



(19)中華民國智慧財產局

(12)發明說明書公開本

(11)公開編號：TW 201945545 A

(43)公開日：中華民國 108 (2019) 年 12 月 01 日

(21)申請案號：108114540

(22)申請日：中華民國 103 (2014) 年 03 月 14 日

(51)Int. Cl.：

C12N15/40 (2006.01)

A61K39/12 (2006.01)

A61K39/295 (2006.01)

A61P37/04 (2006.01)

(30)優先權：2013/03/15

美國

61/800,204

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美國

美國政府 由衛生及公共服務部部長代表 (美國) THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (US)

美國

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申請實體審查：有 申請專利範圍項數：49 項 圖式數：10 共 284 頁

(54)名稱

用於疫苗中之登革熱病毒嵌合式建構物的組成物及方法

(57)摘要

此處實施例實證登革熱病毒建構物及活減毒登革熱病毒之組成物、用途及製造。若干實施例係有關於一種組成物包括但非限制性，四價登革熱病毒組成物。於某些實施例中，組成物可包括一或多個登革熱病毒血清型之建構物，諸如登革熱-1(DEN-1)病毒、登革熱-2(DEN-2)病毒、登革熱-3(DEN-3)病毒、及登革熱-4(DEN-4)病毒建構物。於其它實施例中，如此處揭示的建構物可組合於一組成物以產生對抗多於一種或多種登革熱病毒建構物之疫苗，該建構物可以或可不接續地於哺乳動物細胞內繼代培養。

Embodiments herein report compositions, uses and manufacturing of dengue virus constructs and live attenuated dengue viruses. Some embodiments concern a composition that includes, but is not limited to, a tetravalent dengue virus composition. In certain embodiments, compositions can include constructs of one or more serotypes of dengue virus, such as dengue-1 (DEN-1) virus, dengue-2 (DEN-2) virus, dengue-3 (DEN-3) or dengue-4 (DEN-4) virus constructs. In other embodiments, constructs disclosed herein can be combined in a composition to generate a vaccine against more one or more dengue virus constructs that may or may not be subsequently passaged in mammalian cells.

發明專利說明書

(本說明書格式、順序，請勿任意更動)

【發明名稱】(中文/英文)

用於疫苗中之登革熱病毒嵌合式建構物的組成物及方法
COMPOSITIONS AND METHODS FOR DENGUE
VIRUS CHIMERIC CONSTRUCTS IN VACCINES

【技術領域】

優先權

[0001]本 PCT 申請案請求美國臨時專利申請案第 61/800,204 號申請日 2013 年 3 月 15 日之優先權。本申請案全文爰引於此並融入本說明書之揭示用於全部目的。

聯邦贊助研究

[0002]此處揭示之若干實施例以贊助合約號碼 R43 AI08429-01 獲得美國國家衛生院的部分支援。美國政府對實施本發明擁有某些權利。

發明領域

[0003]此處實施例報告登革熱病毒建構物之組成物、方法、用途及製造程序及其疫苗組成物。若干實施例係有關於一種組成物其包括但非限制性，嵌合式黃病毒建構物其單獨或組合其它建構物可用於疫苗組成物。於某些實施例中，組成物可包括多於一個個登革熱病毒血清型之建構物，諸如登革熱-1(DEN-1)病毒、登革熱-2(DEN-2)病毒、登革熱-3(DEN-3)病毒及/或登革熱-4(DEN-4)病毒建構物。於其它實施例中，製造策略可改良重組活減毒嵌合式登革熱疫苗(DENVax)病毒之安全性及遺傳安定性。某些實施例

包括至少一個活滅毒登革熱病毒組合登革熱病毒嵌合式建構物經識別用於疫苗組成物既安全又有效，於該處該等建構物已經於細胞培養中進行額外繼代培養

【先前技術】

發明背景

[0004]感染登革熱病毒可能導致不等嚴重程度的疼痛發燒。至目前為止已經識別四個登革熱病毒血清型：登革熱-1(DEN-1)、登革熱-2(DEN-2)、登革熱-3(DEN-3)組合登革熱-4(DEN-4)。登革熱係因登革熱病毒之感染所引起。未來可能找到其它血清型(例如DEN-5)。登革熱病毒血清型1-4也可能引發出血性登革熱(DHF)及登革熱休克症候群(DSS)。感染的最嚴重後果亦即DHF及DSS可能引發致命威脅。登革熱病毒每年引發5千萬至1兆個病弱型登革熱病毒病例、500,000個DHF/DSS病例，及多於20,000個死亡病例。至目前為止並無有效疫苗可保護對抗登革熱，且無藥物可用以治療該病。蚊蟲防治努力未能有效地預防登革熱在地方病地區的爆發，或防止該病的進一步地理擴散。估計有35億人受登革熱病毒的感染威脅。此外，登革熱病毒乃於地方病地區，諸如亞洲、中南美洲、及加勒比海地區的旅行者發燒的最常見起因。

