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(54)名稱

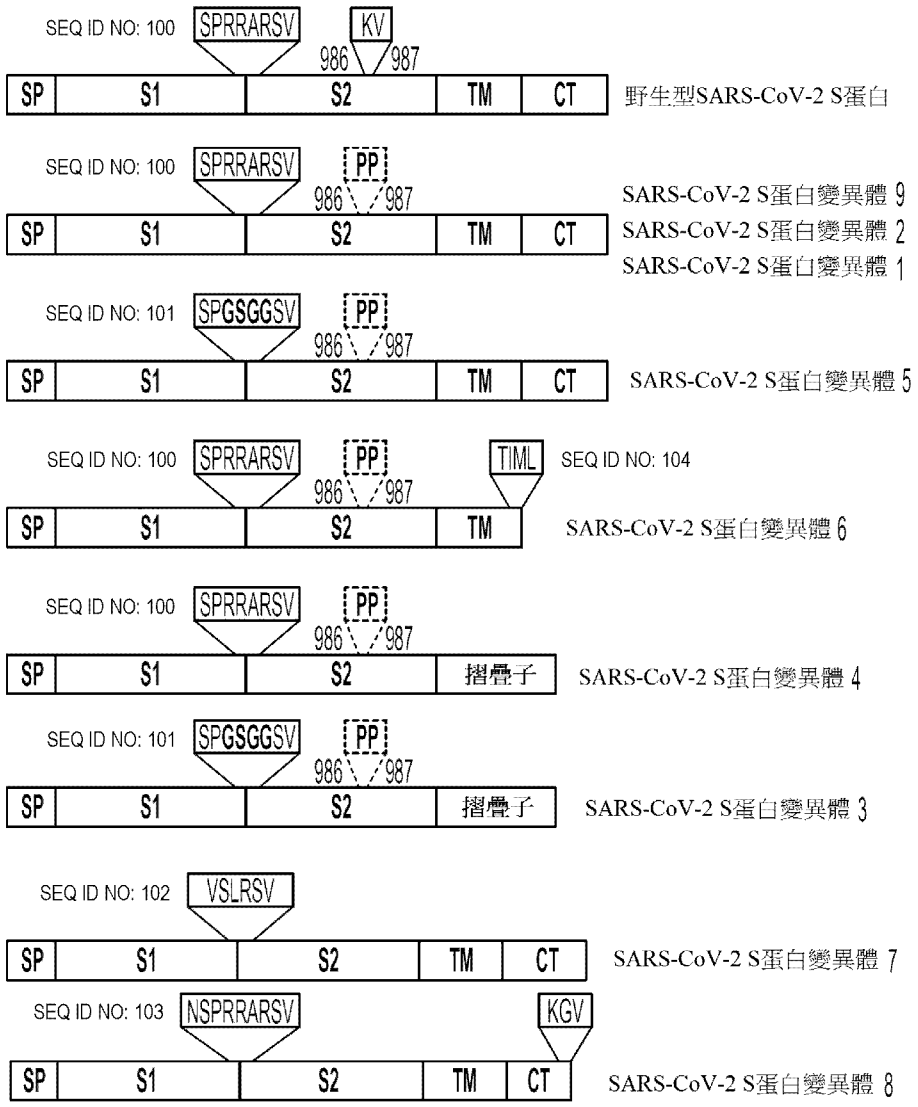
冠狀病毒ＲＮＡ疫苗

(57)摘要

本揭示案係關於冠狀病毒核糖核酸(RNA)疫苗以及使用該等疫苗及包含該等疫苗之組合物之方法。

The disclosure relates to coronavirus ribonucleic acid (RNA) vaccines as well as methods of using the vaccines and compositions comprising the vaccines.

指定代表圖：


SEQ ID NO: 100
SPRRARSV
KV
986
987
SP
S1
S2
TM
CT
野生型SARS-CoV-2 S蛋白
SEQ ID NO: 100
SPRRARSV
PP
986
987
SARS-CoV-2 S蛋白變異體 9
SARS-CoV-2 S蛋白變異體 2
SARS-CoV-2 S蛋白變異體 1
SEQ ID NO: 101
SPGSGGSV
PP
SARS-CoV-2 S蛋白變異體 5
SEQ ID NO: 100
TIML
SEQ ID NO: 104
SARS-CoV-2 S蛋白變異體 6
摺疊子
SARS-CoV-2 S蛋白變異體 4
SARS-CoV-2 S蛋白變異體 3
SEQ ID NO: 102
VSLRSV
SARS-CoV-2 S蛋白變異體 7
SEQ ID NO: 103
NSPRRARSV
KGV
SARS-CoV-2 S蛋白變異體 8

【圖 1】

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【發明摘要】

【中文發明名稱】

冠狀病毒RNA疫苗

【英文發明名稱】

CORONAVIRUS RNA VACCINES

【中文】

本揭示案係關於冠狀病毒核糖核酸(RNA)疫苗以及使用該等疫苗及包含該等疫苗之組合物之方法。

【英文】

The disclosure relates to coronavirus ribonucleic acid (RNA) vaccines as well as methods of using the vaccines and compositions comprising the vaccines.

【指定代表圖】

圖1

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

冠狀病毒RNA疫苗

【英文發明名稱】

CORONAVIRUS RNA VACCINES

【技術領域】

【先前技術】

【0001】 人類冠狀病毒係冠狀病毒科(*Coronaviridae* family)之高度傳染性帶套膜之陽性單股RNA病毒。已知*冠狀病毒科*之兩個亞科引起人類疾病。最重要的亞科為*β*-冠狀病毒(beta-coronavirus)。*β*-冠狀病毒係輕度至中度上呼吸道感染之常見病原體。然而，新型冠狀病毒感染的爆發(諸如武漢冠狀病毒所引起之感染)與高死亡率死亡人數相關。嚴重急性呼吸症候群冠狀病毒2 (SARSCoV-2) (舊稱為「武漢冠狀病毒」、「2019新型冠狀病毒」或「2019-nCoV」)於2019年12月在中國武漢市首先鑑別出，且已迅速感染幾十萬人。SARSCoV-2病毒所引起之大流行性疾病已被世界衛生組織(World Health Organization, WHO)命名為COVID-19 (冠狀病毒疾病(**Co**rona**vi**rus **D**isease) 2019)。SARS-CoV-2分離株(亦稱為2019 nCoV或Wuhan-Hu-1)之首個基因體序列已於2020年1月12日由來自北京的中國CDC之研究人員存入基因庫(GenBank)中。

【0002】 目前，尚無針對COVID-19之特效治療或針對SARS-CoV-2感染之疫苗。與冠狀病毒感染(具體而言SARS-CoV-2大流行)相關之持續健康問題及死亡率在國際上引起極大關注。由SARS-CoV-2所引起之公共健康危機強調了快速開發針對該等病毒之有效且安全的候選疫苗之重要

性。

【發明內容】

【0003】 本文在一些實施例中提供包含RNA之免疫組合物(例如RNA疫苗)，該RNA編碼能夠引發針對冠狀病毒抗原(諸如SARS-CoV-2抗原)之強效中和抗體反應之高度免疫原性抗原。令人驚訝地，此新型冠狀病毒之蛋白質抗原序列與嚴重急性呼吸症候群(SARS)冠狀病毒之蛋白質抗原序列共有小於80%之一致性，且與中東呼吸症候群(MERS)冠狀病毒之蛋白質抗原序列共有小於35%之一致性。

【0004】 在一些實施例中，本文所提供之構築體包括：天然SARS-CoV-2刺突(S)蛋白中之多元裂解位點至一元裂解位點之回復(例如圖1，變異體7，SEQ ID NO: 23)；羧基尾處多元ER/高基氏體(Golgi)信號序列(KXHXX-COOH)之缺失(例如圖1，變異體8，SEQ ID NO: 26)；雙脯胺酸穩定性突變(例如圖1，變異體1至6及9，SEQ ID NO: 5、8、11、14、17、20及29)；經修飾之蛋白酶裂解位點以使蛋白質穩定(例如圖1，變異體3及5，SEQ ID NO: 11及17)；胞質尾區之缺失(例如圖1，變異體3、4及6，SEQ ID NO: 11、14及20)；及/或摺疊子支架(例如圖1，變異體3及4，SEQ ID NO: 11及14)。本文中所揭示之結構特徵包括例如藉由視情況用跨膜區置換弗林蛋白酶(furin)裂解位點來去除弗林蛋白酶裂解位點、移植至刺突蛋白胞外域之C末端部分之摺疊子、缺失C端細胞內尾區(羧基尾區)。因此，在一些實施例中，本文中所提供之mRNA包含編碼變異型三聚刺突蛋白之開放閱讀框，該變異型三聚刺突蛋白包含缺失弗林蛋白酶裂解位點、作為C端之額外摺疊子序列、缺失羧基尾區或其中的序列及/或2脯胺酸突變中之任一或多者。

【0005】 本揭示案之一些態樣提供核糖核酸(RNA)，其包含開放閱讀框(ORF)，該ORF編碼能夠誘導對SARS-CoV-2之免疫反應(例如中和抗體反應)之冠狀病毒抗原(例如S蛋白、膜(M)蛋白、套膜(E)蛋白、核衣殼(NC)蛋白或表1之蛋白)，視情況其中該RNA調配在脂質奈米顆粒中。

【0006】 本揭示案之其他態樣提供密碼子最佳化之RNA，其包含ORF，該ORF包含與編碼SARS-CoV-2抗原之野生型RNA具有至少80%一致性之序列，視情況其中該RNA調配在脂質奈米顆粒中。

【0007】 本揭示案之其他態樣提供經化學修飾之RNA，其包含ORF，該ORF包含與編碼SARS-CoV-2抗原之野生型RNA具有至少80%一致性之序列，視情況其中該RNA調配在脂質奈米顆粒中。

【0008】 本揭示案之其他態樣提供RNA，其包含ORF，該ORF包含與表1序列中之任一者之序列(例如SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或84)具有至少80%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 28之序列具有至少80%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 16之序列具有至少80%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 19之序列具有至少80%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 22之序列具有至少80%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 25之序列具有至少80%一致性之序列。

【0009】 在一些實施例中，ORF包含與表1序列中之任一者之序列(例如SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、

52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或84)具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 28之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO: 28之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 16之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO: 16之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 19之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO: 19之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 22之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO: 22之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO: 25之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO: 25之序列。在一些實施例中，RNA包含ORF，該ORF包含與SEQ ID NO:106之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含ORF，該ORF包含SEQ ID NO:106之序列。在一些實施例中，包含ORF之mRNA統一經修飾(例如，完全修飾、貫穿整個序列中修飾)以獲得特定修飾。舉例而言，RNA可統一經1-甲基-假尿苷修飾，使得序列中之各U為1-甲基-假尿苷。

【0010】 在一些實施例中，RNA進一步包含5' UTR，視情況其中該

5' UTR包含SEQ ID NO: 2或SEQ ID NO: 36之序列。

【0011】 在一些實施例中，RNA進一步包含3' UTR，視情況其中該3' UTR包含SEQ ID NO: 4或SEQ ID NO: 37之序列。

【0012】 在一些實施例中，RNA進一步包含5'帽類似物、視情況7mG(5')ppp(5')NlmpNp帽。可使用其他帽類似物。

【0013】 在一些實施例中，RNA進一步包含聚(A)尾，視情況長度為50至150個核苷酸。

【0014】 在一些實施例中，ORF編碼冠狀病毒抗原。在一些實施例中，冠狀病毒抗原係結構蛋白。在一些實施例中，結構蛋白係刺突(S)蛋白。在一些實施例中，S蛋白係S蛋白之穩定化融合前形式。在一些實施例中，冠狀病毒抗原包含與表1序列中之任一者之序列(例如SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83、或85)具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 29之序列具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 17之序列具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 20之序列具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 23之序列具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 26之序列具有至少80%一致性之序列。在一些實施例中，冠狀病毒抗原包含與表1序列中之任一者之序列(例如SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83、或85)具有至少85%、至少90%、至少95%或

至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 29之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含SEQ ID NO: 29之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 17之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含SEQ ID NO: 17之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 20之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含SEQ ID NO: 20之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 23之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含SEQ ID NO: 23之序列。在一些實施例中，冠狀病毒抗原包含與SEQ ID NO: 26之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，冠狀病毒抗原包含SEQ ID NO: 26之序列。

【0015】 在一些實施例中，結構蛋白係M蛋白。在一些實施例中，M蛋白包含與SEQ ID NO: 81之序列具有至少80%一致性之序列。在一些實施例中，M蛋白包含與SEQ ID NO: 81之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，ORF包含SEQ ID NO: 80之序列。在一些實施例中，RNA包含與SEQ ID NO: 95之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含SEQ ID NO: 95之序列。

【0016】 在一些實施例中，結構蛋白係E蛋白。在一些實施例中，E蛋白包含與SEQ ID NO: 83之序列具有至少80%一致性之序列。在一些實

施例中，E蛋白包含與SEQ ID NO: 83之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，ORF包含SEQ ID NO: 82之序列。在一些實施例中，RNA包含與SEQ ID NO: 96之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含SEQ ID NO: 96之序列。

【0017】在一些實施例中，結構蛋白係NC蛋白。在一些實施例中，NC蛋白包含與SEQ ID NO: 85之序列具有至少80%一致性之序列。在一些實施例中，NC蛋白包含與SEQ ID NO: 85之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，ORF包含SEQ ID NO: 84之序列。在一些實施例中，RNA包含與SEQ ID NO: 97之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含SEQ ID NO: 97之序列。

【0018】在一些實施例中，ORF包含表1序列中之任一者之序列，例如SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、84、或106中之任一者。在一些實施例中，包含ORF之mRNA統一經修飾(例如，完全修飾、貫穿整個序列中修飾)以獲得特定修飾。舉例而言，RNA可統一經1-甲基-假尿苷修飾，使得序列中之各U為1-甲基-假尿苷。

【0019】在一些實施例中，RNA包含與表1序列中之任一者之序列(例如SEQ ID NO: 1、6、9、12、15、18、21、24、27、30、51、53、55、57、58、60、86至97、或105中之任一者)具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 27之序列具有至少85%、至少90%、至少95%或至少98%一

致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 105之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 15之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 18之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 21之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。在一些實施例中，RNA包含與SEQ ID NO: 24之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

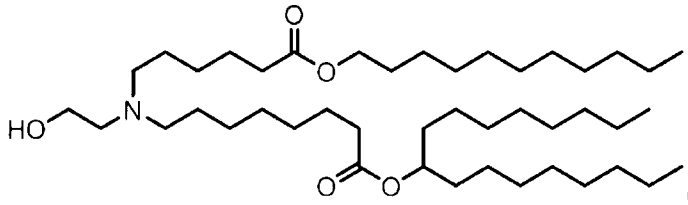
【0020】 在一些實施例中，RNA包含表1序列中之任一者之序列，例如SEQ ID NO: 1、6、9、12、15、18、21、24、27、30、51、53、55、57、58、60、86至97、或105中之任一者。在一些實施例中，RNA包含SEQ ID NO: 27之序列。在一些實施例中，RNA包含SEQ ID NO: 15之序列。在一些實施例中，RNA包含SEQ ID NO: 18之序列。在一些實施例中，RNA包含SEQ ID NO: 21之序列。在一些實施例中，RNA包含SEQ ID NO: 24之序列。在一些實施例中，mRNA統一經修飾(例如，完全修飾、貫穿整個序列中修飾)以獲得特定修飾。舉例而言，RNA可統一經1-甲基-假尿苷修飾，使得序列中之各U為1-甲基-假尿苷。

【0021】 在一些實施例中，RNA包含化學修飾。在一些實施例中，化學修飾係1-甲基假尿苷(例如，完全修飾、貫穿整個序列中修飾)。

【0022】 本揭示案之一些態樣提供方法，其包括使前述實施例中之任一實施例之RNA密碼子最佳化。

【0023】 在一些實施例中，將RNA調配在脂質奈米顆粒中。

【0024】 在一些實施例中，脂質奈米顆粒包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。在一些實施例中，脂質奈米顆粒包含0.5-15 mol% (例如0.5-10 mol%、0.5-5 mol%或1-2 mol%) PEG修飾之脂質；5-25 mol% (例如5-20 mol%或5-15 mol%)非陽離子(例如中性)脂質；25-55 mol% (例如30-45 mol%或35-40 mol%)固醇；及20-60 mol% (例如40-60 mol%、40-50 mol%、45-55 mol%或45-50 mol%)可電離之陽離子脂質。在一些實施例中，PEG修飾之脂質係1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，非陽離子脂質係1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，固醇係膽固醇；且可電離之陽離子脂質具有化合物1之結構：



(化合物1)。

【0025】 本揭示案之其他態樣提供組合物，其包含前述實施例中之任一實施例之RNA及脂質混合物。在一些實施例中，脂質混合物包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。在一些實施例中，脂質混合物包含0.5-15 mol% (例如0.5-10 mol%、0.5-5 mol%或1-2 mol%) PEG修飾之脂質；5-25 mol% (例如5-20 mol%或5-15 mol%)非陽離子(例如中性)脂質；25-55 mol% (例如30-45 mol%或35-40 mol%)固醇；及20-60 mol% (例如40-60 mol%、40-50 mol%、45-55 mol%或45-50 mol%)可電離之陽離子脂質。在一些實施例中，PEG修飾之脂質係1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，非陽離子脂質係1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，固醇係膽固醇；且可電離之陽離子脂質具有化合物1之結構。

【0026】 在一些實施例中，脂質混合物形成脂質奈米顆粒。在一些實施例中，將RNA調配在脂質奈米顆粒中。在一些實施例中，脂質奈米顆粒首先形成為空的脂質奈米顆粒，且在即將投與之前(例如在幾分鐘至一小時內)與疫苗之mRNA組合。

【0027】 本揭示案之其他態樣提供方法，該方法包括向受試者投與前述實施例中之任一實施例之RNA，其量有效誘導該受試者中針對冠狀病毒之中和抗體反應。

【0028】 本揭示案之其他態樣提供方法，該方法包括向受試者投與前述實施例中之任一實施例之組合物，其量有效誘導該受試者中針對冠狀病毒之中和抗體反應及/或T細胞免疫反應、視情況$CD4^+$及/或$CD8^+$ T細胞免疫反應。

【0029】 在一些實施例中，冠狀病毒係SARS-CoV-2。

【0030】 在一些實施例中，受試者係免疫受損的。在一些實施例中，受試者患有肺病。在一些實施例中，受試者為5歲或更小、或65歲或更大。

【0031】 在一些實施例中，該方法包括向受試者投與至少兩個劑量之組合物。

【0032】 在一些實施例中，在投與RNA或包含RNA之組合物後1-72小時，在受試者之血清中產生可偵測水準之冠狀病毒抗原。

【0033】 在一些實施例中，在投與RNA或包含RNA之組合物後1-72小時，在受試者之血清中產生至少100 NU/ml、至少500 NU/ml或至少1000 NU/ml之中和抗體效價。

【0034】 應理解，術語「SARS-CoV-2」、「武漢冠狀病毒」、「2019

新型冠狀病毒」及「2019-nCoV」係指最近出現的、現稱為SARS-CoV-2之相同β冠狀病毒，且其在本文中可互換使用。

【0035】國際申請案第PCT/US2016/058327號(公開案第WO2017/07062號)及國際申請案第PCT/US2018/022777號(公開案第WO2018/170347號)之全部內容係以引用的方式併入本文中。

【圖式簡單說明】

【0036】

圖1顯示由本揭示案之SARS-CoV-2 mRNA編碼的各種例示性S蛋白抗原之示意圖。頂部示意圖代表野生型SARS-CoV-2蛋白；下方示意圖繪示相對於該野生型之SARS-CoV-2蛋白變異體。

圖2顯示由本揭示案之SARS-CoV-2 mRNA編碼的各種SARS-CoV-2蛋白變異體之24小時活體外表現數據之圖表。

圖3顯示由本揭示案之SARS-CoV-2 mRNA編碼的各種SARS-CoV-2蛋白變異體之24小時活體外表現數據之圖表。測試兩種不同量之mRNA。

圖4A至圖4B顯示在不同小鼠品系中用不同劑量之SARS-CoV-2變異體9 mRNA疫苗(圖4A)及在較高劑量下(圖4B)免疫後的血清抗體效價量測值之圖表。

圖5A至圖5C顯示與SARS-CoV-2變異體9 mRNA疫苗及編碼野生型SARS-CoV-2 S蛋白之mRNA (圖5B)相比，在用不同劑量的SARS-CoV-2變異體5 mRNA疫苗(圖5A)免疫後之血清抗體效價量測值之圖表。圖5C係對七種不同的SARS-CoV-2 mRNA疫苗及編碼野生型SARS-CoV-2 S蛋白序列之mRNA之血清抗體效價進行比較之圖表。

圖6顯示在利用不同劑量之SARS-CoV-2變異體9 mRNA進行免疫

後，小鼠中之時程性抗體反應圖表。

圖7顯示繪示投藥時間表之示意圖。

圖8A至 圖8C顯 示 在BALB/c小 鼠(圖8A)、C57BL/6小 鼠(圖8B)及C3B6小鼠(圖8C)中，在初免劑量之SARS-CoV-2變異體9 mRNA疫苗後兩週及在加強劑劑量之Wuahn-Hu-1變異體9 mRNA疫苗後兩週，小鼠中之血清抗體效價圖表。對各種疫苗劑量進行測試。

圖9A至圖9E顯示在BALB/c小鼠(圖9A)及C3B6小鼠(圖9B)中，在初免劑量之SARS-CoV-2變異體5 mRNA疫苗後兩週及在加強劑劑量之SARS-CoV-2變異體5 mRNA疫苗後兩週，或在初免劑量及加強劑量之編碼野生型SARS-CoV-2蛋白之mRNA (圖9C)後，來自小鼠之血清抗體效價圖表。對各種疫苗劑量進行測試。圖9D至圖9E顯示用SARS-CoV-2變異體9 mRNA疫苗、SARS-CoV-2變異體5 mRNA疫苗或編碼野生型SARS-CoV-2 S蛋白之mRNA實施免疫的BALB/c小鼠(圖9D)及C3B6小鼠(圖9E)中之血清抗體效價比較圖表。

圖10顯示用七種不同的SARA-CoV-2 mRNA疫苗中之一者或編碼野生型SARS-CoV-2 S蛋白序列之mRNA實施免疫的小鼠在加強劑劑量後之血清抗體效價比較圖表。

圖11A至 圖11B顯 示 在 利 用SARS-CoV-2變 異 體9 mRNA疫 苗 、SARS-CoV-2變異體5 mRNA疫苗或SARS-CoV-2變異體6 mRNA疫苗對小鼠實施免疫後，使用對SARS-CoV-1 S1子單元之N末端結構域具有特異性之5653-118 (「118」)抗體進行流式細胞術分析之結果之圖表。使用自小鼠獲得之淋巴結(圖11A)及脾(圖11B)樣品實施該分析。

圖12A至 圖12B顯 示 在 利 用SARS-CoV-2變 異 體9 mRNA疫 苗 、

SARS-CoV-2變異體5 mRNA疫苗或SARS-CoV-2變異體6 mRNA疫苗對小鼠實施免疫後，使用對SARS-CoV-1 S蛋白之受體結合結構域具有特異性之5652-109 (「109」)抗體進行流式細胞術分析之結果之圖表。使用自小鼠獲得之淋巴結(圖12A)及脾(圖12B)樣品實施該分析。

圖13A至圖13C顯示在活體外用六種不同的SARS-CoV-2 mRNA疫苗中之一者轉染後的流式細胞術分析結果之圖表。圖13A顯示陽性抗原呈遞細胞(APC+)之百分比，且圖13B顯示平均螢光強度(MFI)。圖13C顯示使用陽性對照(SARS抗體)之結果。

圖14顯示使用mAb118、mAb109及SARS mAb103 (陽性對照)，在活體外用SARS-CoV-2變異體9 mRNA疫苗轉染後來自流式細胞術分析之結果之圖表。陰性對照不包括一級抗體。

圖15顯示不同濃度之mAb118或mAb109與SARS-CoV-2抗原之間的蛋白質結合之圖表。

圖16A至圖16B顯示在第0週及第3週接種1 μg、0.1 μg或0.01 μg之SARS-CoV-2變異體9 mRNA疫苗之BALB/c小鼠中的結合及中和抗體之圖表。圖16A顯示在第2週(初免後)及第5週(加強後)藉由ELISA評價之S-2P結合抗體。圖16B顯示在第5週藉由假病毒中和分析在接受1 μg或0.1 μg之SARS-CoV-2變異體9 mRNA疫苗之小鼠血清中評價之中和活性。

圖17A至圖17C顯示數據圖表，其展示SARS-CoV-2變異體9 mRNA疫苗誘導之免疫性阻止SARS-CoV-2在BALB/c小鼠肺中複製。在第0週及第3週向BALB/c小鼠接種1 μg、0.1 μg或0.01 μg之SARS-CoV-2變異體9 mRNA疫苗，且在第9週利用小鼠適應性SARS-CoV-2進行攻毒(challenge)。圖17A顯示在攻毒後第2天藉由噬斑分析評價之肺中之病毒

效價。圖17B顯示在攻毒後第2天藉由噬斑分析評價之鼻甲中之病毒效價。圖17C顯示在感染後隨時間推移之體重變化(百分比)。

圖18A至圖18C顯示數據圖表，其展示SARS-CoV-2變異體9 mRNA疫苗誘導之免疫性阻止SARS-CoV-2在BALB/c小鼠肺中複製。在第0週向BALB/c小鼠接種1 μg、0.1 μg或0.01 μg之SARS-CoV-2變異體9 mRNA疫苗，且在第7週利用小鼠適應性SARS-CoV-2進行攻毒。圖18A顯示在攻毒後第2天藉由噬斑分析評價之鼻甲中之病毒效價。圖18B顯示在攻毒後第2天藉由噬斑分析評價之肺中之病毒效價。圖18C顯示在感染後隨時間推移之體重變化(百分比)。

圖19顯示實例10中所用之第0週及第3週免疫時間表。

圖20A至圖20C顯示數據圖表，其展示SARS-CoV-2變異體9 mRNA疫苗誘導之免疫性阻止SARS-CoV-2在BALB/c小鼠肺中複製。在第0週及第4週向BALB/c小鼠接種10 μg、1 μg或0.1 μg之SARS-CoV-2變異體9，且在第7週利用小鼠適應性SARS-CoV-2進行攻毒。圖20A顯示在攻毒後第2天藉由噬斑分析評價之鼻甲中之病毒效價。圖20B顯示在攻毒後第2天藉由噬斑分析評價之肺中之病毒效價。圖20C顯示在感染後隨時間推移之體重變化(百分比)。

圖21A至圖21H顯示與在BALB/c小鼠之mRNA免疫後的中和抗體反應相關之數據圖表。在每一血清稀釋度下取一式三份之平均值，自相對螢光素酶單位(RLU)讀數生成S形曲線，且將未感染之細胞視為代表100%中和並將僅經病毒轉導之細胞視為代表0%中和，計算50% (IC_{50}) (圖21A、21C、21E、21G)及80% (IC_{80}) (圖21B、21D、21F、21H)中和活性。每一符號代表個別小鼠，條形代表幾何平均效價(GMT)，且誤差槓指示幾何

標準偏差(SD)。圖21A至圖21F顯示用於比較0.1 μg及1 μg劑量之未配對T測試。圖21G及圖21H顯示藉由單因子ANOVA與克魯斯卡-沃利斯(Kruskal-Wallis)多重比較測試比較之各組。

圖22A至圖22C顯示與利用替代性刺突抗原設計對BALB/c小鼠進行低劑量mRNA免疫後之結合及中和抗體反應相關之數據圖表。圖22A顯示血清終點效價。圖22B顯示將未感染之細胞視為代表100%中和且將僅經病毒轉導之細胞視為代表0%中和所計算之50% (IC_{50})中和活性。每一符號代表個別小鼠，條形代表幾何平均效價(GMT)，且誤差槓指示幾何標準偏差(SD)。在圖22A及圖22B中，藉由單因子ANOVA與克魯斯卡-沃利斯多重比較測試對各組進行比較。圖22C顯示藉由斯皮爾曼關聯(Spearman correlation)比較之抗體結合及中和效價。

【實施方式】

相關申請案

【0037】 本申請案根據35 U.S.C. § 119(e)主張2020年1月28日提出申請之美國臨時申請案第62/967,006號、2020年2月7日提出申請之美國臨時申請案第62/971,825號、2020年3月30日提出申請之美國臨時申請案第63/002,094號、2020年4月13日提出申請之美國臨時申請案第63/009,005號及2020年4月27日提出申請之美國臨時申請案第63/016,175號之權益，該等臨時申請案各自係以全文引用的方式併入本文中。

【0038】 本揭示案提供引發針對冠狀病毒抗原之強效中和抗體之組合物(例如免疫/免疫原性組合物，諸如含RNA疫苗之脂質奈米顆粒)。在一些實施例中，免疫組合物包括編碼冠狀病毒抗原(諸如含SARS-CoV-2抗原之脂質奈米顆粒)之RNA (例如信使RNA (mRNA))。在一些實施例

中，冠狀病毒抗原係結構蛋白。在一些實施例中，冠狀病毒抗原係刺突蛋白、套膜蛋白、核衣殼蛋白或膜蛋白。在一些實施例中，冠狀病毒抗原係穩定化之融合前刺突蛋白。在一些實施例中，mRNA包含編碼變異型三聚刺突蛋白之開放閱讀框。舉例而言，三聚刺突蛋白可包含穩定的融合前刺突蛋白。在一些實施例中，穩定的融合前刺突蛋白包含雙脯胺酸(S2P)突變。

抗原

【0039】 如本文所用之抗原係能夠誘導免疫反應之蛋白質(例如使免疫系統產生針對該等抗原之抗體)。在本文中，除非另有說明，否則使用術語「抗原」涵蓋免疫原性蛋白質及免疫原性片段(誘導(或能夠誘導)對(至少一種)冠狀病毒之免疫反應之免疫原性片段)。應理解，術語「蛋白質」涵蓋肽且術語「抗原」涵蓋抗原性片段。其他分子可為抗原性的，諸如細菌多醣或蛋白質與多醣結構之組合，但對於本文所包括之病毒疫苗而言，病毒蛋白、病毒蛋白片段及源自β冠狀病毒SARS-CoV-2之經設計及/或突變之蛋白質係本文所提供之抗原。

【0040】 在一些實施例中，本文中所提供之mRNA包含編碼變異型三聚刺突蛋白之開放閱讀框。在一些實施例中，開放閱讀框編碼包含穩定的融合前刺突蛋白之變異型三聚刺突蛋白。在一些實施例中，穩定的融合前刺突蛋白包含雙脯胺酸(S2P)突變。

【0041】 冠狀病毒抗原及本揭示案之組合物中編碼冠狀病毒抗原之RNA (例如mRNA)之例示性序列提供於表1中。

【0042】 在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)及視情況選用之脂質奈米顆粒，該冠狀病毒抗原包含與SEQ

ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83、或85中之任一者之胺基酸序列具有至少80%、至少85%、至少90%、至少95%、至少98%或100%一致性之胺基酸序列。在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)，該冠狀病毒抗原包含SEQ ID NO: 29之序列。在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)，該冠狀病毒抗原包含SEQ ID NO: 17之序列。在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)，該冠狀病毒抗原包含SEQ ID NO: 20之序列。在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)，該冠狀病毒抗原包含SEQ ID NO: 23之序列。在一些實施例中，組合物包含編碼冠狀病毒抗原之RNA (例如mRNA)，該冠狀病毒抗原包含SEQ ID NO: 26之序列。

【0043】 應理解，由本文所闡述之RNA編碼的抗原中之任一者可或可不包含信號序列。

核酸

【0044】 本揭示案之組合物包含具有編碼冠狀病毒抗原(例如，變異型三聚刺突蛋白，諸如穩定的融合前刺突蛋白)之開放閱讀框(ORF)之(至少一種) RNA。在一些實施例中，RNA係信使RNA (mRNA)。在一些實施例中，RNA (例如mRNA)進一步包含5' UTR、3' UTR、聚(A)尾及/或5'帽類似物。

【0045】 亦應理解，本揭示案之冠狀病毒疫苗可包括任何5'非轉譯區(UTR)及/或任何3' UTR。例示性UTR序列提供於序列表中(例如SEQ ID NO: 2、36、4或37)；然而，可使用其他UTR序列或用其交換本文所闡述

之UTR序列中之任一者。UTR亦可自本文所提供之RNA多核苷酸中省略。

【0046】 核酸包含核苷酸(核苷酸單體)之聚合物。因此，核酸亦稱為多核苷酸。核酸可為或可包括(例如)去氧核糖核酸(DNA)、核糖核酸(RNA)、蘇糖核酸(TNA)、乙二醇核酸(GNA)、肽核酸(PNA)、鎖核酸(LNA，包括具有β-D-核糖構形之LNA、具有α-L-核糖構形之α-LNA(LNA之非鏡像異構物)、2′-胺基官能化之2′-胺基-LNA及2′-胺基官能化之2′-胺基-α-LNA)、乙烯核酸(ENA)、環己烯基核酸(CeNA)及/或其嵌合體及/或組合。

【0047】 信使RNA (mRNA)係編碼(至少一種)蛋白質(天然、非天然或經修飾之胺基酸聚合物)之任何RNA，且可經轉譯以在活體外、活體內、原位或離體產生所編碼之蛋白質。熟習此項技術者將瞭解，除非另有註明，否則本申請案中所陳述之核酸序列可在代表性DNA序列中列舉「T」，但在該序列代表RNA (例如mRNA)時，「T」將由「U」取代。因此，由本文中之特定序列識別號揭示並識別之任一DNA亦揭示與該DNA互補之相應RNA (例如mRNA)序列，其中DNA序列之每一「T」經「U」取代。

【0048】 開放閱讀框(ORF)係以起始密碼子(例如甲硫胺酸(ATG或AUG))開始且以終止密碼子(例如TAA、TAG或TGA或UAA、UAG或UGA)結束之連續DNA或RNA區段。ORF通常編碼蛋白質。將理解，本文所揭示之序列可進一步包含額外元件，例如5'及3' UTR，但不同於ORF，彼等元件不一定存在於本揭示案之RNA多核苷酸中。

【0049】 在一些實施例中，組合物包含RNA (例如mRNA)，該RNA

包含與SEQ ID NO: 1、6、9、12、15、18、21、24、27、30、51、53、55、57、58、60、或86至97中之任一者之核苷酸序列具有至少80%、至少85%、至少90%、至少95%、至少98%或100%一致性之核苷酸序列。

【0050】 在一些實施例中，組合物包含RNA (例如mRNA)，其包含ORF，該ORF包含與SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或84中之任一者之核苷酸序列具有至少80%、至少85%、至少90%、至少95%、至少98%或100%一致性之核苷酸序列。

變異體

【0051】 在一些實施例中，本揭示案之組合物包括編碼冠狀病毒抗原變異體(例如，變異型三聚刺突蛋白，諸如穩定的融合前刺突蛋白)之RNA。抗原變異體或其他多肽變異體係指其胺基酸序列不同於野生型、天然或參照序列之分子。與天然或參照序列相比，抗原/多肽變異體可在胺基酸序列內之某些位置處具有取代、缺失及/或插入。通常，變異體與野生型、天然或參照序列具有至少50%之一致性。在一些實施例中，變異體與野生型、天然或參照序列共有至少80%或至少90%之一致性。

【0052】 由本揭示案之核酸編碼的變異體抗原/多肽可含有賦予諸多合意性質中之任一者之胺基酸變化，例如增強其在受試者中之免疫原性、增強其表現及/或改良其穩定性或PK/PD性質。變異體抗原/多肽可使用常規誘變技術製得且視需要進行分析以確定其是否具有期望性質。測定表現水準及免疫原性之分析為此項技術中所熟知，且此等例示性分析陳述於實例部分中。類似地，可使用業內公認之技術來量測蛋白質變異體之PK/PD性質，例如藉由測定抗原在接種疫苗之受試者中隨時間推移之表現及/或

藉由觀察所誘導免疫反應之持久性。由變異體核酸編碼的蛋白質之穩定性可藉由分析熱穩定性或尿素變性時之穩定性來量測，或可使用電腦模擬預測來量測。用於此等實驗及電腦模擬測定之方法為此項技術中所已知。

【0053】 在一些實施例中，組合物包含RNA或RNA ORF，其包含本文所提供序列中之任一者之核苷酸序列(例如，參見序列表及表1)，或包含與本文所提供序列中之任一者之核苷酸序列至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%一致之核苷酸序列。

【0054】 術語「一致性」係指如藉由對序列進行比較所確定，兩個或更多個多肽(例如抗原)或多核苷酸(核酸)之序列之間的關係。一致性亦指如藉由兩個或更多個胺基酸殘基或核酸殘基串之間的匹配數所確定的序列間之序列相關性程度。一致性衡量兩個或更多個序列中較小序列之間的一致性匹配之百分比，其中空位比對(若存在)藉由特定數學模型或電腦程式(例如「演算法」)定址。相關抗原或核酸之一致性可藉由已知方法容易地計算。「一致性百分比(%)」在應用於多肽或多核苷酸序列時係定義為在比對序列並引入空位(視需要)以達成最大一致性百分比後，候選胺基酸或核酸序列中與第二序列之胺基酸序列或核酸序列中之殘基(胺基酸殘基或核酸殘基)一致的殘基之百分比。用於比對之方法及電腦程式為此項技術中所熟知。應理解，一致性取決於對一致性百分比之計算，但其值可因在計算中所引入之空位及罰分而有所不同。通常，如藉由本文所闡述且為熟習此項技術者所已知之序列比對程式及參數測定，特定多核苷酸或多肽(例如抗原)之變異體與特定參照多核苷酸或多肽具有至少40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、91%、92%、

93%、94%、95%、96%、97%、98%、99%但小於100%之序列一致性。此等用於比對之工具包括BLAST套件之彼等工具(Stephen F. Altschul等人(1997)，「Gapped BLAST and PSI-BLAST: a new generation of protein database search programs」, Nucleic Acids Res. 25:3389-3402)。另一常用之局部比對技術係基於史密斯-沃特曼演算法(Smith-Waterman algorithm) (Smith, T.F.及Waterman, M.S. (1981) 「Identification of common molecular subsequences.」J. Mol. Biol. 147:195-197)。基於動態程式化之通用整體比對技術係尼德曼-翁施演算法(Needleman-Wunsch algorithm) (Needleman, S.B.及Wunsch, C.D. (1970) 「A general method applicable to the search for similarities in the amino acid sequences of two proteins.」J. Mol. Biol. 48:443-453)。最近，已開發出快速最佳整體序列比對演算法(Fast Optimal Global Sequence Alignment Algorithm, FOGSAA)，據稱，其較其他最佳整體比對方法(包括尼德曼-翁施演算法)更快地產生對核苷酸及蛋白質序列之整體比對。

【0055】 因此，編碼相對於參照序列、尤其本文所揭示之多肽(例如抗原)序列含有取代、插入及/或添加、缺失及共價修飾之肽或多肽之多核苷酸包括在本揭示案之範圍內。舉例而言，可將序列標籤或胺基酸(諸如一或多個離胺酸)添加至肽序列(例如在N末端或C末端處)。序列標籤可用於肽偵測、純化或定位。離胺酸可用於增加肽溶解性或容許進行生物素化。或者，可視情況使位於肽或蛋白質之胺基酸序列之羧基及胺基末端區域處的胺基酸殘基缺失，從而提供截短序列。端視於序列之用途(如例如使序列表現為可溶性或連接至固體支持物之較大序列之一部分)，某些胺基酸(例如C末端或N末端殘基)可替代地缺失。在一些實施例中，用於(或

編碼)信號序列、終止序列、跨膜結構域、連接體、多聚化結構域(諸如摺疊子區)及諸如此類之序列可經達成相同或相似功能之替代序列取代。在一些實施例中，蛋白質核心中之空腔可經填充以改良穩定性，例如藉由引入更大之胺基酸。在其他實施例中，掩埋之氫鍵網路可經疏水性殘基替代以改良穩定性。在其他實施例中，可去除糖基化位點並用適當殘基替代。熟習此項技術者可容易地鑑別出此等序列。亦應理解，本文所提供之一些序列含有序列標籤或末端肽序列(例如在N末端或C末端處)，其可在(例如)用於RNA (例如mRNA)疫苗製劑中之前缺失。

【0056】 如熟習此項技術者所公認，蛋白質片段、功能性蛋白質結構域及同源蛋白質亦視為在所關注之冠狀病毒抗原之範圍內。舉例而言，本文提供參照蛋白質之任何蛋白質片段(意指較參照抗原序列短至少一個胺基酸殘基，但其他方面一致之多肽序列)，條件係該片段為免疫原性的且賦予對冠狀病毒之保護性免疫反應。除與參照蛋白質一致但截短之變異體以外，在一些實施例中，如本文所提供或提及之任一序列中所示，抗原包括2、3、4、5、6、7、8、9、10或更多個突變。抗原/抗原性多肽之長度可在約4、6或8個胺基酸至全長蛋白質範圍內。

穩定性元件

【0057】 除諸如5′-帽結構或3′-聚(A)尾等其他結構特徵以外，天然真核mRNA分子亦可含有穩定性元件，包括(但不限於)在其5′端 (5′ UTR)及/或在其3′端(3′ UTR)之非轉譯區(UTR)。5′ UTR及3′ UTR二者通常均自基因體DNA轉錄，且係成熟前mRNA之元件。成熟mRNA之特徵性結構特徵(諸如5′-帽及3′-聚(A)尾)通常係在mRNA加工期間添加至經轉錄(成熟前)之mRNA。

【0058】 在一些實施例中，組合物包括RNA多核苷酸，其具有編碼至少一種具有至少一種修飾、至少一個5′末端帽之抗原性多肽之開放閱讀框，且調配在脂質奈米顆粒內。可根據製造商方案，使用以下化學RNA帽類似物在活體外轉錄反應期間同時完成對多核苷酸之5′加帽以產生5′-鳥苷帽結構：3′-O-Me-m7G(5')ppp(5') G [ARCA帽]；G(5')ppp(5')A；G(5')ppp(5')G；m7G(5')ppp(5')A；m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA)。可使用牛痘病毒加帽酶在轉錄後完成對經修飾RNA之5′加帽，以產生「帽0」結構：m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA)。可使用牛痘病毒加帽酶及2′-O甲基-轉移酶二者來產生帽1結構，以產生：m7G(5')ppp(5')G-2′-O-甲基。可自帽1結構隨後使用2′-O甲基-轉移酶對5′-倒數第三核苷酸進行2′-O-甲基化來產生帽2結構。可自帽2結構隨後使用2′-O甲基-轉移酶對5′-倒數第四核苷酸進行2′-O-甲基化來產生帽3結構。酶可源自重組來源。

【0059】 3′-聚(A)尾通常係添加至所轉錄mRNA之3′端之腺嘌呤核苷酸區段。在一些情況中，其可包含最多約400個腺嘌呤核苷酸。在一些實施例中，就個別mRNA之穩定性而言，3′-聚(A)尾之長度可為必不可少之要素。

【0060】 在一些實施例中，組合物包括穩定性元件。穩定性元件可包括(例如)組織蛋白莖環。已鑑別出一種莖環結合蛋白(SLBP)，其為32 kDa之蛋白質。該蛋白質與在細胞核及細胞質二者中傳遞訊息的組織蛋白之3'端處之組織蛋白莖環締合。其表現水準受細胞週期調控；其在S期期間達到峰值，此時組織蛋白mRNA水準亦升高。已顯示，該蛋白質對於U7 snRNP對組織蛋白前mRNA進行有效3'端加工必不可少。在加工後，

SLBP繼續與莖環締合，且接著刺激成熟組織蛋白mRNA轉譯成細胞質中之組織蛋白。SLBP之RNA結合結構域在整個後生動物及原生動物中均係保守的；其與組織蛋白莖環之結合取決於環之結構。最小結合位點包括相對於莖環之至少三個5'核苷酸及兩個3'核苷酸。

【0061】 在一些實施例中，RNA (例如mRNA)包括編碼區、至少一個組織蛋白莖環及視情況聚(A)序列或多聚腺苷酸化信號。聚(A)序列或多聚腺苷酸化信號通常應增強所編碼蛋白質之表現水準。在一些實施例中，所編碼之蛋白質不為組織蛋白、報告蛋白(例如螢光素酶、GFP、EGFP、β-半乳糖苷酶、EGFP)或標記物或選擇蛋白(例如α-球蛋白、半乳糖激酶及黃嘌呤:鳥嘌呤磷酸核糖基轉移酶(GPT))。

【0062】 在一些實施例中，RNA (例如mRNA)包括聚(A)序列或多聚腺苷酸化信號與至少一個組織蛋白莖環之組合，儘管兩者在自然界中代表替代機制，但其協同作用使蛋白質表現增加至超過任一個別元件所觀察到之水準。聚(A)與至少一個組織蛋白莖環之組合之協同效應不依賴於元件之次序或聚(A)序列之長度。

【0063】 在一些實施例中，RNA (例如mRNA)不包括組織蛋白下游元件(HDE)。「組織蛋白下游元件」(HDE)包括在天然莖環3′的富含嘌呤之大約15至20個核苷酸之多核苷酸區段，其代表參與將組織蛋白前mRNA加工為成熟組織蛋白mRNA之U7 snRNA之結合位點。在一些實施例中，核酸不包括內含子。

【0064】 RNA (例如mRNA)可或可不含有增強子及/或啟動子序列，其可經修飾或未經修飾或其可經活化或不活化。在一些實施例中，組織蛋白莖環通常源自組織蛋白基因，且包括由間隔區(由短序列組成)分隔的兩

個相鄰部分或完全反向互補序列之分子內鹼基配對，其形成結構之環。未配對之環區通常無法與莖環元件中之任一者進行鹼基配對。由於未配對之環區係許多RNA二級結構之關鍵組分，故其更常見於RNA中，但亦可存在於單股DNA中。莖環結構之穩定性通常取決於長度、失配或膨出部之數目以及配對區之鹼基組成。在一些實施例中，可產生擺動鹼基配對(非沃森-克裡克(non-Watson-Crick)鹼基配對)。在一些實施例中，該至少一個組織蛋白莖環序列包含15至45個核苷酸長度。

【0065】 在一些實施例中，RNA (例如mRNA)之一或多個富含AU之序列被去除。該等序列有時稱為AURES，其係在3'UTR中發現的去穩定化序列。可將AURES自RNA疫苗中去除。或者，可使AURES保留在RNA疫苗中。

信號肽

【0066】 在一些實施例中，組合物包含RNA (例如mRNA)，其具有編碼與冠狀病毒抗原融合之信號肽之ORF。信號肽包含蛋白質之N末端之15-60個胺基酸，其通常為在分泌路徑上進行跨膜易位所需，且因此在真核生物及原核生物二者中普遍控制大多數蛋白質進入分泌路徑。在真核生物中，新生前體蛋白質(前蛋白)之信號肽將核糖體引導至粗面內質網(ER)膜，且起始生長中之肽鏈穿過ER膜轉運以進行加工。ER加工產生成熟蛋白質，其中信號肽通常由宿主細胞之ER駐留信號肽酶自前體蛋白質中裂解，或其保持不裂解並起膜錨之作用。信號肽亦可有助於使蛋白質靶向細胞膜。

【0067】 信號肽之長度可為15-60個胺基酸。舉例而言，信號肽之長度可為15、16、17、18、19、20、21、22、23、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、51、52、53、54、55、56、57、58、59或60個胺基酸。在一些實施例中，信號肽之長度為20-60、25-60、30-60、35- 60、40-60、45- 60、50-60、55-60、15-55、20-55、25-55、30-55、35-55、40-55、45-55、50-55、15-50、20-50、25-50、30-50、35-50、40-50、45-50、15-45、20-45、25-45、30-45、35-45、40-45、15-40、20-40、25-40、30-40、35-40、15-35、20-35、25-35、30-35、15-30、20-30、25-30、15-25、20-25或15-20個胺基酸。

【0068】 來自異源基因之信號肽(其調控自然界中除冠狀病毒抗原以外之基因之表現)為此項技術中所已知，且可測試其期望性質並接著併入至本揭示案之核酸中。在一些實施例中，信號肽可包含以下序列中之一者：MDSKGSSQKGSRLLLLLVVSNLLLPQGVVG (SEQ ID NO: 38)；MDWTWILFLVAAATRVHS (SEQ ID NO: 39)；METPAQLLFLLLLWLPDTTG (SEQ ID NO: 40)；MLGSNSGQRVVFTILLLLVAPAYS (SEQ ID NO: 41)；MKCLLYLAFLFIGVNCA (SEQ ID NO: 42)；MWLVSLAIVTACAGA (SEQ ID NO: 43)；或MFVFLVLLPLVSSQC (SEQ ID NO: 99)。

融合蛋白

【0069】 在一些實施例中，本揭示案之組合物包括編碼抗原性融合蛋白之RNA (例如mRNA)。因此，所編碼之一或多種抗原可包括接合在一起之兩種或更多種蛋白質(例如蛋白質及/或蛋白質片段)。或者，與蛋白質抗原融合之蛋白質不促進對其自身之強免疫反應，而是促進對冠狀病毒抗原之強免疫反應。在一些實施例中，抗原性融合蛋白保留來自每一原始蛋

白質之功能性質。

支架部分

【0070】 在一些實施例中，如本文所提供之RNA (例如mRNA)疫苗編碼包含連接至支架部分之冠狀病毒抗原之融合蛋白。在一些實施例中，此等支架部分賦予由本揭示案之核酸所編碼抗原所期望之性質。舉例而言，支架蛋白可改良抗原之免疫原性，例如藉由改變抗原之結構、改變抗原之攝取及加工及/或使抗原結合至結合搭配物。

【0071】 在一些實施例中，支架部分係可自組裝成高度對稱、穩定且結構有序之蛋白質奈米顆粒之蛋白質，該等蛋白質奈米顆粒之直徑為10-150 nm，其係與免疫系統之各種細胞進行最佳相互作用高度適宜之大小範圍。在一些實施例中，可使用病毒蛋白或類病毒顆粒來形成穩定奈米顆粒結構。此等病毒蛋白之實例為此項技術中所已知。舉例而言，在一些實施例中，支架部分係B型肝炎表面抗原(HBsAg)。HBsAg形成平均直徑為約22 nm之球形顆粒，且其缺乏核酸且因此不具傳染性(Lopez-Sagaseta, J.等人，Computational and Structural Biotechnology Journal 14 (2016) 58-68)。在一些實施例中，支架部分係自組裝成直徑為24-31 nm之顆粒之B型肝炎核心抗原(HBcAg)，其類似於自HBV感染之人類肝臟獲得的病毒核心。HBcAg自組裝產生為具有300 Å及360 Å直徑之兩類不同大小之奈米顆粒，此對應於180或240個單元體。在一些實施例中，使冠狀病毒抗原與HBsAG或HBcAG融合，以促進展示冠狀病毒抗原之奈米顆粒之自組裝。

【0072】 在一些實施例中，可使用細菌蛋白質平臺。該等自組裝蛋白質之非限制性實例包括鐵蛋白、2,4-二氧四氫喋啶(lumazine)及包封蛋

白(encapsulin)。

【0073】 鐵蛋白係主要功能為細胞內鐵儲存之蛋白質。鐵蛋白由24個亞單元組成，其各自由四-α-螺旋束構成，該等亞單元以具有八面體對稱性之四級結構自組裝(Cho K.J.等人，*J Mol Biol*. 2009;390:83-98)。已確定鐵蛋白之若干種高解析度結構，此證實幽門螺旋桿菌(Helicobacter pylori)鐵蛋白係由24個相同單元體組成，而在動物中，存在可單獨組裝或以不同比率組合成24個亞單元顆粒之鐵蛋白輕鏈及重鏈(Granier T.等人，*J Biol Inorg Chem*. 2003;8:105-111；Lawson D.M.等人，*Nature*. 1991;349:541-544)。鐵蛋白自組裝成具有強勁熱及化學穩定性之奈米顆粒。因此，鐵蛋白奈米顆粒非常適合攜帶並暴露抗原。

【0074】 2,4-二氧四氫喋啶合酶(LS)亦非常適合作為用於抗原展示之奈米顆粒平臺。LS負責核黃素之生物合成中之倒數第二個催化步驟，其係存在於眾多種生物體中之酶，包括古細菌、細菌、真菌、植物及真細菌(Weber S.E. Flavins and Flavoproteins. Methods and Protocols, Series: Methods in Molecular Biology. 2014)。LS單體長150個胺基酸，且係由β-摺疊連同其兩側之串聯α-螺旋組成。已報導LS之多種不同的四級結構，此說明其形態之多樣性：自同五聚體至形成直徑為150 Å之衣殼的12個五聚體之對稱組裝體。甚至已闡述超過100個亞單元之LS籠(Zhang X.等人，J Mol Biol. 2006;362:753-770)。

【0075】 包封蛋白係自嗜熱生物海棲熱袍菌(*Thermotoga maritima*)分離出之新型蛋白質籠奈米顆粒，其亦可用作在自組裝奈米顆粒表面上呈遞抗原之平臺。包封蛋白係自60份相同的31 kDa單體組裝而成，該等單體具有薄的二十面體T = 1對稱籠狀結構，其中內徑及外徑分別為20 nm及24

nm (Sutter M.等人，Nat Struct Mol Biol. 2008, 15: 939-947)。儘管尚未明確瞭解包封蛋白在海棲熱袍菌中之確切功能，但其晶體結構已於近期解決，且其功能被假定為一種細胞隔室，其可封裝參與氧化應激反應之蛋白質，諸如DyP (染料去色過氧化酶)及Flp (鐵蛋白樣蛋白) (Rahmanpour R.等人，FEBS J. 2013, 280: 2097-2104)。

【0076】 在一些實施例中，本揭示案之RNA編碼與摺疊子結構域融合之冠狀病毒抗原(例如SARS-CoV-2 S蛋白)。該摺疊子結構域可(例如)自噬菌體T4彈力素獲得(例如，參見Tao Y等人，*Structure*. 1997年6月15日; 5(6):789-98)。

連接體及可裂解肽

【0077】 在一些實施例中，本揭示案之mRNA編碼一種以上多肽，其在本文中稱為融合蛋白。在一些實施例中，該mRNA進一步編碼位於融合蛋白之至少一個或每一結構域之間的連接體。連接體可為(例如)可裂解連接體或蛋白酶敏感性連接體。在一些實施例中，連接體選自由以下組成之群：F2A連接體、P2A連接體、T2A連接體、E2A連接體及其組合。此自裂解肽連接體(稱為2A肽)家族已在此項技術中予以闡述(例如，參見Kim, J.H.等人，(2011) *PLoS ONE* 6:e18556)。在一些實施例中，連接體係F2A連接體。在一些實施例中，連接體係GGGS (SEQ ID NO: 98)連接體。在一些實施例中，融合蛋白含有具有中間連接體之三個結構域，其具有如下結構：結構域-連接體-結構域-連接體-結構域。

【0078】 此項技術中已知之可裂解連接體可結合本揭示案使用。此等例示性連接體包括：F2A連接體、T2A連接體、P2A連接體、E2A連接體(例如，參見WO2017127750)。熟習此項技術者將瞭解，其他業內公認

之連接體可適用於本揭示案之構築體中(例如由本揭示案之核酸編碼)。熟習此項技術者將同樣瞭解，其他多順反子構築體(在同一分子內分別編碼一種以上抗原/多肽之mRNA)可適於如本文所提供之用途。

序列最佳化

【0079】 在一些實施例中，使編碼本揭示案抗原之ORF經密碼子最佳化。密碼子最佳化方法為此項技術中所已知。舉例而言，可使本文所提供序列中之任一或多者之ORF經密碼子最佳化。在一些實施例中，密碼子最佳化可用於匹配靶標及宿主生物體中之密碼子頻率以確保正確摺疊；偏置GC含量以增加mRNA穩定性或減少二級結構；使可能損害基因構築或表現之串聯重複密碼子或鹼基序列最小化；定製轉錄及轉譯控制區；插入或去除蛋白質輸送序列；在編碼蛋白質中去除/添加轉譯後修飾位點(例如糖基化位點)；添加、去除或改組蛋白質結構域；插入或缺失限制位點；修飾核糖體結合位點及mRNA降解位點；調整轉譯速率以容許蛋白質之各個結構域正確摺疊；或減少或消除多核苷酸內之問題二級結構。密碼子最佳化工具、演算法及服務為此項技術中所已知，非限制性實例包括來自GeneArt (Life Technologies)、DNA2.0 (Menlo Park CA)及/或專有方法之服務。在一些實施例中，使用最佳化演算法使開放閱讀框(ORF)序列最佳化。

【0080】 在一些實施例中，密碼子最佳化之序列與天然或野生型序列ORF (例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有小於95%之序列一致性。在一些實施例中，密碼子最佳化之序列與天然或野生型序列(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有小於90%之序列一致性。在一些實施例中，密碼子最佳化之序列與天然或野生型序列

(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有小於85%之序列一致性。在一些實施例中，密碼子最佳化之序列與天然或野生型序列(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有小於80%之序列一致性。在一些實施例中，密碼子最佳化之序列與天然或野生型序列(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有小於75%之序列一致性。

【0081】 在一些實施例中，密碼子最佳化之序列與天然或野生型序列(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有介於65%與85%之間(例如介於約67%與約85%之間或介於約67%與約80%之間)的序列一致性。在一些實施例中，密碼子最佳化之序列與天然或野生型序列(例如編碼冠狀病毒抗原之天然或野生型mRNA序列)共有介於65%與75%或約80%之間的序列一致性。

【0082】 在一些實施例中，密碼子最佳化之序列編碼的抗原與非密碼子最佳化之序列編碼的冠狀病毒抗原具有相同免疫原性，或其免疫原性較非密碼子最佳化之序列編碼的冠狀病毒抗原高(例如高至少10%、至少20%、至少30%、至少40%、至少50%、至少100%或至少200%)。

【0083】 當轉染至哺乳動物宿主細胞中時，經修飾之mRNA具有介於12至18小時之間或大於18小時(例如24、36、48、60、72或大於72小時)之穩定性，且能夠由哺乳動物宿主細胞表現。

【0084】 在一些實施例中，密碼子最佳化之RNA可為其中G/C水準增強之RNA。核酸分子(例如mRNA)之G/C含量可影響RNA之穩定性。鳥嘌呤(G)及/或胞嘧啶(C)殘基量增加之RNA可在功能上較含有大量腺嘌呤(A)及胸腺嘧啶(T)或尿嘧啶(U)核苷酸之RNA更穩定。作為實例，

WO02/098443揭示一種醫藥組合物，其含有藉由轉譯區中之序列修飾而穩定化之mRNA。由於遺傳密碼之簡併性，該等修飾藉由用現有密碼子取代促進更高RNA穩定性而不改變所得胺基酸之彼等密碼子來發揮作用。該方法限於RNA之編碼區。

