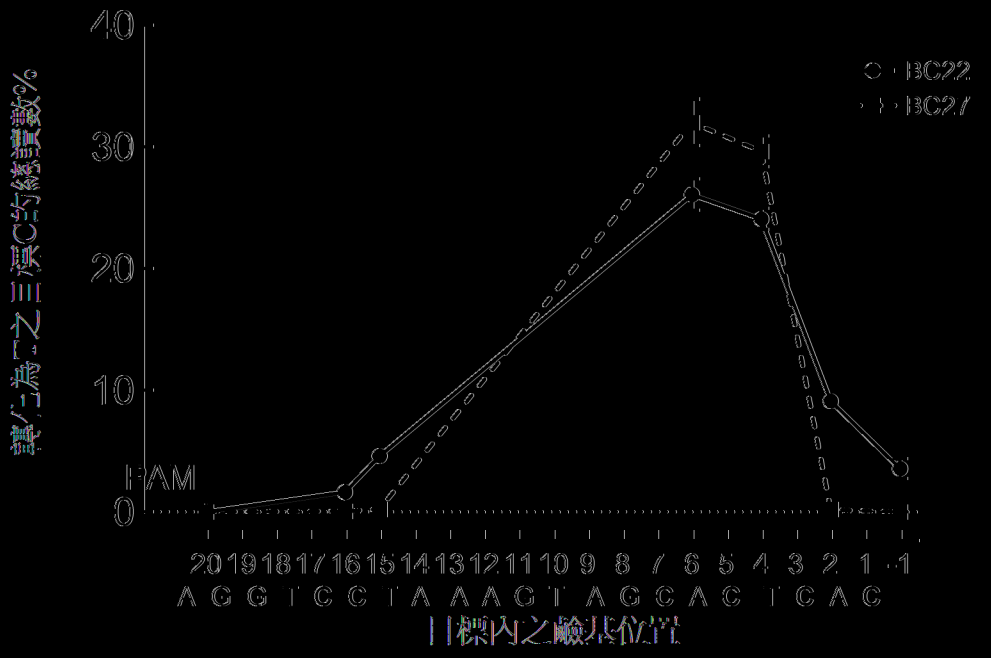
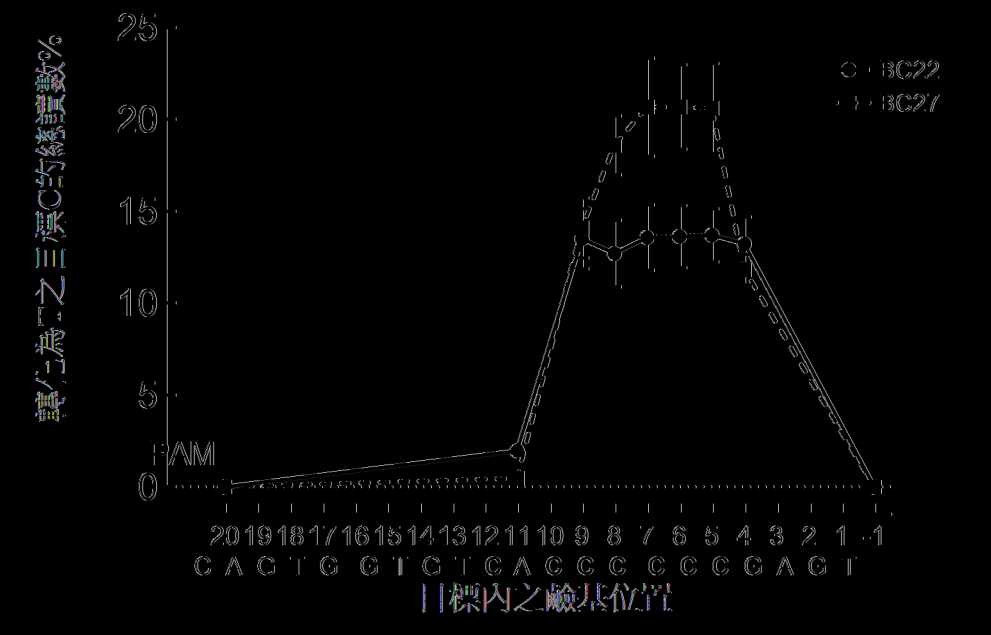

25
20
15
10
5
0
FAM
BC22
BC27
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 -1
A C C C C C T A G G A G T C G G T C C C T C

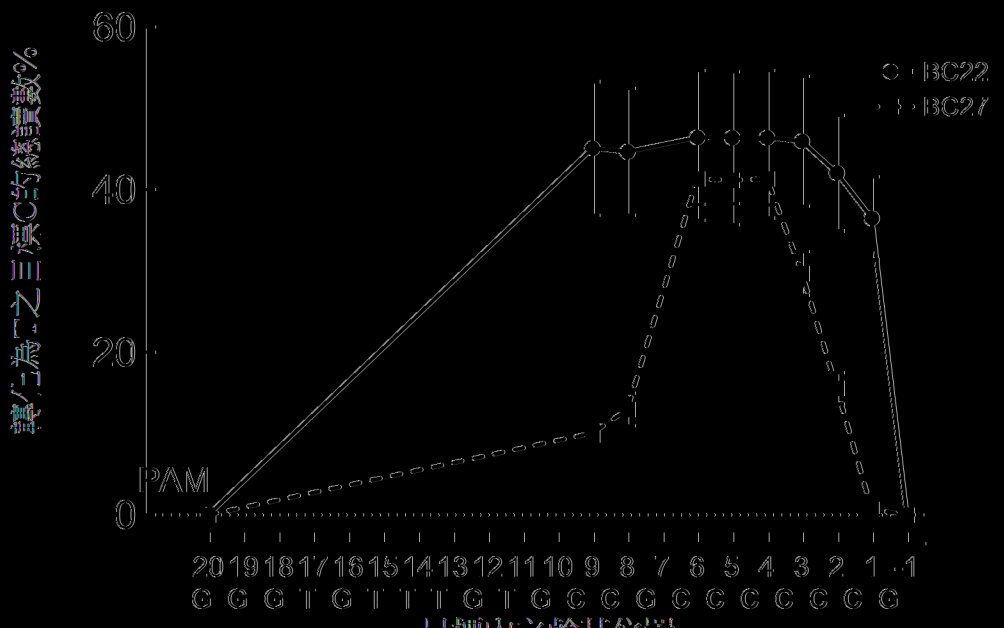
圖3B


40
30
20
10
0
PAM
BC22
BC27
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 -1
A G G T C C T A A A G T A G C A C T C A C

[圖3C]

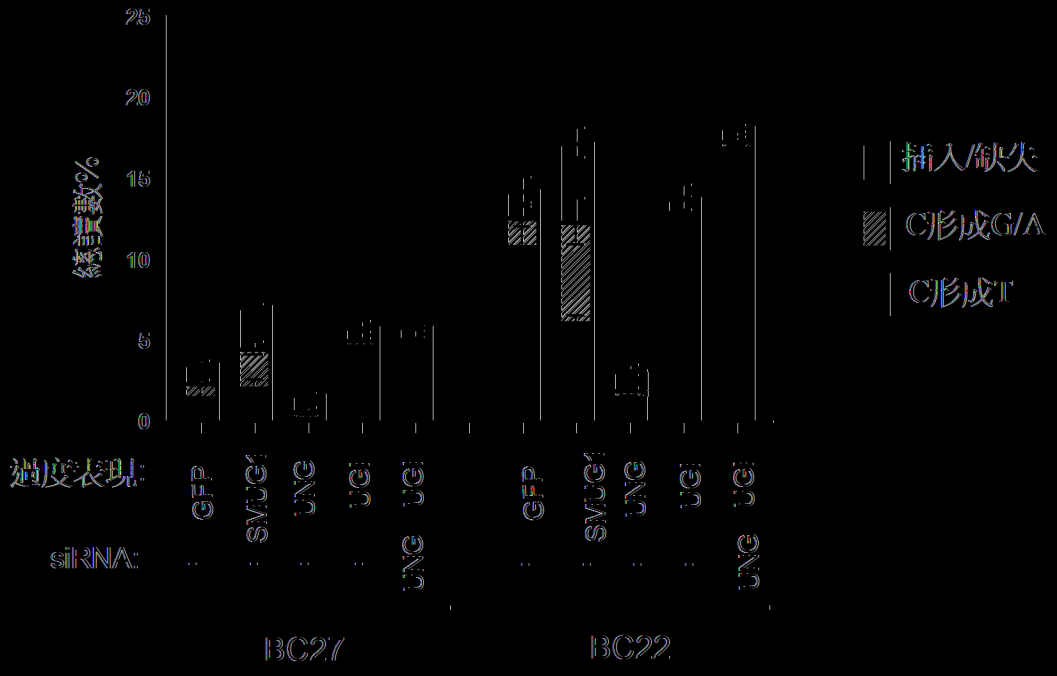

25
20
15
10
5
0
PAM
BC22
BC27
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 -1
C A C T G G T G T C A C C C C C C G A G T

[圖3D]

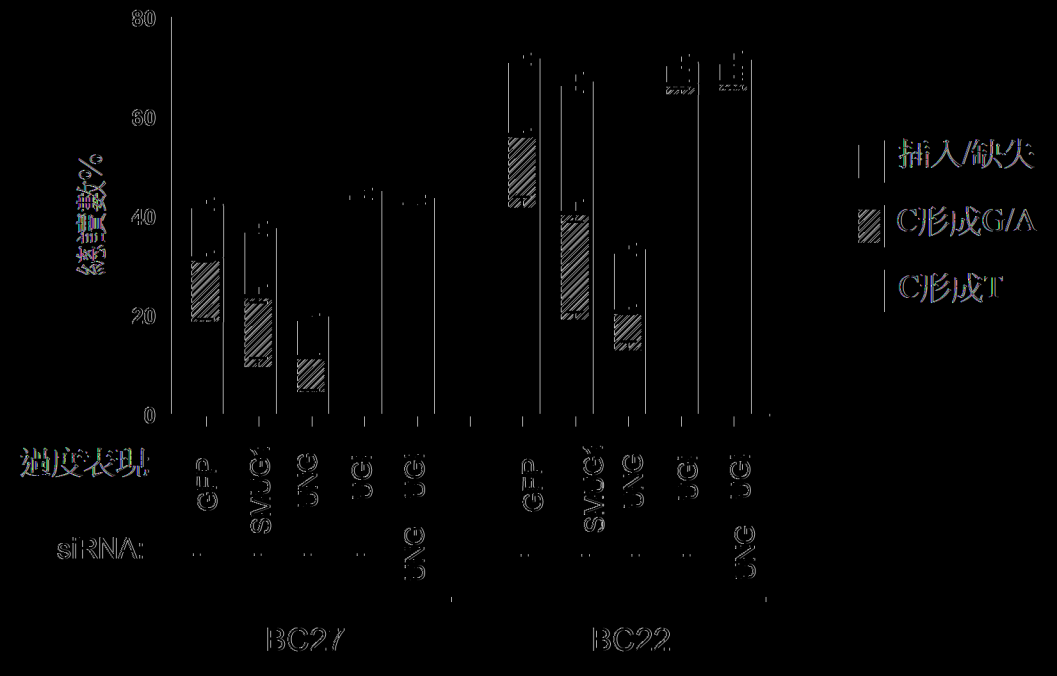


目標內之鹼基位置

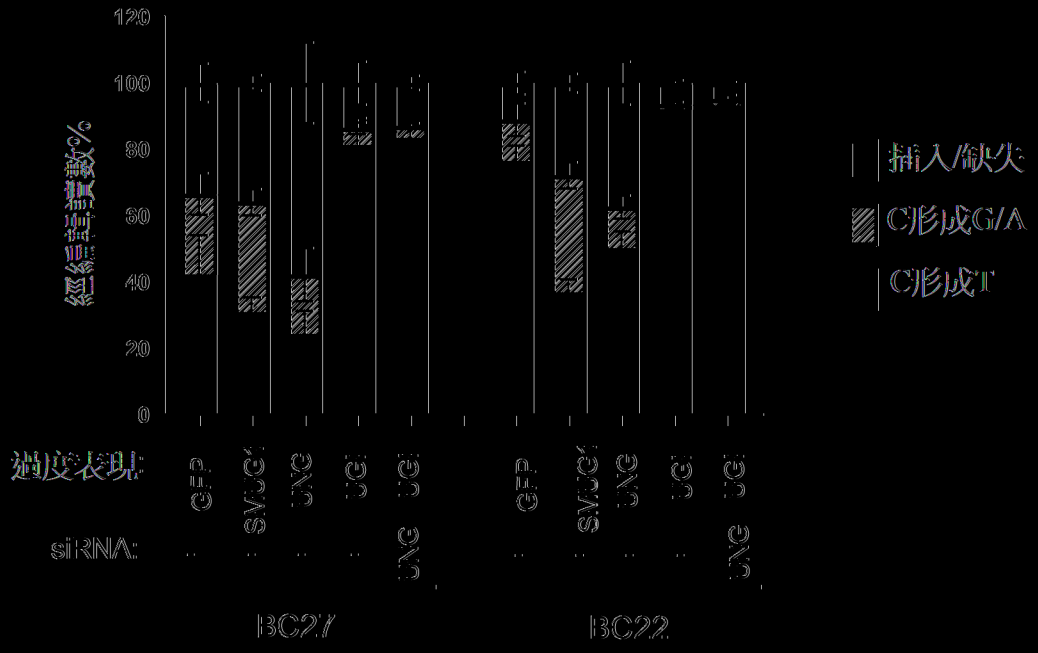
[圖3E]


25
20
15
10
5
0
總讀數%
插入/缺失
C形成G/A
C形成T
過度表現:
siRNA:
GFP
SMUG1
UNG
UGI
UNG
UGI
GFP
SMUG1
UNG
UGI
UNG
UGI
BC27
BC22

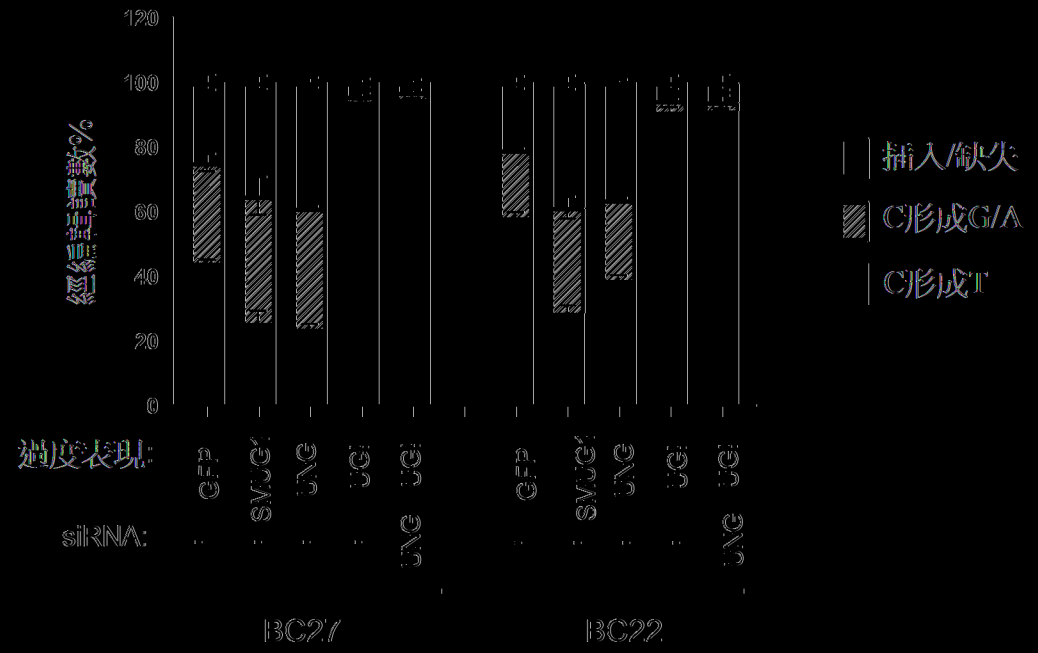
|(圖4A)|


80
60
40
20
0
總讀數%
插入/缺失
C形成G/A
C形成T
過度表現:
siRNA:
GFP
SMUG1
UNG
UGI
UNG
UGI
GFP
SMUG1
UNG
UGI
UNG
UGI
BC27
BC22

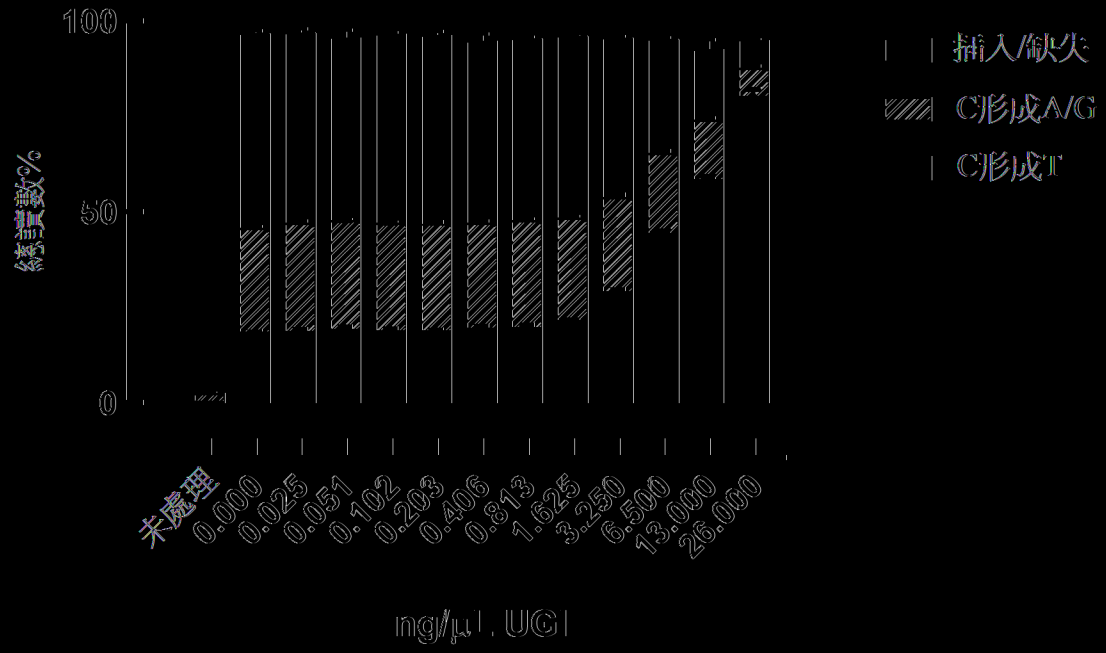
|(圖4B)|


120
100
80
60
40
20
0
過度表現:
siRNA:
BC27
BC22
插入/缺失
C形成G/A
C形成T

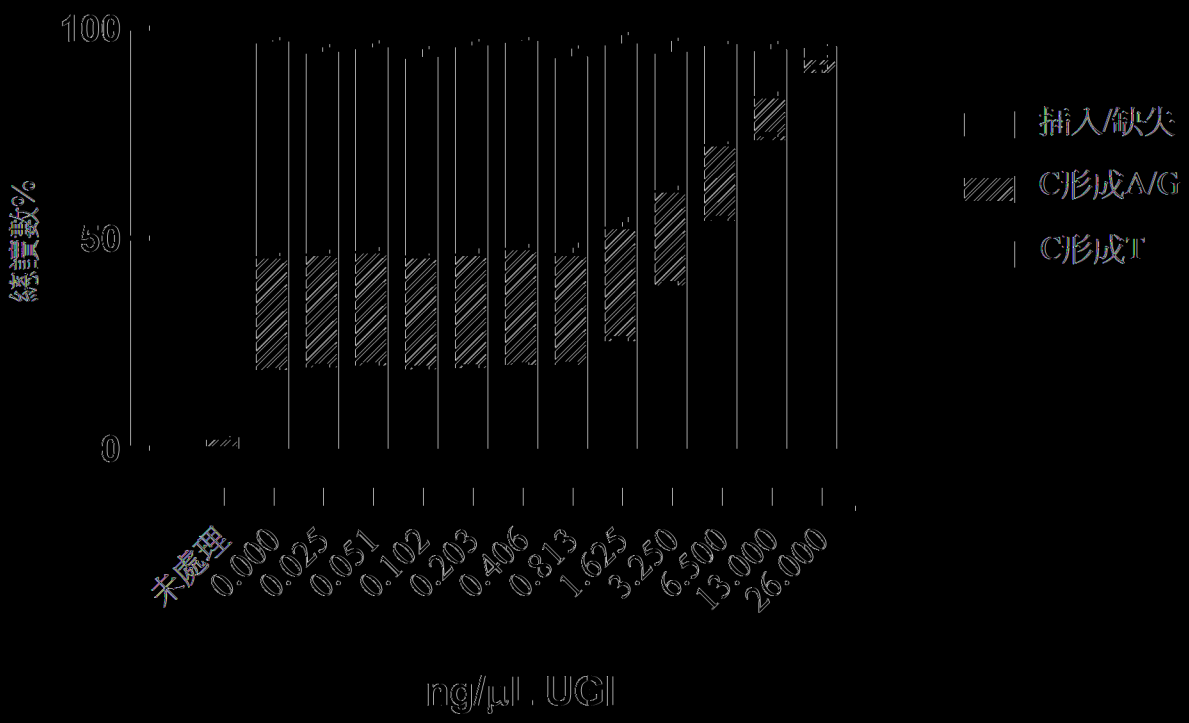
|(圖5A)|


120
100
80
60
40
20
0
過度表現:
siRNA:
BC27
BC22
插入/缺失
C形成G/A
C形成T

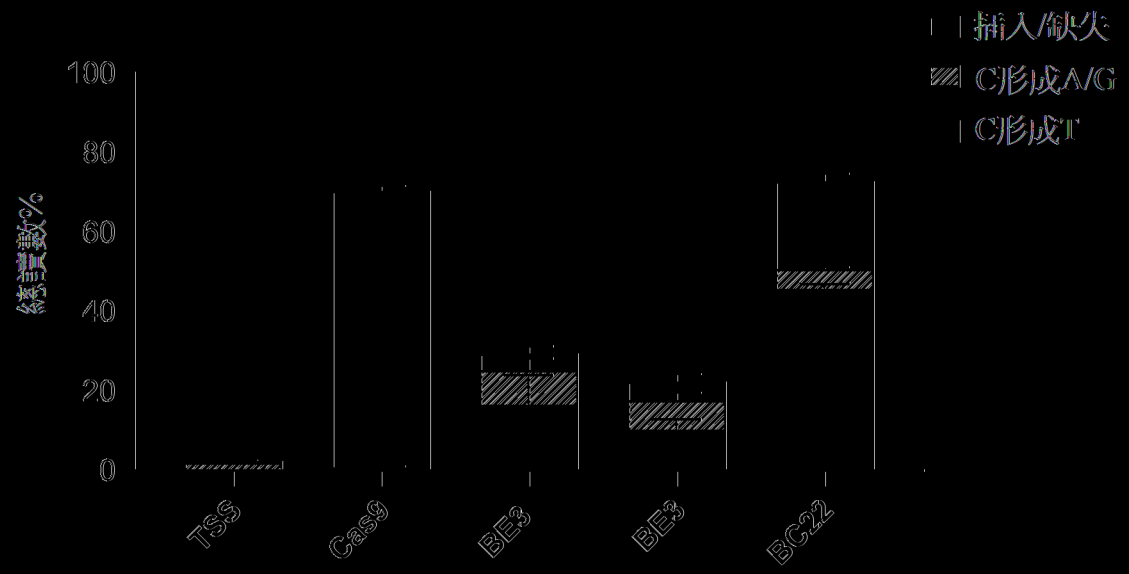
|(圖5B)|


100
50
0
總讀數%
未處理
0.000
0.025
0.051
0.102
0.203
0.406
0.813
1.625
3.250
6.500
13.000
26.000
ng/μl . UGI
插入/缺失
C形成A/G
C形成T

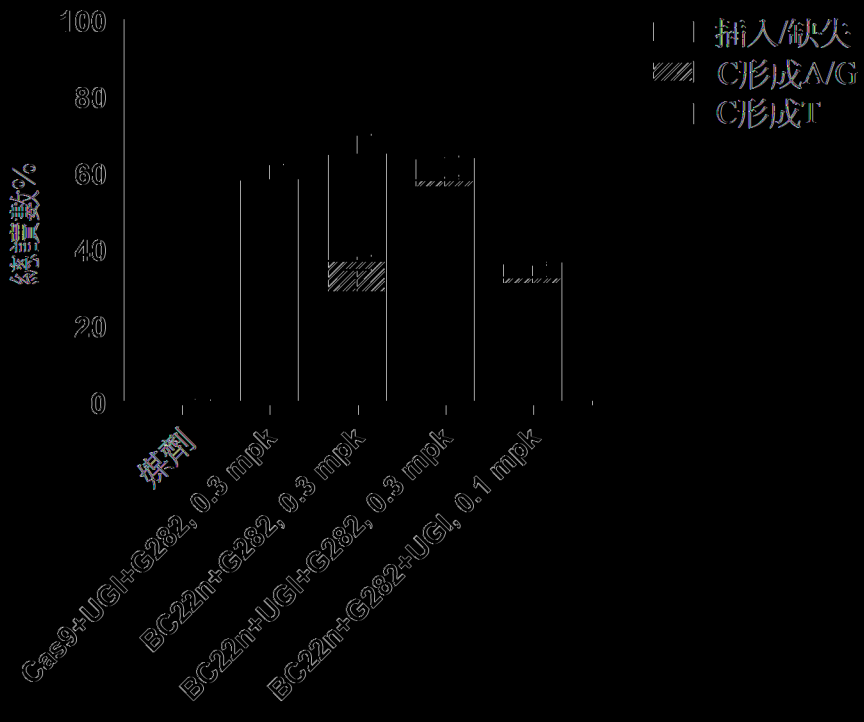
|(圖6A)|


100
50
0
總讀數%
未處理
0.000
0.025
0.051
0.102
0.203
0.406
0.813
1.625
3.250
6.500
13.000
26.000
ng/μl . UGI
插入/缺失
C形成A/G
C形成T

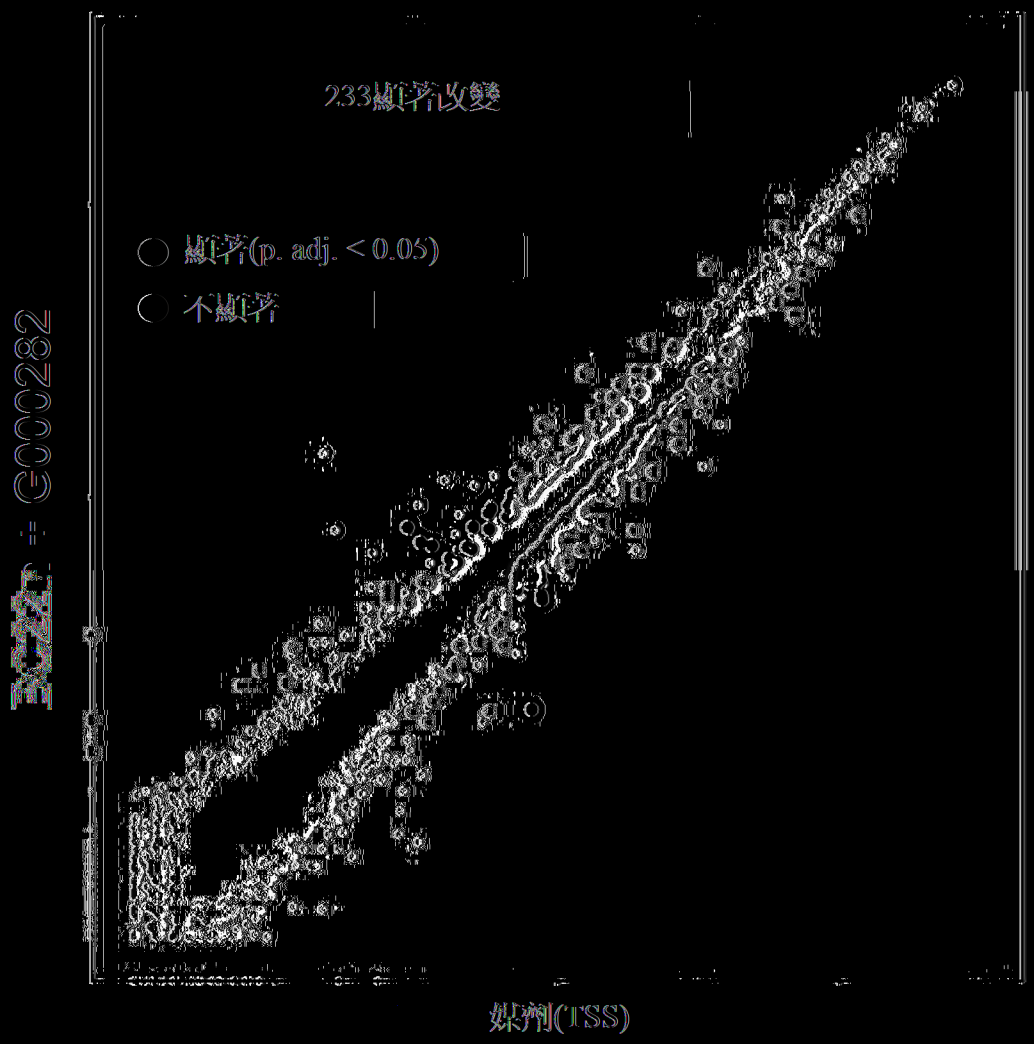
|(圖6B)|


插入/缺失
C形成A/G
C形成T
100
80
60
40
20
0
TS5
Cas9
BE3
BE3
BC22

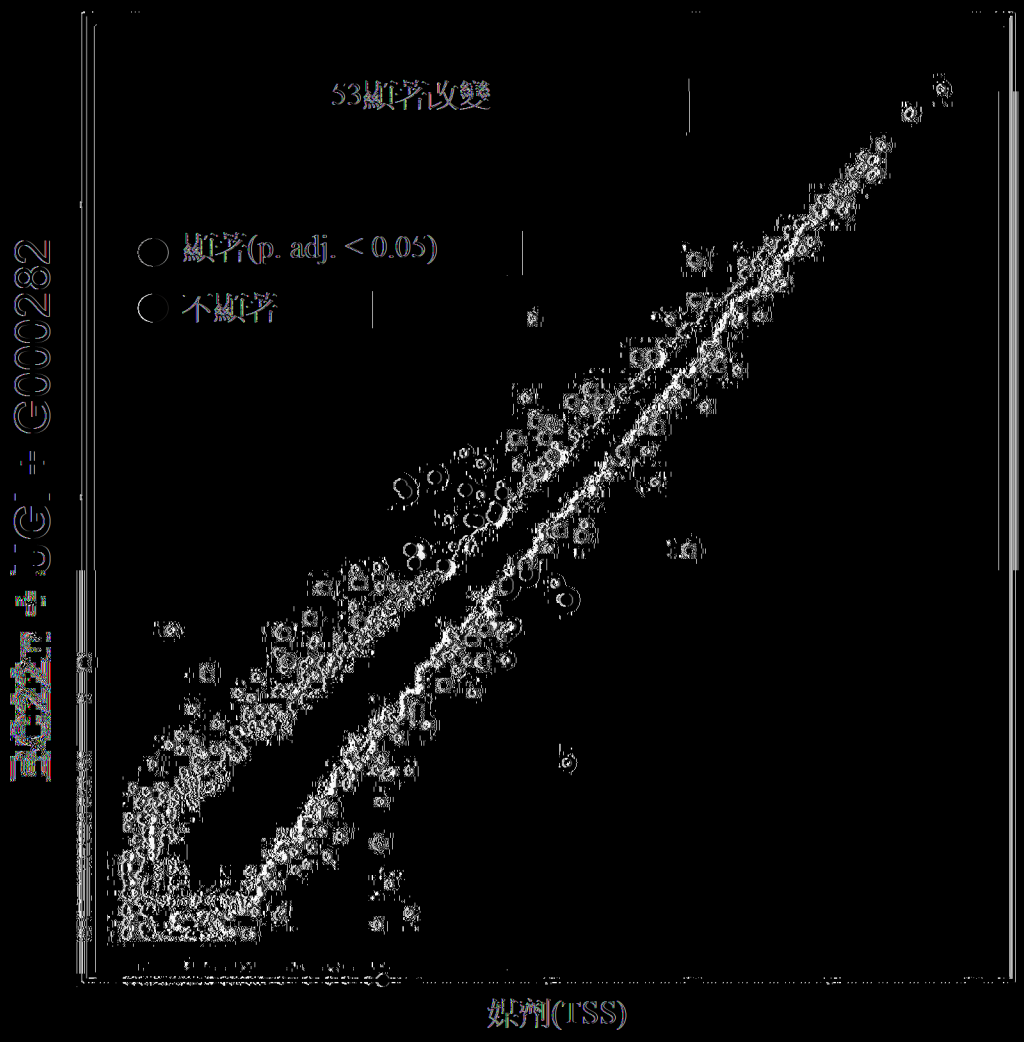
|(圖7)|


插入/缺失
C形成A/G
C形成T
100
80
60
40
20
0
控制
Cas9+UGI+G282, 0.3 mpk
BC22n+G282, 0.3 mpk
BC22n+UGI+G282, 0.3 mpk
BC22n+G282+UGI, 0.1 mpk

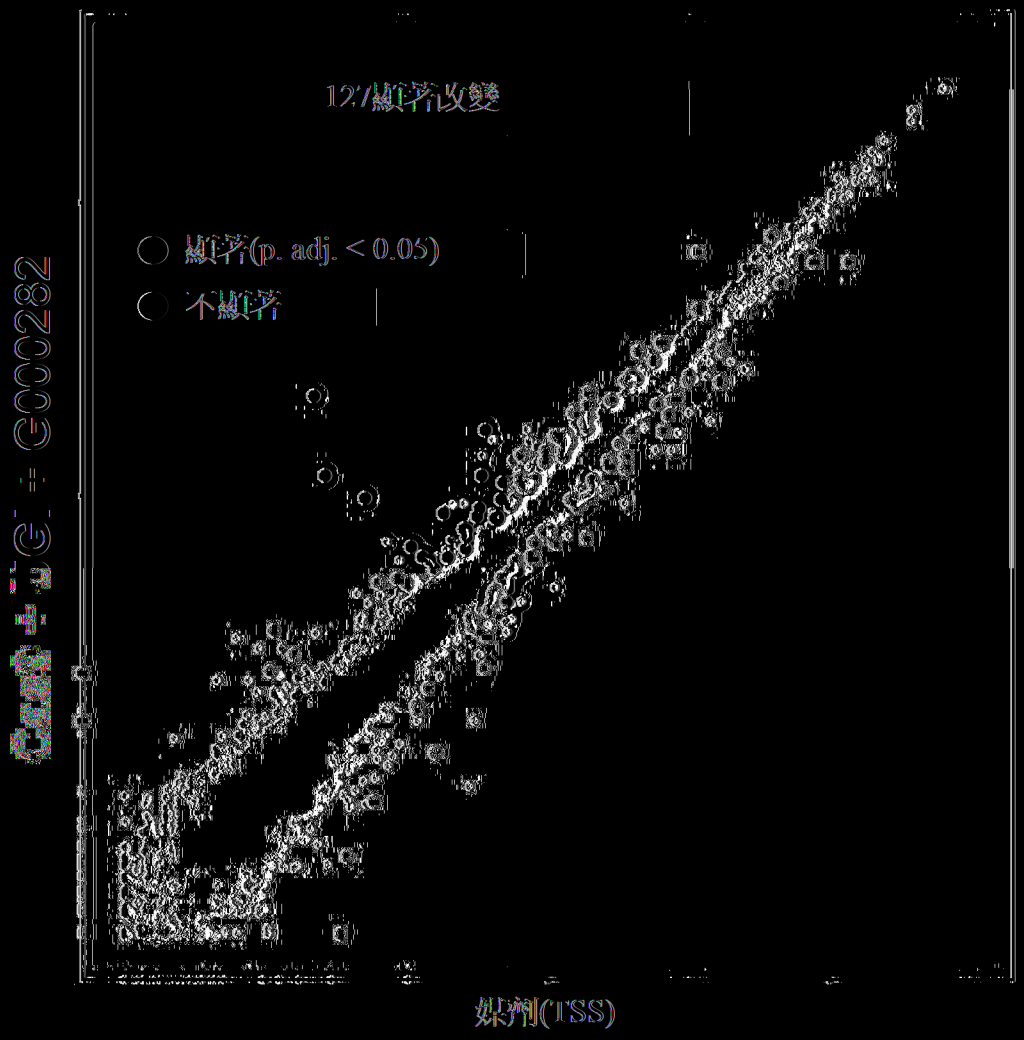
|(圖8)|



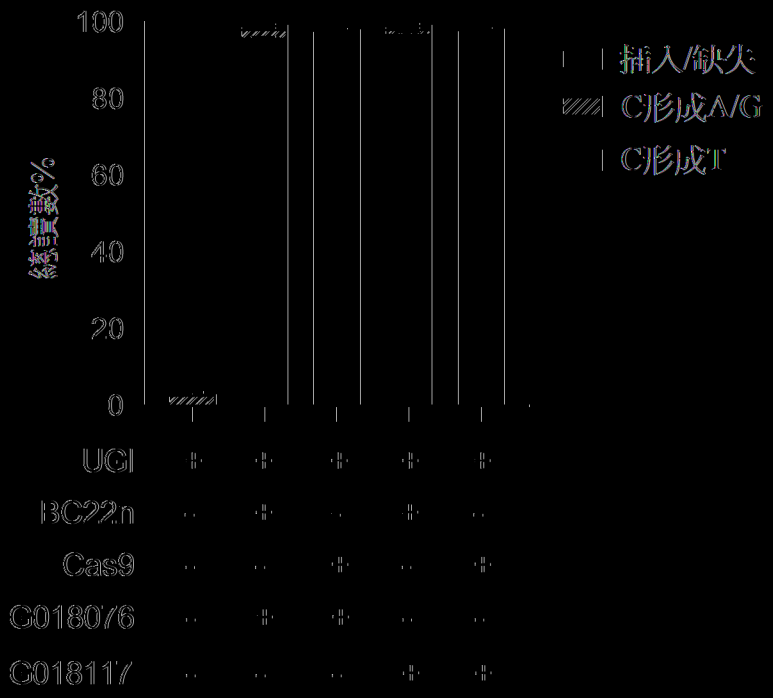
|(圖9A)|



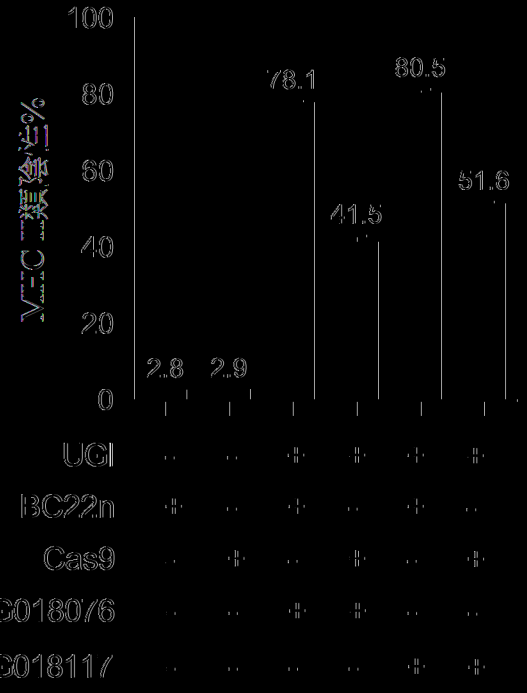
[圖9B]