[0005]全部四種登革熱病毒血清型在全球熱帶地區皆為地方病，且構成全球熱帶地區對人類有最大威脅的蚊媒病毒。登革熱病毒主要係由埃及斑蚊(*Aedes aegypti*)蚊子傳播給人類。感染一型登革熱病毒血清型導致終生保護免於

再受該血清型的重複感染，但無法保護免於另外三型登革熱病毒血清型中之一者的二度感染。實際上，先前感染一型登革熱病毒血清型結果導致當二度感染不同血清型時重症(DHF/DSS)的風險增高。有效疫苗的發展代表此種全球性疾病的預防及控制上的重要辦法。多重免疫接種使得針對在登革熱病毒地方病國家的公共衛生努力以及旅行者兩者受完整疫苗覆蓋率的困難。

【發明內容】

發明概要

[0006]此處實施例係有關於嵌合式登革熱病毒建構物之組成物、方法及用途。於若干實施例中，一種組成物可包括嵌合式登革熱病毒建構物具有減毒登革熱病毒骨架帶有來自至少另一個登革熱病毒血清型的結構基因。其它實施例係有關於至少一個活減毒病毒組合一或多個嵌合式登革熱病毒。其它實施例可包括一種嵌合式登革熱病毒之組成物具有改性DEN-2骨架(例如PDK-53作為P1(繼代培養-1)的起始骨架及繼代培養變異度(在一許可細胞系上試管內繼代培養及生長之後)如針對P2、P3、...、P8、...P10等指示)及一或多個DEN-1、DEN-2、DEN-3、或DEN-4之結構成分。於其它實施例中，生成免疫原性組成物，於該處當導入個體體內時，該組成物對個體體內的一或多個登革熱病毒產生免疫反應。因此，此處預期涵蓋之建構物可經生成及於試管內繼代培養，及該等繼代培養各自提供預期用在藥學上可接受之疫苗組成物的減毒登革熱病毒。於某些實

施例中，活減毒病毒可為單獨活減毒登革熱-2病毒或組合一或多個嵌合式登革熱病毒。

[0007]於某些實施例中，登革熱病毒血清型之嵌合式登革熱病毒建構物可包括繼代培養7(P7)活減毒病毒或嵌合式病毒，具有由SEQ ID NO: 1、9、17及25識別的核酸序列或由SEQ ID NO: 2、10、18及26指示的多肽序列。此處預期涵蓋針對此處描述的活減毒病毒中之任一者的繼代培養中之任一者可用於免疫原性組成物以對呈示的登革熱病毒(例如血清型1-4)誘生免疫反應。依據此等實施例，取決於所選用的建構物，包括P-8分離的活減毒病毒之免疫原性組成物可投予一個體以誘生對抗一或多個登革熱病毒血清型的免疫原性反應。此外，活減毒病毒可組合此等嵌合式病毒中之一或多者。此點預期涵蓋針對在各次接續細胞繼代培養(例如非洲綠猴腎Vero細胞製造，後文稱作：Vero細胞)所分離/製造的活減毒病毒中之各者。此處預期涵蓋能夠製造登革熱病毒的任何細胞系(例如GMP製造的細胞存庫、經FDA或EMA核准)係以製造規模用於病毒建構物中之任一者的繼代培養，或若屬適宜此處預期涵蓋隨後用在對抗登革熱病毒的疫苗或免疫原性組成物。

[0008]於其它實施例中，此處預期涵蓋之組成物可組合對抗其它黃病毒諸如西尼羅病毒、日本腦炎病毒或任何其它黃病毒嵌合式建構物及/或活減毒病毒的其它免疫原性組成物。單於某些實施例中，單一組成物可用以對抗多種黃病毒。

[0009]於某些實施例中，本發明之免疫原性組成物可包括對抗DEN-1、DEN-2、DEN-3、及/或DEN-4中之一或多者的嵌合式登革熱病毒，單獨或組合活減毒登革熱病毒組成物。

[0010]於其它實施例中，一種建構物可包括在病毒的結構區或非結構區具有適應性突變的建構物，該突變增加生長或製造而不影響導入個體體內時病毒的減毒或安全性。於某些實施例中，預期的嵌合式登革熱病毒建構物中之任一者可包括具有特定突變的活減毒DEN-2病毒用作為骨架，於該處活減毒DEN-2 PDK病毒進一步包括其它登革熱病毒血清型的prM(前膜)及E(被膜)結構蛋白質中之一或多者的結構蛋白質。此外，DEN-2骨架可包括額外突變以對一預定組成物當投予一個體時增加製造或促進免疫反應(例如嵌合式登革熱病毒2/1、2/3或2/4)。