未經化學修飾之核苷酸

【0085】 在一些實施例中，RNA (例如mRNA)未經化學修飾，且包含由腺苷、鳥苷、胞嘧啶及尿苷組成之標準核糖核苷酸。在一些實施例中，本揭示案之核苷酸及核苷包含標準核苷殘基，諸如存在於所轉錄RNA中之彼等殘基(例如A、G、C或U)。在一些實施例中，本揭示案之核苷酸及核苷包含標準去氧核糖核苷，諸如存在於DNA中之彼等去氧核糖核苷(例如dA、dG、dC或dT)。

化學修飾

【0086】 在一些實施例中，本揭示案之組合物包含具有編碼冠狀病毒抗原之開放閱讀框之RNA，其中核酸包含可為標準(未經修飾)或如此項技術中所已知經修飾之核苷酸及/或核苷。在一些實施例中，本揭示案之核苷酸及核苷包含經修飾之核苷酸或核苷。此等經修飾之核苷酸及核苷可為經修飾之天然核苷酸及核苷或經修飾之非天然核苷酸及核苷。此等修飾可包括如此項技術中所公認的在核苷酸及/或核苷之糖、主鏈或核鹼基部分處之彼等修飾。

【0087】 在一些實施例中，本揭示案之經修飾之天然核苷酸或核苷係如此項技術中所通常已知或公認之核苷酸或核苷。此等經修飾之天然核苷酸及核苷之非限制性實例可尤其在廣泛認可之MODOMICS資料庫中找到。

【0088】 在一些實施例中，本揭示案之經修飾之非天然核苷酸或核苷係如此項技術中所通常已知或公認之核苷酸或核苷。此等經修飾之非天然核苷酸及核苷之非限制性實例可尤其在如下已公開之美國申請案中找到：第PCT/US2012/058519號；第PCT/US2013/075177號；第PCT/US2014/058897號；第PCT/US2014/058891號；第PCT/US2014/070413號；第PCT/US2015/36773號；第PCT/US2015/36759號；第PCT/US2015/36771號；或第PCT/IB2017/051367號，所有該等申請案均係以引用的方式併入本文中。

【0089】 因此，本揭示案之核酸(例如DNA核酸及RNA核酸，諸如mRNA核酸)可包含標準核苷酸及核苷、天然核苷酸及核苷、非天然核苷酸及核苷或其任何組合。

【0090】 在一些實施例中，本揭示案之核酸(例如DNA核酸及RNA核酸，諸如mRNA核酸)包含各種(一種以上)不同類型之標準及/或經修飾之核苷酸及核苷。在一些實施例中，核酸之特定區域含有一個、兩個或更多個(視情況不同)類型之標準及/或經修飾之核苷酸及核苷。

【0091】 在一些實施例中，相對於包含標準核苷酸及核苷的未經修飾之核酸，引入至細胞或生物體中之經修飾之RNA核酸(例如經修飾之mRNA核酸)分別在該細胞或生物體中展現降低之降解。

【0092】 在一些實施例中，相對於包含標準核苷酸及核苷的未經修飾之核酸，引入至細胞或生物體中之經修飾之RNA核酸(例如經修飾之mRNA核酸)可分別在該細胞或生物體中展現降低之免疫原性(例如降低之先天性反應)。

【0093】 在一些實施例中，核酸(例如RNA核酸，諸如mRNA核酸)

包含非天然修飾之核苷酸，其係在核酸之合成期間或合成後引入，以達成期望功能或性質。該等修飾可存在於核苷酸間鍵聯、嘌呤或嘧啶鹼基或糖上。修飾可利用化學合成或利用聚合酶在鏈末端或鏈中之任何其他位置處引入。核酸中之任一區域均可經化學修飾。

【0094】 本揭示案提供核酸(例如RNA核酸，諸如mRNA核酸)之經修飾之核苷及核苷酸。「核苷」係指含有糖分子(例如戊糖或核糖)或其衍生物與有機鹼基(例如嘌呤或嘧啶)或其衍生物(在本文中亦稱為「核鹼基」)之組合的化合物。「核苷酸」係指包括磷酸基之核苷。經修飾之核苷酸可藉由任何可用方法(諸如化學、酶促或重組地)來合成，以包括一或多個經修飾或非天然之核苷。核酸可包含一或多個連接之核苷區域。此等區域可具有可變之主鏈鍵聯。該等鍵聯可為標準磷酸二酯鍵聯，在該情形中，核酸將包含核苷酸區域。

【0095】 經修飾之核苷酸鹼基配對不僅涵蓋標準腺苷-胸腺嘧啶、腺苷-尿嘧啶或鳥苷-胞嘧啶鹼基對，且亦涵蓋在核苷酸及/或包含非標準或經修飾鹼基之經修飾核苷酸之間形成的鹼基對，其中氫鍵供體及氫鍵受體之排列允許在非標準鹼基與標準鹼基之間或在兩個互補非標準鹼基結構之間(諸如在具有至少一種化學修飾之彼等核酸中)形成氫鍵。此非標準鹼基配對之一個實例係在經修飾之核苷酸肌苷與腺嘌呤、胞嘧啶或尿嘧啶之間的鹼基配對。鹼基/糖或連接體之任何組合可併入至本揭示案之核酸中。

【0096】 在一些實施例中，核酸(例如RNA核酸，諸如mRNA核酸)中之經修飾之核鹼基包含1-甲基-假尿苷(m1ψ)、1-乙基-假尿苷(e1ψ)、5-甲氧基-尿苷(mo5U)、5-甲基-胞苷(m5C)及/或假尿苷(ψ)。在一些實施例中，核酸(例如RNA核酸，諸如mRNA核酸)中之經修飾之核鹼基包含5-甲

氧基甲基尿苷、5-甲硫基尿苷、1-甲氧基甲基假尿苷、5-甲基胞苷及/或5-甲氧基胞苷。在一些實施例中，多聚核糖核苷酸包括上文所提及之任何經修飾核鹼基中之至少兩者(例如2者、3者、4者或更多者)之組合，包括(但不限於)化學修飾。

【0097】 在一些實施例中，本揭示案之mRNA包含在核酸之一或多個或所有尿苷位置處之1-甲基-假尿苷(m1ψ)取代。

【0098】 在一些實施例中，本揭示案之mRNA包含在核酸之一或多個或所有尿苷位置處之1-甲基-假尿苷(m1ψ)取代及在核酸之一或多個或所有胞苷位置處之5-甲基胞苷取代。

【0099】 在一些實施例中，本揭示案之mRNA包含在核酸之一或多個或所有尿苷位置處之假尿苷(ψ)取代。

【0100】 在一些實施例中，本揭示案之mRNA包含在核酸之一或多個或所有尿苷位置處之假尿苷(ψ)取代及在核酸之一或多個或所有胞苷位置處之5-甲基胞苷取代。

【0101】 在一些實施例中，本揭示案之mRNA包含在核酸之一或多個或所有尿苷位置處之尿苷。

【0102】 在一些實施例中，mRNA統一經修飾(例如完全修飾、貫穿整個序列中修飾)以獲得特定修飾。舉例而言，核酸可統一經1-甲基-假尿苷修飾，此意味著mRNA序列中之所有尿苷殘基均經1-甲基-假尿苷替代。類似地，可針對序列中所存在的任一類型之核苷殘基對核酸進行統一修飾，其係藉由用經修飾之殘基(諸如上文所陳述之彼等殘基)進行替代來實施。

【0103】 本揭示案之核酸可沿著整個分子長度部分或完全地經修

飾。舉例而言，在本揭示案之核酸中或在其預定序列區域中(例如在包括或不包括聚(A)尾之mRNA中)，一或多個或全部或給定類型之核苷酸(例如嘌呤或嘧啶，或A、G、U、C中之任一或多者或全部)可統一經修飾。在一些實施例中，本揭示案之核酸中(或其序列區域中)之所有核苷酸X均係經修飾之核苷酸，其中X可為核苷酸A、G、U、C中之任一者，或組合A+G、A+U、A+C、G+U、G+C、U+C、A+G+U、A+G+C、G+U+C或A+G+C中之任一者。

【0104】 核酸可含有約1%至約100%之經修飾核苷酸(相對於總核苷酸含量，或相對於一或多種類型之核苷酸，亦即A、G、U或C中之任一或多者)或任何中間百分比(例如1%至20%、1%至25%、1%至50%、1%至60%、1%至70%、1%至80%、1%至90%、1%至95%、10%至20%、10%至25%、10%至50%、10%至60%、10%至70%、10%至80%、10%至90%、10%至95%、10%至100%、20%至25%、20%至50%、20%至60%、20%至70%、20%至80%、20%至90%、20%至95%、20%至100%、50%至60%、50%至70%、50%至80%、50%至90%、50%至95%、50%至100%、70%至80%、70%至90%、70%至95%、70%至100%、80%至90%、80%至95%、80%至100%、90%至95%、90%至100%及95%至100%)。將理解，任何剩餘之百分比係由存在未經修飾之A、G、U或C引起。

【0105】 mRNA可含有最少1%且最多100%之經修飾核苷酸，或任何中間百分比，諸如至少5%之經修飾核苷酸、至少10%之經修飾核苷酸、至少25%之經修飾核苷酸、至少50%之經修飾核苷酸、至少80%之經修飾核苷酸或至少90%之經修飾核苷酸。舉例而言，核酸可含有經修飾之

嘧啶，諸如經修飾之尿嘧啶或胞嘧啶。在一些實施例中，核酸中至少5%、至少10%、至少25%、至少50%、至少80%、至少90%或100%之尿嘧啶由經修飾之尿嘧啶(例如5-取代之尿嘧啶)替代。經修飾之尿嘧啶可由具有單一獨特結構之化合物替代，或可由複數種具有不同結構(例如2、3、4或更多種獨特結構)之化合物替代。在一些實施例中，核酸中至少5%、至少10%、至少25%、至少50%、至少80%、至少90%或100%之胞嘧啶由經修飾之胞嘧啶(例如5-取代之胞嘧啶)替代。經修飾之胞嘧啶可由具有單一獨特結構之化合物替代，或可由複數種具有不同結構(例如2、3、4或更多種獨特結構)之化合物替代。

非轉譯區(UTR)

【0106】 本揭示案之mRNA可包含一或多個充當非轉譯區或起非轉譯區作用之區域或部分。倘若mRNA經設計以編碼至少一種所關注抗原，則核酸可包含該等非轉譯區(UTR)中之一或多者。核酸之野生型非轉譯區經轉錄但不轉譯。在mRNA中，5′ UTR起始於轉錄起始位點且延續至起始密碼子但不包括起始密碼子；而3′ UTR緊接著終止密碼子起始且延續至轉錄終止信號。愈來愈多之證據表明，UTR在核酸分子之穩定性及轉譯方面起調控作用。可將UTR之調控性特徵併入至本揭示案之多核苷酸中，以尤其增強分子之穩定性。亦可併入該等特定特徵，以確保轉錄本在錯引導至不期望之器官位點時使其受控下調。此項技術中已知且可獲得多種5'UTR及3'UTR序列。

【0107】 5' UTR係位於起始密碼子(由核糖體轉譯之mRNA轉錄本之第一個密碼子)正上游(5')之mRNA區域。5' UTR不編碼蛋白質(係非編碼的)。天然5′UTR具有在轉譯起始中起作用之特徵。其帶有如Kozak序列之

印記，眾所周知該等序列與核糖體啟動許多基因轉譯之過程有關。Kozak序列具有一致性CCR(A/G)CCAUGG (SEQ ID NO: 44)，其中R係在起始密碼子(AUG)上游三個鹼基之嘌呤(腺嘌呤或鳥嘌呤)，該起始密碼子(AUG)後接另一『G』。亦已知5'UTR形成參與延長因子結合之二級結構。

【0108】 在本揭示案之一些實施例中，5' UTR係異源性UTR，亦即係在自然界中發現的與不同ORF締合之UTR。在另一實施例中，5' UTR係合成性UTR，亦即不存在於自然界中。合成性UTR包括已經突變以改良其性質之UTR，例如增加基因表現之UTR以及完全合成之彼等UTR。例示性5' UTR包括爪蟾(*Xenopus*)或人類源性a-球蛋白或b-球蛋白(8278063；9012219)、人類細胞色素b-245 a多肽及羥基類固醇(17b)去氫酶以及煙草蝕紋病毒(US8278063、9012219)。亦可使用CMV即刻早期1(IE1)基因(US2014/0206753、WO2013/185069)、序列GGGAUCCUACC (SEQ ID NO: 45) (WO2014/144196)。在另一實施例中，TOP基因之5' UTR係缺少5' TOP基元(寡嘧啶帶)之TOP基因之5' UTR (例如WO/2015/101414、WO2015/101415、WO/2015/062738、WO2015/024667、WO2015/024667)；可使用源自核糖體蛋白質大32(L32)基因之5' UTR元件(WO/2015/101414、WO2015/101415、WO/2015/062738)、源自羥基類固醇(17-β)去氫酶4基因(HSD17B4)之5'UTR之5' UTR元件(WO2015/024667)或源自ATP5A1之5' UTR之5' UTR元件(WO2015/024667)。在一些實施例中，使用內部核糖體進入位點(IRES)代替5' UTR。

【0109】 在一些實施例中，本揭示案之5' UTR包含選自SEQ ID NO: 2及SEQ ID NO: 36之序列。

【0110】 3' UTR係位於終止密碼子(mRNA轉錄本中發出終止轉譯信號之密碼子)正下游(3')之mRNA區域。3' UTR不編碼蛋白質(係非編碼的)。已知天然或野生型3′ UTR中內嵌有腺苷及尿苷區段。該等富含AU之印記在具有高更替率之基因中尤為普遍。基於其序列特徵及功能性質，可將富含AU之元件(ARE)分成三類(Chen等人，1995): I類ARE在U富集區內含有AUUUA基元之若干個分散拷貝。C-Myc及MyoD含有I類ARE。II類ARE具有兩個或更多個重疊UUAUUUA(U/A)(U/A) (SEQ ID NO: 46)九聚體。含有此類ARE之分子包括GM-CSF及TNF-a。III類ARES之定義較不明確。該等U富集區不含AUUUA基元。c-Jun及Myogenin係此類別之兩個充分研究之實例。已知大多數結合至ARE之蛋白質使信使不穩定，而ELAV家族之成員(最著名的為HuR)已被證明增加mRNA之穩定性。HuR結合至所有三個類別之ARE。將HuR特異性結合位點工程化至核酸分子之3′ UTR中將導致HuR結合，且由此使活體內訊息穩定。

【0111】 引入、去除或修飾3′ UTR富含AU之元件(ARE)可用於調節本揭示案之核酸(例如RNA)之穩定性。當工程化特定核酸時，可引入一或多個ARE拷貝以使本揭示案之核酸較不穩定，且藉此縮減轉譯並減少所得蛋白質之產生。同樣，可鑑別並去除ARE或使其突變以增加細胞內穩定性，且由此增加所得蛋白質之轉譯及產生。使用本揭示案之核酸，可在相關細胞株中進行轉染實驗，且可在轉染後之各個時間點對蛋白質產生進行分析。舉例而言，可利用不同ARE工程化分子轉染細胞，且藉由使用針對相關蛋白質之ELISA套組並分析在轉染後6小時、12小時、24小時、48小時及7天產生之蛋白質。

【0112】 3' UTR可為異源的或合成的。關於3' UTR，球蛋白UTR

(包括爪蟾β-球蛋白UTR及人類β-球蛋白UTR)為此項技術中所已知(8278063、9012219、US2011/0086907)。藉由自頭至尾選殖兩個連續人類β-球蛋白3'UTR，已開發出在一些細胞類型中具有增強的穩定性之經修飾之β-球蛋白構築體，且其為此項技術中所熟知(US2012/0195936、WO2014/071963)。另外，a2-球蛋白、a1-球蛋白、UTR及其突變體亦為此項技術中所已知(WO2015/101415、WO2015/024667)。在非專利文獻中之mRNA構築體中所描述之其他3' UTR包括CYBA (Ferizi等人，2015)及白蛋白(Thess等人，2015)。其他例示性3' UTR、包括牛或人類生長激素(野生型或經修飾)之3′ UTR (WO2013/185069、US2014/0206753、WO2014152774)、兔β球蛋白及B型肝炎病毒(HBV)之3' UTR、α-球蛋白3' UTR及病毒VEEV 3' UTR序列亦為此項技術中所已知。在一些實施例中，使用序列UUUGAAUU (WO2014/144196)。在一些實施例中，使用人類及小鼠核糖體蛋白質之3' UTR。其他實例包括rps9 3'UTR (WO2015/101414)、FIG4 (WO2015/101415)及人類白蛋白7 (WO2015/101415)。

【0113】 在一些實施例中，本揭示案之3' UTR包含選自SEQ ID NO: 4及SEQ ID NO: 37之序列。

【0114】 熟習此項技術者將理解，異源性或合成性5'UTR可與任一期望之3' UTR序列一起使用。舉例而言，異源性5'UTR可與合成性3'UTR及異源性3' UTR一起使用。

【0115】 非UTR序列亦可用作核酸內之區域或亞區。舉例而言，可將內含子或內含子序列之一部分併入至本揭示案核酸之區域中。併入內含子序列可增加蛋白質產生以及核酸水準。

【0116】 特徵之組合可包括在側接區域中且可含於其他特徵內。舉例而言，ORF可側接有5' UTR (其可含有強Kozak轉譯起始信號)及/或3' UTR (其可包括用於模板化添加聚A尾之寡(dT)序列)。5' UTR可包含來自相同及/或不同基因之第一多核苷酸片段及第二多核苷酸片段，諸如美國專利申請公開案第2010/0293625號及PCT/US2014/069155中所闡述之5' UTR，該等專利係以全文引用的方式併入本文中。

【0117】 應理解，來自任何基因之任何UTR均可併入至核酸之區域中。此外，可利用任何已知基因之多種野生型UTR。提供不為野生型區域變異體之人工UTR亦在本揭示案之範圍內。可將該等UTR或其部分以與在從中選擇其之轉錄本相同之定向放置，或可改變其定向或位置。因此，5′或3′ UTR可倒置、縮短、加長、用一或多個其他5′ UTR或3′ UTR製得。如本文所用，術語「經改變」在涉及UTR序列時，意指UTR相對於參照序列已以某種方式改變。舉例而言，3′ UTR或5′ UTR可如上文所教示藉由改變定向或位置而相對於野生型或天然UTR發生改變，或可藉由納入額外核苷酸、使核苷酸缺失、使核苷酸交換或轉座而發生改變。產生「經改變」UTR (無論3′抑或5′)之該等變化中之任一者構成變異體UTR。

【0118】 在一些實施例中，可使用雙、三或四UTR (諸如5′ UTR或3′ UTR)。如本文所用，「雙」UTR係兩個相同UTR拷貝串聯或實質上串聯編碼之UTR。舉例而言，可如美國專利公開案2010/0129877中所闡述使用雙β-球蛋白3′ UTR，該專利公開案之內容係以全文引用的方式併入本文中。

【0119】 模式化之UTR亦在本揭示案之範圍內。如本文所用，「模式化UTR」係反映重複或交替模式之彼等UTR，諸如重複一次、兩次或3

次以上之ABABAB或AABBAABBAABB或ABCABCABC或其變異體。在該等模式中，每一字母A、B或C代表核苷酸層面上之不同UTR。

【0120】 在一些實施例中，側接區域選自其蛋白質共有共同功能、結構、特徵或性質之轉錄本家族。舉例而言，所關注之多肽可屬於在特定細胞、組織中或有時在發育期間表現之蛋白質家族。可將來自該等基因中之任一者之UTR換成相同或不同蛋白質家族之任何其他UTR，以產生新的多核苷酸。如本文所用，「蛋白質家族」係以最廣泛意義使用，其指一組共有至少一種功能、結構、特徵、定位、起源或表現模式之兩種或更多種所關注多肽。

【0121】 非轉譯區亦可包括轉譯增強子元件(TEE)。作為非限制性實例，TEE可包括以全文引用方式併入本文中之美國申請案第2009/0226470號中所闡述之彼等TEE，及此項技術中已知之彼等TEE。

RNA之活體外轉錄

【0122】 可使用活體外轉錄(IVT)系統來轉錄編碼本文所闡述多核苷酸之cDNA。RNA之活體外轉錄為此項技術中所已知且闡述於國際公開案WO 2014/152027中，該公開案係以全文引用的方式併入本文中。在一些實施例中，本揭示案之RNA係根據WO 2018/053209及WO 2019/036682中所闡述方法中之任一或多者來製備，該等專利各自係以引用的方式併入本文中。

【0123】 在一些實施例中，使用未擴增之線性化DNA模板，在用以產生RNA轉錄本之活體外轉錄反應中來產生RNA轉錄本。在一些實施例中，模板DNA係經分離之DNA。在一些實施例中，模板DNA係cDNA。在一些實施例中，藉由RNA多核苷酸(例如(但不限於)冠狀病毒mRNA)之

反轉錄來形成cDNA。在一些實施例中，使細胞(例如細菌細胞，例如大腸桿菌(E. coli)，例如DH-1細胞)經質體DNA模板轉染。在一些實施例中，培養經轉染之細胞以複製質體DNA，接著將其分離並純化。在一些實施例中，DNA模板包括RNA聚合酶啟動子，例如位於所關注基因之5'且與其可操作地連接之T7啟動子。

【0124】在一些實施例中，活體外轉錄模板編碼5′非轉譯(UTR)區，含有開放閱讀框，且編碼3′ UTR及聚(A)尾。活體外轉錄模板之具體核酸序列組成及長度將取決於該模板所編碼之mRNA。

【0125】「5′非轉譯區」(UTR)係指位於起始密碼子(亦即由核糖體轉譯之mRNA轉錄本之第一個密碼子)正上游(亦即5')之不編碼多肽之mRNA區域。產生RNA轉錄本時，5′ UTR可包含啟動子序列。此等啟動子序列為此項技術中所已知。應理解，此等啟動子序列將不存在於本揭示案之疫苗中。

【0126】「3′非轉譯區」(UTR)係指位於終止密碼子(亦即mRNA轉錄本中發出終止轉譯信號之密碼子)正下游(亦即3')之不編碼多肽之mRNA區域。

【0127】「開放閱讀框」係以起始密碼子(例如甲硫胺酸(ATG))開始，且以終止密碼子(例如TAA、TAG或TGA)結束並編碼多肽之連續DNA區段。

【0128】「聚(A)尾」係位於3′ UTR下游(例如正下游(亦即3′))之含有多個連續單磷酸腺苷之mRNA區域。聚(A)尾可含有10至300個單磷酸腺苷。舉例而言，聚(A)尾可含有10、20、30、40、50、60、70、80、90、100、110、120、130、140、150、160、170、180、190、200、210、

220、230、240、250、260、270、280、290或300個單磷酸腺苷。在一些實施例中，聚(A)尾含有50至250個單磷酸腺苷。在相關生物學環境中(例如在細胞中、在活體內)，聚(A)尾起保護mRNA免受酶促降解(例如在細胞質中)之作用，且有助於轉錄終止及/或mRNA自細胞核之輸出及轉譯。

【0129】 在一些實施例中，核酸包括200至3,000個核苷酸。舉例而言，核酸可包括200至500、200至1000、200至1500、200至3000、500至1000、500至1500、500至2000、500至3000、1000至1500、1000至2000、1000至3000、1500至3000或2000至3000個核苷酸。

【0130】 活體外轉錄系統通常包含轉錄緩衝液、核苷酸三磷酸(NTP)、RNA酶抑制劑及聚合酶。

【0131】 NTP可在內部製造，可自供應商選擇，或可如本文所闡述進行合成。NTP可選自(但不限於)本文所闡述之彼等NTP，包括天然及非天然(經修飾) NTP。

【0132】 許多RNA聚合酶或變異體可用於本揭示案之方法中。聚合酶可選自(但不限於)噬菌體RNA聚合酶，例如T7 RNA聚合酶、T3 RNA聚合酶、SP6 RNA聚合酶及/或突變體聚合酶，諸如(但不限於)能夠併入經修飾核酸及/或經修飾核苷酸(包括經化學修飾之核酸及/或核苷酸)之聚合酶。一些實施例排除DNA酶之使用。

【0133】 在一些實施例中，經由酶促加帽使RNA轉錄本加帽。在一些實施例中，RNA包含5'末端帽，例如7mG(5')ppp(5')NlmpNp。

化學合成

【0134】 固相化學合成。本揭示案之核酸可使用固相技術全部或部

分地製造。核酸之固相化學合成係自動化方法，其中將分子固定在固體支持物上且在反應物溶液中逐步合成。固相合成可用於在核酸序列中位點特異性引入化學修飾。

【0135】 **液相化學合成**。藉由依序添加單體構建單元來合成本揭示案之核酸可在液相中進行。

【0136】 **合成方法之組合**。上文所論述之合成方法各自具有其自身之優點及侷限性。已嘗試將該等方法組合以克服侷限性。此等方法組合在本揭示案之範圍內。使用固相或液相化學合成與酶促連接之組合提供有效產生無法藉由單獨之化學合成獲得長鏈核酸之方式。

核酸區域或亞區之連接

【0137】 亦可使用藉由連接酶組裝核酸。DNA或RNA連接酶經由形成磷酸二酯鍵而促進多核苷酸鏈之5'及3'端之分子間連接。可藉由連接一或多個區域或亞區來製備諸如嵌合多核苷酸及/或環狀核酸等核酸。DNA片段可藉由連接酶催化之反應而接合，以產生具有不同功能之重組DNA。兩個寡去氧核苷酸(一個具有5'磷醯基且另一個具有游離3'羥基)用作DNA連接酶之受質。

純化

【0138】 本文所闡述核酸之純化可包括(但不限於)核酸清除、品質保證及品質控制。清除可藉由此項技術中已知之方法來實施，諸如(但不限於) AGENCOURT®珠粒(Beckman Coulter Genomics, Danvers, MA)、聚T珠粒、LNATM寡T捕獲探針(EXIQON® Inc, Vedbaek, Denmark)或基於HPLC之純化方法，諸如(但不限於)強陰離子交換HPLC、弱陰離子交換HPLC、反相HPLC (RP-HPLC)及疏水性相互作用HPLC (HIC-HPLC)。術

語「經純化」在關於核酸使用時(諸如「經純化之核酸」)係指與至少一種污染物分離之核酸。「污染物」係使另一物質不合格、不純或劣質之任何物質。因此，經純化之核酸(例如DNA及RNA)係以不同於其在自然界中所發現之形式或環境存在，或以不同於使其經受處理或純化方法之前所存在的形式或環境存在。

【0139】 可使用諸如(但不限於)凝膠電泳、UV吸光度或分析型HPLC等方法來進行品質保證及/或品質控制檢查。

【0140】 在一些實施例中，可藉由包括(但不限於)反轉錄酶-PCR等方法對核酸進行測序。

量化

【0141】 在一些實施例中，本揭示案之核酸可在外泌體中或在源自一或多種體液時進行量化。體液包括外周血、血清、血漿、腹水、尿液、腦脊髓液(CSF)、痰液、唾液、骨髓、滑液、水樣液、羊水、耵聹、母乳、支氣管肺泡灌洗液、精液、前列腺液、考珀液(cowper's fluid)或預射精液、汗液、糞便物、毛髮、淚液、囊腫液、胸膜及腹膜液、心包液、淋巴、食糜、乳糜、膽汁、間隙液、月經、膿、皮脂、嘔吐物、陰道分泌物、黏膜分泌物、糞便水、胰液、來自竇腔之灌洗液、支氣管肺抽吸物、胚泡腔液及臍帶血。或者，可自選自由以下組成之群之器官中獲取外泌體：肺、心臟、胰臟、胃、腸、膀胱、腎臟、卵巢、睪丸、皮膚、結腸、乳房、前列腺、腦、食管、肝臟及胎盤。

【0142】 可使用構築體特異性探針、細胞計數法、qRT-PCR、即時PCR、PCR、流式細胞術、電泳、質譜或其組合來實施分析，而外泌體可使用諸如酶聯免疫吸附分析(ELISA)方法等免疫組織化學方法來分離。外

泌體亦可藉由粒徑篩析層析、密度梯度離心、差速離心、奈米膜超濾、免疫吸收劑捕獲、親和純化、微流體分離或其組合來分離。

【0143】該等方法使得研究者能夠即時監測剩餘或遞送之核酸水準。此係可能的，此乃因在一些實施例中，本揭示案之核酸由於結構或化學修飾而與內源性形式不同。

【0144】在一些實施例中，可使用諸如(但不限於)紫外可見光譜法(UV/Vis)等方法對核酸進行量化。UV/Vis光譜儀之非限制性實例係NANODROP®光譜儀(ThermoFisher, Waltham, MA)。可對量化之核酸進行分析，以確定該核酸是否可具有適當大小，檢查有沒有發生核酸降解。可藉由諸如(但不限於)以下等方法來檢查核酸之降解：瓊脂糖凝膠電泳、基於HPLC之純化方法(諸如(但不限於)強陰離子交換HPLC、弱陰離子交換HPLC、反相HPLC (RP-HPLC)及疏水性相互作用HPLC (HIC-HPLC))、液相層析-質譜(LCMS)、毛細管電泳(CE)及毛細管凝膠電泳(CGE)。

脂質奈米顆粒(LNP)

【0145】在一些實施例中，將本揭示案之RNA (例如mRNA)調配在脂質奈米顆粒(LNP)中。脂質奈米顆粒通常包含可電離之陽離子脂質、非陽離子脂質、固醇及PEG脂質組分以及所關注之核酸負荷。可使用如此項技術中通常已知之組分、組合物及方法來產生本揭示案之脂質奈米顆粒，例如，參見PCT/US2016/052352；PCT/US2016/068300；PCT/US2017/037551；PCT/US2015/027400；PCT/US2016/047406；PCT/US2016000129；PCT/US2016/014280；PCT/US2016/014280；PCT/US2017/038426；PCT/US2014/027077；PCT/US2014/055394；

PCT/US2016/52117；PCT/US2012/069610；PCT/US2017/027492；PCT/US2016/059575及PCT/US2016/069491，所有其均係以全文引用的方式併入本文中。

【0146】 通常將本揭示案之疫苗調配在脂質奈米顆粒中。在一些實施例中，脂質奈米顆粒包含至少一種可電離之陽離子脂質、至少一種非陽離子脂質、至少一種固醇及/或至少一種聚乙二醇(PEG)修飾之脂質。

【0147】 在一些實施例中，脂質奈米顆粒包含20-60 mol%可電離之陽離子脂質。舉例而言，脂質奈米顆粒可包含20-50 mol%、20-40 mol%、20-30 mol%、30-60 mol%、30-50 mol%、30-40 mol%、40-60 mol%、40-50 mol%或50-60 mol%可電離之陽離子脂質。在一些實施例中，脂質奈米顆粒包含20 mol%、30 mol%、40 mol%、50 mol%或60 mol%可電離之陽離子脂質。

【0148】 在一些實施例中，脂質奈米顆粒包含5-25 mol%非陽離子脂質。舉例而言，脂質奈米顆粒可包含5-20 mol%、5-15 mol%、5-10 mol%、10-25 mol%、10-20 mol%、10-25 mol%、15-25 mol%、15-20 mol%或20-25 mol%非陽離子脂質。在一些實施例中，脂質奈米顆粒包含5 mol%、10 mol%、15 mol%、20 mol%或25 mol%非陽離子脂質。

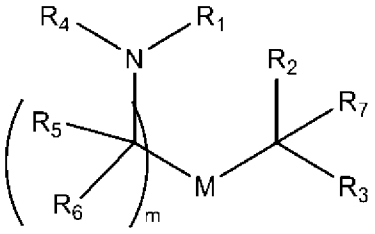
【0149】 在一些實施例中，脂質奈米顆粒包含25-55 mol%固醇。舉例而言，脂質奈米顆粒可包含25-50 mol%、25-45 mol%、25-40 mol%、25-35 mol%、25-30 mol%、30-55 mol%、30-50 mol%、30-45 mol%、30-40 mol%、30-35 mol%、35-55 mol%、35-50 mol%、35-45 mol%、35-40 mol%、40-55 mol%、40-50 mol%、40-45 mol%、45-55 mol%、45-50 mol%或50-55 mol%固醇。在一些實施例中，脂質奈米顆粒包含25

mol%、30 mol%、35 mol%、40 mol%、45 mol%、50 mol%或55 mol%固醇。

【0150】 在一些實施例中，脂質奈米顆粒包含0.5-15 mol% PEG修飾之脂質。舉例而言，脂質奈米顆粒可包含0.5-10 mol%、0.5-5 mol%、1-15 mol%、1-10 mol%、1-5 mol%、2-15 mol%、2-10 mol%、2-5 mol%、5-15 mol%、5-10 mol%或10-15 mol% PEG修飾之脂質。在一些實施例中，脂質奈米顆粒包含0.5 mol%、1 mol%、2 mol%、3 mol%、4 mol%、5 mol%、6 mol%、7 mol%、8 mol%、9 mol%、10 mol%、11 mol%、12 mol%、13 mol%、14 mol%或15 mol% PEG修飾之脂質。

【0151】 在一些實施例中，脂質奈米顆粒包含20-60 mol%可電離之陽離子脂質、5-25 mol%非陽離子脂質、25-55 mol%固醇及0.5-15 mol% PEG修飾之脂質。

【0152】 在一些實施例中，本揭示案之可電離之陽離子脂質包含式(I)化合物：



(I)，

或其鹽或異構物，其中：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4選自由以下組成之群：C_{3-6}碳環、-$(CH_2)_nQ$、-$(CH_2)_nCHQR$、-CHQR、-$CQ(R)_2$及未經取代之C_{1-6}烷基，其中Q選自碳環、雜環、-OR、-$O(CH_2)_nN(R)_2$、-C(O)OR、-OC(O)R、-CX_3、-CX_2H、-CXH_2、-CN、-$N(R)_2$、-$C(O)N(R)_2$、-N(R)C(O)R、-$N(R)S(O)_2R$、-$N(R)C(O)N(R)_2$、-$N(R)C(S)N(R)_2$、-$N(R)R_8$、-$O(CH_2)_nOR$、-$N(R)C(=NR_9)N(R)_2$、-$N(R)C(=CHR_9)N(R)_2$、-$OC(O)N(R)_2$、-$N(R)C(O)OR$、-N(OR)C(O)R、-$N(OR)S(O)_2R$、-N(OR)C(O)OR、-$N(OR)C(O)N(R)_2$、-$N(OR)C(S)N(R)_2$、-$N(OR)C(=NR_9)N(R)_2$、-$N(OR)C(=CHR_9)N(R)_2$、-$C(=NR_9)N(R)_2$、-$C(=NR_9)R$、-C(O)N(R)OR及-$C(R)N(R)_2C(O)OR$，且每一n獨立地選自1、2、3、4及5；

每一R_5獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R_6獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-N(R')C(O)-、-C(O)-、-C(S)-、-C(S)S-、-SC(S)-、-CH(OH)-、-P(O)(OR')O-、-$S(O)_2$-、-S-S-、芳基及雜芳基；

R_7選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

R_8選自由C_{3-6}碳環及雜環組成之群；

R_9選自由以下組成之群：H、CN、NO_2、C_{1-6}烷基、-OR、-$S(O)_2R$、-$S(O)_2N(R)_2$、C_{2-6}烯基、C_{3-6}碳環及雜環；

每一R獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R'獨立地選自由以下組成之群：C_{1-18}烷基、C_{2-18}烯基、-R*YR''、-YR''及H；

每一R''獨立地選自由C_{3-14}烷基及C_{3-14}烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{2-12}烯基組成之群；

每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13。

【0153】 在一些實施例中，式(I)化合物之子集包括如下之彼等化合物：當R_4係$-(CH_2)_nQ$、$-(CH_2)_nCHQR$、-CHQR或$-CQ(R)_2$時，則(i)在n為1、2、3、4或5時，Q不為$-N(R)_2$，或(ii)在n為1或2時，Q不為5員、6員或7員雜環烷基。

【0154】 在一些實施例中，式(I)化合物之另一子集包括如下之彼等化合物：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4選自由以下組成之群：C_{3-6}碳環、$-(CH_2)_nQ$、$-(CH_2)_nCHQR$、-CHQR、$-CQ(R)_2$及未經取代之C_{1-6}烷基，其中Q選自C_{3-6}碳環、具有一或多個選自N、O及S之雜原子之5員至14員雜芳基、-OR、$-O(CH_2)_nN(R)_2$、$-C(O)OR$、$-OC(O)R$、$-CX_3$、$-CX_2H$、$-CXH_2$、-CN、$-C(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)S(O)_2R$、$-N(R)C(O)N(R)_2$、$-N(R)C(S)N(R)_2$、$-CRN(R)_2C(O)OR$、$-N(R)R_8$、$-O(CH_2)_nOR$、$-N(R)C(=NR_9)N(R)_2$、$-N(R)C(=CHR_9)N(R)_2$、$-OC(O)N(R)_2$、$-N(R)C(O)OR$、$-N(OR)C(O)R$、$-N(OR)S(O)_2R$、$-N(OR)C(O)OR$、$-N(OR)C(O)N(R)_2$、-

$N(OR)C(S)N(R)_2$、$-N(OR)C(=NR_9)N(R)_2$、$-N(OR)C(=CHR_9)N(R)_2$、$-C(=NR_9)N(R)_2$、$-C(=NR_9)R$、$-C(O)N(R)OR$及具有一或多個選自N、O及S之雜原子之5員至14員雜環烷基，其經一或多個選自側氧基(=O)、OH、胺基、單-或二-烷基胺基及C_{1-3}烷基之取代基取代，且每一n獨立地選自1、2、3、4及5；

每一R_5獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R_6獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

M及M'獨立地選自$-C(O)O-$、$-OC(O)-$、$-C(O)N(R')-$、$-N(R')C(O)-$、$-C(O)-$、$-C(S)-$、$-C(S)S-$、$-SC(S)-$、$-CH(OH)-$、$-P(O)(OR')O-$、$-S(O)_2-$、-S-S-、芳基及雜芳基；

R_7選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

R_8選自由C_{3-6}碳環及雜環組成之群；

R_9選自由以下組成之群：H、CN、NO_2、C_{1-6}烷基、-OR、$-S(O)_2R$、$-S(O)_2N(R)_2$、C_{2-6}烯基、C_{3-6}碳環及雜環；

每一R獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R'獨立地選自由以下組成之群：C_{1-18}烷基、C_{2-18}烯基、$-R^*YR''$、$-YR''$及H；

每一R''獨立地選自由C_{3-14}烷基及C_{3-14}烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{2-12}烯基組成之群；

每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13，

或其鹽或異構物。

【0155】在一些實施例中，式(I)化合物之另一子集包括如下之彼等化合物：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4選自由以下組成之群：C_{3-6}碳環、$-(CH_2)_nQ$、$-(CH_2)_nCHQR$、-CHQR、$-CQ(R)_2$及未經取代之C_{1-6}烷基，其中Q選自C_{3-6}碳環、具有一或多個選自N、O及S之雜原子之5員至14員雜環、-OR、$-O(CH_2)_nN(R)_2$、-C(O)OR、-OC(O)R、$-CX_3$、$-CX_2H$、$-CXH_2$、-CN、$-C(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)S(O)_2R$、$-N(R)C(O)N(R)_2$、$-N(R)C(S)N(R)_2$、$-CRN(R)_2C(O)OR$、$-N(R)R_8$、$-O(CH_2)_nOR$、$-N(R)C(=NR_9)N(R)_2$、$-N(R)C(=CHR_9)N(R)_2$、$-OC(O)N(R)_2$、$-N(R)C(O)OR$、$-N(OR)C(O)R$、$-N(OR)S(O)_2R$、$-N(OR)C(O)OR$、$-N(OR)C(O)N(R)_2$、$-N(OR)C(S)N(R)_2$、$-N(OR)C(=NR_9)N(R)_2$、$-N(OR)C(=CHR_9)N(R)_2$、$-C(=NR_9)R$、-C(O)N(R)OR及$-C(=NR_9)N(R)_2$，且每一n獨立地選自1、2、3、4及5；且當Q係5員至14員雜環且(i) R_4係$-(CH_2)_nQ$，其中n係1或2，或(ii) R_4係$-(CH_2)_nCHQR$，其中n係1，或(iii) R_4係-CHQR及$-CQ(R)_2$時，則Q係5員至14員雜芳基或8員至14員雜環烷基；

每一R_5獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R_6獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-

N(R')C(O)-、-C(O)-、-C(S)-、-C(S)S-、-SC(S)-、-CH(OH)-、-P(O)(OR')O-、-$S(O)_2$-、-S-S-、芳基及雜芳基；

R_7選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

R_8選自由C_{3-6}碳環及雜環組成之群；

R_9選自由以下組成之群：H、CN、NO_2、C_{1-6}烷基、-OR、-$S(O)_2R$、-$S(O)_2N(R)_2$、C_{2-6}烯基、C_{3-6}碳環及雜環；

每一R獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R'獨立地選自由以下組成之群：C_{1-18}烷基、C_{2-18}烯基、-R*YR''、-YR''及H；

每一R''獨立地選自由C_{3-14}烷基及C_{3-14}烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{2-12}烯基組成之群；

每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13，

或其鹽或異構物。

【0156】在一些實施例中，式(I)化合物之另一子集包括如下之彼等化合物：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4選自由以下組成之群：C_{3-6}碳環、-$(CH_2)_nQ$、-$(CH_2)_nCHQR$、-

CHQR、-CQ(R)$_2$及未經取代之C$_{1-6}$烷基，其中Q選自C$_{3-6}$碳環、具有一或多個選自N、O及S之雜原子之5員至14員雜芳基、-OR、-O(CH$_2$)$_n$N(R)$_2$、-C(O)OR、-OC(O)R、-CX$_3$、-CX$_2$H、-CXH$_2$、-CN、-C(O)N(R)$_2$、-N(R)C(O)R、-N(R)S(O)$_2$R、-N(R)C(O)N(R)$_2$、-N(R)C(S)N(R)$_2$、-CRN(R)$_2$C(O)OR、-N(R)R$_8$、-O(CH$_2$)$_n$OR、-N(R)C(=NR$_9$)N(R)$_2$、-N(R)C(=CHR$_9$)N(R)$_2$、-OC(O)N(R)$_2$、-N(R)C(O)OR、-N(OR)C(O)R、-N(OR)S(O)$_2$R、-N(OR)C(O)OR、-N(OR)C(O)N(R)$_2$、-N(OR)C(S)N(R)$_2$、-N(OR)C(=NR$_9$)N(R)$_2$、-N(OR)C(=CHR$_9$)N(R)$_2$、-C(=NR$_9$)R、-C(O)N(R)OR及-C(=NR$_9$)N(R)$_2$，且每一n獨立地選自1、2、3、4及5；

每一R$_5$獨立地選自由以下組成之群：C$_{1-3}$烷基、C$_{2-3}$烯基及H；

每一R$_6$獨立地選自由以下組成之群：C$_{1-3}$烷基、C$_{2-3}$烯基及H；

M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-N(R')C(O)-、-C(O)-、-C(S)-、-C(S)S-、-SC(S)-、-CH(OH)-、-P(O)(OR')O-、-S(O)$_2$-、-S-S-、芳基及雜芳基；

R$_7$選自由以下組成之群：C$_{1-3}$烷基、C$_{2-3}$烯基及H；

R$_8$選自由C$_{3-6}$碳環及雜環組成之群；

R$_9$選自由以下組成之群：H、CN、NO$_2$、C$_{1-6}$烷基、-OR、-S(O)$_2$R、-S(O)$_2$N(R)$_2$、C$_{2-6}$烯基、C$_{3-6}$碳環及雜環；

每一R獨立地選自由以下組成之群：C$_{1-3}$烷基、C$_{2-3}$烯基及H；

每一R'獨立地選自由以下組成之群：C$_{1-18}$烷基、C$_{2-18}$烯基、-R*YR''、-YR''及H；

每一R''獨立地選自由C$_{3-14}$烷基及C$_{3-14}$烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{2-12}烯基組成之群；

每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13，

或其鹽或異構物。

【0157】 在一些實施例中，式(I)化合物之另一子集包括如下之彼等化合物：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：H、C_{2-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4係$-(CH_2)_nQ$或$-(CH_2)_nCHQR$，其中Q係$-N(R)_2$，且n選自3、4及5；

每一R_5獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R_6獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-N(R')C(O)-、-C(O)-、-C(S)-、-C(S)S-、-SC(S)-、-CH(OH)-、-P(O)(OR')O-、$-S(O)_2-$、-S-S-、芳基及雜芳基；

R_7選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R'獨立地選自由以下組成之群：C_{1-18}烷基、C_{2-18}烯基、-R*YR''、-YR''及H；

每一R''獨立地選自由C_{3-14}烷基及C_{3-14}烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{1-12}烯基組成之群；

每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13，

或其鹽或異構物。

【0158】 在一些實施例中，式(I)化合物之另一子集包括如下之彼等化合物：

R_1選自由以下組成之群：C_{5-30}烷基、C_{5-20}烯基、-R*YR''、-YR''及-R''M'R'；

R_2及R_3獨立地選自由以下組成之群：C_{1-14}烷基、C_{2-14}烯基、-R*YR''、-YR''及-R*OR''，或R_2及R_3與其所連接之原子一起形成雜環或碳環；

R_4選自由以下組成之群：$-(CH_2)_nQ$、$-(CH_2)_nCHQR$、-CHQR及$-CQ(R)_2$，其中Q係$-N(R)_2$，且n選自1、2、3、4及5；

每一R_5獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R_6獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-N(R')C(O)-、-C(O)-、-C(S)-、-C(S)S-、-SC(S)-、-CH(OH)-、-P(O)(OR')O-、$-S(O)_2-$、-S-S-、芳基及雜芳基；

R_7選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R獨立地選自由以下組成之群：C_{1-3}烷基、C_{2-3}烯基及H；

每一R'獨立地選自由以下組成之群：C_{1-18}烷基、C_{2-18}烯基、-

R*YR''、-YR''及H；

每一R''獨立地選自由C_{3-14}烷基及C_{3-14}烯基組成之群；

每一R*獨立地選自由C_{1-12}烷基及C_{1-12}烯基組成之群；

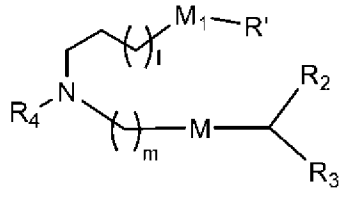
每一Y獨立地係C_{3-6}碳環；

每一X獨立地選自由以下組成之群：F、Cl、Br及I；且

m選自5、6、7、8、9、10、11、12及13，

或其鹽或異構物。

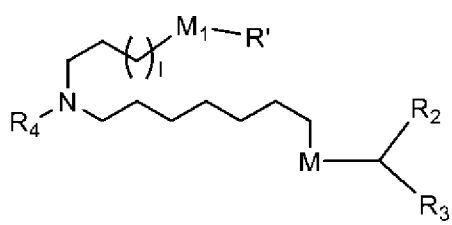
【0159】 在一些實施例中，式(I)化合物之子集包括式(IA)之彼等化合物：



(IA)，

或其鹽或異構物，其中l選自1、2、3、4及5；m選自5、6、7、8及9；M_1係鍵或M'；R_4係未經取代之C_{1-3}烷基或$-(CH_2)_nQ$，其中Q係OH、-NHC(S)N$(R)_2$、-NHC(O)N$(R)_2$、-N(R)C(O)R、-N(R)S$(O)_2$R、-N(R)R_8、-NHC(=NR_9)N$(R)_2$、-NHC(=CHR_9)N$(R)_2$、-OC(O)N$(R)_2$、-N(R)C(O)OR、雜芳基或雜環烷基；M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-P(O)(OR')O-、-S-S-、芳基及雜芳基；且R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基及C_{2-14}烯基。

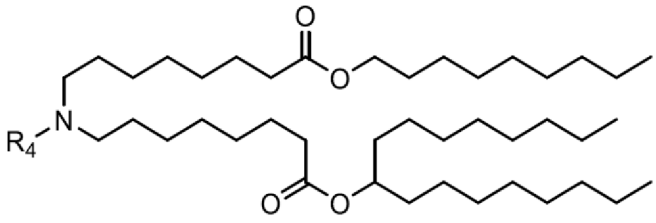
【0160】 在一些實施例中，式(I)化合物之子集包括式(II)之彼等化合物：



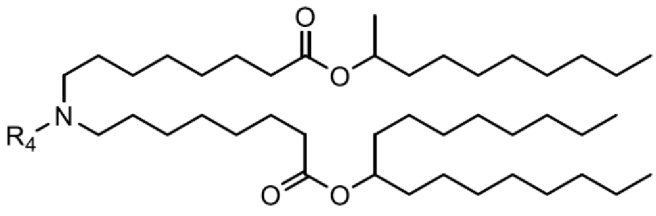
(II)或其鹽或異構物，其中l選自1、2、3、

4及5；M_1係鍵或M'；R_4係未經取代之C_{1-3}烷基或-$(CH_2)_nQ$，其中n係2、3或4，且Q係OH、-NHC(S)$N(R)_2$、-NHC(O)$N(R)_2$、-N(R)C(O)R、-N(R)$S(O)_2R$、-N(R)R_8、-NHC(=NR_9)$N(R)_2$、-NHC(=CHR_9)$N(R)_2$、-OC(O)$N(R)_2$、-N(R)C(O)OR、雜芳基或雜環烷基；M及M'獨立地選自-C(O)O-、-OC(O)-、-C(O)N(R')-、-P(O)(OR')O-、-S-S-、芳基及雜芳基；且R_2及R_3獨立地選自由以下組成之群：H、C_{1-14}烷基及C_{2-14}烯基。

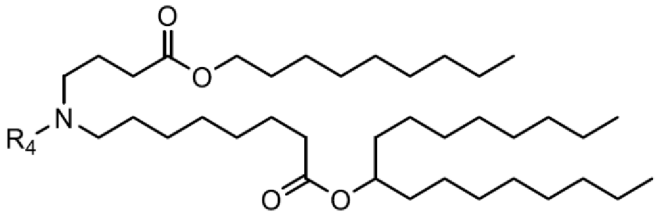
【0161】 在一些實施例中，式(I)化合物之子集包括式(IIa)、(IIb)、(IIc)或(IIe)之彼等化合物：



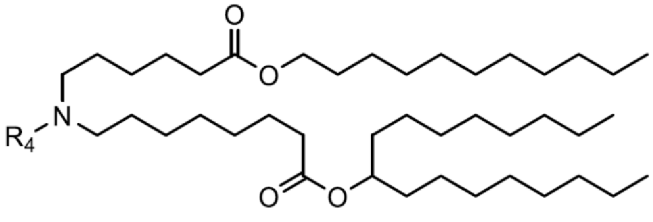
(IIa)、



(IIb)、



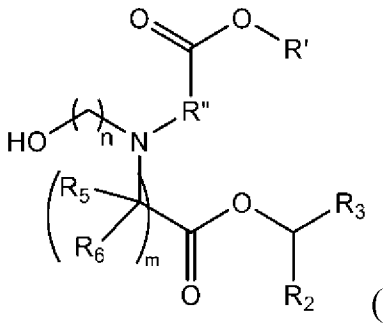
(IIc)或



(IIe)，

或其鹽或異構物，其中R_4係如本文所闡述。

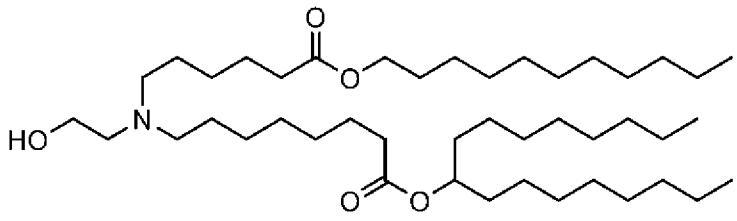
【0162】 在一些實施例中，式(I)化合物之子集包括式(IId)之彼等化合物：



(IId)，

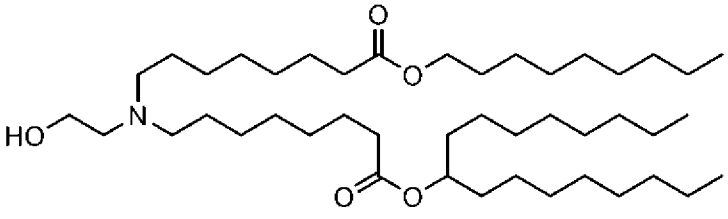
或其鹽或異構物，其中n係2、3或4；且m、R'、R''及R_2至R_6係如本文所闡述。舉例而言，R_2及R_3中之每一者可獨立地選自由C_{5-14}烷基及C_{5-14}烯基組成之群。

【0163】 在一些實施例中，本揭示案之可電離之陽離子脂質包含具有如下結構之化合物：



(化合物I)。

【0164】 在一些實施例中，本揭示案之可電離之陽離子脂質包含具有如下結構之化合物：



(化合物II)。

【0165】 在一些實施例中，本揭示案之非陽離子脂質包含1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)、1,2-二油醯基-sn-甘油-3-磷酸乙醇胺(DOPE)、1,2-二亞油醯基-sn-甘油-3-磷酸膽鹼(DLPC)、1,2-二肉豆蔻醯基-sn-甘油-磷酸膽鹼(DMPC)、1,2-二油醯基-sn-甘油-3-磷酸膽鹼(DOPC)、1,2-二棕櫚醯基-sn-甘油-3-磷酸膽鹼(DPPC)、1,2-二-十一醯基-sn-甘油-磷酸膽鹼(DUPC)、1-棕櫚醯基-2-油醯基-sn-甘油-3-磷酸膽鹼

(POPC)、1,2-二-O-十八烯基-sn-甘油-3-磷酸膽鹼(18:0二醚PC)、1-油醯基-2膽固醇基半琥珀醯基-sn-甘油-3-磷酸膽鹼(OChemsPC)、1-十六烷基-sn-甘油-3-磷酸膽鹼(C16 Lyso PC)、1,2-二亞麻醯基-sn-甘油-3-磷酸膽鹼、1,2-二花生四烯醯基-sn-甘油-3-磷酸膽鹼、1,2-二-二十二碳六烯醯基-sn-甘油-3-磷酸膽鹼、1,2-二植烷醯基-sn-甘油-3-磷酸乙醇胺(ME 16.0 PE)、1,2-二硬脂醯基-sn-甘油-3-磷酸乙醇胺、1,2-二亞油醯基-sn-甘油-3-磷酸乙醇胺、1,2-二亞麻醯基-sn-甘油-3-磷酸乙醇胺、1,2-二花生四烯醯基-sn-甘油-3-磷酸乙醇胺、1,2-二-二十二碳六烯醯基-sn-甘油-3-磷酸乙醇胺、1,2-二油醯基-sn-甘油-3-磷酸-外消旋-(1-甘油)鈉鹽(DOPG)、鞘磷脂及其混合物。

【0166】 在一些實施例中，本揭示案之PEG修飾之脂質包含PEG修飾之磷脂醯乙醇胺、PEG修飾之磷脂酸、PEG修飾之神經醯胺、PEG修飾之二烷基胺、PEG修飾之二醯基甘油、PEG修飾之二烷基甘油及其混合物。在一些實施例中，PEG修飾之脂質係DMG-PEG、PEG-c-DOMG (亦稱為PEG-DOMG)、PEG-DSG及/或PEG-DPG。

【0167】 在一些實施例中，本揭示案之固醇包含膽固醇、糞固醇、植固醇、麥角固醇、菜油固醇、豆固醇、菜子固醇、番茄鹼、熊果酸、α-生育酚及其混合物。

【0168】 在一些實施例中，本揭示案之LNP包含化合物1之可電離之陽離子脂質，其中非陽離子脂質係DSPC，結構脂質係膽固醇，且PEG脂質係DMG-PEG。

【0169】 在一些實施例中，脂質奈米顆粒包含45至55莫耳百分比(mol%)之可電離之陽離子脂質。舉例而言，脂質奈米顆粒可包含45

mol%、46 mol%、47 mol%、48 mol%、49 mol%、50 mol%、51 mol%、52 mol%、53 mol%、54 mol%或55 mol%可電離之陽離子脂質。

【0170】在一些實施例中，脂質奈米顆粒包含5 - 15 mol% DSPC。舉例而言，脂質奈米顆粒可包含5 mol%、6 mol%、7 mol%、8 mol%、9 mol%、10 mol%、11 mol%、12 mol%、13 mol%、14 mol%或15 mol% DSPC。

【0171】在一些實施例中，脂質奈米顆粒包含35 - 40 mol%膽固醇。舉例而言，脂質奈米顆粒可包含35 mol%、36 mol%、37 mol%、38 mol%、39 mol%或40 mol%膽固醇。

【0172】在一些實施例中，脂質奈米顆粒包含1 - 2 mol% DMG-PEG。舉例而言，脂質奈米顆粒可包含1 mol%、1.5 mol%或2 mol% DMG-PEG。

【0173】在一些實施例中，脂質奈米顆粒包含50 mol%可電離之陽離子脂質、10 mol% DSPC、38.5 mol%膽固醇及1.5 mol% DMG-PEG。

【0174】在一些實施例中，本揭示案之LNP包含約2:1至約30:1之N:P比率。

【0175】在一些實施例中，本揭示案之LNP包含約6:1之N:P比率。

【0176】在一些實施例中，本揭示案之LNP包含約3:1之N:P比率。

【0177】在一些實施例中，本揭示案之LNP包含約10:1至約100:1之可電離之陽離子脂質組分對RNA之wt/wt比率。

【0178】在一些實施例中，本揭示案之LNP包含約20:1之可電離之陽離子脂質組分對RNA之wt/wt比率。

【0179】在一些實施例中，本揭示案之LNP包含約10:1之可電離之

陽離子脂質組分對RNA之wt/wt比率。

【0180】 在一些實施例中，本揭示案之LNP之平均直徑為約50 nm至約150 nm。

【0181】 在一些實施例中，本揭示案之LNP之平均直徑為約70 nm至約120 nm。

多價疫苗

【0182】 如本文所提供之組合物可包括編碼相同或不同物種之兩種或更多種抗原之RNA或多種RNA。在一些實施例中，組合物包括編碼兩種或更多種冠狀病毒抗原之RNA或多種RNA。在一些實施例中，RNA可編碼1、2、3、4、5、6、7、8、9、10、11、12種或更多種冠狀病毒抗原。

【0183】 在一些實施例中，可將兩種或更多種編碼抗原之不同RNA(例如mRNA)調配在同一脂質奈米顆粒中。在其他實施例中，可將兩種或更多種編碼抗原之不同RNA調配在單獨脂質奈米顆粒中(每一RNA調配在單一脂質奈米顆粒中)。接著可將脂質奈米顆粒組合且以單一疫苗組合物形式(例如，包含編碼多種抗原之多種RNA)投與或可分開投與。

組合疫苗

【0184】 如本文所提供之組合物可包括編碼相同或不同病毒株之兩種或更多種抗原之RNA或多種RNA。本文亦提供組合疫苗，其包括編碼一或多種冠狀病毒及不同生物體之一或多種抗原之RNA。因此，本揭示案之疫苗可為靶向相同毒株/物種之一或多種抗原或不同毒株/物種之一或多種抗原之組合疫苗，該(等)抗原係例如誘導對在冠狀病毒感染風險高之同一地理區域中發現的生物體或個體在暴露於冠狀病毒時有可能暴露於其