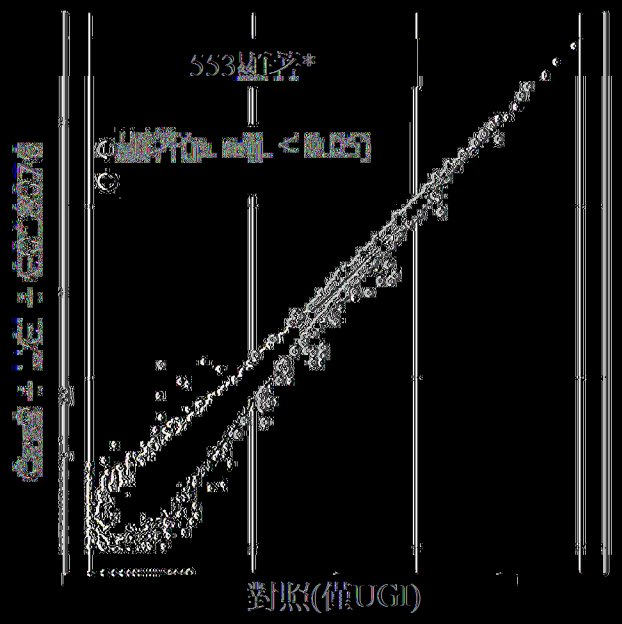
|(|9C)|


100
80
60
40
20
0
插入/缺失
C形成A/G
C形成T
UGI
BC22n
Cas9
G018076
G018117

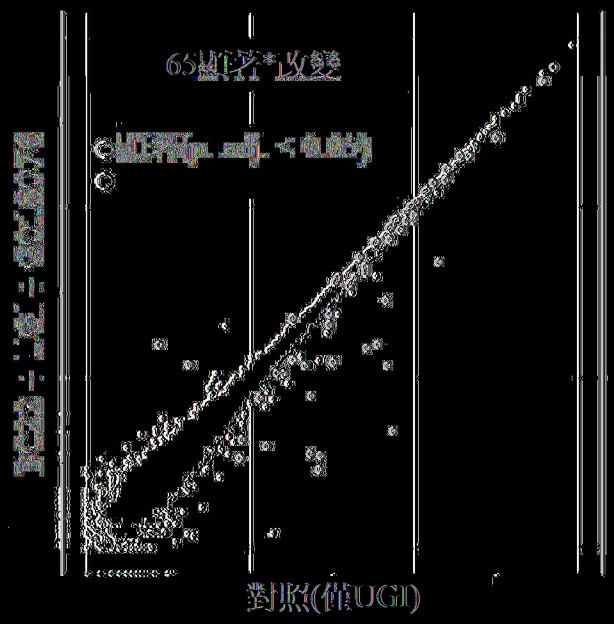
|(圖10)|


100
80
60
40
20
0
2.8
2.9
78.1
41.5
80.5
51.6
UGI
BC22n
Cas9
G018076
G018117

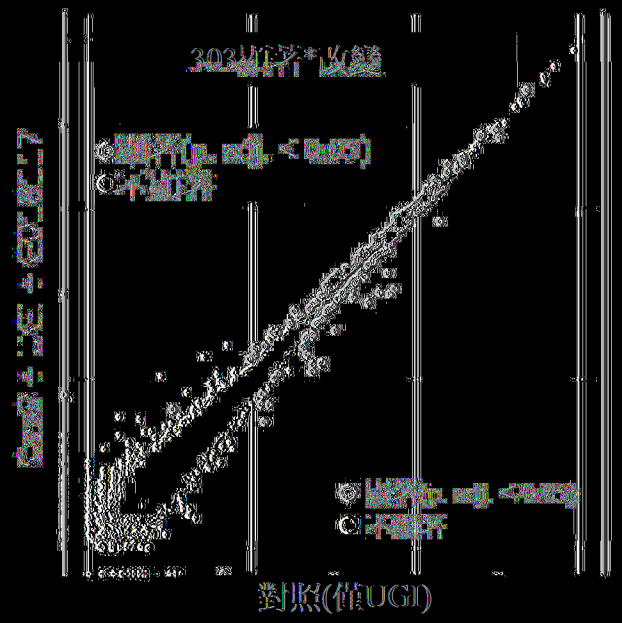
|(圖11)|



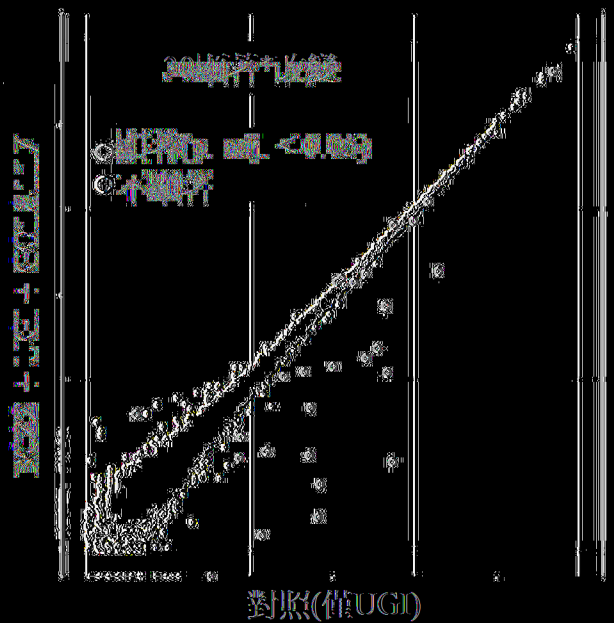
|(圖12A)|



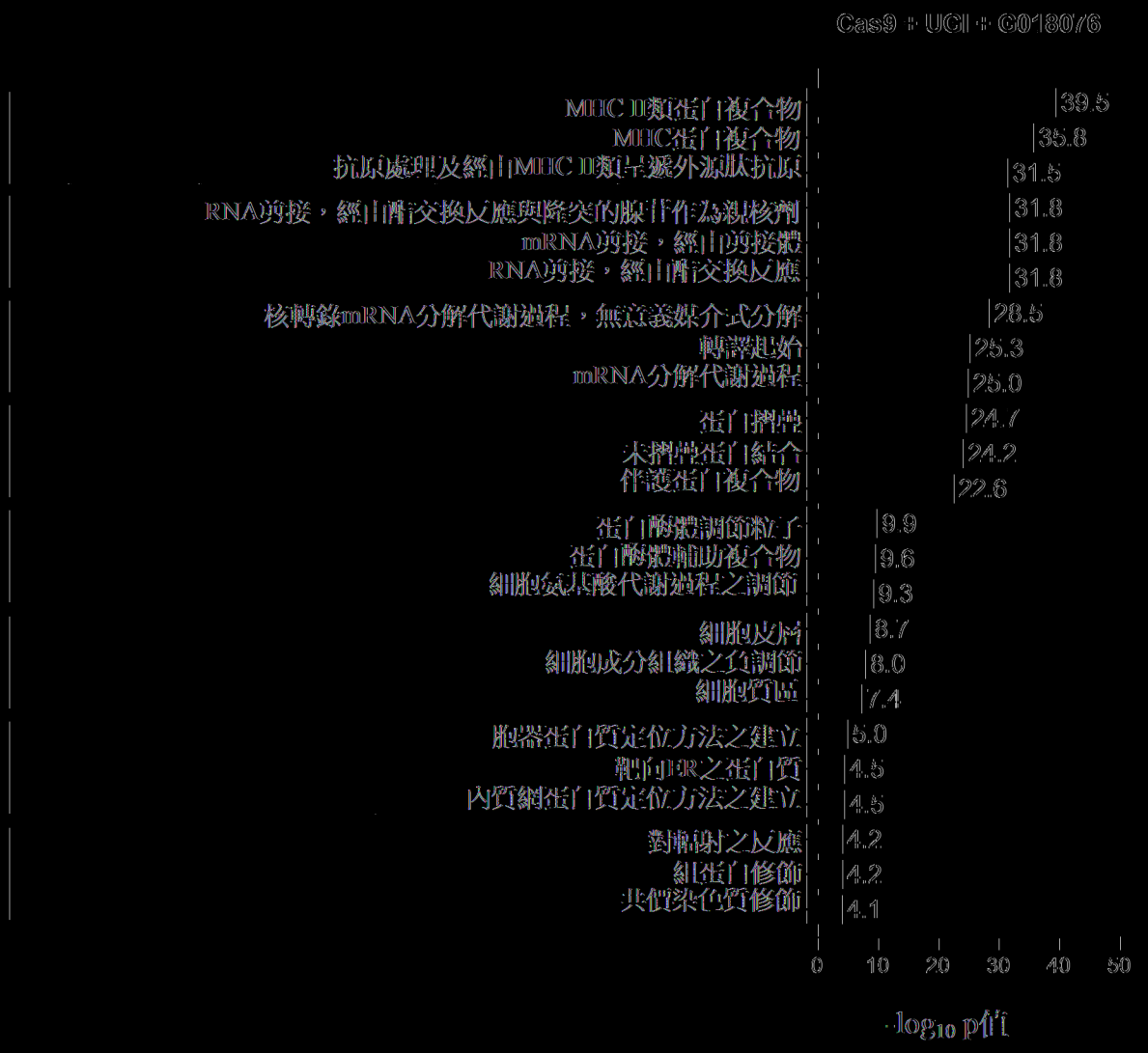
|(圖12B)|



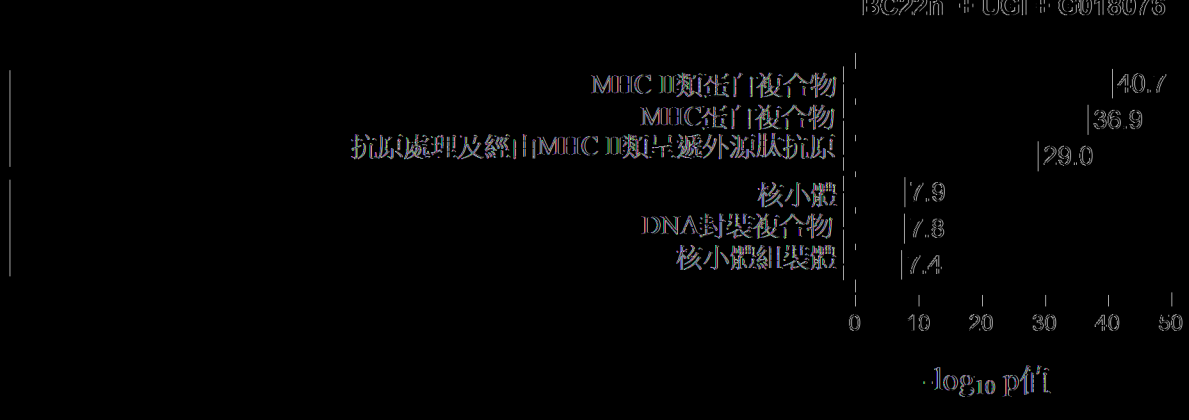
|(圖13A)|



|(圖13B)|


Cas9 + UGI + G018076
MHC II類蛋白複合物
MHC蛋白複合物
抗原處理及經由MHC II類呈遞外源肽抗原
RNA剪接，經由酯交換反應與隆突的腺苷作為親核劑
mRNA剪接，經由剪接體
RNA剪接，經由酯交換反應
核轉錄mRNA分解代謝過程，無意義媒介式分解
轉譯起始
mRNA分解代謝過程
蛋白摺疊
未摺疊蛋白結合
伴護蛋白複合物
蛋白酶體調節粒子
蛋白酶體輔助複合物
細胞氨基酸代謝過程之調節
細胞皮層
細胞成分組織之負調節
細胞質區
胞器蛋白質定位方法之建立
靶向ER之蛋白質
內質網蛋白質定位方法之建立
對輻射之反應
組蛋白修飾
共價染色質修飾
39.5
35.8
31.5
31.8
31.8
31.8
28.5
25.3
25.0
24.7
24.2
22.6
9.9
9.6
9.3
8.7
8.0
7.4
5.0
4.5
4.5
4.2
4.2
4.1
0
10
20
30
40
50
-log10 p值

(圖14A)


BC22n + UGI + G018076
MHC II類蛋白複合物
MHC蛋白複合物
抗原處理及經由MHC II類呈遞外源肽抗原
核小體
DNA封裝複合物
核小體組裝體
40.7
36.9
29.0
7.9
7.8
7.4
0
10
20
30
40
50
-log10 p值

(圖14B)

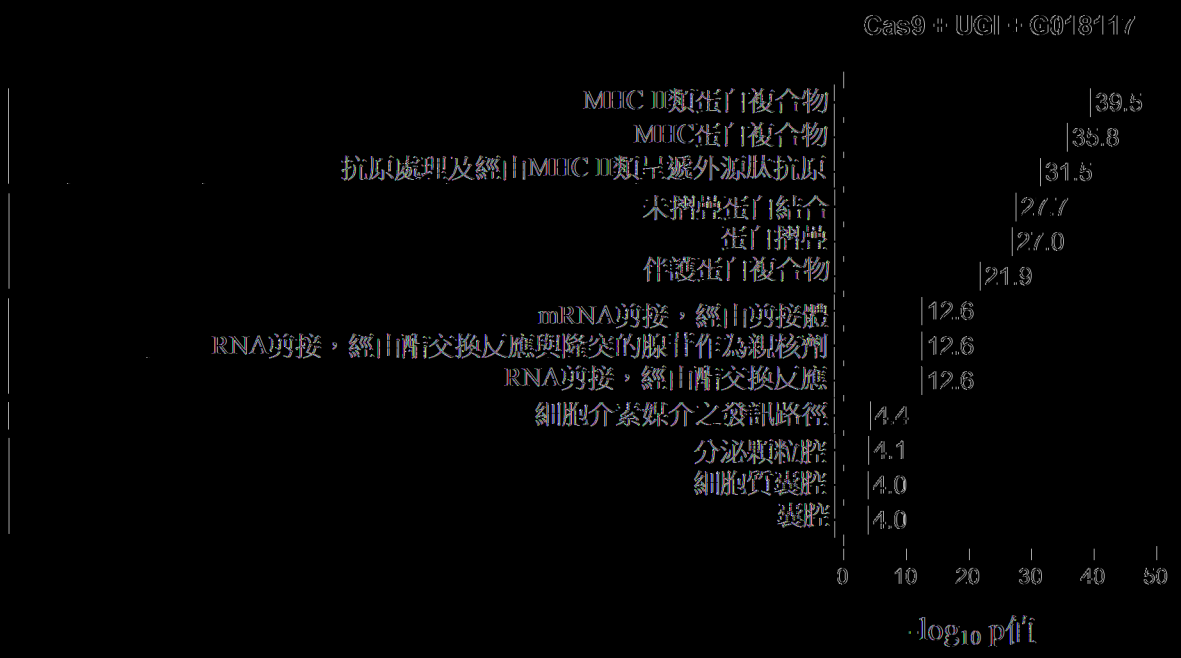

Cas9 + UGI + G018117
MHC II類蛋白複合物
MHC蛋白複合物
抗原處理及經由MHC II類呈遞外源肽抗原
未摺疊蛋白結合
蛋白摺疊
伴護蛋白複合物
mRNA剪接，經由剪接體
RNA剪接，經由酯交換反應與腺苷作為親核劑
RNA剪接，經由酯交換反應
細胞介素媒介之發訊路徑
分泌顆粒腔
細胞質囊腔
囊腔
39.5
35.8
31.5
27.7
27.0
21.9
12.6
12.6
12.6
4.4
4.1
4.0
4.0
0
10
20
30
40
50
-log10 p值

圖15A

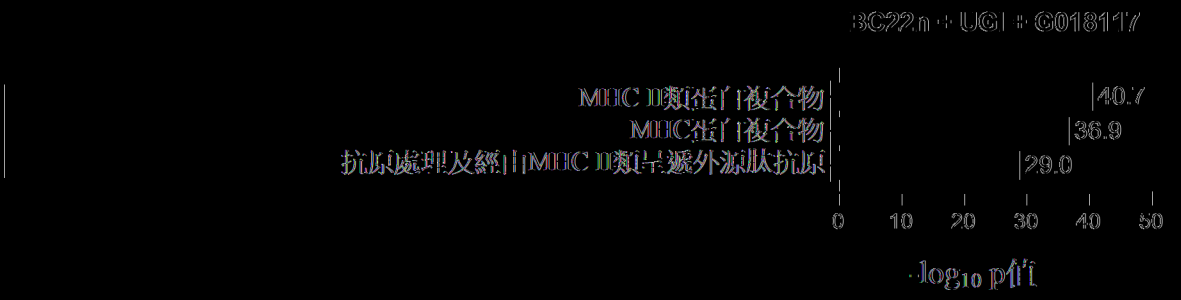
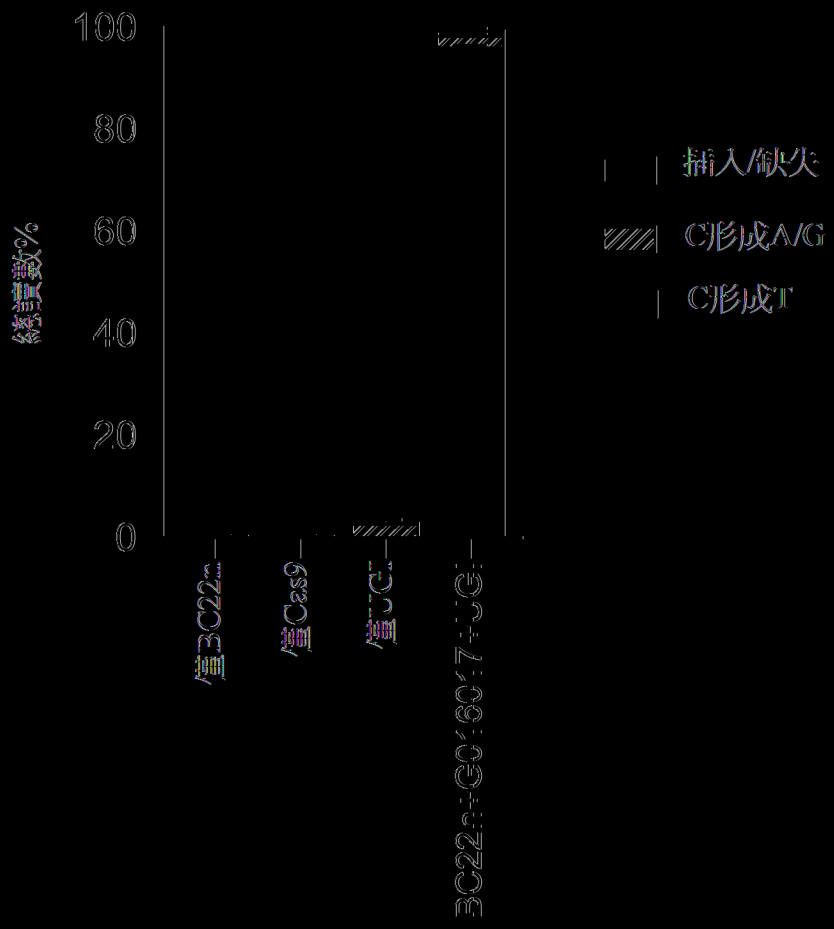
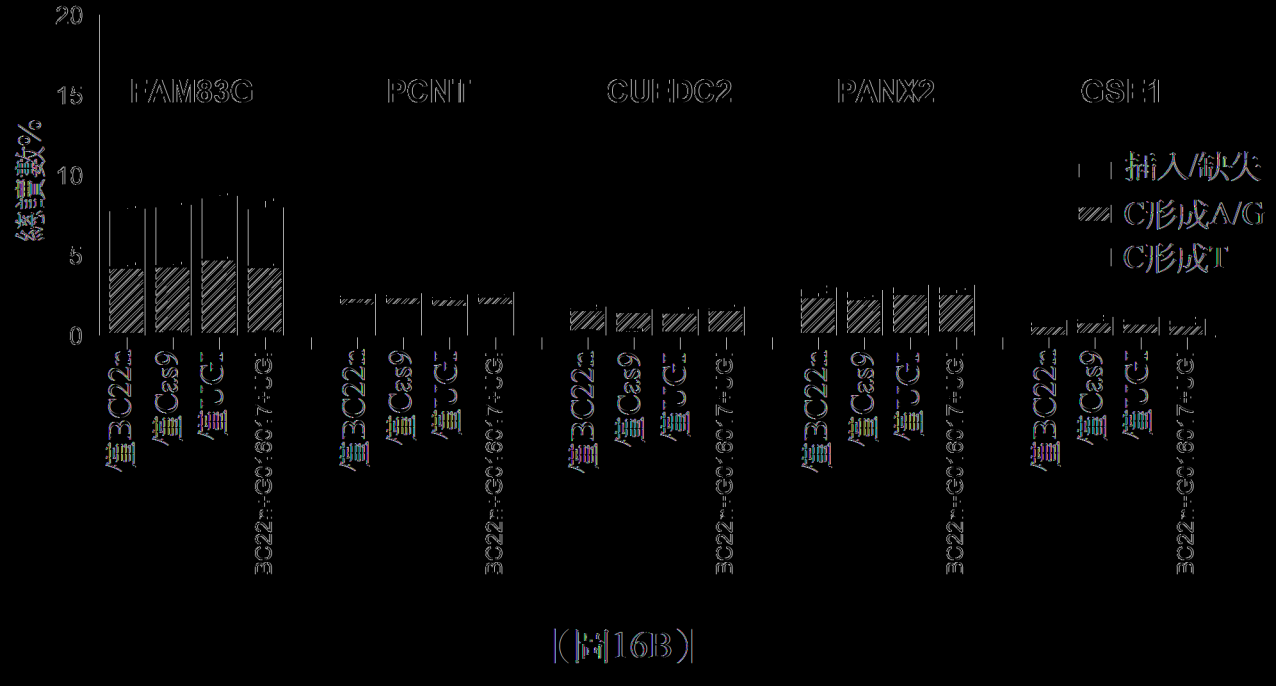

BC22n + UGI + G018117
MHC II類蛋白複合物
MHC蛋白複合物
抗原處理及經由MHC II類呈遞外源肽抗原
40.7
36.9
29.0
0
10
20
30
40
50
-log10 p值

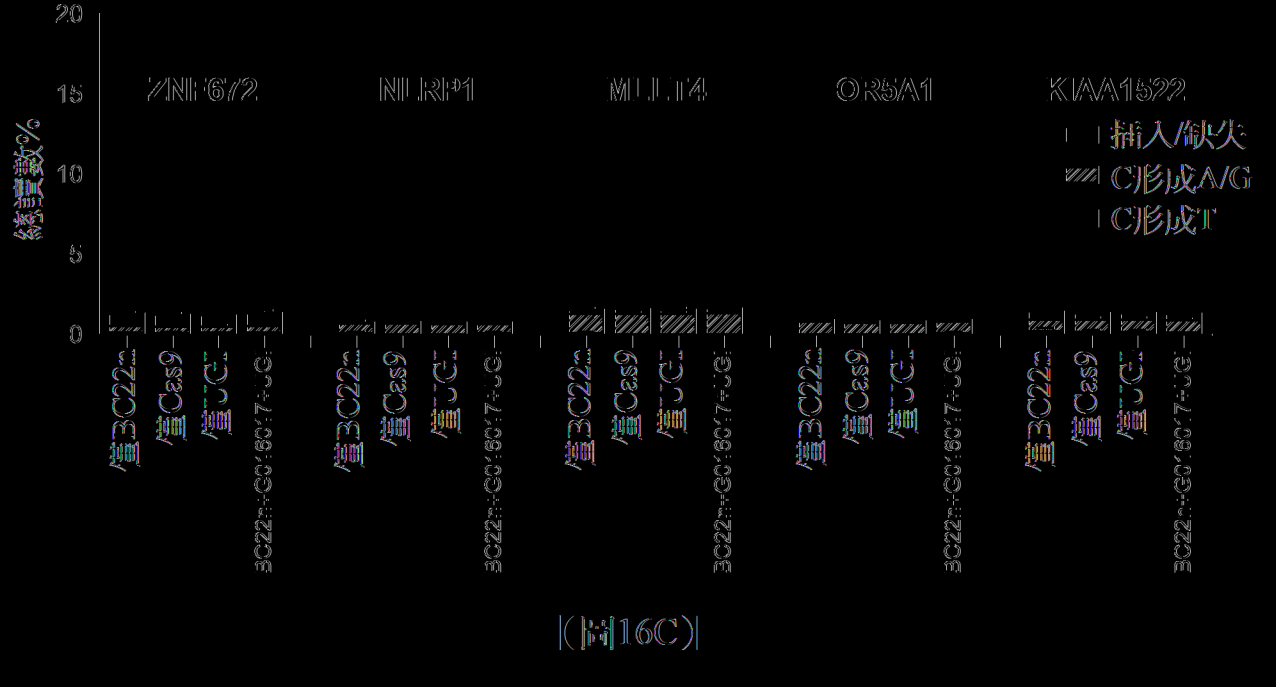
圖15B


100
80
60
40
20
0
總讀數%
插入/缺失
C形成A/G
C形成T
BC22n
Cas9
UGI
BC22n+G016017+UGI

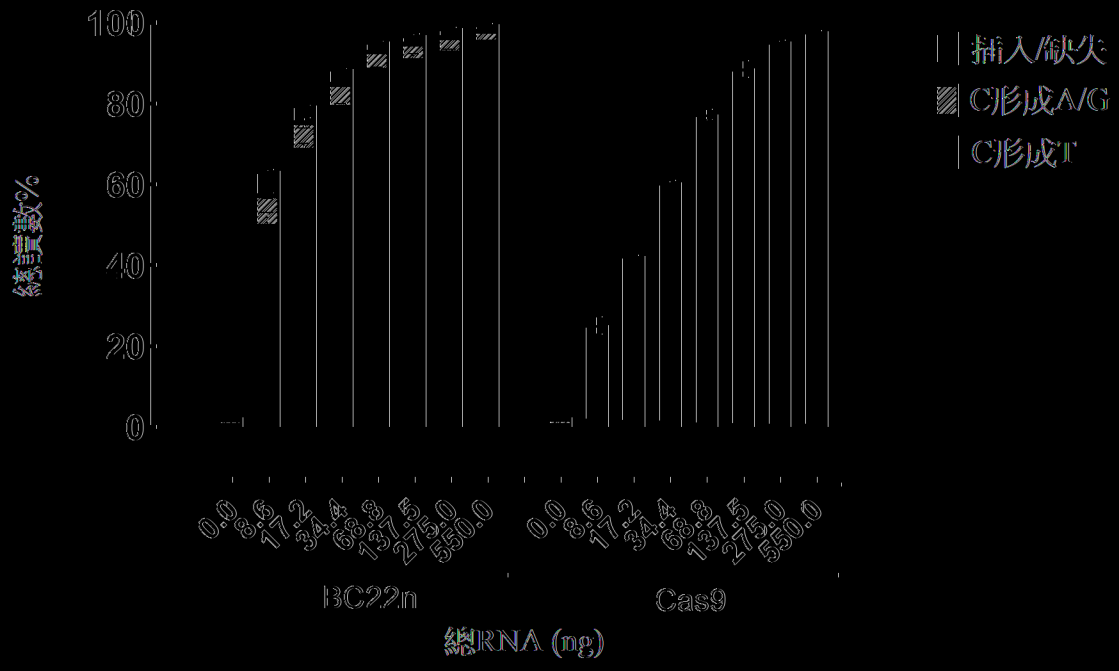
(圖16A)


20
15
10
5
0
FAM83C
PCNT
CUL3
PANX2
CSF1
插入/缺失
C形成A/G
C形成T

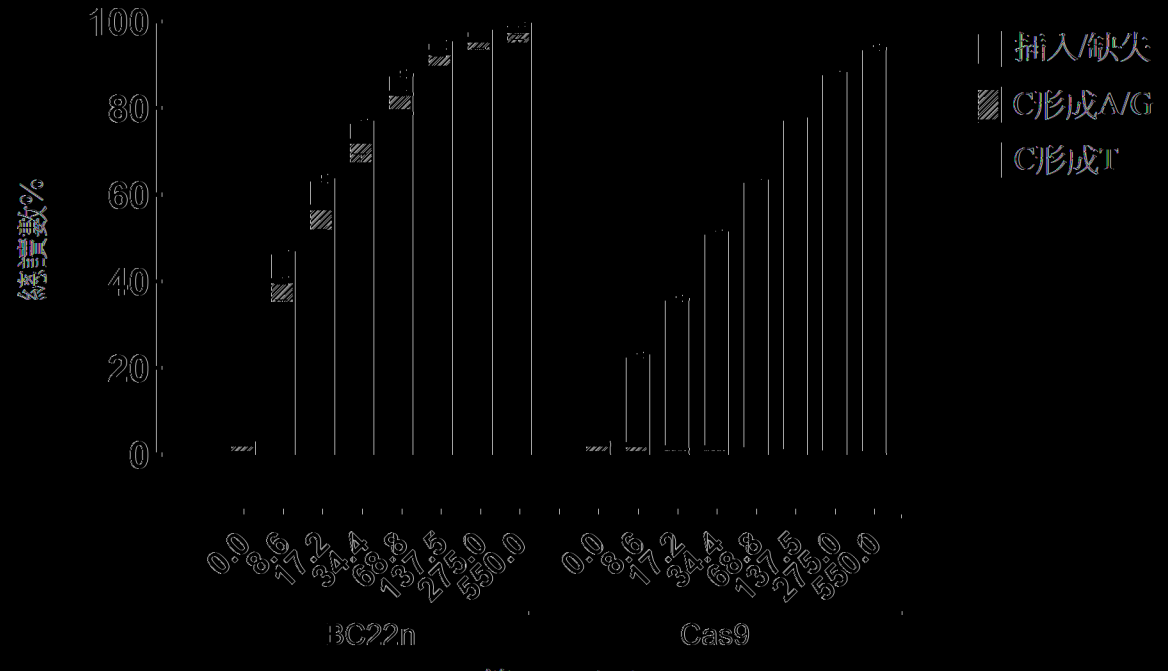
(圖16B)


20
15
10
5
0
ZNF672
NLRP1
MLL4
OR5A1
KIAA1522
插入/缺失
C形成A/G
C形成T

(圖16C)


100
80
60
40
20
0
%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

|(圖17A)|


100
80
60
40
20
0
%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

|(圖17B)|

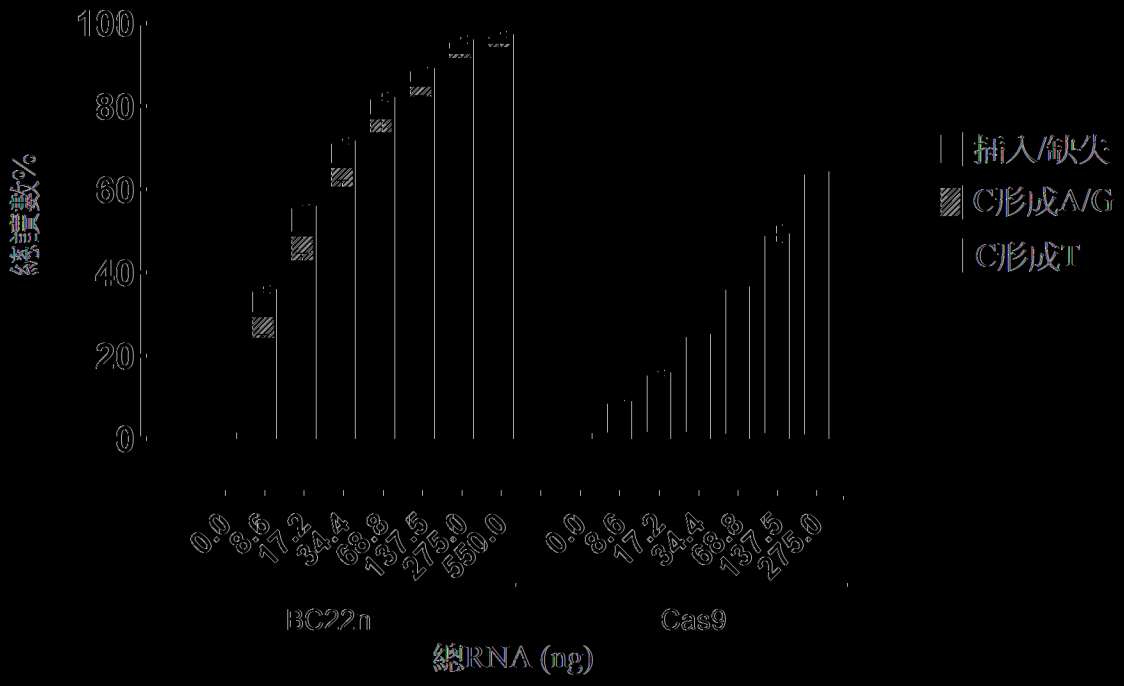

100
80
60
40
20
0
%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

圖17C

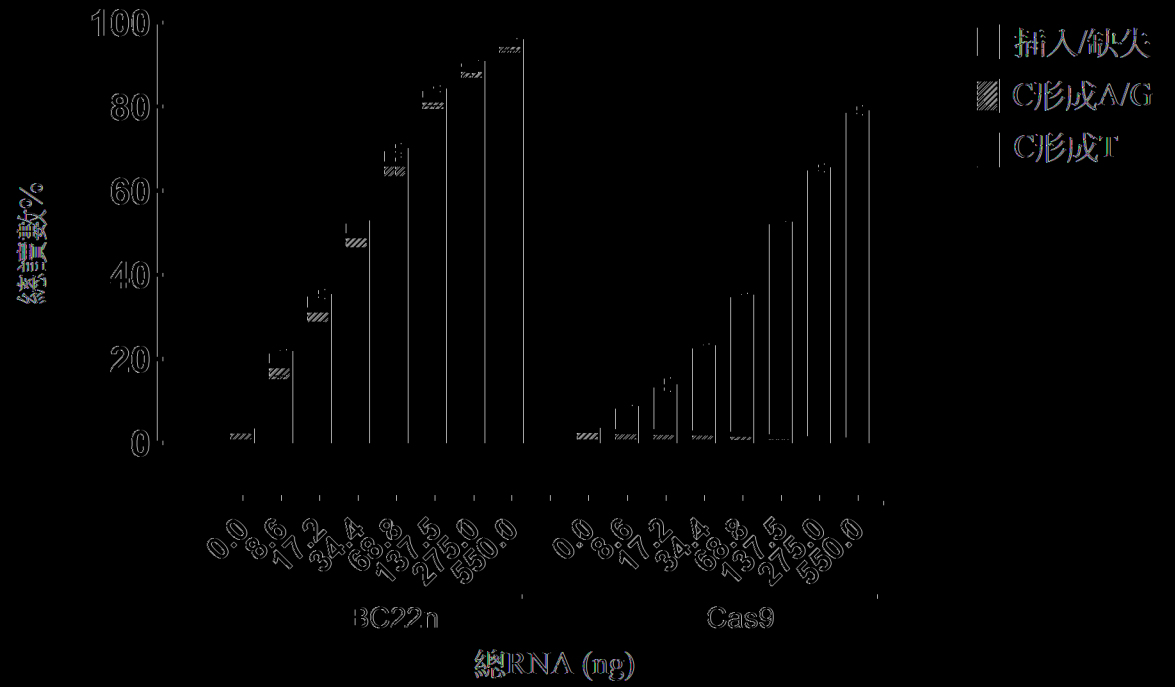
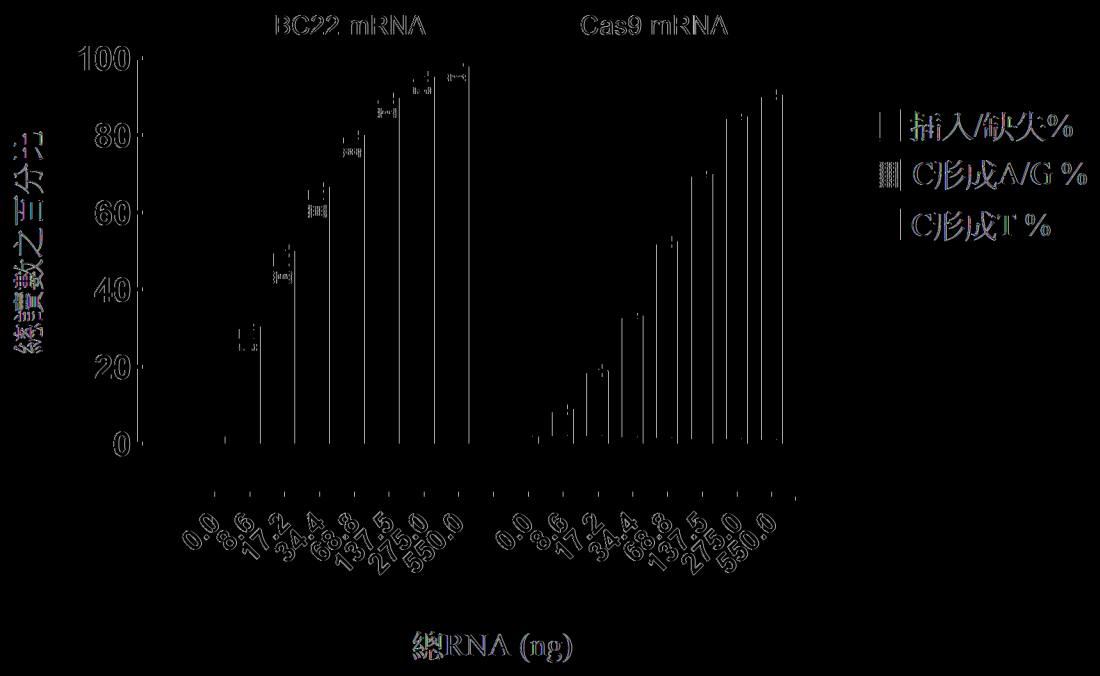