的生物體之免疫性之抗原。

醫藥調配物

【0185】 本文提供用於預防或治療(例如)人類及其他哺乳動物中之冠狀病毒之組合物(例如醫藥組合物)、方法、套組及試劑。本文所提供之組合物可用作治療劑或預防劑。其可用於藥物中以預防及/或治療冠狀病毒感染。

【0186】 在一些實施例中，可將含有如本文所闡述之RNA之冠狀病毒疫苗投與給受試者(例如哺乳動物受試者，諸如人類受試者)，且RNA多核苷酸在活體內轉譯以產生抗原性多肽(抗原)。

【0187】 組合物(例如包含RNA)之「有效量」至少部分地基於靶組織、靶細胞類型、投與方式、RNA之物理特徵(例如長度、核苷酸組成及/或經修飾核苷之程度)、疫苗之其他組分及其他決定因素，諸如受試者之年齡、體重、身高、性別及一般健康狀況。通常，有效量之組合物提供經誘導或加強之免疫反應，其隨受試者細胞中之抗原產生而變化。在一些實施例中，有效量的含有具有至少一種化學修飾之RNA多核苷酸之組合物較含有編碼相同抗原或肽抗原之相應未經修飾之多核苷酸之組合物更有效。增加之抗原產生可藉由以下來證明：細胞轉染增加(經RNA疫苗轉染之細胞百分比)、自多核苷酸之蛋白質轉譯及/或表現增加、核酸降解減少(如(例如)藉由自經修飾之多核苷酸的蛋白質轉譯之持續時間延長所證明)或宿主細胞之抗原特異性免疫反應改變。

【0188】 術語「醫藥組合物」係指活性劑與惰性或活性載劑之組合，使得組合物尤其適於活體內或離體之診斷性或治療性用途。「醫藥學上可接受之載劑」在投與給受試者後或投與給受試者時不會引起不合意之

生理學效應。醫藥組合物中之載劑亦必須在與活性成分相容且可能夠使其穩定之意義上為「可接受的」。可利用一或多種增溶劑作為用於遞送活性劑之醫藥載劑。醫藥學上可接受之載劑之實例包括(但不限於)生物相容性媒劑、佐劑、添加劑及稀釋劑，以達成可用作劑型之組合物。其他載劑之實例包括膠體氧化矽、硬脂酸鎂、纖維素及月桂基硫酸鈉。其他適宜醫藥載劑及稀釋劑以及使用其之醫藥必需品闡述於Remington's Pharmaceutical Sciences中。

【0189】 在一些實施例中，本揭示案之組合物(包含多核苷酸及其編碼之多肽)可用於治療或預防冠狀病毒感染。組合物可作為主動免疫方案之一部分預防性地或治療性地投與給健康個體，或在感染早期之潛伏期期間或症狀發作後之活動性感染期間投與。在一些實施例中，向細胞、組織或受試者提供之RNA量可為有效用於免疫預防之量。

【0190】 組合物可與其他預防性或治療性化合物一起投與。作為非限制性實例，預防性或治療性化合物可為佐劑或加強劑。如本文所用，當提及預防性組合物(諸如疫苗)時，術語「加強劑」係指預防性(疫苗)組合物之額外投與。可在早期投與預防性組合物之後給予加強劑(或加強疫苗)。預防性組合物之初始投與與加強劑之間的投與時間可為(但不限於) 1分鐘、2分鐘、3分鐘、4分鐘、5分鐘、6分鐘、7分鐘、8分鐘、9分鐘、10分鐘、15分鐘、20分鐘、35分鐘、40分鐘、45分鐘、50分鐘、55分鐘、1小時、2小時、3小時、4小時、5小時、6小時、7小時、8小時、9小時、10小時、11小時、12小時、13小時、14小時、15小時、16小時、17小時、18小時、19小時、20小時、21小時、22小時、23小時、1天、36小時、2天、3天、4天、5天、6天、1週、10天、2週、3週、1個月、2個

月、3個月、4個月、5個月、6個月、7個月、8個月、9個月、10個月、11個月、1年、18個月、2年、3年、4年、5年、6年、7年、8年、9年、10年、11年、12年、13年、14年、15年、16年、17年、18年、19年、20年、25年、30年、35年、40年、45年、50年、55年、60年、65年、70年、75年、80年、85年、90年、95年或99年以上。在例示性實施例中，預防性組合物之初始投與與加強劑之間的投與時間可為(但不限於) 1週、2週、3週、1個月、2個月、3個月、6個月或1年。

【0191】 在一些實施例中，與此項技術中已知之不活化疫苗之投與類似，組合物可肌內、鼻內或真皮內投與。

【0192】 端視於感染之盛行率或未滿足醫療需求之程度或水準，組合物可用於各種環境中。作為非限制性實例，RNA疫苗可用於治療及/或預防多種傳染病。RNA疫苗具有優良性質，此乃因其產生顯著更大之抗體效價、更佳之中和免疫性、產生更持久之免疫反應及/或較市售疫苗更早地產生反應。

【0193】 本文提供醫藥組合物，其包括RNA及/或視情況與一或多種醫藥學上可接受之賦形劑組合之複合物。

【0194】 RNA可單獨或與一或多種其他組分聯合調配或投與。舉例而言，免疫組合物可包含其他組分，包括(但不限於)佐劑。

【0195】 在一些實施例中，免疫組合物不包括佐劑(其不含佐劑)。

【0196】 RNA可與一或多種醫藥學上可接受之賦形劑組合調配或投與。在一些實施例中，疫苗組合物包含至少一種額外活性物質，諸如治療活性物質、預防活性物質或二者之組合。疫苗組合物可為無菌的、無熱原的或既無菌又無熱原的。醫藥劑(諸如疫苗組合物)之調配及/或製造中之一

般考慮因素可參見(例如) Remington: The Science and Practice of Pharmacy，第21版，Lippincott Williams & Wilkins, 2005 (以全文引用的方式併入本文中)。

【0197】 在一些實施例中，將免疫組合物投與給人類、人類患者或受試者。出於本揭示案之目的，片語「活性成分」通常係指RNA疫苗或其中所含之多核苷酸，例如編碼抗原之RNA多核苷酸(例如mRNA多核苷酸)。

【0198】 本文所闡述疫苗組合物之調配物可藉由藥理學技術中已知或以後開發之任何方法來製備。一般而言，此等製備方法包括以下步驟：使活性成分(例如mRNA多核苷酸)與賦形劑及/或一或多種其他輔助成分締合，且接著視需要及/或期望，將產品分割、成型及/或包裝成期望單一或多劑量單元。

【0199】 本揭示案之醫藥組合物中之活性成分、醫藥學上可接受之賦形劑及/或任何其他成分之相對量將端視於所治療受試者之屬性(identity)、體型及/或狀況且進一步端視於擬投與組合物之途徑而變化。舉例而言，組合物可包含介於0.1%與100%之間、例如介於0.5%與50%之間、介於1%至30%之間、介於5%至80%之間、至少80% (w/w)之活性成分。

【0200】 在一些實施例中，使用一或多種賦形劑調配RNA，以：(1)增加穩定性；(2)增加細胞轉染；(3)允許持續或延遲釋放(例如自儲積調配物)；(4)改變生物分佈(例如靶向至特異性組織或細胞類型)；(5)增加所編碼蛋白質在活體內之轉譯；及/或(6)改變所編碼蛋白質(抗原)在活體內之釋放特徵。除傳統賦形劑(諸如任何及所有溶劑、分散介質、稀釋劑

或其他液體媒劑)以外，分散或懸浮助劑、表面活性劑、等滲劑、增稠或乳化劑、防腐劑、賦形劑可包括(但不限於)類脂質、脂質體、脂質奈米顆粒、聚合物、脂質複合物(lipoplex)、核心-殼體奈米顆粒、肽、蛋白質、經RNA轉染之細胞(例如用於移植至受試者中)、玻尿酸酶、奈米顆粒模擬物及其組合。

投藥/投與

【0201】 本文提供用於預防及/或治療人類及其他哺乳動物中之冠狀病毒感染之免疫組合物(例如RNA疫苗)、方法、套組及試劑。免疫組合物可用作治療劑或預防劑。在一些實施例中，免疫組合物用於提供針對冠狀病毒感染之預防性保護。在一些實施例中，免疫組合物用於治療冠狀病毒感染。在一些實施例中，免疫組合物用於啟動免疫效應細胞，例如使外周血單核細胞(PBMC)離體活化，接著將其輸注(再輸注)至受試者中。

【0202】 受試者可為任何哺乳動物，包括非人類靈長類動物及人類受試者。通常，受試者係人類受試者。

【0203】 在一些實施例中，將免疫組合物(例如RNA疫苗)以有效量投與給受試者(例如哺乳動物受試者，諸如人類受試者)，以誘導抗原特異性免疫反應。使編碼冠狀病毒抗原之RNA在活體內表現並轉譯以產生抗原，其隨後刺激受試者中之免疫反應。

【0204】 在投與本揭示案之免疫組合物(例如RNA疫苗)後，可達成針對冠狀病毒之預防性保護。可將免疫組合物投與一次、兩次、三次、四次或更多次，但有可能投與一次疫苗(視情況之後為單一加強劑)即為足夠的。儘管較不合意，但可將免疫組合物投與給受感染個體以達成治療性反應。可能需要相應地調整投藥。

【0205】 本揭示案之態樣中提供在受試者中引發針對冠狀病毒抗原(或多種抗原)之免疫反應之方法。在一些實施例中，方法涉及向受試者投與包含具有編碼冠狀病毒抗原之開放閱讀框的RNA (例如mRNA)之免疫組合物，藉此在該受試者中誘導特異性針對該冠狀病毒抗原之免疫反應，其中在疫苗接種後，該受試者中之抗抗原抗體效價相對於接種預防有效劑量的針對該抗原之傳統疫苗的受試者中之抗抗原抗體效價有所增加。「抗抗原抗體」係特異性地結合至抗原之血清抗體。

【0206】 預防有效劑量係以臨床上可接受之水準防止病毒感染之有效劑量。在一些實施例中，有效劑量係在疫苗之包裝插頁中所列示之劑量。如本文所用，傳統疫苗係指除本揭示案之mRNA疫苗以外之疫苗。舉例而言，傳統疫苗包括(但不限於)活微生物疫苗、殺滅之微生物疫苗、亞單位疫苗、蛋白質抗原疫苗、DNA疫苗、類病毒顆粒(VLP)疫苗等。在例示性實施例中，傳統疫苗係已取得監管批准及/或由國家藥品管理機構(例如美國食品藥品管理局(Food and Drug Administration, FDA)或歐洲藥物管理局(European Medicines Agency, EMA))註冊之疫苗。

【0207】 在一些實施例中，在疫苗接種後，受試者中之抗抗原抗體效價相對於接種預防有效劑量的針對冠狀病毒之傳統疫苗的受試者或未接種疫苗的受試者中之抗抗原抗體效價增加1 log至10 log。在一些實施例中，在疫苗接種後，受試者中之抗抗原抗體效價相對於接種預防有效劑量的針對冠狀病毒之傳統疫苗的受試者或未接種疫苗的受試者中之抗抗原抗體效價增加1 log、2 log、3 log、4 log、5 log或10 log。

【0208】 本揭示案之其他態樣中提供在受試者中引發針對冠狀病毒之免疫反應之方法。該方法涉及向受試者投與包含RNA多核苷酸(其包含

編碼冠狀病毒抗原之開放閱讀框)之免疫組合物(例如RNA疫苗)，藉此在該受試者中誘導特異性針對該冠狀病毒之免疫反應，其中該受試者中之免疫反應等效於以相對於該免疫組合物2倍至100倍之劑量水準接種針對冠狀病毒之傳統疫苗的受試者中之免疫反應。

【0209】 在一些實施例中，受試者中之免疫反應等效於以相對於本揭示案之免疫組合物兩倍之劑量水準接種傳統疫苗的受試者中之免疫反應。在一些實施例中，受試者中之免疫反應等效於以相對於本揭示案之免疫組合物三倍之劑量水準接種傳統疫苗的受試者中之免疫反應。在一些實施例中，受試者中之免疫反應等效於以相對於本揭示案之免疫組合物4倍、5倍、10倍、50倍或100倍之劑量水準接種傳統疫苗的受試者中之免疫反應。在一些實施例中，受試者中之免疫反應等效於以相對於本揭示案之免疫組合物10倍至1000倍之劑量水準接種傳統疫苗的受試者中之免疫反應。在一些實施例中，受試者中之免疫反應等效於以相對於本揭示案之免疫組合物100倍至1000倍之劑量水準接種傳統疫苗的受試者中之免疫反應。

【0210】 在其他實施例中，藉由測定受試者中之[蛋白質]抗體效價來評價免疫反應。在其他實施例中，測試來自經免疫受試者之血清或抗體能夠中和病毒攝取或減少人類B淋巴球之冠狀病毒轉型之能力。在其他實施例中，使用業內公認之技術量測促進強勁T細胞反應之能力。

【0211】 本揭示案之其他態樣提供在受試者中引發針對冠狀病毒之免疫反應之方法，其係藉由向該受試者投與包含具有編碼冠狀病毒抗原之開放閱讀框的RNA之免疫組合物(例如RNA疫苗)來實施，藉此在該受試者中誘導特異性針對該冠狀病毒抗原之免疫反應，其中相對於在接種預防有

效劑量的針對冠狀病毒之傳統疫苗的受試者中誘導之免疫反應，該受試者中之免疫反應提前誘導2天至10週。在一些實施例中，在以相對於本揭示案之免疫組合物2倍至100倍之劑量水準接種預防有效劑量之傳統疫苗的受試者中誘導出該受試者中之免疫反應。

【0212】 在一些實施例中，相對於在接種預防有效劑量的傳統疫苗之受試者中誘導之免疫反應，該受試者中之免疫反應提前誘導2天、3天、1週、2週、3週、5週或10週。

【0213】 本文亦提供在受試者中引發針對冠狀病毒之免疫反應之方法，其係藉由向該受試者投與具有編碼第一抗原之開放閱讀框之RNA來實施，其中該RNA不包括穩定元件，且其中佐劑不與疫苗共調配或共投與。

【0214】 免疫組合物(例如RNA疫苗)可藉由產生治療有效結果之任何途徑來投與。該等途徑包括(但不限於)真皮內、肌內、鼻內及/或皮下投與。本揭示案提供包括向有需要之受試者投與RNA疫苗之方法。所需之確切量將因受試者而異，此取決於受試者之物種、年齡及一般狀況、疾病之嚴重程度、具體組合物、其投與模式、其活性模式及諸如此類。通常以劑量單位形式調配RNA以便於投與及統一劑量。然而，將理解，RNA之總日用量可由主治醫師在合理的醫學判斷範圍內決定。用於任何特定患者之具體治療有效、預防有效或適當成像劑量水準將取決於多種因素，包括所治療之病症及病症之嚴重程度；所採用之具體化合物之活性；所採用之具體組合物；患者之年齡、體重、一般健康狀況、性別及飲食；所採用之具體化合物之投與時間、投與途徑及排泄速率；治療之持續時間；與所採用之具體化合物組合或同時使用之藥物；及醫學技術中所熟知之類似因

素。

【0215】 如本文所提供的RNA之有效量可低至20 μg，例如作為單一劑量或作為兩個10 μg劑量投與。在一些實施例中，有效量為20 μg-300 μg或25 μg-300 μg之總劑量。舉例而言，有效量可為20 μg、25 μg、30 μg、35 μg、40 μg、45 μg、50 μg、55 μg、60 μg、65 μg、70 μg、75 μg、80 μg、85 μg、90 μg、95 μg、100 μg、110 μg、120 μg、130 μg、140 μg、150 μg、160 μg、170 μg、180 μg、190 μg、200 μg、250 μg或300 μg之總劑量。在一些實施例中，有效量為20 μg之總劑量。在一些實施例中，有效量為25 μg之總劑量。在一些實施例中，有效量為75 μg之總劑量。在一些實施例中，有效量為150 μg之總劑量。在一些實施例中，有效量為300 μg之總劑量。

【0216】 可將本文所闡述之RNA調配成本文所闡述之劑型，諸如鼻內、氣管內或可注射的(例如靜脈內、眼內、玻璃體內、肌內、真皮內、心內、腹膜內及皮下)。

疫苗效能

【0217】 本揭示案之一些態樣提供免疫組合物(例如RNA疫苗)之調配物，其中RNA係以有效量調配，以在受試者中產生抗原特異性免疫反應(例如產生對冠狀病毒抗原具有特異性之抗體)。「有效量」係有效產生抗原特異性免疫反應之RNA劑量。本文亦提供在受試者中誘導抗原特異性免疫反應之方法。

【0218】 如本文所用，對本揭示案之疫苗或LNP之免疫反應係受試者對疫苗中所存在之(一或多種)冠狀病毒蛋白產生體液性及/或細胞性免疫反應。出於本揭示案之目的，「體液性」免疫反應係指由包括(例如)分泌

性(IgA)或IgG分子在內之抗體分子介導之免疫反應，而「細胞性」免疫反應係由T淋巴球(例如CD4+輔助性及/或CD8+ T細胞(例如CTL))及/或其他白血球介導之免疫反應。細胞免疫之一個重要態樣涉及細胞溶解性T細胞(CTL)之抗原特異性反應。CTL對與由主要組織相容性複合體(MHC)編碼之蛋白質一起呈遞並在細胞表面上表現之肽抗原具有特異性。CTL有助於誘導並促進細胞內微生物之破壞或感染此等微生物之細胞之溶解。細胞免疫之另一態樣涉及輔助性T細胞之抗原特異性反應。輔助性T細胞起幫助刺激功能之作用，且將非特異性效應細胞之活性集中於對抗在表面上展示與MHC分子締合之肽抗原之細胞。細胞性免疫反應亦導致產生細胞介素、趨化介素及由經活化之T細胞及/或其他白血球(包括源自CD4+及CD8+ T細胞之彼等細胞)產生的其他此類分子。

【0219】 在一些實施例中，藉由量測在投與如本文所提供之免疫組合物的受試者中所產生之抗冠狀病毒抗原抗體效價來表徵抗原特異性免疫反應。抗體效價係受試者體內抗體量之量度，該等抗體係例如對特定抗原或抗原之抗原決定基具有特異性之抗體。抗體效價通常表示為提供陽性結果之最大稀釋度之倒數。舉例而言，酶聯免疫吸附分析(ELISA)係用於測定抗體效價之常用分析。

【0220】 在一些實施例中，使用抗體效價來評價受試者是否已感染或確定是否需要實施免疫。在一些實施例中，使用抗體效價來確定自體免疫反應之強度、確定是否需要加強免疫、確定先前疫苗是否有效並鑑別任何近期或在前之感染。根據本揭示案，可使用抗體效價來確定免疫組合物(例如RNA疫苗)在受試者中所誘導之免疫反應之強度。

【0221】 在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體

效價相對於對照增加至少1 log。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照可增加至少1.5 log、至少2 log、至少2.5 log或至少3 log。在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照增加1 log、1.5 log、2 log、2.5 log或3 log。在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照增加1至3 log。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照可增加1至1.5 log、1至2 log、1至2.5 log、1至3 log、1.5至2 log、1.5至2.5 log、1.5至3 log、2至2.5 log、2至3 log或2.5至3 log。

【0222】 在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照為至少2倍。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照可為至少3倍、至少4倍、至少5倍、至少6倍、至少7倍、至少8倍、至少9倍或至少10倍。在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照為2倍、3倍、4倍、5倍、6倍、7倍、8倍、9倍或10倍。在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照為2至10倍。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照可為2至10倍、2至9倍、2至8倍、2至7倍、2至6倍、2至5倍、2至4倍、2至3倍、3至10倍、3至9倍、3至8倍、3至7倍、3至6倍、3至5倍、3至4倍、4至10倍、4至9倍、4至8倍、4至7倍、4至6倍、4至5倍、5至10倍、5至9倍、5至8倍、5至7倍、5至6倍、6至10倍、6至9倍、6至8倍、6至7倍、7至10倍、7至9倍、7至8倍、8至10倍、8至9倍或9至10倍。

【0223】 在一些實施例中，將抗原特異性免疫反應量測為血清中和抗體效價對冠狀病毒之幾何平均效價(GMT)比率，稱為幾何平均值比率

(GMR)。幾何平均效價(GMT)係一組受試者之平均抗體效價，其係藉由將所有值相乘並取該數值之*n*次方根來計算，其中*n*係具有可用數據之受試者數量。

【0224】 在一些實施例中，對照係未投與免疫組合物(例如RNA疫苗)之受試者中所產生之抗冠狀病毒抗原抗體效價。在一些實施例中，對照係投與重組或經純化蛋白質疫苗之受試者中所產生之抗冠狀病毒抗原抗體效價。重組蛋白質疫苗通常包括在異源表現系統(例如細菌或酵母)中產生或自大量致病性生物體純化之蛋白質抗原。

【0225】 在一些實施例中，在鼠類模型中量測免疫組合物(例如RNA疫苗)有效之能力。舉例而言，可將免疫組合物投與給鼠類模型且分析該鼠類模型對中和抗體效價之誘導。亦可使用病毒攻毒研究來評價本揭示案之疫苗之效能。舉例而言，可將免疫組合物投與給鼠類模型，利用病毒攻毒該鼠類模型，且分析該鼠類模型之存活及/或免疫反應(例如中和抗體反應、T細胞反應(例如細胞介素反應))。

【0226】 在一些實施例中，免疫組合物(例如RNA疫苗)之有效量係與重組蛋白質疫苗之照護標準劑量相比降低之劑量。如本文所提供之「照護標準」係指醫學或心理學治療指引，且可為一般性的或特定性的。「照護標準」指定基於科學證據及參與治療既定疾患之醫學專業人士之間的合作之適當治療。其係醫師/臨床醫師對某一類型之患者、疾病或臨床情況應遵循之診斷及治療過程。如本文所提供之「照護標準劑量」係指醫師/臨床醫師或其他醫學專業人士在遵循用於治療或預防冠狀病毒感染或相關疾患之照護標準指引的同時將投與給受試者以治療或預防冠狀病毒感染或相關疾患之重組或經純化蛋白質疫苗、或減毒活疫苗或不活化疫苗、或

VLP疫苗之劑量。

【0227】 在一些實施例中，投與有效量之免疫組合物的受試者中所產生之抗冠狀病毒抗原抗體效價等效於投與照護標準劑量之重組或經純化蛋白質疫苗、或減毒活疫苗或不活化疫苗、或VLP疫苗之對照受試者中所產生的抗冠狀病毒抗原抗體效價。

【0228】 可使用標準分析來評價疫苗效能(例如，參見Weinberg等人，J Infect Dis. 2010年6月1日;201(11):1607-10)。舉例而言，可藉由雙盲、隨機化之臨床對照試驗來量測疫苗效能。疫苗效能可表示為未接種疫苗(ARU)與接種疫苗(ARV)研究群組之間的疾病發作率(AR)之成比例降低，且可使用以下公式自接種疫苗組中之疾病相對風險(RR)進行計算：

效能= (ARU - ARV)/ARU × 100；及

效能= (1-RR) × 100。

【0229】 同樣，可使用標準分析來評價疫苗有效性(例如，參見Weinberg等人，J Infect Dis. 2010年6月1日;201(11):1607-10)。疫苗有效性係對疫苗(其可能已證明具有高疫苗效能)如何減少群體疾病之評價。此量度可評價疫苗接種計劃(不僅僅為疫苗自身)在自然現場條件下而非在受控臨床試驗中之益處與不良效應之淨平衡。疫苗有效性與疫苗效能(功效)成正比，但亦受群體中目標群組之免疫程度之影響，以及受影響住院、門診就診或費用之『現實世界』結果之其他非疫苗相關因素之影響。舉例而言，可使用回溯性病例對照分析，其中比較一組感染病例與適當對照之間的疫苗接種率。疫苗有效性可表示為率差，其中使用針對疫苗接種後發生感染之勝算比(OR)：

有效性= (1 - OR) × 100。

【0230】 在一些實施例中，相對於未接種疫苗之對照受試者，免疫組合物(例如RNA疫苗)之效能為至少60%。舉例而言，相對於未接種疫苗之對照受試者，免疫組合物之效能可為至少65%、至少70%、至少75%、至少80%、至少85%、至少95%、至少98%或100%。

【0231】 消除性免疫。消除性免疫係指防止有效病原體感染進入至宿主中之獨特免疫狀態。在一些實施例中，本揭示案之免疫組合物之有效量足以在受試者中提供至少1年之消除性免疫。舉例而言，本揭示案之免疫組合物之有效量足以在受試者中提供至少2年、至少3年、至少4年或至少5年之消除性免疫。在一些實施例中，本揭示案之免疫組合物之有效量足以在受試者中以相對於對照低至少5倍之劑量提供消除性免疫。舉例而言，有效量可足以在受試者中以相對於對照低至少10倍、低15倍或低20倍之劑量提供消除性免疫。

【0232】 可偵測抗原。在一些實施例中，如在投與後1-72小時在受試者血清中所量測，本揭示案之免疫組合物之有效量足以產生可偵測水準之冠狀病毒抗原。

【0233】 效價。抗體效價係受試者體內抗體量之量度，該等抗體係例如對特定抗原(例如抗冠狀病毒抗原)具有特異性之抗體。抗體效價通常表示為提供陽性結果之最大稀釋度之倒數。舉例而言，酶聯免疫吸附分析(ELISA)係用於測定抗體效價之常用分析。

【0234】 在一些實施例中，如在投與後1-72小時在受試者血清中所量測，本揭示案之免疫組合物之有效量足以產生1,000-10,000個中和抗體效價，該效價係由針對冠狀病毒抗原之中和抗體產生。在一些實施例中，如在投與後1-72小時在受試者血清中所量測，有效量足以產生1,000-

5,000個中和抗體效價，該效價係由針對冠狀病毒抗原之中和抗體產生。在一些實施例中，如在投與後1-72小時在受試者血清中所量測，有效量足以產生5,000-10,000個中和抗體效價，該效價係由針對冠狀病毒抗原之中和抗體產生。

【0235】 在一些實施例中，中和抗體效價為至少100 NT_{50}。舉例而言，中和抗體效價可為至少200、300、400、500、600、700、800、900或1000 NT_{50}。在一些實施例中，中和抗體效價為至少10,000 NT_{50}。

【0236】 在一些實施例中，中和抗體效價為至少100個中和單位/毫升(NU/mL)。舉例而言，中和抗體效價可為至少200 NU/mL、300 NU/mL、400 NU/mL、500 NU/mL、600 NU/mL、700 NU/mL、800 NU/mL、900 NU/mL或1000 NU/mL。在一些實施例中，中和抗體效價為至少10,000 NU/mL。

【0237】 在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照增加至少1 log。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照可增加至少2 log、3 log、4 log、5 log、6 log、7 log、8 log、9 log或10 log。

【0238】 在一些實施例中，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照為至少2倍。舉例而言，受試者中所產生之抗冠狀病毒抗原抗體效價相對於對照為至少3倍、4倍、5倍、6倍、7倍、8倍、9倍或10倍。

【0239】 在一些實施例中，通常使用幾何平均值(其係n個數之乘積之n次方根)來描述成比例增長。在一些實施例中，使用幾何平均值來表徵在受試者中產生之抗體效價。

【0240】 對照可為(例如)未接種疫苗之受試者，或投與減毒活病毒疫苗、不活化之病毒疫苗或蛋白質亞單位疫苗之受試者。

實例

實例1：nCoV活體外表現 - DNA

【0241】 此實驗中測試之構築體係與T7聚合酶質體共轉染之Norwood DNA，以使來自Norwood之2019-nCoV質體上之啟動子反式活化。使用SARS作為陽性對照DNA。分析條件如下：

DNA構築體：	SARS-CoV-2變異體6至10
細胞類型：	HEK293T細胞
板格式：	12孔，600,000個細胞/孔
每孔之DNA：	2.5 μg/孔(構築體:T7 =1:1)
培育時間：	24小時、72小時
細胞外染色：	單一色彩
儀器：	LSR Fortessa
ACE2-FLAG, His:	200 μg母液，10 μg/ml FACS濃度
抗FLAG-FITC：	1 mg，5 μg/ml FACS濃度

實例2：nCoV活體外表現 - mRNA

【0242】 測試實例1中構築體之mRNA。分析條件如下：

mRNA構築體：	SARS-CoV-2變異體6至10
細胞類型：	HEK293T細胞
板格式：	24孔，300,000個細胞/孔
每孔之mRNA：	0.5 μg，0.1 μg/孔
培育時間：	24小時、48小時

細胞外染色：　　單一色彩

儀器：　　LSR Fortessa

ACE2-FLAG, His:　　200 μg母液，10 μg/ml FACS濃度

抗FLAG-FITC：　　1 mg，5 μg/ml FACS濃度

【0243】 在所有構築體中，與其他低劑量之構築體相比，SARS-CoV-2變異體5顯示最佳表現。參見圖2及3。

實例3：免疫原性研究

【0244】 本研究經設計以測試候選冠狀病毒疫苗在小鼠及/或兔中之免疫原性，該等候選冠狀病毒疫苗包含**表1**中之編碼諸如SARS-CoV-2抗原等冠狀病毒抗原(例如刺突(S)蛋白、刺突蛋白之S1亞單元(S1)或刺突蛋白之S2亞單元(S2))之mRNA。

【0245】 在第0週及第3週經由靜脈內(IV)、肌內(IM)或真皮內(ID)途徑對動物接種疫苗。作為對照，一組保持不接種疫苗，且一組投與不活化之冠狀病毒。在第1週、第3週(投藥前)及第5週自每一動物收集血清。經由所有三個時間點之病毒中和分析測試個別出血之抗S、抗S1或抗S2活性，且使用不活化之冠狀病毒藉由西方墨點(Western blot)對僅來自第5週之合併樣品進行測試。

【0246】 在使用脂質奈米顆粒(LNP)調配物之實驗中，調配物可包括0.5-15% PEG修飾之脂質；5-25%非陽離子脂質；25-55%固醇；及20-60%可電離之陽離子脂質。舉例而言，PEG修飾之脂質可為1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，非陽離子脂質可為1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，固醇可為膽固醇；且可電離之陽離子脂質可具有化合物1之結構。

實例4：冠狀病毒攻毒

【0247】 本研究經設計以測試候選冠狀病毒疫苗在小鼠及/或兔中對抗冠狀病毒之致死性攻毒之效能，該等候選冠狀病毒疫苗包含**表1**中之編碼諸如SARS-CoV-2抗原等冠狀病毒抗原(例如刺突(S)蛋白、刺突蛋白之S1亞單元(S1)或刺突蛋白之S2亞單元(S2))之mRNA。動物經致死性劑量(10×LD90；約100個噬斑形成單位；PFU)之冠狀病毒攻毒。

【0248】 所用動物為6-8週齡之雌性動物，每組10隻。動物在第0週及第3週經由IM、ID或IV投與途徑接種疫苗。候選疫苗經化學修飾或未經修飾。測試動物血清之微量中和(參見實例14)。接著在第7週用約1 LD90之冠狀病毒經由IN、IM、ID或IV投與途徑攻毒動物。終點為感染後第13天、死亡或安樂死。對如藉由體重減輕>30%、極度嗜睡或癱瘓所確定的展示嚴重疾病之動物實施安樂死。每天評價並記錄體溫及體重。

實例5 - SARS-CoV-2變異體9在小鼠中之免疫原性(一個劑量)

【0249】 利用各種劑量的SARS-CoV-2變異體9 mRNA疫苗(「變異體9」)於50 μL 1× PBS中肌內注射至右後腿中對C3B6、C57/BL6及BALB/c小鼠實施免疫。免疫後兩週，收集血清且使其經受ELISA，以評價抗體與SARS-CoV-2穩定化之融合前刺突蛋白(SARS-CoV-2 pre-S)之結合。

【0250】 變異體9之資料示於圖4A至圖4B中。小鼠品系之間無顯著差異。如圖4A中所示，接受1 μg變異體9之C3B6小鼠較接受0.1 μg或0.01 μg劑量之C3B6小鼠具有顯著更高之抗體反應(p值 < 0.05)。圖4B顯示，接受10 μg變異體9之BALB/c小鼠較接受1 μg劑量(p值 < 0.05)或0.1 μg劑量(p值 < 0.0001)之BALB/c小鼠具有顯著更高之抗體反應。

【0251】如圖5A至圖5C中所示，以上文所闡述之方式測試其他mRNA候選者。圖5A展示，在投與一個劑量後，SARS-CoV-2變異體5 mRNA疫苗(「變異體5」)在C3B6及BALB/c小鼠中引發類似之抗體反應。與接受0.1 μg或0.01 μg劑量之BALB/c小鼠相比，接受1 μg變異體9或變異體5之BALB/c小鼠具有顯著更高之抗體反應(p值 < 0.05) (圖5B)。在0.1 μg下，變異體9對mRNA遞送之各種其他SARS-CoV-2疫苗抗原引發類似之反應。此外，在0.1 μg劑量下，SARS-CoV-2變異體8 mRNA疫苗(「變異體8」)及SARS-CoV-2變異體6 mRNA疫苗(「變異體6」)較可溶性刺突蛋白(S)序列引發顯著更高之抗體反應(* = p值 < 0.05；** = p值 < 0.01)。

時程性分析

【0252】利用藉由臨床代表性製程製造之各種劑量的變異體9於50 μL 1× PBS中肌內注射至右後腿中對BALB/c小鼠實施免疫。每兩週收集初免後血清且使其經受ELISA，以評價抗體與SARS-CoV-2穩定化之融合前刺突蛋白(SARS-CoV-2 pre-S)之結合。結果示於圖6中。每一符號代表幾何平均效價(GMT)且誤差槓指示幾何標準偏差(SD)。使用二因子ANOVA來比較隨時間及每一劑量而變之抗體反應。發現10 μg劑量之變異體9較所有其他劑量引發顯著更高之抗體反應(p值 < 0.0001)且在初免後4週內顯著衰減(p值 < 0.001)。

實例6 - 變異體9在小鼠中之免疫原性(兩個劑量)

小鼠品系之比較

【0253】在第0週及第3週，利用各種劑量的變異體9於50 μL 1× PBS中肌內注射至右後腿中對小鼠(BALB/c、C57BL/6及C3B6)實施免疫

(圖7)。在初免後及加強後兩週(例如第2週及第5週)，收集血清且使其經受ELISA，以評價抗體與SARS-CoV-2穩定化之融合前刺突蛋白(SARS-CoV-2 pre-S)之結合。

【0254】 結果示於圖8A至圖8C中。每一符號代表個別小鼠，條形代表幾何平均效價(GMT)，且誤差槓指示幾何標準偏差(SD)。使用二因子ANOVA來比較初免後及加強後之反應。在1 μg劑量下，用變異體9免疫之BALB/c (圖8A)及C57/BL6 (圖8B)小鼠在加強後具有顯著更高之抗體反應(p值 < 0.0001)。

SARS-CoV-2 mRNA疫苗構築體之比較

【0255】 在第0週及第3週，利用各種劑量的變異體9、變異體5或SARS-CoV-2野生型刺突蛋白mRNA於50 μL 1× PBS中肌內注射至右後腿中對小鼠(BALB/c及C3B6)實施免疫(圖7)。在初免後及加強後兩週(例如第2週及第5週)，收集血清且使其經受ELISA，以評價抗體與SARS-CoV-2穩定化之融合前刺突蛋白(SARS-CoV-2 pre-S)之結合。

【0256】 結果示於圖9A至圖9E中。每一符號代表個別小鼠，條形代表幾何平均效價(GMT)，且誤差槓指示幾何標準偏差(SD)。使用二因子ANOVA來比較初免後及加強後之反應。在1 μg劑量下，用變異體5及刺突野生型序列(S WT)免疫之小鼠在加強後具有顯著更高之抗體反應(p值 < 0.0001) (圖9A至圖9C)。此外，在1 μg劑量下，用變異體9免疫之BALB/c小鼠較用GMP備份序列(p值 < 0.01)及S WT (p值 < 0.05)免疫之小鼠具有顯著更高之抗體反應(圖9D)。在C3B6小鼠中，由任一構築體引發之抗體反應之間無顯著差異(圖9E)。對於所測試之所有三個序列，存在顯著之時程性反應(例如初免後劑量對加強後劑量)。

【0257】 對其他研究序列進行分析。在第0週及第3週，利用各種劑量的編碼變異體9或其他研究序列之mRNA於50 μL 1× PBS中肌內注射至右後腿中對BALB/c小鼠實施免疫(圖7)。在加強後兩週(例如第5週)，收集血清且使其經受ELISA，以評價抗體與SARS-CoV-2穩定化之融合前刺突蛋白(SARS-CoV-2 pre-S)之結合。

【0258】 結果示於圖10中。每一符號代表個別小鼠，條形代表幾何平均效價(GMT)，且誤差槓指示幾何標準偏差(SD)。使用單因子ANOVA來比較所有免疫原。用變異體8、變異體7及變異體6免疫之小鼠較用變異體9及S WT免疫之小鼠具有顯著更高之抗體效價(* = p值 < 0.05；** = p值 < 0.01；**** = p值 < 0.0001)。

實例7 - SARS-CoV-2 mRNA疫苗構築體之活體內表現

【0259】 向6-8週齡雌性BALB/c小鼠之每一後腿中肌內投與2 μg或10 μg之COVID-19構築體或Tris緩衝液(作為對照)。該等構築體包含於陽離子脂質奈米顆粒中之變異體9、10.7 mM乙酸鈉、8.7%蔗糖、20 mM Tris (pH 7.5)。測試三種構築體：變異體9、變異體5及變異體6。將構築體儲存在-70℃下(變異體9)或-20℃下(其他構築體)。一天後，收集脾及淋巴結以使用流式細胞術偵測蛋白質表現。

【0260】 圖11A至圖11B顯示使用5653-118 (「118」)抗體之結果，該抗體對SARS-CoV-1 S1子單元蛋白之N末端結構域具有特異性。所測試之所有構築體均具有良好表現，且觀察到表現呈劑量依賴性下降。在淋巴結(圖11A)及脾(圖11B)中，變異體5較任一其他構築體顯示顯著更高之表現(α = 0.05)。在較低劑量(2 μg)下，變異體9較變異體6具有顯著更高之表現(α = 0.05)。

【0261】 圖12A至圖12B顯示使用5652-109 (「109」)抗體之結果，該抗體對SARS-CoV-1 S蛋白之受體結合結構域具有特異性。所測試之所有構築體均具有良好表現，且觀察到表現呈劑量依賴性下降。在淋巴結或脾中，變異體9及變異體5在10 μg劑量下無顯著差異。在2 μg劑量下，在淋巴結(圖12A)及脾(圖12B)中，變異體9較另兩種構築體具有顯著更高之表現($\alpha = 0.05$)。

實例8 - SARS-CoV-2 mRNA疫苗構築體之活體外表現

【0262】 在活體外測試六種SARS-CoV-2 mRNA疫苗構築體。將HEK293t細胞平鋪(30,000個細胞/孔)於96孔板上。將200 ng構築體添加至每一孔中，且將板培育24小時。接著，將細胞用「118」抗體(稀釋度為1:100、1:300或1:600)、「109」抗體(稀釋度為1:100、1:300或1:600)或SARS-103 (結合來自SARS-CoV-1之RBD，稀釋度為1:100；作為對照)染色。接著利用抗人類FC AL647以1:500之稀釋度實施染色，且使用LSR Fortessa讀取樣品。結果示於圖13A至圖13C中。變異體9之結果提供於圖14中。

實例9 - 活體外功效分析開發

【0263】 開發分析以檢查不同構築體之功效。測試抗體，亦即118(對SARS-CoV-1 S1子單元之N末端結構域具有特異性)及109 (對SARS-CoV-1 S蛋白之受體結合結構域具有特異性)。如圖15中所示，在不同濃度及劑量下僅118抗體結合SARS-CoV-2抗原。

實例10 - SARS-CoV-2變異體9 mRNA疫苗小鼠免疫原性研究

【0264】 起始研究以評估低劑量之SARS-CoV-2變異體9 mRNA疫苗(「變異體9」)在BALB/c小鼠中之免疫原性及效能。在第0週及第3週向

BALB/c小鼠接種1 μg、0.1 μg或0.01 μg之變異體9。在第2週及第5週對穩定化之S-2P蛋白之結合抗體進行量化。在單一劑量後兩週，在接受1 μg變異體9之小鼠中，藉由ELISA量測存在大量之S-2P蛋白結合抗體(圖16A)。在接受1 μg或0.1 μg變異體9之小鼠中，第二劑量之變異體9顯著地增加結合抗體之水準(圖16A)。使用假型慢病毒報告子中和分析評價針對SARS-CoV-2之中和活性。與接受0.1 μg變異體9之小鼠相比，變異體9在1 μg劑量下引發顯著之中和活性(圖16B)。

【0265】 在第0週及第3週，利用1 μg或0.1 μg之變異體9、變異體5或不含2個脯胺酸突變之野生型(WT)對BALB/c小鼠實施免疫。在加強後兩週，收集血清且藉由針對同源性SARS-CoV-2之假型慢病毒報告子中和分析進行分析。在每一血清稀釋度下取一式三份之平均值，自相對螢光素酶單位(RLU)讀數生成S形曲線，且將未感染之細胞視為代表100%中和並將僅經病毒轉導之細胞視為代表0%中和，計算50% (IC_{50}) (圖21A、21C、21E、21G)及80% (IC_{80}) (圖21B、21D、21F、21H)中和活性。如圖21A至圖21F中所示，用1 μg SARS-CoV-2 S mRNA免疫之小鼠較用0.1 μg免疫之小鼠具有顯著更高之中和抗體反應(*** = p值 < 0.001，**** = p值 < 0.0001)。此外，用0.1 μg劑量免疫之小鼠不具有可偵測到之中和活性，此表明亞保護性抗體水準。此外，具有2P突變的穩定化之SARS-CoV-2 S (變異體5及變異體9)較WT S誘導更強效之IC_{50}中和活性(*p值 < 0.05)。納入天然S1/S2弗林蛋白酶(furin)裂解位點或用GS連接體替代弗林蛋白酶裂解位點以產生單鏈構築體對免疫原性不具有顯著效應(圖21G、圖21H)。

【0266】 在第0週及第3週，利用1 μg、0.1 μg或0.01 μg之變異體9

於50 μL 1× PBS中肌內注射至右後腿中對BALB/c小鼠實施免疫，且在第9週利用1 × 10^5 PFU之小鼠適應性SARS-CoV-2進行鼻內攻毒，該SARS-CoV-2在受體結合結構域中含有兩個靶向胺基酸變化以消除與小鼠ACE-2受體之衝突(關於時間表參見圖19)。在攻毒後第2天，對小鼠肺及鼻進行勻漿且藉由噬斑分析評價病毒負荷。一個肺葉(圖17A)及鼻甲(圖17B)中之噬斑形成單位顯示，1 μg劑量組受到完全保護，其中與對照組相比效價降低60倍。相比之下，未經免疫之攻毒小鼠之病毒負荷為約10^6 PFU/肺葉。觀察到如下劑量效應：0.1 μg變異體9劑量使肺病毒負荷降低大約2 log且0.01 μg變異體9劑量使肺病毒負荷降低大約0.5 log。

【0267】 在另一研究中，向小鼠一次性接種10 μg、1 μg或0.1 μg於50 μL 1× PBS中肌內注射至右後腿中之變異體9 (第0週)，且在第7週利用1×10^5 PFU之小鼠適應性SARS-CoV-2進行鼻內攻毒，該SARS-CoV-2在受體結合結構域中含有兩個靶向胺基酸變化以消除與小鼠ACE-2受體之衝突。在攻毒後第2天，對小鼠肺(圖18A)及鼻(圖18B)進行勻漿且藉由噬斑分析評價病毒負荷。如圖18A中可見，在攻毒後，10 μg劑量及1 μg劑量組受到完全保護免於肺中之病毒複製，其中與對照組相比效價降低60倍。體重百分比示於圖18C中。

【0268】 在另一研究中，在第0週及第4週向小鼠接種1 μg、0.1 μg或0.01 μg之變異體9，且在第7週利用小鼠適應性SARS-CoV-2進行攻毒，該SARS-CoV-2在受體結合結構域中含有兩個靶向胺基酸變化以消除與小鼠ACE-2受體之衝突。在攻毒後第二天，一個肺葉(圖20A)及鼻甲(圖20B)中之噬斑形成單位顯示，1 μg劑量組及0.1 μg劑量組受到完全保護，其中與對照組相比效價降低大約60倍。體重百分比示於圖20C中。

實例11 - SARS-CoV-2變異體9 mRNA疫苗與替代序列之比較

【0269】此實例提供關於利用替代性刺突抗原設計進行低劑量mRNA免疫後之結合及中和抗體反應之資料。利用0.1 μg編碼不同SARS-CoV-2 S-2P變異體之mRNA對BALB/c小鼠實施免疫。在第0週及第3週對小鼠實施兩次免疫。在加強後兩週，收集血清且藉由針對同源性SARS-CoV-2穩定刺突之摺疊競爭ELISA (圖22A)及假型慢病毒報告子中和分析(圖22B)進行分析。圖22A顯示血清終點結合效價，其係藉由在每一血清稀釋度下取一式兩份之平均值而得到，且計算為背景光學密度之4倍。此外，在每一血清稀釋度下取一式三份之平均值，自相對螢光素酶單位(RLU)讀數生成S形曲線，且將未感染之細胞視為代表100%中和並將僅經病毒轉導之細胞視為代表0%中和，計算50% (IC_{50})中和活性(圖22B)。另外，藉由斯皮爾曼關聯比較抗體結合及中和效價(圖22C)。已發現，編碼含有胞質尾區突變之序列之mRNA引發最強效之抗體反應。另外，在適用情況下，結合抗體效價與中和抗體效價之間存在強關聯性。

方法

SARS-CoV-2 ELISA

【0270】為量測抗體結合，實施ELISA。在4℃下將SARS-CoV-2 pre-S於100 μL 1× PBS中包覆至96孔Nunc MaxiSorp™平底板上(ThermoFisher，目錄號：44-2401-21)達16小時。將板用250 μL PBS-Tween (PBST) (Medicago AB，目錄號：09-9410-100)洗滌3次。為防止非特異性結合，用200 μL補充有5%脫脂乳(BD Difco™，目錄號：232100)之PBST (封阻緩衝液)將板在室溫(RT)下封阻1小時。將板用250 μL PBST洗滌3次。將血清連續稀釋(1:100，4倍，8次)於100 μL封阻緩衝

液中，且使其在室溫下以一式兩份與抗原結合1小時。將板用250 μL PBST洗滌3次。在室溫下添加100 mL於封阻緩衝液中稀釋的與HRP結合之山羊抗小鼠IgG (H+L)交叉吸附之二級抗體(ThermoFisher，目錄號：G-21040)達1小時。將板用250 μL PBST洗滌3次。利用100 μL KPL SureBlue 1-組分TMB微孔過氧化酶受質(Sure Blue，目錄號：5120-0077)使酶聯反應顯色10分鐘，且利用100 μL 1 N硫酸(ThermoFisher，目錄號：SA 212-1)終止。使用Spectramax Paradigm (Molecular Devices)來偵測OD_{450}。血清終點效價計算為非特異性二級抗體與抗原結合之4倍。

其他實施例

1. 一種核糖核酸(RNA)，其包含編碼冠狀病毒抗原之開放閱讀框(ORF)，該冠狀病毒抗原能夠誘導對SARS-CoV-2之免疫反應、諸如中和抗體反應，視情況其中該RNA調配在脂質奈米顆粒中。

2. 一種經化學修飾之核糖核酸(RNA)，其包含開放閱讀框(ORF)，該ORF包含與編碼SARS-CoV-2抗原之野生型RNA具有至少80%一致性之序列，視情況其中該RNA調配在脂質奈米顆粒中。

3. 一種密碼子最佳化之核糖核酸(RNA)，其包含開放閱讀框(ORF)，該ORF包含與編碼SARS-CoV-2抗原之野生型RNA具有至少80%一致性之序列，視情況其中該RNA調配在脂質奈米顆粒中。

4. 如段落2或3之RNA，其中由該野生型RNA編碼之該SARS-CoV-2抗原包含SEQ ID NO: 31之序列。

5. 一種核糖核酸(RNA)，其包含開放閱讀框(ORF)，該ORF包含與SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或

84中之任一者之序列具有至少80%一致性之序列。

6. 如段落5之RNA，其中該ORF包含與SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或84中之任一者之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

7. 如段落5或6之RNA，其進一步包含5' UTR，視情況其中該5' UTR包含SEQ ID NO: 2或SEQ ID NO: 36之序列。

8. 如前述段落中之任一段落之RNA，其進一步包含3' UTR，視情況其中該3' UTR包含SEQ ID NO: 4或SEQ ID NO: 37之序列。

9. 如前述段落中之任一段落之RNA，其進一步包含5'帽類似物、視情況7mG(5')ppp(5')NlmpNp帽。

10. 如前述段落中之任一段落之RNA，其進一步包含聚(A)尾，視情況長度為50至150個核苷酸。

11. 如段落5至10中之任一段落之RNA，其中該ORF編碼SARS-CoV-2抗原。

12. 如段落11之RNA，其中該冠狀病毒抗原係結構蛋白。

13. 如段落12之RNA，其中該結構蛋白係刺突蛋白。

14. 如段落11至13中之任一段落之RNA，其中該冠狀病毒抗原包含與SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83、或85中之任一者之序列具有至少80%一致性之序列。

15. 如段落14之RNA，其中該冠狀病毒抗原包含與SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、

63、65、67、69、71、73、75、77、79、81、83、或85中之任一者之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

16. 如段落1至13中之任一段落之RNA，其中該ORF包含SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、或84中之任一者之序列。

17. 如段落1至13中之任一段落之RNA，其中該RNA包含與SEQ ID NO: 1、6、9、12、15、18、21、24、27、30、51、53、55、57至58、60、或86至97中之任一者之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

18. 如段落1至13中之任一段落之RNA，其中該RNA包含SEQ ID NO: 1、6、9、12、15、18、21、24、27、30、51、53、55、57至58、60、或86至97中之任一者之序列。

19. 如前述段落中之任一段落之RNA，其中該RNA包含化學修飾且視情況經完全化學修飾。

20. 如段落19之RNA，其中該化學修飾係1-甲基假尿苷且視情況各尿苷是1-甲基假尿苷。

21. 如段落19之RNA，其中各尿苷是1-甲基假尿苷。

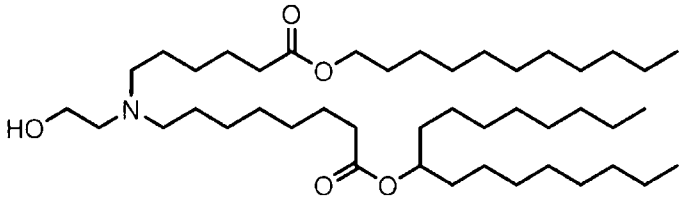
22. 如前述段落中之任一段落之RNA，其調配在脂質奈米顆粒中。

23. 如段落22之RNA，其中該脂質奈米顆粒包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

24. 如段落23之RNA，其中該脂質奈米顆粒包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60

mol%可電離之陽離子脂質。

25. 如段落24之RNA，其中該PEG修飾之脂質係1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，該非陽離子脂質係1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，該固醇係膽固醇；且該可電離之陽離子脂質具有化合物1之結構：



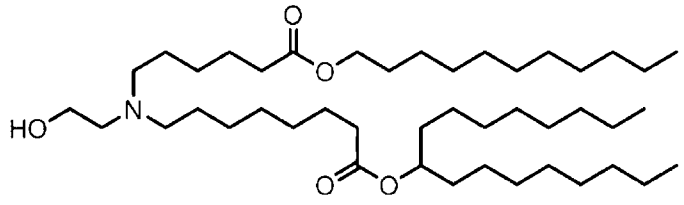
(化合物1)。

26. 一種組合物，其包含如段落1至21中之任一段落之RNA及脂質混合物。

27. 如段落26之組合物，其中該脂質混合物包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

28. 如段落27之組合物，其中該脂質混合物包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60 mol%可電離之陽離子脂質。

29. 如段落28之組合物，其中該PEG修飾之脂質係1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，該非陽離子脂質係1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，該固醇係膽固醇；且該可電離之陽離子脂質具有化合物1之結構：



(化合物1)。

30. 如段落26至29中之任一段落之組合物，其中該脂質混合物形成脂質奈米顆粒。

31. 如段落30之組合物，其中該RNA調配在該等脂質奈米顆粒中。

32. 如段落1至13中之任一段落之RNA，其中該ORF包含與SEQ ID NO: 28之序列具有至少80%、至少85%、至少90%、至少95%、至少98%或100%一致性之核苷酸序列。

33. 如段落1至13中之任一段落之RNA，其中該冠狀病毒抗原包含與SEQ ID NO: 29之序列具有至少80%、至少85%、至少90%、至少95%、至少98%或100%一致性之胺基酸序列。

33. 如段落1至13中之任一段落之RNA，其中該RNA包含與SEQ ID NO: 27之序列具有至少85%、至少90%、至少95%、至少98%或100%一致性之核苷酸序列。

34. 一種方法，其包括向受試者投與如前述段落中之任一段落之RNA或組合物，其量有效誘導該受試者中針對冠狀病毒之中和抗體反應。

35. 一種方法，其包括向受試者投與如前述段落中之任一段落之RNA或組合物，其量有效誘導該受試者中針對冠狀病毒之中和抗體反應及/或T細胞免疫反應、視情況$CD4^+$及/或$CD8^+$ T細胞免疫反應。

36. 如段落34及35之方法，其中該冠狀病毒係SARS-CoV-2。

37. 如前述段落中之任一段落之方法，其中該受試者係免疫受損的。

38. 如前述段落中之任一段落之方法，其中該受試者患有肺病。

39. 如前述段落中之任一段落之方法，其中該受試者為5歲或更小、或65歲或更大。

40. 如前述段落中之任一段落之方法，其包括向該受試者投與至少

兩個劑量之該組合物。

41. 如前述段落中之任一段落之方法，其中在投與該RNA或包含該RNA之組合物後1-72小時，在該受試者之血清中產生可偵測水準之該冠狀病毒抗原。

42. 如前述段落中之任一段落之方法，其中在投與該RNA或包含該RNA之組合物後1-72小時，在該受試者之血清中產生至少100 NU/ml、至少500 NU/ml或至少1000 NU/ml之中和抗體效價。

43. 一種免疫組合物，其包含：脂質奈米顆粒，其包含(a)信使RNA，其包含與SEQ ID NO: 28之序列具有至少90%、至少95%、至少98%或100%一致性之開放閱讀框(ORF)，及(b)脂質混合物，其包含0.5-15 mol% PEG修飾之脂質、5-25 mol%非陽離子脂質、25-55 mol%固醇及20-60 mol%可電離之陽離子脂質。

44. 一種免疫組合物，其包含：脂質奈米顆粒，其包含(a)信使RNA，其包含與SEQ ID NO: 27之序列具有至少90%、至少95%、至少98%或100%一致性之序列，及(b)脂質混合物，其包含0.5-15 mol% PEG修飾之脂質、5-25 mol%非陽離子脂質、25-55 mol%固醇及20-60 mol%可電離之陽離子脂質。

45. 一種免疫組合物，其包含：

(a) 第一核糖核酸(RNA)，其包含編碼能夠誘導對SARS-CoV-2之免疫反應、諸如中和抗體反應之冠狀病毒抗原之開放閱讀框(ORF)；及

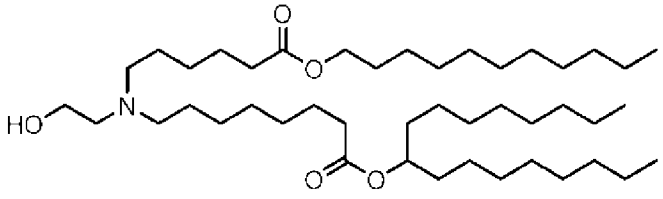
(b) 第二核糖核酸(RNA)，其包含編碼能夠誘導對SARS-CoV-2之免疫反應、諸如中和抗體反應之冠狀病毒抗原之開放閱讀框(ORF)，其中該第一RNA之ORF不同於該第二RNA之ORF。

46. 如段落45之免疫組合物，其進一步包含含有脂質混合物之脂質奈米顆粒。

47. 如段落46之免疫組合物，其中該脂質混合物包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

48. 如段落47之免疫組合物，其中該脂質混合物包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60 mol%可電離之陽離子脂質。

49. 如段落46或47之免疫組合物，其中該PEG修飾之脂質係1,2-二肉豆蔻醯基-sn-甘油，甲氧基聚乙二醇(PEG2000 DMG)，該非陽離子脂質係1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，該固醇係膽固醇，且該可電離之陽離子脂質具有化合物1之結構：



(化合物1)。

50. 如段落45至49中之任一段落之免疫組合物，其中由該第一RNA之ORF編碼之冠狀病毒抗原包含與SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83、及85中之任一者之胺基酸序列具有至少80%、至少85%、至少90%或至少95%一致性之胺基酸序列。

51. 如段落45至49中之任一段落之免疫組合物，其中該第一RNA之ORF包含與SEQ ID NO: 3、7、10、13、16、19、22、25、28、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、及84中之任一者之胺基酸序列具有至少80%、至少85%、至少90%或至少95%一致性之核苷酸序列。

52. 如段落1至13中之任一段落之RNA，其中該ORF編碼SARS-CoV-2抗原。

53. 如段落52之RNA，其中該SARS-CoV-2抗原係結構蛋白。

54. 如段落53之RNA，其中該結構蛋白選自由以下組成之群：刺突(S)蛋白、膜(M)蛋白、包膜(E)蛋白及(NC)核殼體蛋白。

55. 如段落54之RNA，其中該結構蛋白係S蛋白，視情況為S蛋白之穩定化融合前形式。

56. 如段落55之RNA，其中該S蛋白係S蛋白變異體，其相對於S蛋白包含SEQ ID NO: 32之胺基酸序列。

57. 如段落56之RNA，其中該S蛋白變異體包含多元裂解位點至一元裂解位點之回復。

58. 如段落56之RNA，其中該S蛋白變異體包含在該S蛋白變異體之羧基尾處多元ER/高基氏體(Golgi)信號序列(KXHXX-COOH)之缺失。

59. 如段落57至58中之任一段落之RNA，其中該S蛋白包含雙脯胺酸穩定性突變。

60. 如段落57至58中之任一段落之RNA，其中該S蛋白包含經修飾之蛋白酶裂解位點以使該蛋白質穩定。

61. 如段落57至60中之任一段落之RNA，其中該S蛋白包含胞質尾區之缺失。

62. 如段落57至61中之任一段落之RNA，其中該S蛋白包含摺疊子支架。

63. 如段落57之RNA，其中該S蛋白包含與SEQ ID NO: 5、8、11、14、17、20、23、26、29、32、33、34、35、47、49、59、63、

65、67、69、71、73、75、77、79、81、83、或85中之任一者之序列具有至少80%一致性之序列。

64. 如段落58之RNA，其中該結構蛋白係M蛋白。

65. 如段落64之RNA，其中該M蛋白包含與SEQ ID NO: 81之序列具有至少80%一致性之序列。

66. 如段落65之RNA，其中該M蛋白包含與SEQ ID NO:81之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

67. 如段落57至66中之任一段落之RNA，其中該ORF包含SEQ ID NO: 80之序列。

68. 如段落57至67中之任一段落之RNA，其中該RNA包含與SEQ ID NO: 95之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

69. 如段落68之RNA，其中該RNA包含SEQ ID NO: 95之序列。

70. 如段落54之RNA，其中該結構蛋白係E蛋白。

71. 如段落70之RNA，其中該E蛋白包含與SEQ ID NO: 83之序列具有至少80%一致性之序列。

72. 如段落71之RNA，其中該E蛋白包含與SEQ ID NO: 83之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

73. 如段落70至72中之任一段落之RNA，其中該ORF包含SEQ ID NO: 82之序列。

74. 如段落70至73中之任一段落之RNA，其中該RNA包含與SEQ ID NO: 96之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

75. 如段落74之RNA，其中該RNA包含SEQ ID NO: 96之序列。

76. 如段落54之RNA，其中該結構蛋白係NC蛋白。

77. 如段落76之RNA，其中該NC蛋白包含與SEQ ID NO: 85之序列具有至少80%一致性之序列。

78. 如段落77之RNA，其中該NC蛋白包含與SEQ ID NO: 85之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

79. 如段落76至78中之任一段落之RNA，其中該ORF包含SEQ ID NO: 84之序列。

80. 如段落76至78中之任一段落之RNA，其中該RNA包含與SEQ ID NO: 97之序列具有至少85%、至少90%、至少95%或至少98%一致性之序列。

81. 如段落80之RNA，其中該RNA包含SEQ ID NO: 97之序列。

82. 如段落53之RNA，其中該SARS-CoV-2抗原係融合蛋白。

83. 如段落82之RNA，其中該融合蛋白包含SARS-CoV-2多肽及來自不同病毒之多肽。

84. 一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 106之核苷酸序列具有至少80%一致性之核苷酸序列。

85. 一種信使核糖核酸(mRNA)，其包含與SEQ ID NO: 105之核苷酸序列具有至少80%一致性之核苷酸序列。

86. 一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 106之核苷酸序列具有至少95%一致性之核苷酸序列。

87　一種信使核糖核酸(mRNA)，其包含與SEQ ID NO: 105之核苷酸序列具有至少95%一致性之核苷酸序列。

88.　一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 106之核苷酸序列具有至少99%一致性之核苷酸序列。

89.　一種信使核糖核酸(mRNA)，其包含與SEQ ID NO: 105之核苷酸序列具有至少99%一致性之核苷酸序列。

序列表

【0271】 應理解，本文所闡述之任一mRNA序列可包括5' UTR及/或3' UTR。UTR序列可選自以下序列，或可使用其他已知UTR序列。亦應理解，本文所闡述之任一mRNA構築體可進一步包含聚(A)尾及/或帽(例如7mG(5')ppp(5')NlmpNp)。此外，儘管本文所闡述之許多mRNA及所編碼之抗原序列包括信號肽及/或肽標籤(例如C末端His標籤)，但應理解，所指示之信號肽及/或肽標籤可取代不同信號肽及/或肽標籤，或可省略信號肽及/或肽標籤。

5′ UTR: GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAGCCACC (SEQ ID NO: 36)

5′ UTR: GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGACCCCGGCGCCGCCACC (SEQ ID NO: 2)

3′ UTR: UGAUAAUAGGCUGGAGCCUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC (SEQ ID NO: 37)

3′ UTR: UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCCCCUUGGGCCUCCCCCCAGCC CCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC (SEQ ID NO: 4)

表1.