100
80
60
40
20
0
%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

圖17D


BC22 mRNA
Cas9 mRNA
100
80
60
40
20
0
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
插入/缺失%
C形成A/G %
C形成T %
總RNA (ng)

|(圖17E)|

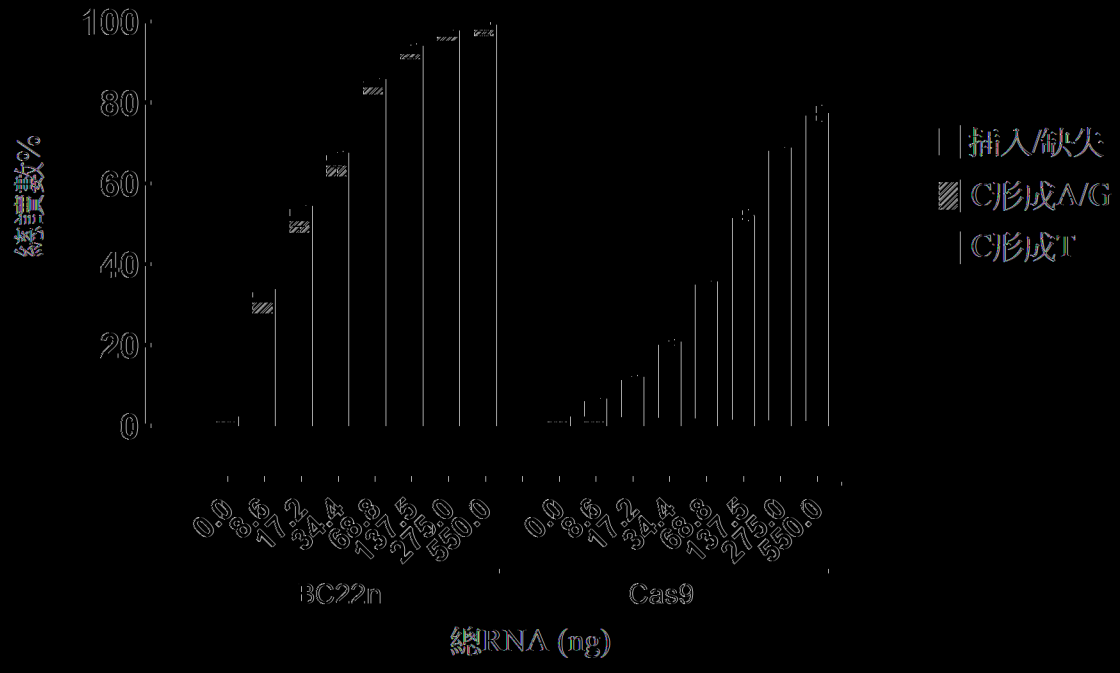

100
80
60
40
20
0
編輯效率%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

圖18A

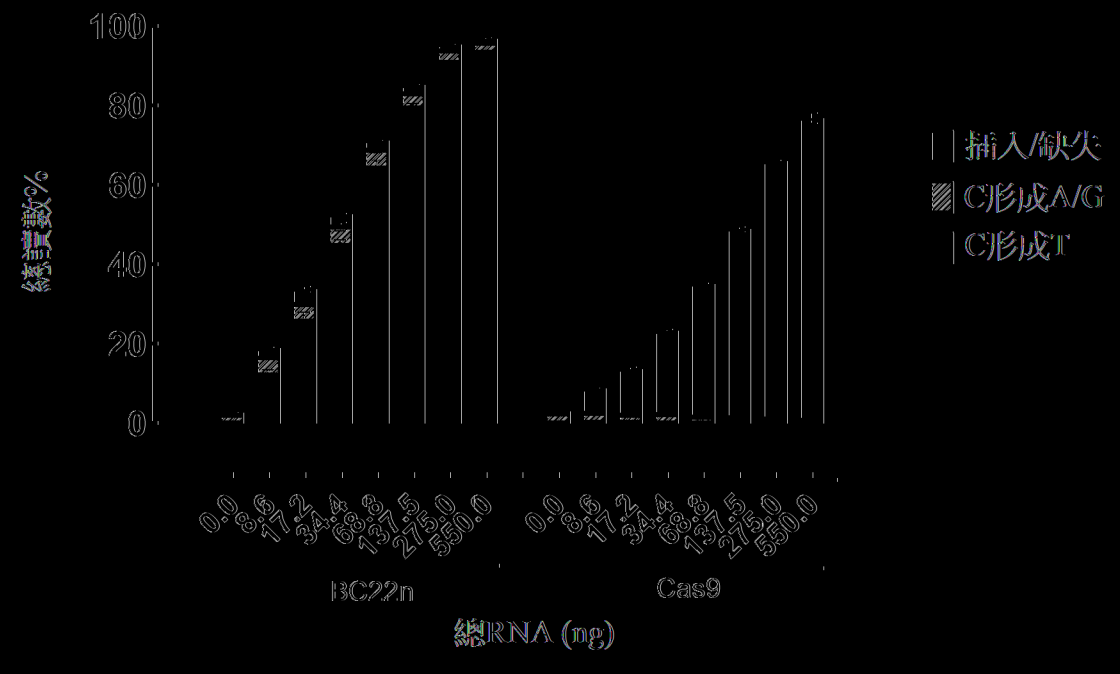
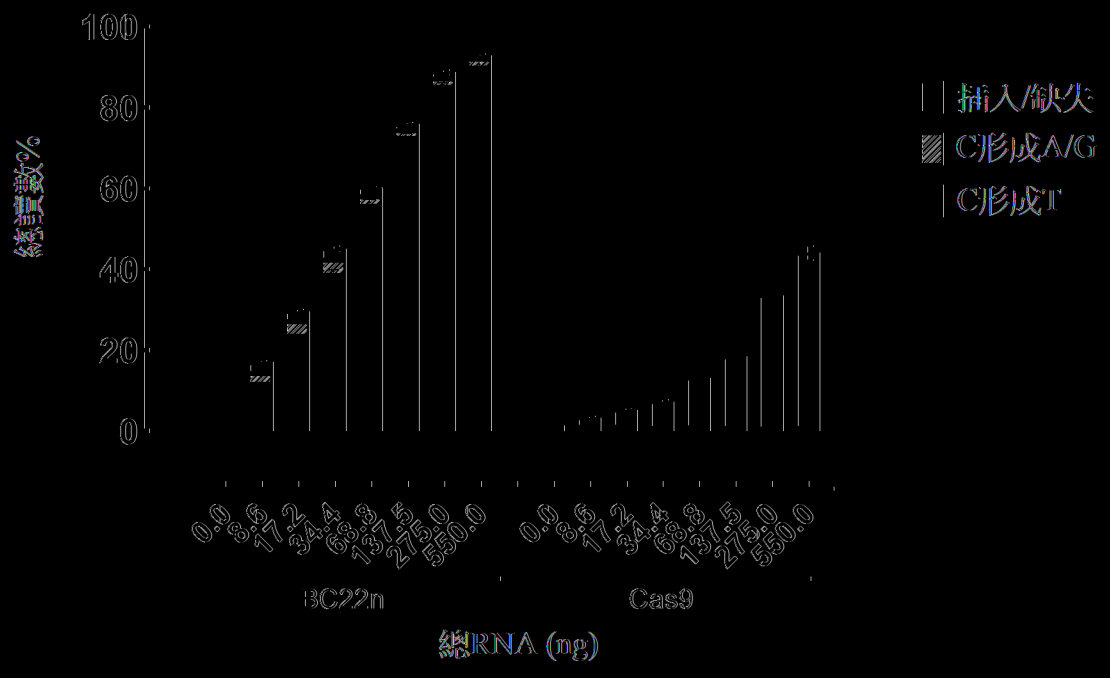
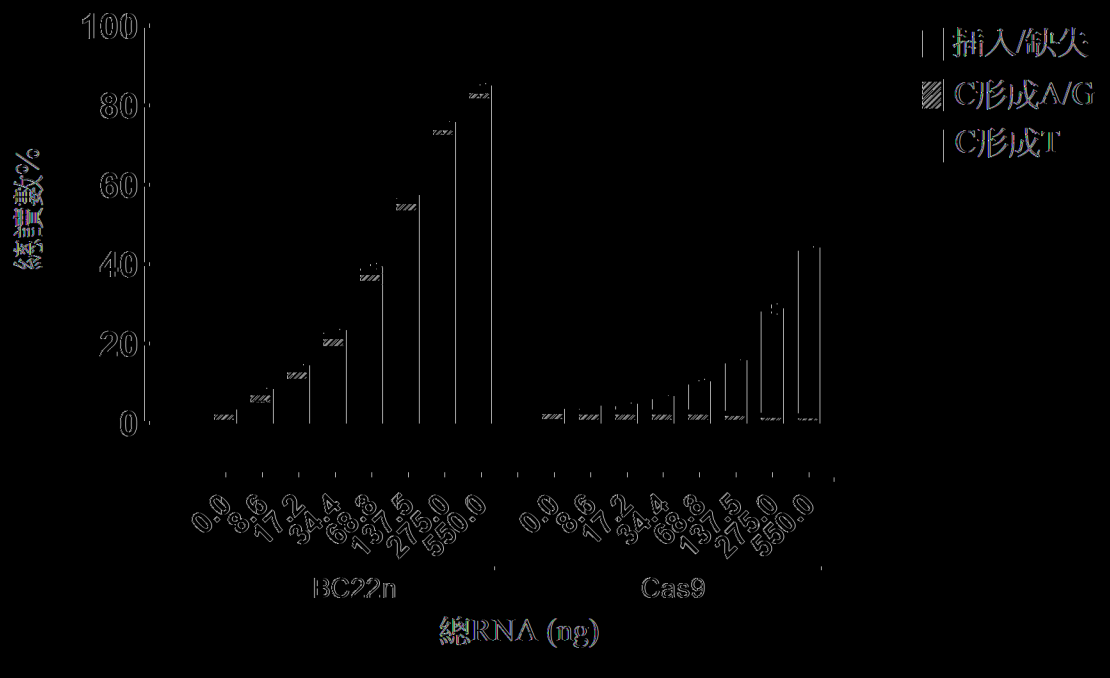

100
80
60
40
20
0
編輯效率%
插入/缺失
C形成A/G
C形成T
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)

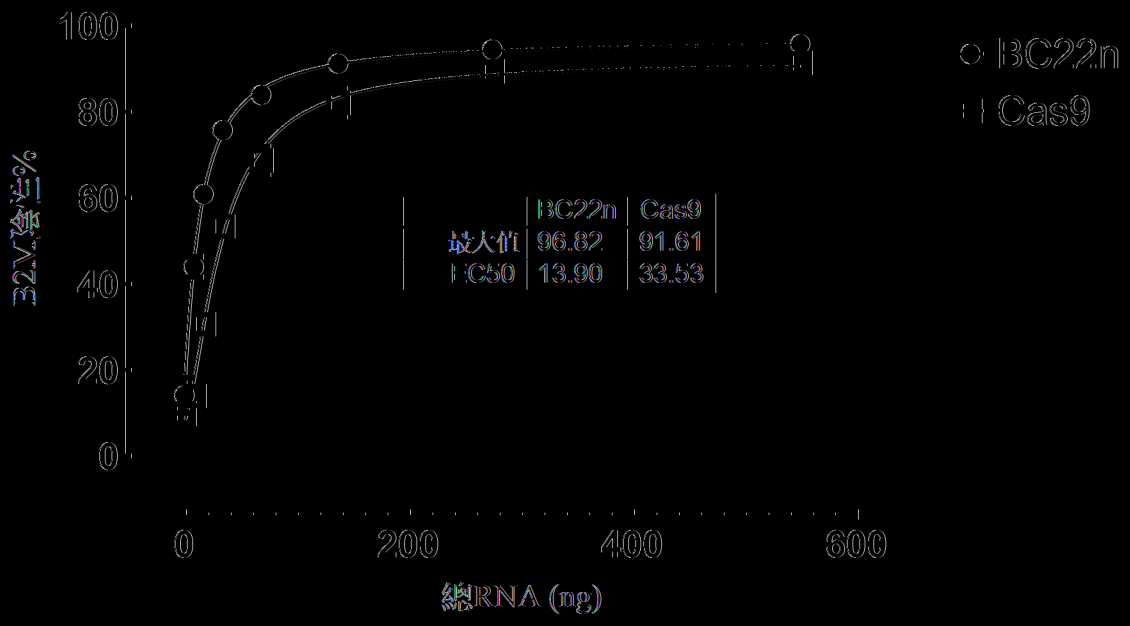
圖18B


100
80
60
40
20
0
總讀數%
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)
插入/缺失
C形成A/G
C形成T

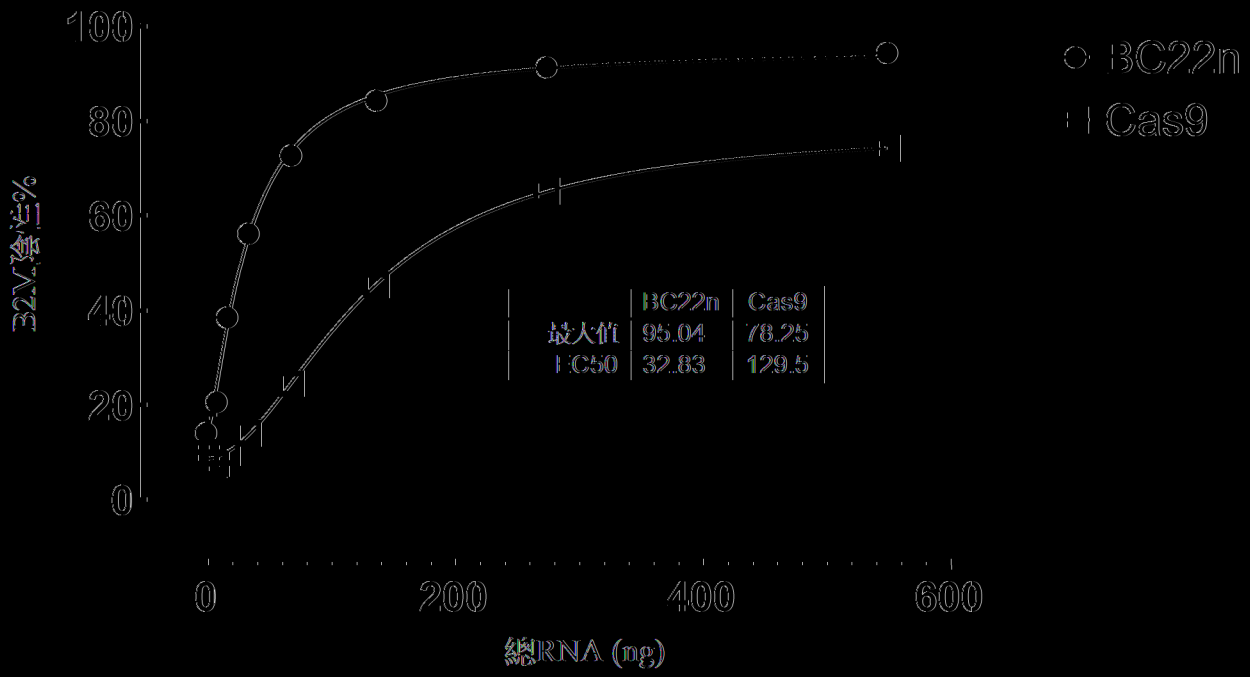
|(圖18C)|


100
80
60
40
20
0
總讀數%
0.0
8.6
17.2
34.4
68.8
137.5
275.0
550.0
BC22n
Cas9
總RNA (ng)
插入/缺失
C形成A/G
C形成T

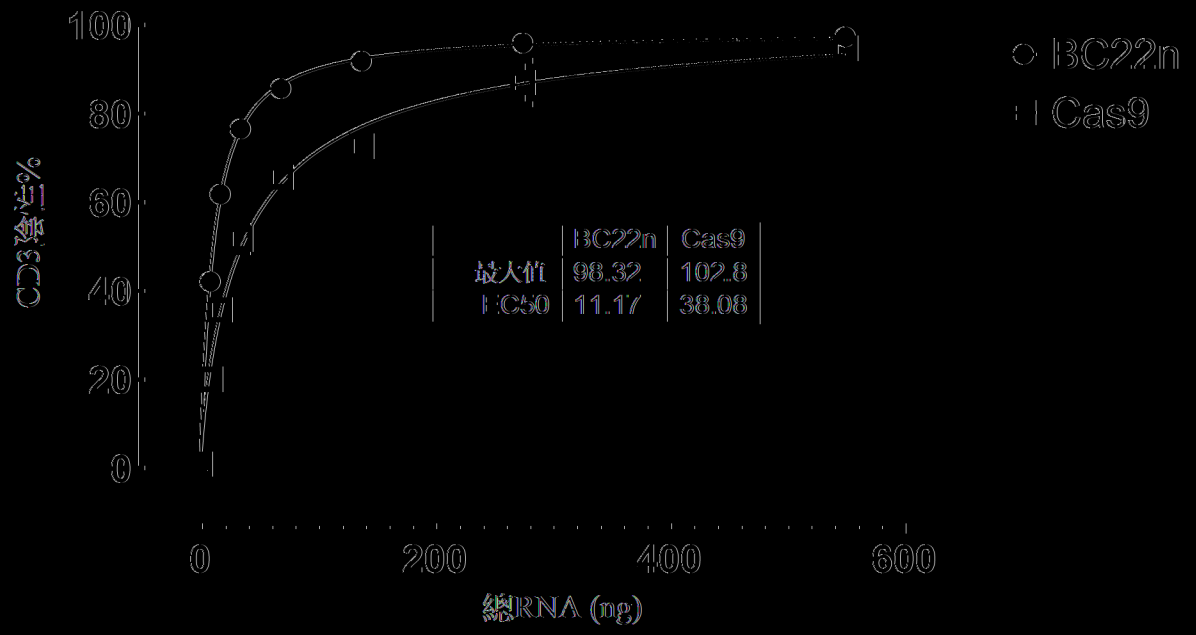
|(圖18D)|


100
80
60
40
20
0
B2V.陰性%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 96.82 91.61
EC50 13.90 33.53

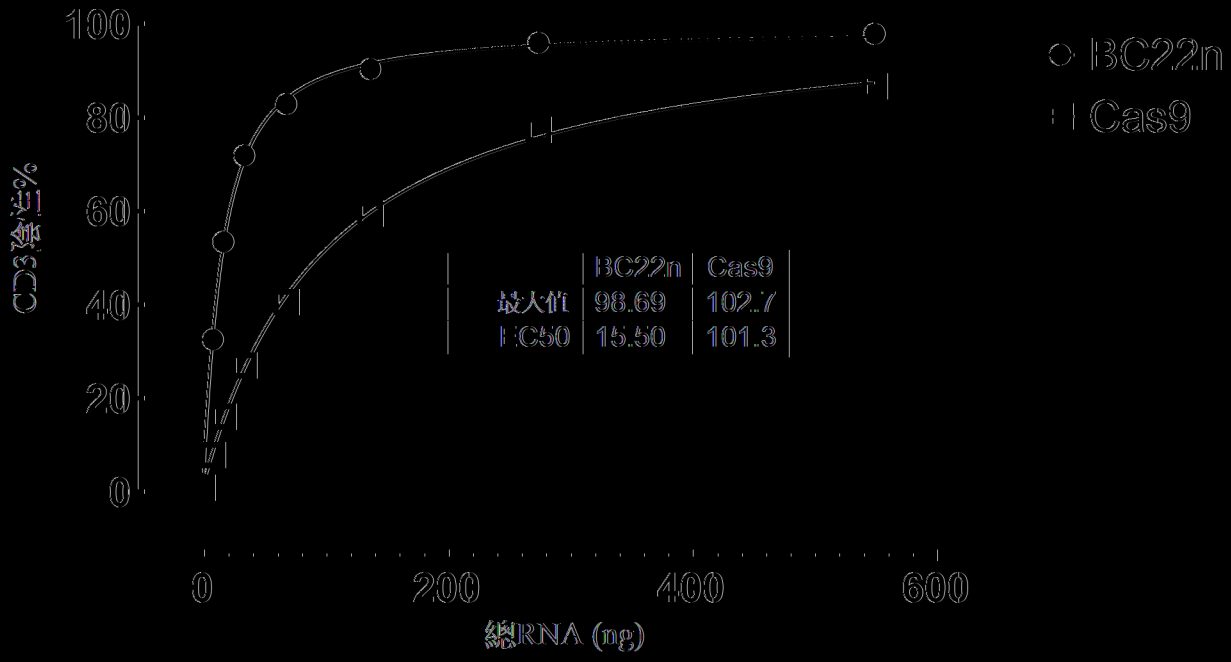
|(圖19A)|


100
80
60
40
20
0
B2V.陰性%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 95.04 78.25
EC50 32.83 129.5

|(圖19B)|


100
80
60
40
20
0
CD3活化%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 98.32 102.8
EC50 11.17 38.08

|(圖19C)|


100
80
60
40
20
0
CD3活化%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 98.69 102.7
EC50 15.50 101.3

|(圖19D)|

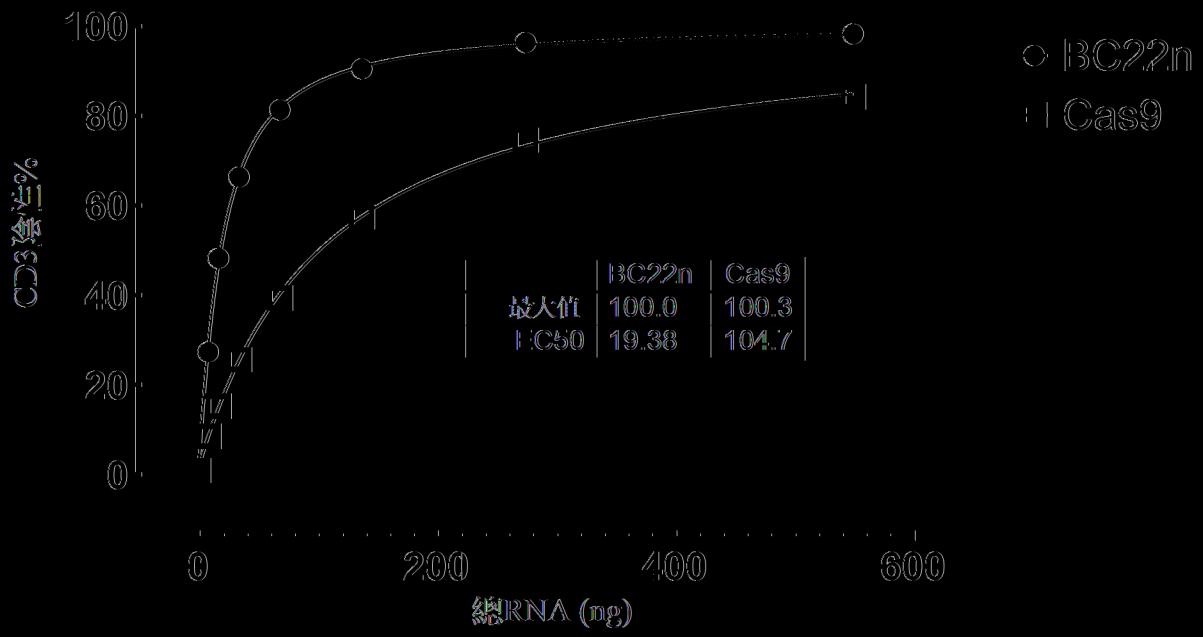

100
80
60
40
20
0
CD3+細胞%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 100.0 100.3
EC50 19.38 104.7

圖19E

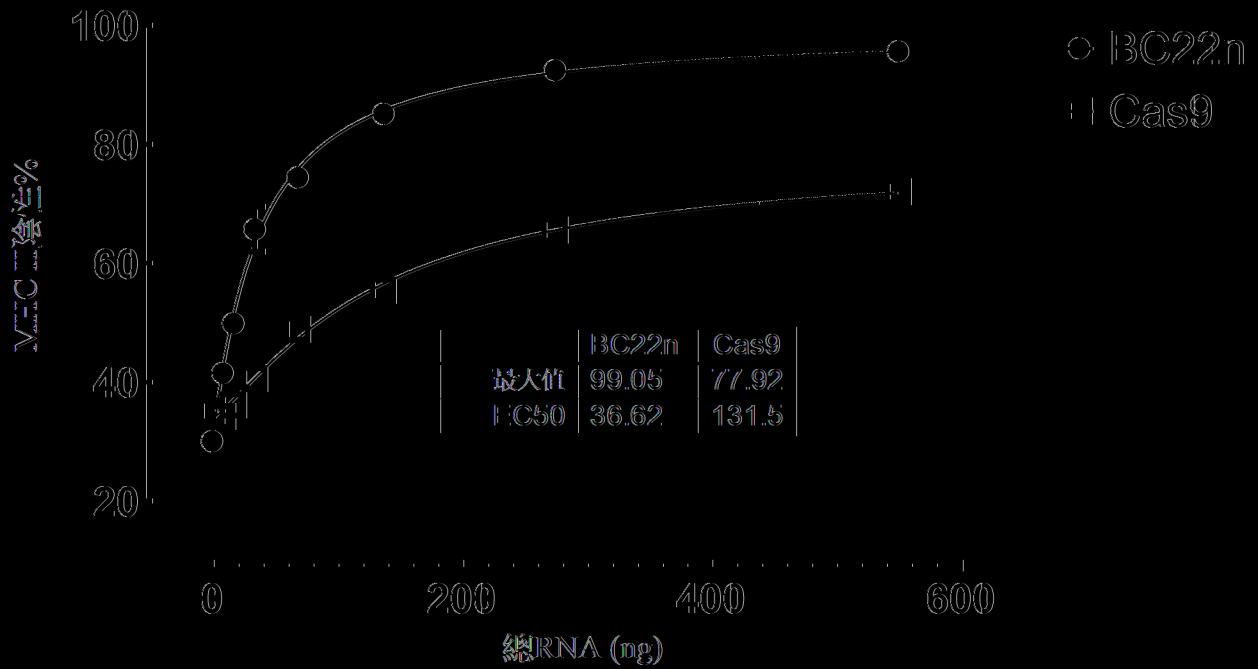

100
80
60
40
20
VEC+細胞%
0
200
400
600
總RNA (ng)
BC22n
Cas9
BC22n Cas9
最大值 99.05 77.92
EC50 36.62 131.5

圖19F

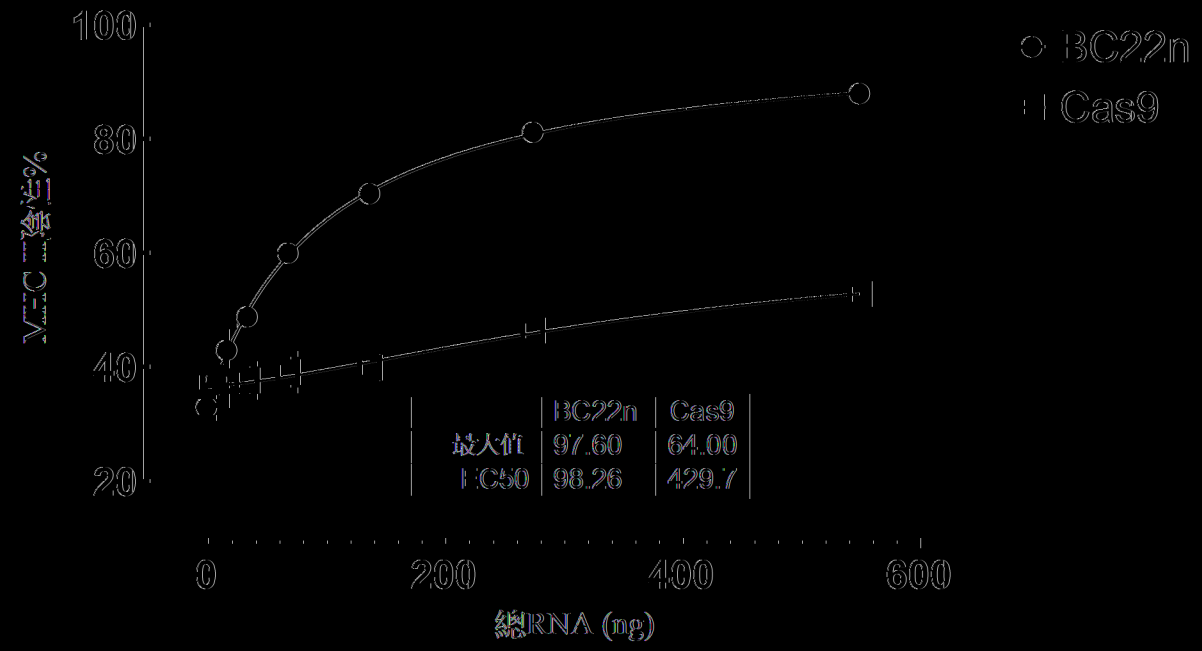

100
80
60
40
20
0
200
400
600
總RNA (ng)
BC22n
Cas9
最大值 97.60 64.00
IC50 98.26 429.7

圖19G

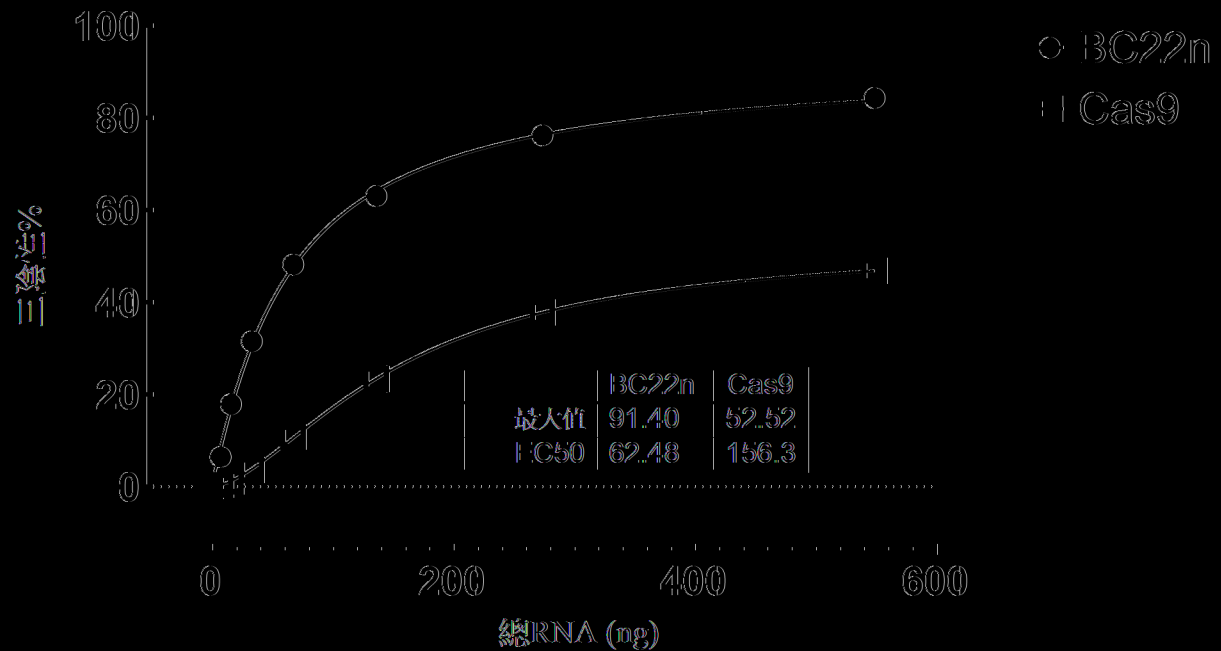

100
80
60
40
20
0
0
200
400
600
總RNA (ng)
BC22n
Cas9
最大值 91.40 52.52
IC50 62.48 156.3

圖19H

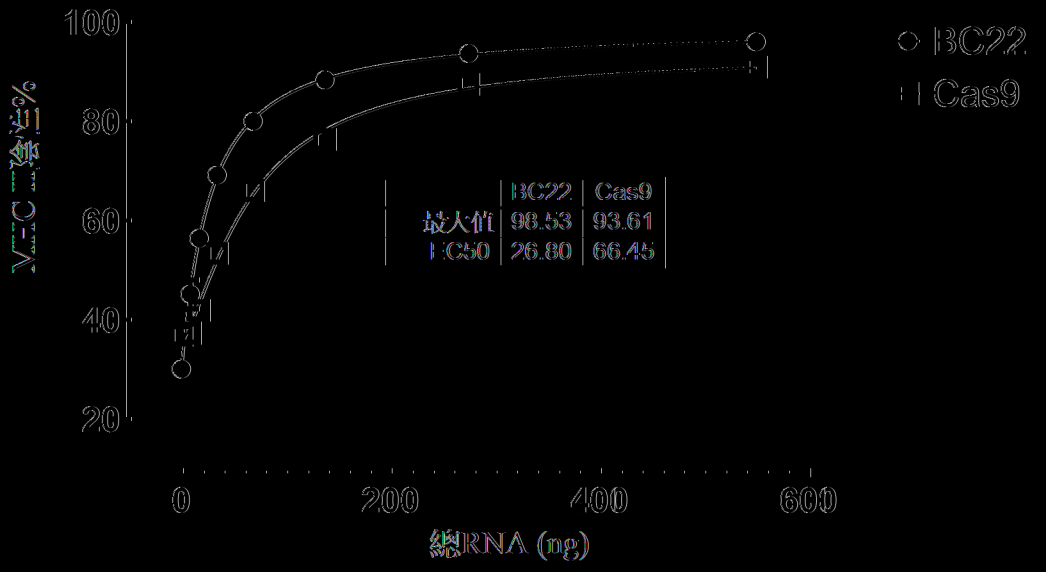
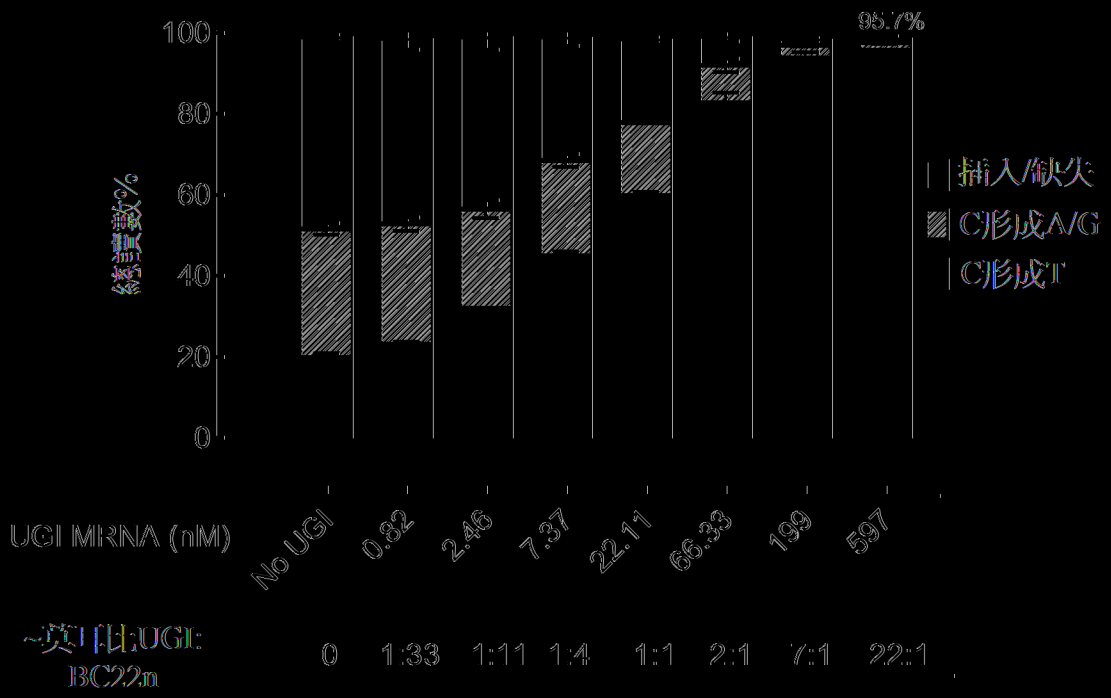
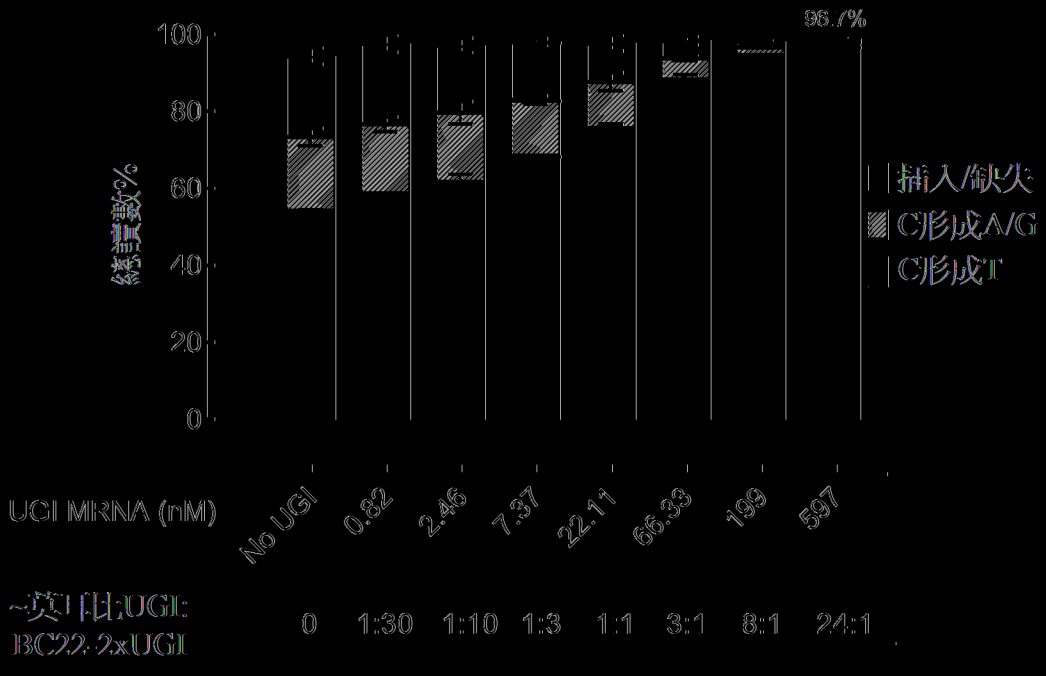

100
80
60
40
20
0
200
400
600
總RNA (ng)
BC22
Cas9
BC22 Cas9
最大值 98.53 93.61
IC50 26.80 66.45

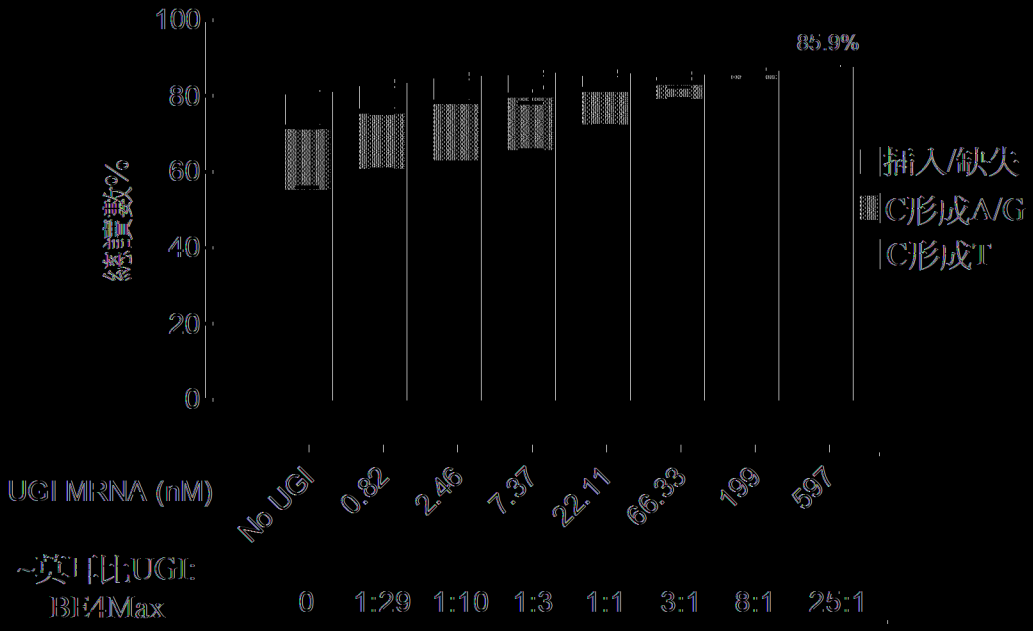
圖19D


95.7%
100
80
60
40
20
0
總讀數%
插入/缺失
C形成A/G
C形成T
UGI MRNA (nM)
No UGI
0.82
2.46
7.37
22.11
66.33
199
597
~莫耳比UGI:
BC22n
0
1:33
1:11
1:4
1:1
2:1
7:1
22:1

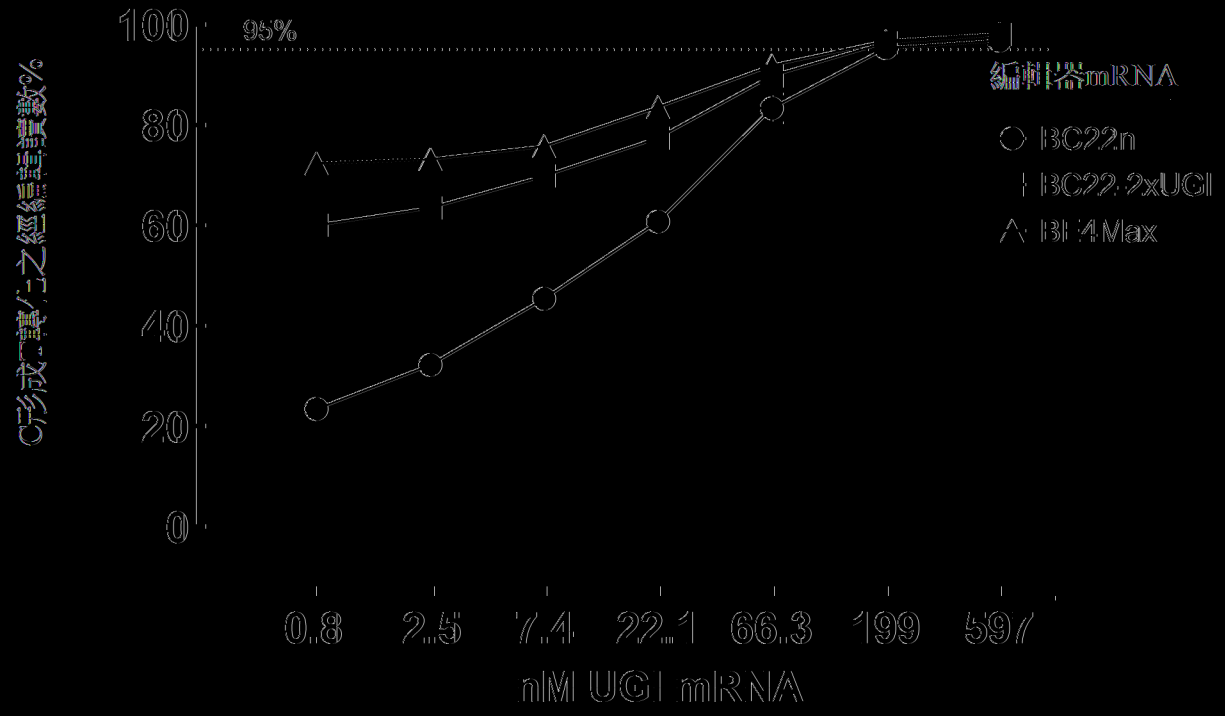
|(圖20A)|


96.7%
100
80
60
40
20
0
總讀數%
插入/缺失
C形成A/G
C形成T
UGI MRNA (nM)
No UGI
0.82
2.46
7.37
22.11
66.33
199
597
~莫耳比UGI:
BC22-2xUGI
0
1:30
1:10
1:3
1:1
3:1
8:1
24:1

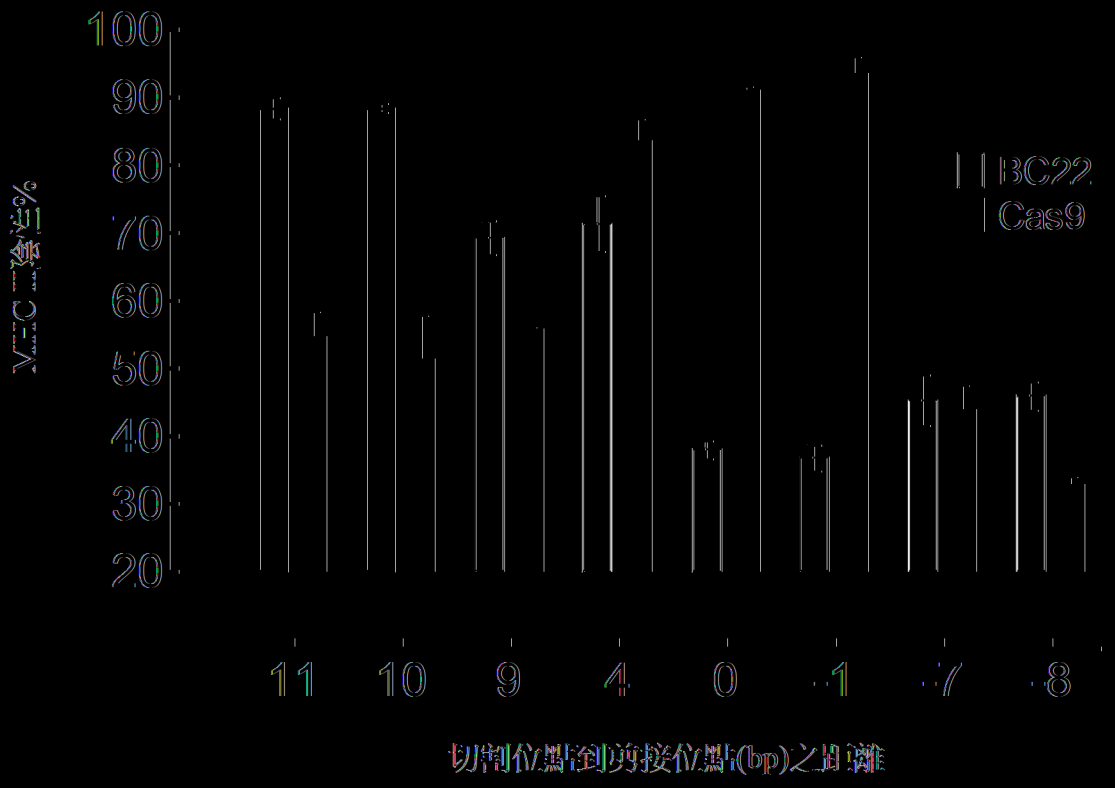
|(圖20B)|


100
80
60
40
20
0
總讀數%
85.9%
插入/缺失
C形成A/G
C形成T
UGI MRNA (nM)
No UGI
0.82
2.46
7.37
22.11
66.33
199
597
~莫耳比UGI:
BE4Max
0
1:29
1:10
1:3
1:1
3:1
8:1
25:1

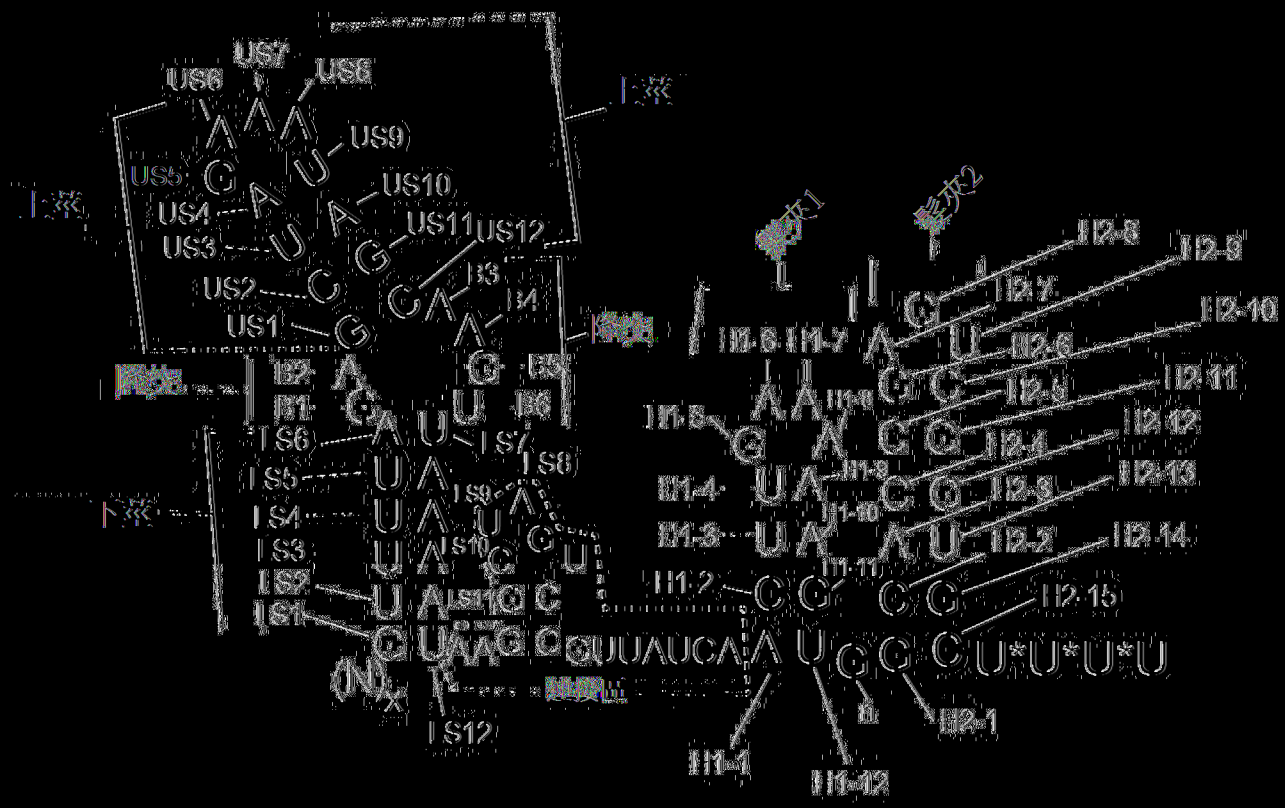
(圖20C)


100
80
60
40
20
0
95%
C形成口轉爪之經編輯實數%
編輯器mRNA
BC22n
BC22-2xUGI
BE4Max
0.8
2.5
7.4
22.1
66.3
199
597
nM UGI mRNA

(圖21)

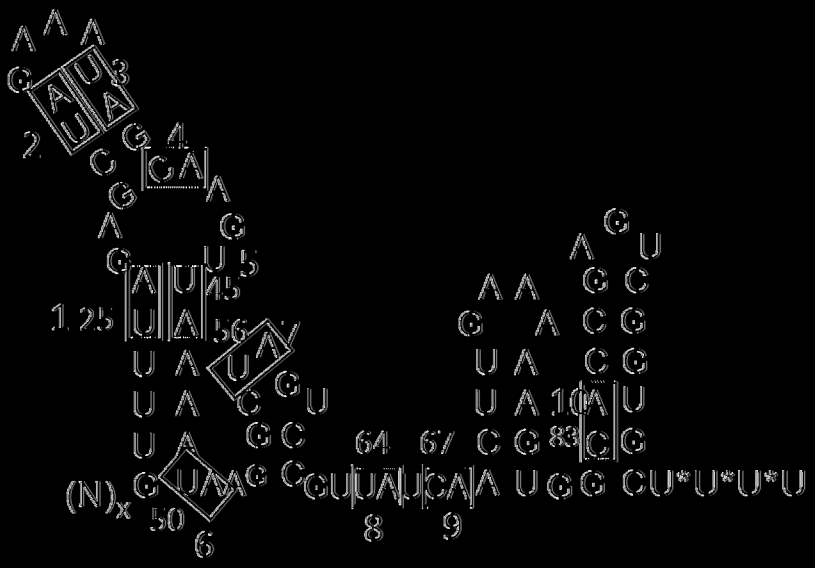

100
90
80
70
60
50
40
30
20
MHC 二陰性%
BC22
Cas9
11
10
9
4
0
-1
-7
-8
切割位點到剪接位點(bp)之距離

(圖22)



|(圖23A)|

骨架Y/A



|(圖23B)|

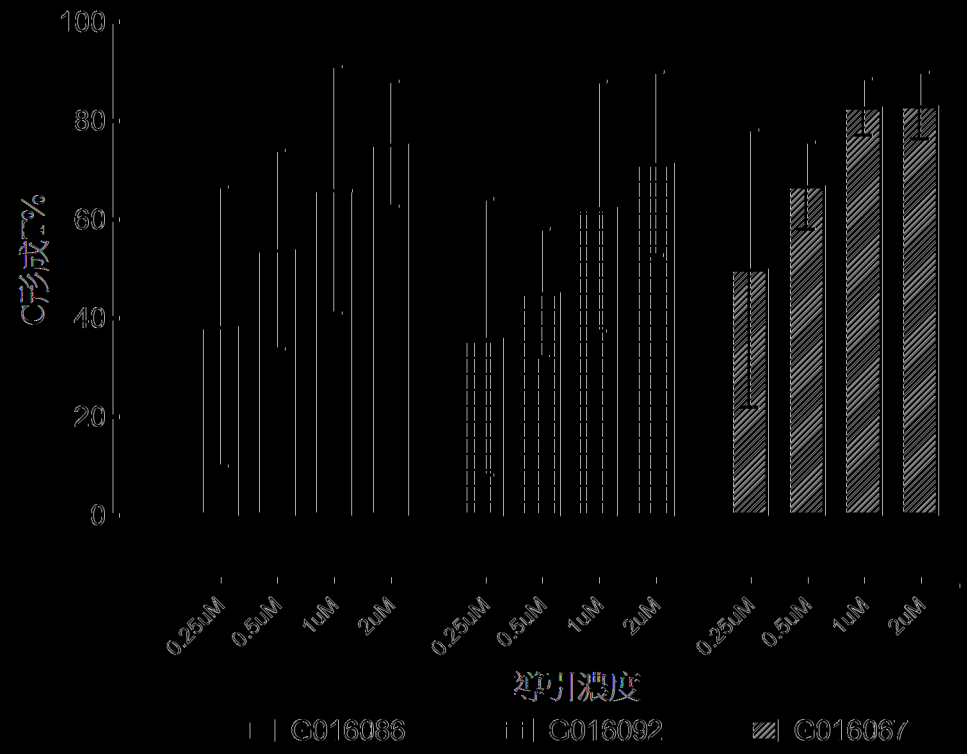

100
80
60
40
20
0
C活成%
0.25uM
0.5uM
1uM
2uM
0.25uM
0.5uM
1uM
2uM
0.25uM
0.5uM
1uM
2uM
導引濃度
C016086
C016092
C016067

圖24A

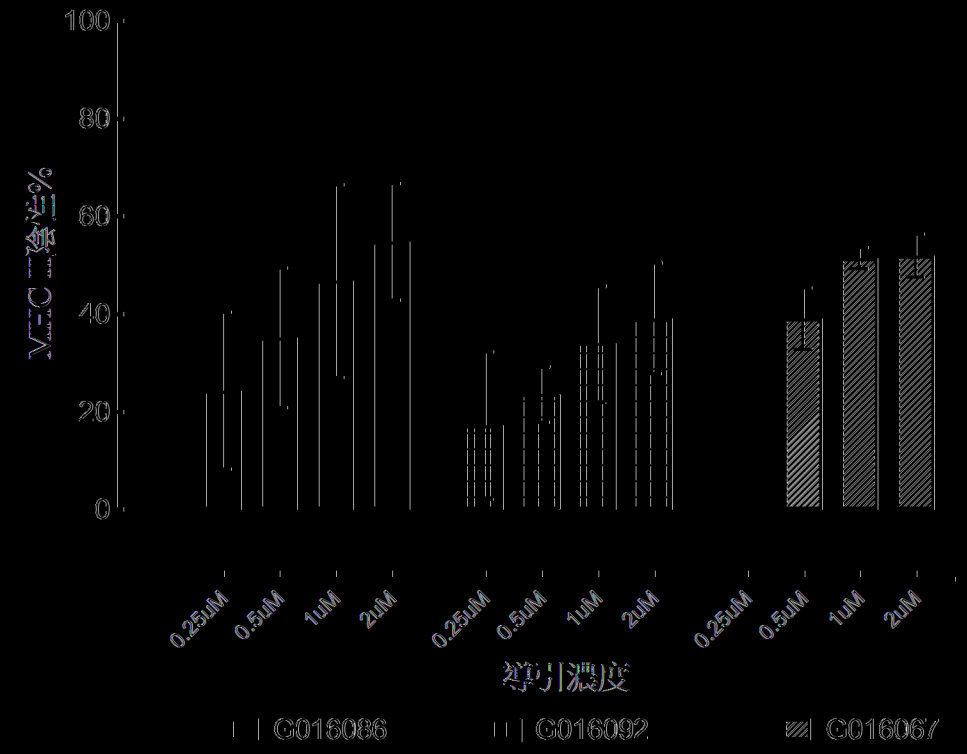
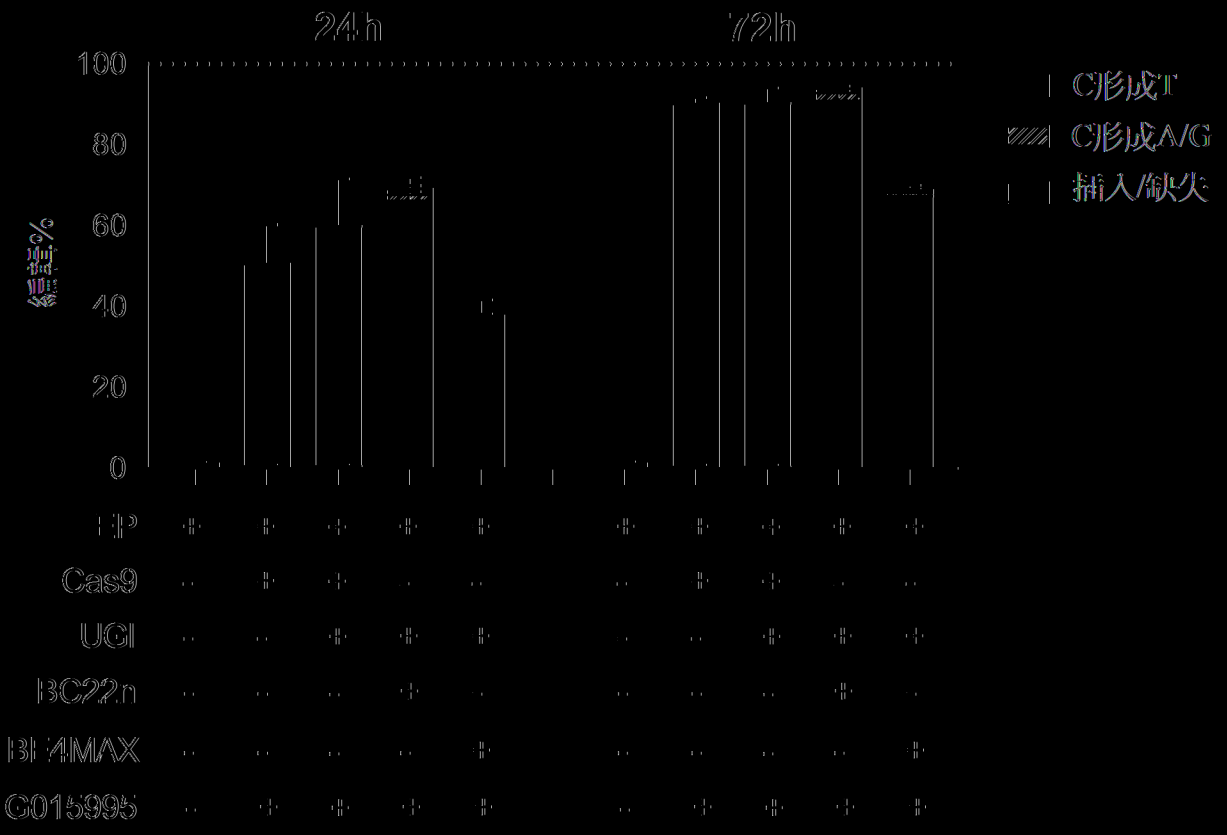
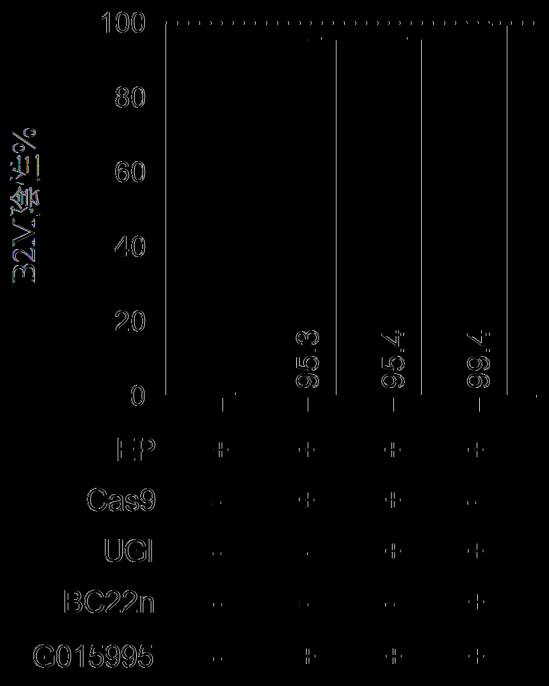

100
80
60
40
20
0
VEC C活%
0.25uM
0.5uM
1uM
2uM
0.25uM
0.5uM
1uM
2uM
0.25uM
0.5uM
1uM
2uM
導引濃度
C016086
C016092
C016067

圖24B

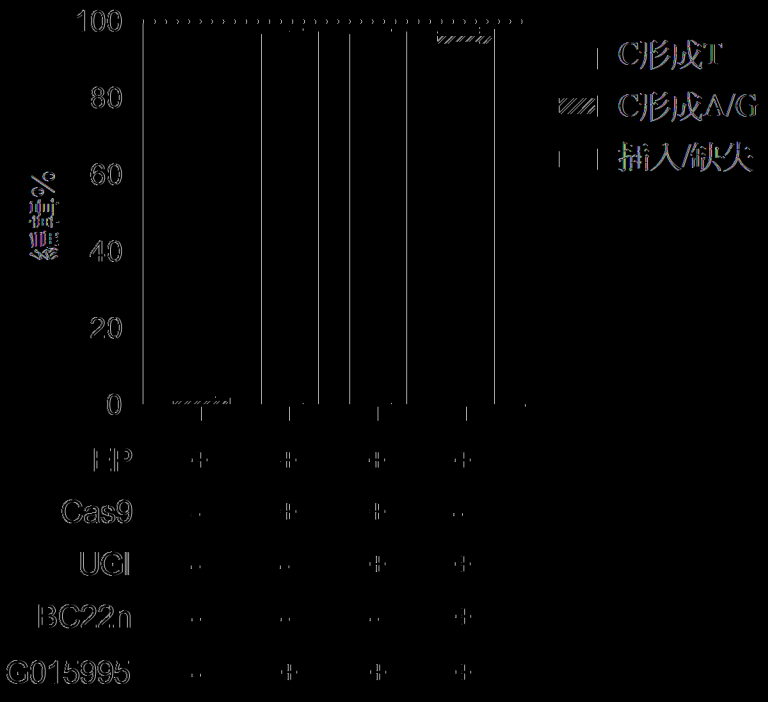

24h
72h
100
80
60
40
20
0
編輯%
EP
Cas9
UGI
BC22n
BE4MAX
G015995
C形成T
C形成A/G
插入/缺失

【圖25】

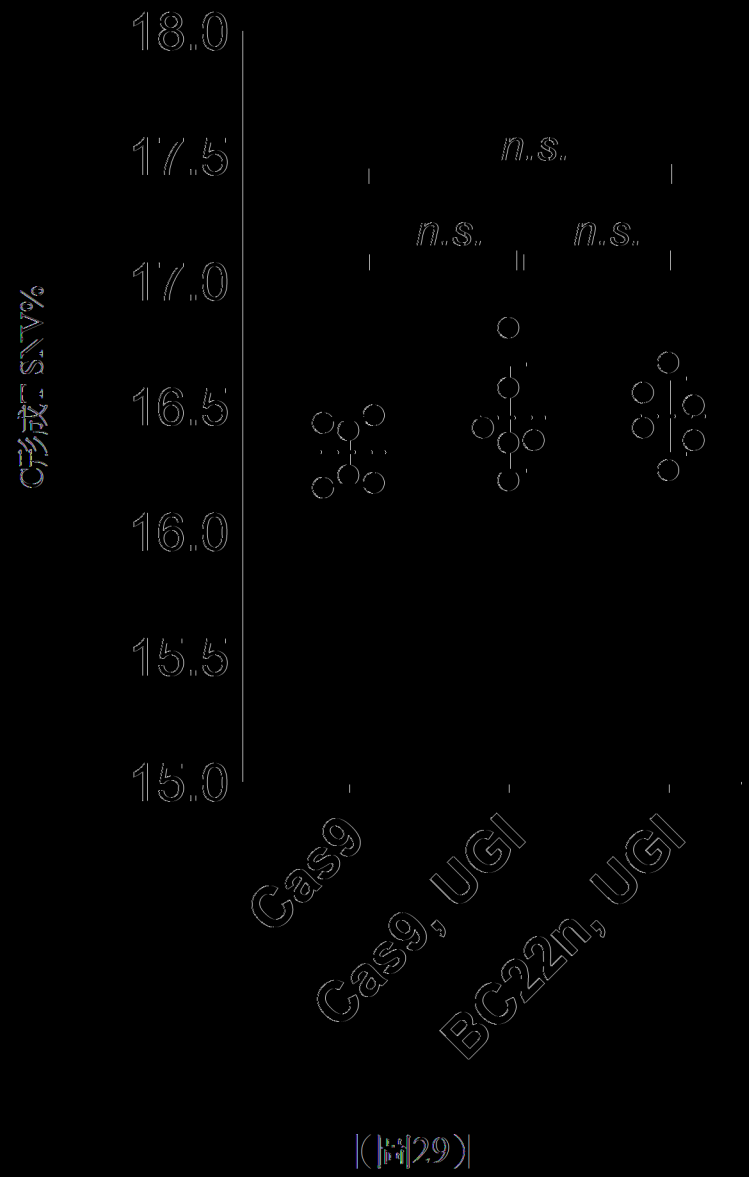
|(圖2.6)|


100
80
60
40
20
0
B2M陰性%
95.3
95.4
99.4
EP
Cas9
UGI
BC22n
G015995

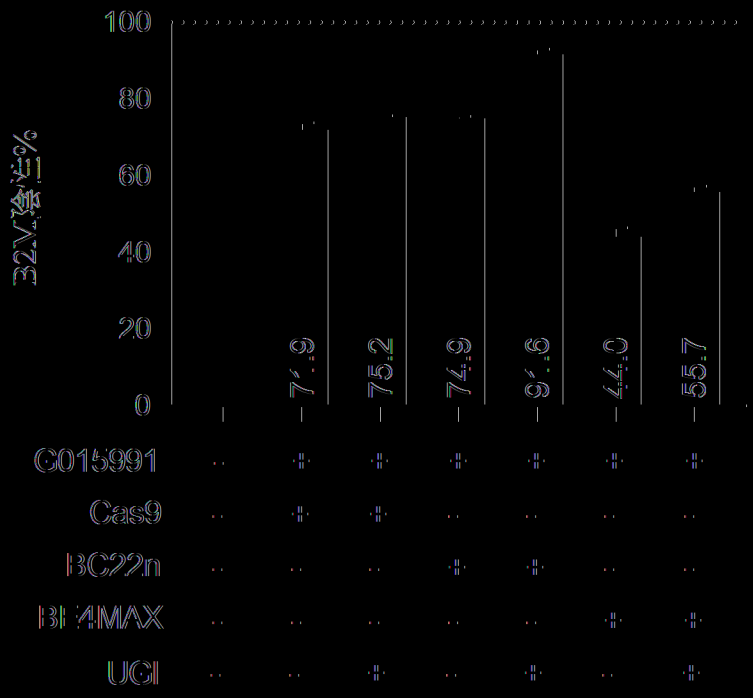
|(圖27)|


100
80
60
40
20
0
鎖鏈%
C形成T
C形成A/G
插入/缺失
EP
Cas9
UGI
BC22n
G015995

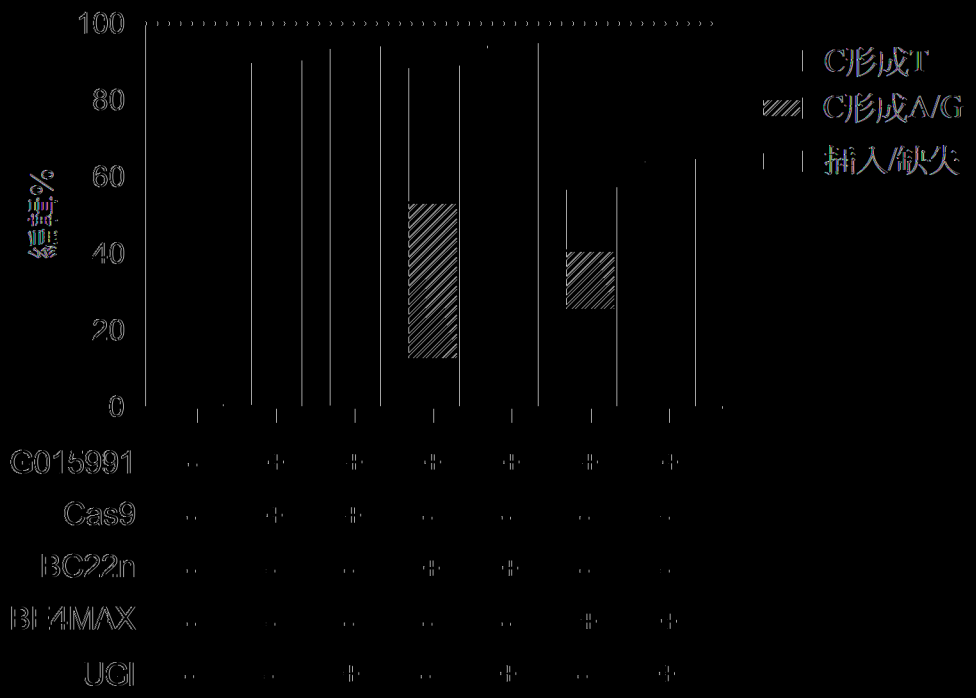
|(圖28)|



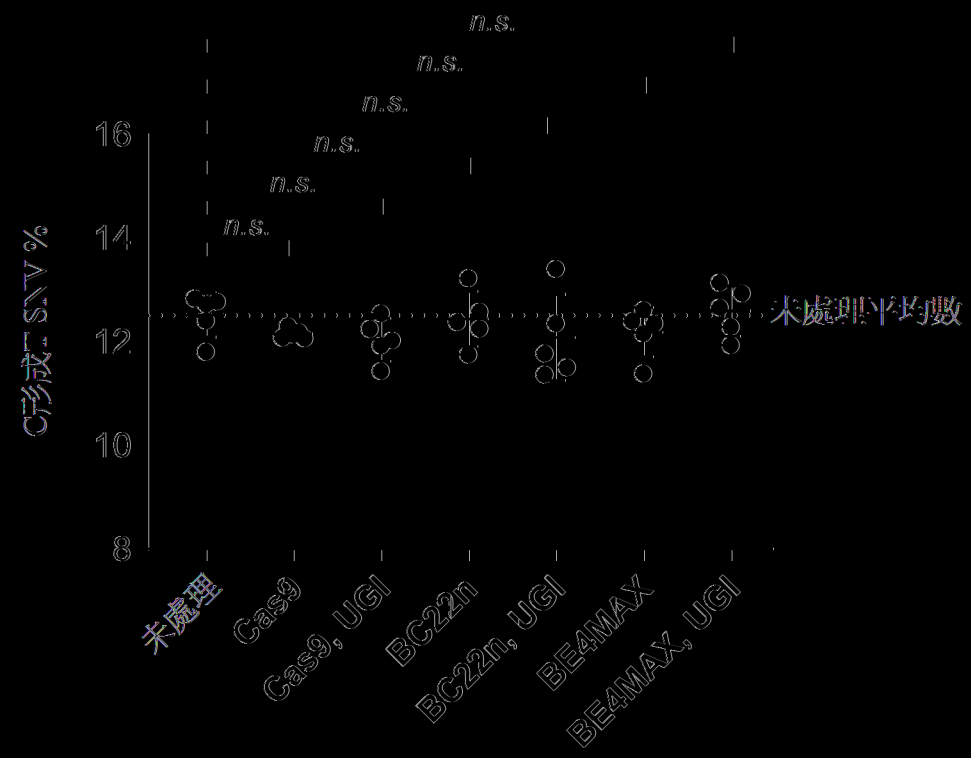
|(圖29)|


100
80
60
40
20
0
B2V含性%
71.9
75.2
74.9
91.6
44.0
55.7
G015991
Cas9
BC22n
BE4MAX
UGI