SARS-CoV-2刺突(S)蛋白		
SEQ ID NO: 30自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 31及3' UTR SEQ ID NO: 4。		30
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA	31

	ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACAAGG UGGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCC GGCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGA UCCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGC CACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCG GGUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUU UCCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUG ACCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCC CAGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGA GGGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGAC CCAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGAC AACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGC AUCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGC UGGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGA AUCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGG CAUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGA UCGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCU GAUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAU CAAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGG CCUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUG CAUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAG CUGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGA GCCCGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG	32

	STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGVKLHYT	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體1		
SEQ ID NO: 1自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 3及3' UTR SEQ ID NO: 4。		1
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUCUUCCUCGUCUUGCUGCCGCUGGUGUCGAGC CAGUGCGUGAACCUCACCACAAGGACGCAGCUCCCACCGG CCUACACGAACAGCUUCACGCGCGGCGUGUACUACCCCGA CAAGGUGUUCCGGUCGUCGGUCCUCCACUCCACGCAGGAC CUCUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCACG CCAUCCACGUCUCCGGGACGAACGGGACGAAGCGGUUCG ACAACCCGGUCCUCCCGUUCAACGACGGCGUCUACUUCGC GAGCACGGAGAAGUCGAACAUCAUCCGGGGCUGGAUCUU CGGCACGACCCUGGACUCGAAGACCCAGUCCCUACUUAUC GUGAACAACGCCACCAACGUCGUCAUCAAGGUCUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUCGGCGUCUACUACC ACAAGAACAACAAGUCGUGGAUGGAGUCGGAGUUCCGGG UGUACAGCUCGGCGAACAACUGCACCUUCGAGUACGUGU CGCAGCCGUUCCUCAUGGACCUCGAGGGCAAGCAGGGUA ACUUCAAGAACCUGCGCGAGUUCGUCUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACUCCAAGCACACGCCCAUCAA CCUGGUCCGCGACCUCCCGCAAGGCUUCUCCGCCCUCGAG CCUCUGGUCGACCUGCCGAUCGGCAUCAACAUCACGAGG UUCCAGACGCUCCUGGCGCUGCACCGGUCGUACCUGACGC CAGGCGACUCCUCCUCGGGCUGGACAGCAGGCGCGGCUGC CUACUACGUCGGGUACCUGCAGCCCCGCACGUUCCUCCUG AAGUACAACGAGAACGGCACUAUCACGGACGCCGUCGAC UGCGCCCUGGACCCACUGUCGGAGACGAAGUGCACGCUG AAGUCGUUCACCGUGGAGAAGGGUAUCUACCAGACCUCC AACUUCCGGGUCCAGCCGACGGAGUCGAUCGUGCGGUUC CCCAACAUCACGAACCUGUGCCCCUUCGGUGAGGUCUUCA ACGCCACCCGGUUCGCGUCGGUCUACGCGUGGAACCGUA AGCGCAUCUCGAACUGCGUGGCGGACUACUCCGUCCUCU ACAACAGCGCGUCCUUCAGCACCUUCAAGUGCUACGGCG UCAGCCCCACGAAGCUGAACGACCUCUGCUUCACCAACGU CUACGCAGACUCCUUCGUGAUCCGGGGUGACGAGGUGCG ACAGAUCGCCCCUGGUCAGACCGGGAAGAUCGCCGACUA	3

	CAACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCGUGGAACAGCAACAACCUGGACUCCAAGGUCGGAGGU AACUACAACUACCUCUACCGGCUGUUCCGCAAGUCCAACC UGAAGCCGUUCGAGCGGGACAUCUCCACGGAGAUCUACC AAGCCGGCUCGACCCCUUGUAACGGGGUGGAGGGGUUCA ACUGCUACUUCCCACUGCAGUCCUACGGGUUCCAGCCCAC CAACGGGGUCGGGUACCAGCCGUACCGCGUGGUGGUCCU GUCCUUCGAGCUGCUGCACGCGCCAGCCACGGUGUGCGG GCCAAAGAAGAGCACGAACCUGGUCAAGAACAAGUGCGU CAACUUCAACUUCAACGGCCUGACGGGGACAGGGGUCCU CACGGAGUCGAACAAGAAGUUCCUGCCGUUCCAGCAGUU CGGCCGUGACAUCGCAGACACGACUGACGCCGUCCGCGAC CCUCAGACCCUCGAGAUCCUCGACAUCACCCCGUGCUCGU UCGGCGGAGUGAGCGUCAUCACCCCGGGGACCAACACAU CGAACCAGGUGGCCGUCCUGUACCAGGACGUCAACUGCA CGGAGGUCCCUGUGGCGAUCCACGCCGACCAGCUCACGCC CACCUGGCGCGUCUACUCCACCGGGUCCAACGUGUUCCAG ACCCGCGCAGGCUGCCUGAUCGGGGCCGAGCACGUCAACA ACAGCUACGAGUGCGACAUCCCCAUCGGAGCGGGCAUCU GCGCCAGCUACCAGACGCAGACGAACUCUCCAAGGCGCGC UCGUAGCGUGGCCUCCCAGUCCAUCAUCGCGUACACGAU GUCCCUUGGGGCCGAGAACUCGGUCGCAUACAGCAACAA CUCCAUCGCCAUCCCCACCAACUUCACGAUCUCGGUCACC ACCGAGAUCCUCCCGGUCAGCAUGACGAAGACGUCGGUG GACUGCACCAUGUACAUCUGCGGGGACAGCACGGAGUGC UCGAACCUGCUCCUGCAGUACGGGAGCUUCUGCACCCAGC UGAACAGGGCGCUGACGGGGAUCGCGGUGGAGCAGGACA AGAACACCCAGGAGGUGUUCGCGCAGGUGAAGCAGAUCU ACAAGACGCCUCCAAUCAAGGACUUCGGCGGGUUCAACU UCUCGCAGAUCCUCCCCGACCCGUCCAAGCCGUCGAAGCG GUCGUUCAUCGAGGACCUGCUCUUCAACAAGGUGACGUU GGCCGACGCGGGCUUCAUCAAGCAGUACGGGGACUGCCU UGGGGACAUCGCUGCCCGCGACCUCAUCUGCGCCCAGAAG UUCAACGGGCUGACUGUGCUCCCGCCCCUGCUGACGGACG AGAUGAUCGCGCAGUACACGUCCGCGCUGCUCGCUGGAA CGAUCACCUCCGGGUGGACCUUCGGCGCUGGAGCGGCUC UGCAGAUCCCGUUCGCGAUGCAGAUGGCGUACCGGUUCA ACGGCAUCGGGGUGACCCAGAACGUCCUCUACGAGAACC AGAAGCUGAUCGCCAACCAGUUCAACUCCGCGAUCGGCA AGAUCCAGGACUCGCUGAGCUCCACGGCUUCCGCCCUCGG GAAGCUUCAGGACGUGGUGAACCAGAACGCCCAGGCCCU CAACACCCUGGUGAAGCAGCUGAGCUCGAACUUCGGCGC CAUCUCGAGCGUGCUCAACGACAUCCUGAGCCGUCUGGA CCCUCCCGAGGCGGAGGUGCAGAUCGACCGGCUCAUCACG GGCCGGCUUCAGUCCCUGCAGACGUACGUGACCCAGCAGC UCAUACGGGCGGCGGAGAUACGCGCCUCCGCCAACCUGGC CGCGACGAAGAUGUCCGAGUGCGUCCUCGGACAGAGCAA GCGCGUGGACUUCUGCGGCAAGGGGUACCACCUCAUGAG CUUUCCCCAGUCGGCUCCUCACGGGGUCGUCUUCCUGCAC GUGACGUACGUCCCGGCGCAGGAGAAGAACUUCACCACC GCCCCAGCGAUCUGCCACGACGGGAAGGCGCACUUCCCGC GCGAGGGCGUCUUCGUCUCCAACGGGACCCACUGGUUCG UCACCCAGCGGAACUUCUACGAGCCGCAGAUCAUCACGAC CGACAACACGUUCGUAUCCGGGAACUGCGACGUCGUCAU CGGCAUCGUCAACAACACGGUCUACGACCCACUGCAGCCG GAGCUGGACUCGUUCAAGGAGGAGCUGGACAAGUAUUUC AAGAACCACACCUCGCCCGACGUGGACCUGGGCGACAUCA GCGGGAUCAACGCGUCGGUCGUGAACAUCCAGAAGGAGA UCGACCGACUGAACGAGGUCGCCAAGAACCUGAACGAGU CCCUGAUCGACCUGCAAGAGCUCGGCAAGUACGAGCAGU ACAUCAAGUGGCCUUGGUACAUCUGGCUCGGCUUCAUCG CGGGGCUGAUCGCCAUCGUGAUGGUCACCAUCAUGUUGU	

	GCUGCAUGACCUCCUGCUGCUCGUGCCUCAAGGGGUGCU GCAGCUGCGGGUCCUGCUGCAAGUUCGACGAGGACGACU CGGAGCCGGUCCUCAAGGGCGUCAAGCUCCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGVKLHYT	5
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體2		
SEQ ID NO: 6自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 7及3' UTR SEQ ID NO: 4。		6
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCAGGACCCAGCUGCCGCCUG CCUACACCAACAGCUUCACCCGCGGUGUGUACUACCCCGA CAAGGUGUUCAGGUCCAGCGUGCUGCACAGCACCCAGGA CCUGUUCCUCCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACACUCGACAGCAAGACCCAGAGCCUGCUGAUC GUGAACAACGCCACCAACGUGGUGAUCAAGGUGUGCGAA UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGCG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA	7

	AUUUCAAGAACCUGAGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACGCCCAUCA ACCUGGUGCGGGACUUGCCCCAGGGCUUCAGCGCCCUGG AGCCCUUAGUGGACCUGCCUAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACU CCCGGCGACAGCAGCUCCGGGUGGACUGCCGGUGCUGCCG CCUACUACGUGGGGUACCUGCAGCCCCGGACCUUCCUGCU GAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGGA CUGCGCCCUGGAUCCACUGAGCGAGACCAAGUGCACCCUG AAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAGC AACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGAGGUUC CCCAACAUCACCAACCUGUGCCCUUUCGGCGAGGUGUUCA ACGCCACCCGCUUCGCCUCCGUGUACGCCUGGAACAGGAA GAGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGUA CAACAGCGCCAGCUUCUCCACCUUCAAGUGCUACGGCGUG AGCCCAACCAAGCUGAACGACCUGUGCUUUACCAACGUG UACGCCGAUAGCUUCGUGAUCCGCGGCGACGAAGUGCGG CAGAUCGCUCCUGGGCAGACCGGAAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGGUGCGUGAUC GCUUGGAACAGCAACAACCUGGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGCGACAUCUCCACCGAGAUCUACC AGGCCGGCUCCACACCCUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUUCCCCUGCAGUCCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCAUACCGCGUGGUGGUGCU GUCCUUCGAGCUGCUGCACGCUCCCGCCACCGUUUGCGGC CCCAAGAAGUCCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGUCUCACGGGCACCGGGGUGCUG ACCGAGAGCAACAAGAAGUUCCUGCCCUUUCAGCAGUUC GGCAGGGACAUCGCCGACACCACAGACGCCGUGCGGGAU CCCCAGACCCUGGAGAUCCUGGACAUCACCCCGUGCAGCU UCGGCGGCGUGAGCGUGAUCACGCCCGGCACCAACACCAG CAACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCAC CGAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACUCCC ACCUGGCGCGUGUAUAGCACCGGCAGCAACGUGUUCCAG ACACGGGCCGGCUGCCUGAUCGGCGCCGAGCACGUGAAC AACUCCUACGAGUGCGACAUCCCCAUCGGCGCUGGCAUCU GCGCCAGCUACCAGACCCAGACCAACAGCCCCAGACGGGC CAGGUCCGUGGCUUCCCAGAGCAUCAUCGCCUACACCAUG UCCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC UCCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUCCUGCCCGUGAGCAUGACCAAGACCUCCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACAGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACUCCACCUAUCAAGGACUUCGGCGGGUUCAACUU CAGCCAGAUCCUCCCCGACCCCUCCAAGCCCAGCAAGCGG AGCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUG GCUGACGCCGGCUUUAUCAAGCAGUACGGCGACUGCCUU GGCGACAUCGCCGCCAGGGACCUGAUCUGCGCCCAGAAG UUCAACGGCCUGACCGUGCUGCCGCCACUGCUGACCGACG AGAUGAUCGCCCAGUACACCUCUGCCCUGCUGGCCGGUAC CAUCACCUCCGGCUGGACAUUUGGUGCUGGCGCUGCGCU GCAGAUCCCCUUCGCCAUGCAGAUGGCCUACCGCUUCAAC GGCAUCGGGGUGACCCAGAACGUGCUGUACGAGAACCAG AAGCUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAG AUCCAGGACAGCCUGAGCAGCACCGCCAGCGCUCUGGGCA AGCUGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGA ACACCCUGGUGAAGCAGCUGUCCAGCAACUUCGGCGCCA UCAGCUCCGUGCUGAACGACAUCCUGAGCCGGCUGGAUC CACCAGAGGCCGAGGUGCAGAUCGACCGUCUGAUCACCG	

	GUCGGCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGC UGAUCCGCGCCGCCGAAAUCCGCGCCUCCGCCAACCUGGC CGCCACCAAGAUGUCCGAGUGCGUGCUGGGCCAGAGCAA GCGGGUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAG CUUCCCACAGAGCGCUCCCCACGGGGUAGUGUUCCUGCAC GUGACCUACGUGCCCGCCCAGGAGAAGAACUUCACCACU GCACCCGCCAUCUGCCACGACGGCAAGGCCCACUUCCCUC GGGAGGGCGUGUUCGUGAGCAACGGCACCCACUGGUUCG UGACCCAGAGGAACUUCUACGAGCCCCAGAUCAUCACCAC CGACAACACCUUCGUGUCCGGCAACUGCGACGUGGUGAU CGGCAUAGUGAACAACACCGUGUACGACCCACUGCAGCCC GAGCUGGACAGCUUCAAGGAGGAGCUGGACAAGUACUUC AAGAACCACACCAGCCCAGACGUGGACCUGGGCGACAUC UCCGGCAUCAACGCCUCCGUGGUGAACAUCCAGAAGGAG AUCGACCGGCUGAACGAGGUGGCCAAGAACCUGAACGAG AGCCUGAUCGACCUGCAGGAGCUGGGGAAGUACGAGCAG UACAUCAAGUGGCCUUGGUACAUCUGGCUGGGCUUCAUC GCCGGCCUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUG UGCUGCAUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGU UGCAGCUGCGGCAGCUGCUGCAAGUUCGACGAGGACGAC AGCGAGCCCGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGVKLHYT	8
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體3		
SEQ ID NO: 9自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 10及3' UTR SEQ ID NO: 4。		9

化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCGGCAGCGGC GGCAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA	10

	GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGGGCAGC GGCUACAUCCCCGAGGCCCCUAGAGACGGCCAGGCCUACG UGCGGAAGGACGGCGAGUGGGUGCUGCUGAGCACCUUCC UG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSGGSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM	11

	IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQGSGYIP EAPRDGQAYVRKDGEWVLLSTFL	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體4		
SEQ ID NO: 12自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 13及3' UTR SEQ ID NO: 4。		12
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG	13

	ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGGGCAGC GGCUACAUCCCCGAGGCCCCUAGAGACGGCCAGGCCUACG UGCGGAAGGACGGCGAGUGGGUGCUGCUGAGCACCUUCC UG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD	14

	LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQGSGYIP EAPRDGQAYVRKDGEWVLLSTFL	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體5		
SEQ ID NO: 15自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 16及3' UTR SEQ ID NO: 4。		15
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA	16

	AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCGGCAGCGGC GGCAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC	

	AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUC AAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGC CUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGC AUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGC UGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAG CCCGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSGGSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGVKLHYT	17
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體6		
SEQ ID NO: 18自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 19及3' UTR SEQ ID NO: 4。		18
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC	19

	GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC	

	AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUC AAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGC CUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIML	20
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體7		
SEQ ID NO: 21自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 22及3' UTR SEQ ID NO: 4。		21

化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC	22

	UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACAAGGUGGAG GCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUG CAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGG GCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCA AGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGG ACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCC AGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCU ACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGC CAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGC GUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAG CGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACA CCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCG UGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGG ACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUC ACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAU CAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCG GCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAU CGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAA GUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCU GAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGCAU GACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGCUG CGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAGCC CGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA	23

	QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGR LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFD EDDSEPVLKGVKLHYT	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體8		
SEQ ID NO: 24自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 25及3' UTR SEQ ID NO: 4。		24
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU	25

	GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACAAGG UGGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCC GGCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGA UCCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGC CACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCG GGUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUU UCCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUG ACCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCC CAGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGA GGGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGAC CCAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGAC AACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGC AUCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGC UGGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGA AUCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGG CAUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGA UCGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCU GAUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAU CAAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGG CCUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUG CAUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAG CUGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGA GCCCGUGCUGAAGGGCGUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4

相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGV	26
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體9		
SEQ ID NO: 27自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 28及3' UTR SEQ ID NO: 4。		27
化學	1-甲基假尿苷；SEQ ID NO: 105對應於包括5' UTR、mRNA ORF及3' UTR之經完全修飾之RNA序列；SEQ ID NO: 106對應於mRNA構築體之經完全修飾之ORF。	105 106
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG	28

	AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG	

	GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUC AAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGC CUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGC AUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGC UGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAG CCCGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDDSEPVLKGVKLHYT	29
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體10		
SEQ ID NO: 51自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 52及3' UTR SEQ ID NO: 4。		51
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA	2

	AGACCCCGGCGCCGCCACC	
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC	52

	AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACAAGG UGGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCC GGCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGA UCCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGC CACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCG GGUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUU UCCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUG ACCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCC CAGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGA GGGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGAC CCAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGAC AACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGC AUCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGC UGGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGA AUCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGG CAUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGA UCGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCU GAUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAU CAAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGG CCUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUG CAUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAG CUGCGGCAGCUGCUGCAAGUUCGACGAGGACGAC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG	33

	RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDD	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體11		
SEQ ID NO: 53自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 54及3' UTR SEQ ID NO: 4。		53
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC	54

	CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUC AAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGC CUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGC AUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGC UGCGGCAGCUGCUGCAAGUUCGACGAGGACGAC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA	34

	GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDD	
聚A尾	100 nt	
SARS-CoV-2 S蛋白變異體12		
SEQ ID NO: 55自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 56及3' UTR SEQ ID NO: 4。		55
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	UUUCAACGACGGCGUGUACUUCGCCAGCACCGAGAAGAG CAACAUCAUCCGGGGCUGGAUCUUCGGCACCACCCUGGAC AGCAAGACCCAGAGCCUGCUGAUCGUGAAUAACGCCACC AACGUGGUGAUCAAGGUGUGCGAGUUCCAGUUCUGCAAC GACCCCUUCCUGGGCGUGUACUACCACAAGAACAACAAG AGCUGGAUGGAGAGCGAGUUCCGGGUGUACAGCAGCGCC AACAACUGCACCUUCGAGUACGUGAGCCAGCCCUUCCUG AUGGACCUGGAGGGCAAGCAGGGCAACUUCAAGAACCUG CGGGAGUUCGUGUUCAAGAACAUCGACGGCUACUUCAAG AUCUACAGCAAGCACACCCCAAUCAACCUGGUGCGGGAU CUGCCCCAGGGCUUCUCAGCCCUGGAGCCCCUGGUGGACC UGCCCAUCGGCAUCAACAUCACCCGGUUCCAGACCCUGCU GGCCCUGCACCGGAGCUACCUGACCCCAGGCGACAGCAGC AGCGGGUGGACAGCAGGCGCGGCUGCUUACUACGUGGGC UACCUGCAGCCCCGGACCUUCCUGCUGAAGUACAACGAG AACGGCACCAUCACCGACGCCGUGGACUGCGCCCUGGACC CUCUGAGCGAGACCAAGUGCACCCUGAAGAGCUUCACCG UGGAGAAGGGCAUCUACCAGACCAGCAACUUCCGGGUGC AGCCCACCGAGAGCAUCGUGCGGUUCCCCAACAUCACCAA CCUGUGCCCCUUCGGCGAGGUGUUCAACGCCACCCGGUUC GCCAGCGUGUACGCCUGGAACCGGAAGCGGAUCAGCAAC UGCGUGGCCGACUACAGCGUGCUGUACAACAGCGCCAGC UUCAGCACCUUCAAGUGCUACGGCGUGAGCCCCACCAAGC UGAACGACCUGUGCUUCACCAACGUGUACGCCGACAGCU UCGUGAUCCGUGGCGACGAGGUGCGGCAGAUCGCACCCG GCCAGACAGGCAAGAUCGCCGACUACAACUACAAGCUGC CCGACGACUUCACCGGCUGCGUGAUCGCCUGGAACAGCA	56

	ACAACCUCGACAGCAAGGUGGGCGGCAACUACAACUACC UGUACCGGCUGUUCCGGAAGAGCAACCUGAAGCCCUUCG AGCGGGACAUCAGCACCGAGAUCUACCAAGCCGGCUCCAC CCCUUGCAACGGCGUGGAGGGCUUCAACUGCUACUUCCC UCUGCAGAGCUACGGCUUCCAGCCCACCAACGGCGUGGGC UACCAGCCCUACCGGGUGGUGGUGCUGAGCUUCGAGCUG CUGCACGCCCCAGCCACCGUGUGUGGCCCCAAGAAGAGCA CCAACCUGGUGAAGAACAAGUGCGUGAACUUCAACUUCA ACGGCCUUACCGGCACCGGCGUGCUGACCGAGAGCAACA AGAAAUUCCUGCCCUUUCAGCAGUUCGGCCGGGACAUCG CCGACACCACCGACGCUGUGCGGGAUCCCCAGACCCUGGA GAUCCUGGACAUCACCCCUUGCAGCUUCGGCGGCGUGAG CGUGAUCACCCCAGGCACCAACACCAGCAACCAGGUGGCC GUGCUGUACCAGGACGUGAACUGCACCGAGGUGCCCGUG GCCAUCCACGCCGACCAGCUGACACCCACCUGGCGGGUCU ACAGCACCGGCAGCAACGUGUUCCAGACCCGGGCCGGUU GCCUGAUCGGCGCCGAGCACGUGAACAACAGCUACGAGU GCGACAUCCCCAUCGGCGCCGGCAUCUGUGCCAGCUACCA GACCCAGACCAAUUCACCCGGCAGCGGCGGCAGCGUGGCC AGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGCGCCG AGAACAGCGUGGCCUACAGCAACAACAGCAUCGCCAUCCC CACCAACUUCACCAUCAGCGUGACCACCGAGAUUCUGCCC GUGAGCAUGACCAAGACCAGCGUGGACUGCACCAUGUAC AUCUGCGGCGACAGCACCGAGUGCAGCAACCUGCUGCUG CAGUACGGCAGCUUCUGCACCCAGCUGAACCGGGCCCUGA CCGGCAUCGCCGUGGAGCAGGACAAGAACACCCAGGAGG UGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCCUCCCA UCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAUCCUGC CCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUCGAGGA CCUGCUGUUCAACAAGGUGACCCUAGCCGACGCCGGCUUC AUCAAGCAGUACGGCGACUGCCUCGGCGACAUAGCCGCCC GGGACCUGAUCUGCGCCCAGAAGUUCAACGGCCUGACCG UGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGCCCAGUA CACCAGCGCCCUGUUAGCCGGAACCAUCACCAGCGGCUGG ACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCCUUCGCCA UGCAGAUGGCCUACCGGUUCAACGGCAUCGGCGUGACCC AGAACGUGCUGUACGAGAACCAGAAGCUGAUCGCCAACC AGUUCAACAGCGCCAUCGGCAAGAUCCAGGACAGCCUGA GCAGCACCGCUAGCGCCCUGGGCAAGCUGCAGGACGUGG UGAACCAGAACGCCCAGGCCCUGAACACCCUGGUGAAGC AGCUGAGCAGCAACUUCGGCGCCAUCAGCAGCGUGCUGA ACGACAUCCUGAGCCGGCUGGACCCUCCCGAGGCCGAGGU GCAGAUCGACCGGCUGAUCACUGGCCGGCUGCAGAGCCU GCAGACCUACGUGACCCAGCAGCUGAUCCGGGCCGCCGAG AUUCGGGCCAGCGCCAACCUGGCCGCCACCAAGAUGAGCG AGUGCGUGCUGGGCCAGAGCAAGCGGGUGGACUUCUGCG GCAAGGGCUACCACCUGAUGAGCUUUCCCCAGAGCGCACC CCACGGAGUGGUGUUCCUGCACGUGACCUACGUGCCCGCC CAGGAGAAGAACUUCACCACCGCCCCAGCCAUCUGCCACG ACGGCAAGGCCCACUUUCCCCGGGAGGGCGUGUUCGUGA GCAACGGCACCCACUGGUUCGUGACCCAGCGGAACUUCU ACGAGCCCCAGAUCAUCACCACCGACAACACCUUCGUGAG CGGCAACUGCGACGUGGUGAUCGGCAUCGUGAACAACAC CGUGUACGAUCCCCUGCAGCCCGAGCUGGACAGCUUCAA GGAGGAGCUGGACAAGUACUUCAAGAAUCACACCAGCCC CGACGUGGACCUGGGCGACAUCAGCGGCAUCAACGCCAG CGUGGUGAACAUCCAGAAGGAGAUCGAUCGGCUGAACGA GGUGGCCAAGAACCUGAACGAGAGCCUGAUCGACCUGCA GGAGCUGGGCAAGUACGAGCAGUACAUCAAGUGGCCCUG GUACAUCUGGCUGGGCUUCAUCGCCGGCCUGAUCGCCAU CGUGAUGGUGACCAUCAUGCUGUGCUGCAUGACCAGCUG CUGCAGCUGCCUGAAGGGCUGUUGCAGCUGCGGCAGCUG	

	CUGCAAGUUCGACGAGGACGAC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSGGSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF DEDD	35
聚A尾	100 nt	
WIV16 S蛋白變異體1		
SEQ ID NO: 57自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 48及3' UTR SEQ ID NO: 4。		57
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUUAUCUUCCUGUUCUUCCUGACCCUGACCAGCGGC AGCGACCUGGAAAGCUGCACCACCUUCGACGACGUGCAG GCCCCCAACUACCCUCAGCACAGCUCUAGCAGACGGGGCG UGUACUACCCCGACGAGAUCUUCAGAAGCGACACCCUGU ACCUGACCCAGGACCUGUUCCUGCCCUUCUACAGCAACGU GACCGGCUUCCACACCAUCAACCACAGAUUCGACAACCCC GUGAUCCCCUUCAAGGACGGGGUGUACUUUGCCGCCACC GAGAAGUCCAAUGUCGUGCGGGGAUGGGUGUUCGGCAGC ACCAUGAACAACAAGAGCCAGAGCGUGAUCAUCAUCAAC AACAGCACCAACGUCGUGAUCCGGGCCUGCAACUUCGAG CUGUGCGACAACCCAUUCUUCGCCGUGUCCAAGCCCACCG GCACCCAGACCCACACCAUGAUCUUCGACAACGCCUUCAA CUGCACCUUCGAGUACAUCAGCGACAGCUUCAGCCUGGA CGUGGCCGAGAAAAGCGGCAACUUCAAGCACCUGAGAGA AUUCGUGUUCAAGAACAAGGACGGCUUCCUGUACGUGUA CAAGGGCUACCAGCCCAUCGACGUCGUGCGCGAUCUGCCC	48

	AGCGGCUUCAACAUCCUGAAGCCCAUCUUCAAGCUGCCCC UGGGCAUCAACAUCACCAACUUCCGGGCUAUCCUGACCGC CUUCCUGCCCGCCCAGGAUACCUGGGGAACAAGCGCCGCU GCCUACUUCGUGGGCUACCUGAAGCCUGCCACCUUCAUGC UGAAGUACGACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCAGCCAGAAUCCUCUGGCCGAGCUGAAGUGCAGCG UGAAGUCCUUCGAGAUCGACAAGGGCAUCUACCAGACCA GCAACUUCAGAGUGGCCCCCAGCAAAGAAGUCGUGCGGU UCCCCAAUAUCACCAACCUGUGCCCCUUCGGCGAGGUGUU CAACGCCACCACCUUUCCCAGCGUGUACGCCUGGGAGCGG AAGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUG UACAACUCCACCAGCUUCUCCACCUUCAAGUGCUACGGCG UGUCCGCCACCAAGCUGAACGACCUGUGCUUCAGCAAUG UGUACGCCGACUCCUUCGUCGUGAAGGGCGACGAUGUGC GCCAGAUCGCCCCUGGACAGACAGGCGUGAUCGCCGAUU ACAACUACAAGCUGCCUGACGACUUCACCGGCUGCGUGC UGGCCUGGAACACCAGAAACAUCGACGCCACCCAGACAG GCAACUACAAUUACAAGUACAGAAGCCUGCGGCACGGCA AGCUGCGGCCCUUCGAGAGGGACAUCUCCAACGUGCCCU UCAGCCCCGACGGCAAGCCUUGUACCCCCCCUGCCUUUAA CUGCUACUGGCCCCUGAACGACUACGGCUUCUACAUCACA AACGGCAUCGGCUAUCAGCCCUACCGGGUGGUGGUGCUG UCCUUUGAGCUGCUGAAUGCCCCUGCCACCGUGUGCGGCC CUAAGCUGAGCACCGACCUGAUCAAGAACCAGUGCGUGA ACUUCAACUUCAACGGCCUGACCGGCACCGGCGUGCUGAC ACCUAGCAGCAAGAGAUUCCAGCCCUUCCAGCAGUUCGG CCGGGACGUGCUGGAUUUCACCGACAGCGUGCGGGACCC CAAGACCAGCGAGAUCCUGGACAUCAGCCCCUGCAGCUUC GGCGGAGUGUCCGUGAUCACCCCCGGCACCAAUACCAGCU CUGAGGUGGCCGUGCUGUAUCAGGACGUGAACUGCACCG AUGUGCCCGUGGCCAUCCACGCCGAUCAGCUGACCCCAUC UUGGCGGGUGUACUCCACCGGCAACAACGUGUUCCAGAC ACAAGCCGGCUGCCUGAUCGGAGCCGAGCACGUGGACAC CAGCUACGAGUGCGACAUCCCUAUCGGCGCUGGCAUCUG CGCCAGCUACCACACCGUGUCCAGCCUGAGAAGCACCAGC CAGAAAUCUAUCGUGGCCUACACCAUGAGCCUGGGCGCC GACAGCUCUAUCGCCUACUCCAACAACACAAUCGCCAUCC CCACCAAUUUCAGCAUCUCCAUCACCACCGAAGUGAUGCC CGUGUCCAUGGCCAAGACCUCCGUGGAUUGCAACAUGUA CAUCUGCGGCGACAGCACCGAGUGCGCCAACCUGCUGCUG CAGUACGGCAGCUUCUGCACCCAGCUGAACAGAGCCCUG AGCGGAAUCGCCGUGGAACAGGACAGAAACACCCGGGAA GUGUUCGCCCAAGUGAAGCAGAUGUAUAAGACCCCCACC CUGAAGGAUUUCGGCGGCUUUAACUUCAGCCAGAUCCUG CCCGACCCUCUGAAGCCUACCAAGCGGAGCUUCAUCGAGG ACCUGCUGUUCAACAAAGUGACCCUGGCCGACGCCGGCU UUAUGAAGCAGUAUGGCGAGUGCCUGGGCGACAUCAACG CCCGGGAUCUGAUCUGCGCCCAGAAGUUUAACGGACUGA CCGUGCUGCCCCCUCUGCUGACCGACGAUAUGAUCGCCGC CUACACAGCCGCCCUGGUGUCUGGCACAGCUACCGCCGGA UGGACAUUUGGAGCUGGCGCCGCUCUGCAGAUCCCCUUU GCCAUGCAGAUGGCCUACCGGUUCAAUGGCAUCGGCGUG ACCCAGAAUGUGCUGUACGAGAACCAGAAGCAGAUCGCC AACCAGUUCAACAAGGCCAUUAGCCAGAUUCAGGAAAGC CUGACCACCACCAGCACCGCCCUGGGCAAACUGCAGGACG UCGUGAACCAGAACGCCCAGGCCCUGAACACCCUCGUGAA GCAGCUGAGCAGCAAUUUCGGCGCCAUCAGCUCCGUGCU GAACGAUAUCCUGAGCAGACUGGACAAGGUGGAAGCAGA GGUGCAGAUCGACCGGCUGAUCACCGGCAGACUGCAGAG CCUGCAGACCUACGUGACACAGCAGCUGAUUAGAGCCGC CGAGAUCAGGGCCAGCGCCAAUCUGGCCGCCACAAAGAU GAGCGAGUGUGUGCUGGGCCAGAGCAAGCGGGUGGACUU	

	CUGCGGCAAGGGCUAUCACCUGAUGAGCUUCCCCCAGGCC GCUCCUCACGGCGUGGUGUUUCUGCACGUGACAUACGUG CCCAGCCAGGAACGGAACUUCACCACCGCCCCAGCCAUCU GCCACGAGGGCAAGGCCUACUUCCCCCGGGAAGGCGUGU UCGUGUUUAACGGCACCUCCUGGUUUAUCACCCAGCGGA AUUUCUUCAGUCCGCAGAUCAUCACCACAGACAACACCU UCGUGUCCGGCAGCUGCGACGUCGUGAUUGGCAUCAUUA ACAACACCGUGUACGACCCCCUGCAGCCCGAGCUGGACAG CUUCAAAGAGGAACUGGACAAGUACUUCAAGAACCACAC CUCCCCCGACGUGGACCUGGGCGAUAUCUCCGGCAUCAAU GCCAGCGUCGUGAAUAUCCAGAAAGAGAUCGAUCGCCUG AACGAGGUGGCCAAGAACCUGAAUGAGAGCCUGAUCGAC CUGCAGGAACUGGGGAAGUACGAGCAGUACAUCAAGUGG CCUUGGUACGUGUGGCUGGGCUUUAUCGCCGGCCUGAUC GCCAUCGUGAUGGUCACCAUCCUGCUGUGCUGCAUGACC AGCUGUUGCAGCUGUCUGAAGGGCGCCUGCAGCUGUGGC UCCUGCUGCAAGUUCGAUGAGGACGACAGCGAGCCUGUG CUGAAAGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFIFLFFLTLTSGSDLESCTTFDDVQAPNYPQHSSSRRGVYYPD EIFRSDTLYLTQDLFLPFYSNVTGFHTINHRFDNPVIPFKDGVYF AATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFEL CDNPFFAVSKPTGTQTHTMIFDNAFNCTFEYISDSFSLDVAEKS GNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGFNILKPI FKLPLGINITNFRAILTAFLPAQDTWGTSAAAYFVGYLKPATFM LKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGIYQTSNFRV APSKEVVRFPNITNLCPFGEVFNATTFPSVYAWERKRISNCVAD YSVLYNSTSFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDD VRQIAPGQTGVIADYNYKLPDDFTGCVLAWNTRNIDATQTGN YNYKYRSLRHGKLRPFERDISNVPFSPDGKPCTPPAFNCYWPL NDYGFYITNGIGYQPYRVVVLSFELLNAPATVCGPKLSTDLIKN QCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDVLDFTDSVRDP KTSEILDISPCSFGGVSVITPGTNTSSEVAVLYQDVNCTDVPVAI HADQLTPSWRVYSTGNNVFQTQAGCLIGAEHVDTSYECDIPIG AGICASYHTVSSLRSTSQKSIVAYTMSLGADSSIAYSNNTIAIPT NFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSF CTQLNRALSGIAVEQDRNTREVFAQVKQMYKTPTLKDFGGFN FSQILPDPLKPTKRSFIEDLLFNKVTLADAGFMKQYGECLGDIN ARDLICAQKFNGLTVLPPLLTDDMIAAYTAALVSGTATAGWTF GAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQIANQFNKA ISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAIS SVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEI RASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHG VVFLHVTYVPSQERNFTTAPAICHEGKAYFPREGVFVFNGTSW FITQRNFFSPQIITTDNTFVSGSCDVVIGIINNTVYDPLQPELDSF KEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAK NLNESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMVTILL CCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT	47
聚A尾	100 nt	
WIV16 S蛋白變異體2		
SEQ ID NO: 58自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 50及3' UTR SEQ ID NO: 4。		58
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2

mRNA構築體之ORF (不包括終止密碼子)	AUGUUCAUCUUCCUGUUCUUCCUGACCCUGACCAGCGGC AGCGACCUGGAGAGCUGCACCACCUUCGACGACGUGCAG GCCCCUAACUACCCUCAGCACAGCAGCAGCAGAAGAGGCG UGUACUACCCUGACGAGAUCUUCAGAAGCGACACCCUGU ACCUGACCCAGGACCUGUUCCUGCCUUUCUACAGCAACGU GACCGGCUUCCACACCAUCAACCACAGAUUCGACAACCCU GUGAUCCCUUUCAAGGACGGCGUGUACUUCGCCGCCACC GAGAAGAGCAACGUGGUGAGAGGCUGGGUGUUCGGCAGC ACCAUGAACAACAAGAGCCAGAGCGUGAUCAUCAUCAAC AACAGCACCAACGUGGUGAUCAGAGCCUGCAACUUCGAG CUGUGCGACAACCCUUUCUUCGCCGUGAGCAAGCCUACCG GCACCCAGACCCACACCAUGAUCUUCGACAACGCCUUCAA CUGCACCUUCGAGUACAUCAGCGACAGCUUCAGCCUGGA CGUGGCCGAGAAGAGCGGCAACUUCAAGCACCUGAGAGA GUUCGUGUUCAAGAACAAGGACGGCUUCCUGUACGUGUA CAAGGGCUACCAGCCUAUCGACGUGGUGAGAGACCUGCC UAGCGGCUUCAACAUCCUGAAGCCUAUCUUCAAGCUGCC UCUGGGCAUCAACAUCACCAACUUCAGAGCCAUCCUGACC GCCUUCCUGCCUGCCCAGGACACCUGGGGCACCAGCGCCG CCGCCUACUUCGUGGGCUACCUGAAGCCUGCCACCUUCAU GCUGAAGUACGACGAGAACGGCACCAUCACCGACGCCGU GGACUGCAGCCAGAACCCUCUGGCCGAGCUGAAGUGCAG CGUGAAGAGCUUCGAGAUCGACAAGGGCAUCUACCAGAC CAGCAACUUCAGAGUGGCCCCUAGCAAGGAGGUGGUGAG AUUCCCUAACAUCACCAACCUGUGCCCUUUCGGCGAGGU GUUCAACGCCACCACCUUCCCUAGCGUGUACGCCUGGGAG AGAAAGAGAAUCAGCAACUGCGUGGCCGACUACAGCGUG CUGUACAACAGCACCAGCUUCAGCACCUUCAAGUGCUAC GGCGUGAGCGCCACCAAGCUGAACGACCUGUGCUUCAGC AACGUGUACGCCGACAGCUUCGUGGUGAAGGGCGACGAC GUGAGACAGAUCGCCCCUGGCCAGACCGGCGUGAUCGCC GACUACAACUACAAGCUGCCUGACGACUUCACCGGCUGC GUGCUGGCCUGGAACACCAGAAACAUCGACGCCACCCAG ACCGGCAACUACAACUACAAGUACAGAAGCCUGAGACAC GGCAAGCUGAGACCUUUCGAGAGAGACAUCAGCAACGUG CCUUUCAGCCCUGACGGCAAGCCUUGCACCCCUCCUGCCU UCAACUGCUACUGGCCUCUGAACGACUACGGCUUCUACA UCACCAACGGCAUCGGCUACCAGCCUUACAGAGUGGUGG UGCUGAGCUUCGAGCUGCUGAACGCCCCUGCCACCGUGU GCGGCCCUAAGCUGAGCACCGACCUGAUCAAGAACCAGU GCGUGAACUUCAACUUCAACGGCCUGACCGGCACCGGCG UGCUGACCCCUAGCAGCAAGAGAUUCCAGCCUUUCCAGC AGUUCGGCAGAGACGUGCUGGACUUCACCGACAGCGUGA GAGACCCUAAGACCAGCGAGAUCCUGGACAUCAGCCCUU GCAGCUUCGGCGGCGUGAGCGUGAUCACCCCUGGCACCA ACACCAGCAGCGAGGUGGCCGUGCUGUACCAGGACGUGA ACUGCACCGACGUGCCUGUGGCCAUCCACGCCGACCAGCU GACCCCUAGCUGGAGAGUGUACAGCACCGGCAACAACGU GUUCCAGACCCAGGCCGGCUGCCUGAUCGGCGCCGAGCAC GUGGACACCAGCUACGAGUGCGACAUCCCUAUCGGCGCC GGCAUCUGCGCCAGCUACCACACCGUGAGCAGCCUGAGA AGCACCAGCCAGAAGAGCAUCGUGGCCUACACCAUGAGC CUGGGCGCCGACAGCAGCAUCGCCUACAGCAACAACACCA UCGCCAUCCCUACCAACUUCAGCAUCAGCAUCACCACCGA GGUGAUGCCUGUGAGCAUGGCCAAGACCAGCGUGGACUG CAACAUGUACAUCUGCGGCGACAGCACCGAGUGCGCCAA CCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAAC AGAGCCCUGAGCGGCAUCGCCGUGGAGCAGGACAGAAAC ACCAGAGAGGUGUUCGCCCAGGUGAAGCAGAUGUACAAG ACCCCUACCCUGAAGGACUUCGGCGGCUUCAACUUCAGCC AGAUCCUGCCUGACCCUCUGAAGCCUACCAAGAGAAGCU UCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUGGCCG	50

	ACGCCGGCUUCAUGAAGCAGUACGGCGAGUGCCUGGGCG ACAUCAACGCCAGAGACCUGAUCUGCGCCCAGAAGUUCA ACGGCCUGACCGUGCUGCCUCCUCUGCUGACCGACGACAU GAUCGCCGCCUACACCGCCGCCCUGGUGAGCGGCACCGCC ACCGCCGGCUGGACCUUCGGCGCCGGCGCCGCCCUGCAGA UCCCUUUCGCCAUGCAGAUGGCCUACAGAUUCAACGGCA UCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAGC AGAUCGCCAACCAGUUCAACAAGGCCAUCAGCCAGAUCC AGGAGAGCCUGACCACCACCAGCACCGCCCUGGGCAAGCU GCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACAC CCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAG CAGCGUGCUGAACGACAUCCUGAGCAGACUGGACCCUCC UGAGGCCGAGGUGCAGAUCGACAGACUGAUCACCGGCAG ACUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CAGAGCCGCCGAGAUCAGAGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGAGA GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUC CCUCAGGCCGCCCCUCACGGCGUGGUGUUCCUGCACGUGA CCUACGUGCCUAGCCAGGAGAGAAACUUCACCACCGCCCC UGCCAUCUGCCACGAGGGCAAGGCCUACUUCCCUAGAGA GGGCGUGUUCGUGUUCAACGGCACCAGCUGGUUCAUCAC CCAGAGAAACUUCUUCAGCCCUCAGAUCAUCACCACCGAC AACACCUUCGUGAGCGGCAGCUGCGACGUGGUGAUCGGC AUCAUCAACAACACCGUGUACGACCCUCUGCAGCCUGAGC UGGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGA ACCACACCAGCCCUGACGUGGACCUGGGCGACAUCAGCGG CAUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGA CAGACUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCU GAUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAU CAAGUGGCCUUGGUACGUGUGGCUGGGCUUCAUCGCCGG CCUGAUCGCCAUCGUGAUGGUGACCAUCCUGCUGUGCUG CAUGACCAGCUGCUGCAGCUGCCUGAAGGGCGCCUGCAG CUGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGA GCCUGUGCUGAAGGGCGUGAAGCUGCACUACACC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFIFLFFLTLTSGSDLESCTTFDDVQAPNYPQHSSSRRGVYYPD EIFRSDTLYLTQDLFLPFYSNVTGFHTINHRFDNPVIPFKDGVYF AATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFEL CDNPFFAVSKPTGTQTHTMIFDNAFNCTFEYISDSFSLDVAEKS GNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGFNILKPI FKLPLGINITNFRAILTAFLPAQDTWGTSAAAYFVGYLKPATFM LKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGIYQTSNFRV APSKEVVRFPNITNLCPFGEVFNATTFPSVYAWERKRISNCVAD YSVLYNSTSFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDD VRQIAPGQTGVIADYNYKLPDDFTGCVLAWNTRNIDATQTGN YNYKYRSLRHGKLRPFERDISNVPFSPDGKPCTPPAFNCYWPL NDYGFYITNGIGYQPYRVVVLSFELLNAPATVCGPKLSTDLIKN QCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDVLDFTDSVRDP KTSEILDISPCSFGGVSVITPGTNTSSEVAVLYQDVNCTDVPVAI HADQLTPSWRVYSTGNNVFQTQAGCLIGAEHVDTSYECDIPIG AGICASYHTVSSLRSTSQKSIVAYTMSLGADSSIAYSNNTIAIPT NFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSF CTQLNRALSGIAVEQDRNTREVFAQVKQMYKTPTLKDFGGFN FSQILPDPLKPTKRSFIEDLLFNKVTLADAGFMKQYGECLGDIN ARDLICAQKFNGLTVLPPLLTDDMIAAYTAALVSGTATAGWTF GAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQIANQFNKA ISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAIS SVLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIR ASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGV	49

	VFLHVTYVPSQERNFTTAPAICHEGKAYFPREGVFVFNGTSWFI TQRNFFSPQIITTDNTFVSGSCDVVIGIINNTVYDPLQPELDSFK EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKN LNESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLC CMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT	
聚A尾	100 nt	
MERS S蛋白變異體1		
SEQ ID NO: 60自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 61及3' UTR SEQ ID NO: 4。		60
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGAUCCACAGCGUGUUCCUGCUGAUGUUCCUCCUUACC CCUACCGAGAGCUACGUGGACGUCGGCCCUGACAGCGUU AAGAGCGCUUGCAUCGAGGUGGACAUCCAGCAGACCUUC UUCGACAAGACCUGGCCUAGACCUAUCGACGUGAGCAAG GCCGACGGCAUCAUCUACCCUCAGGGCAGAACCUACAGCA ACAUCACCAUCACCUACCAGGGCCUGUUCCCUUAUCAGGG CGACCACGGCGACAUGUACGUGUACAGCGCCGGCCACGCC ACCGGCACAACGCCCCAGAAGCUUUUCGUGGCCAACUACU CCCAGGACGUGAAGCAGUUCGCCAACGGCUUCGUGGUGA GAAUCGGCGCCGCCGCCAACUCCACUGGAACCGUGAUCAU CAGCCCUAGCACCAGCGCCACCAUCAGAAAGAUUUAUCCU GCCUUUAUGCUGGGCUCCAGCGUGGGUAACUUCAGCGAC GGCAAGAUGGGCAGAUUCUUCAACCACACCCUGGUGCUG CUGCCUGACGGCUGCGGCACCCUGCUGAGAGCCUUCUACU GCAUCCUGGAGCCUAGAAGCGGCAACCACUGCCCUGCCGG CAACAGCUACACCAGCUUCGCAACCUAUCACACCCCUGCC ACCGACUGUUCUGACGGUAACUACAACAGAAACGCCAGC CUGAACAGCUUCAAGGAGUACUUCAACCUGAGAAACUGC ACCUUCAUGUACACCUAUAAUAUCACCGAGGACGAGAUC CUCGAGUGGUUCGGCAUAACCCAGACCGCCCAAGGCGUG CACCUGUUCAGCAGCAGAUACGUUGAUCUGUACGGCGGC AACAUGUUCCAGUUCGCUACCCUGCCUGUGUACGACACC AUCAAGUACUACAGCAUCAUCCCUCAUUCUAUUAGAAGC AUCCAGAGCGACAGAAAGGCCUGGGCCGCUUUCUACGUA UACAAGCUGCAGCCUCUCACAUUCUUGCUCGACUUCUCU GUGGACGGCUAUAUCCGCAGGGCCAUCGACUGCGGCUUC AACGACCUGAGCCAGCUGCACUGCAGCUACGAGAGCUUC GACGUGGAGAGCGGAGUUUAUUCCGUGAGCAGCUUCGAG GCCAAGCCUAGCGGCUCUGUAGUGGAGCAGGCCGAGGGC GUGGAGUGCGAUUUCAGCCCUCUGCUGAGCGGUACCCCU CCUCAGGUGUACAACUUCAAGAGACUGGUGUUCACGAAC UGCAACUACAAUCUGACCAAACUGCUUUCGCUUUUCUCC GUGAACGACUUCACCUGCAGCCAGAUUUCUCCGGCAGCC AUCGCCAGCAACUGCUACAGCAGCUUGAUCCUUGACUAC UUCAGCUACCCUCUGAGCAUGAAGUCCGACUUAAGUGUA UCCUCAGCCGGCCCUAUCAGCCAGUUCAAUUACAAGCAG AGCUUCAGCAACCCUACCUGCCUAAUUUUGGCCACCGUGC CUCACAACCUGACUACAAUUACCAAGCCACUCAAGUAUU CCUACAUUAACAAGUGUAGCCGAUUCCUGAGCGACGACA GAACCGAGGUGCCUCAGCUGGUGAACGCCAACCAGUACA GCCCUUGCGUGUCGAUCGUGCCAAGUACCGUGUGGGAGG ACGGCGACUACUACAGAAAGCAGCUGUCUCCUCUCGAAG GCGGCGGGUGGCUGGUGGCAAGCGGAAGCACAGUGGCCA UGACCGAGCAGCUGCAGAUGGGCUUCGGAAUUACCGUGC AGUACGGCACCGACACCAAUAGUGUCUGCCCUAAGCUGG AAUUCGCGAACGACACUAAGAUUGCCUCCCAACUGGGAA	61

	AUUGCGUAGAGUACUCUCUGUACGGAGUGUCCGGCAGAG GUGUCUUCCAGAAUUGCACAGCCGUGGGCGUGAGACAGC AGAGAUUCGUCUACGACGCCUACCAGAACCUGGUGGGCU AUUAUAGUGACGACGGCAACUACUACUGCCUGCGGGCCU GCGUUAGUGUGCCUGUCUCCGUUAUCUACGACAAGGAGA CAAAGACUCACGCCACACUUUUCGGAUCUGUCGCCUGCG AGCACAUCAGUAGUACCAUGUCUCAGUAUAGCAGAAGCA CCAGGUCUAUGCUGAAGAGACGGGACUCAACCUACGGAC CACUUCAGACCCCUGUGGGCUGCGUGCUGGGCCUCGUAA AUAGCUCUCUGUUUGUGGAGGACUGUAAACUGCCACUGG GCCAGAGCCUGUGUGCUUUACCUGACACACCUAGUACAC UGACACCAGCGAGCGUGGGUAGUGUACCAGGCGAGAUGA GACUGGCCAGCAUCGCUUUCAAUCACCCUAUCCAGGUGG ACCAGCUCAAUUCCUCUUACUUCAAGCUGAGCAUCCCUAC CAAUUUCUCUUUCGGCGUGACCCAGGAGUACAUCCAGAC CACAAUACAGAAGGUGACCGUAGAUUGCAAGCAGUACGU GUGUAACGGAUUCCAGAAGUGCGAGCAAUUGCUCAGGGA GUACGGCCAGUUCUGUAGCAAGAUCAACCAGGCUCUGCA CGGGGCCAAUCUGCGACAGGACGACAGCGUAAGAAACCU GUUCGCCAGCGUAAAGUCUAGCCAGUCGAGUCCAAUCAU ACCAGGCUUCGGCGGAGAUUUCAAUCUCACCUUAUUGGA GCCAGUUUCCAUCUCUACGGGUUCGAGGAGCGCUAGGAG CGCAAUCGAGGACCUGCUGUUCGAUAAGGUCACCAUCGC CGACCCUGGCUACAUGCAGGGCUACGACGACUGCAUGCA GCAGGGCCCAGCCUCCGCCAGAGAUCUGAUCUGCGCCCAG UACGUCGCCGGCUACAAGGUGCUGCCUCCUCUGAUGGAC GUUAACAUGGAGGCCGCCUAUACUAGUAGUCUUCUGGGA AGCAUUGCAGGCGUGGGCUGGACCGCCGGCCUGUCUAGC UUCGCGGCCAUACCUUUCGCCCAGAGCAUCUUCUACAGAC UGAACGGUGUGGGCAUCACACAACAGGUACUGUCUGAGA AUCAGAAGCUGAUCGCCAACAAGUUCAAUCAGGCACUUG GCGCCAUGCAGACCGGCUUCACCACCACCAACGAGGCCUU CCACAAGGUCCAGGACGCCGUGAACAACAACGCUCAGGCC UUGAGCAAGUUAGCGAGCGAACUUAGCAACACCUUCGGC GCCAUCAGUGCAAGCAUUGGAGACAUUAUCCAGAGGCUC GACCCUCCUGAGCAGGACGCUCAGAUCGAUCGGUUGAUC AACGGCAGACUGACCACUCUGAACGCCUUCGUUGCCCAAC AACUGGUGCGGUCUGAGAGCGCCGCUUUAUCCGCCCAGC UGGCCAAGGACAAGGUUAACGAGUGCGUGAAGGCACAGU CGAAGCGUUCAGGAUUCUGCGGCCAGGGCACCCACAUCG UGAGCUUCGUCGUGAACGCCCCUAACGGCCUGUACUUCA UGCACGUCGGAUAUUACCCUAGCAACCAUAUUGAAGUGG UGAGCGCGUACGGCCUCUGUGACGCAGCUAAUCCUACAA ACUGCAUCGCCCCUGUGAACGGUUACUUCAUCAAGACCA ACAACACCAGAAUCGUGGACGAGUGGUCAUACACGGGCA GUUCAUUCUACGCCCCUGAGCCGAUCACUAGCCUUAACAC CAAGUACGUGGCCCCACAAGUGACAUACCAGAACAUUAG CACAAACCUGCCUCCACCGCUGUUAGGUAACAGCACGGGC AUCGACUUCCAGGACGAAUUAGACGAGUUCUUCAAGAAC GUGUCCACCAGCAUCCCAAACUUCGGCAGCCUGACCCAGA UCAACACAACCUUACUCGACCUGACCUACGAGAUGCUGA GCCUCCAGCAGGUUGUCAAGGCCCUCAACGAAUCAUAUA UCGACUUGAAGGAGCUUGGCAAUUACACUUACUACAACA AGUGGCCUUGGUACAUCUGGCUCGGCUUCAUCGCCGGGC UGGUCGCCCUCGCCCUGUGCGUCUUCUUCAUCCUGUGCUG CACAGGUUGUGGAACCAACUGUAUGGGCAAGCUGAAGUG CAACCGUUGCUGUGAUAGAUACGAGGAGUACGAUCUGGA ACCACAUAAGGUGCACGUGCAC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4