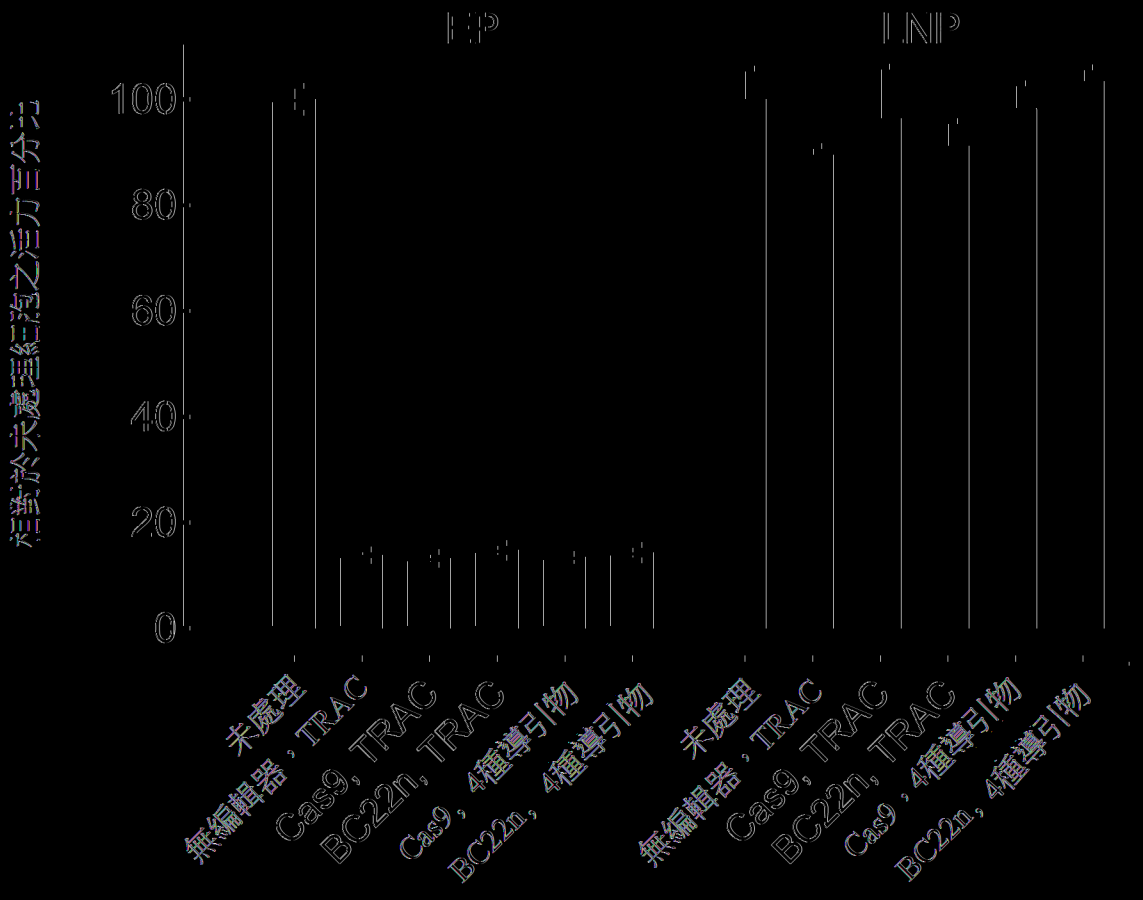
|(圖30)|


100
80
60
40
20
0
編輯%
C形成T
C形成A/G
插入/缺失
G015991
Cas9
BC22n
BE4MAX
UGI

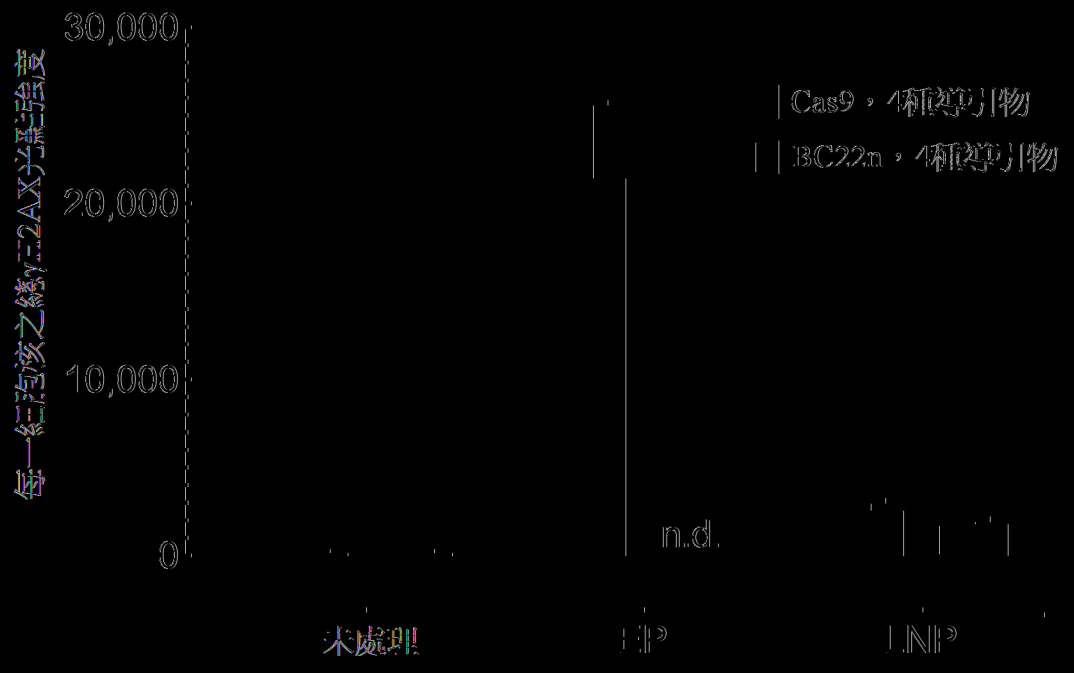
|(圖31)|


n.s.
n.s.
n.s.
n.s.
n.s.
n.s.
16
14
12
10
8
C形成口 SNV %
未處理平均數
未處理
Cas9
Cas9, UGI
BC22n
BC22n, UGI
BE4MAX
BE4MAX, UGI

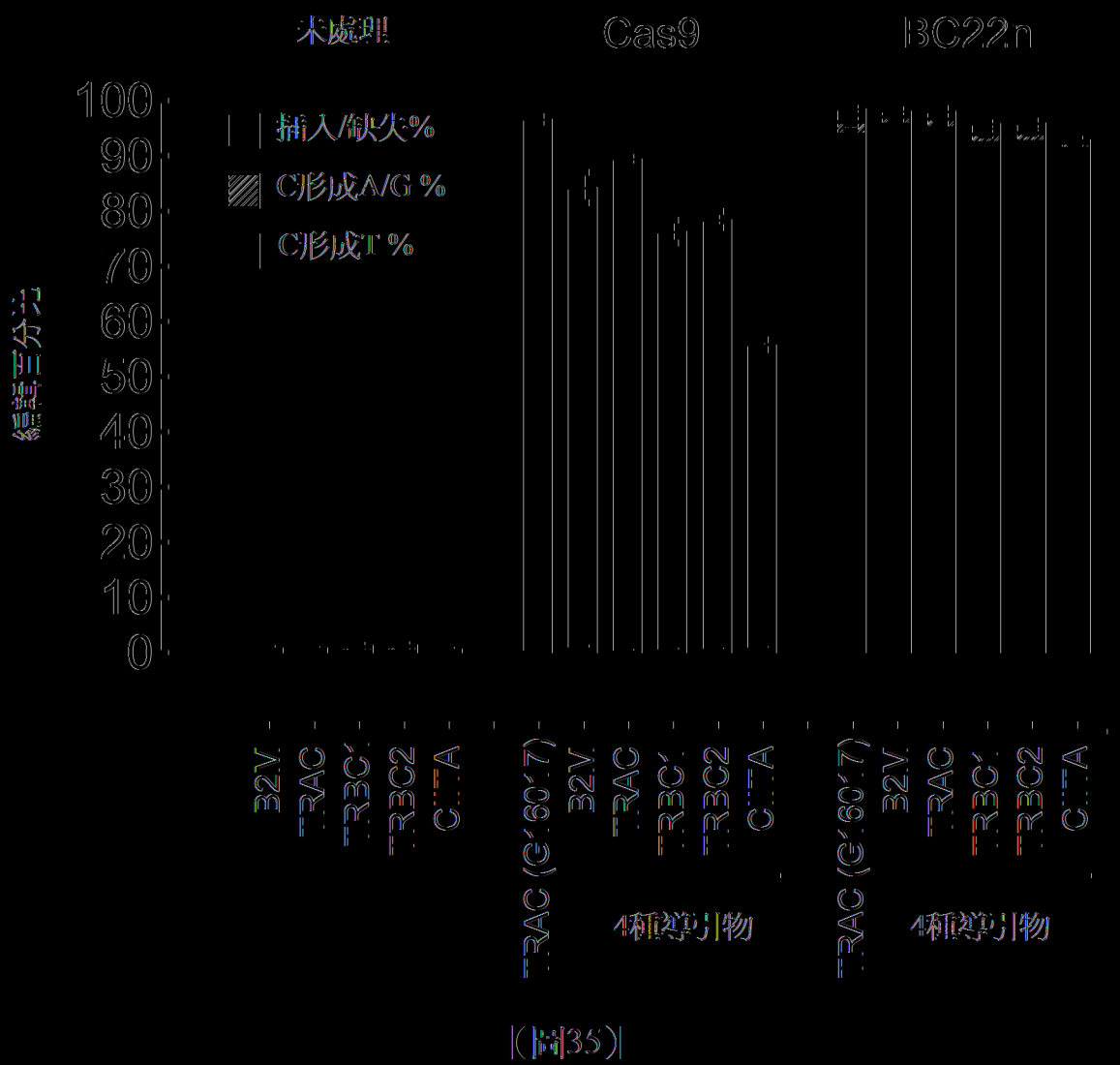
|(圖32)|


EP
LNP
相對於未處理細胞之活力百分比
100
80
60
40
20
0
未處理
無編輯器，TRAC
Cas9, TRAC
BC22n, TRAC
Cas9，4種導引物
BC22n，4種導引物
未處理
無編輯器，TRAC
Cas9, TRAC
BC22n, TRAC
Cas9，4種導引物
BC22n，4種導引物

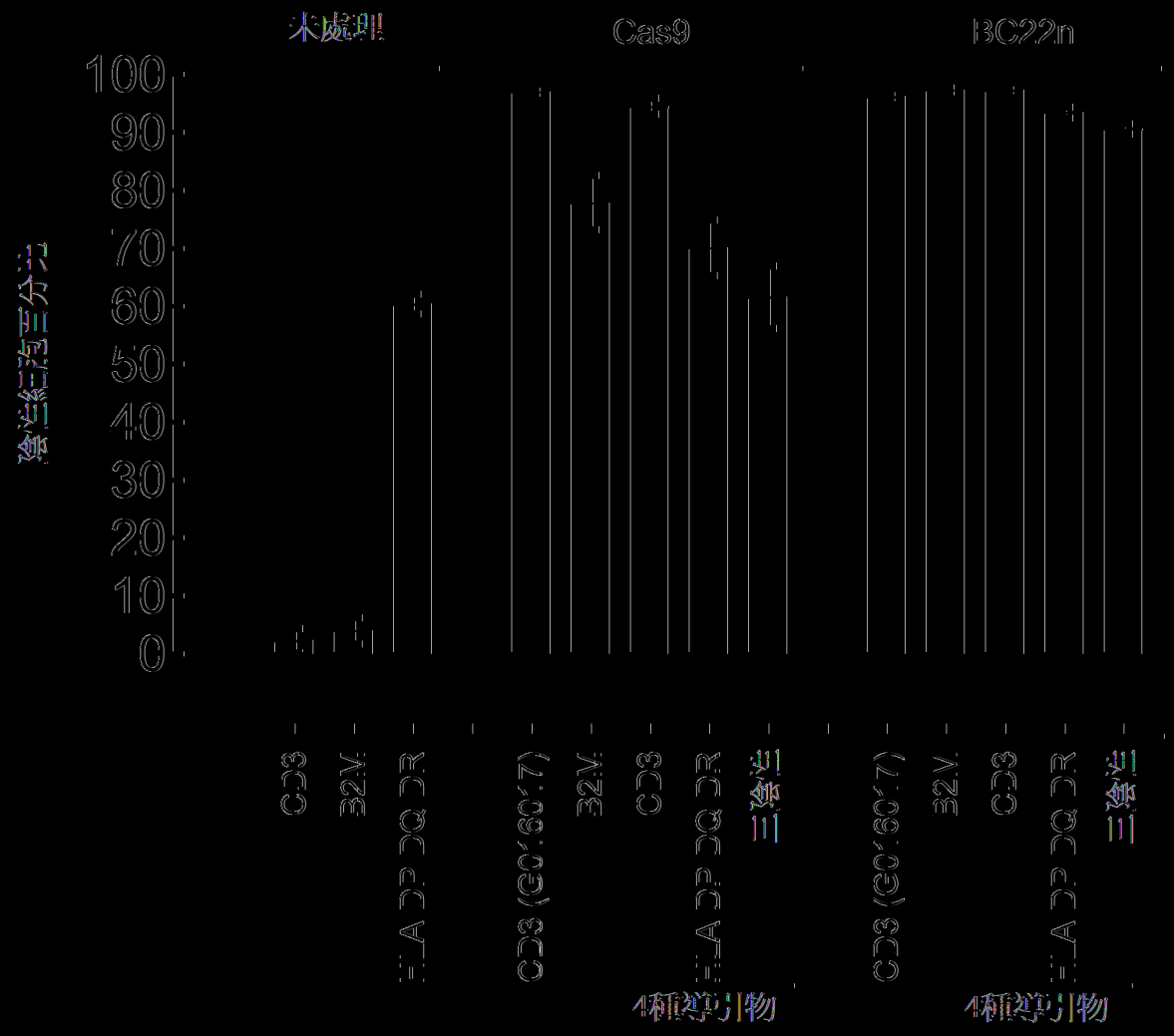
【圖33】


30,000
20,000
10,000
0
每一細胞核之總γH2AX光點強度
Cas9，4種導引物
BC22n，4種導引物
n.d.
未處理
EP
LNP

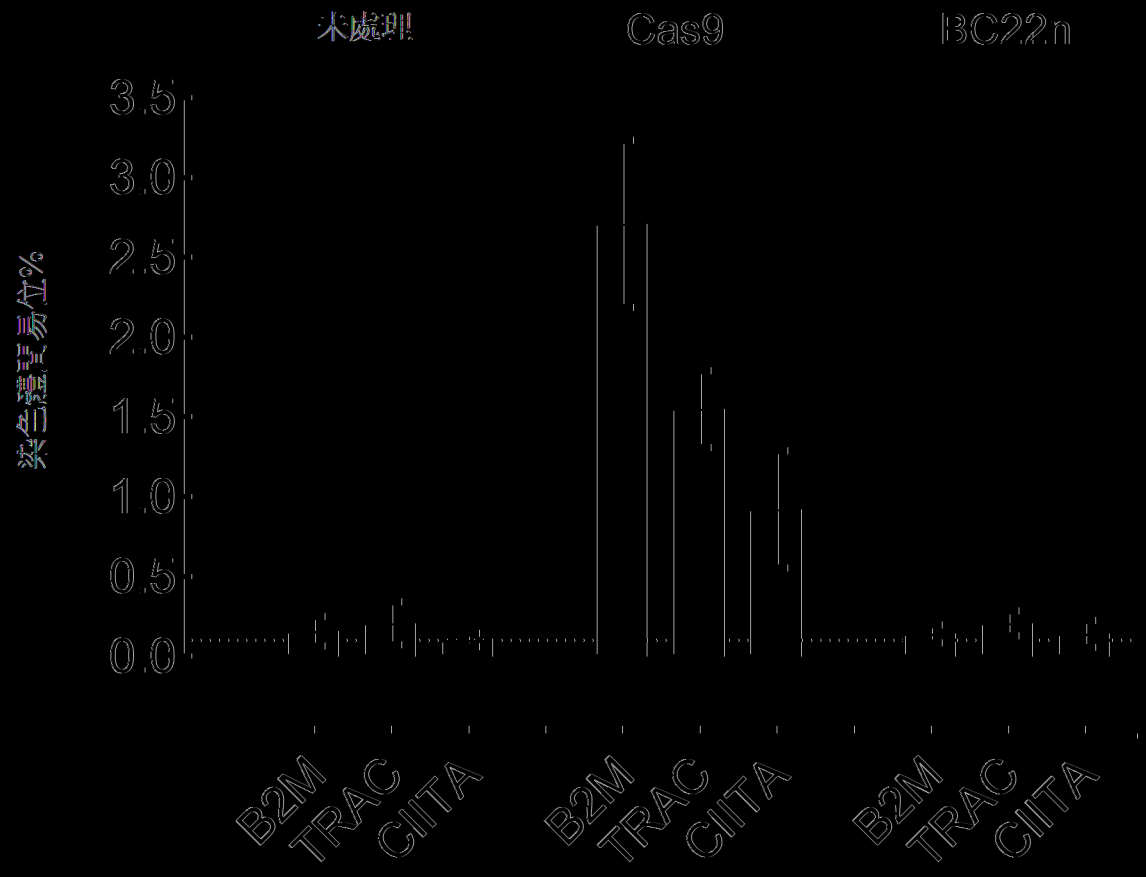
(圖34)


未處理
Cas9
BC22n
100
90
80
70
60
50
40
30
20
10
0
插入/缺失%
C形成A/G %
C形成T %
編輯百分比
B2V
TRAC
TRBC1
TRBC2
CTTA
TRAC (G16017)
4種導引物

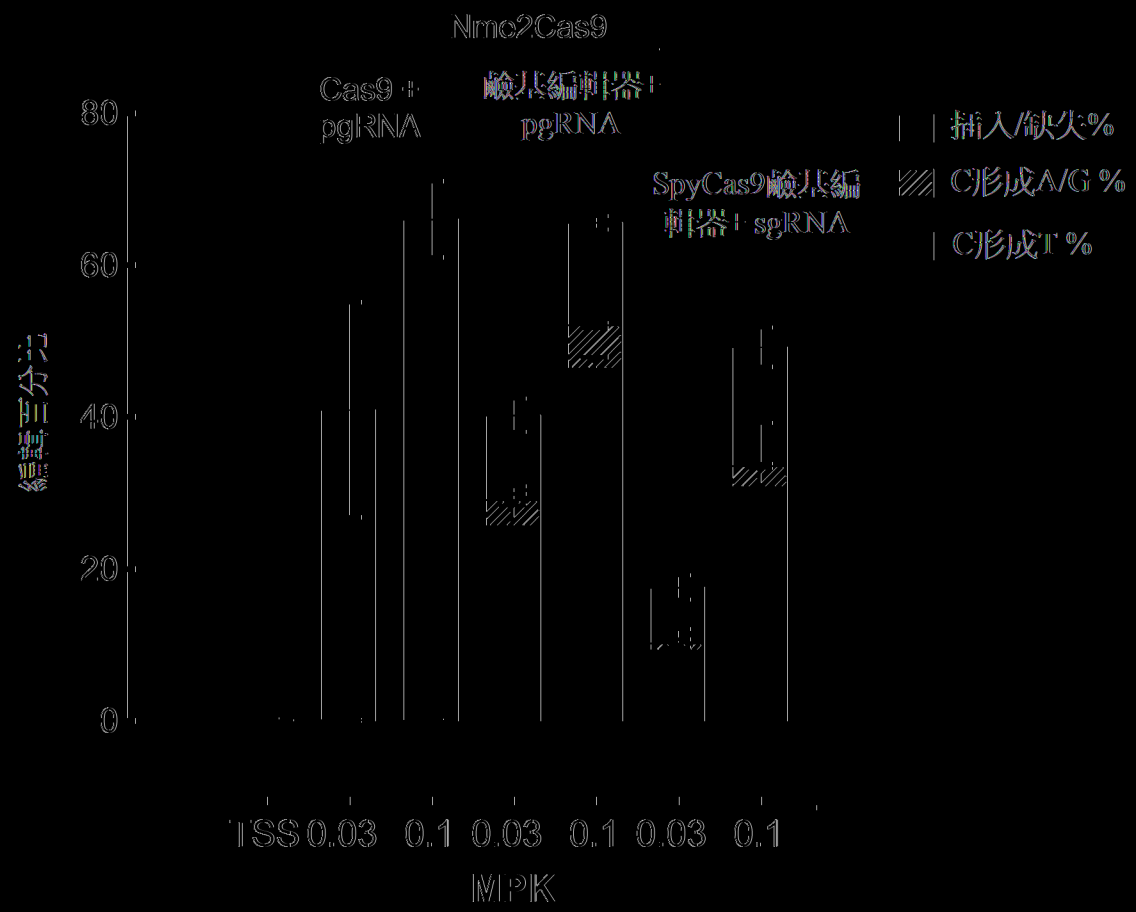
(圖35)


未處理
Cas9
BC22n
100
90
80
70
60
50
40
30
20
10
0
陰性細胞百分比
CD3
B2M
HLA DP DQ DR
CD3 (G01601.7)
B2M
CD3
HLA DP DQ DR
三陰性
CD3 (G01601.7)
B2M
CD3
HLA DP DQ DR
三陰性
4種導引物
4種導引物

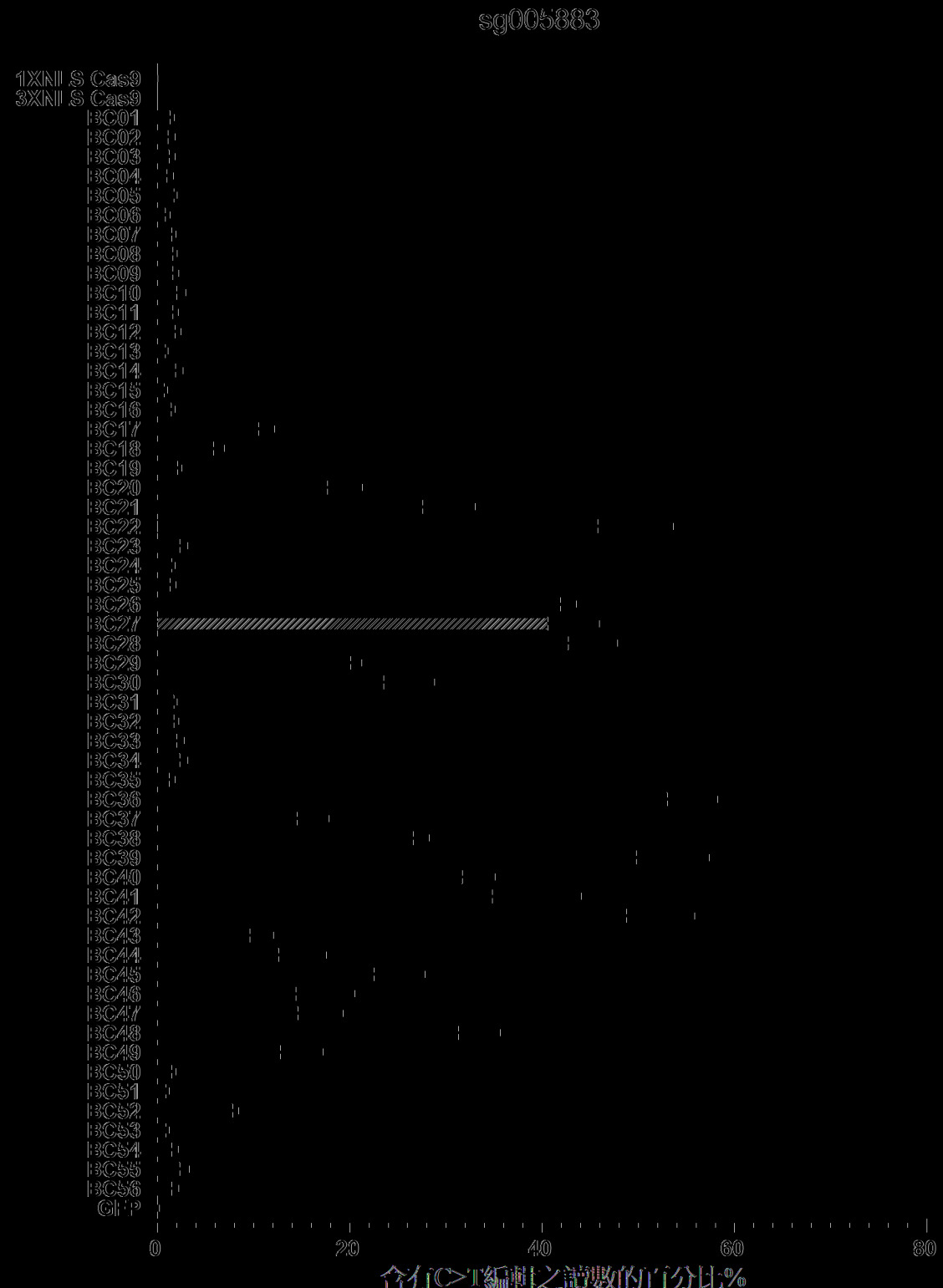
|(圖36)|


未處理
Cas9
BC22n
突合讀長百分比%
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
B2M
TRAC
CITA
B2M
TRAC
CITA
B2M
TRAC
CITA

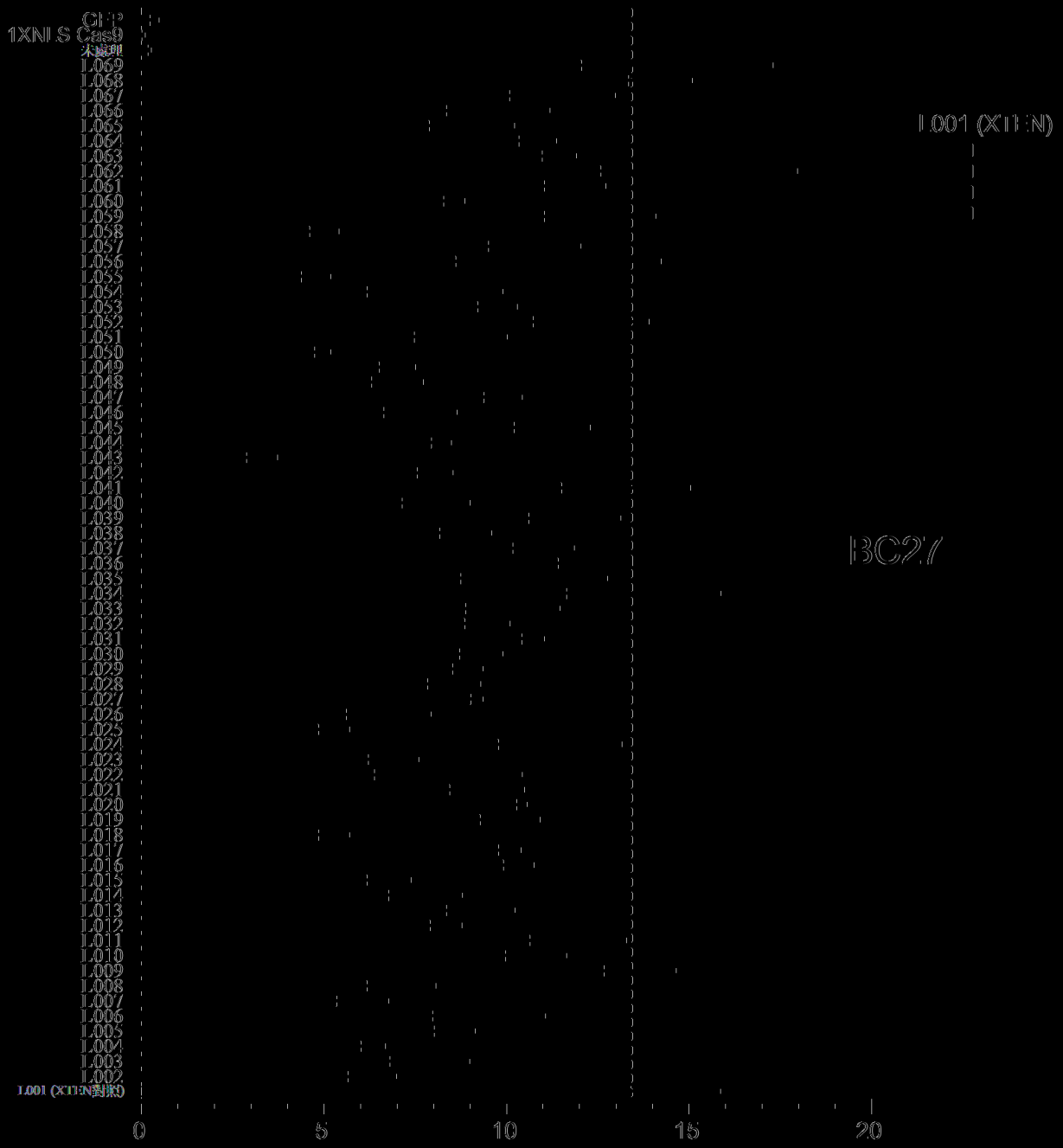
|(圖3’)|


Nmc2Cas9
Cas9+pgRNA
鹼基編輯器+pgRNA
SpyCas9鹼基編輯器+sgRNA
插入/缺失%
C形成A/G %
C形成T %
編輯效率%
80
60
40
20
0
TSS 0.03 0.1 0.03 0.1 0.03 0.1
MPK

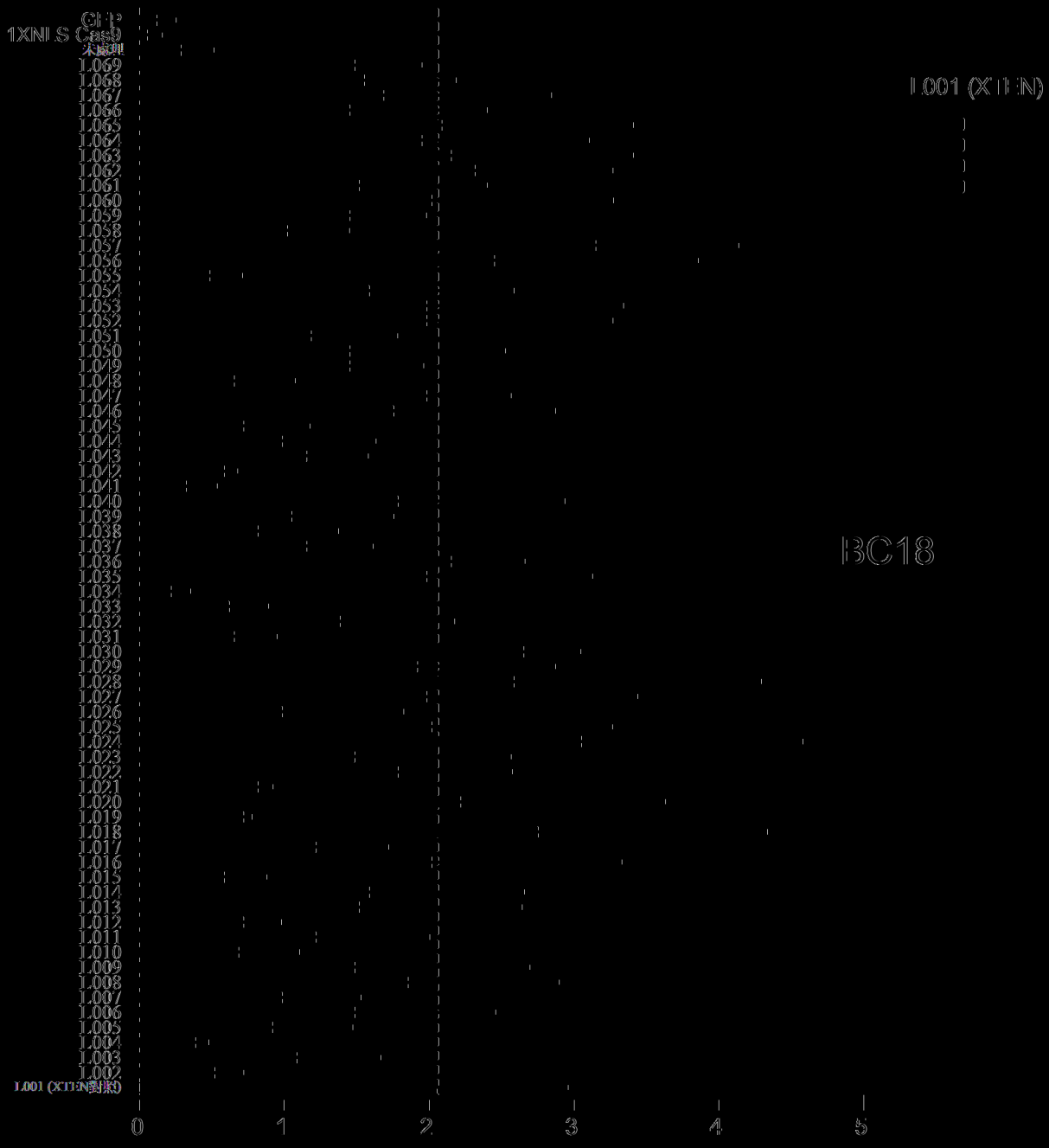
|(圖38)|


sg005883
1XNI S Cas9
3XNI S Cas9
BC01
BC02
BC03
BC04
BC05
BC06
BC07
BC08
BC09
BC10
BC11
BC12
BC13
BC14
BC15
BC16
BC17
BC18
BC19
BC20
BC21
BC22
BC23
BC24
BC25
BC26
BC27
BC28
BC29
BC30
BC31
BC32
BC33
BC34
BC35
BC36
BC37
BC38
BC39
BC40
BC41
BC42
BC43
BC44
BC45
BC46
BC47
BC48
BC49
BC50
BC51
BC52
BC53
BC54
BC55
BC56
GFP
0
20
40
60
80
含有C>T編輯之讀數的百分比%