相應胺基酸序列	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYV YSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANSTG TVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTLVLLP DGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPATDCSDG NYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEWFGITQTA QGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSIIPHSIRSIQS DRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDCGFNDLSQLH CSYESFDVESGVYSVSSFEAKPSGSVVEQAEGVECDFSPLLSG TPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFTCSQISPAAIAS NCYSSLILDYFSYPLSMKSDLSVSSAGPISQFNYKQSFSNPTCLI LATVPHNLTTITKPLKYSYINKCSRFLSDDRTEVPQLVNANQYS PCVSIVPSTVWEDGDYYRKQLSPLEGGGWLVASGSTVAMTEQ LQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLGNCVEYSLY GVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNYYC LRACVSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTR SMLKRRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLC ALPDTPSTLTPASVGSVPGEMRLASIAFNHPIQVDQLNSSYFKL SIPTNFSFGVTQEYIQTTIQKVTVDCKQYVCNGFQKCEQLLRE YGQFCSKINQALHGANLRQDDSVRNLFASVKSSQSSPIIPGFGG DFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADPGYMQGYDD CMQQGPASARDLICAQYVAGYKVLPPLMDVNMEAAYTSSLL GSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKL IANKFNQALGAMQTGFTTTNEAFHKVQDAVNNNAQALSKLA SELSNTFGAISASIGDIIQRLDPPEQDAQIDRLINGRLTTLNAFVA QQLVRSESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVS FVVNAPNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAP VNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTY QNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINT TLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYI WLGFIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYE EYDLEPHKVHVH	59
聚A尾	100 nt	
SARS-CoV-2變異體25		
SEQ ID NO: 86自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 62及3' UTR SEQ ID NO: 4。		86
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC	62

	CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACAAGGUGGAG GCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUG CAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGG GCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCA AGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGG ACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCC AGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCU	

	ACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGC CAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGC GUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAG CGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACA CCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCG UGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGG ACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUC ACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAU CAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCG GCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAU CGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAA GUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCU GAUCGCCAUCGUGAUGGUGACCAUCAUGCUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGR LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIML	63
聚A尾	100 nt	
SARS-CoV-2變異體26		
SEQ ID NO: 87自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 64及3' UTR SEQ ID NO: 4。		87
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC	64

	GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC	

	GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACAAGGUGGAG GCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUG CAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGG GCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCA AGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGG ACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCC AGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCU ACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGC CAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGC GUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAG CGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACA CCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCG UGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGG ACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUC ACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAU CAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCG GCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAU CGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAA GUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCU GAUCGCCAUCGUGAUGGUGACCAUCAUGCUGAAGAAGAA GAAGCGGCCACGGAACUCCUACAAGUGCGGCACCAACACC AUGGAGCGGGAGGAGAGCGAGCAGACCAAGAAGCGGGAG AAGAUCCACAUUCCUGAACGGUCCGACGAAGCCCAGCGG GUGUUCAAGAGCAGCAAGACCAGCAGCUGCGACAAGAGC GACACCUGCUUC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGR LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV	65

	VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLKKKKRPRNSYKCGTNTMEREESE QTKKREKIHIPERSDEAQRVFKSSKTSSCDKSDTCF	
聚A尾	100 nt	
SARS-CoV-2變異體27		
SEQ ID NO: 88自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 66及3' UTR SEQ ID NO: 4。		88
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC	66

	GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACAAGGUGGAG GCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUG CAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGG GCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCA AGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGG ACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCC AGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCU ACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGC CAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGC GUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAG CGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACA CCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCG UGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGG ACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUC ACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAU CAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCG GCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAU CGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAA GUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCU GAUCGCCAUCGUGAUGGUGACCAUCAUGCUGAAGCGGCA GUACAAGGACAUGAUGAGCGAGGGAGGACCACCUGGCGC UGAGCCACAG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL	67

	CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGR LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLKRQYKDMMSEGGPPGAEPQ	
聚A尾	100 nt	
SARS-CoV-2變異體28		
SEQ ID NO: 89自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 68及3' UTR SEQ ID NO: 4。		89
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG	68

	GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACCCCCCCGAGG CCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUGC AGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGGG CCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCAA GAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGGA CUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCCA GAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCUA CGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGCC AUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGCG UGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAGC GGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACAC CUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCGU GAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGGAC AGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUCAC ACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAUCA ACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCGGC UGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAUCG ACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAAGU GGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCUGA	

	UCGCCAUCGUGAUGGUGACCAUCAUGCUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRL QSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIML	69
聚A尾	100 nt	
SARS-CoV-2變異體29		
SEQ ID NO: 90自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 70及3' UTR SEQ ID NO: 4。		90
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG	70

	AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACCCCCCCGAGG CCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUGC AGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGGG CCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCAA GAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGGA	

	CUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCCA GAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCUA CGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGCC AUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGCG UGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAGC GGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACAC CUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCGU GAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGGAC AGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUCAC ACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAUCA ACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCGGC UGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAUCG ACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAAGU GGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCUGA UCGCCAUCGUGAUGGUGACCAUCAUGCUGAAGAAGAAGA AGCGGCCACGGAACUCCUACAAGUGCGGCACCAACACCAU GGAGCGGGAGGAGAGCGAGCAGACCAAGAAGCGGGAGAA GAUCCACAUUCCUGAACGGUCCGACGAAGCCCAGCGGGU GUUCAAGAGCAGCAAGACCAGCAGCUGCGACAAGAGCGA CACCUGCUUC	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRL QSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLKKKKRPRNSYKCGTNTMEREESE QTKKREKIHIPERSDEAQRVFKSSKTSSCDKSDTCF	71
聚A尾	100 nt	
SARS-CoV-2變異體30		
SEQ ID NO: 91自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 72及3' UTR SEQ ID NO: 4。		91
化學	1-甲基假尿苷	

帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG	72

	CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACCCCCCCGAGG CCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUGC AGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGGG CCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCAA GAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGGA CUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCCA GAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCUA CGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGCC AUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGCG UGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAGC GGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACAC CUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCGU GAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGGAC AGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUCAC ACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAUCA ACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCGGC UGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAUCG ACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAAGU GGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCUGA UCGCCAUCGUGAUGGUGACCAUCAUGCUGAAGCGGCAGU ACAAGGACAUGAUGAGCGAGGGAGGACCACCUGGCGCUG AGCCACAG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA	73

	QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRL QSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLKRQYKDMMSEGGPPGAEPQ	
聚A尾	100 nt	
SARS-CoV-2變異體31		
SEQ ID NO: 92自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 74及3' UTR SEQ ID NO: 4。		92
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG	74

	ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACAAGGUGGAG GCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUG CAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGG GCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCA AGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGG ACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCC AGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCU ACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGC CAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGC GUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAG CGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACA CCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCG UGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGG ACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUC ACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAU CAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCG GCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAU CGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAA GUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCU GAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGCAU GACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGCUG CGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAGCC CGUGCUGAAGGGCGUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV	75

	CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGR LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFD EDDSEPVLKGV	
聚A尾	100 nt	
SARS-CoV-2變異體32		
SEQ ID NO: 93自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 76及3' UTR SEQ ID NO: 4。		93
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG	76

	CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCGUGUCACUGAGGAGCGU GGCCAGCCAGAGCAUCAUCGCCUACACCAUGAGCCUGGGC GCCGAGAACAGCGUGGCCUACAGCAACAACAGCAUCGCC AUCCCCACCAACUUCACCAUCAGCGUGACCACCGAGAUUC UGCCCGUGAGCAUGACCAAGACCAGCGUGGACUGCACCA UGUACAUCUGCGGCGACAGCACCGAGUGCAGCAACCUGC UGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAACCGGG CCCUGACCGGCAUCGCCGUGGAGCAGGACAAGAACACCCA GGAGGUGUUCGCCCAGGUGAAGCAGAUCUACAAGACCCC UCCCAUCAAGGACUUCGGCGGCUUCAACUUCAGCCAGAU CCUGCCCGACCCCAGCAAGCCCAGCAAGCGGAGCUUCAUC GAGGACCUGCUGUUCAACAAGGUGACCCUAGCCGACGCC GGCUUCAUCAAGCAGUACGGCGACUGCCUCGGCGACAUA GCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUCAACGGCC UGACCGUGCUGCCUCCCCUGCUGACCGACGAGAUGAUCGC CCAGUACACCAGCGCCCUGUUAGCCGGAACCAUCACCAGC GGCUGGACUUUCGGCGCUGGAGCCGCUCUGCAGAUCCCC UUCGCCAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGC GUGACCCAGAACGUGCUGUACGAGAACCAGAAGCUGAUC GCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGAC AGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGCUGCAG GACGUGGUGAACCAGAACGCCCAGGCCCUGAACACCCUG GUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCAGCAGC GUGCUGAACGACAUCCUGAGCCGGCUGGACCCCCCCGAGG CCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCGGCUGC AGAGCCUGCAGACCUACGUGACCCAGCAGCUGAUCCGGG CCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCCACCAA GAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGGGUGGA CUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUUCCCCA GAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGACCUA CGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCCAGCC AUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAGGGCG UGUUCGUGAGCAACGGCACCCACUGGUUCGUGACCCAGC GGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACAC CUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCAUCGU	

	GAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCUGGAC AGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAAUCAC ACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGCAUCA ACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAUCGGC UGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUGAUCG ACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUCAAGU GGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGCCUGA UCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGCAUGA CCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGCUGCG GCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAGCCCG UGCUGAAGGGCGUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTVSLRSVASQSIIAYT MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM YICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFA QVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTL ADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIA QYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRL QSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFC GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDG KAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGI NASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPW YIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFD EDDSEPVLKGV	77
聚A尾	100 nt	
SARS-CoV-2變異體33		
SEQ ID NO: 94自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 78及3' UTR SEQ ID NO: 4。		94
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUUCGUGUUCCUGGUGCUGCUGCCCCUGGUGAGCAGC CAGUGCGUGAACCUGACCACCCGGACCCAGCUGCCACCAG CCUACACCAACAGCUUCACCCGGGGCGUCUACUACCCCGA CAAGGUGUUCCGGAGCAGCGUCCUGCACAGCACCCAGGA CCUGUUCCUGCCCUUCUUCAGCAACGUGACCUGGUUCCAC GCCAUCCACGUGAGCGGCACCAACGGCACCAAGCGGUUCG	78

	ACAACCCCGUGCUGCCCUUCAACGACGGCGUGUACUUCGC CAGCACCGAGAAGAGCAACAUCAUCCGGGGCUGGAUCUU CGGCACCACCCUGGACAGCAAGACCCAGAGCCUGCUGAUC GUGAAUAACGCCACCAACGUGGUGAUCAAGGUGUGCGAG UUCCAGUUCUGCAACGACCCCUUCCUGGGCGUGUACUACC ACAAGAACAACAAGAGCUGGAUGGAGAGCGAGUUCCGGG UGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGA GCCAGCCCUUCCUGAUGGACCUGGAGGGCAAGCAGGGCA ACUUCAAGAACCUGCGGGAGUUCGUGUUCAAGAACAUCG ACGGCUACUUCAAGAUCUACAGCAAGCACACCCCAAUCA ACCUGGUGCGGGAUCUGCCCCAGGGCUUCUCAGCCCUGG AGCCCCUGGUGGACCUGCCCAUCGGCAUCAACAUCACCCG GUUCCAGACCCUGCUGGCCCUGCACCGGAGCUACCUGACC CCAGGCGACAGCAGCAGCGGGUGGACAGCAGGCGCGGCU GCUUACUACGUGGGCUACCUGCAGCCCCGGACCUUCCUGC UGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGG ACUGCGCCCUGGACCCUCUGAGCGAGACCAAGUGCACCCU GAAGAGCUUCACCGUGGAGAAGGGCAUCUACCAGACCAG CAACUUCCGGGUGCAGCCCACCGAGAGCAUCGUGCGGUU CCCCAACAUCACCAACCUGUGCCCCUUCGGCGAGGUGUUC AACGCCACCCGGUUCGCCAGCGUGUACGCCUGGAACCGGA AGCGGAUCAGCAACUGCGUGGCCGACUACAGCGUGCUGU ACAACAGCGCCAGCUUCAGCACCUUCAAGUGCUACGGCG UGAGCCCCACCAAGCUGAACGACCUGUGCUUCACCAACGU GUACGCCGACAGCUUCGUGAUCCGUGGCGACGAGGUGCG GCAGAUCGCACCCGGCCAGACAGGCAAGAUCGCCGACUAC AACUACAAGCUGCCCGACGACUUCACCGGCUGCGUGAUC GCCUGGAACAGCAACAACCUCGACAGCAAGGUGGGCGGC AACUACAACUACCUGUACCGGCUGUUCCGGAAGAGCAAC CUGAAGCCCUUCGAGCGGGACAUCAGCACCGAGAUCUAC CAAGCCGGCUCCACCCCUUGCAACGGCGUGGAGGGCUUCA ACUGCUACUUCCCUCUGCAGAGCUACGGCUUCCAGCCCAC CAACGGCGUGGGCUACCAGCCCUACCGGGUGGUGGUGCU GAGCUUCGAGCUGCUGCACGCCCCAGCCACCGUGUGUGGC CCCAAGAAGAGCACCAACCUGGUGAAGAACAAGUGCGUG AACUUCAACUUCAACGGCCUUACCGGCACCGGCGUGCUG ACCGAGAGCAACAAGAAAUUCCUGCCCUUUCAGCAGUUC GGCCGGGACAUCGCCGACACCACCGACGCUGUGCGGGAUC CCCAGACCCUGGAGAUCCUGGACAUCACCCCUUGCAGCUU CGGCGGCGUGAGCGUGAUCACCCCAGGCACCAACACCAGC AACCAGGUGGCCGUGCUGUACCAGGACGUGAACUGCACC GAGGUGCCCGUGGCCAUCCACGCCGACCAGCUGACACCCA CCUGGCGGGUCUACAGCACCGGCAGCAACGUGUUCCAGA CCCGGGCCGGUUGCCUGAUCGGCGCCGAGCACGUGAACA ACAGCUACGAGUGCGACAUCCCCAUCGGCGCCGGCAUCUG UGCCAGCUACCAGACCCAGACCAAUUCACCCCGGAGGGCA AGGAGCGUGGCCAGCCAGAGCAUCAUCGCCUACACCAUG AGCCUGGGCGCCGAGAACAGCGUGGCCUACAGCAACAAC AGCAUCGCCAUCCCCACCAACUUCACCAUCAGCGUGACCA CCGAGAUUCUGCCCGUGAGCAUGACCAAGACCAGCGUGG ACUGCACCAUGUACAUCUGCGGCGACAGCACCGAGUGCA GCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACCCAGCU GAACCGGGCCCUGACCGGCAUCGCCGUGGAGCAGGACAA GAACACCCAGGAGGUGUUCGCCCAGGUGAAGCAGAUCUA CAAGACCCCUCCCAUCAAGGACUUCGGCGGCUUCAACUUC AGCCAGAUCCUGCCCGACCCCAGCAAGCCCAGCAAGCGGA GCUUCAUCGAGGACCUGCUGUUCAACAAGGUGACCCUAG CCGACGCCGGCUUCAUCAAGCAGUACGGCGACUGCCUCGG CGACAUAGCCGCCCGGGACCUGAUCUGCGCCCAGAAGUUC AACGGCCUGACCGUGCUGCCUCCCCUGCUGACCGACGAGA UGAUCGCCCAGUACACCAGCGCCCUGUUAGCCGGAACCAU CACCAGCGGCUGGACUUUCGGCGCUGGAGCCGCUCUGCA	

	GAUCCCCUUCGCCAUGCAGAUGGCCUACCGGUUCAACGGC AUCGGCGUGACCCAGAACGUGCUGUACGAGAACCAGAAG CUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCC AGGACAGCCUGAGCAGCACCGCUAGCGCCCUGGGCAAGC UGCAGGACGUGGUGAACCAGAACGCCCAGGCCCUGAACA CCCUGGUGAAGCAGCUGAGCAGCAACUUCGGCGCCAUCA GCAGCGUGCUGAACGACAUCCUGAGCCGGCUGGACCCUCC CGAGGCCGAGGUGCAGAUCGACCGGCUGAUCACUGGCCG GCUGCAGAGCCUGCAGACCUACGUGACCCAGCAGCUGAU CCGGGCCGCCGAGAUUCGGGCCAGCGCCAACCUGGCCGCC ACCAAGAUGAGCGAGUGCGUGCUGGGCCAGAGCAAGCGG GUGGACUUCUGCGGCAAGGGCUACCACCUGAUGAGCUUU CCCCAGAGCGCACCCCACGGAGUGGUGUUCCUGCACGUGA CCUACGUGCCCGCCCAGGAGAAGAACUUCACCACCGCCCC AGCCAUCUGCCACGACGGCAAGGCCCACUUUCCCCGGGAG GGCGUGUUCGUGAGCAACGGCACCCACUGGUUCGUGACC CAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACA ACACCUUCGUGAGCGGCAACUGCGACGUGGUGAUCGGCA UCGUGAACAACACCGUGUACGAUCCCCUGCAGCCCGAGCU GGACAGCUUCAAGGAGGAGCUGGACAAGUACUUCAAGAA UCACACCAGCCCCGACGUGGACCUGGGCGACAUCAGCGGC AUCAACGCCAGCGUGGUGAACAUCCAGAAGGAGAUCGAU CGGCUGAACGAGGUGGCCAAGAACCUGAACGAGAGCCUG AUCGACCUGCAGGAGCUGGGCAAGUACGAGCAGUACAUC AAGUGGCCCUGGUACAUCUGGCUGGGCUUCAUCGCCGGC CUGAUCGCCAUCGUGAUGGUGACCAUCAUGCUGUGCUGC AUGACCAGCUGCUGCAGCUGCCUGAAGGGCUGUUGCAGC UGCGGCAGCUGCUGCAAGUUCGACGAGGACGACAGCGAG CCCGUGCUGAAGGGCGUG	
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVF RSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPF NDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKV CEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRD LPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTA GAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCV IAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAG STPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSN QVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAG CLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSII AYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDC TMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEV FAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEM IAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT QNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHD GKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCD VVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDIS GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKF	79

	DEDDSEPVLKGV	
聚A尾	100 nt	
CoV2膜蛋白		
SEQ ID NO: 95自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 80及3' UTR SEQ ID NO: 4。		95
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGGCCGACAGCAACGGCACCAUCACCGUGGAGGAGCUG AAGAAGCUGCUGGAGCAGUGGAACCUGGUGAUCGGCUUC CUGUUCCUGACCUGGAUCUGCCUGCUGCAGUUCGCCUAC GCCAACCGGAACCGUUUCCUGUACAUCAUCAAGCUGAUC UUCCUGUGGCUGCUGUGGCCCGUGACCCUGGCCUGCUUC GUGCUGGCCGCCGUGUACCGGAUCAACUGGAUCACCGGC GGCAUCGCCAUCGCCAUGGCCUGCCUGGUGGGCCUGAUG UGGCUGAGCUACUUCAUCGCCAGCUUCCGGCUGUUCGCCC GGACCCGGAGCAUGUGGAGCUUCAACCCCGAGACCAACA UCCUGCUGAACGUGCCCCUGCACGGCACAAUCCUGACCCG GCCCCUGCUGGAGAGCGAGCUUGUGAUCGGCGCCGUGAU CCUGCGGGGCCACCUGAGGAUCGCCGGCCAUCACCUGGGC CGGUGCGACAUCAAGGACCUGCCCAAGGAGAUCACCGUG GCCACCAGCCGGACCCUGAGCUACUACAAACUGGGCGCCA GCCAGAGAGUGGCCGGAGACAGCGGCUUCGCCGCCUACA GCCGGUACCGGAUCGGCAACUACAAGCUGAACACCGACC ACAGCAGCAGCAGCGACAACAUCGCCCUGCUGGUGCAG	80
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MADSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRN RFLYIIKLIFLWLLWPVTLACFVLAAVYRINWITGGIAIAMACL VGLMWLSYFIASFRLFARTRSMWSFNPETNILLNVPLHGTILTR PLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLS YYKLGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALL VQ	81
聚A尾	100 nt	
CoV2包膜蛋白		
SEQ ID NO: 96自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 82及3' UTR SEQ ID NO: 4。		96
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGUACAGCUUCGUGAGCGAGGAGACCGGCACCCUGAUC GUGAACAGCGUGCUGCUGUUCCUGGCCUUCGUGGUGUUC CUGCUGGUGACCCUGGCCAUCCUGACCGCCCUGCGGCUGU GUGCCUACUGCUGCAACAUCGUGAACGUGAGCCUGGUGA AGCCCAGCUUCUACGUGUACAGCCGGGUGAAGAACCUGA ACAGCAGCCGGGUGCCUGACCUGCUGGUG	82
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
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聚A尾	100 nt	
CoV2核殼體蛋白		
SEQ ID NO: 97自5'端至3'端係由以下組成：5' UTR SEQ ID NO: 2、mRNA ORF SEQ ID NO: 84及3' UTR SEQ ID NO: 4。		97
化學	1-甲基假尿苷	
帽	7mG(5')ppp(5')NlmpNp	
5' UTR	GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUA AGACCCCGGCGCCGCCACC	2
mRNA構築體之ORF (不包括終止密碼子)	AUGAGCGACAACGGCCCUCAGAACCAGCGGAACGCACCCC GGAUCACCUUUGGCGGCCCCAGCGAUAGCACCGGCAGCA ACCAGAACGGCGAGAGAUCAGGGGCCCGGAGCAAGCAGC GGCGUCCUCAGGGCCUGCCCAACAACACCGCCAGCUGGUU CACCGCCCUGACCCAGCACGGCAAGGAGGACCUGAAGUUC CCUCGGGGCCAAGGAGUGCCCAUCAACACCAACAGCAGCC CCGACGACCAGAUCGGCUACUACAGAAGGGCCACCCGGA GGAUCCGGGGAGGGGACGGCAAGAUGAAGGACCUGUCUC CCCGGUGGUACUUCUACUAUCUUGGCACGGGCCCUGAAG CUGGCCUGCCGUACGGCGCAAACAAGGACGGCAUCAUCU GGGUCGCCACCGAGGGAGCCCUGAACACCCCGAAGGACCA CAUCGGCACCCGGAAUCCCGCCAACAACGCCGCCAUCGUU CUGCAGCUGCCCCAGGGCACCACCCUGCCCAAGGGCUUCU ACGCCGAGGGCAGCAGAGGCGGCUCACAGGCCAGCAGCC GGUCAAGCAGCCGGAGCCGGAACAGCAGCCGGAACUCCA CACCCGGCUCUAGCCGAGGCACAAGCCCCGCCAGAAUGGC AGGAAACGGCGGCGACGCUGCCUUAGCCCUGCUGUUGCU GGACCGGCUGAACCAGCUCGAGAGCAAGAUGAGCGGCAA GGGUCAGCAGCAGCAAGGCCAAACCGUGACCAAGAAGAG CGCCGCCGAGGCUAGCAAGAAGCCCCGGCAGAAGCGGACC GCCACCAAGGCCUACAACGUGACCCAGGCCUUCGGUCGGA GAGGCCCCGAGCAGACCCAGGGCAACUUCGGCGACCAGG AGCUGAUCCGGCAGGGCACCGACUACAAGCACUGGCCCCA GAUCGCCCAGUUCGCCCCUAGCGCCUCAGCCUUCUUCGGC AUGAGCCGGAUCGGCAUGGAGGUGACUCCCAGCGGCACC UGGCUGACCUACACCGGCGCCAUCAAGCUGGACGACAAG GACCCCAACUUCAAGGACCAGGUGAUCCUGCUGAACAAG CACAUCGACGCCUACAAGACCUUUCCGCCCACCGAGCCCA AGAAGGACAAGAAGAAGAAGGCCGACGAGACCCAGGCCC UGCCCCAACGGCAGAAGAAGCAGCAGACCGUCACCUUAC UGCCCGCAGCCGACCUGGACGACUUCAGCAAGCAGCUGCA GCAGAGCAUGAGCAGCGCCGACAGCACCCAGGCC	84
3' UTR	UGAUAAUAGGCUGGAGCCUCGGUGGCCUAGCUUCUUGCC CCUUGGGCCUCCCCCCAGCCCCUCCUCCCCUUCCUGCACC CGUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG C	4
相應胺基酸序列	MSDNGPQNQRNAPRITFGGPSDSTGSNQNGERSGARSKQRRP QGLPNNTASWFTALTQHGKEDLKFPRGQGVPINTNSSPDDQIG YYRRATRRIRGGDGKMKDLSPRWYFYYLGTGPEAGLPYGAN KDGIIWVATEGALNTPKDHIGTRNPANNAAIVLQLPQGTTLPK GFYAEGSRGGSQASSRSSSRSRNSSRNSTPGSSRGTSPARMAG NGGDAALALLLLDRLNQLESKMSGKGQQQQGQTVTKKSAAE ASKKPRQKRTATKAYNVTQAFGRRGPEQTQGNFGDQELIRQG TDYKHWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTYTGAIK LDDKDPNFKDQVILLNKHIDAYKTFPPTEPKKDKKKKADETQ ALPQRQKKQQTVTLLPAADLDDFSKQLQQSMSSADSTQA	85
聚A尾	100 nt	

*應理解，表1中所闡述之任一開放閱讀框及/或相應胺基酸序列可包

括或不包括信號序列。亦應理解，信號序列可由不同信號序列(例如SEQ ID NO: 38-43中之任一者)替代。

等效形式

【0272】 本文所揭示之所有參考文獻、專利及專利申請案關於其各自所列舉之標的物均係以引用的方式併入，其在一些情形中可涵蓋整個文檔。

【0273】 除非明確指示相反情形，否則如本文在說明書及在申請專利範圍中所用之不定冠詞「一(a及an)」應理解為意指「至少一種」。

【0274】 亦應理解，除非明確指示相反情形，否則在本文所主張之包括一個以上步驟或動作之任何方法中，方法之步驟或動作次序不一定受限於該方法中所列舉之步驟或動作次序。

【0275】 在申請專利範圍以及在上文說明書中，所有過渡性片語(諸如「包含」、「包括」、「攜帶」、「具有」、「含有」、「涉及」、「持有」、「由……構成」及諸如此類)應理解為係開放式的，亦即意指包括但不限於。如美國專利局專利審查程序手冊(United States Patent Office Manual of Patent Examining Procedures)第2111.03節中所陳述，僅過渡性片語「由……組成」及「基本上由……組成」應分別係封閉式或半封閉式過渡性片語。

【0276】 數值前之術語「約」及「實質上」意指所列舉數值之±10%。

【0277】 在提供值範圍之情形下，本文明確考慮並描述該範圍之上限與下限之間的每一值。

【0278】 以下國際申請案之全部內容係以引用的方式併入本文中：

第PCT/US2015/02740號、第PCT/US2016/043348號、第PCT/US2016/043332號、第PCT/US2016/058327號、第PCT/US2016/058324號、第PCT/US2016/058314號、第PCT/US2016/058310號、第PCT/US2016/058321號、第PCT/US2016/058297號、第PCT/US2016/058319號及第PCT/US2016/058314號。

【序列表】

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<130> M1378.70145WO00

<140> TW 110103314
<141> 2021-01-28

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<151> 2020-01-28

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<150> US 63/002,094
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gugaccuggu uccacgccau ccacgucucc gggacgaacg ggacgaagcg guucgacaac 300

ccgguccucc cguucaacga cggcgucuac uucgcgagca cggagaaguc gaacaucauc 360

cggggcugga ucuucggcac gacccuggac ucgaagaccc agucccuacu uaucgugaac 420

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<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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<210> 3
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<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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ugcucgugcc ucaaggggug cugcagcugc ggguccugcu gcaaguucga cgaggacgac 3780

ucggagccgg uccucaaggg cgucaagcuc cacuacacc 3819

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<211> 119
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
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cuccuccccu uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 119

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<211> 1273
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 5

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly

405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser

805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu

1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

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Val Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<212> RNA
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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala

340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu

740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
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Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
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Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
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Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
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Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro

1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
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Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
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Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val

305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

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645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gly Ser Gly Gly Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile

705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
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Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
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Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
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Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
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Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
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Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
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Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln

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Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
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Gly Lys Tyr Glu Gln Gly Ser Gly Tyr Ile Pro Glu Ala Pro Arg
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cucggcgaca uagccgcccg ggaccugauc ugcgcccaga aguucaacgg ccugaccgug 2580

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val

305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile

705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln

1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Gly Ser Gly Tyr Ile Pro Glu Ala Pro Arg
1205 1210 1215

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ugcagcugcc ugaagggcug uugcagcugc ggcagcugcu gcaaguucga cgaggacgac 3780

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<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala

275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gly Ser Gly Gly Ser Val Ala

675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His

1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1250 1255 1260

Val Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 18
<211> 3878
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 18
gggaaauaag agagaaaaga agaguaagaa gaaauauaag accccggcgc cgccaccaug 60

uucguguucc uggugcugcu gccccuggug agcagccagu gcgugaaccu gaccacccgg 120

acccagcugc caccagccua caccaacagc uucacccggg gcgucuacua ccccgacaag 180

guguuccgga gcagcguccu gcacagcacc caggaccugu uccugcccuu cuucagcaac 240

gugaccuggu uccacgccau ccacgugagc ggcaccaacg gcaccaagcg guucgacaac 300

cccgugcugc ccuucaacga cggcguguac uucgccagca ccgagaagag caacaucauc 360

cggggcugga ucuucggcac cacccuggac agcaagaccc agagccugcu gaucgugaau 420

aacgccacca acguggugau caaggugugc gaguuccagu ucugcaacga ccccuuccug 480

ggcguguacu accacaagaa caacaagagc uggauggaga gcgaguuccg gguguacagc 540

agcgccaaca acugcaccuu cgaguacgug agccagcccu uccugaugga ccuggagggc 600

aagcagggca acuucaagaa ccugcgggag uucguguuca agaacaucga cggcuacuuc 660

aagaucuaca gcaagcacac cccaaucaac cuggugcggg aucugcccca gggcuucuca 720

gcccuggagc cccuggugga ccugcccauc ggcaucaaca ucacccgguu ccagacccug 780

cuggcccugc accggagcua ccugacccca ggcgacagca gcagcgggug gacagcaggc 840

gcggcugcuu acuacguggg cuaccugcag ccccggaccu uccugcugaa guacaacgag 900

aacggcacca ucaccgacgc cguggacugc gcccuggacc cucugagcga gaccaagugc 960

acccugaaga gcuucaccgu ggagaagggc aucuaccaga ccagcaacuu ccgggugcag 1020

cccaccgaga gcaucgugcg guuccccaac aucaccaacc ugugccccuu cggcgaggug 1080

uucaacgcca cccgguucgc cagcguguac gccuggaacc ggaagcggau cagcaacugc 1140

guggccgacu acagcgugcu guacaacagc gccagcuuca gcaccuucaa gugcuacggc 1200

gugagcccca ccaagcugaa cgaccugugc uucaccaacg uguacgccga cagcuucgug 1260

auccguggcg acgaggugcg gcagaucgca cccggccaga caggcaagau cgccgacuac 1320

aacuacaagc ugcccgacga cuucaccggc ugcgugaucg ccuggaacag caacaaccuc 1380

gacagcaagg ugggcggcaa cuacaacuac cuguaccggc uguuccggaa gagcaaccug 1440

aagcccuucg agcgggacau cagcaccgag aucuaccaag ccggcuccac cccuugcaac 1500

ggcguggagg gcuucaacug cuacuucccu cugcagagcu acggcuucca gcccaccaac 1560

ggcgugggcu accagcccua ccggguggug gugcugagcu ucgagcugcu gcacgcccca 1620

gccaccgugu guggccccaa gaagagcacc aaccugguga agaacaagug cgugaacuuc 1680

aacuucaacg gccuuaccgg caccggcgug cugaccgaga gcaacaagaa auuccugccc 1740

uuucagcagu ucggccggga caucgccgac accaccgacg cugugcggga uccccagacc 1800

cuggagaucc uggacaucac cccuugcagc uucggcggcg ugagcgugau caccccaggc 1860

accaacacca gcaaccaggu ggccgugcug uaccaggacg ugaacugcac cgaggugccc 1920

guggccaucc acgccgacca gcugacaccc accuggcggg ucuacagcac cggcagcaac 1980

guguuccaga cccgggccgg uugccugauc ggcgccgagc acgugaacaa cagcuacgag 2040

ugcgacaucc ccaucggcgc cggcaucugu gccagcuacc agacccagac caauucaccc 2100

cggagggcaa ggagcguggc cagccagagc aucaucgccu acaccaugag ccuggggcgcc 2160

gagaacagcg uggccuacag caacaacagc aucgccaucc ccaccaacuu caccaucagc 2220

gugaccaccg agauucugcc cgugagcaug accaagacca gcguggacug caccauguac 2280

aucugcggcg acagcaccga gugcagcaac cugcugcugc aguacggcag cuucugcacc 2340

cagcugaacc gggcccugac cggcaucgcc guggagcagg acaagaacac ccaggaggug 2400

uucgcccagg ugaagcagau cuacaagacc ccucccauca aggacuucgg cggcuucaac 2460

uucagccaga uccugcccga ccccagcaag cccagcaagc ggagcuucau cgaggaccug 2520

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ccucccccugc ugaccgacga gaugaucgcc caguacacca gcgcccuguu agccggaacc 2700

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gccaaccugg ccgccaccaa gaugagcgag ugcgugcugg gccagagcaa gcggguggac 3180

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uuccugcacg ugaccuacgu gcccgcccag gagaagaacu ucaccaccgc cccagccauc 3300

ugccacgacg gcaaggccca cuuuccccgg gagggcgugu ucgugagcaa cggcacccac 3360

ugguucguga cccagcggaa cuucuacgag ccccagauca ucaccaccga caacaccuuc 3420

gugagcggca acugcgacgu ggugaucggc aucgugaaca acaccgugua cgaucccccug 3480

cagcccgagc uggacagcuu caaggaggag cuggacaagu acuucaagaa ucacaccagc 3540

cccgacgugg accugggcga caucagcggc aucaacgcca gcguggugaa cauccagaag 3600

gagaucgauc ggcugaacga gguggccaag aaccugaacg agagccugau cgaccugcag 3660

gagcugggca aguacgagca guacaucaag uggcccuggu acaucuggcu gggcuucauc 3720

gccggccuga ucgccaucgu gauggugacc aucaugcugu gauaauaggc uggagccucg 3780

guggccuagc uucuugcccc uugggccucc ccccagcccc uccuccccuu ccugcacccg 3840

uacccccgug gucuuugaau aaagucugag ugggcggc 3878

<210> 19
<211> 3702
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 19
auguucgugu uccuggugcu gcugccccug gugagcagcc agugcgugaa ccugaccacc 60

cggacccagc ugccaccagc cuacaccaac agcuucaccc ggggcgucua cuaccccgac 120

aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

cugggcgugu acuaccacaa gaacaacaag agcuggaugg agagcgaguu ccggguguac 480

agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgcccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

ggcgugagcc ccaccaagcu gaacgaccug ugcuucacca acguguacgc cgacagcuuc 1200

gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

uacaacuaca agcugcccga cgacuucacc ggcugcguga ucgccuggaa cagcaacaac 1320

cucgacagca agguggggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

uucaacuuca acggccuuac cggcaccggc gugcugaccg agagcaacaa gaaauuccug 1680

cccuuucagc aguucggccg ggacaucgcc gacaccaccg acgcugugcg ggauccccag 1740

acccuggaga uccuggacau cacccccuugc agcuucggcg gcgugagcgu gaucacccca 1800

ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

aacguguucc agacccgggc cgguugccug aucggcgccg agcacgugaa caacagcuac 1980

gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccaauuca 2040

ccccggaggg caaggagcgu ggccagccag agcaucaucg ccuacaccau gagccugggc 2100

gccgagaaca gcguggccua cagcaacaac agcaucgcca uccccaccaa cuucaccauc 2160

agcgugacca ccgagauucu gcccgugagc augaccaaga ccagcgugga cugcaccaug 2220

uacaucugcg gcgacagcac cgagugcagc aaccugcugc ugcaguacgg cagcuucugc 2280

acccagcuga accgggcccu gaccggcauc gccguggagc aggacaagaa cacccaggag 2340

guguucgccc aggugaagca gaucuacaag accccuccca ucaaggacuu cggcggcuuc 2400

aacuucagcc agauccugcc cgaccccagc aagcccagca agcggagcuu caucgaggac 2460

cugcuguuca acaaggugac ccuagccgac gccggcuuca ucaagcagua cggcgacugc 2520

cucggcgaca uagccgcccg ggaccugauc ugcgcccaga aguucaacgg ccugaccgug 2580

cugccucccc ugcugaccga cgagaugauc gcccaguaca ccagcgcccu guuagccgga 2640

accaucacca gcggcuggac uuucggcgcu ggagccgcuc ugcagauccc cuucgccaug 2700

cagauggccu accgguucaa cggcaucggc gugacccaga acgugcugua cgagaaccag 2760

aagcugaucg ccaaccaguu caacagcgcc aucggcaaga uccaggacag ccugagcagc 2820

accgcuagcg cccugggcaa gcugcaggac guggugaacc agaacgccca ggcccugaac 2880

acccugguga agcagcugag cagcaacuuc ggcgccauca gcagcgugcu gaacgacauc 2940

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cugcagagcc ugcagaccua cgugacccag cagcugaucc gggccgccga gauucgggcc 3060

agcgccaacc uggccgccac caagaugagc gagugcgugc uggggccagag caagcgggug 3120

gacuucugcg gcaagggcua ccaccugaug agcuuucccc agagcgcacc ccacggagug 3180

guguuccugc acgugaccua cgugcccgcc caggagaaga acuucaccac cgccccagcc 3240

aucugccacg acggcaaggc ccacuuuccc cgggagggcg uguucgugag caacggcacc 3300

cacugguucg ugacccagcg gaacuucuac gagccccaga ucaucaccac cgacaacacc 3360

uucgugagcg gcaacugcga cguggugauc ggcaucguga acaacaccgu guacgauccc 3420

cugcagcccg agcuggacag cuucaaggag gagcuggaca aguacuucaa gaaucacacc 3480

agccccgacg uggaccuggg cgacaucagc ggcaucaacg ccagcguggu gaacauccag 3540

aaggagaucg aucggcugaa cgagguggcc aagaaccuga acgagagccu gaucgaccug 3600

caggagcugg gcaaguacga gcaguacauc aaguggcccu gguacaucug gcugggcuuc 3660

aucgccggcc ugaucgccau cgugauggug accaucaugc ug 3702

<210> 20
<211> 1234
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 20

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

```
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
    50                  55                  60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
                165                 170                 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
            180                 185                 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
        195                 200                 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
    210                 215                 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225                 230                 235                 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
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245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val

645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro

1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu

<210> 21
<211> 3986
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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acccagcugc caccagccua caccaacagc uucacccggg gcgucuacua ccccgacaag 180

guguuccgga gcagcguccu gcacagcacc caggaccugu uccugcccuu cuucagcaac 240

gugaccuggu uccacgccau ccacgugagc ggcaccaacg gcaccaagcg guucgacaac 300

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cggggcugga ucuucggcac cacccuggac agcaagaccc agagccugcu gaucgugaau 420

aacgccacca acguggugau caaggugugc gaguuccagu ucugcaacga ccccuuccug 480

ggcguguacu accacaagaa caacaagagc uggauggaga gcgaguuccg gguguacagc 540

agcgccaaca acugcaccuu cgaguacgug agccagcccu uccugaugga ccuggagggc 600

aagcagggca acuucaagaa ccugcgggag uucguguuca agaacaucga cggcuacuuc 660

aagaucuaca gcaagcacac cccaaucaac cuggugcggg aucugcccca gggcuucuca 720

gcccuggagc cccuggugga ccugcccauc ggcaucaaca ucacccgguu ccagacccug 780

cuggcccugc accggagcua ccugacccca ggcgacagca gcagcgggug gacagcaggc 840

gcggcugcuu acuacguggg cuaccugcag ccccggaccu uccugcugaa guacaacgag 900

aacggcacca ucaccgacgc cguggacugc gcccuggacc cucugagcga gaccaagugc 960

acccugaaga gcuucaccgu ggagaagggc aucuaccaga ccagcaacuu ccgggugcag 1020

cccaccgaga gcaucgugcg guuccccaac aucaccaacc ugugccccuu cggcgaggug 1080

uucaacgcca cccgguucgc cagcguguac gccuggaacc ggaagcggau cagcaacugc 1140

guggccgacu acagcgugcu guacaacagc gccagcuuca gcaccuucaa gugcuacggc 1200

gugagcccca ccaagcugaa cgaccugugc uucaccaacg uguacgccga cagcuucgug 1260

auccguggcg acgaggugcg gcagaucgca cccggccaga caggcaagau cgccgacuac 1320

aacuacaagc ugcccgacga cuucaccggc ugcgugaucg ccuggaacag caacaaccuc 1380

gacagcaagg ugggcggcaa cuacaacuac cuguaccggc uguuccggaa gagcaaccug 1440

aagcccuucg agcgggacau cagcaccgag aucuaccaag ccggcuccac cccuugcaac 1500

ggcguggagg gcuucaacug cuacuucccu cugcagagcu acggcuucca gcccaccaac 1560

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aacuucaacg gccuuaccgg caccggcgug cugaccgaga gcaacaagaa auuccugccc 1740

uuucagcagu ucggccggga caucgccgac accaccgacg cugugcggga uccccagacc 1800

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gacagcaccg agugcagcaa ccugcugcug caguacggca gcuucugcac ccagcugaac 2340

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gugaagcaga ucuacaagac cccucccauc aaggacuucg gcggcuucaa cuucagccag 2460

auccugcccg accccagcaa gcccagcaag cggagcuuca ucgaggaccu gcuguucaac 2520

aaggugaccc uagccgacgc cggcuucauc aagcaguacg gcgacugccu cggcgacaua 2580

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cugaagggcg ugaagcugca cuacaccuga uaauaggcug gagccucggu ggccuagcuu 3900

cuugccccuu gggccucccc ccagccccuc cuccccuucc ugcacccgua cccccguggu 3960

cuuugaauaa agucugagug ggcggc 3986

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<211> 3810
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<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

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uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

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ggcaagggcu accaccugau gagcuuuccc cagagcgcac cccacggagu gguguuccug 3180

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ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugugcugca ugaccagcug cugcagcugc 3720

cugaagggcu guugcagcug cggcagcugc ugcaaguucg acgaggacga cagcgagccc 3780

gugcugaagg gcgugaagcu gcacuacacc 3810

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<211> 1270
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 23

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
        35                  40                  45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
    50                  55                  60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
                165                 170                 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
            180                 185                 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
        195                 200                 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile

610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785 790 795 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
805 810 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
820 825 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
835 840 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
850 855 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865 870 875 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
885 890 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
900 905 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
915 920 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala

1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys
1220 1225 1230

Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys Ser Cys Gly
1235 1240 1245

Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys
1250 1255 1260

Gly Val Lys Leu His Tyr Thr
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<211> 3980
<212> RNA
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<223> 合成

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
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His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr

145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
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Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
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Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
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Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
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Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
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595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
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675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
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Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
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755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
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Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
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Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn

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Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
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Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
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Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
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Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
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His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
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Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
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Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
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Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
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Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
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35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu

85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly

485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

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Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

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Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
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Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
                725                 730                 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
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Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
        755                 760                 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785                 790                 795                 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
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Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
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Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
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Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
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Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865                 870                 875                 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
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Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
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Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
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Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
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Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
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His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
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Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
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gccggccuga ucgccaucgu gauggugacc aucaugcugu gcugcaugac cagcugcugc 3780

agcugccuga agggcuguug cagcugcggc agcugcugca aguucgacga ggacgacagc 3840

gagcccgugc ugaagggcgu gaagcugcac uacaccugau aauaggcugg agccucggug 3900

gccuagcuuc uugccccuug ggccucccccc cagccccucc uccccuuccu gcacccguac 3960

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<211> 3819
<212> RNA

<213> 人工序列(Artificial Sequence)

<220>
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aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

cugggcgugu acuaccacaa gaacaacaag agcuggaugg agagcgaguu ccggguguac 480

agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgccccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

ggcgugagcc ccaccaagcu gaacgaccug ugcuucacca acguguacgc cgacagcuuc 1200

gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

uacaacuaca agcugcccga cgacuucacc ggcugcguga ucgccuggaa cagcaacaac 1320

cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

uucaacuuca acggccuuac cggcaccggc gugcugaccg agagcaacaa gaaauuccug 1680

cccuuucagc aguucggccg ggacaucgcc gacaccaccg acgcugugcg ggauccccag 1740

acccuggaga uccuggacau cacccccuugc agcuucggcg gcgugagcgu gaucacccca 1800

ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

aacguguucc agacccgggc cgguugccug aucggcgccg agcacgugaa caacagcuac 1980

gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccaauuca 2040

ccccggaggg caaggagcgu ggccagccag agcaucaucg ccuacaccau gagccugggc 2100

gccgagaaca gcguggccua cagcaacaac agcaucgcca uccccaccaa cuucaccauc 2160

agcgugacca ccgagauucu gcccgugagc augaccaaga ccagcgugga cugcaccaug 2220

uacaucugcg gcgacagcac cgagugcagc aaccugcugc ugcaguacgg cagcuucugc 2280

acccagcuga accgggcccu gaccggcauc gccguggagc aggacaagaa cacccaggag 2340

guguucgccc aggugaagca gaucuacaag accccuccca ucaaggacuu cggcggcuuc 2400

aacuucagcc agauccugcc cgaccccagc aagcccagca agcggagcuu caucgaggac 2460

cugcuguuca acaaggugac ccuagccgac gccggcuuca ucaagcagua cggcgacugc 2520

cucggcgaca uagccgcccg ggaccugauc ugcgcccaga aguucaacgg ccugaccgug 2580

cugccucccc ugcugaccga cgagaugauc gcccaguaca ccagcgcccu guuagccgga 2640

accaucacca gcggcuggac uuucggcgcu ggagccgcuc ugcagauccc cuucgccaug 2700

cagauggccu accgguucaa cggcaucggc gugacccaga acgugcugua cgagaaccag 2760

aagcugaucg ccaaccaguu caacagcgcc aucggcaaga uccaggacag ccugagcagc 2820

accgcuagcg cccugggcaa gcugcaggac guggugaacc agaacgccca ggcccugaac 2880

acccugguga agcagcugag cagcaacuuc ggcgccauca gcagcgugcu gaacgacauc 2940

cugagccggc uggacaaggu ggaggccgag gugcagaucg accggcugau cacuggccgg 3000

cugcagagcc ugcagaccua cgugacccag cagcugaucc gggccgccga gauucgggcc 3060

agcgccaacc uggccgccac caagaugagc gagugcgugc uggggccagag caagcgggug 3120

gacuucugcg gcaagggcua ccaccugaug agcuuucccc agagcgcacc ccacggagug 3180

guguuccugc acgugaccua cgugcccgcc caggagaaga acuucaccac cgccccagcc 3240

aucugccacg acggcaaggc ccacuuuccc cgggagggcg uguucgugag caacggcacc 3300

cacugguucg ugacccagcg gaacuucuac gagccccaga ucaucaccac cgacaacacc 3360

uucgugagcg gcaacugcga cguggugauc ggcaucguga acaacaccgu guacgauccc 3420

cugcagcccg agcuggacag cuucaaggag gagcuggaca aguacuucaa gaaucacacc 3480

agccccgacg uggaccuggg cgacaucagc ggcaucaacg ccagcguggu gaacauccag 3540

aaggagaucg aucggcugaa cgagguggcc aagaaccuga acgagagccu gaucgaccug 3600

caggagcugg gcaaguacga gcaguacauc aaguggcccu gguacaucug gcugggcuuc 3660

aucgccggcc ugaucgccau cgugauggug accaucaugc ugugcugcau gaccagcugc 3720

ugcagcugcc ugaagggcug uugcagcugc ggcagcugcu gcaaguucga cgaggacgac 3780

agcgagcccg ugcugaaggg cgugaagcug cacuacacc 3819

<210> 32
<211> 1273
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 32

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe

20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225                 230                 235                 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
                245                 250                 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
            260                 265                 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
        275                 280                 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
    290                 295                 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305                 310                 315                 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
                325                 330                 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
            340                 345                 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
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420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly

820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu

1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1250 1255 1260

Val Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu

85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly

485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile

885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp
1250 1255 1260

<210> 34

<211> 1260
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 34

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Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
            20                  25                  30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
        35                  40                  45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
    50                  55                  60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545                 550                 555                 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
```

565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

```
Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
    770                 775                 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785                 790                 795                 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
                805                 810                 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
            820                 825                 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
        835                 840                 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
    850                 855                 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865                 870                 875                 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
                885                 890                 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
            900                 905                 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
        915                 920                 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
    930                 935                 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945                 950                 955                 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
```

965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp
1250 1255 1260

<210> 35
<211> 1260
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 35

Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
1 5 10 15

Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

```
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
    50                  55                  60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
                165                 170                 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
            180                 185                 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
        195                 200                 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
    210                 215                 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225                 230                 235                 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
```

245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val

645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gly Ser Gly Gly Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro

1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp
1250 1255 1260

<210> 36
<211> 47
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 36
gggaaauaag agagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 37
<211> 119
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 37
ugauaaauagg cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagccc 60

cuccucccccu uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 119

<210> 38
<211> 30
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 38

Met Asp Ser Lys Gly Ser Ser Gln Lys Gly Ser Arg Leu Leu Leu Leu
1 5 10 15

Leu Val Val Ser Asn Leu Leu Leu Pro Gln Gly Val Val Gly

20 25 30

<210> 39
<211> 18
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 39

Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser

<210> 40
<211> 20
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 40

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly
20

<210> 41
<211> 24
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 41

Met Leu Gly Ser Asn Ser Gly Gln Arg Val Val Phe Thr Ile Leu Leu

1 5 10 15

Leu Leu Val Ala Pro Ala Tyr Ser
20

<210> 42
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 42

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
1 5 10 15

Ala

<210> 43
<211> 15
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 43

Met Trp Leu Val Ser Leu Ala Ile Val Thr Ala Cys Ala Gly Ala
1 5 10 15

<210> 44
<211> 9
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 44
ccrccaugg 9

<210> 45
<211> 11
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 45
gggauccuac c 11

<210> 46
<211> 9
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 46
uuauuuaww 9

<210> 47
<211> 1255
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 47

Met Phe Ile Phe Leu Phe Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu
1 5 10 15

Glu Ser Cys Thr Thr Phe Asp Asp Val Gln Ala Pro Asn Tyr Pro Gln
20 25 30

His Ser Ser Ser Arg Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg
35 40 45

Ser Asp Thr Leu Tyr Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser
50 55 60

```
Asn Val Thr Gly Phe His Thr Ile Asn His Arg Phe Asp Asn Pro Val
65                  70                  75                  80

Ile Pro Phe Lys Asp Gly Val Tyr Phe Ala Ala Thr Glu Lys Ser Asn
                85                  90                  95

Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln
            100                 105                 110

Ser Val Ile Ile Ile Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys
        115                 120                 125

Asn Phe Glu Leu Cys Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Thr
    130                 135                 140

Gly Thr Gln Thr His Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr
145                 150                 155                 160

Phe Glu Tyr Ile Ser Asp Ser Phe Ser Leu Asp Val Ala Glu Lys Ser
                165                 170                 175

Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly
            180                 185                 190

Phe Leu Tyr Val Tyr Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp
        195                 200                 205

Leu Pro Ser Gly Phe Asn Ile Leu Lys Pro Ile Phe Lys Leu Pro Leu
    210                 215                 220

Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala Phe Leu Pro
225                 230                 235                 240

Ala Gln Asp Thr Trp Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr
                245                 250                 255

Leu Lys Pro Ala Thr Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile
```

260 265 270

Thr Asp Ala Val Asp Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys
275 280 285

Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn
290 295 300

Phe Arg Val Ala Pro Ser Lys Glu Val Val Arg Phe Pro Asn Ile Thr
305 310 315 320

Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Thr Phe Pro Ser
325 330 335

Val Tyr Ala Trp Glu Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr
340 345 350

Ser Val Leu Tyr Asn Ser Thr Ser Phe Ser Thr Phe Lys Cys Tyr Gly
355 360 365

Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn Val Tyr Ala
370 375 380

Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly
385 390 395 400

Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe
405 410 415

Thr Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Gln
420 425 430

Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Ser Leu Arg His Gly Lys Leu
435 440 445

Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly
450 455 460

```
Lys Pro Cys Thr Pro Pro Ala Phe Asn Cys Tyr Trp Pro Leu Asn Asp
465                 470                 475                 480

Tyr Gly Phe Tyr Ile Thr Asn Gly Ile Gly Tyr Gln Pro Tyr Arg Val
                485                 490                 495

Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly
            500                 505                 510

Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn
        515                 520                 525

Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg
    530                 535                 540

Phe Gln Pro Phe Gln Gln Phe Gly Arg Asp Val Leu Asp Phe Thr Asp
545                 550                 555                 560

Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys
                565                 570                 575

Ser Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Ser
            580                 585                 590

Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Pro Val
        595                 600                 605

Ala Ile His Ala Asp Gln Leu Thr Pro Ser Trp Arg Val Tyr Ser Thr
    610                 615                 620

Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu
625                 630                 635                 640

His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile
                645                 650                 655

Cys Ala Ser Tyr His Thr Val Ser Ser Leu Arg Ser Thr Ser Gln Lys
```

660 665 670

Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser Ser Ile Ala
675 680 685

Tyr Ser Asn Asn Thr Ile Ala Ile Pro Thr Asn Phe Ser Ile Ser Ile
690 695 700

Thr Thr Glu Val Met Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys
705 710 715 720

Asn Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu
725 730 735

Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile
740 745 750

Ala Val Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys
755 760 765

Gln Met Tyr Lys Thr Pro Thr Leu Lys Asp Phe Gly Gly Phe Asn Phe
770 775 780

Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile
785 790 795 800

Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met
805 810 815

Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile
820 825 830

Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr
835 840 845

Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala
850 855 860

```
Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe
865                 870                 875                 880

Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn
                885                 890                 895

Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala
            900                 905                 910

Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly
        915                 920                 925

Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu
    930                 935                 940

Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn
945                 950                 955                 960

Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp
                965                 970                 975

Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln
            980                 985                 990

Gln Leu Ile Arg Ala Ala Glu Ile  Arg Ala Ser Ala Asn  Leu Ala Ala
        995                 1000                1005

Thr Lys  Met Ser Glu Cys Val  Leu Gly Gln Ser Lys  Arg Val Asp
    1010                1015                1020

Phe Cys  Gly Lys Gly Tyr His  Leu Met Ser Phe Pro  Gln Ala Ala
    1025                1030                1035

Pro His  Gly Val Val Phe Leu  His Val Thr Tyr Val  Pro Ser Gln
    1040                1045                1050

Glu Arg  Asn Phe Thr Thr Ala  Pro Ala Ile Cys His  Glu Gly Lys
```

1055 1060 1065

Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser
1070 1075 1080

Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr
1085 1090 1095

Thr Asp Asn Thr Phe Val Ser Gly Ser Cys Asp Val Val Ile Gly
1100 1105 1110

Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1115 1120 1125

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1130 1135 1140

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1145 1150 1155

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1160 1165 1170

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1175 1180 1185

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile
1190 1195 1200

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Leu Leu Cys Cys
1205 1210 1215

Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Ala Cys Ser Cys Gly
1220 1225 1230

Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys
1235 1240 1245

Gly Val Lys Leu His Tyr Thr
1250 1255

<210> 48
<211> 3765
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 48
auguuuaucu uccuguucuu ccugacccug accagcggca gcgaccugga aagcugcacc 60

accuucgacg acgugcaggc ccccaacuac ccucagcaca gcucuagcag acggggcgug 120

uacuaccccg acgagaucuu cagaagcgac acccuguacc ugacccagga ccuguuccug 180

cccuucuaca gcaacgugac cggcuuccac accaucaacc acagauucga caaccccgug 240

aucccccuuca aggacggggu guacuuugcc gccaccgaga aguccaaugu cgugcgggga 300

uggguguucg gcagcaccau gaacaacaag agccagagcg ugaucaucau caacaacagc 360

accaacgucg ugauccgggc cugcaacuuc gagcugugcg acaacccauu cuucgccgug 420

uccaagccca ccggcaccca gacccacacc augaucuucg acaacgccuu caacugcacc 480

uucgaguaca ucagcgacag cuucagccug gacguggccg agaaaagcgg caacuucaag 540

caccugagag aauucguguu caagaacaag gacggcuucc uguacgugua caagggcuac 600

cagcccaucg acgucgugcg cgaucugccc agcggcuuca acauccugaa gcccaucuuc 660

aagcugcccc ugggcaucaa caucaccaac uuccgggcua uccugaccgc cuuccugccc 720

gcccaggaua ccuggggaac aagcgccgcu gccuacuucg ugggcuaccu gaagccugcc 780

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Asn Val Thr Gly Phe His Thr Ile Asn His Arg Phe Asp Asn Pro Val
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Ile Pro Phe Lys Asp Gly Val Tyr Phe Ala Ala Thr Glu Lys Ser Asn
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Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln
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Gly Thr Gln Thr His Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr
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Phe Glu Tyr Ile Ser Asp Ser Phe Ser Leu Asp Val Ala Glu Lys Ser
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Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly
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Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn
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Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly
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Thr Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Gln
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Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Ser Leu Arg His Gly Lys Leu
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gccggccuga ucgccaucgu gauggugacc aucaugcugu gcugcaugac cagcugcugc 3780

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<212> RNA
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<220>
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<212> RNA
<213> 人工序列(Artificial Sequence)

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acccagcugc caccagccua caccaacagc uucacccggg gcgucuacua ccccgacaag 180

guguuccgga gcagcguccu gcacagcacc caggaccugu uccugcccuu cuucagcaac 240

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gcacacccca aucaaccugg ugcgggaucu gccccagggc uucucagccc uggagccccu 480

gguggaccug cccaucggca ucaacaucac ccgguuccag acccugcugg cccugcaccg 540

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cgugggcuac cugcagcccc ggaccuuccu gcugaaguac aacgagaacg gcaccaucac 660

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cgagcaguac aucaaguggc ccugguacau cuggcugggc uucaucgccg gccugaucgc 3480

caucgugaug gugaccauca ugcugugcug caugaccagc ugcugcagcu gccugaaggg 3540

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<210> 56
<211> 3526
<212> RNA

<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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cguggugauc aaggugugcg aguuccaguu cugcaacgac cccuuccugg gcguguacua 180

ccacaagaac aacaagagcu ggauggagag cgaguuccgg guguacagca gcgccaacaa 240

cugcaccuuc gaguacguga gccagcccuu ccugauggac cuggagggca agcagggcaa 300

cuucaagaac cugcgggagu ucguguucaa gaacaucgac ggcuacuuca agaucuacag 360

caagcacacc ccaaucaacc uggugcggga ucugccccag ggcuucucag cccuggagcc 420

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caccgacgcc guggacugcg cccuggaccc ucugagcgag accaagugca cccugaagag 660

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<211> 3941
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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uucgacgacg ugcaggcccc caacuacccu cagcacagcu cuagcagacg gggcguguac 180

uaccccgacg agaucuucag aagcgacacc cuguaccuga cccaggaccu guuccugccc 240

uucuacagca acgugaccgg cuuccacacc aucaaccaca gauucgacaa ccccgugauc 300

cccuucaagg acggggugua cuuugccgcc accgagaagu ccaaugucgu gcggggaugg 360

guguucggca gcaccaugaa caacaagagc cagagcguga ucaucaucaa caacagcacc 420

aacgucguga uccgggccug caacuucgag cugugcgaca acccauucuu cgccgugucc 480

aagcccaccg gcacccagac ccacaccaug aucuucgaca acgccuucaa cugcaccuuc 540

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cugagagaau ucguguucaa gaacaaggac ggcuuccugu acguguacaa gggcuaccag 660