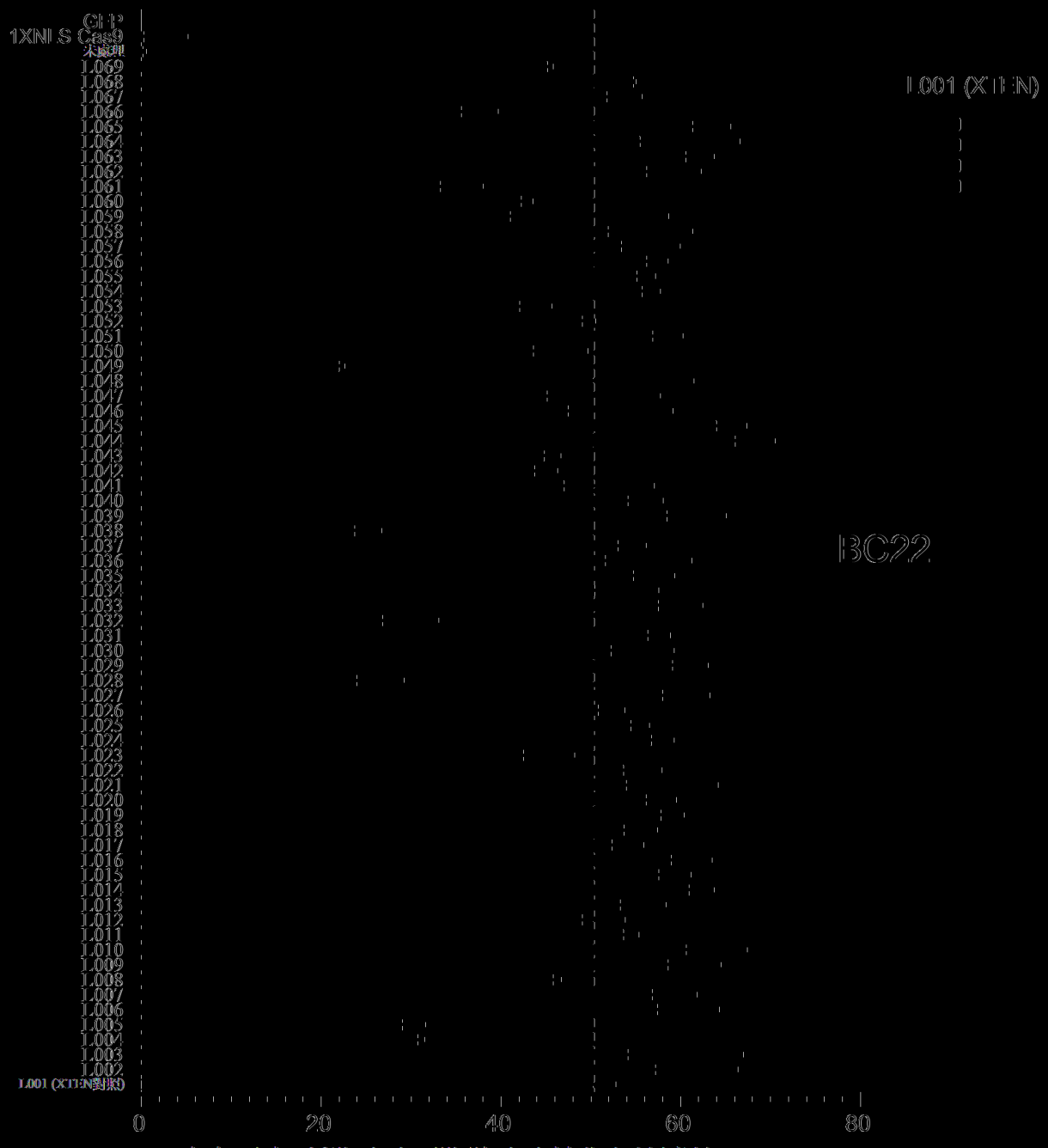
|(時39)|


GFP
1XNLS Cas9
未處理
L069
L068
L067
L066
L065
L064
L063
L062
L061
L060
L059
L058
L057
L056
L055
L054
L053
L052
L051
L050
L049
L048
L047
L046
L045
L044
L043
L042
L041
L040
L039
L038
L037
L036
L035
L034
L033
L032
L031
L030
L029
L028
L027
L026
L025
L024
L023
L022
L021
L020
L019
L018
L017
L016
L015
L014
L013
L012
L011
L010
L009
L008
L007
L006
L005
L004
L003
L002
L001 (XTEN對照)
L001 (XTEN)
BC27
0
5
10
15
20
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

|(圖40A)|

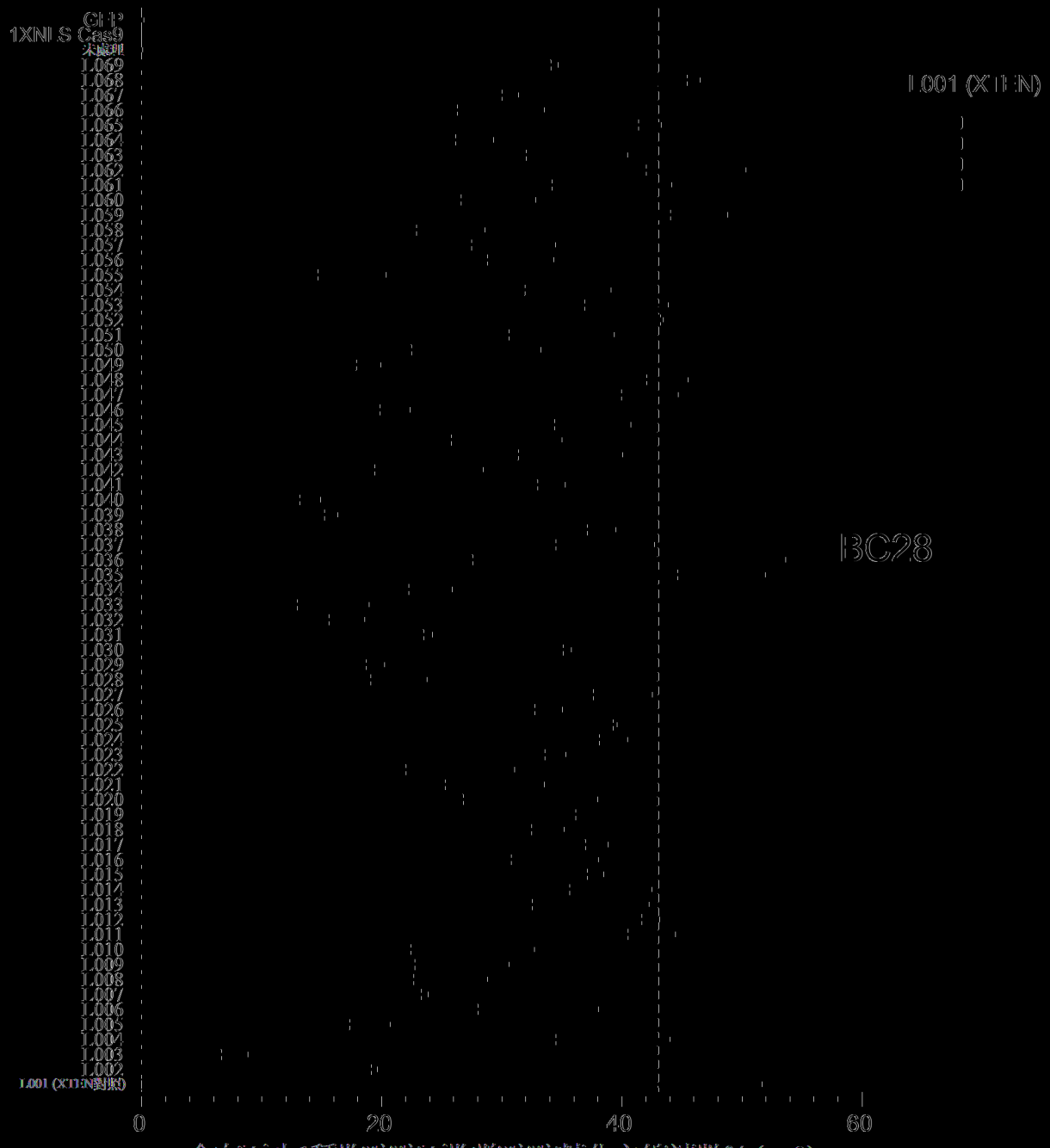

GFP
1XNLS Cas9
未處理
L001 (XTEN)
BC18
L001 (XTEN對照)
0
1
2
3
4
5
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

|(圖40B)|

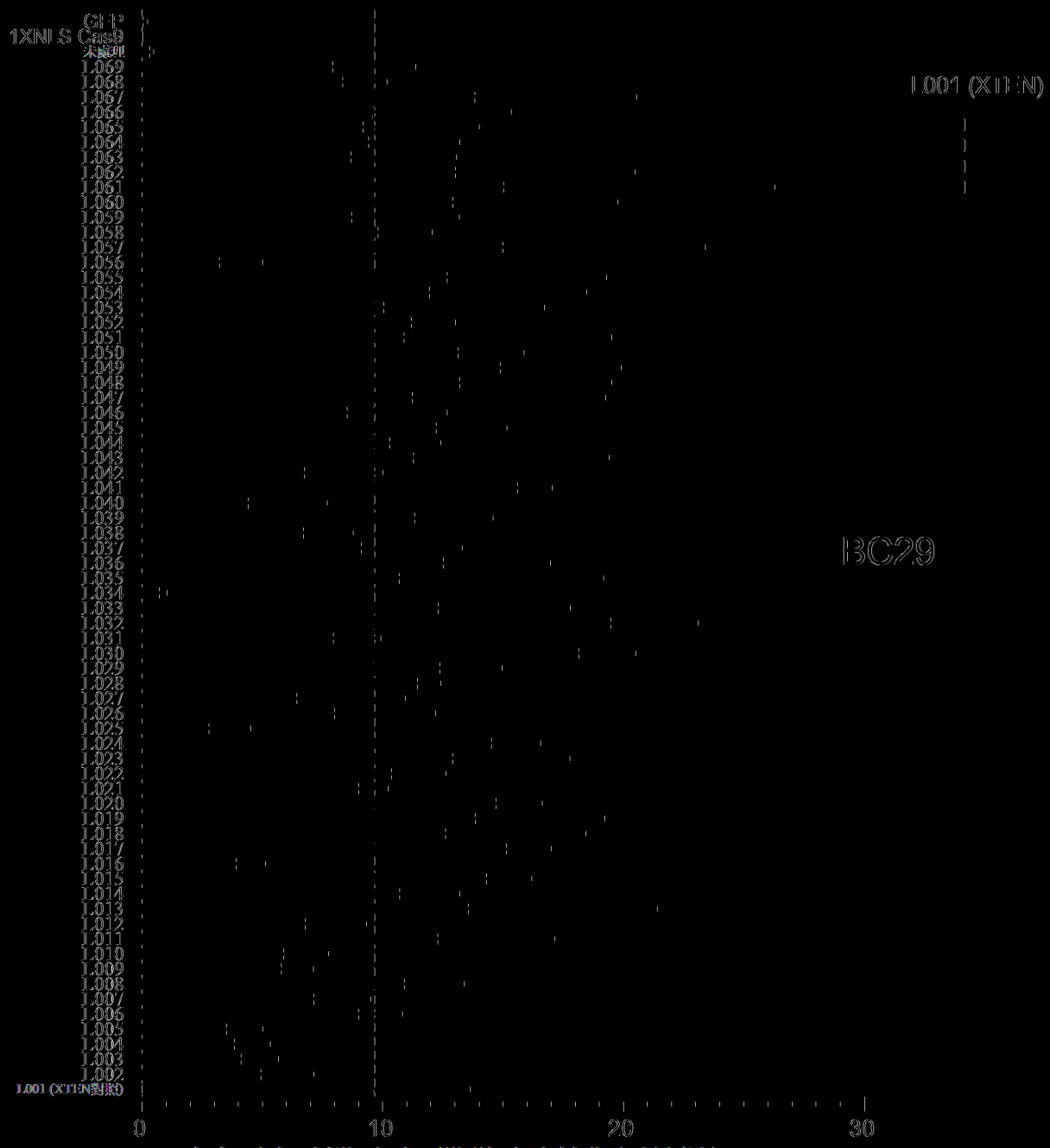


含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

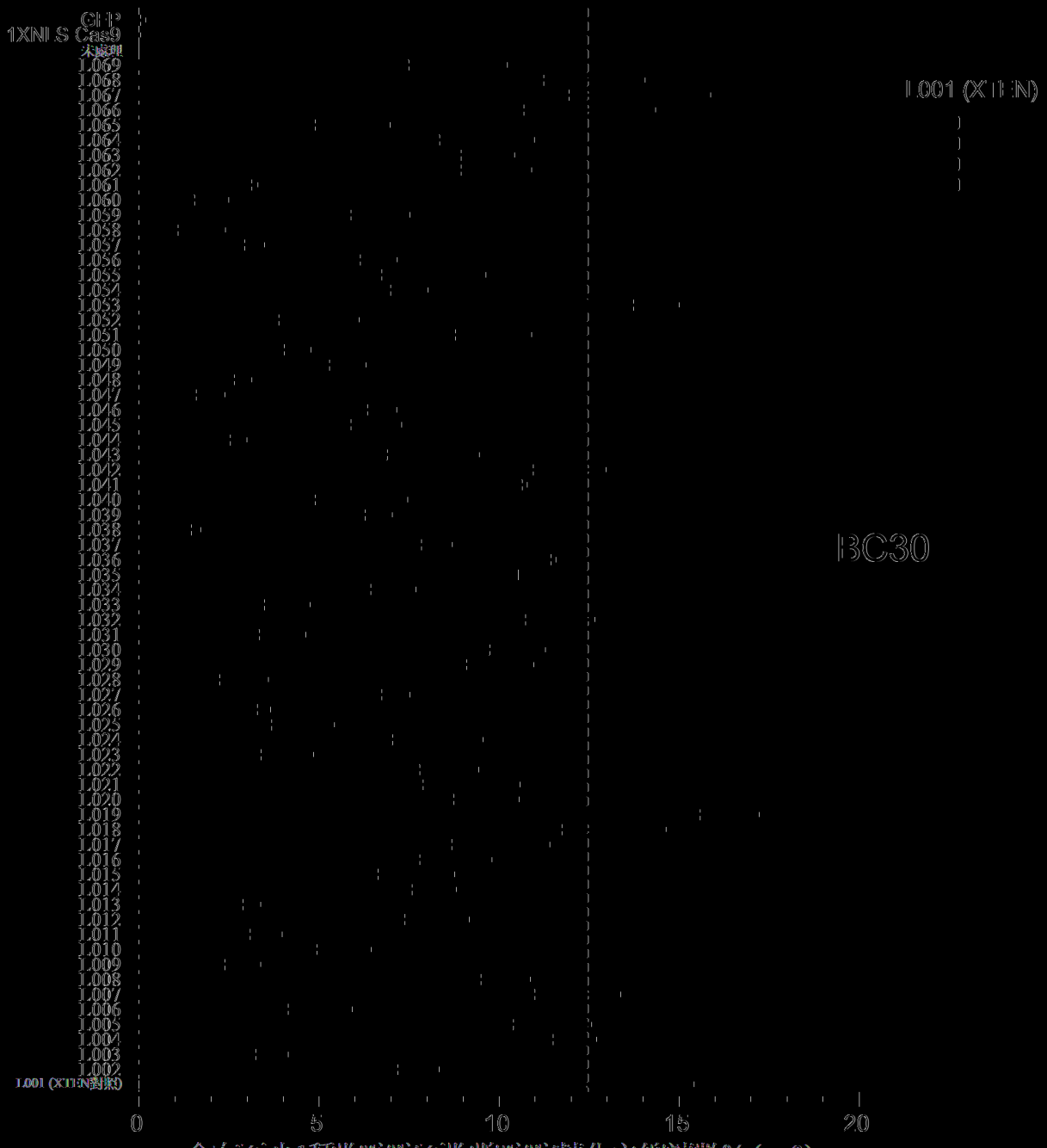
[圖40C]


GHP
1XNLS Cas9
未處理
1.069
1.068
1.067
1.066
1.065
1.064
1.063
1.062
1.061
1.060
1.059
1.058
1.057
1.056
1.055
1.054
1.053
1.052
1.051
1.050
1.049
1.048
1.047
1.046
1.045
1.044
1.043
1.042
1.041
1.040
1.039
1.038
1.037
1.036
1.035
1.034
1.033
1.032
1.031
1.030
1.029
1.028
1.027
1.026
1.025
1.024
1.023
1.022
1.021
1.020
1.019
1.018
1.017
1.016
1.015
1.014
1.013
1.012
1.011
1.010
1.009
1.008
1.007
1.006
1.005
1.004
1.003
1.002
1.001 (XTEN對照)
1.001 (XTEN)
BC28
0
20
40
60
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

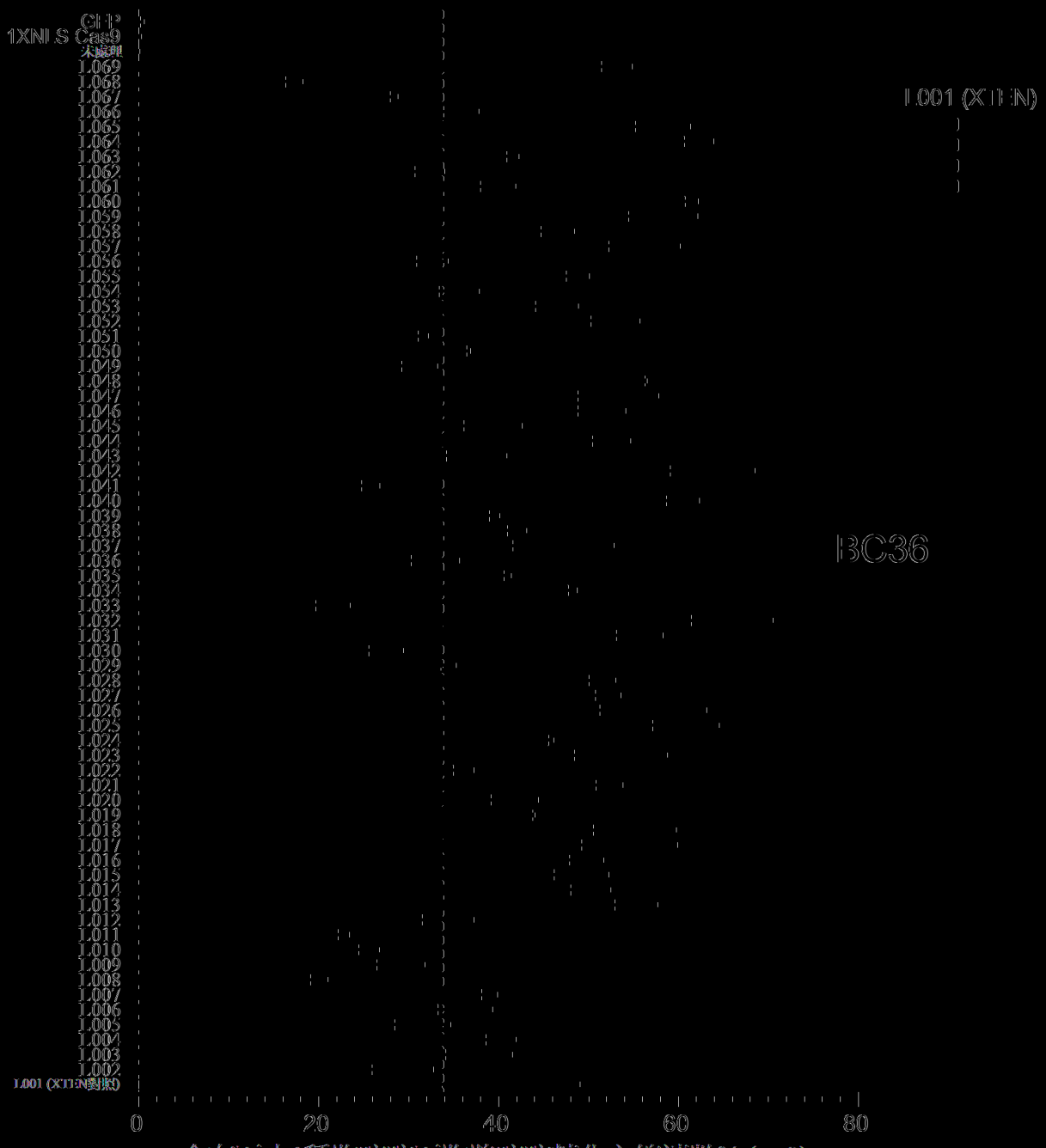
|(圖40D)|


GHP
1XNLS Cas9
未處理
L069
L068
L067
L066
L065
L064
L063
L062
L061
L060
L059
L058
L057
L056
L055
L054
L053
L052
L051
L050
L049
L048
L047
L046
L045
L044
L043
L042
L041
L040
L039
L038
L037
L036
L035
L034
L033
L032
L031
L030
L029
L028
L027
L026
L025
L024
L023
L022
L021
L020
L019
L018
L017
L016
L015
L014
L013
L012
L011
L010
L009
L008
L007
L006
L005
L004
L003
L002
L001 (XTEN對照)
L001 (XTEN)
BC29
0
10
20
30
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

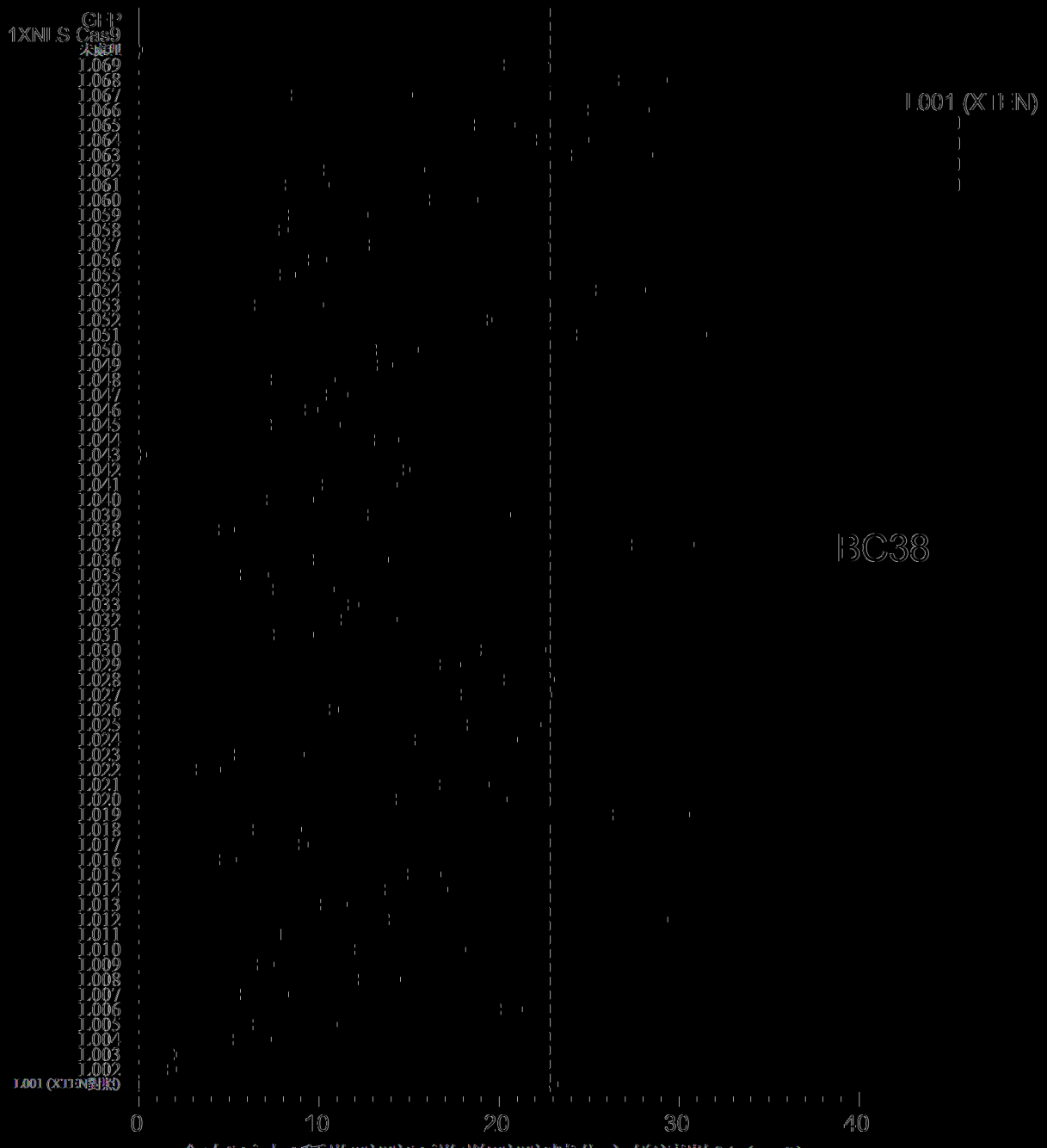
|(圖|40E)|


GFP
1XNLS Cas9
未處理
1.069
1.068
1.067
1.066
1.065
1.064
1.063
1.062
1.061
1.060
1.059
1.058
1.057
1.056
1.055
1.054
1.053
1.052
1.051
1.050
1.049
1.048
1.047
1.046
1.045
1.044
1.043
1.042
1.041
1.040
1.039
1.038
1.037
1.036
1.035
1.034
1.033
1.032
1.031
1.030
1.029
1.028
1.027
1.026
1.025
1.024
1.023
1.022
1.021
1.020
1.019
1.018
1.017
1.016
1.015
1.014
1.013
1.012
1.011
1.010
1.009
1.008
1.007
1.006
1.005
1.004
1.003
1.002
1.001 (XTEN對照)
1.001 (XTEN)
BC30
0
5
10
15
20
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

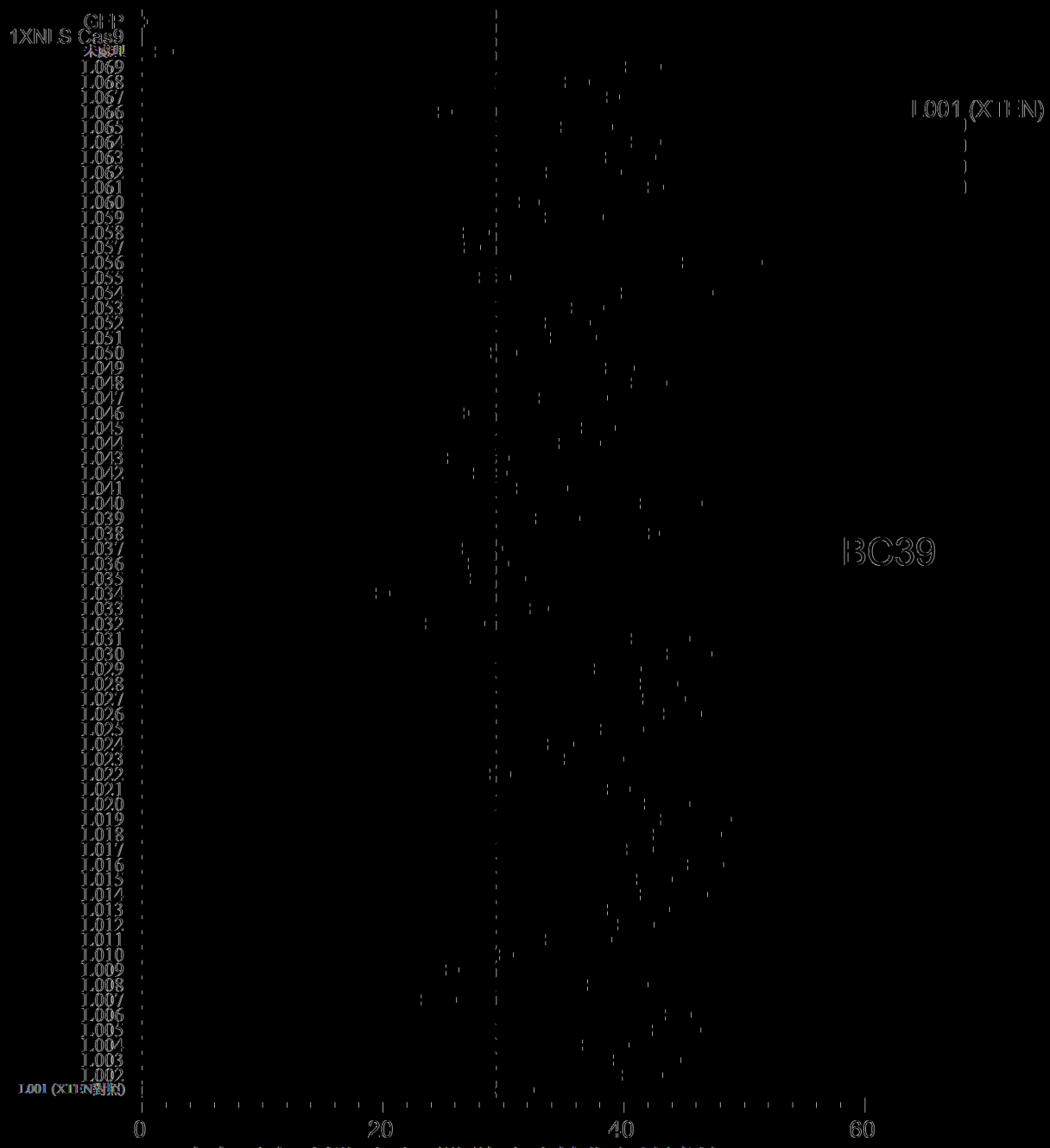
(圖40F)


GHP
1XNLS Cas9
未處理
L001 (XTEN)
BC36
L001 (XTEN對照)
0
20
40
60
80
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

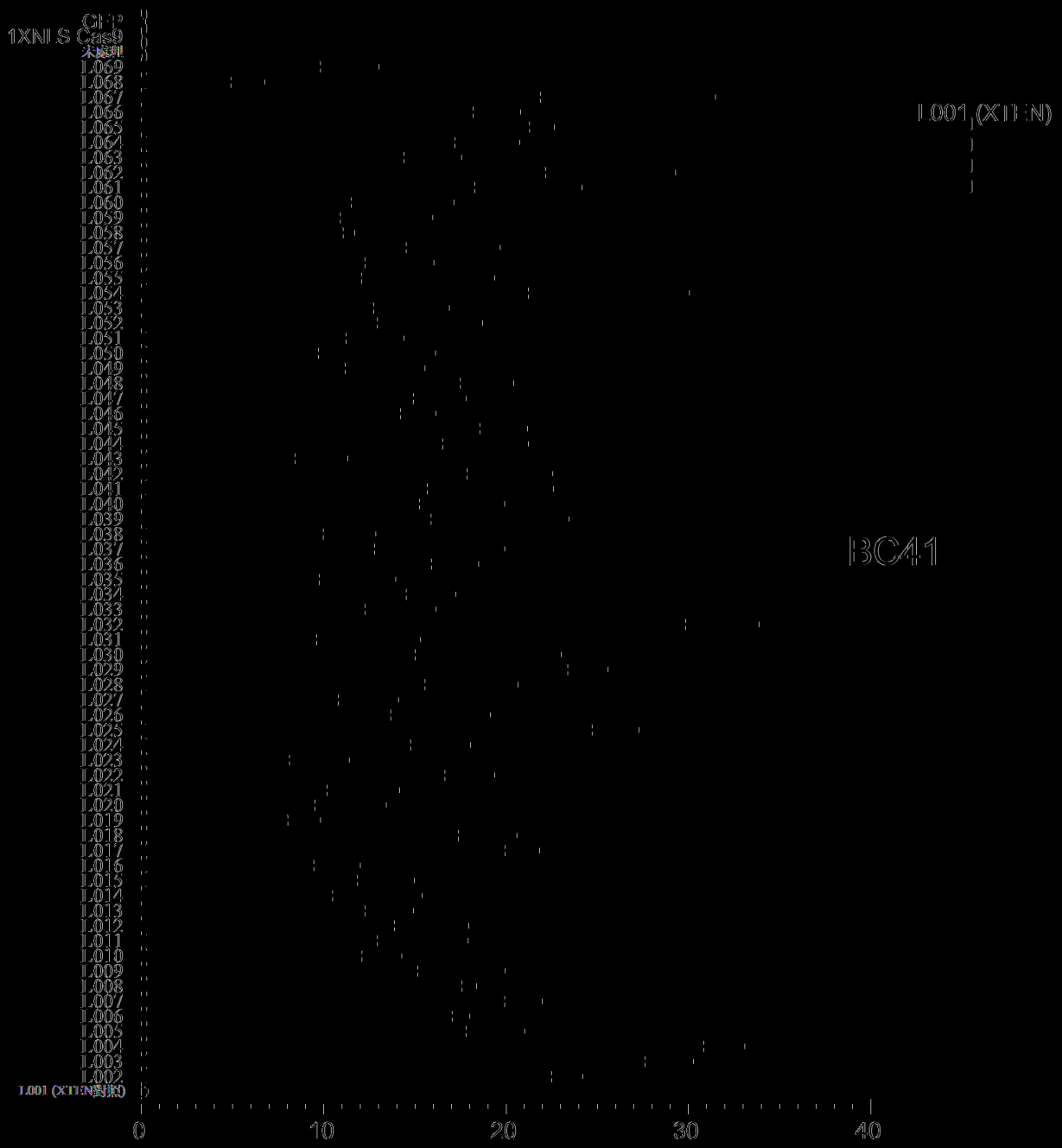
【圖40G】


GFP
1XNLS Cas9
未處理
1.069
1.068
1.067
1.066
1.065
1.064
1.063
1.062
1.061
1.060
1.059
1.058
1.057
1.056
1.055
1.054
1.053
1.052
1.051
1.050
1.049
1.048
1.047
1.046
1.045
1.044
1.043
1.042
1.041
1.040
1.039
1.038
1.037
1.036
1.035
1.034
1.033
1.032
1.031
1.030
1.029
1.028
1.027
1.026
1.025
1.024
1.023
1.022
1.021
1.020
1.019
1.018
1.017
1.016
1.015
1.014
1.013
1.012
1.011
1.010
1.009
1.008
1.007
1.006
1.005
1.004
1.003
1.002
1.001 (XTEN對照)
1.001 (XTEN)
BC38
0
10
20
30
40
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

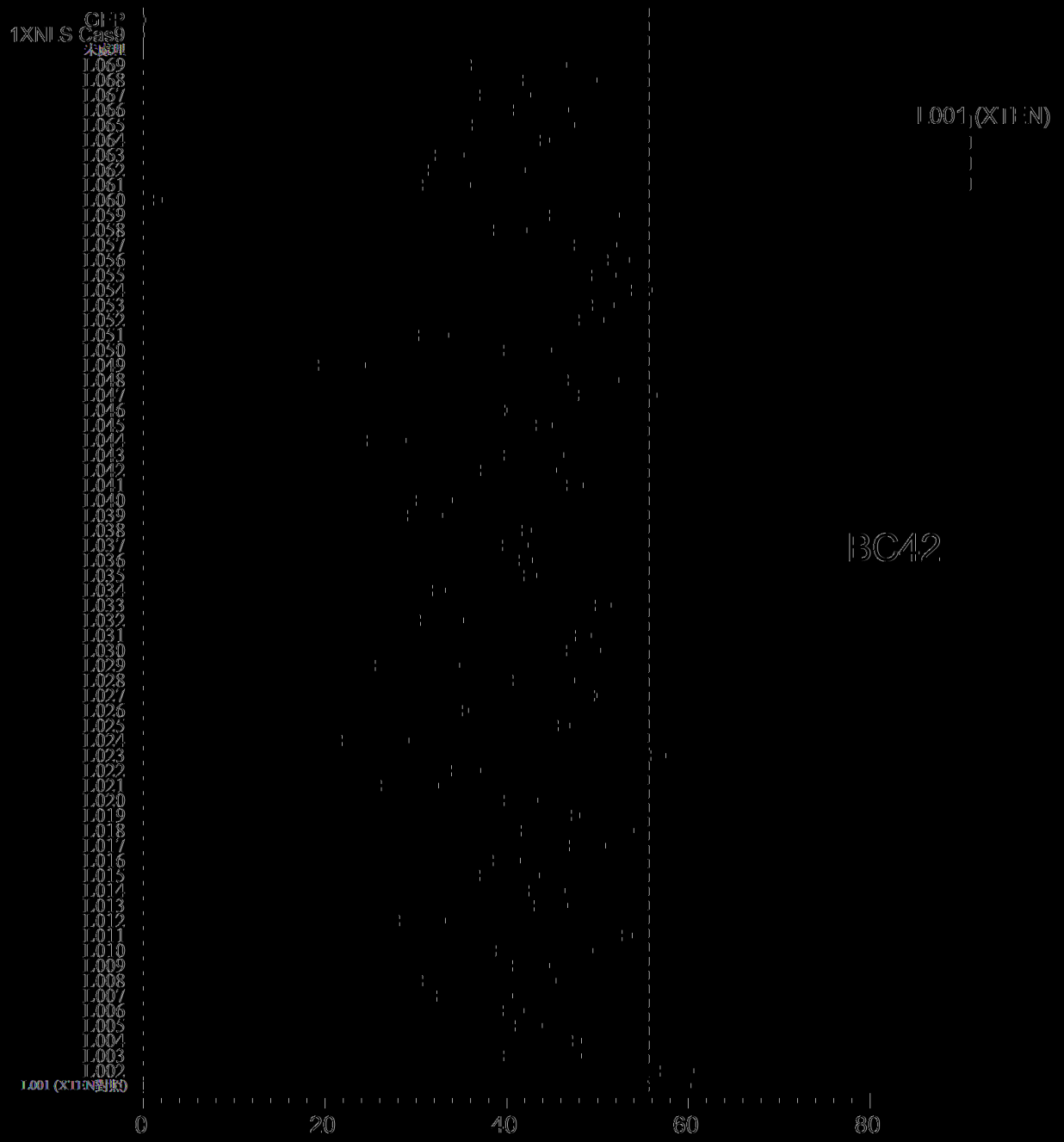
|(圖40H)|


GFP
1XNLS Cas9
未處理
1.069
1.068
1.067
1.066
1.065
1.064
1.063
1.062
1.061
1.060
1.059
1.058
1.057
1.056
1.055
1.054
1.053
1.052
1.051
1.050
1.049
1.048
1.047
1.046
1.045
1.044
1.043
1.042
1.041
1.040
1.039
1.038
1.037
1.036
1.035
1.034
1.033
1.032
1.031
1.030
1.029
1.028
1.027
1.026
1.025
1.024
1.023
1.022
1.021
1.020
1.019
1.018
1.017
1.016
1.015
1.014
1.013
1.012
1.011
1.010
1.009
1.008
1.007
1.006
1.005
1.004
1.003
1.002
1.001 (XTEN對照)
1.001 (XTEN)
BC39
0
20
40
60
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

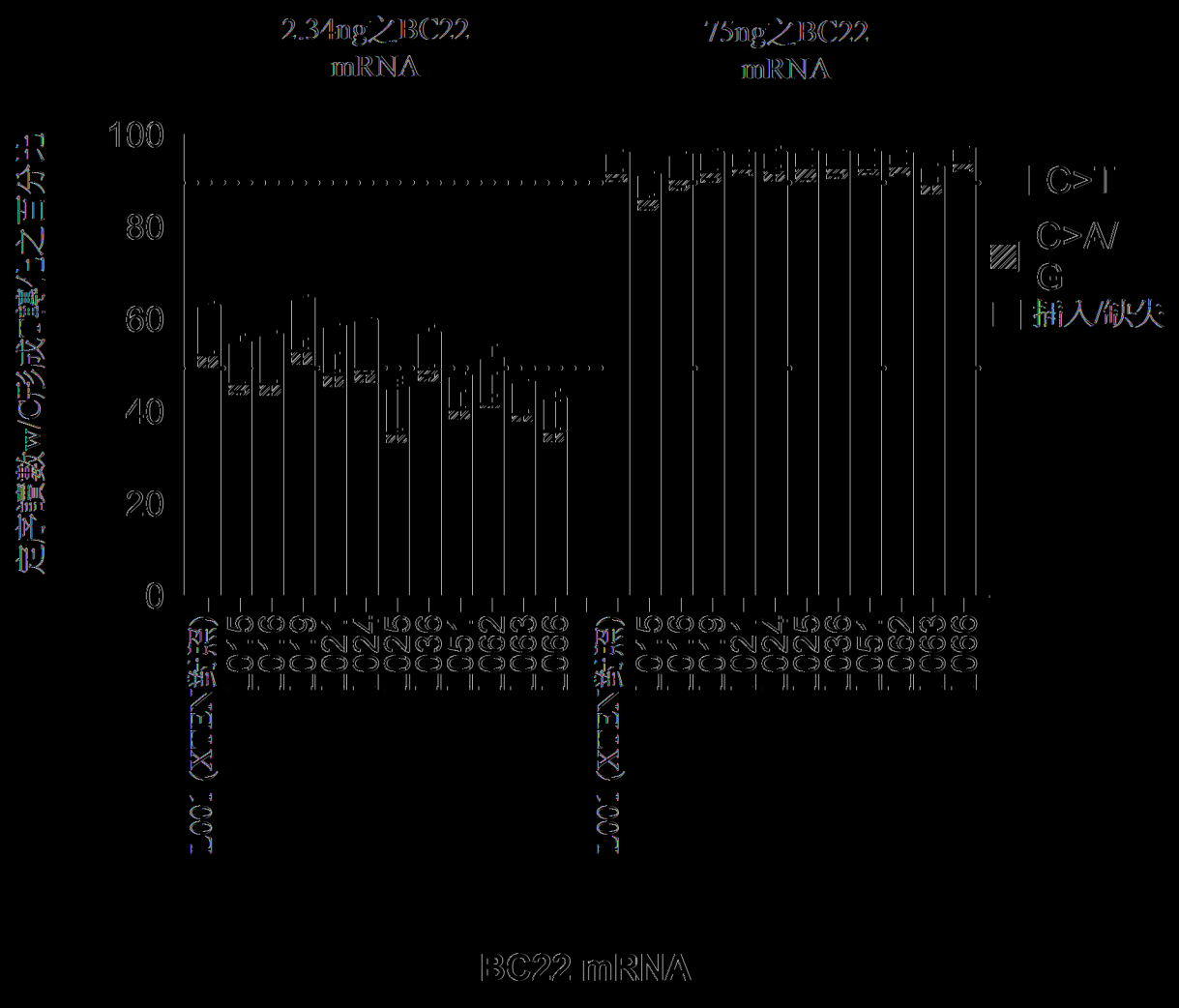
【圖401】


GFP
1XNLS Cas9
未處理
L069
L068
L067
L066
L065
L064
L063
L062
L061
L060
L059
L058
L057
L056
L055
L054
L053
L052
L051
L050
L049
L048
L047
L046
L045
L044
L043
L042
L041
L040
L039
L038
L037
L036
L035
L034
L033
L032
L031
L030
L029
L028
L027
L026
L025
L024
L023
L022
L021
L020
L019
L018
L017
L016
L015
L014
L013
L012
L011
L010
L009
L008
L007
L006
L005
L004
L003
L002
L001 (XTEN對照)
L001 (XTEN)
BC41
0
10
20
30
40
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

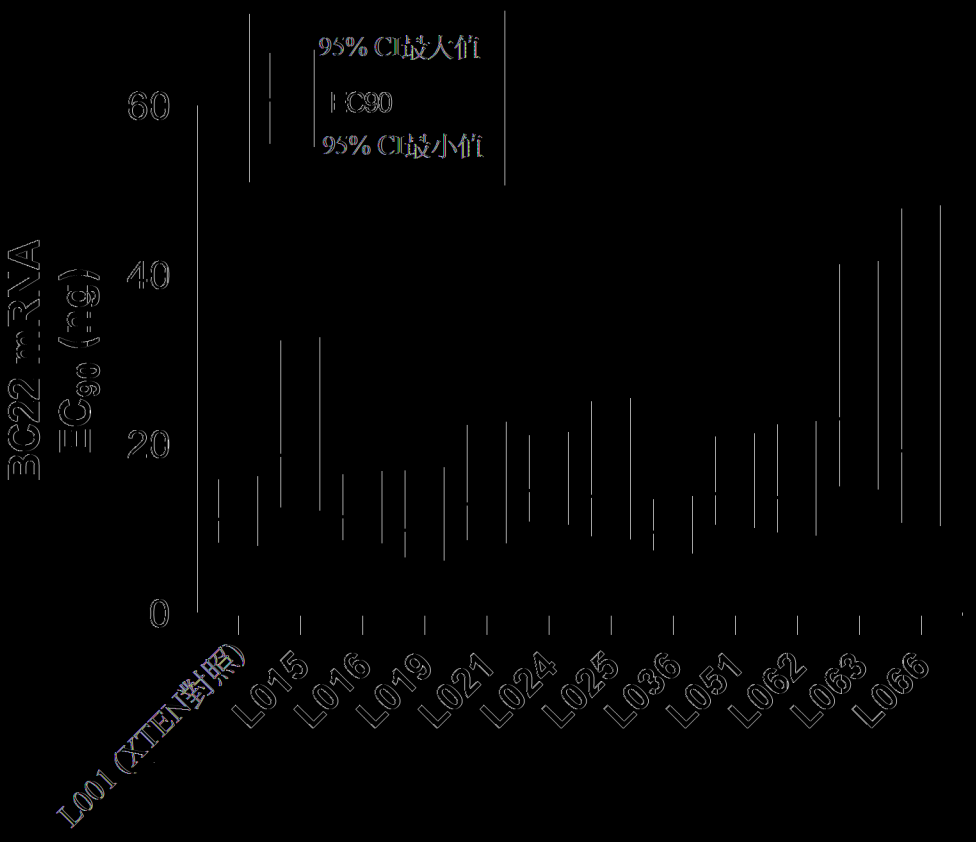
|(圖40J)|


GFP
1XNLS Cas9
未處理
L069
L068
L067
L066
L065
L064
L063
L062
L061
L060
L059
L058
L057
L056
L055
L054
L053
L052
L051
L050
L049
L048
L047
L046
L045
L044
L043
L042
L041
L040
L039
L038
L037
L036
L035
L034
L033
L032
L031
L030
L029
L028
L027
L026
L025
L024
L023
L022
L021
L020
L019
L018
L017
L016
L015
L014
L013
L012
L011
L010
L009
L008
L007
L006
L005
L004
L003
L002
L001 (XTEN對照)
L001 (XTEN)
BC42
0
20
40
60
80
含有至少1種胞嘧啶至胸腺嘧啶轉化之總讀數% (n=3)

【圖40K】


2.34ng之BC22 mRNA
75ng之BC22 mRNA
定序讀數w/C形成T轉化之百分比
100
80
60
40
20
0
C>T
C>A/G
插入/缺失
BC22 mRNA

[圖41]


95% CI最大值
EC90
95% CI最小值
60
40
20
0
BC22 mRNA
EC90 (ng)
L001 (XTEN對照)
L015
L016
L019
L021
L024
L025
L036
L051
L062
L063
L066

(圖42)

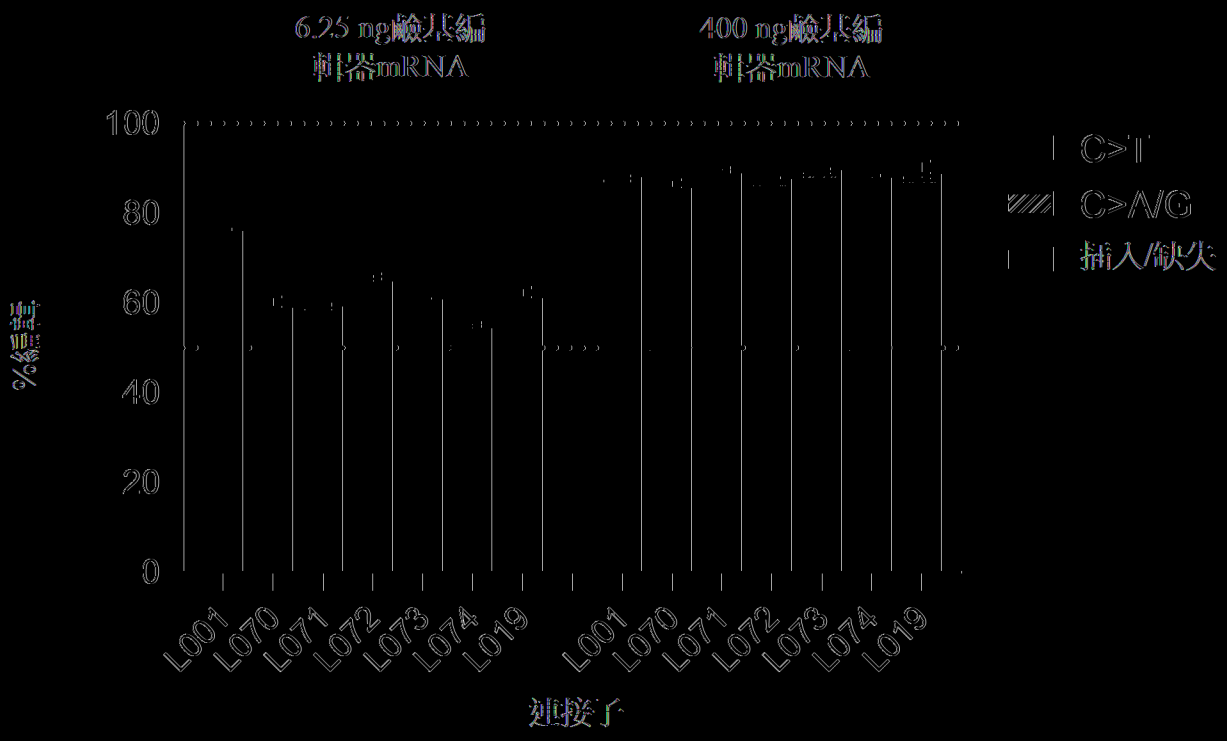

6.25 ng脂質編
輯器mRNA
400 ng脂質編
輯器mRNA
100
80
60
40
20
0
%編輯效率
C>T
C>A/G
插入/缺失
L001
L070
L071
L072
L073
L074
L019
連接子

圖43

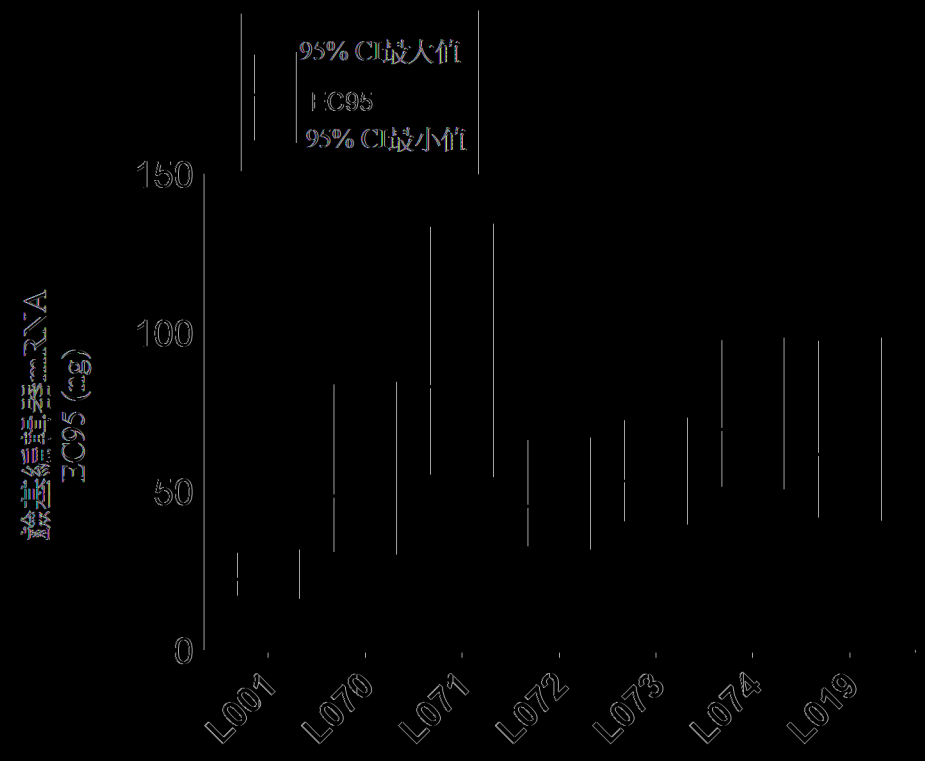
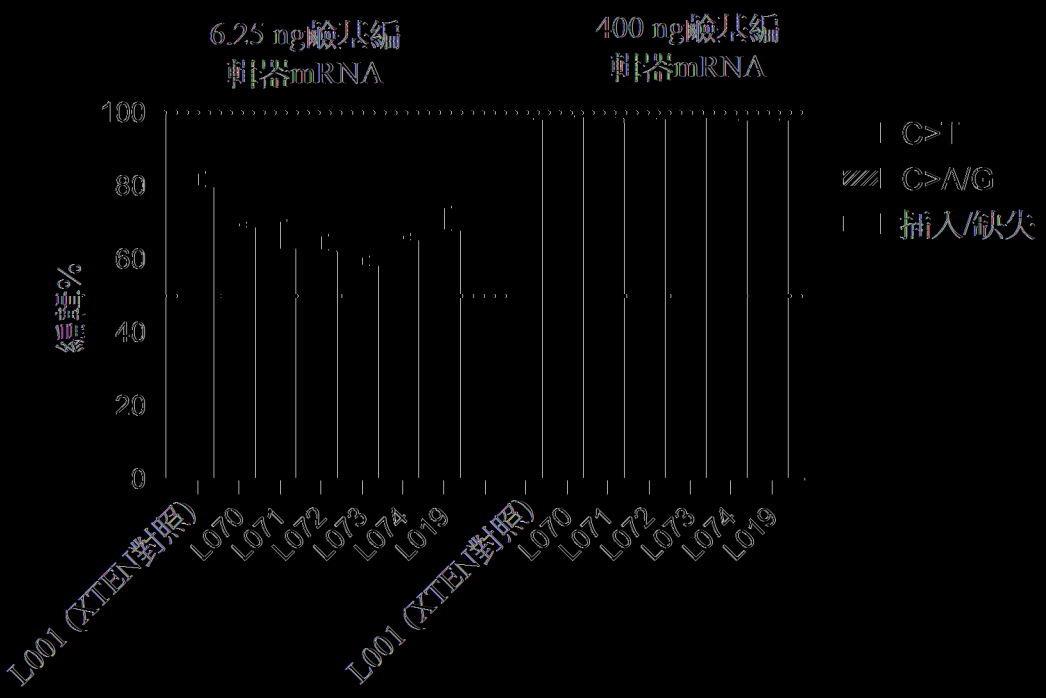
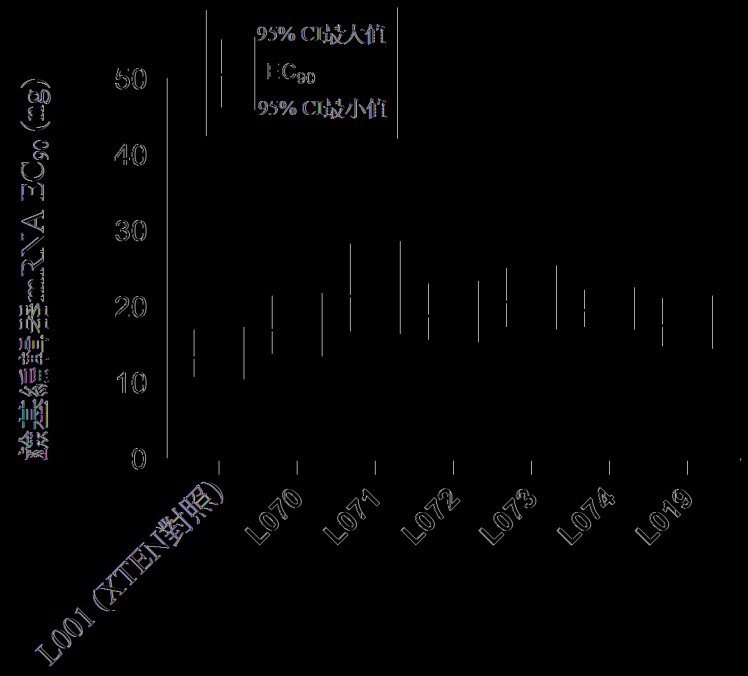

95% CI最大值
EC95
95% CI最小值
150
100
50
0
編輯mRNA的EC95 (ng)
L001
L070
L071
L072
L073
L074
L019

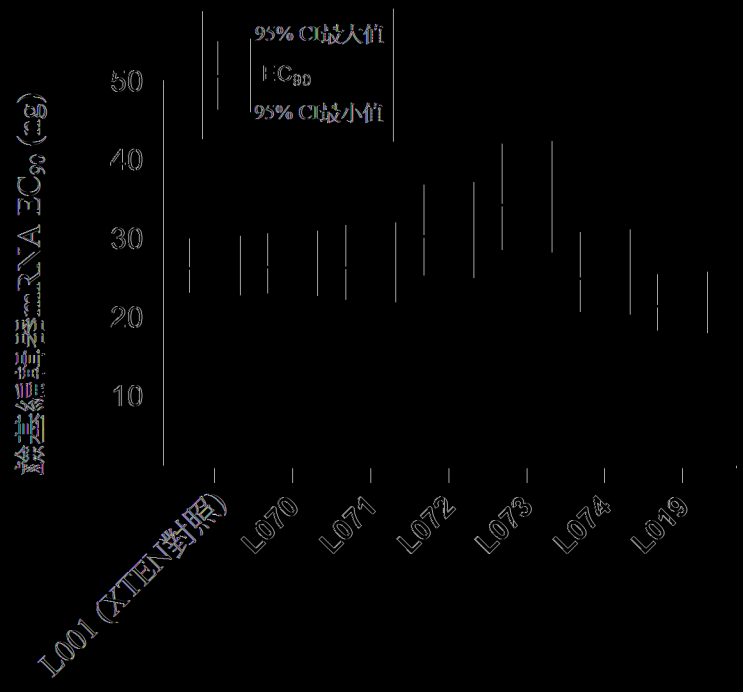
圖44


6.25 ng脫氨編
輯器mRNA
400 ng脫氨編
輯器mRNA
100
80
60
40
20
0
%
C>T
C>A/G
插入/缺失
L001 (XTEN對照)
L070
L071
L072
L073
L074
L019

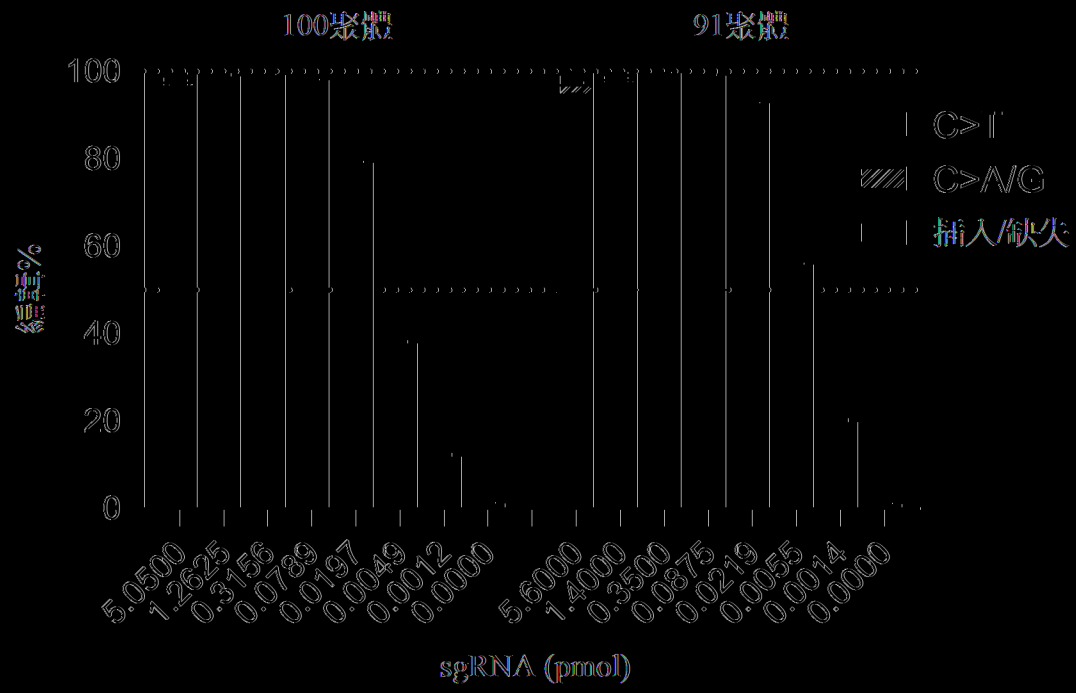
|(圖45)|


95% CI最大值
EC50
95% CI最小值
50
40
30
20
10
0
L001 (XTEN對照)
L070
L071
L072
L073
L074
L019

|(圖46)|


95% CI最大值
IC90
95% CI最小值
50
40
30
20
10
L001 (GTEN對照)
L070
L071
L072
L073
L074
L019

|(圖47)|


100聚體
91聚體
100
80
60
40
20
0
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.6000
1.4000
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

|(圖48)|

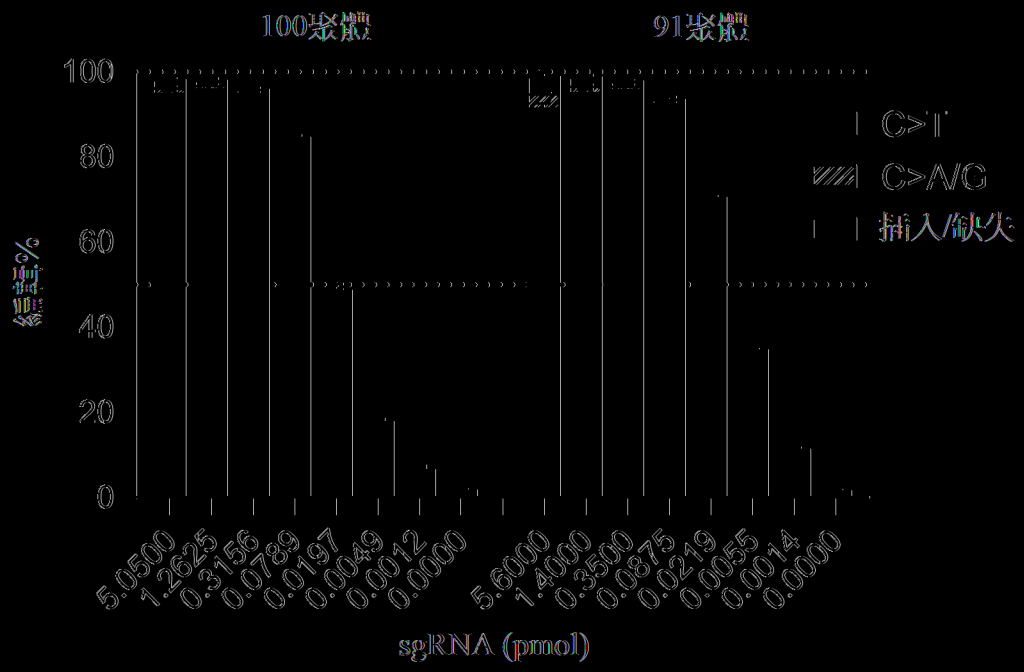

100毫微克
91毫微克
100
80
60
40
20
0
%
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.600
1.400
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

圖49A

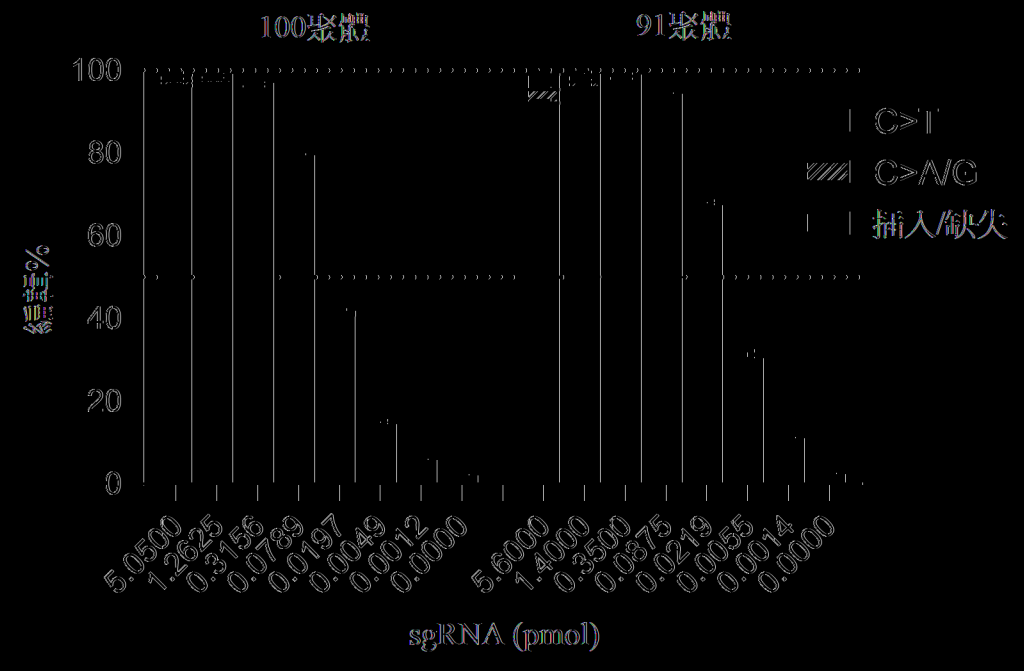
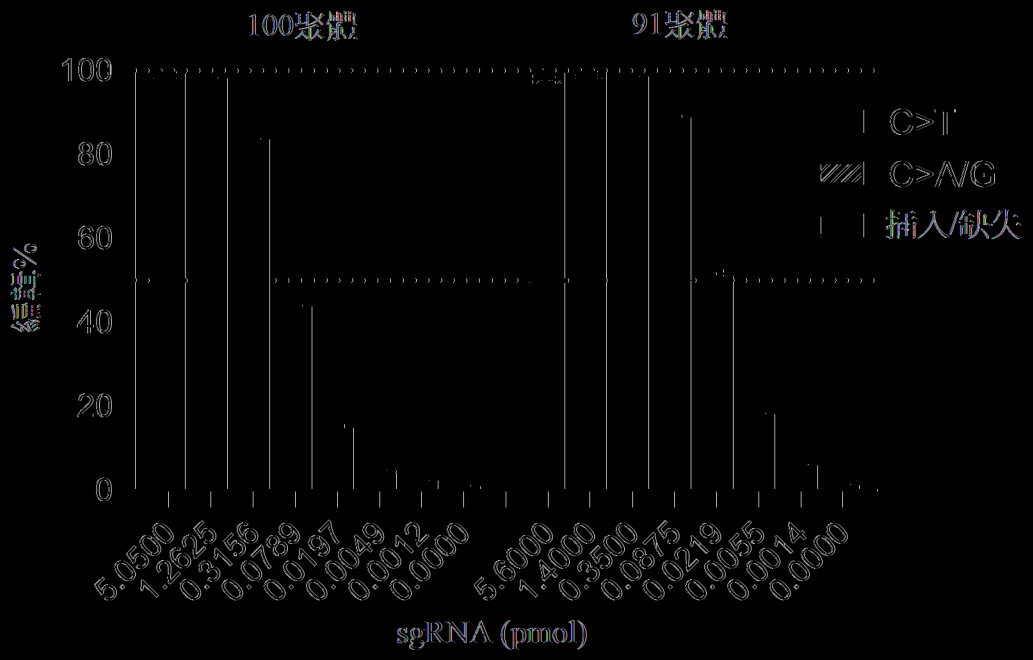
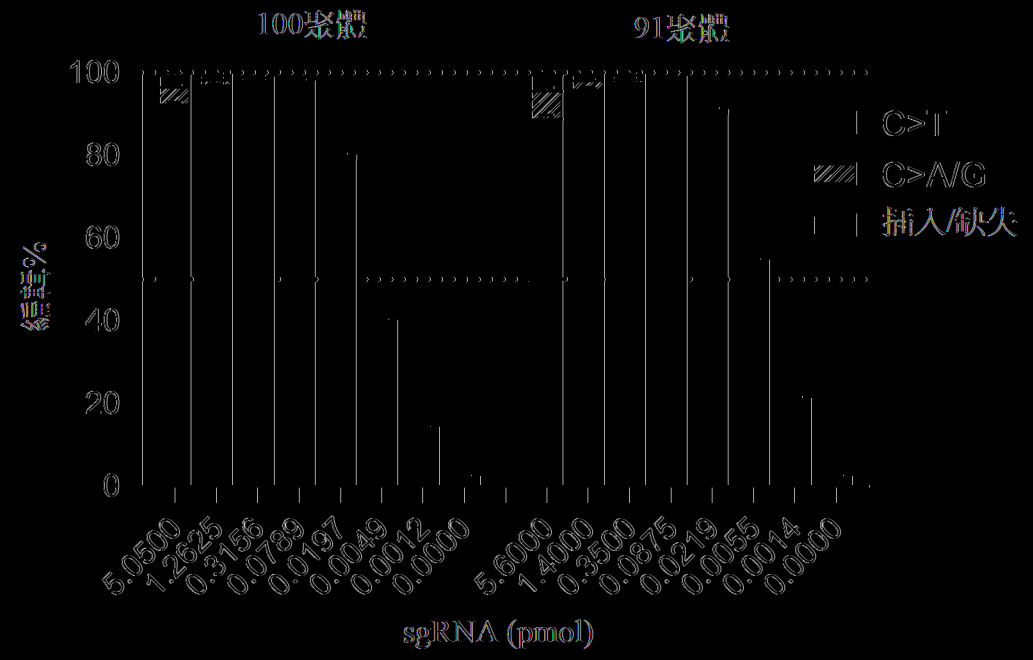

100毫微克
91毫微克
100
80
60
40
20
0
%
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.600
1.400
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

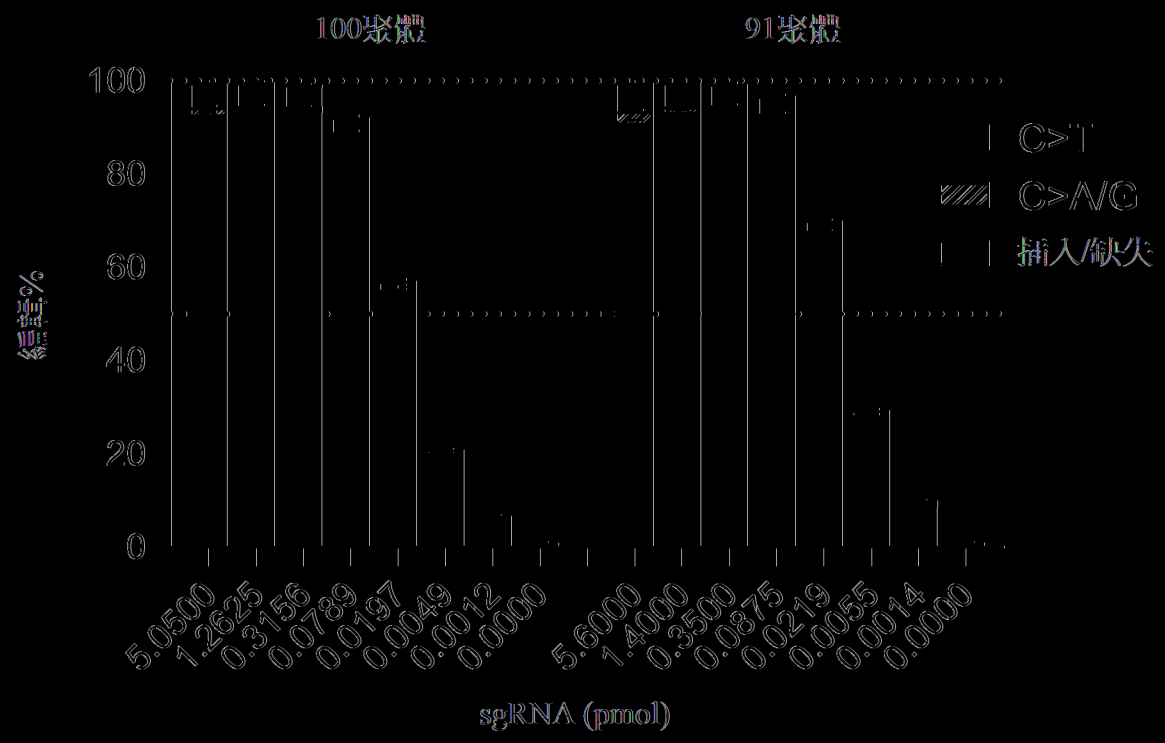
圖49B


100紫癜
91紫癜
100
80
60
40
20
0
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.6000
1.4000
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

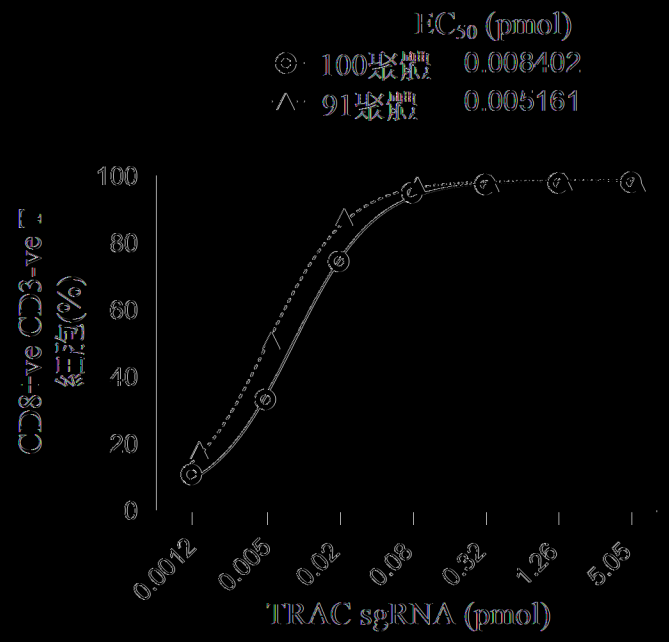
|(圖50)|


100紫癜
91紫癜
100
80
60
40
20
0
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.6000
1.4000
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

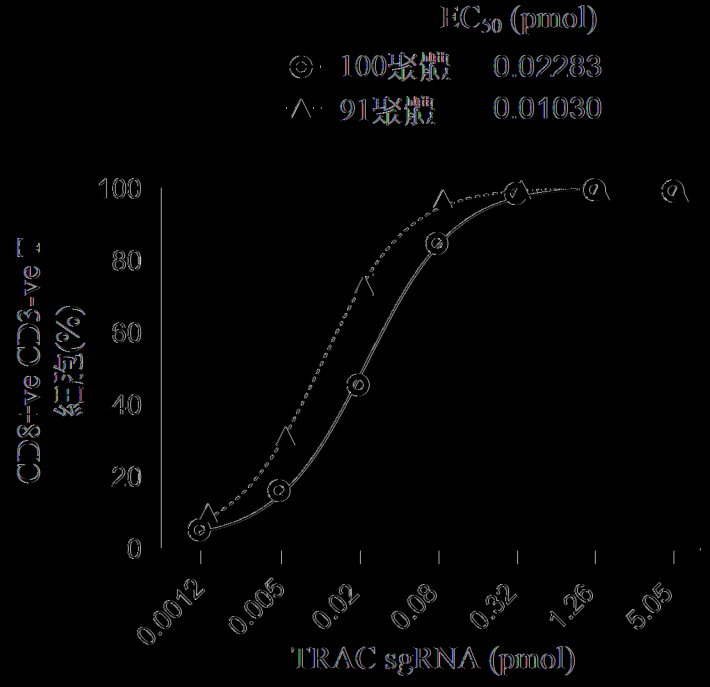
|(圖51)|


100聚體
91聚體
100
80
60
40
20
0
編輯%
C>T
C>A/G
插入/缺失
5.0500
1.2625
0.3156
0.0789
0.0197
0.0049
0.0012
0.0000
5.6000
1.4000
0.3500
0.0875
0.0219
0.0055
0.0014
0.0000
sgRNA (pmol)

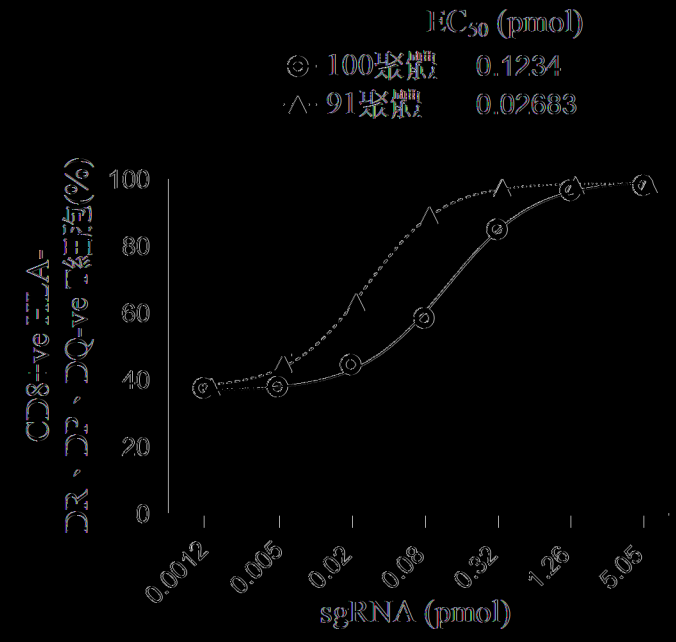
|(圖52)|


EC50 (pmol)
100聚體 0.008402
91聚體 0.005161
CD8+ve CD3-ve T
紅泡(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
TRAC sgRNA (pmol)