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caggauaccu ggggaacaag cgccgcugcc uacuucgugg gcuaccugaa gccugccacc 840

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ccucuggccg agcugaagug cagcgugaag uccuucgaga ucgacaaggg caucuaccag 960

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<210> 58
<211> 3941
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 58
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uucgacgacg ugcaggcccc uaacuacccu cagcacagca gcagcagaag aggcguguac 180

uacccugacg agaucuucag aagcgacacc cuguaccuga cccaggaccu guuccugccu 240

uucuacagca acgugaccgg cuuccacacc aucaaccaca gauucgacaa cccugugauc 300

ccuuucaagg acggcgugua cuucgccgcc accgagaaga gcaacguggu gagaggcugg 360

guguucggca gcaccaugaa caacaagagc cagagcguga ucaucaucaa caacagcacc 420

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35 40 45

Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
50 55 60

Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
65 70 75 80

His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
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Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
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Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
115 120 125

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Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
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Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
                165                 170                 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
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Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
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Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
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Leu Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met
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Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
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Thr Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp
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Leu Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp
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Thr Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln
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Ser Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro
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Leu Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala
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325 330 335

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Lys Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp
370 375 380

Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys
385 390 395 400

Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser
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Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala
420 425 430

Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr
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Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
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Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
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Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
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Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Phe Leu Ser Asp Asp Arg Thr
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Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
515 520 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
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Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
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Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln
565 570 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
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Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu
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Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
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Val Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr
660 665 670

Leu Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln
675 680 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
690 695 700

Gly Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser
705 710 715 720

Ser Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys

725 730 735

Ala Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Ala Ser Val Gly Ser
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Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
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Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
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Lys Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys
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Cys Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn
820 825 830

Gln Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn
835 840 845

Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
850 855 860

Phe Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser
865 870 875 880

Thr Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp
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915 920 925

Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu
930 935 940

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Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile
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Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu
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Asn Gln Lys Leu Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met
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Ile Ile Gln Arg Leu Asp Pro Pro Glu Gln Asp Ala Gln Ile Asp
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Arg Leu Ile Asn Gly Arg Leu Thr Thr Leu Asn Ala Phe Val Ala
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Ala Lys Asp Lys Val Asn Glu Cys Val Lys Ala Gln Ser Lys Arg
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Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val Ser Phe Val Val

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Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly Tyr Tyr Pro
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Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
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Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys
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Pro Pro Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp
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Glu Leu Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn
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Phe Gly Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr
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Tyr Glu Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu
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Ser Tyr Ile Asp Leu Lys Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn
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Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val
1295 1300 1305

Ala Leu Ala Leu Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys
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agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgccccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

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gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

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cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

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ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

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gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccguguca 2040

cugaggagcg uggccagcca gagcaucauc gccuacacca ugagccuggg cgccgagaac 2100

agcguggccu acagcaacaa cagcaucgcc auccccacca acuucaccau cagcgugacc 2160

accgagauuc ugcccgugag caugaccaag accagcgugg acugcaccau guacaucugc 2220

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aaccgggccc ugaccggcau cgccguggag caggacaaga acacccagga gguguucgcc 2340

caggugaagc agaucuacaa gaccccuccc aucaaggacu ucggcggcuu caacuucagc 2400

cagauccugc ccgaccccag caagcccagc aagcggagcu ucaucgagga ccugcuguuc 2460

aacaagguga cccuagccga cgccggcuuc aucaagcagu acggcgacug ccucggcgac 2520

auagccgccc gggaccugau cugcgcccag aaguucaacg gccugaccgu gcugccuccc 2580

cugcugaccg acgagaugau cgcccaguac accagcgccc uguuagccgg aaccaucacc 2640

agcggcugga cuuucggcgc uggagccgcu cugcagaucc ccuucgccau gcagauggcc 2700

uaccgguuca acggcaucgg cgugacccag aacgugcugu acgagaacca gaagcugauc 2760

gccaaccagu ucaacagcgc caucggcaag auccaggaca gccugagcag caccgcuagc 2820

gcccugggca agcugcagga cguggugaac cagaacgccc aggcccugaa cacccuggug 2880

aagcagcuga gcagcaacuu cggcgccauc agcagcgugc ugaacgacau ccugagccgg 2940

cuggacaagg uggaggccga ggugcagauc gaccggcuga ucacuggccg gcugcagagc 3000

cugcagaccu acgugaccca gcagcugauc cgggccgccg agauucgggc cagcgccaac 3060

cuggccgcca ccaagaugag cgagugcgug cuggccaga gcaagcgggu ggacuucugc 3120

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cacgugaccu acgugcccgc ccaggagaag aacuucacca ccgccccagc caucugccac 3240

gacggcaagg cccacuuucc ccgggagggc guguucguga gcaacggcac ccacugguuc 3300

gugacccagc ggaacuucua cgagccccag aucaucacca ccgacaacac cuucgugagc 3360

ggcaacugcg acguggugau cggcaucgug aacaacaccg uguacgaucc ccugcagccc 3420

gagcuggaca gcuucaagga ggagcuggac aaguacuuca agaaucacac cagccccgac 3480

guggaccugg gcgacaucag cggcaucaac gccagcgugg ugaacaucca gaaggagauc 3540

gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cug 3693

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<211> 1231
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 63

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe

180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545                 550                 555                 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
                565                 570                 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
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580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

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Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785                 790                 795                 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
                805                 810                 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
            820                 825                 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
        835                 840                 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
    850                 855                 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865                 870                 875                 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
                885                 890                 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
            900                 905                 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
        915                 920                 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
    930                 935                 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945                 950                 955                 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
                965                 970                 975

Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg
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980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu
1220 1225 1230

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<211> 3870
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 64
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cggacccagc ugccaccagc cuacaccaac agcuucaccc ggggcgucua cuaccccgac 120

aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

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ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgcccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

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gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

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cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

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cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

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cugaggagcg uggccagcca gagcaucauc gccuacacca ugagccuggg cgccgagaac 2100

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cuggccgcca ccaagaugag cgagugcgug cugggccaga gcaagcgggu ggacuucugc 3120

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gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugaagaaga agaagcggcc acggaacucc 3720

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aagauccaca uuccugaacg guccgacgaa gcccagcggg uguucaagag cagcaagacc 3840

agcagcugcg acaagagcga caccugcuuc 3870

<210> 65
<211> 1290
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 65

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20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr

130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
            340                 345                 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

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Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
            740                 745                 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
        755                 760                 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
    770                 775                 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785                 790                 795                 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
                805                 810                 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
            820                 825                 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
        835                 840                 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
    850                 855                 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865                 870                 875                 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
                885                 890                 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
            900                 905                 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
        915                 920                 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
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930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Lys Lys
1220 1225 1230

Lys Lys Arg Pro Arg Asn Ser Tyr Lys Cys Gly Thr Asn Thr Met
1235 1240 1245

Glu Arg Glu Glu Ser Glu Gln Thr Lys Lys Arg Glu Lys Ile His
1250 1255 1260

Ile Pro Glu Arg Ser Asp Glu Ala Gln Arg Val Phe Lys Ser Ser
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Lys Thr Ser Ser Cys Asp Lys Ser Asp Thr Cys Phe
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aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

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gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu

35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn

435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785 790 795 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
805 810 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
820 825 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys

835 840 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
850 855 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865 870 875 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
885 890 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
900 905 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
915 920 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
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Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Lys Arg

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Gln Tyr Lys Asp Met Met Ser Glu Gly Gly Pro Pro Gly Ala Glu
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uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

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gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

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cugaucgcca ucgugauggu gaccaucaug cug 3693

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe

180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545                 550                 555                 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
                565                 570                 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
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580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785 790 795 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
805 810 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
820 825 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
835 840 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
850 855 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865 870 875 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
885 890 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
900 905 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
915 920 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg

980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu
1220 1225 1230

<210> 70
<211> 3870
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 70
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cggacccagc ugccaccagc cuacaccaac agcuucaccc ggggcgucua cuaccccgac 120

aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

cugggcgugu acuaccacaa gaacaacaag agcuggaugg agagcgaguu ccggguguac 480

agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgcccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

ggcgugagcc ccaccaagcu gaacgaccug ugcuucacca acguguacgc cgacagcuuc 1200

gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

uacaacuaca agcugcccga cgacuucacc ggcugcguga ucgccuggaa cagcaacaac 1320

cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

uucaacuuca acggccuuac cggcaccggc gugcugaccg agagcaacaa gaaauuccug 1680

cccuuucagc aguucggccg ggacaucgcc gacaccaccg acgcugugcg ggauccccag 1740

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ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

aacguguucc agacccgggc cgguugccug aucggcgccg agcacgugaa caacagcuac 1980

gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccguguca 2040

cugaggagcg uggccagcca gagcaucauc gccuacacca ugagccuggg cgccgagaac 2100

agcguggccu acagcaacaa cagcaucgcc auccccacca acuucaccau cagcgugacc 2160

accgagauuc ugcccgugag caugaccaag accagcgugg acugcaccau guacaucugc 2220

ggcgacagca ccgagugcag caaccugcug cugcaguacg gcagcuucug cacccagcug 2280

aaccgggccc ugaccggcau cgccguggag caggacaaga acacccagga gguguucgcc 2340

caggugaagc agaucuacaa gaccccuccc aucaaggacu ucggcggcuu caacuucagc 2400

cagauccugc ccgaccccag caagcccagc aagcggagcu ucaucgagga ccugcuguuc 2460

aacaagguga cccuagccga cgccggcuuc aucaagcagu acggcgacug ccucggcgac 2520

auagccgccc gggaccugau cugcgcccag aaguucaacg gccugaccgu gcugccuccc 2580

cugcugaccg acgagaugau cgcccaguac accagcgccc uguuagccgg aaccaucacc 2640

agcggcugga cuuucggcgc uggagccgcu cugcagaucc ccuucgccau gcagauggcc 2700

uaccgguuca acggcaucgg cgugacccag aacgugcugu acgagaacca gaagcugauc 2760

gccaaccagu ucaacagcgc caucggcaag auccaggaca gccugagcag caccgcuagc 2820

gcccugggca agcugcagga cguggugaac cagaacgccc aggcccugaa cacccuggug 2880

aagcagcuga gcagcaacuu cggcgccauc agcagcgugc ugaacgacau ccugagccgg 2940

cuggaccccc ccgaggccga ggugcagauc gaccggcuga ucacuggccg gcugcagagc 3000

cugcagaccu acgugaccca gcagcugauc cgggccgccg agauucgggc cagcgccaac 3060

cuggccgcca ccaagaugag cgagugcgug cugggccaga gcaagcgggu ggacuucugc 3120

ggcaagggcu accaccugau gagcuuuccc cagagcgcac cccacggagu gguguuccug 3180

cacgugaccu acgugcccgc ccaggagaag aacuucacca ccgccccagc caucugccac 3240

gacggcaagg cccacuuucc ccgggagggc guguucguga gcaacggcac ccacugguuc 3300

gugacccagc ggaacuucua cgagccccag aucaucacca ccgacaacac cuucgugagc 3360

ggcaacugcg acguggugau cggcaucgug aacaacaccg uguacgaucc ccugcagccc 3420

gagcuggaca gcuucaagga ggagcuggac aaguacuuca agaaucacac cagccccgac 3480

guggaccugg gcgacaucag cggcaucaac gccagcgugg ugaacaucca gaaggagauc 3540

gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugaagaaga agaagcggcc acggaacucc 3720

uacaagugcg gcaccaacac cauggagcgg gaggagagcg agcagaccaa gaagcgggag 3780

aagauccaca uuccugaacg guccgacgaa gcccagcggg uguucaagag cagcaagacc 3840

agcagcugcg acaagagcga caccugcuuc 3870

<210> 71
<211> 1290
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 71

Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr

130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
            340                 345                 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

```
Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
            740                 745                 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
        755                 760                 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
    770                 775                 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785                 790                 795                 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
                805                 810                 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
            820                 825                 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
        835                 840                 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
    850                 855                 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865                 870                 875                 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
                885                 890                 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
            900                 905                 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
        915                 920                 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
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930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Lys Lys
1220 1225 1230

Lys Lys Arg Pro Arg Asn Ser Tyr Lys Cys Gly Thr Asn Thr Met
1235 1240 1245

Glu Arg Glu Glu Ser Glu Gln Thr Lys Lys Arg Glu Lys Ile His
1250 1255 1260

Ile Pro Glu Arg Ser Asp Glu Ala Gln Arg Val Phe Lys Ser Ser
1265 1270 1275

Lys Thr Ser Ser Cys Asp Lys Ser Asp Thr Cys Phe
1280 1285 1290

<210> 72
<211> 3750
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 72
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cggacccagc ugccaccagc cuacaccaac agcuucaccc ggggcgucua cuaccccgac 120

aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

cugggcgugu acuaccacaa gaacaacaag agcuggaugg agagcgaguu ccggguguac 480

agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgcccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

ggcgugagcc ccaccaagcu gaacgaccug ugcuucacca acguguacgc cgacagcuuc 1200

gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

uacaacuaca agcugcccga cgacuucacc ggcugcguga ucgccuggaa cagcaacaac 1320

cucgacagca agguggggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

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cccuuucagc aguucggccg ggacaucgcc gacaccaccg acgcugugcg ggauccccag 1740

acccuggaga uccuggacau cacccccuugc agcuucggcg gcgugagcgu gaucacccca 1800

ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

aacguguucc agacccgggc cgguugccug aucggcgccg agcacgugaa caacagcuac 1980

gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccguguca 2040

cugaggagcg uggccagcca gagcaucauc gccuacacca ugagccuggg cgccgagaac 2100

agcguggccu acagcaacaa cagcaucgcc aucccccacca acuucaccau cagcgugacc 2160

accgagauuc ugcccgugag caugaccaag accagcgugg acugcaccau guacaucugc 2220

ggcgacagca ccgagugcag caaccugcug cugcaguacg gcagcuucug cacccagcug 2280

aaccgggccc ugaccggcau cgccguggag caggacaaga acacccagga gguguucgcc 2340

caggugaagc agaucuacaa gaccccuccc aucaaggacu ucggcggcuu caacuucagc 2400

cagauccugc ccgaccccag caagcccagc aagcggagcu ucaucgagga ccugcuguuc 2460

aacaagguga cccuagccga cgccggcuuc aucaagcagu acggcgacug ccucggcgac 2520

auagccgccc gggaccugau cugcgcccag aaguucaacg gccugaccgu gcugccuccc 2580

cugcugaccg acgagaugau cgcccaguac accagcgccc uguuagccgg aaccaucacc 2640

agcggcugga cuuucggcgc uggagccgcu cugcagaucc ccuucgccau gcagauggcc 2700

uaccgguuca acggcaucgg cgugacccag aacgugcugu acgagaacca gaagcugauc 2760

gccaaccagu ucaacagcgc caucggcaag auccaggaca gccugagcag caccgcuagc 2820

gcccugggca agcugcagga cguggugaac cagaacgccc aggcccugaa cacccuggug 2880

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cuggaccccc ccgaggccga ggugcagauc gaccggcuga ucacuggccg gcugcagagc 3000

cugcagaccu acgugaccca gcagcugauc cgggccgccg agauucgggc cagcgccaac 3060

cuggccgcca ccaagaugag cgagugcgug cuggggccaga gcaagcgggu ggacuucugc 3120

ggcaagggcu accaccugau gagcuuuccc cagagcgcac cccacggagu gguguuccug 3180

cacgugaccu acgugcccgc ccaggagaag aacuucacca ccgccccagc caucugccac 3240

gacggcaagg cccacuuucc ccgggagggc guguucguga gcaacggcac ccacugguuc 3300

gugacccagc ggaacuucua cgagccccag aucaucacca ccgacaacac cuucgugagc 3360

ggcaacugcg acguggugau cggcaucgug aacaacaccg uguacgaucc ccugcagccc 3420

gagcuggaca gcuucaagga ggagcuggac aaguacuuca agaaucacac cagccccgac 3480

guggaccugg gcgacaucag cggcaucaac gccagcgugg ugaacaucca gaaggagauc 3540

gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugaagcggc aguacaagga caugaugagc 3720

gagggaggac caccuggcgc ugagccacag 3750

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<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 73

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu

35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn

435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785 790 795 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
805 810 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
820 825 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys

835 840 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
850 855 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865 870 875 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
885 890 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
900 905 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
915 920 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Lys Arg

1220 1225 1230

Gln Tyr Lys Asp Met Met Ser Glu Gly Gly Pro Pro Gly Ala Glu
1235 1240 1245

Pro Gln
1250

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<211> 3795
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
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<400> 74
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cggacccagc ugccaccagc cuacaccaac agcuucaccc ggggcgucua cuaccccgac 120

aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

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uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

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ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

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gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

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cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

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aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

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accgagauuc ugcccgugag caugaccaag accagcgugg acugcaccau guacaucugc 2220

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gugacccagc ggaacuucua cgagccccag aucaucacca ccgacaacac cuucgugagc 3360

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gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugugcugca ugaccagcug cugcagcugc 3720

cugaagggcu guugcagcug cggcagcugc ugcaaguucg acgaggacga cagcgagccc 3780

gugcugaagg gcgug 3795

<210> 75

<211> 1265
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 75

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
            20                  25                  30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
        35                  40                  45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
    50                  55                  60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val

565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser
675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

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Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
    770                 775                 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785                 790                 795                 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
                805                 810                 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
            820                 825                 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
        835                 840                 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
    850                 855                 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865                 870                 875                 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
                885                 890                 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
            900                 905                 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
        915                 920                 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
    930                 935                 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945                 950                 955                 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
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965 970 975

Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys
1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys
1220 1225 1230

Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys Ser Cys Gly
1235 1240 1245

Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys
1250 1255 1260

Gly Val
1265

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<211> 3795
<212> RNA
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<220>
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aagguguucc ggagcagcgu ccugcacagc acccaggacc uguuccugcc cuucuucagc 180

aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

aaccccgugc ugcccuucaa cgacggcgug uacuucgcca gcaccgagaa gagcaacauc 300

auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

aauaacgcca ccaacguggu gaucaaggug ugcgaguucc aguucugcaa cgaccccuuc 420

cugggcgugu acuaccacaa gaacaacaag agcuggaugg agagcgaguu ccggguguac 480

agcagcgcca acaacugcac cuucgaguac gugagccagc ccuuccugau ggaccuggag 540

ggcaagcagg gcaacuucaa gaaccugcgg gaguucgugu ucaagaacau cgacggcuac 600

uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agcccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

gagaacggca ccaucaccga cgccguggac ugcgcccugg acccucugag cgagaccaag 900

ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

ugcguggccg acuacagcgu gcuguacaac agcgccagcu ucagcaccuu caagugcuac 1140

ggcgugagcc ccaccaagcu gaacgaccug ugcuucacca acguguacgc cgacagcuuc 1200

gugauccgug gcgacgaggu gcggcagauc gcacccggcc agacaggcaa gaucgccgac 1260

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cucgacagca agguggggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

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gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccguguca 2040

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agcguggccu acagcaacaa cagcaucgcc aucccccacca acuucaccau cagcgugacc 2160

accgagauuc ugcccgugag caugaccaag accagcgugg acugcaccau guacaucugc 2220

ggcgacagca ccgagugcag caaccugcug cugcaguacg gcagcuucug cacccagcug 2280

aaccgggccc ugaccggcau cgccguggag caggacaaga acacccagga gguguucgcc 2340

caggugaagc agaucuacaa gaccccuccc aucaaggacu ucggcggcuu caacuucagc 2400

cagauccugc ccgaccccag caagcccagc aagcggagcu ucaucgagga ccugcuguuc 2460

aacaagguga cccuagccga cgccggcuuc aucaagcagu acggcgacug ccucggcgac 2520

auagccgccc gggaccugau cugcgcccag aaguucaacg gccugaccgu gcugccuccc 2580

cugcugaccg acgagaugau cgcccaguac accagcgccc uguuagccgg aaccaucacc 2640

agcggcugga cuuucggcgc uggagccgcu cugcagaucc ccuucgccau gcagauggcc 2700

uaccgguuca acggcaucgg cgugacccag aacgugcugu acgagaacca gaagcugauc 2760

gccaaccagu ucaacagcgc caucggcaag auccaggaca gccugagcag caccgcuagc 2820

gcccugggca agcugcagga cguggugaac cagaacgccc aggcccugaa cacccuggug 2880

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cuggaccccc ccgaggccga ggugcagauc gaccggcuga ucacuggccg gcugcagagc 3000

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cuggccgcca ccaagaugag cgagugcgug cuggggccaga gcaagcgggu ggacuucugc 3120

ggcaagggcu accaccugau gagcuuuccc cagagcgcac cccacggagu gguguuccug 3180

cacgugaccu acgugcccgc ccaggagaag aacuucacca ccgccccagc caucugccac 3240

gacggcaagg cccacuuucc ccgggagggc guguucguga gcaacggcac ccacugguuc 3300

gugacccagc ggaacuucua cgagccccag aucaucacca ccgacaacac cuucgugagc 3360

ggcaacugcg acguggugau cggcaucgug aacaacaccg uguacgaucc ccugcagccc 3420

gagcuggaca gcuucaagga ggagcuggac aaguacuuca agaaucacac cagccccgac 3480

guggaccugg gcgacaucag cggcaucaac gccagcgugg ugaacaucca gaaggagauc 3540

gaucggcuga acgagguggc caagaaccug aacgagagcc ugaucgaccu gcaggagcug 3600

ggcaaguacg agcaguacau caaguggccc ugguacaucu ggcugggcuu caucgccggc 3660

cugaucgcca ucgugauggu gaccaucaug cugugcugca ugaccagcug cugcagcugc 3720

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gugcugaagg gcgug 3795

<210> 77
<211> 1265
<212> PRT
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<220>
<223> 合成

<400> 77

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala

275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Val Ser Leu Arg Ser Val Ala Ser Gln Ser

675 680 685

Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr
690 695 700

Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr
705 710 715 720

Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr
725 730 735

Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln
740 745 750

Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala
755 760 765

Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln
770 775 780

Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser
785 790 795 800

Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu
805 810 815

Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys
820 825 830

Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys
835 840 845

Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp
850 855 860

Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr
865 870 875 880

Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala
885 890 895

Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val
900 905 910

Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile
915 920 925

Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys
930 935 940

Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val
945 950 955 960

Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp
965 970 975

Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg
980 985 990

Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln
995 1000 1005

Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala
1010 1015 1020

Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp
1025 1030 1035

Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1040 1045 1050

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln
1055 1060 1065

Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys

1070 1075 1080

Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His
1085 1090 1095

Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr
1100 1105 1110

Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly
1115 1120 1125

Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp
1130 1135 1140

Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser
1145 1150 1155

Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val
1160 1165 1170

Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
1175 1180 1185

Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr
1190 1195 1200

Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile
1205 1210 1215

Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys
1220 1225 1230

Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys Ser Cys Gly
1235 1240 1245

Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys
1250 1255 1260

Gly Val
1265

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aacgugaccu gguuccacgc cauccacgug agcggcacca acggcaccaa gcgguucgac 240

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auccggggcu ggaucuucgg caccacccug gacagcaaga cccagagccu gcugaucgug 360

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uucaagaucu acagcaagca caccccaauc aaccuggugc gggaucugcc ccagggcuuc 660

ucagcccugg agccccuggu ggaccugccc aucggcauca acaucacccg guuccagacc 720

cugcuggccc ugcaccggag cuaccugacc ccaggcgaca gcagcagcgg guggacagca 780

ggcgcggcug cuuacuacgu gggcuaccug cagccccgga ccuuccugcu gaaguacaac 840

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ugcacccuga agagcuucac cguggagaag ggcaucuacc agaccagcaa cuuccgggug 960

cagcccaccg agagcaucgu gcgguucccc aacaucacca accugugccc cuucggcgag 1020

guguucaacg ccacccgguu cgccagcgug uacgccugga accggaagcg gaucagcaac 1080

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cucgacagca aggugggcgg caacuacaac uaccuguacc ggcuguuccg gaagagcaac 1380

cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

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caggagcugg gcaaguacga gcaguacauc aaguggcccu gguacaucug gcuggggcuuc 3660

aucgccggcc ugaucgccau cgugauggug accaucaugc ugugcugcau gaccagcugc 3720

ugcagcugcc ugaaggggcug uugcagcugc ggcagcugcu gcaaguucga cgaggacgac 3780

agcgagcccg ugcugaaggg cgug 3804

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<211> 1268
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 79

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20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320

Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe

385 390 395 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
690 695 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe

785 790 795 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
805 810 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
835 840 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975

Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
1010 1015 1020

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1025 1030 1035

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1040 1045 1050

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1055 1060 1065

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1070 1075 1080

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1085 1090 1095

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1100 1105 1110

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1115 1120 1125

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1130 1135 1140

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1145 1150 1155

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1160 1165 1170

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu

1175 1180 1185

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1205 1210 1215

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1220 1225 1230

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1250 1255 1260

Val Leu Lys Gly Val
1265

<210> 80
<211> 666
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

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aaccugguga ucggcuuccu guuccugacc uggaucugcc ugcugcaguu cgccuacgcc 120

aaccggaacc guuuccugua caucaucaag cugaucuucc uguggcugcu guggcccgug 180

acccuggccu gcuucgugcu ggccgccgug uaccggauca acuggaucac cggcggcauc 240

gccaucgcca uggccugccu ggugggccug auguggcuga gcuacuucau cgccagcuuc 300

cggcuguucg cccggacccg gagcaugugg agcuucaacc ccgagaccaa cauccugcug 360

aacgugcccc ugcacggcac aauccugacc cggccccugc uggagagcga gcuugugauc 420

ggcgccguga uccugcgggg ccaccugagg aucgccggcc aucaccuggg ccggugcgac 480

aucaaggacc ugcccaagga gaucaccgug gccaccagcc ggacccugag cuacuacaaa 540

cugggcgcca gccagagagu ggccggagac agcggcuucg ccgccuacag ccgguaccgg 600

aucggcaacu acaagcugaa caccgaccac agcagcagca gcgacaacau cgcccugcug 660

gugcag 666

<210> 81
<211> 222
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 81

Met Ala Asp Ser Asn Gly Thr Ile Thr Val Glu Glu Leu Lys Lys Leu
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Leu Glu Gln Trp Asn Leu Val Ile Gly Phe Leu Phe Leu Thr Trp Ile
20 25 30

Cys Leu Leu Gln Phe Ala Tyr Ala Asn Arg Asn Arg Phe Leu Tyr Ile
35 40 45

Ile Lys Leu Ile Phe Leu Trp Leu Leu Trp Pro Val Thr Leu Ala Cys
50 55 60

Phe Val Leu Ala Ala Val Tyr Arg Ile Asn Trp Ile Thr Gly Gly Ile
65 70 75 80

Ala Ile Ala Met Ala Cys Leu Val Gly Leu Met Trp Leu Ser Tyr Phe
85 90 95

Ile Ala Ser Phe Arg Leu Phe Ala Arg Thr Arg Ser Met Trp Ser Phe
100 105 110

Asn Pro Glu Thr Asn Ile Leu Leu Asn Val Pro Leu His Gly Thr Ile

115 120 125

Leu Thr Arg Pro Leu Leu Glu Ser Glu Leu Val Ile Gly Ala Val Ile
130 135 140

Leu Arg Gly His Leu Arg Ile Ala Gly His His Leu Gly Arg Cys Asp
145 150 155 160

Ile Lys Asp Leu Pro Lys Glu Ile Thr Val Ala Thr Ser Arg Thr Leu
165 170 175

Ser Tyr Tyr Lys Leu Gly Ala Ser Gln Arg Val Ala Gly Asp Ser Gly
180 185 190

Phe Ala Ala Tyr Ser Arg Tyr Arg Ile Gly Asn Tyr Lys Leu Asn Thr
195 200 205

Asp His Ser Ser Ser Ser Asp Asn Ile Ala Leu Leu Val Gln
210 215 220

<210> 82
<211> 225
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 82
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cuggccuucg ugguguuccu gcuggugacc cuggccaucc ugaccgcccu gcggcugugu 120

gccuacugcu gcaacaucgu gaacgugagc cuggugaagc ccagcuucua cguguacagc 180

cgggugaaga accugaacag cagccgggug ccugaccugc uggug 225

<210> 83
<211> 75
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 83

Met Tyr Ser Phe Val Ser Glu Glu Thr Gly Thr Leu Ile Val Asn Ser
1 5 10 15

Val Leu Leu Phe Leu Ala Phe Val Val Phe Leu Leu Val Thr Leu Ala
20 25 30

Ile Leu Thr Ala Leu Arg Leu Cys Ala Tyr Cys Cys Asn Ile Val Asn
35 40 45

Val Ser Leu Val Lys Pro Ser Phe Tyr Val Tyr Ser Arg Val Lys Asn
50 55 60

Leu Asn Ser Ser Arg Val Pro Asp Leu Leu Val
65 70 75

<210> 84
<211> 1257
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 84
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cguccucagg gccugcccaa caacaccgcc agcugguuca ccgcccugac ccagcacggc 180

aaggaggacc ugaaguuccc ucggggccaa ggagugccca ucaacaccaa cagcagcccc 240

gacgaccaga ucggcuacua cagaagggcc acccggagga uccggggagg ggacggcaag 300

augaaggacc ugucucccccg gugguacuuc uacuaucuug gcacgggccc ugaagcuggc 360

cugccguacg gcgcaaacaa ggacggcauc aucugggucg ccaccgaggg agcccugaac 420

accccgaagg accacaucgg cacccggaau cccgccaaca acgccgccau cguucugcag 480

cugccccagg gcaccacccu gcccaagggc uucuacgccg agggcagcag aggcggcuca 540

caggccagca gccggucaag cagccggagc cggaacagca gccggaacuc cacacccggc 600

ucuagccgag gcacaagccc cgccagaaug gcaggaaacg gcggcgacgc ugccuuagcc 660

cugcuguugc uggaccggcu gaaccagcuc gagagcaaga ugagcggcaa gggucagcag 720

cagcaaggcc aaaccgugac caagaagagc gccgccgagg cuagcaagaa gccccggcag 780

aagcggaccg ccaccaaggc cuacaacgug acccaggccu ucggucggag aggccccgag 840

cagacccagg gcaacuucgg cgaccaggag cugauccggc agggcaccga cuacaagcac 900

uggccccaga ucgcccaguu cgccccuagc gccucagccu ucuucggcau gagccggauc 960

ggcauggagg ugacucccag cggcaccugg cugaccuaca ccggcgccau caagcuggac 1020

gacaaggacc ccaacuucaa ggaccaggug auccugcuga acaagcacau cgacgccuac 1080

aagaccuuuc cgcccaccga gcccaagaag gacaagaaga agaaggccga cgagacccag 1140

gcccugcccc aacggcagaa gaagcagcag accgucaccu uacugcccgc agccgaccug 1200

gacgacuuca gcaagcagcu gcagcagagc augagcagcg ccgacagcac ccaggcc 1257