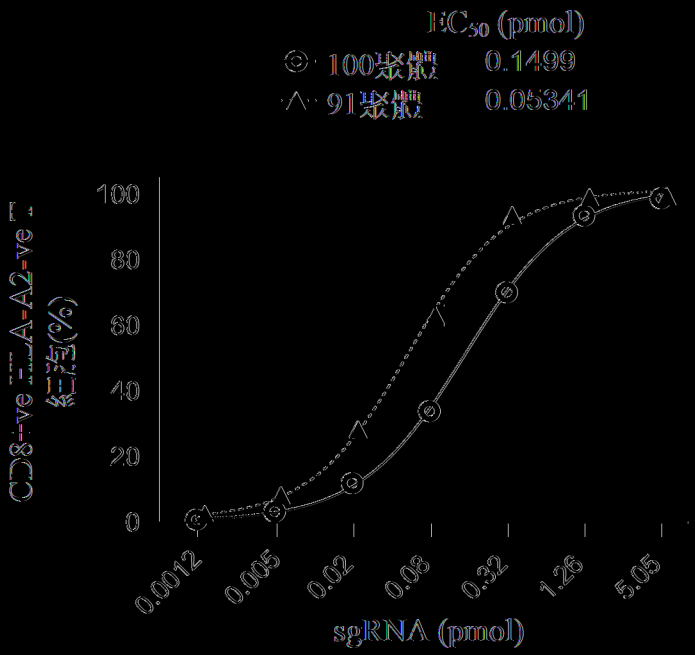
[圖53A]


EC50 (pmol)
100聚體 0.02283
91聚體 0.01030
CD8+ve CD3-ve T
紅泡(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
TRAC sgRNA (pmol)

[圖53B]


EC50 (pmol)
100聚體 0.1234
91聚體 0.02683
CD8+ve HLA-DR、DP、DQ-ve T細胞(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
sgRNA (pmol)

|(圖54A)|


EC50 (pmol)
100聚體 0.1499
91聚體 0.05341
CD8+ve HLA-A2-ve T細胞(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
sgRNA (pmol)

|(圖54B)|

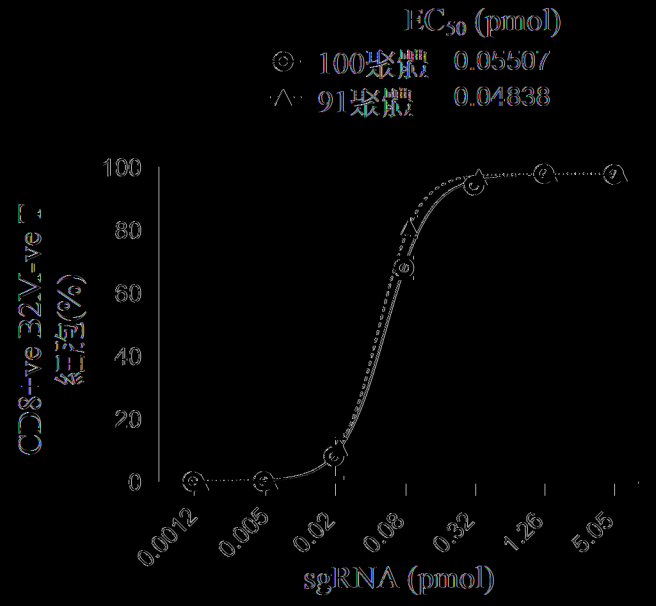

EC50 (pmol)
100聚體 0.05507
91聚體 0.04838
CD8+-ve B2M-ve 細胞(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
sgRNA (pmol)

圖55A

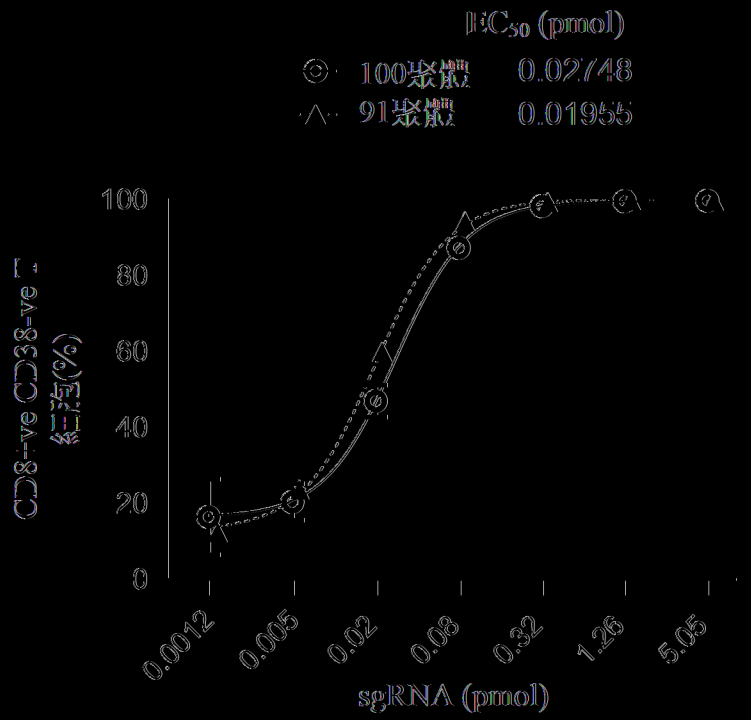
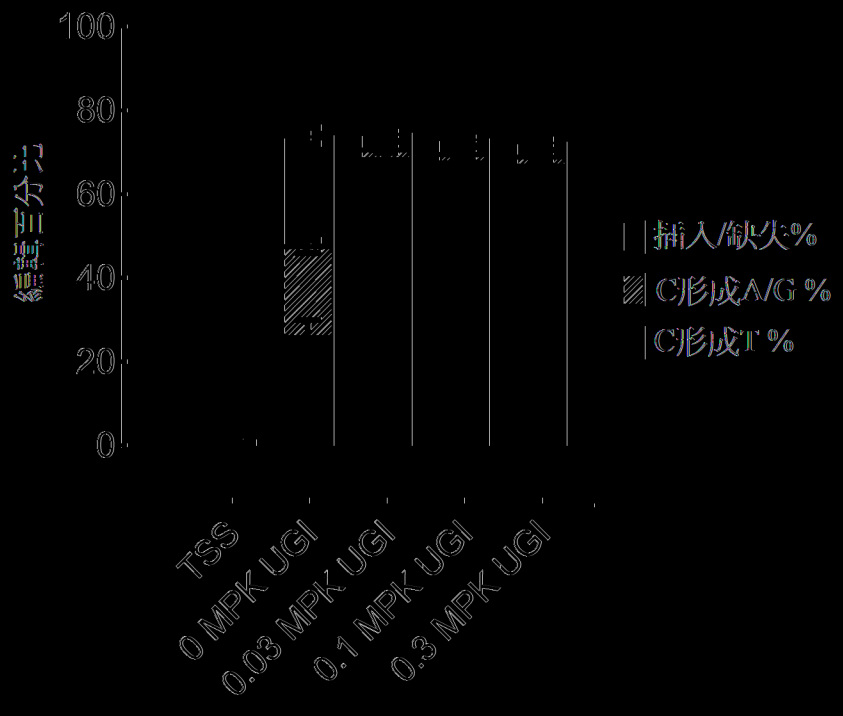
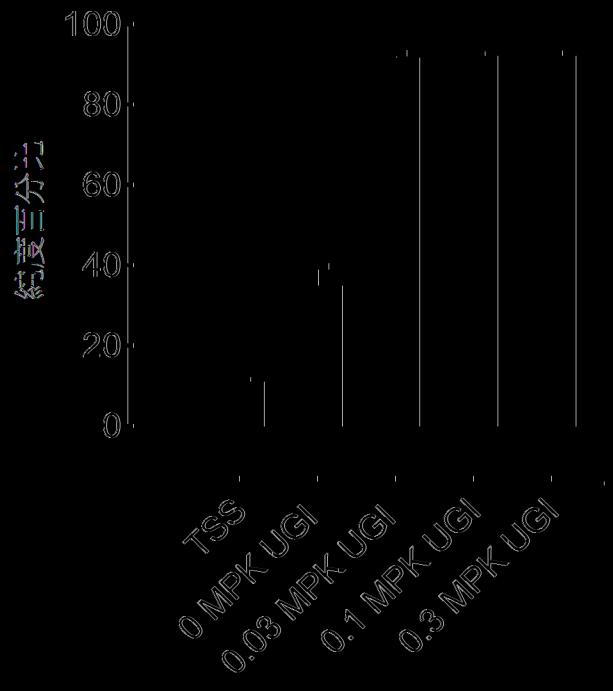

EC50 (pmol)
100聚體 0.02748
91聚體 0.01955
CD8+-ve CD38-ve 細胞(%)
100
80
60
40
20
0
0.0012
0.005
0.02
0.08
0.32
1.26
5.05
sgRNA (pmol)

圖55B


100
80
60
40
20
0
編輯百分比
TSS
0 MPK UGI
0.03 MPK UGI
0.1 MPK UGI
0.3 MPK UGI
插入/缺失%
C形成A/G %
C形成T %

|(圖56)|


100
80
60
40
20
0
編度百分比
TSS
0 MPK UGI
0.03 MPK UGI
0.1 MPK UGI
0.3 MPK UGI

|(圖57)|

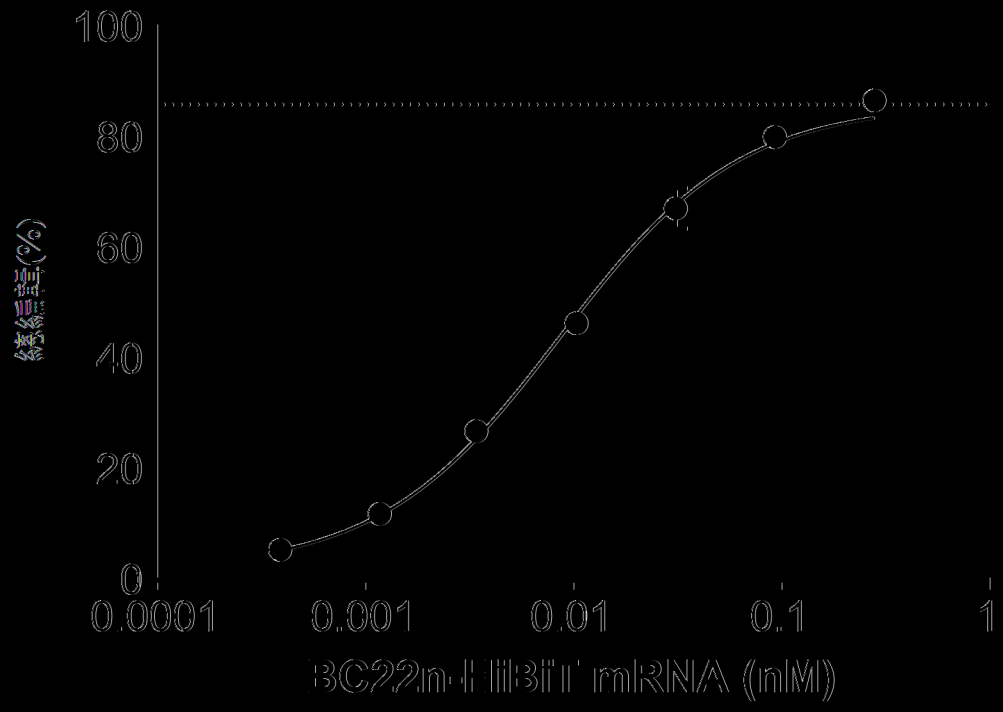

100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
BC22m-HiBiT mRNA (nM)

圖58A

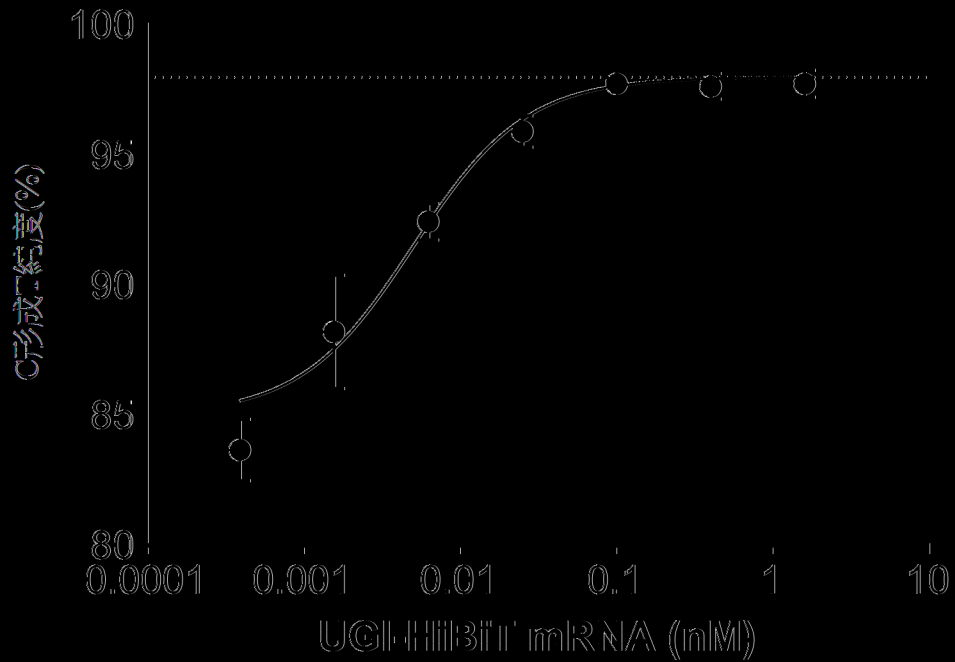

100
95
90
85
80
0.0001
0.001
0.01
0.1
1
10
UGI-HiBiT mRNA (nM)

圖58B

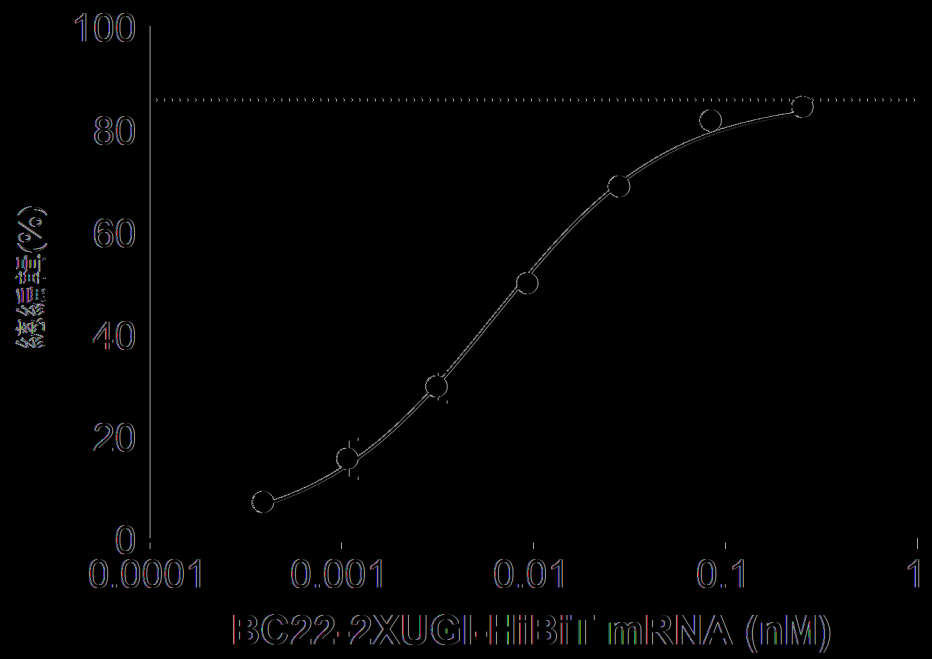

100
80
60
40
20
0
0..0001
0..001
0..01
0..1
1
BC22.2XUGI-HiBiT mRNA (nM)

圖58C

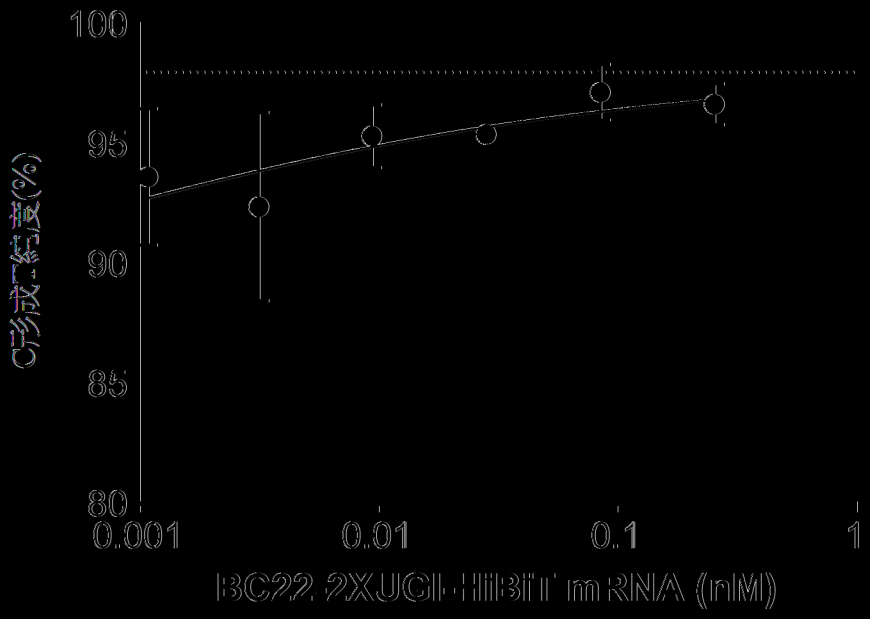
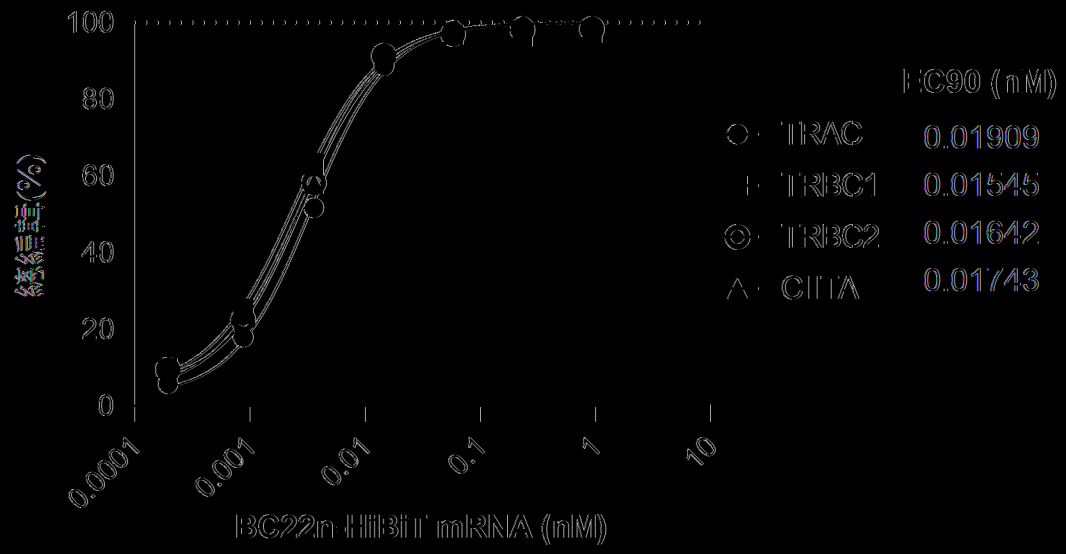
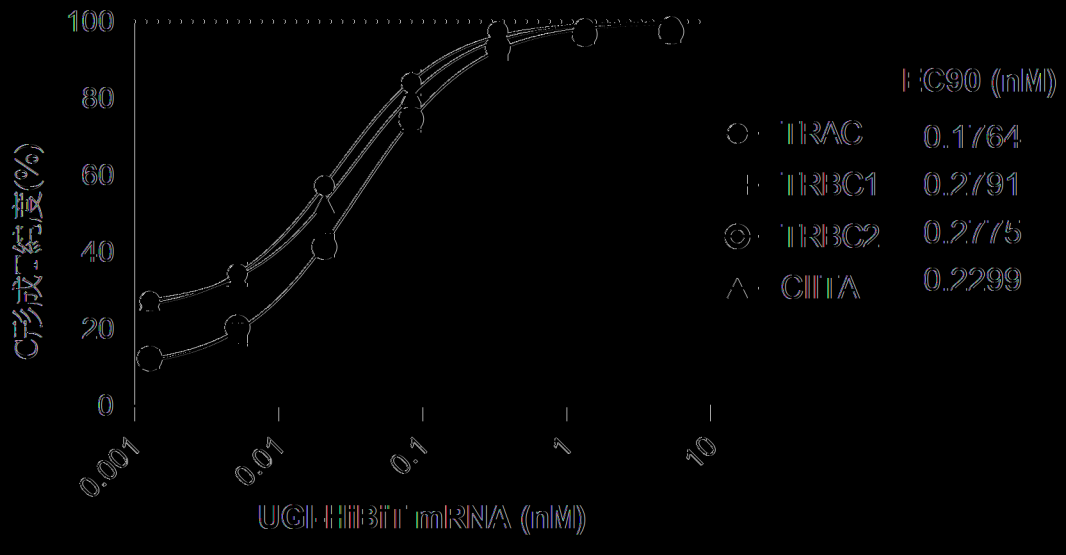

100
95
90
85
80
0.001
0..01
0..1
1
BC22.2XUGI-HiBiT mRNA (nM)

圖58D


100
80
60
40
20
0
總結轉(%)
0.0001
0.001
0.01
0.1
1
10
BC22n-HiBiT mRNA (nM)
EC90 (nM)
TRAC 0.01909
TRBC1 0.01545
TRBC2 0.01642
CITA 0.01743

(圖59A)


100
80
60
40
20
0
C形成口結度(%)
0.001
0.01
0.1
1
10
UGI-HiBiT mRNA (nM)
EC90 (nM)
TRAC 0.1764
TRBC1 0.2791
TRBC2 0.2775
CITA 0.2299

(圖59B)

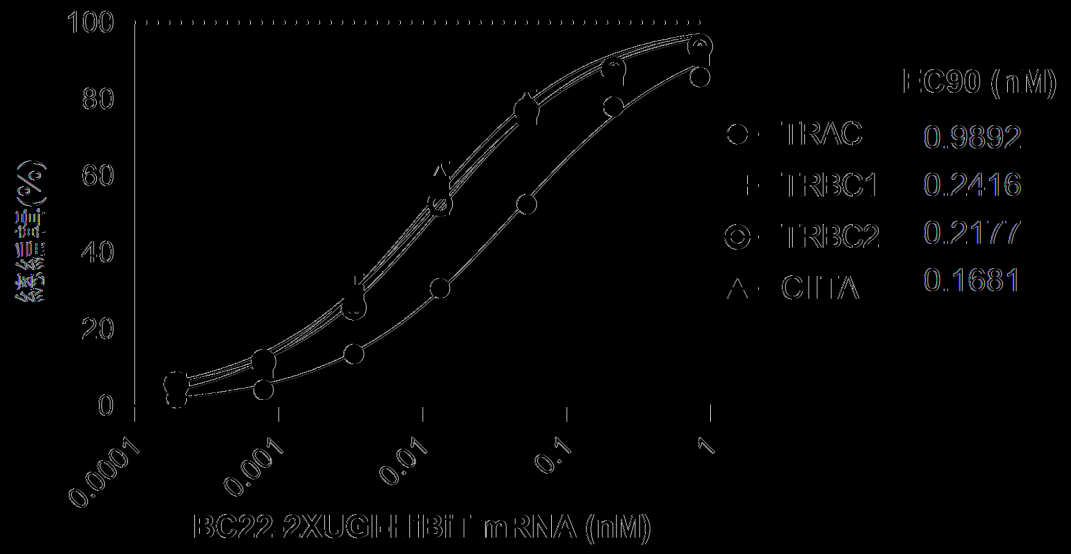

100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
IC90 (nM)
TRAC 0.9892
TRBC1 0.2416
TRBC2 0.2177
CIITA 0.1681

圖59C

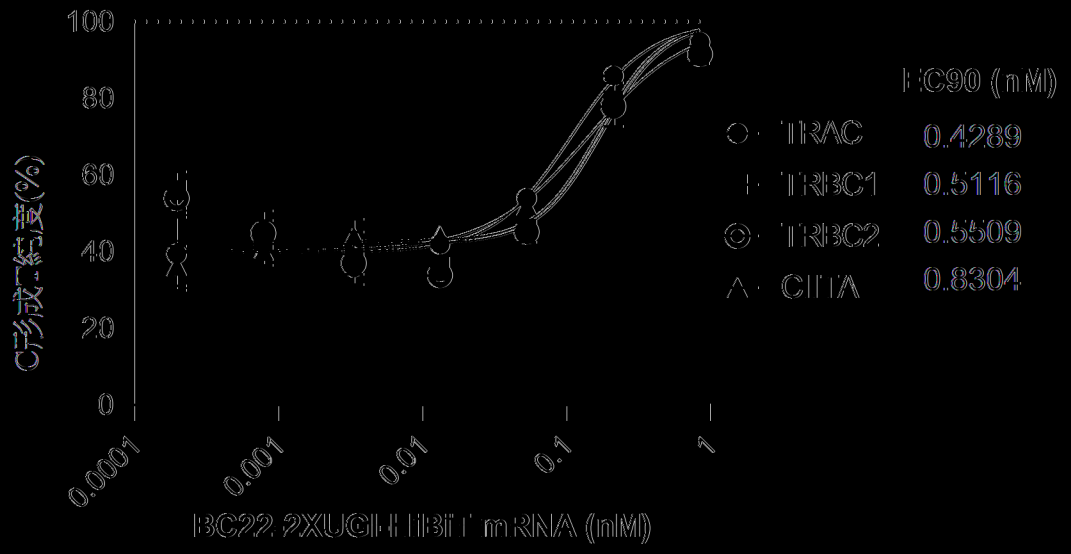

100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
IC90 (nM)
TRAC 0.4289
TRBC1 0.5116
TRBC2 0.5509
CIITA 0.8304

圖59D

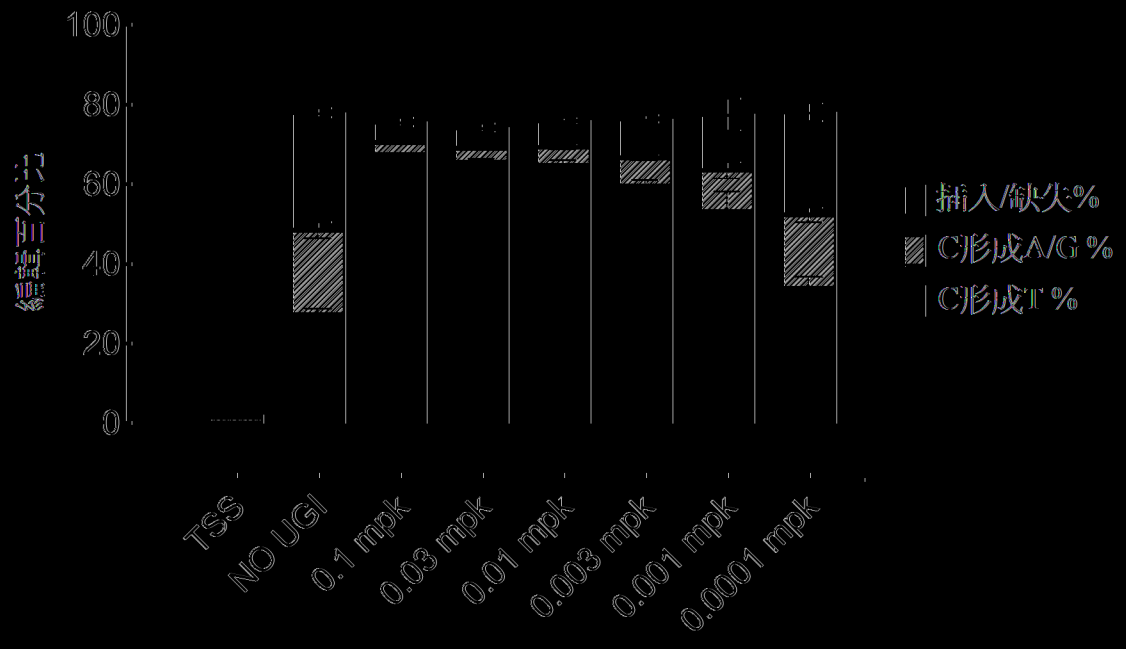

編輯百分比
100
80
60
40
20
0
TSS
NO UGI
0.1 mpk
0.03 mpk
0.01 mpk
0.003 mpk
0.001 mpk
0.0001 mpk
插入/缺失%
C形成A/G %
C形成T %

圖60

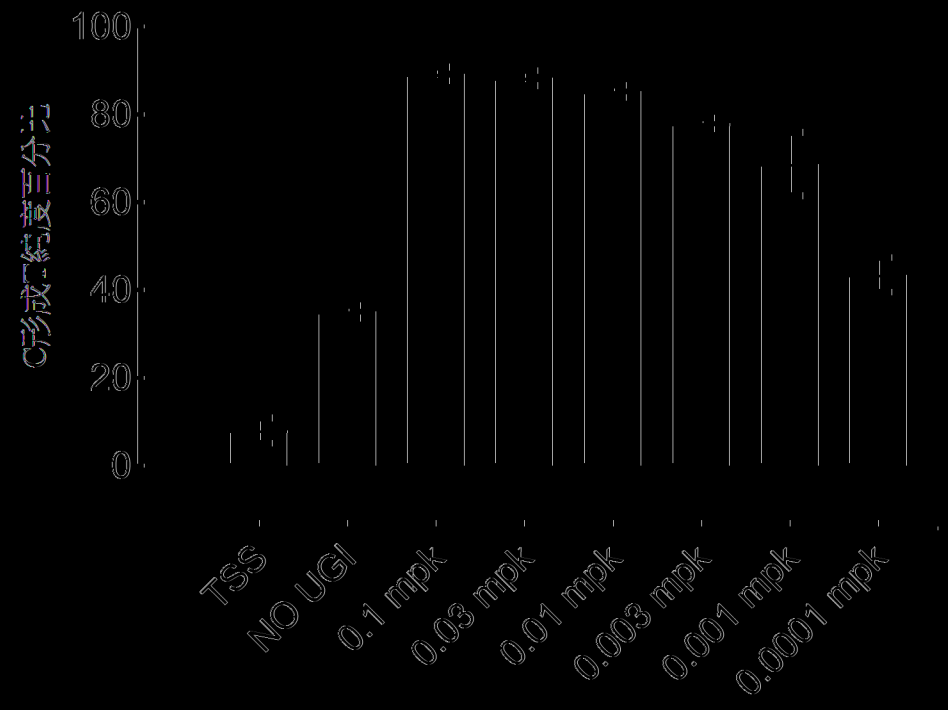
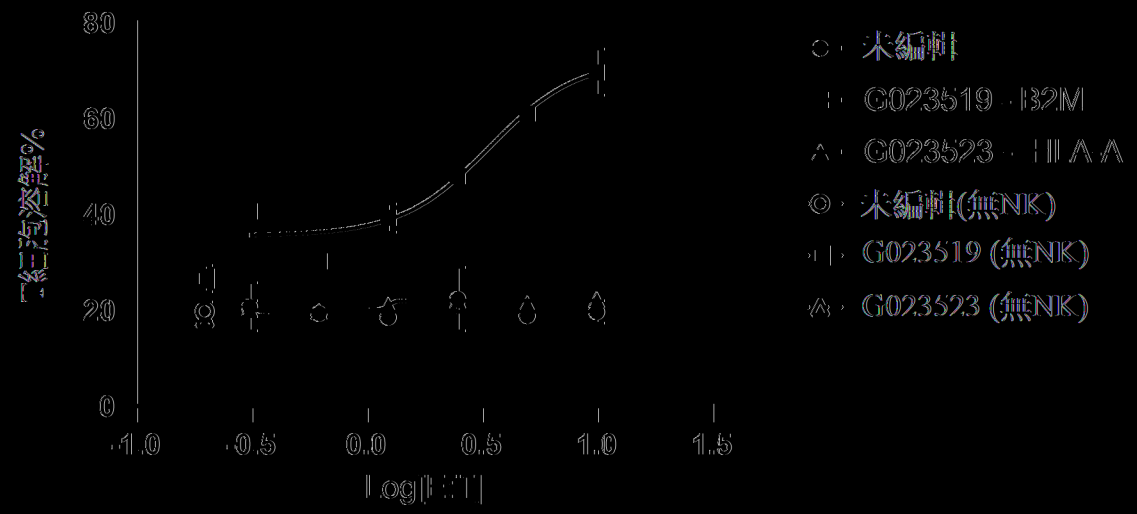
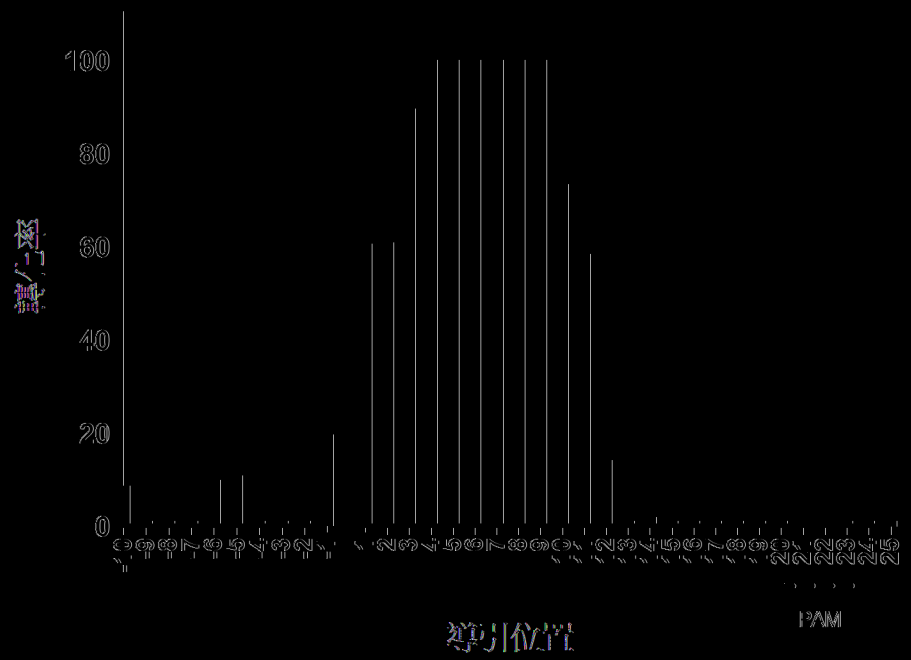

C形成T編輯百分比
100
80
60
40
20
0
TSS
NO UGI
0.1 mpk
0.03 mpk
0.01 mpk
0.003 mpk
0.001 mpk
0.0001 mpk

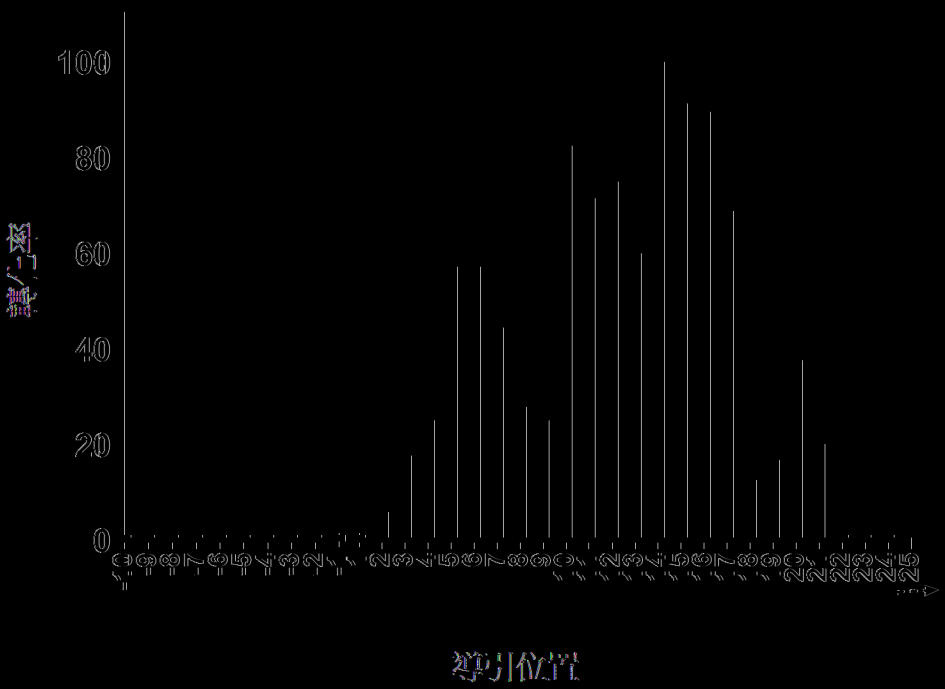
圖61


80
60
40
20
0
-1.0
-0.5
0.0
0.5
1.0
1.5
Log[E:T]
未編輯
G023519 - B2M
G023523 - HLA
未編輯(無NK)
G023519 (無NK)
G023523 (無NK)

|(圖62)|



(圖63)



(圖64)