<210> 85
<211> 419
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 85

Met Ser Asp Asn Gly Pro Gln Asn Gln Arg Asn Ala Pro Arg Ile Thr
1 5 10 15

Phe Gly Gly Pro Ser Asp Ser Thr Gly Ser Asn Gln Asn Gly Glu Arg
20 25 30

Ser Gly Ala Arg Ser Lys Gln Arg Arg Pro Gln Gly Leu Pro Asn Asn
35 40 45

Thr Ala Ser Trp Phe Thr Ala Leu Thr Gln His Gly Lys Glu Asp Leu

50 55 60

Lys Phe Pro Arg Gly Gln Gly Val Pro Ile Asn Thr Asn Ser Ser Pro
65 70 75 80

Asp Asp Gln Ile Gly Tyr Tyr Arg Arg Ala Thr Arg Arg Ile Arg Gly
85 90 95

Gly Asp Gly Lys Met Lys Asp Leu Ser Pro Arg Trp Tyr Phe Tyr Tyr
100 105 110

Leu Gly Thr Gly Pro Glu Ala Gly Leu Pro Tyr Gly Ala Asn Lys Asp
115 120 125

Gly Ile Ile Trp Val Ala Thr Glu Gly Ala Leu Asn Thr Pro Lys Asp
130 135 140

His Ile Gly Thr Arg Asn Pro Ala Asn Asn Ala Ala Ile Val Leu Gln
145 150 155 160

Leu Pro Gln Gly Thr Thr Leu Pro Lys Gly Phe Tyr Ala Glu Gly Ser
165 170 175

Arg Gly Gly Ser Gln Ala Ser Ser Arg Ser Ser Ser Arg Ser Arg Asn
180 185 190

Ser Ser Arg Asn Ser Thr Pro Gly Ser Ser Arg Gly Thr Ser Pro Ala
195 200 205

Arg Met Ala Gly Asn Gly Gly Asp Ala Ala Leu Ala Leu Leu Leu Leu
210 215 220

Asp Arg Leu Asn Gln Leu Glu Ser Lys Met Ser Gly Lys Gly Gln Gln
225 230 235 240

Gln Gln Gly Gln Thr Val Thr Lys Lys Ser Ala Ala Glu Ala Ser Lys
245 250 255

Lys Pro Arg Gln Lys Arg Thr Ala Thr Lys Ala Tyr Asn Val Thr Gln
260 265 270

Ala Phe Gly Arg Arg Gly Pro Glu Gln Thr Gln Gly Asn Phe Gly Asp
275 280 285

Gln Glu Leu Ile Arg Gln Gly Thr Asp Tyr Lys His Trp Pro Gln Ile
290 295 300

Ala Gln Phe Ala Pro Ser Ala Ser Ala Phe Phe Gly Met Ser Arg Ile
305 310 315 320

Gly Met Glu Val Thr Pro Ser Gly Thr Trp Leu Thr Tyr Thr Gly Ala
325 330 335

Ile Lys Leu Asp Asp Lys Asp Pro Asn Phe Lys Asp Gln Val Ile Leu
340 345 350

Leu Asn Lys His Ile Asp Ala Tyr Lys Thr Phe Pro Pro Thr Glu Pro
355 360 365

Lys Lys Asp Lys Lys Lys Lys Ala Asp Glu Thr Gln Ala Leu Pro Gln
370 375 380

Arg Gln Lys Lys Gln Gln Thr Val Thr Leu Leu Pro Ala Ala Asp Leu
385 390 395 400

Asp Asp Phe Ser Lys Gln Leu Gln Gln Ser Met Ser Ser Ala Asp Ser
405 410 415

Thr Gln Ala

<210> 86
<211> 3869
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 86
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acccagcugc caccagccua caccaacagc uucacccggg gcgucuacua ccccgacaag 180

guguuccgga gcagcguccu gcacagcacc caggaccugu uccugcccuu cuucagcaac 240

gugaccuggu uccacgccau ccacgugagc ggcaccaacg gcaccaagcg guucgacaac 300

cccgugcugc ccuucaacga cggcguguac uucgccagca ccgagaagag caacaucauc 360

cggggcugga ucuucggcac cacccuggac agcaagaccc agagccugcu gaucgugaau 420

aacgccacca acguggugau caaggugugc gaguuccagu ucugcaacga ccccuuccug 480

ggcguguacu accacaagaa caacaagagc uggauggaga gcgaguuccg gguguacagc 540

agcgccaaca acugcaccuu cgaguacgug agccagcccu uccugaugga ccuggagggc 600

aagcagggca acuucaagaa ccugcgggag uucguguuca agaacaucga cggcuacuuc 660

aagaucuaca gcaagcacac cccaaucaac cuggugcggg aucugcccca gggcuucuca 720

gcccuggagc cccuggugga ccugcccauc ggcaucaaca ucaccccguu ccagacccug 780

cuggcccugc accggagcua ccugacccca ggcgacagca gcagcgggug gacagcaggc 840

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aacggcacca ucaccgacgc cguggacugc gcccuggacc cucugagcga gaccaagugc 960

acccugaaga gcuucaccgu ggagaagggc aucuaccaga ccagcaacuu ccgggugcag 1020

cccaccgaga gcaucgugcg guuccccaac aucaccaacc ugugccccuu cggcgaggug 1080

uucaacgcca cccgguucgc cagcguguac gccuggaacc ggaagcggau cagcaacugc 1140

guggccgacu acagcgugcu guacaacagc gccagcuuca gcaccuucaa gugcuacggc 1200

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gacagcaagg ugggcggcaa cuacaacuac cuguaccggc uguuccggaa gagcaaccug 1440

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ggcguggagg gcuucaacug cuacuucccu cugcagagcu acggcuucca gcccaccaac 1560

ggcgugggcu accagcccua ccggguggug gugcugagcu ucgagcugcu gcacgcccca 1620

gccaccgugu guggccccaa gaagagcacc aaccugguga agaacaagug cgugaacuuc 1680

aacuucaacg gccuuaccgg caccggcgug cugaccgaga gcaacaagaa auuccugccc 1740

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guguuccaga cccgggccgg uugccugauc ggcgccgagc acgugaacaa cagcuacgag 2040

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aaggugaccc uagccgacgc cggcuucauc aagcaguacg gcgacugccu cggcgacaua 2580

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gacaaggugg aggccgaggu gcagaucgac cggcugauca cuggccggcu gcagagccug 3060

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cggcugaacg agguggccaa gaaccugaac gagagccuga ucgaccugca ggagcugggc 3660

aaguacgagc aguacaucaa guggcccugg uacaucuggc ugggcuucau cgccggccug 3720

aucgccaucg ugauggugac caucaugcug ugauaauagg cuggagccuc gguggccuag 3780

cuucuugccc cuugggccuc cccccagccc cuccucccca uccugcaccc guacccccgu 3840

ggucuuugaa uaaagucuga gugggcggc 3869

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<211> 4046
<212> RNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 合成

<400> 87
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acccagcugc caccagccua caccaacagc uucacccggg gcgucuacua ccccgacaag 180

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cggggcugga ucuucggcac cacccuggac agcaagaccc agagccugcu gaucgugaau 420

aacgccacca acguggugau caaggugugc gaguuccagu ucugcaacga ccccuuccug 480

ggcguguacu accacaagaa caacaagagc uggauggaga gcgaguuccg gguguacagc 540

agcgccaaca acugcaccuu cgaguacgug agccagcccu uccugaugga ccuggagggc 600

aagcagggca acuucaagaa ccugcgggag uucguguuca agaacaucga cggcuacuuc 660

aagaucuaca gcaagcacac cccaaucaac cuggugcggg aucugcccca gggcuucuca 720

gcccuggagc cccuggugga ccugcccauc ggcaucaaca ucacccgguu ccagacccug 780

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aacggcacca ucaccgacgc cguggacugc gcccuggacc cucugagcga gaccaagugc 960

acccugaaga gcuucaccgu ggagaagggc aucuaccaga ccagcaacuu ccgggugcag 1020

cccaccgaga gcaucgugcg guuccccaac aucaccaacc ugugccccuu cggcgaggug 1080

uucaacgcca cccgguucgc cagcguguac gccuggaacc ggaagcggau cagcaacugc 1140

guggccgacu acagcgugcu guacaacagc gccagcuuca gcaccuucaa gugcuacggc 1200

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aacuacaagc ugcccgacga cuucaccggc ugcgugaucg ccuggaacag caacaaccuc 1380

gacagcaagg ugggcggcaa cuacaacuac cuguaccggc uguuccggaa gagcaaccug 1440

aagcccuucg agcgggacau cagcaccgag aucuaccaag ccggcuccac cccuugcaac 1500

ggcguggagg gcuucaacug cuacuucccu cugcagagcu acggcuucca gcccaccaac 1560

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aacuucaacg gccuuaccgg caccggcgug cugaccgaga gcaacaagaa auuccugccc 1740

uuucagcagu ucggccggga caucgccgac accaccgacg cugugcggga uccccagacc 1800

cuggagaucc uggacaucac cccuugcagc uucggcggcg ugagcgugau caccccaggc 1860

accaacacca gcaaccaggu ggccgugcug uaccaggacg ugaacugcac cgaggugccc 1920

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aggagcgugg ccagccagag caucaucgcc uacaccauga gccugggcgc cgagaacagc 2160

guggccuaca gcaacaacag caucgccauc cccaccaacu ucaccaucag cgugaccacc 2220

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gacagcaccg agugcagcaa ccugcugcug caguacggca gcuucugcac ccagcugaac 2340

cgggcccuga ccggcaucgc cguggagcag gacaagaaca cccaggaggu guucgcccag 2400

gugaagcaga ucuacaagac cccucccauc aaggacuucg gcggcuucaa cuucagccag 2460

auccugcccg accccagcaa gcccagcaag cggagcuuca ucgaggaccu gcuguucaac 2520

aaggugaccc uagccgacgc cggcuucauc aagcaguacg gcgacugccu cggcgacaua 2580

gccgcccggg accugaucug cgcccagaag uucaacggcc ugaccgugcu gccuccccug 2640

cugaccgacg agaugaucgc ccaguacacc agcgcccugu uagccggaac caucaccagc 2700

ggcuggacuu ucggcgcugg agccgcucug cagauccccu ucgccaugca gauggccuac 2760

cgguucaacg gcaucggcgu gacccagaac gugcuguacg agaaccagaa gcugaucgcc 2820

aaccaguuca acagcgccau cggcaagauc caggacagcc ugagcagcac cgcuagcgcc 2880

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ggcgccagcc agagaguggc cggagacagc ggcuucgccg ccuacagccg guaccggauc 660

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uacugcugca acaucgugaa cgugagccug gugaagccca gcuucuacgu guacagccgg 240

gugaagaacc ugaacagcag ccgggugccu gaccugcugg ugugauaaua ggcuggagcc 300

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ccucagggcc ugcccaacaa caccgccagc ugguucaccg cccugaccca gcacggcaag 240

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cugaagcccu ucgagcggga caucagcacc gagaucuacc aagccggcuc caccccuugc 1440

aacggcgugg agggcuucaa cugcuacuuc ccucugcaga gcuacggcuu ccagcccacc 1500

aacggcgugg gcuaccagcc cuaccgggug guggugcuga gcuucgagcu gcugcacgcc 1560

ccagccaccg uguguggccc caagaagagc accaaccugg ugaagaacaa gugcgugaac 1620

uucaacuuca acggccuuac cggcaccggc gugcugaccg agagcaacaa gaaauuccug 1680

cccuuucagc aguucggccg ggacaucgcc gacaccaccg acgcugugcg ggaucccccag 1740

acccuggaga uccuggacau cacccccuugc agcuucggcg gcgugagcgu gaucacccca 1800

ggcaccaaca ccagcaacca gguggccgug cuguaccagg acgugaacug caccgaggug 1860

cccguggcca uccacgccga ccagcugaca cccaccuggc gggucuacag caccggcagc 1920

aacguguucc agacccgggc cgguugccug aucggcgccg agcacgugaa caacagcuac 1980

gagugcgaca uccccaucgg cgccggcauc ugugccagcu accagaccca gaccaauuca 2040

ccccggaggg caaggagcgu ggccagccag agcaucaucg ccuacaccau gagccugggc 2100

gccgagaaca gcguggccua cagcaacaac agcaucgcca uccccaccaa cuucaccauc 2160

agcgugacca ccgagauucu gcccgugagc augaccaaga ccagcgugga cugcaccaug 2220

uacaucugcg gcgacagcac cgagugcagc aaccugcugc ugcaguacgg cagcuucugc 2280

acccagcuga accgggcccu gaccggcauc gccguggagc aggacaagaa cacccaggag 2340

guguucgccc aggugaagca gaucuacaag accccuccca ucaaggacuu cggcggcuuc 2400

aacuucagcc agauccugcc cgaccccagc aagcccagca agcggagcuu caucgaggac 2460

cugcuguuca acaaggugac ccuagccgac gccggcuuca ucaagcagua cggcgacugc 2520

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cugccucccc ugcugaccga cgagaugauc gcccaguaca ccagcgcccu guuagccgga 2640

accaucacca gcggcuggac uuucggcgcu ggagccgcuc ugcagauccc cuucgccaug 2700

cagauggccu accgguucaa cggcaucggc gugacccaga acgugcugua cgagaaccag 2760

aagcugaucg ccaaccaguu caacagcgcc aucggcaaga uccaggacag ccugagcagc 2820

accgcuagcg cccugggcaa gcugcaggac guggugaacc agaacgccca ggcccugaac 2880

acccugguga agcagcugag cagcaacuuc ggcgccauca gcagcgugcu gaacgacauc 2940

cugagccggc uggacccucc cgaggccgag gugcagaucg accggcugau cacuggccgg 3000

cugcagagcc ugcagaccua cgugacccag cagcugaucc gggccgccga gauucgggcc 3060

agcgccaacc uggccgccac caagaugagc gagugcgugc uggggccagag caagcgggug 3120

gacuucugcg gcaagggcua ccaccugaug agcuuucccc agagcgcacc ccacggagug 3180

guguuccugc acgugaccua cgugcccgcc caggagaaga acuucaccac cgccccagcc 3240

aucugccacg acggcaaggc ccacuuuccc cgggagggcg uguucgugag caacggcacc 3300

cacugguucg ugacccagcg gaacuucuac gagccccaga ucaucaccac cgacaacacc 3360

uucgugagcg gcaacugcga cguggugauc ggcaucguga acaacaccgu guacgauccc 3420

cugcagcccg agcuggacag cuucaaggag gagcuggaca aguacuucaa gaaucacacc 3480

agccccgacg uggaccuggg cgacaucagc ggcaucaacg ccagcguggu gaacauccag 3540

aaggagaucg aucggcugaa cgagguggcc aagaaccuga acgagagccu gaucgaccug 3600

caggagcugg gcaaguacga gcaguacauc aaguggcccu gguacaucug gcugggcuuc 3660

aucgccggcc ugaucgccau cgugauggug accaucaugc ugugcugcau gaccagcugc 3720

ugcagcugcc ugaagggcug uugcagcugc ggcagcugcu gcaaguucga cgaggacgac 3780

agcgagcccg ugcugaaggg cgugaagcug cacuacacc 3819

【發明申請專利範圍】

【請求項1】

一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框編碼具有雙脯胺酸穩定性突變之SARS-CoV-2刺突(S)蛋白。

【請求項2】

如請求項1之mRNA，其中該雙脯胺酸穩定性突變位於對應於野生型SARS-CoV-2 S蛋白之K986及V987的位置。

【請求項3】

如請求項1之mRNA，其中該冠狀病毒抗原包含與SEQ ID NO: 29之胺基酸序列具有至少80%、至少85%、至少90%、至少95%或至少98%一致性之胺基酸序列。

【請求項4】

如請求項1之mRNA，其中該SARS-CoV-2 S蛋白包含SEQ ID NO: 29之胺基酸序列。

【請求項5】

如請求項1之mRNA，其中該mRNA包含5'非轉譯區(UTR)及3' UTR。

【請求項6】

如請求項5之mRNA，其中該5' UTR包含SEQ ID NO: 2或SEQ ID NO: 36之核苷酸序列及/或該3' UTR包含SEQ ID NO: 4或SEQ ID NO: 37之核苷酸序列。

【請求項7】

一種組合物，其包含脂質奈米顆粒及信使RNA (mRNA)，該信使

RNA包含編碼SARS-CoV-2刺突(S)蛋白之開放閱讀框(ORF)，該SARS-CoV-2刺突(S)蛋白具有野生型SARS-CoV-2 S蛋白之雙脯胺酸穩定性突變。

【請求項8】

如請求項7之組合物，其中該脂質奈米顆粒包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

【請求項9】

如請求項8之組合物，其中該脂質奈米顆粒包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60 mol%可電離之陽離子脂質。

【請求項10】

一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 28之核苷酸序列具有至少80%一致性之核苷酸序列且編碼包含SEQ ID NO: 29之胺基酸序列之多肽。

【請求項11】

如請求項10之mRNA，其中該ORF包含與SEQ ID NO: 28之核苷酸序列具有至少85%、至少90%、至少95%或至少98%一致性之核苷酸序列。

【請求項12】

如請求項10之mRNA，其中該ORF包含SEQ ID NO: 28之核苷酸序列。

【請求項13】

如請求項10之mRNA，其中該mRNA包含與SEQ ID NO: 27之核苷酸序列具有至少80%、至少85%、至少90%、至少95%或至少98%一致性之

核苷酸序列。

【請求項14】

如請求項10之mRNA，其中該mRNA包含SEQ ID NO: 27之核苷酸序列。

【請求項15】

如請求項10之mRNA，其中該mRNA包含5'非轉譯區(UTR)及3' UTR。

【請求項16】

如請求項15之mRNA，其中該5' UTR包含SEQ ID NO: 2或SEQ ID NO: 36之核苷酸序列。

【請求項17】

如請求項15之mRNA，其中該3' UTR包含SEQ ID NO: 4或SEQ ID NO: 37之核苷酸序列。

【請求項18】

如請求項10至17中任一項之mRNA，其中該mRNA包含化學修飾。

【請求項19】

如請求項18之mRNA，其中該mRNA經1-甲基-假尿苷化學修飾，使得序列中之各U為1-甲基-假尿苷。

【請求項20】

一種組合物，其包含脂質奈米顆粒及信使RNA (mRNA)，該信使RNA包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 28之核苷酸序列具有至少80%一致性之核苷酸序列且編碼包含SEQ ID NO: 29之胺基酸序列之多肽。

【請求項21】

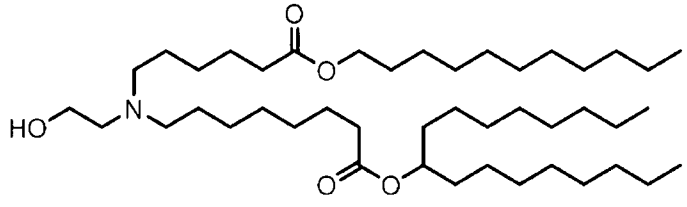
如請求項20之組合物，其中該脂質奈米顆粒包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

【請求項22】

如請求項21之組合物，其中該脂質奈米顆粒包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60 mol%可電離之陽離子脂質。

【請求項23】

如請求項22之組合物，其中該PEG修飾之脂質為1,2-二肉豆蔻醯基-sn-甘油、甲氧基聚乙二醇(PEG2000 DMG)，該非陽離子脂質為1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，該固醇為膽固醇；且該可電離之陽離子脂質具有化合物1之結構：



(化合物1)。

【請求項24】

一種信使核糖核酸(mRNA)，其包含開放閱讀框(ORF)，該開放閱讀框包含與SEQ ID NO: 3、7、10、13、16、19、22、25、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、84或106中之任一者之核苷酸序列具有至少80%一致性之核苷酸序列。

【請求項25】

如請求項24之mRNA，其中該ORF包含與SEQ ID NO: 3、7、10、13、16、19、22、25、31、48、50、52、54、56、61、62、64、66、68、70、72、74、76、78、80、82、84或106中之任一者之核苷酸序列

具有至少85%、至少90%、至少95%、至少98%或至少100%一致性之核苷酸序列。

【請求項26】

如請求項24之mRNA，其中該ORF編碼包含SEQ ID NO: 5、8、11、14、17、20、23、26、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83或85中之任一者之胺基酸序列之多肽。

【請求項27】

如請求項24之mRNA，其中該ORF編碼多肽，該多肽包含與SEQ ID NO: 5、8、11、14、17、20、23、26、32、33、34、35、47、49、59、63、65、67、69、71、73、75、77、79、81、83或85中之任一者具有至少80%、至少85%、至少90%、至少95%或至少98%一致性之胺基酸序列。

【請求項28】

如請求項24之mRNA，其中該mRNA包含5'非轉譯區(UTR)及3' UTR。

【請求項29】

如請求項28之mRNA，其中該5' UTR包含SEQ ID NO: 2或SEQ ID NO: 36之核苷酸序列。

【請求項30】

如請求項28之mRNA，其中該3' UTR包含SEQ ID NO: 4或SEQ ID NO: 37之核苷酸序列。

【請求項31】

如請求項24之mRNA，其中該mRNA包含化學修飾。

【請求項32】

如請求項31之mRNA，其中該mRNA經1-甲基-假尿苷化學修飾，使得序列中之各U為1-甲基-假尿苷。

【請求項33】

一種組合物，其包含脂質奈米顆粒及信使RNA (mRNA)，其中該mRNA為如請求項24至33中任一項之mRNA。

【請求項34】

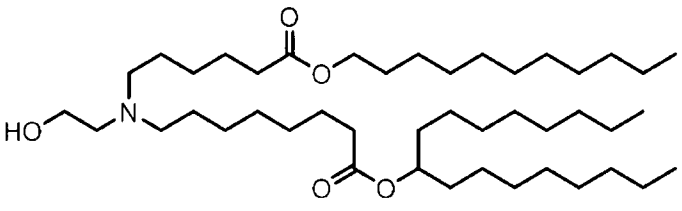
如請求項33之組合物，其中該脂質奈米顆粒包含PEG修飾之脂質、非陽離子脂質、固醇、可電離之陽離子脂質或其任何組合。

【請求項35】

如請求項34之組合物，其中該脂質奈米顆粒包含0.5-15 mol% PEG修飾之脂質；5-25 mol%非陽離子脂質；25-55 mol%固醇；及20-60 mol%可電離之陽離子脂質。

【請求項36】

如請求項35之組合物，其中該PEG修飾之脂質為1,2-二肉豆蔻醯基-sn-甘油、甲氧基聚乙二醇(PEG2000 DMG)，該非陽離子脂質為1,2-二硬脂醯基-sn-甘油-3-磷酸膽鹼(DSPC)，該固醇為膽固醇；且該可電離之陽離子脂質具有化合物1之結構：



(化合物1)。

【請求項37】

一種方法，其包含向受試者投與可有效誘導針對該受試者中之

SARS-CoV-2的中和抗體反應之量的信使核糖核酸(mRNA)，該信使核糖核酸包含開放閱讀框(ORF)，該開放閱讀框編碼具有雙脯胺酸穩定性突變之SARS-CoV-2刺突(S)蛋白抗原。

【請求項38】

如請求項37之方法，其中該雙脯胺酸穩定性突變位於對應於野生型SARS-CoV-2 S蛋白之K986及V987的位置。

【請求項39】

如請求項37至38中任一項之方法，其中該mRNA係以可有效誘導針對該受試者中之SARS-CoV-2的T細胞免疫反應，視情況$CD4^+$及/或$CD8^+$ T細胞免疫反應之量投與。

【請求項40】

如請求項37至39中任一項之方法，其中該受試者係免疫受損的。

【請求項41】

如請求項37至39中任一項之方法，其中該受試者患有肺病。

【請求項42】

如請求項37至39中任一項之方法，其中該受試者為65歲或更大。

【請求項43】

如請求項37至39中任一項之方法，其包含向該受試者投與至少兩個劑量之該組合物。

【請求項44】

如請求項37至43中任一項之方法，其中在投與該mRNA或包含該mRNA之組合物後1-72小時，在該受試者之血清中產生可偵測水準之該SARS-CoV-2 S蛋白。

【請求項45】

如請求項37至43中任一項之方法，其中在投與該mRNA後1-72小時，在該受試者之血清中產生至少100 NU/ml、至少500 NU/ml或至少1000 NU/ml之中和抗體效價。

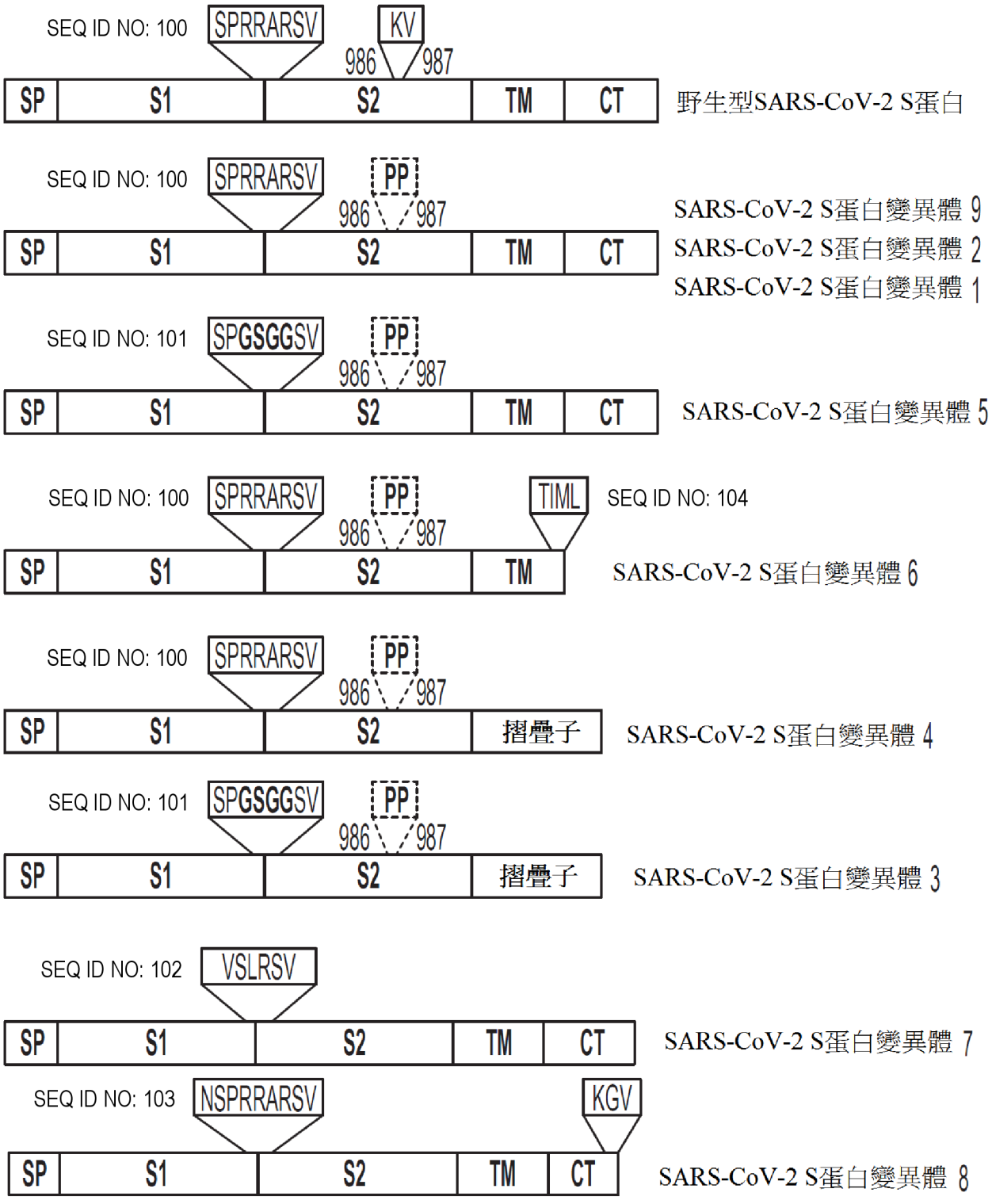
【請求項46】

一種免疫組合物，其包含：

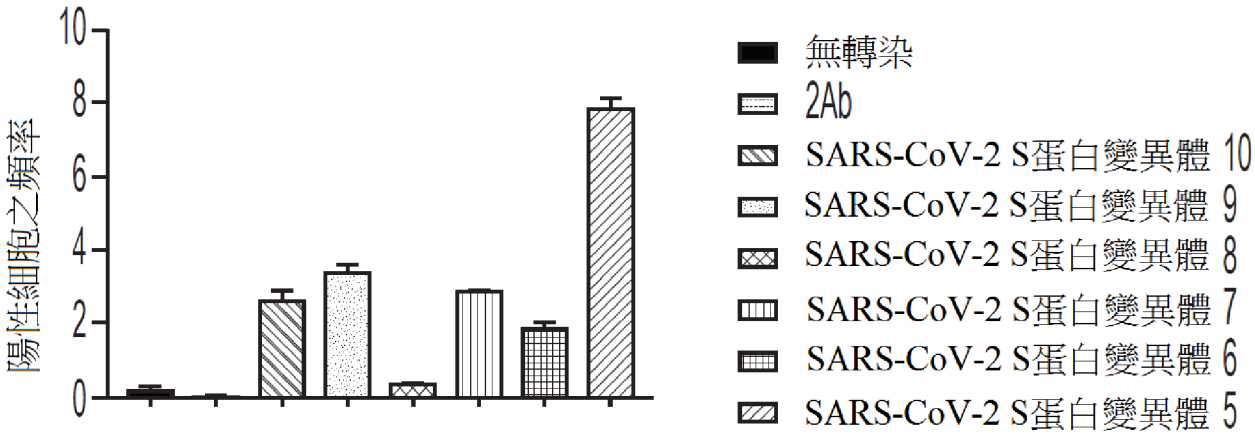
(a) 第一核糖核酸(RNA)，其包含編碼能夠誘導對SARS-CoV-2之免疫反應、諸如中和抗體反應之冠狀病毒抗原之開放閱讀框(ORF)；及

(b) 第二核糖核酸(RNA)，其包含編碼能夠誘導對SARS-CoV-2之免疫反應、諸如中和抗體反應之冠狀病毒抗原之開放閱讀框(ORF)，其中該第一RNA之ORF不同於該第二RNA之ORF。

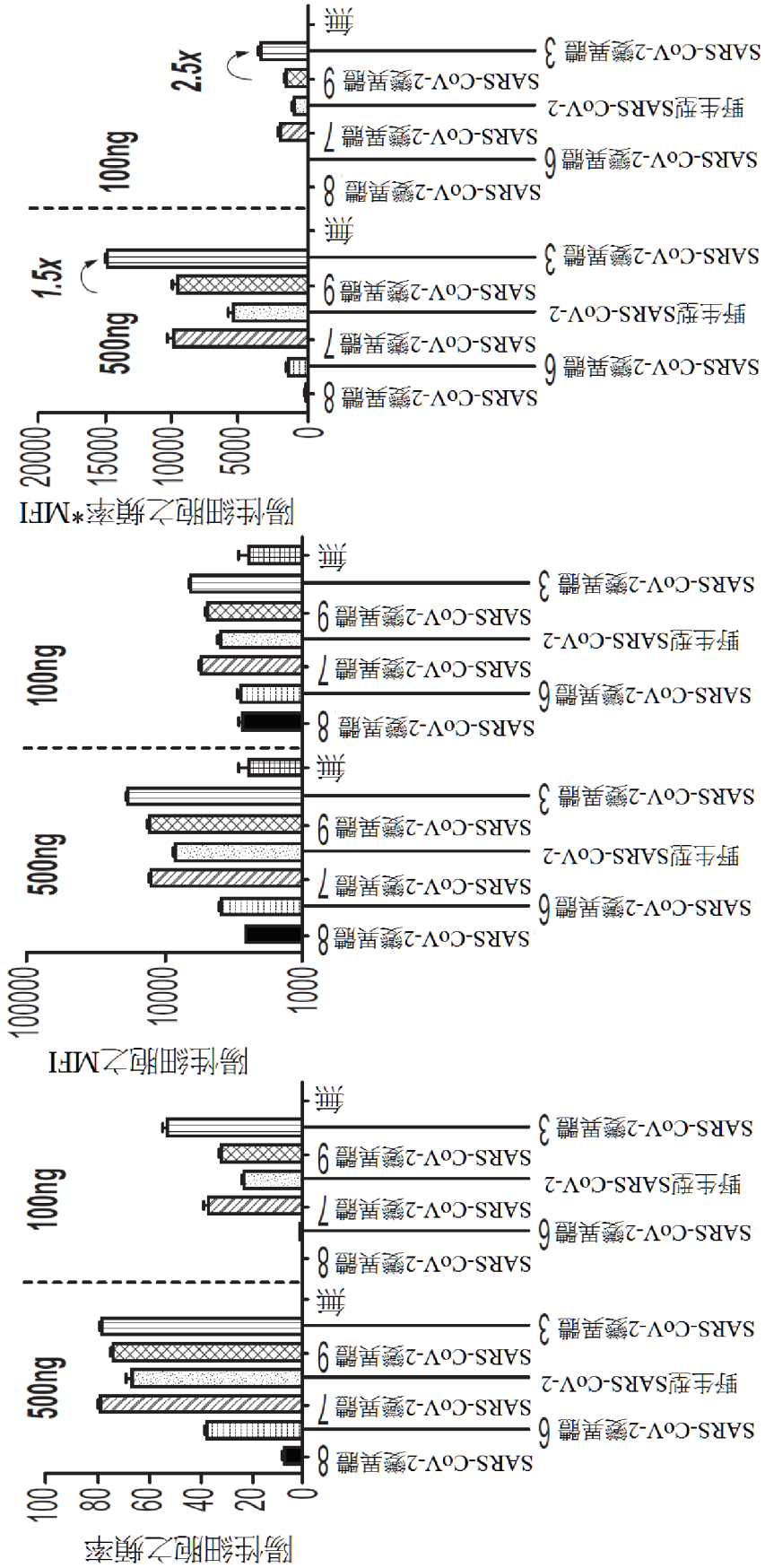
【發明圖式】


SEQ ID NO: 100
SPRRARSV
KV
986
987
SP
S1
S2
TM
CT
野生型SARS-CoV-2 S蛋白
SEQ ID NO: 100
SPRRARSV
PP
986
987
SP
S1
S2
TM
CT
SARS-CoV-2 S蛋白變異體 9
SARS-CoV-2 S蛋白變異體 2
SARS-CoV-2 S蛋白變異體 1
SEQ ID NO: 101
SPGSGGSV
PP
986
987
SP
S1
S2
TM
CT
SARS-CoV-2 S蛋白變異體 5
SEQ ID NO: 100
SPRRARSV
PP
986
987
TIML
SEQ ID NO: 104
SP
S1
S2
TM
SARS-CoV-2 S蛋白變異體 6
SEQ ID NO: 100
SPRRARSV
PP
986
987
SP
S1
S2
摺疊子
SARS-CoV-2 S蛋白變異體 4
SEQ ID NO: 101
SPGSGGSV
PP
986
987
SP
S1
S2
摺疊子
SARS-CoV-2 S蛋白變異體 3
SEQ ID NO: 102
VSLRSV
SP
S1
S2
TM
CT
SARS-CoV-2 S蛋白變異體 7
SEQ ID NO: 103
NSPRRARSV
KGV
SP
S1
S2
TM
CT
SARS-CoV-2 S蛋白變異體 8

【圖 1】

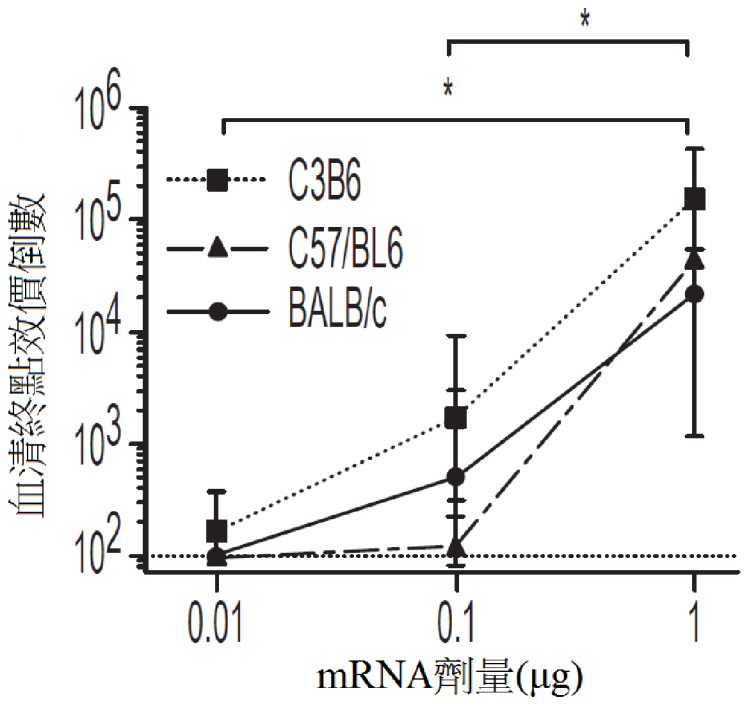

陽性細胞之頻率
10
8
6
4
2
0
無轉染
2Ab
SARS-CoV-2 S蛋白變異體 10
SARS-CoV-2 S蛋白變異體 9
SARS-CoV-2 S蛋白變異體 8
SARS-CoV-2 S蛋白變異體 7
SARS-CoV-2 S蛋白變異體 6
SARS-CoV-2 S蛋白變異體 5

【圖 2】


陽性細胞之頻率
100
80
60
40
20
0
500ng
100ng
無
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
野生型SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 3
陽性細胞之MFI
100000
10000
1000
500ng
100ng
無
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
野生型SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 3
陽性細胞之頻率*MFI
20000
15000
10000
5000
0
500ng
100ng
1.5x
2.5x
無
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
野生型SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 3

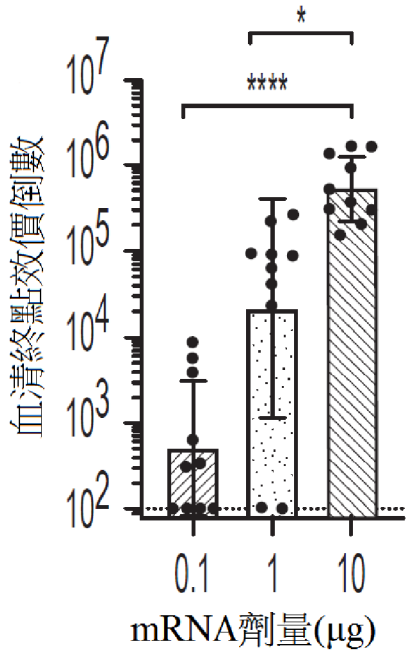
【圖 3】

SARS-CoV-2變異體9在
C3B6、C57/BL6及BALB/c小鼠中



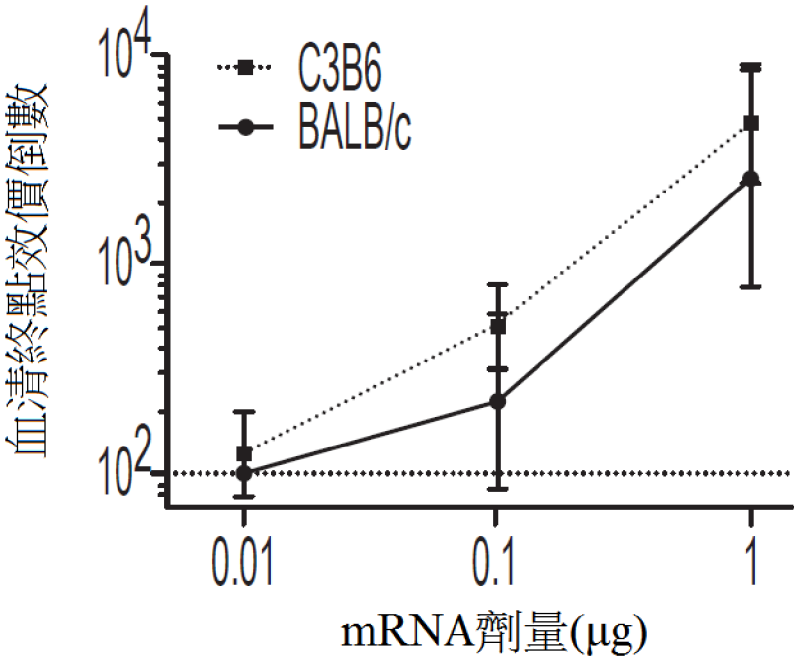
【圖 4A】

高劑量之SARS-CoV-2
變異體9



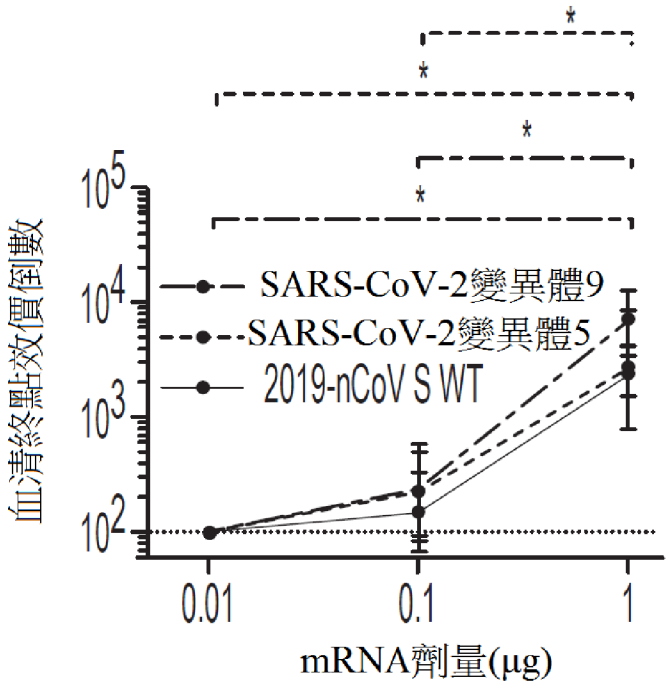
【圖 4B】

SARS-CoV-2變異體5在C3B6及BALB/c小鼠中



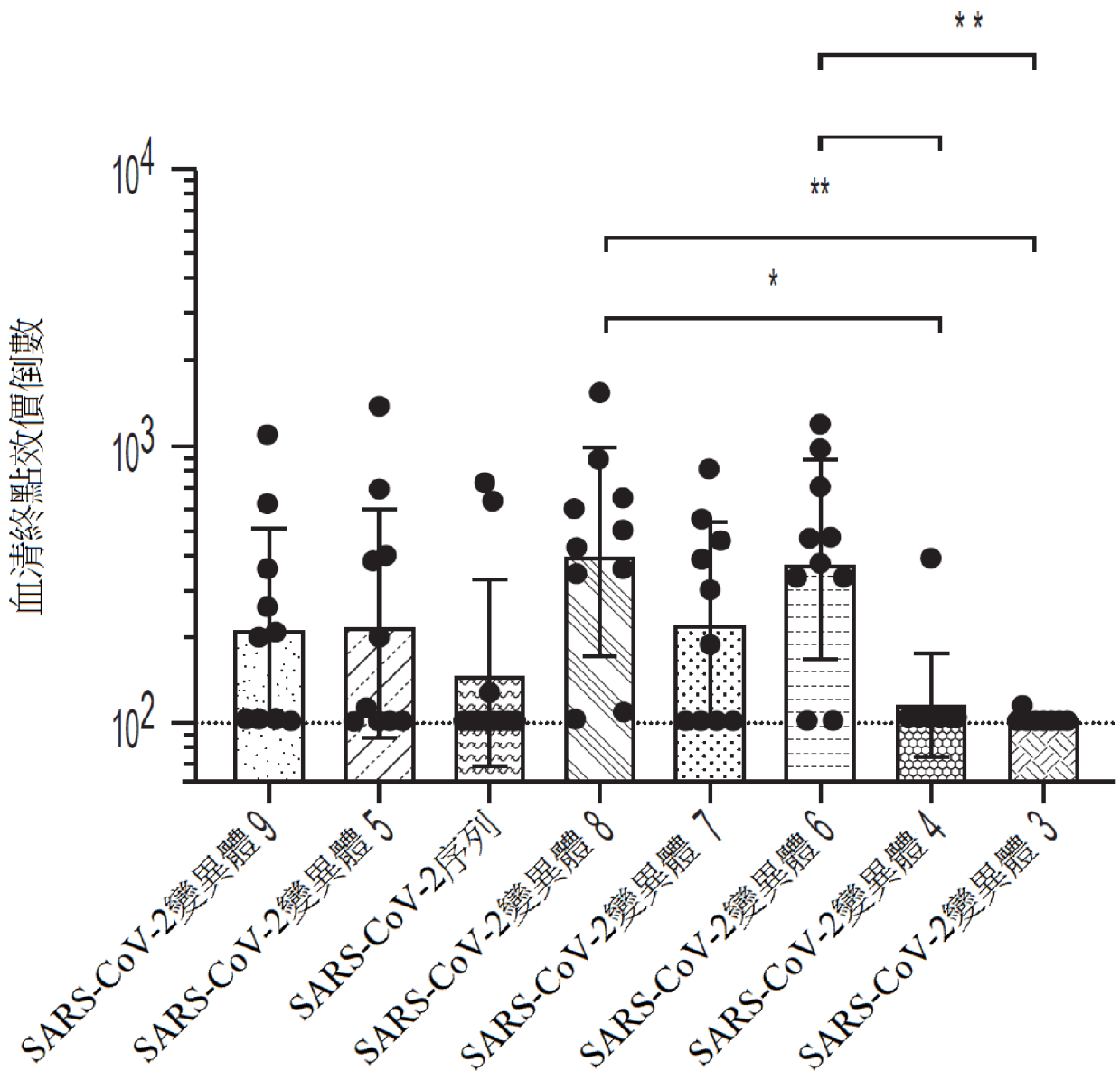
【圖 5A】

SARS-CoV-2變異體9
SARS-CoV-2變異體5
及野生型刺突序列

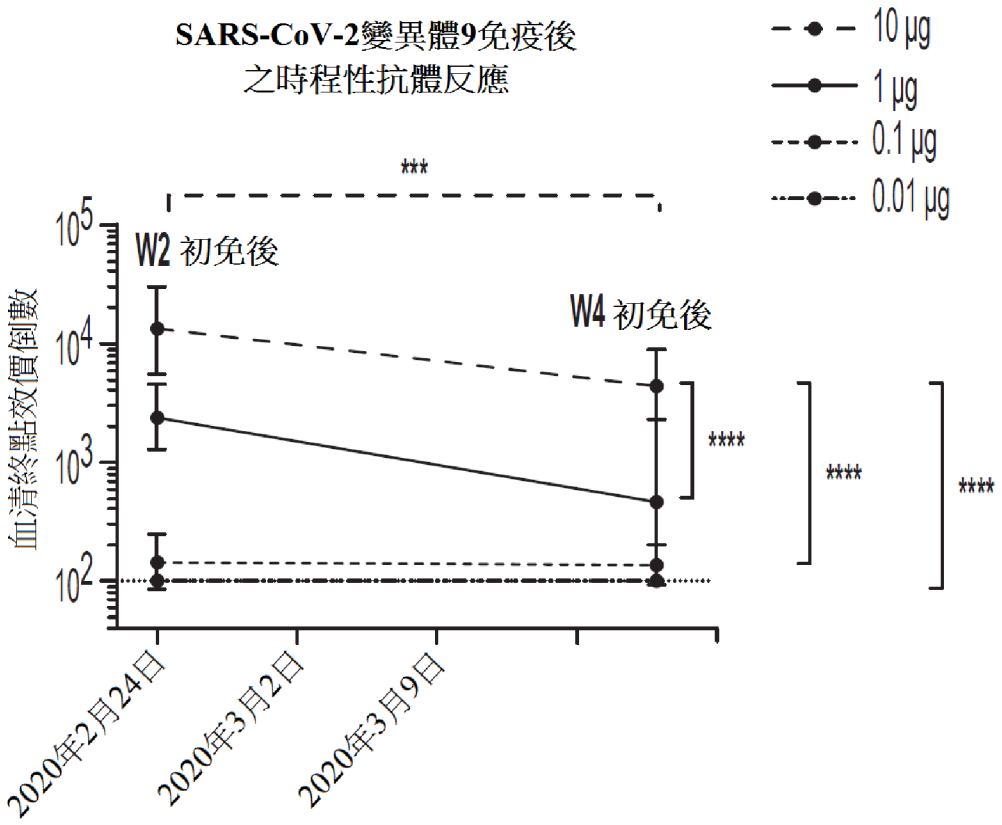


【圖 5B】

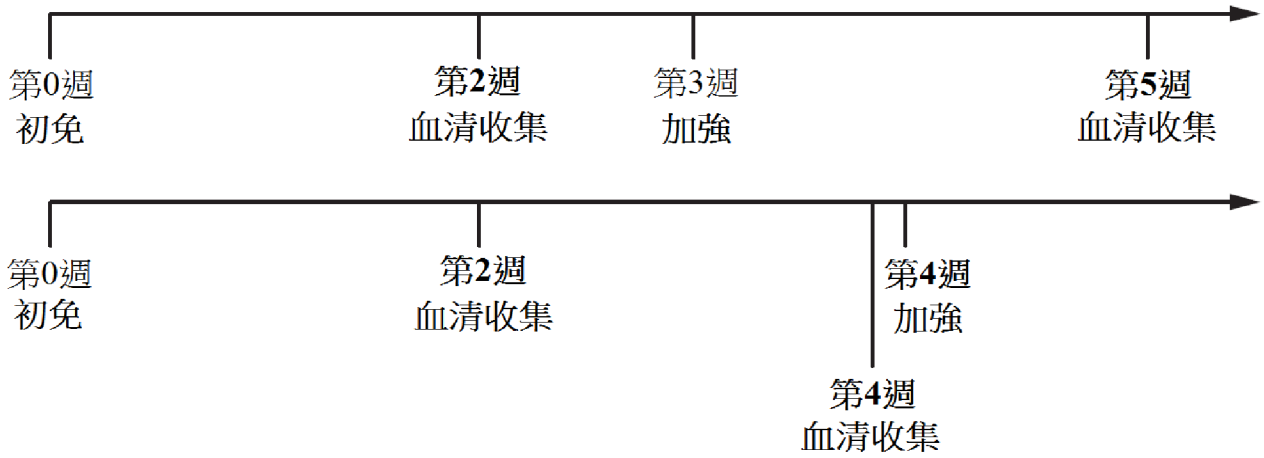
0.1 μg劑量下多個序列之比較



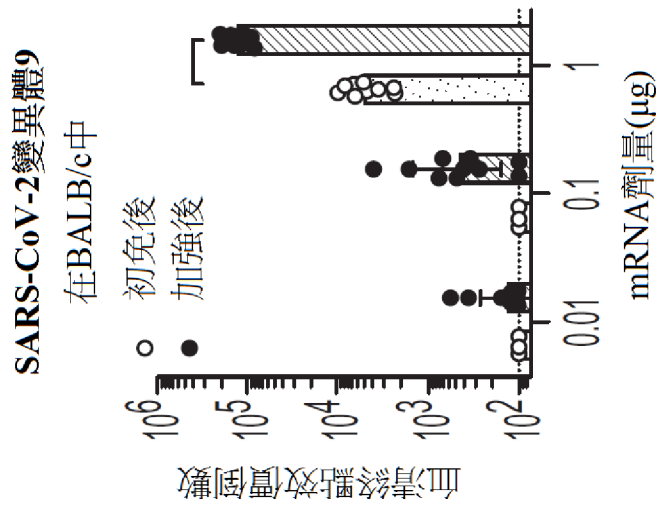
【圖 5C】


SARS-CoV-2變異體9免疫後
之時程性抗體反應
10 μg
1 μg
0.1 μg
0.01 μg
***
W2 初免後
W4 初免後
血清終點效價倒數
10^5
10^4
10^3
10^2
****
****
****
2020年2月24日
2020年3月2日
2020年3月9日

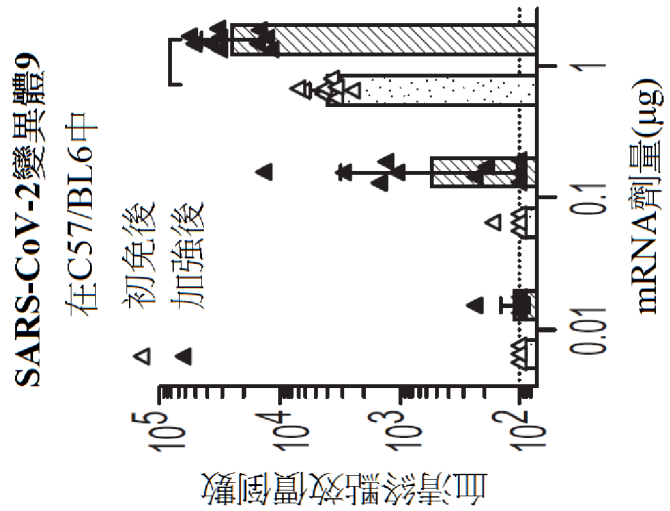
【圖 6】


第0週
初免
第2週
血清收集
第3週
加強
第5週
血清收集
第0週
初免
第2週
血清收集
第4週
加強
第4週
血清收集

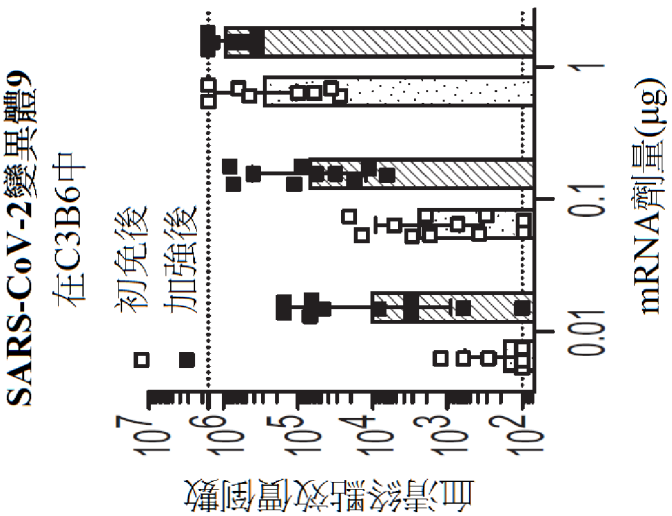
【圖 7】


SARS-CoV-2變異體9
在BALB/c中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)

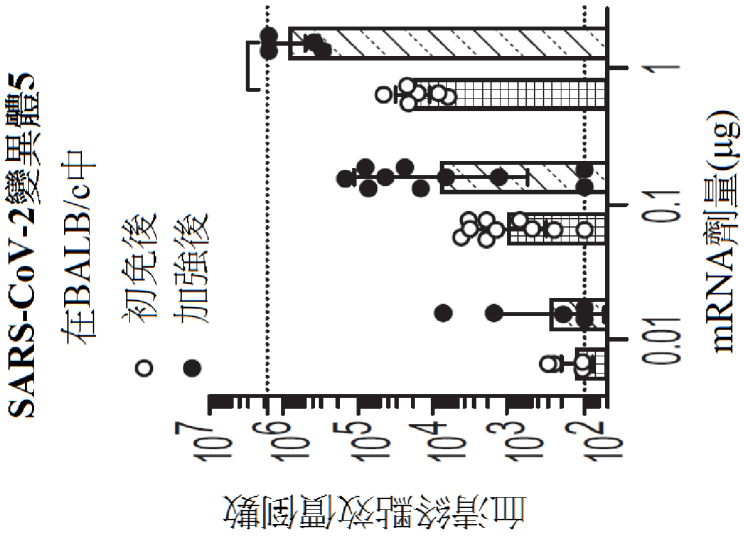
【圖 8A】


SARS-CoV-2變異體9
在C57/BL6中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)

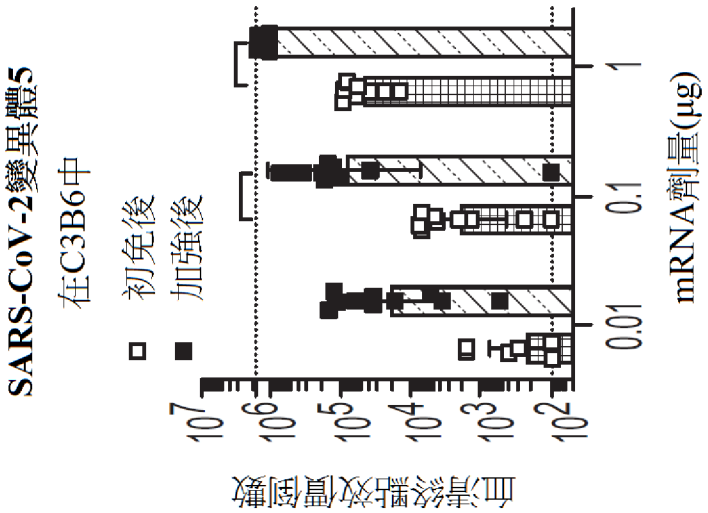
【圖 8B】


SARS-CoV-2變異體9
在C3B6中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)

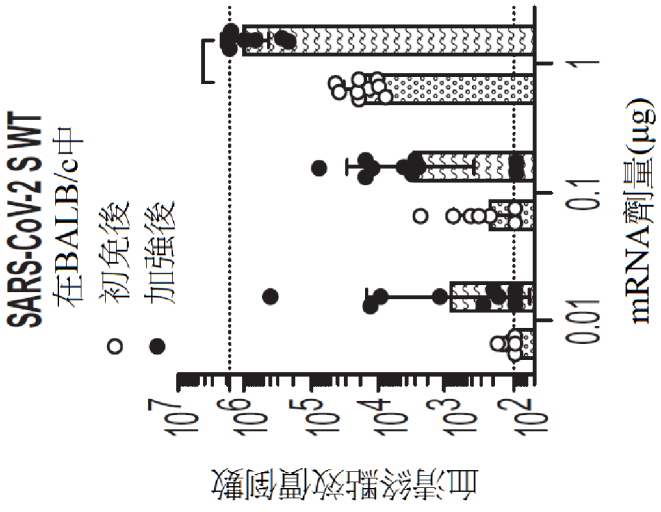
【圖 8C】


SARS-CoV-2變異體5
在BALB/c中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)
0.01
0.1
1

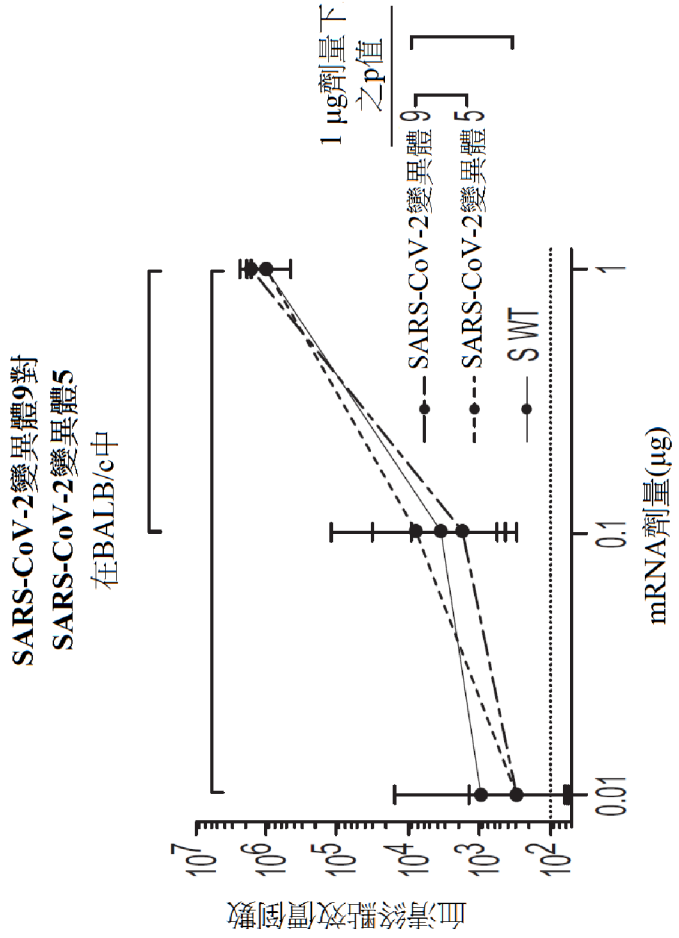
【圖 9A】


SARS-CoV-2變異體5
在C3B6中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)
0.01
0.1
1

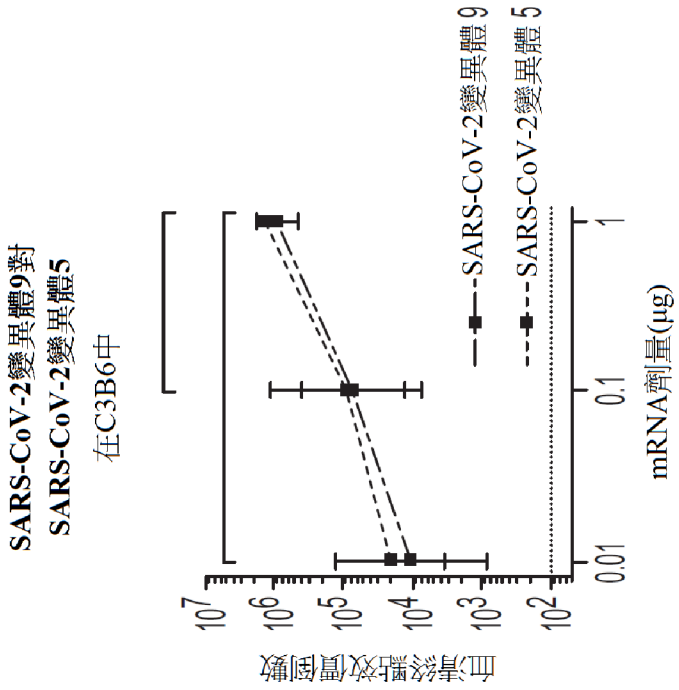
【圖 9B】


SARS-CoV-2 S WT
在BALB/c中
初免後
加強後
血清終點效價倒數
mRNA劑量(μg)
0.01
0.1
1

【圖 9C】

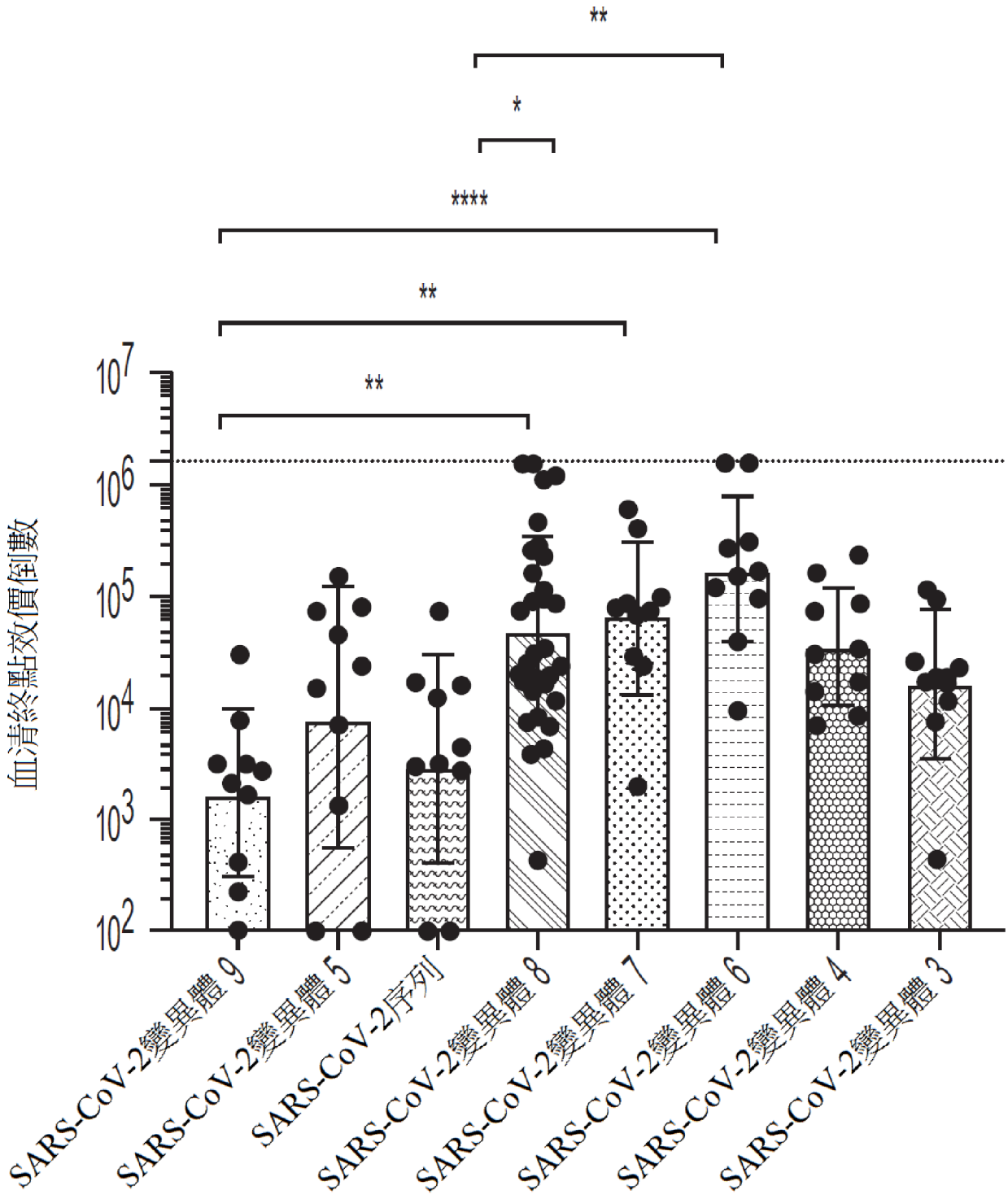

SARS-CoV-2變異體9對
SARS-CoV-2變異體5
在BALB/c中
1 μg劑量下之p值
SARS-CoV-2變異體 9
SARS-CoV-2變異體 5
S WT
血清終點效價倒數
mRNA劑量(μg)
0.01
0.1
1
10^2
10^3
10^4
10^5
10^6
10^7

【圖 9D】

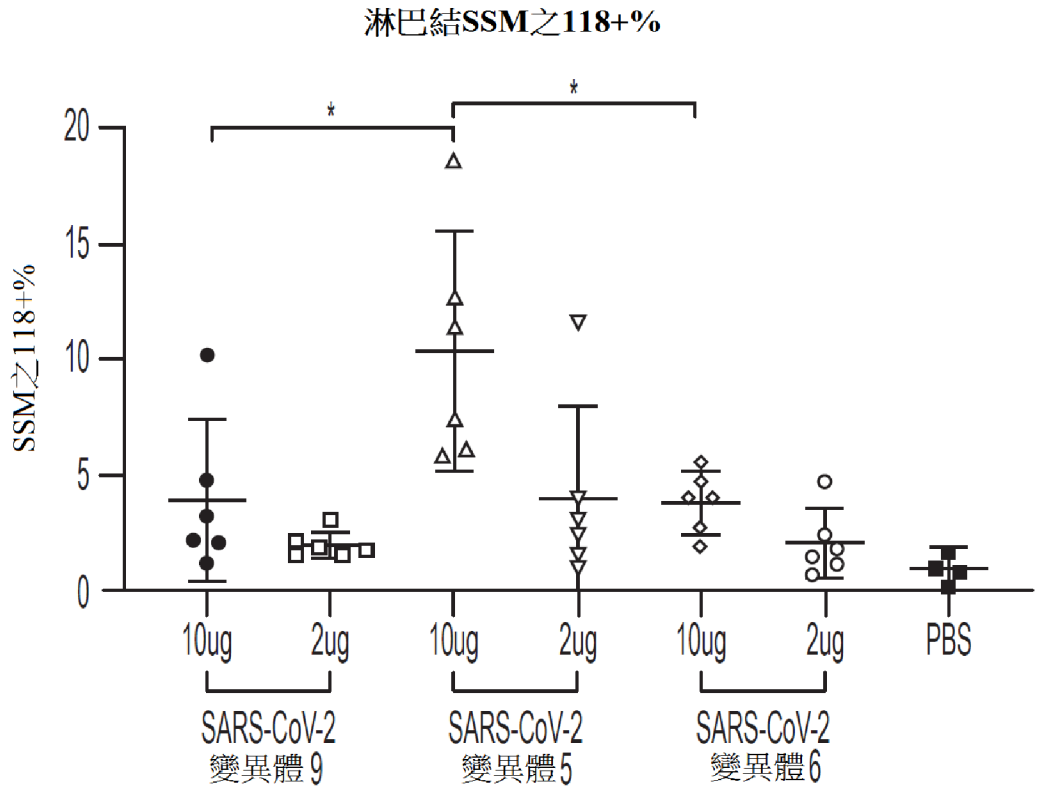

SARS-CoV-2變異體9對
SARS-CoV-2變異體5
在C3B6中
SARS-CoV-2變異體 9
SARS-CoV-2變異體 5
血清終點效價倒數
mRNA劑量(μg)
0.01
0.1
1
10^2
10^3
10^4
10^5
10^6
10^7

【圖 9E】

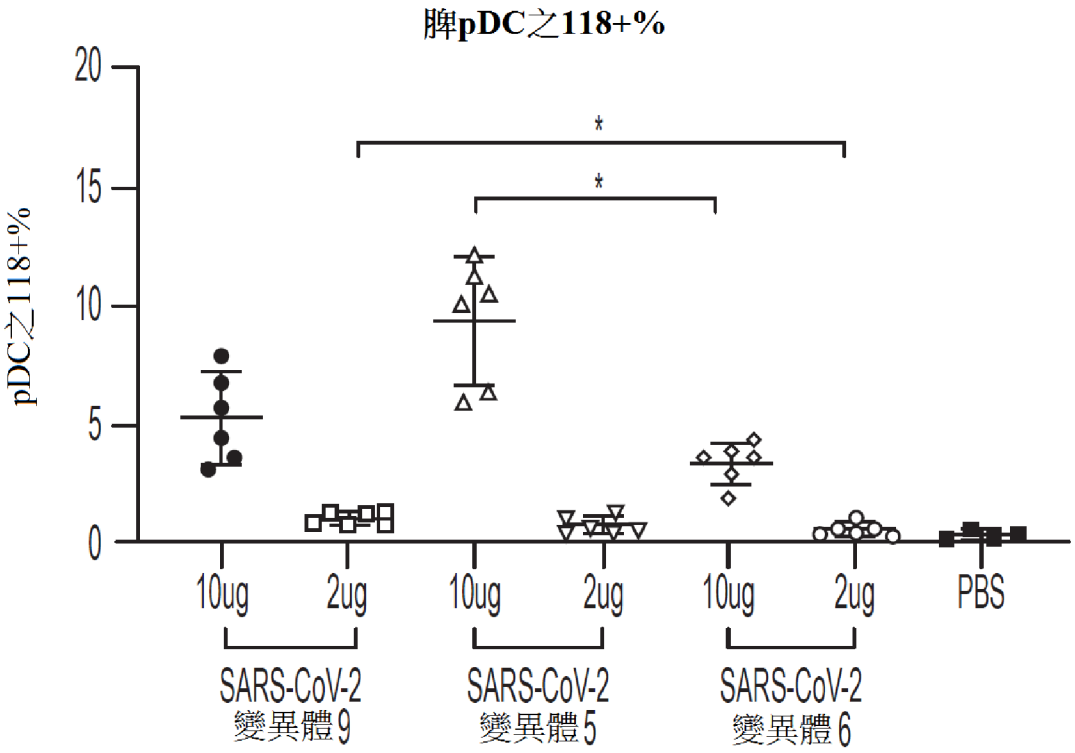
加強後所有序列之比較



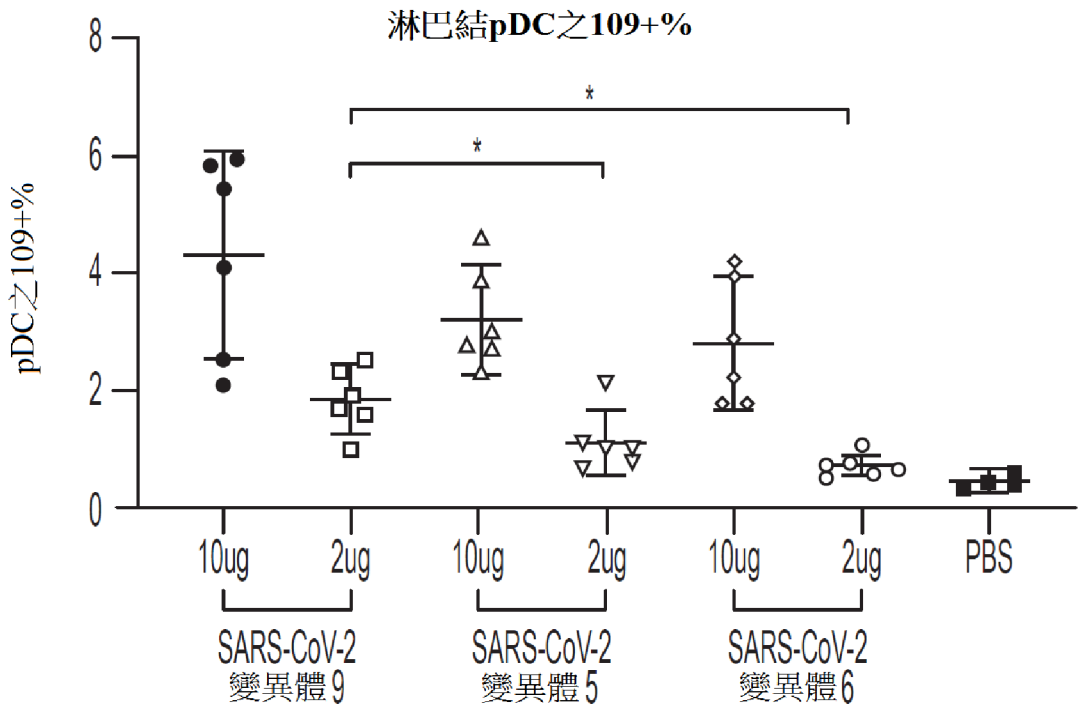
【圖 10】


淋巴結SSM之118+%
SSM之118+%
20
15
10
5
0
*
*
10ug
2ug
10ug
2ug
10ug
2ug
PBS
SARS-CoV-2
變異體9
SARS-CoV-2
變異體5
SARS-CoV-2
變異體6

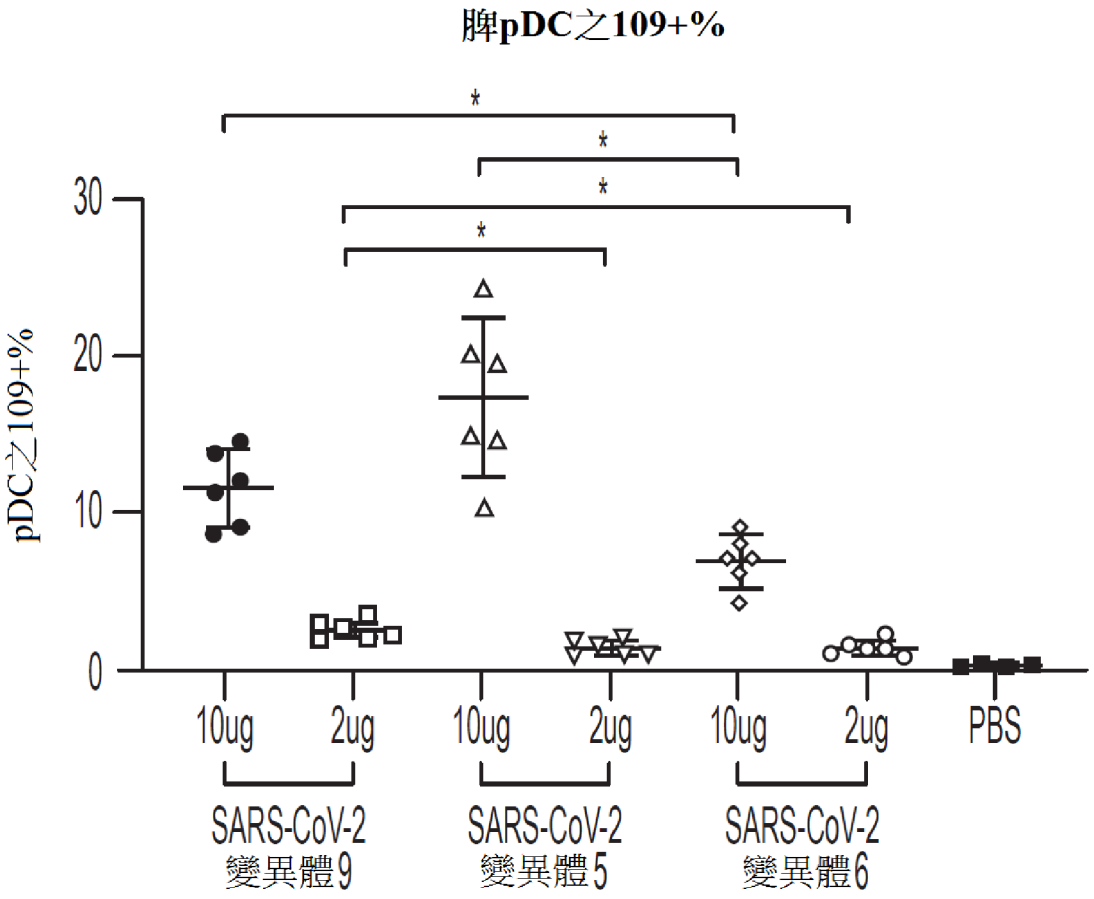
【圖 11A】


脾pDC之118+%
pDC之118+%
20
15
10
5
0
*
*
10ug
2ug
10ug
2ug
10ug
2ug
PBS
SARS-CoV-2
變異體9
SARS-CoV-2
變異體5
SARS-CoV-2
變異體6

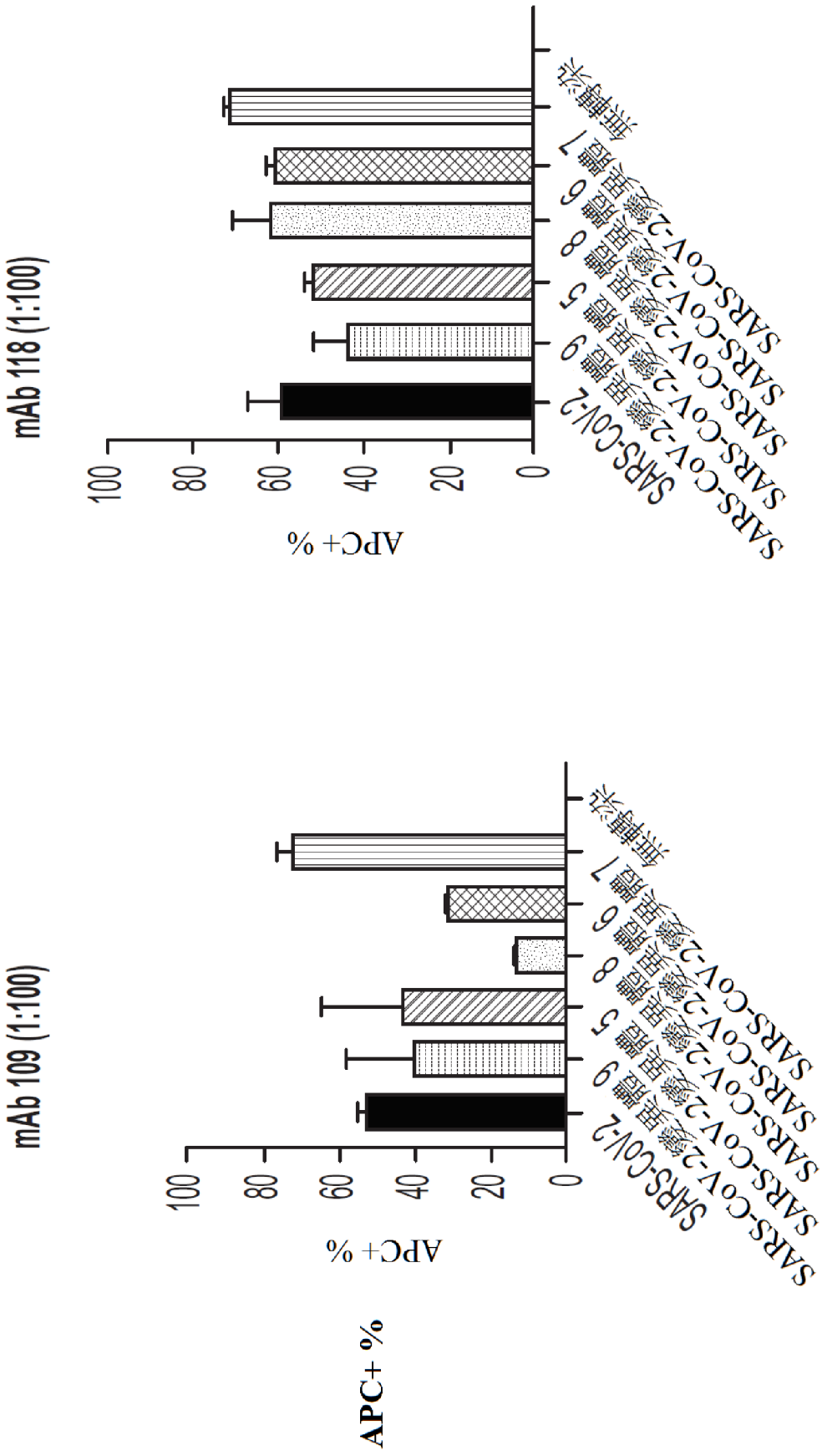
【圖 11B】


淋巴結pDC之109+%
pDC之109+%
8
6
4
2
0
*
*
10ug
2ug
10ug
2ug
10ug
2ug
PBS
SARS-CoV-2
變異體9
SARS-CoV-2
變異體5
SARS-CoV-2
變異體6

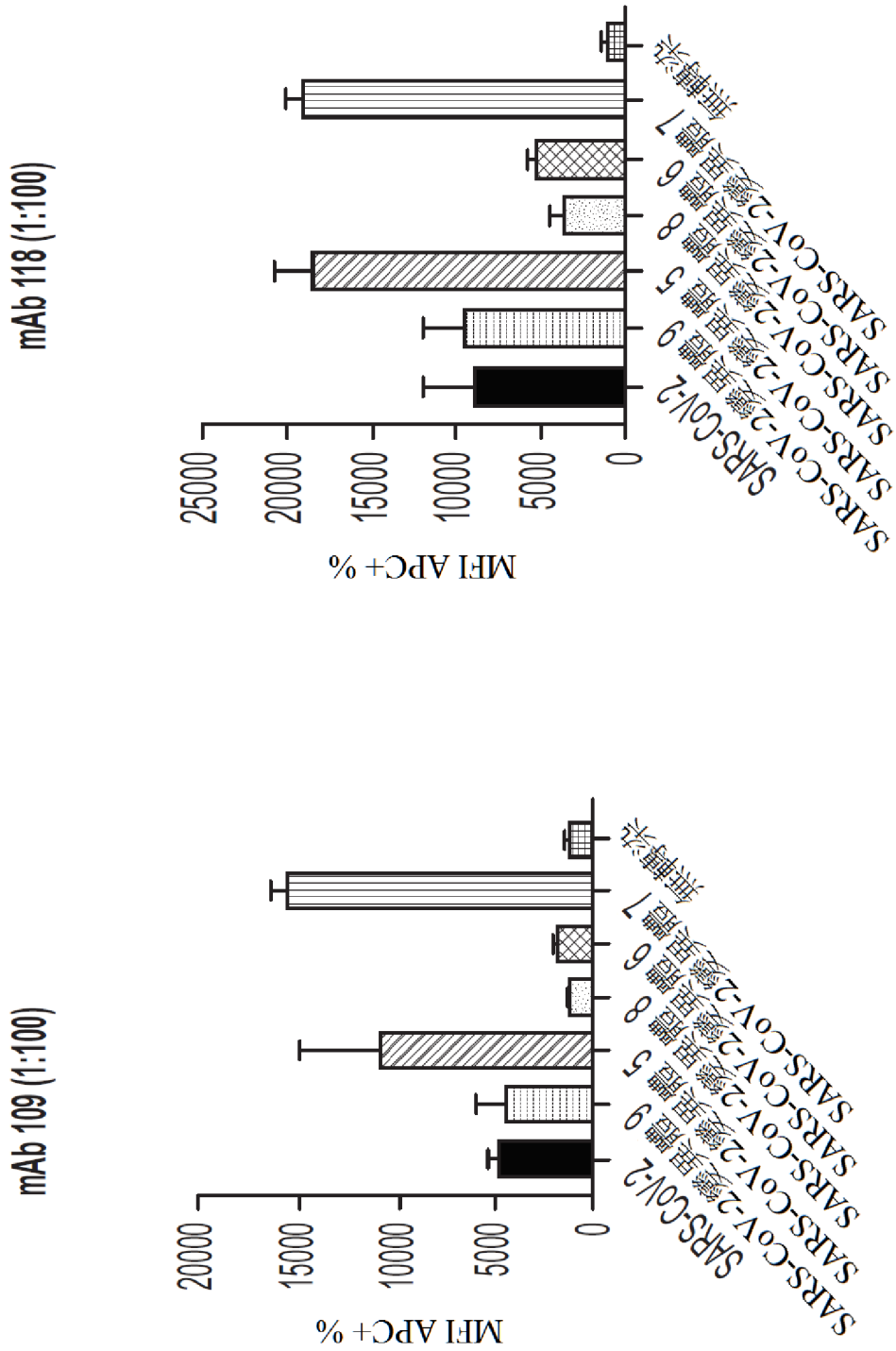
【圖 12A】


脾pDC之109+%
pDC之109+%
30
20
10
0
*
*
*
*
10ug
2ug
10ug
2ug
10ug
2ug
PBS
SARS-CoV-2
變異體9
SARS-CoV-2
變異體5
SARS-CoV-2
變異體6

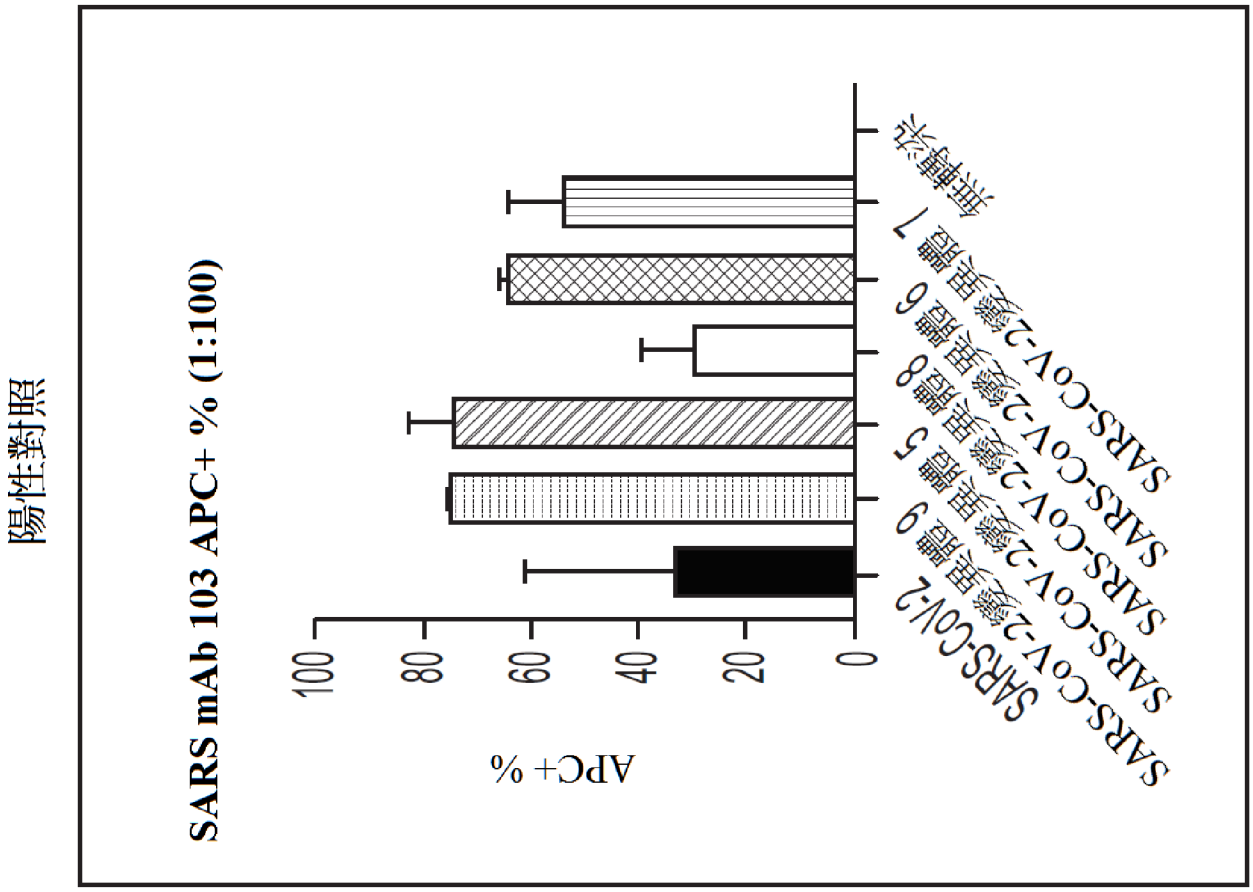
【圖 12B】


mAb 118 (1:100)
mAb 109 (1:100)
APC+ %
100
80
60
40
20
0
SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 5
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
無轉染

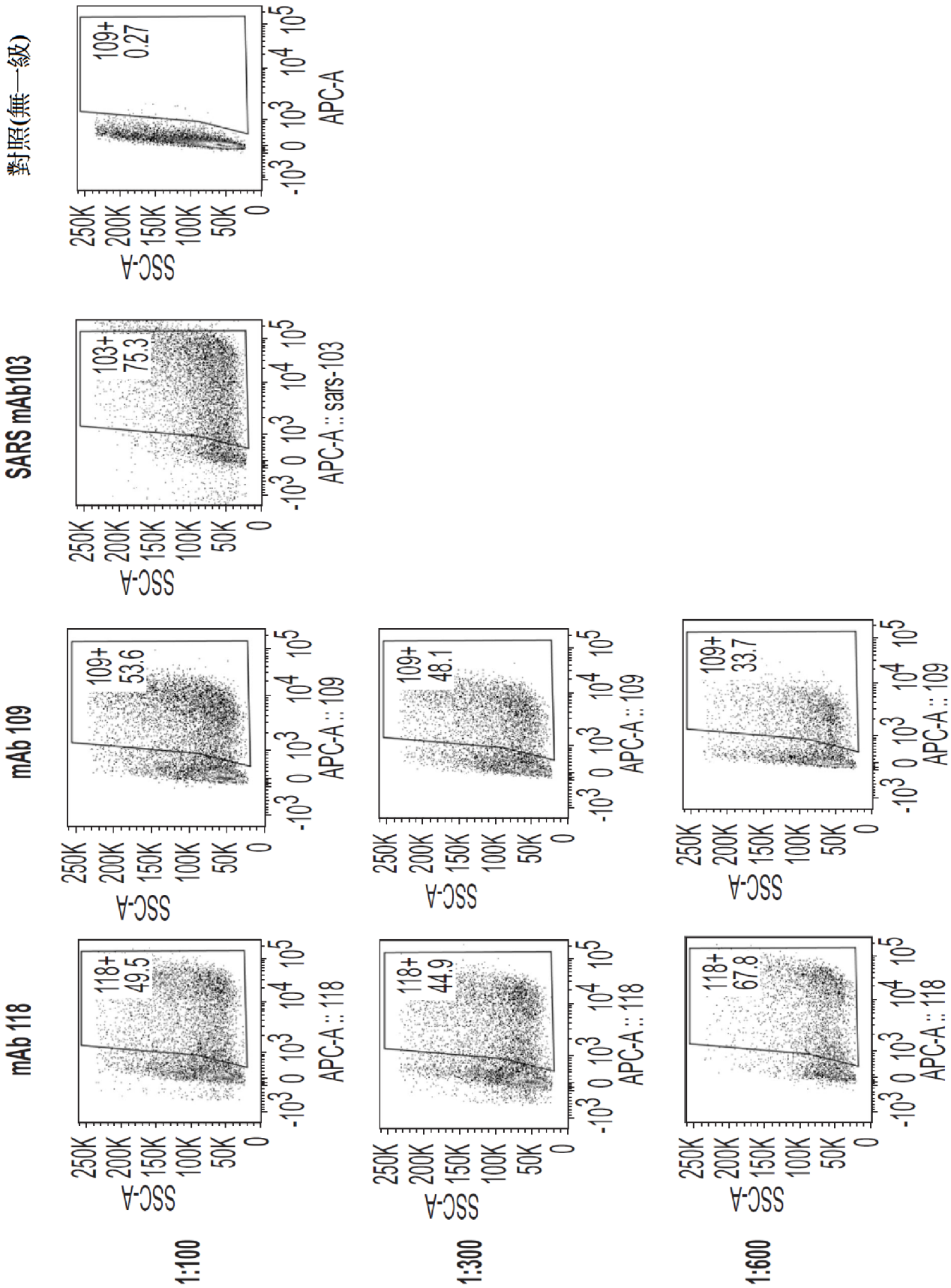
【圖 13A】


mAb 118 (1:100)
MFI APC+ %
25000
20000
15000
10000
5000
0
SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 5
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
無轉染
mAb 109 (1:100)
MFI APC+ %
20000
15000
10000
5000
0
SARS-CoV-2
SARS-CoV-2變異體 9
SARS-CoV-2變異體 5
SARS-CoV-2變異體 8
SARS-CoV-2變異體 6
SARS-CoV-2變異體 7
無轉染
MFI %

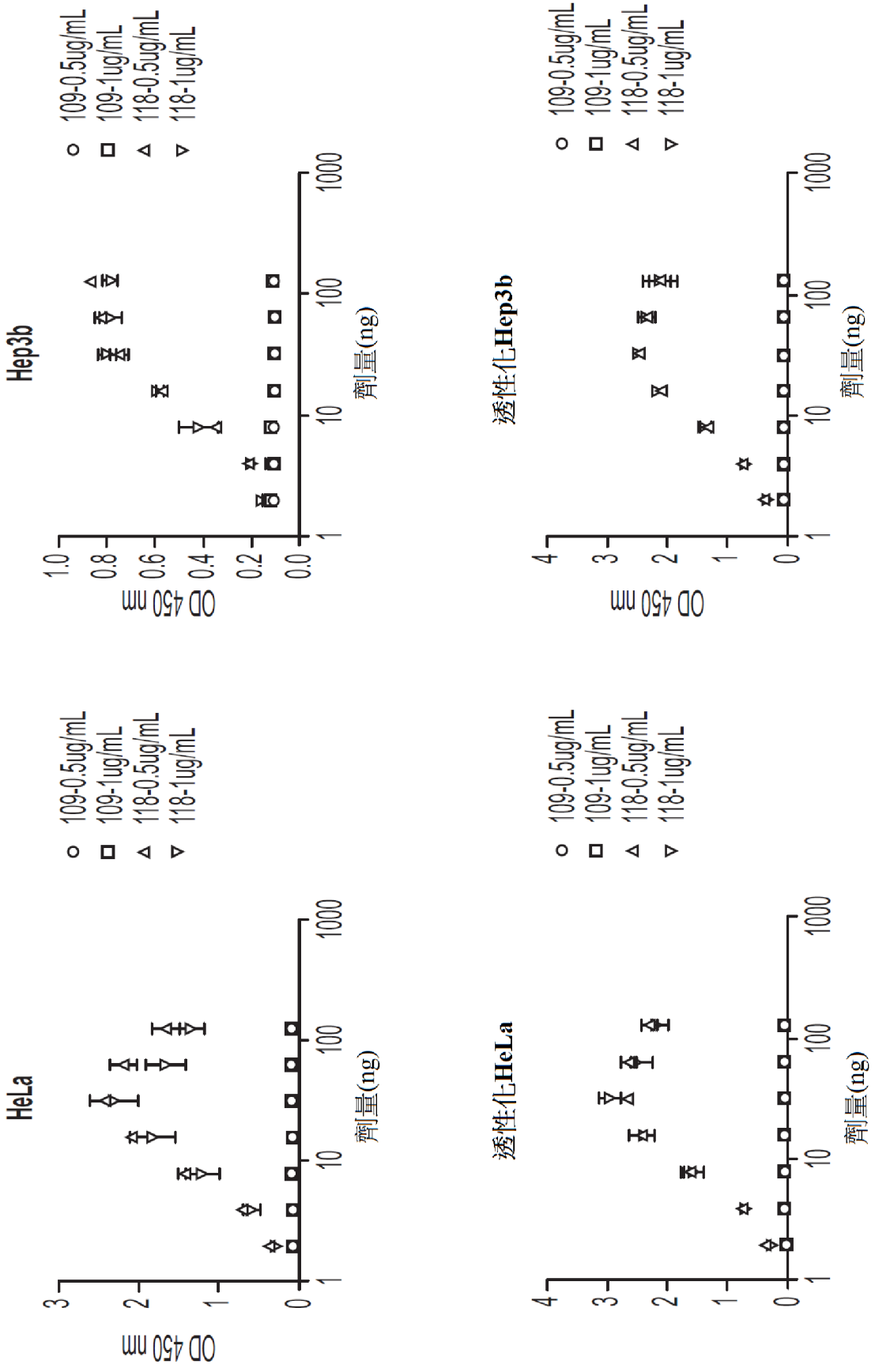
【圖 13B】


陽性對照
SARS mAb 103 APC+ % (1:100)
APC+ %
100
80
60
40
20
0
SARS-CoV-2
SARS-CoV-2變異體9
SARS-CoV-2變異體5
SARS-CoV-2變異體8
SARS-CoV-2變異體6
SARS-CoV-2變異體7
無轉染

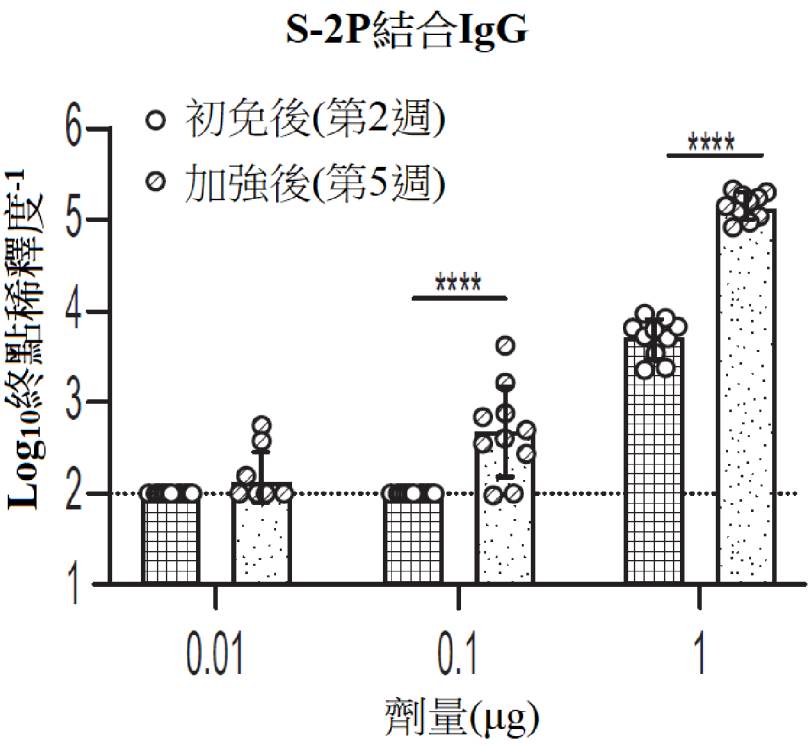
【圖 13C】


對照(無一級)
SARS mAb103
mAb 109
mAb 118
1:100
1:300
1:600
SSC-A
APC-A
APC-A :: sars-103
APC-A :: 109
APC-A :: 118
109+ 0.27
103+ 75.3
109+ 53.6
109+ 48.1
109+ 33.7
118+ 49.5
118+ 44.9
118+ 67.8

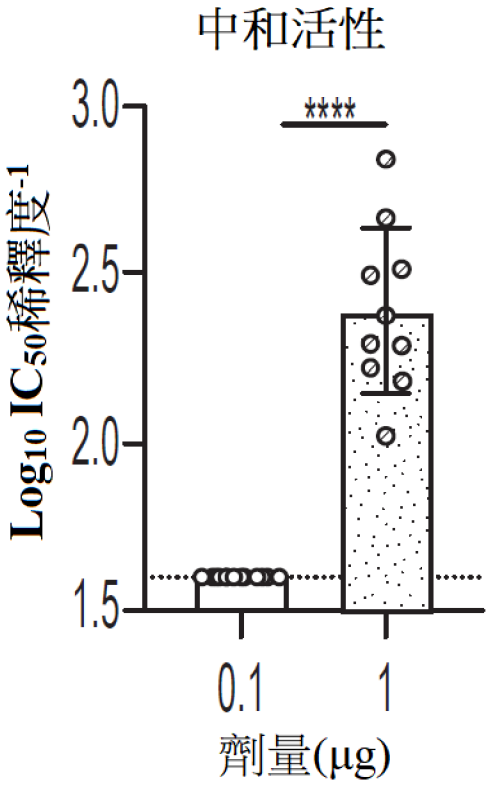
【圖 14】


Hep3b
透性化Hep3b
HeLa
透性化HeLa
109-0.5ug/mL
109-1ug/mL
118-0.5ug/mL
118-1ug/mL
OD 450 nm
劑量(ng)

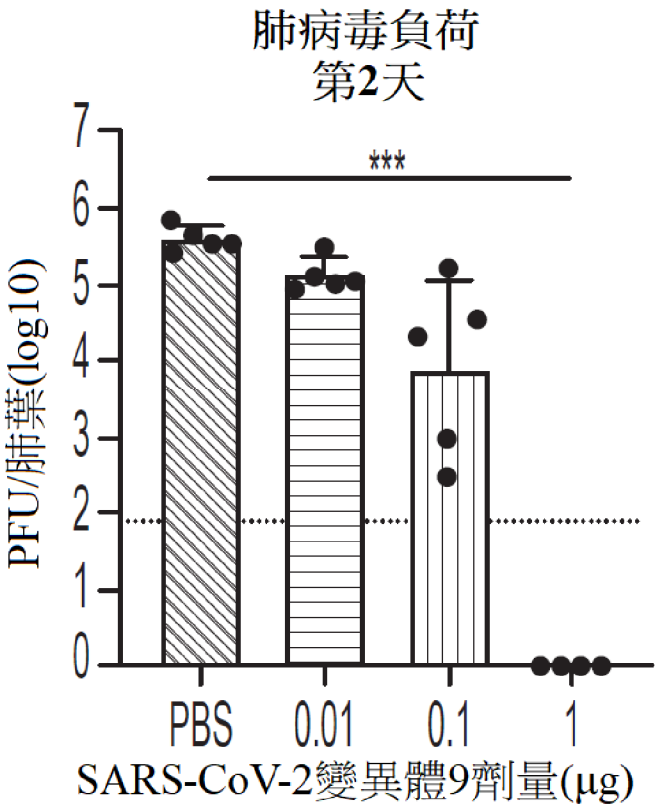
【圖 15】


S-2P結合IgG
初免後(第2週)
加強後(第5週)
Log10終點稀釋度-1
6
5
4
3
2
1
****
****
0.01
0.1
1
劑量(μg)

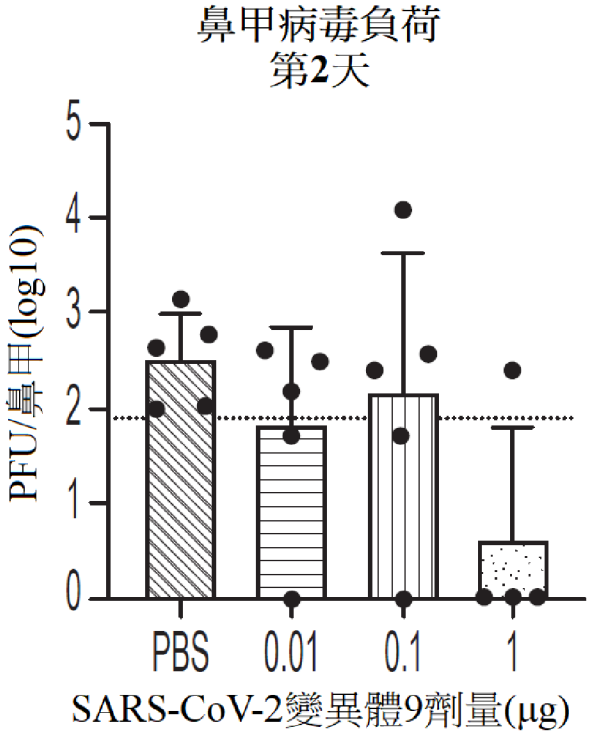
【圖 16A】


中和活性
Log10 IC50稀釋度-1
3.0
2.5
2.0
1.5
****
0.1
1
劑量(μg)

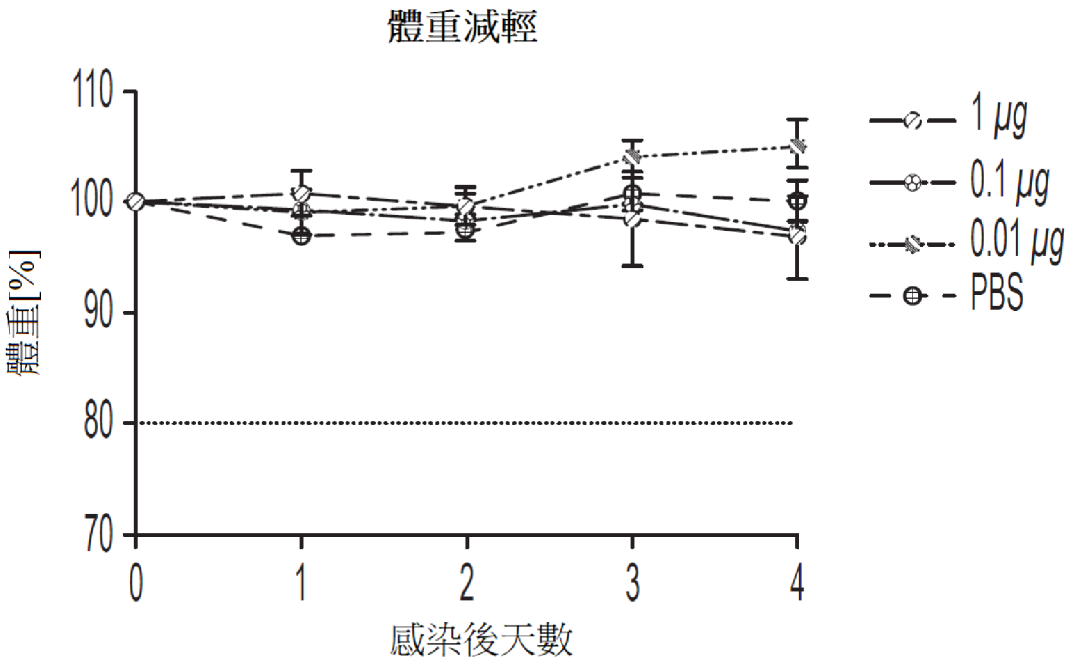
【圖 16B】


肺病毒負荷
第2天
***
PFU/肺葉(log10)
0
1
2
3
4
5
6
7
PBS
0.01
0.1
1
SARS-CoV-2變異體9劑量(μg)

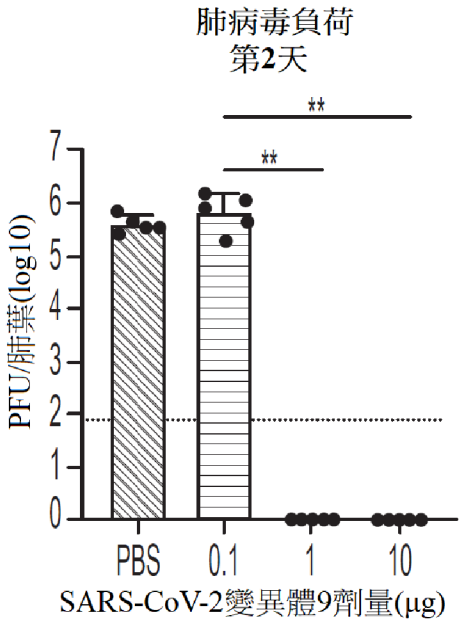
【圖 17A】


鼻甲病毒負荷
第2天
PFU/鼻甲(log10)
0
1
2
3
4
5
PBS
0.01
0.1
1
SARS-CoV-2變異體9劑量(μg)

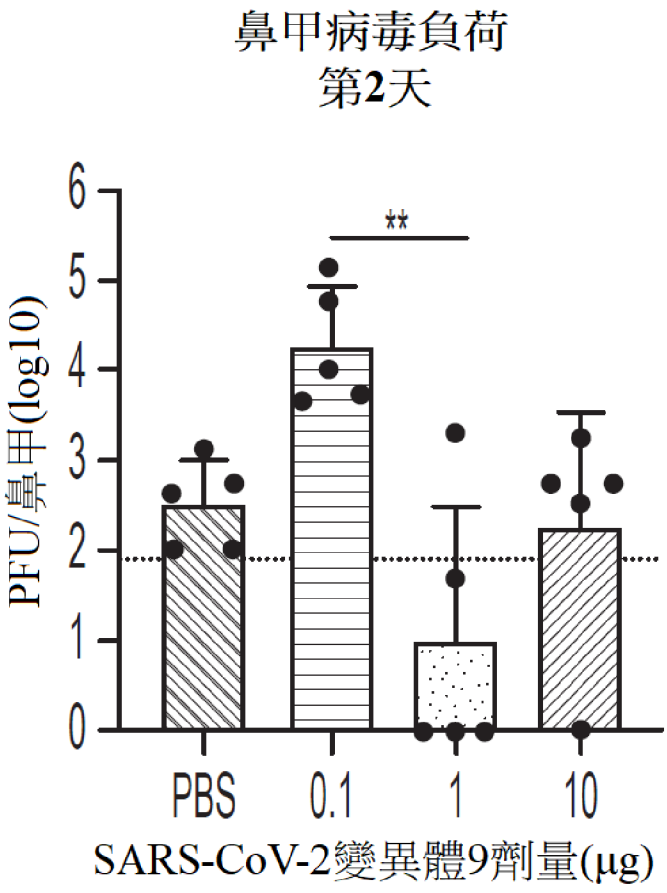
【圖 17B】



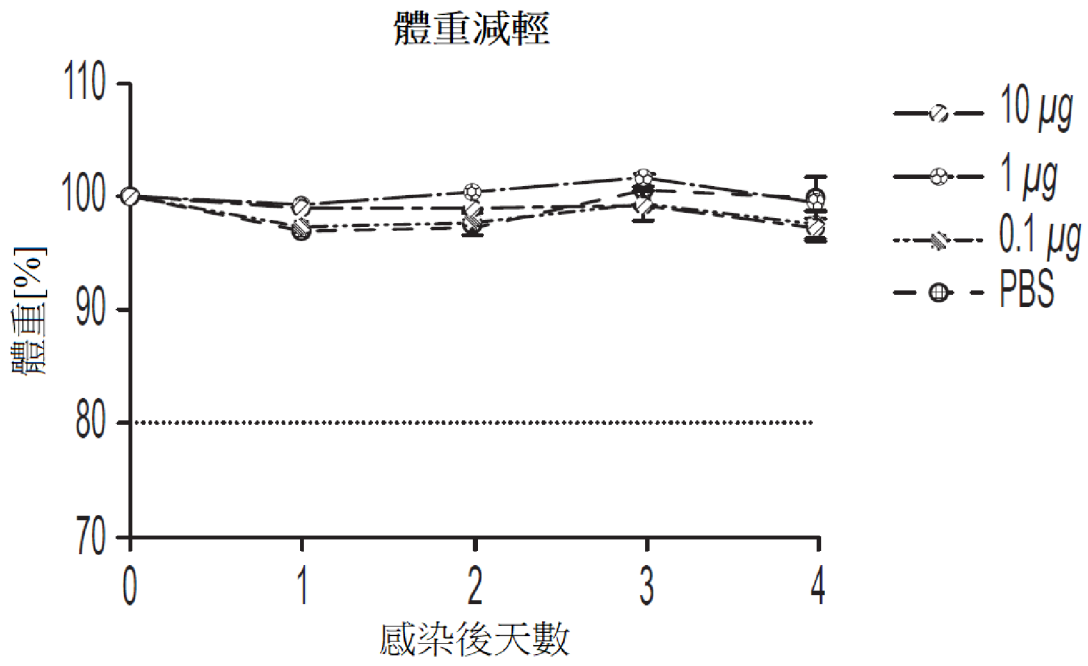
【圖 17C】


肺病毒負荷
第2天
**
**
PFU/肺葉(log10)
0
1
2
3
4
5
6
7
PBS
0.1
1
10
SARS-CoV-2變異體9劑量(μg)

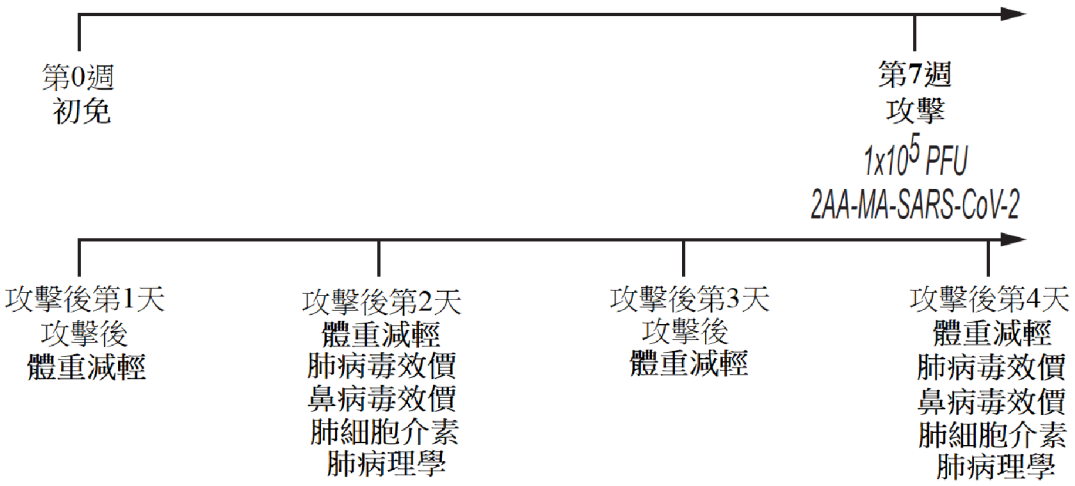
【圖 18A】


鼻甲病毒負荷
第2天
**
PFU/鼻甲(log10)
0
1
2
3
4
5
6
PBS
0.1
1
10
SARS-CoV-2變異體9劑量(μg)

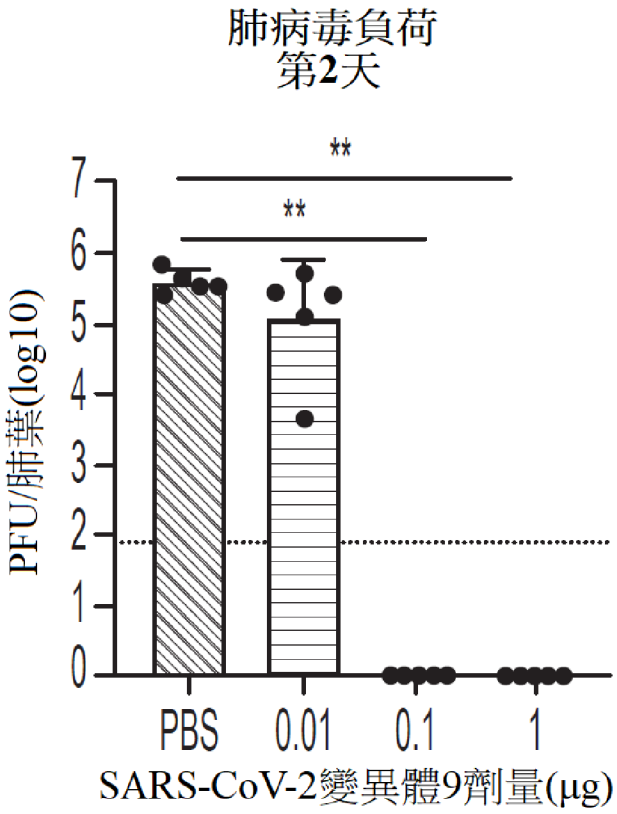
【圖 18B】


體重減輕
110
100
90
80
70
體重[%]
0
1
2
3
4
感染後天數
10 μg
1 μg
0.1 μg
PBS

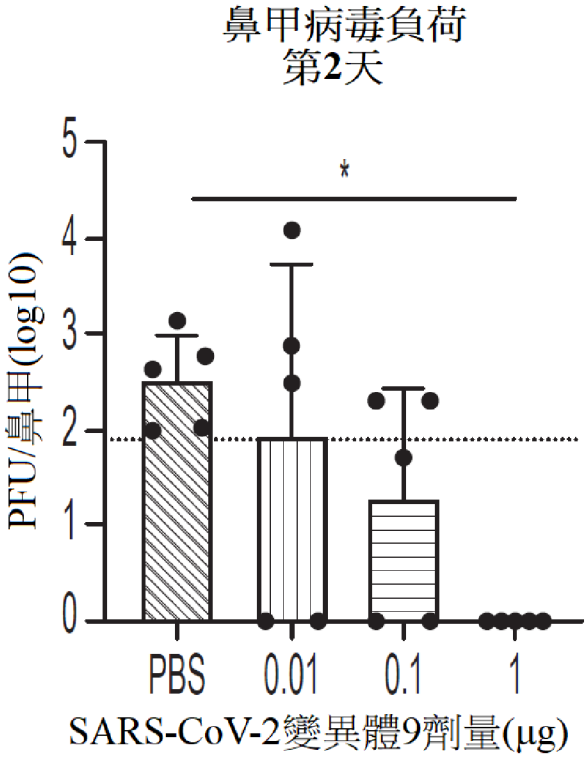
【圖 18C】


第0週
初免
第7週
攻擊
1x10^5 PFU
2AA-MA-SARS-CoV-2
攻擊後第1天
攻擊後
體重減輕
攻擊後第2天
體重減輕
肺病毒效價
鼻病毒效價
肺細胞介素
肺病理學
攻擊後第3天
攻擊後
體重減輕
攻擊後第4天
體重減輕
肺病毒效價
鼻病毒效價
肺細胞介素
肺病理學

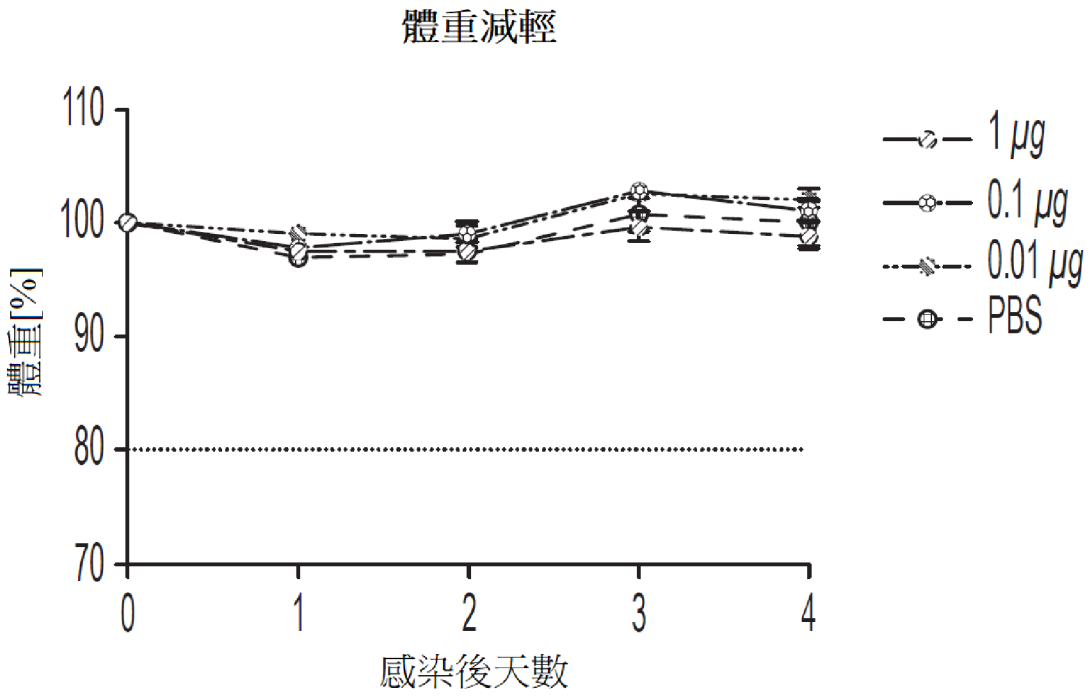
【圖 19】


肺病毒負荷
第2天
**
**
PFU/肺葉(log10)
0
1
2
3
4
5
6
7
PBS
0.01
0.1
1
SARS-CoV-2變異體9劑量(μg)

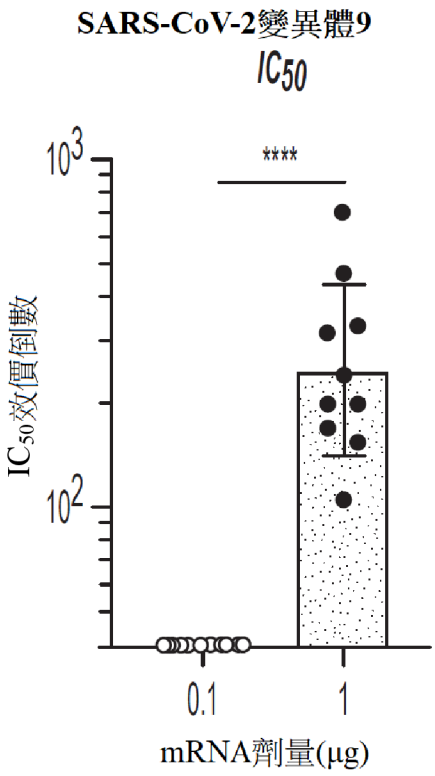
【圖 20A】


鼻甲病毒負荷
第2天
*
PFU/鼻甲(log10)
0
1
2
3
4
5
PBS
0.01
0.1
1
SARS-CoV-2變異體9劑量(μg)

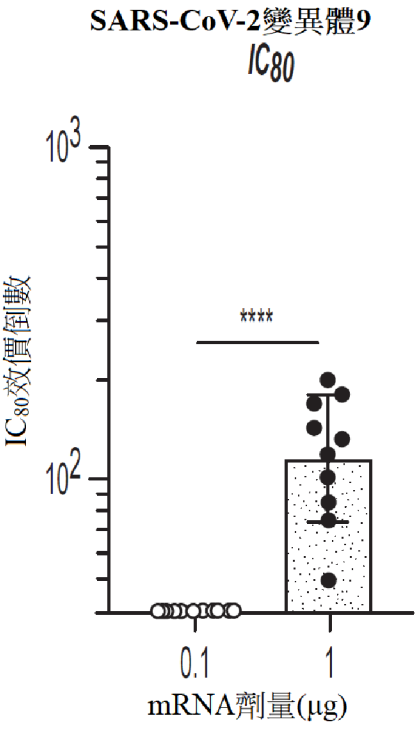
【圖 20B】



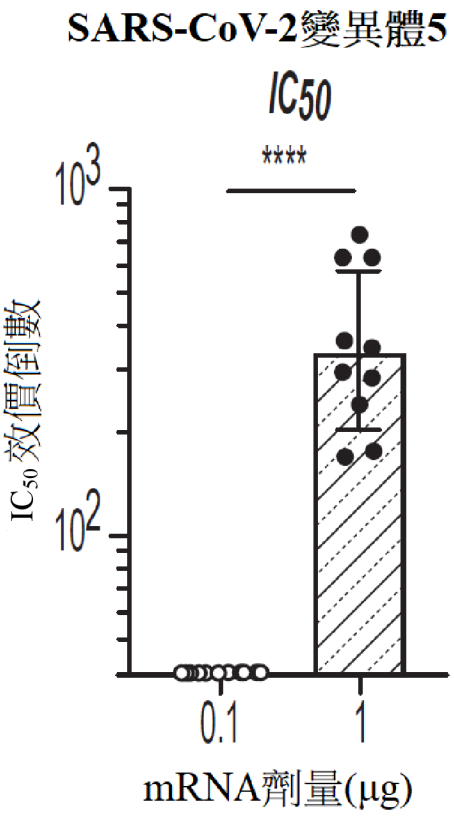
【圖 20C】


SARS-CoV-2變異體9
IC50
****
10^3
10^2
IC50效價倒數
0.1
1
mRNA劑量(μg)

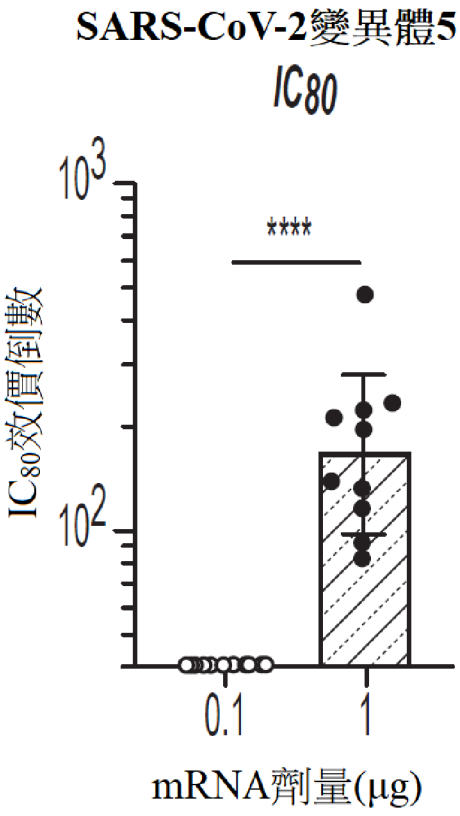
【圖 21A】


SARS-CoV-2變異體9
IC80
****
10^3
10^2
IC80效價倒數
0.1
1
mRNA劑量(μg)

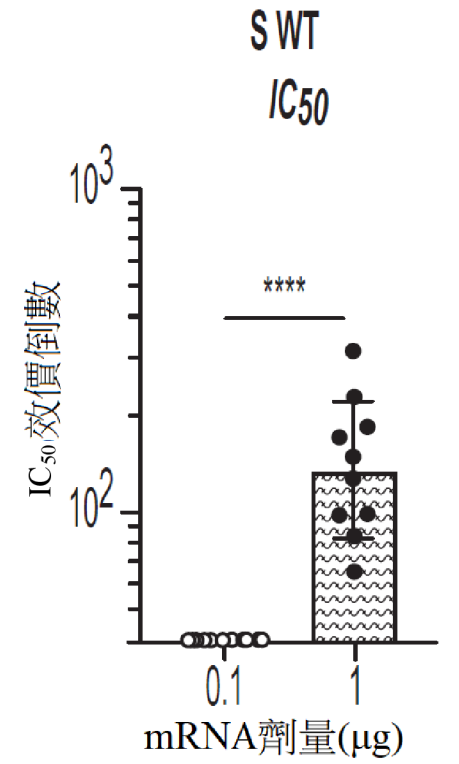
【圖 21B】


SARS-CoV-2變異體5
IC50
****
10^3
10^2
IC50 效價倒數
0.1
1
mRNA劑量(μg)

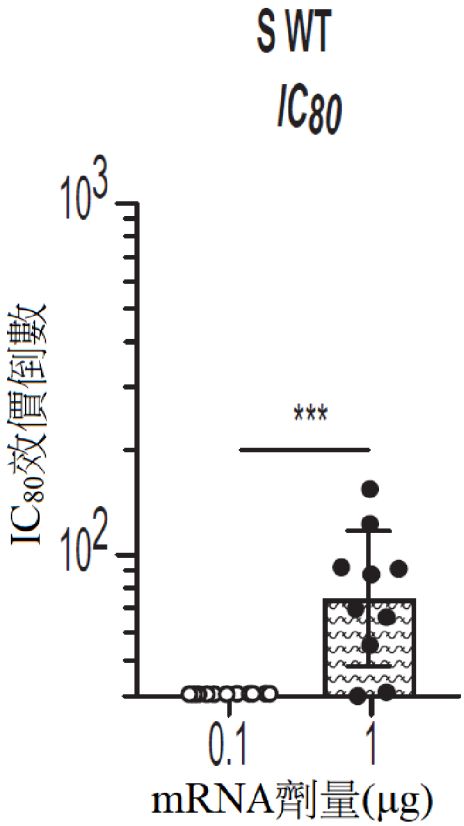
【圖 21C】


SARS-CoV-2變異體5
IC80
****
10^3
10^2
IC80效價倒數
0.1
1
mRNA劑量(μg)

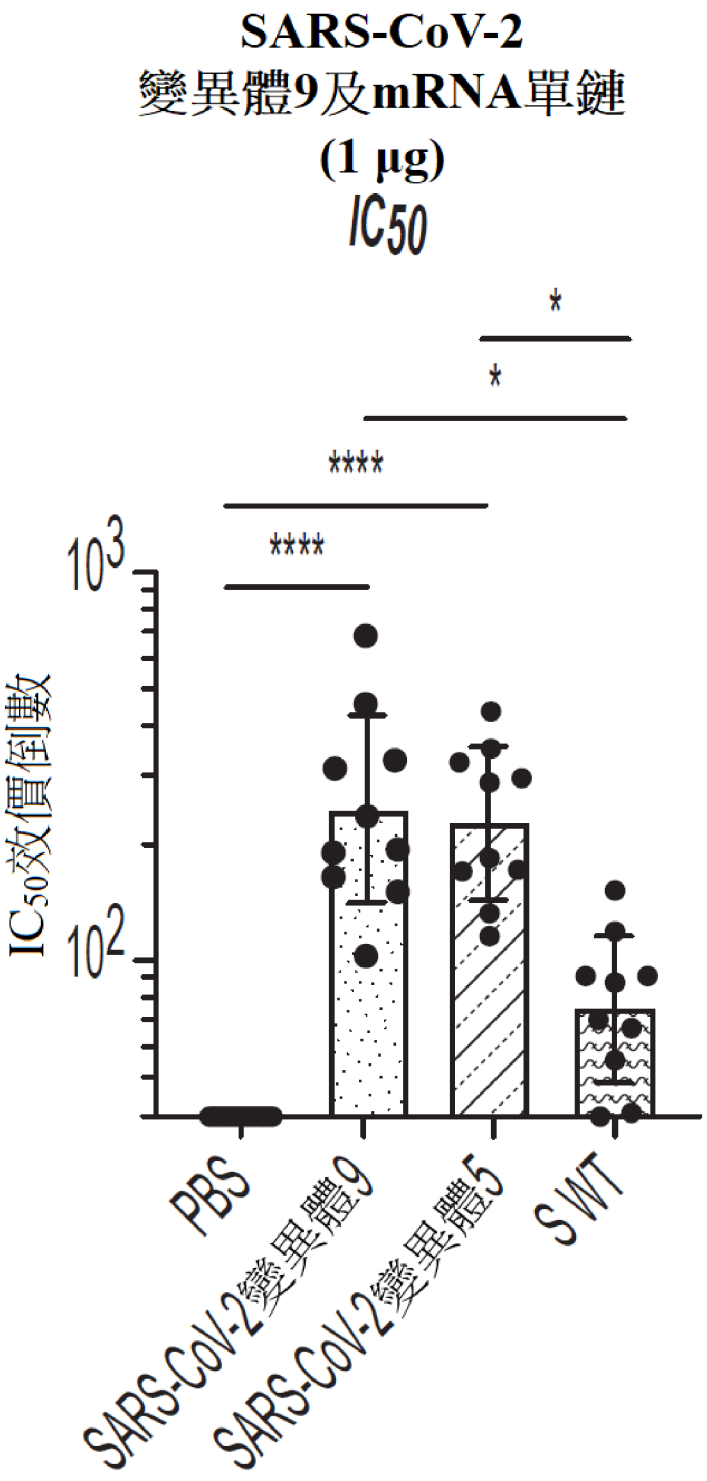
【圖 21D】


S WT
IC50
10^3
10^2
IC50效價倒數
****
0.1
1
mRNA劑量(μg)

【圖 21E】

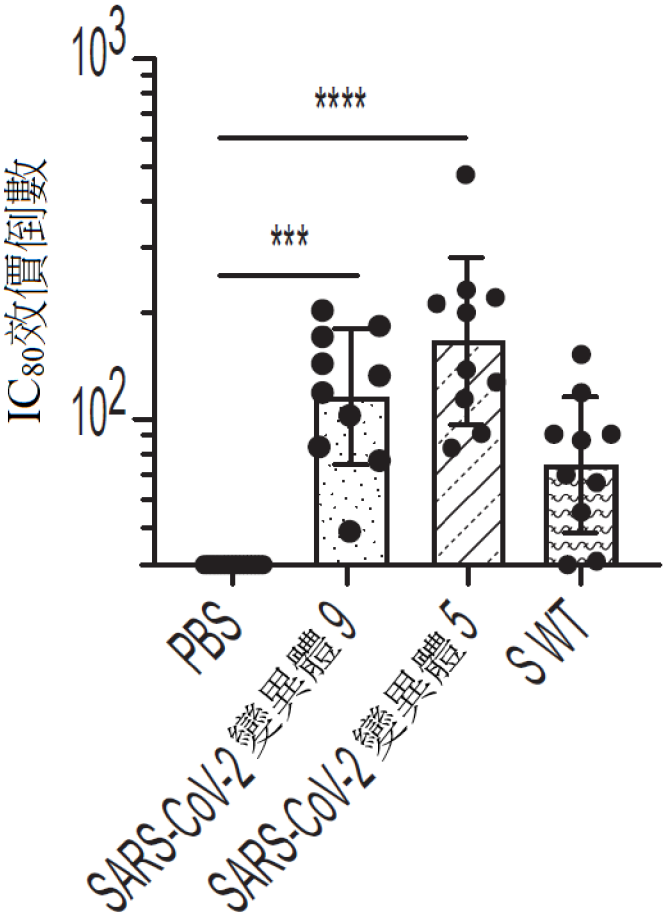

S WT
IC80
10^3
10^2
IC80效價倒數
***
0.1
1
mRNA劑量(μg)

【圖 21F】

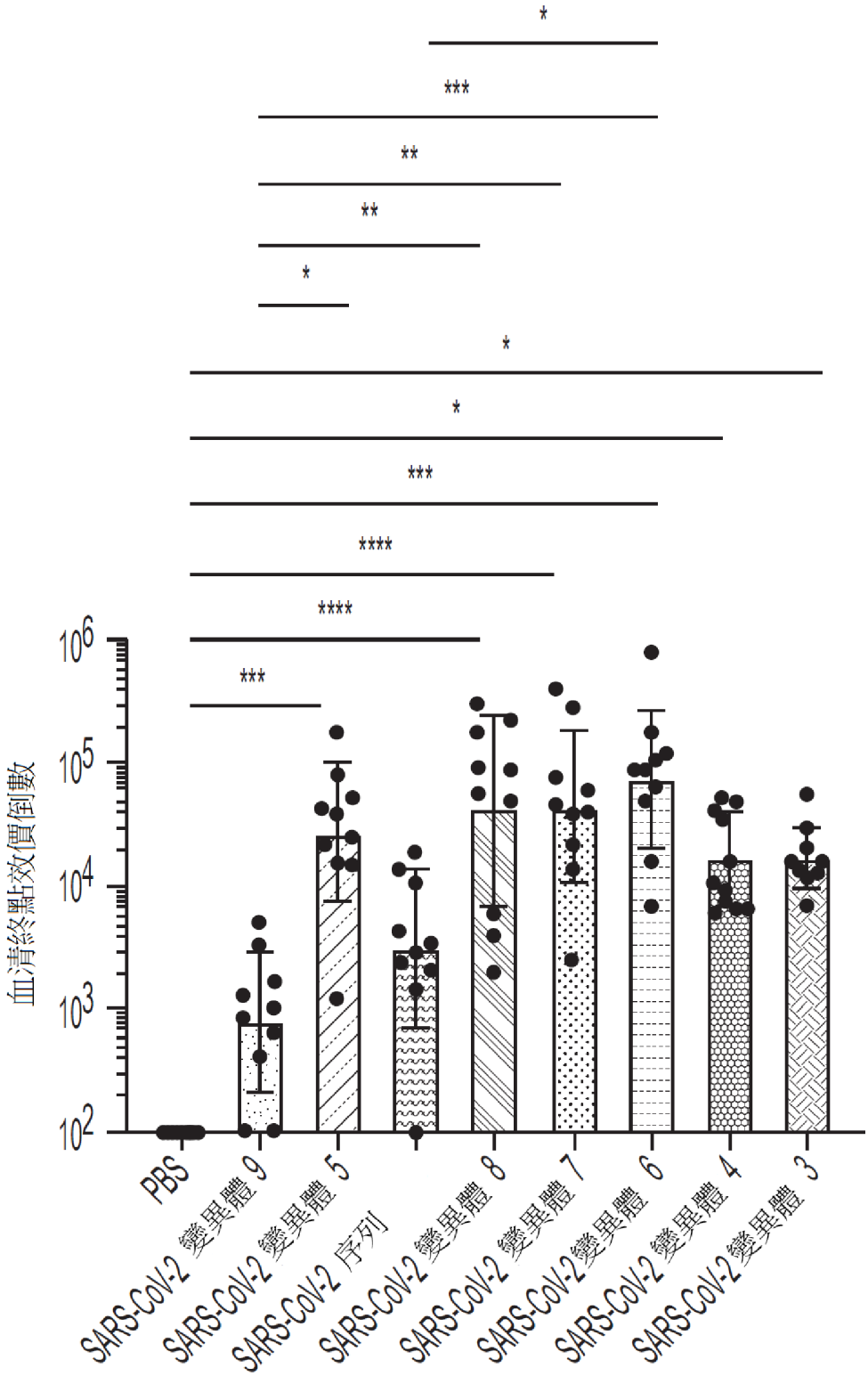

SARS-CoV-2
變異體9及mRNA單鏈
(1 μg)
IC50
*
*
****
****
10^3
10^2
IC50效價倒數
PBS
SARS-CoV-2變異體9
SARS-CoV-2變異體5
S WT

【圖 21G】

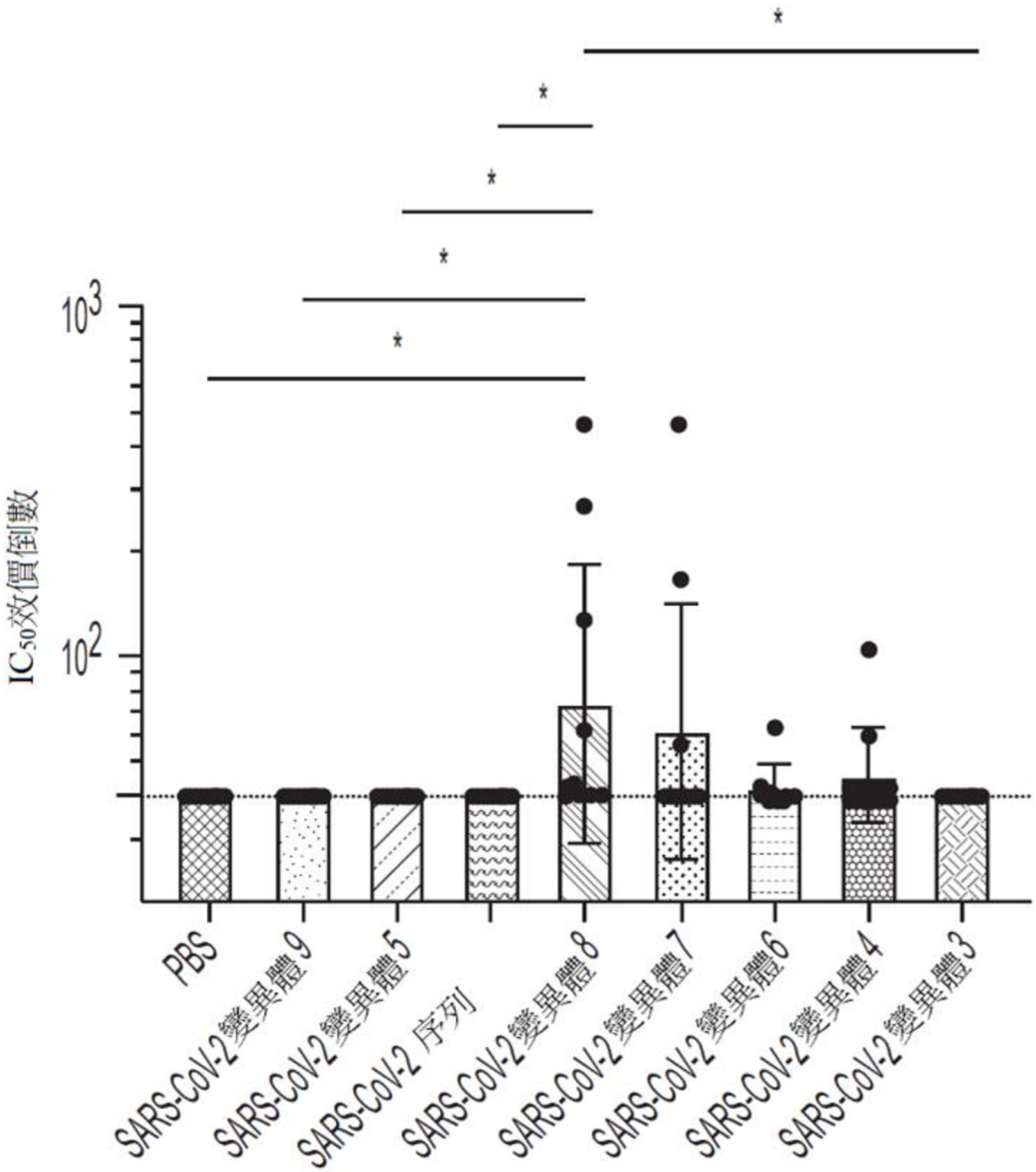
SARS-CoV-2
變異體9及mRNA單鏈
(1 μg)
IC80



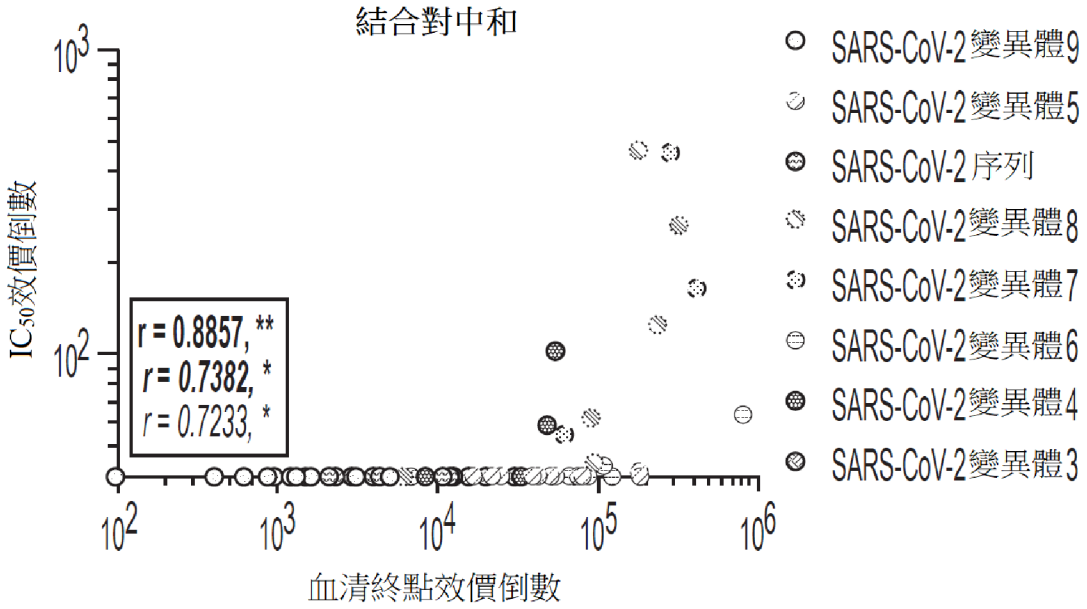
【圖 21H】


*
***
**
**
*
*
*
***
****
****
***
血清終點效價倒數
10^6
10^5
10^4
10^3
10^2
PBS
SARS-CoV-2 變異體 9
SARS-CoV-2 變異體 5
SARS-CoV-2 序列
SARS-CoV-2 變異體 8
SARS-CoV-2 變異體 7
SARS-CoV-2 變異體 6
SARS-CoV-2 變異體 4
SARS-CoV-2 變異體 3

【圖 22A】


IC_{50}效價倒數
10^3
10^2
PBS
SARS-CoV-2變異體9
SARS-CoV-2變異體5
SARS-CoV-2 序列
SARS-CoV-2變異體8
SARS-CoV-2變異體7
SARS-CoV-2變異體6
SARS-CoV-2變異體4
SARS-CoV-2變異體3

【圖 22B】


結合對中和
10^3
10^2
IC_{50}效價倒數
r = 0.8857, **
r = 0.7382, *
r = 0.7233, *
10^2
10^3
10^4
10^5
10^6
血清終點效價倒數
SARS-CoV-2變異體9
SARS-CoV-2變異體5
SARS-CoV-2 序列
SARS-CoV-2變異體8
SARS-CoV-2變異體7
SARS-CoV-2變異體6
SARS-CoV-2變異體4
SARS-CoV-2變異體3

【圖 22C】