[0011]於若干實施例中，結構蛋白質基因可包括在DEN-2骨架上的DEN-1、DEN-2、DEN-3或DEN-4之prM及E基因具有一或二個突變構成活減毒登革熱病毒的一部分。舉例言之，於某些實施例中，登革熱建構物可包括定名為DENVax-1-A、DENVax-2-F、DENVax-3-F、及DENVax-4-F(參考實施例章節)的該等建構物，於該處DEN-2骨架具有來自DEN-2活減毒病毒的一或多個突變(例如未見於P1或其它先前繼代培養之病毒或PDK-53)，先前驗證為安全有效地誘生免疫反應。本案的DEN-2活減毒病毒乃原先使用的DEN-2活減毒病毒之改良版本。本發明之嵌合式建構物可包括改

性減毒DEN-2 PDK-53骨架，具有第二登革熱病毒血清型之一或多個結構蛋白質，其中該等結構蛋白質可包括額外突變以增加對嵌合式建構物的免疫原性反應。於若干實施例中，藉減毒DEN-2 PDK-53獲得的某些突變在與P1建構物不同的一建構物中可產生保守性胺基酸變化可能導致期望的製造特徵等。

[0012]於其它實施例中，活減毒DEN-2基因體可用以生成登革熱病毒血清型1(DEN-1)、登革熱病毒血清型3(DEN-3)、及登革熱病毒血清型4(DEN-4)之建構物，於該處DEN-2病毒基因體之一或多個結構蛋白質基因可分別地由DEN-1、DEN-3或DEN-4的一或多個結構蛋白質基因置換。於若干實施例中，結構蛋白質可為第二登革熱病毒之C、prM或E蛋白。於某些實施例中，結構蛋白質基因包括DEN-1、DEN-3或DEN-4之prM或E蛋白。混合型病毒表現DEN-1、DEN-3或DEN-4的表面抗原，同時保有親代減毒DEN-2之減毒表現型。

[0013]此處揭示的建構物可包括使用減毒DEN-2病毒作為骨架表示DEN-1、DEN-3或DEN-4之表面抗原的DEN-4、DEN-2、DEN-1、及DEN-3之嵌合式建構物。

[0014]於某些實施例中，本發明之組成物可包括包含單一此處揭示的嵌合式登革熱病毒建構物及藥學上可接受之載劑或賦形劑之一組成物。另外，本發明之組成物可包括包含二或多種、或三或多種此處揭示的嵌合式登革熱病毒建構物及藥學上可接受之載劑或賦形劑之一組成物。依據

此等實施例，此處預期涵蓋的一或多個登革熱病毒嵌合式建構物可組合一或多個活減毒登革熱病毒。於某些實施例中，活減毒病毒可為活減毒DEN-2病毒，其中在NCR、NS1區或其它區的額外突變可提高免疫反應，增加病毒生長，或針對活減毒登革熱病毒之其它改良。

[0015]於某些實施例中，DENV-2疫苗的減毒基因座亦即核苷酸5'NCR-57-T、NS1-53-Asp、及NS3-250-Val先前已經決定，而全部此等變化皆由四種DENVax病毒的共通PDK-53特定病毒遺傳背景所分享。三個減毒基因座之基因序列以及此等疫苗候選者先前建立的試管內及活體內減毒表現型係針對cGMP製造的DENVax種病毒小心監控。本報告描述用以生成主種病毒(MVS)以及其用於登革熱病毒疫苗組成物的製造上使用的基因型及表現型特徵。此等MVS可用以製造臨床材料及最終供應商業疫苗。

【圖式簡單說明】

[0016]下列圖式形成本文說明書之一部分，且係含括於其中以進一步驗證某些實施例。若干實施例藉單獨參考此等圖式中之一或多者或組合所呈示之特定實施例之詳細說明部分將更明白瞭解。

[0017]圖1表示一圖表實施例，反映比較先前生成的建構物及野生型登革熱病毒，本發明之嵌合式建構物之實施例DEN-2/DEN-4。

[0018]圖2表示之直方圖實施例，比較使用活減毒DEN-2骨架(帶有額外突變)及第二登革熱病毒血清型作為

結構成分取代登革熱-2結構成分(例如DENVax-1 MVS)之各種反應。本圖例示DENVax MVS之溶菌斑大小。野生型登革熱病毒及先前公開的研究級疫苗候選者病毒係包括用於對照及比較。本圖例示比較對照組登革熱病毒嵌合式建構物，登革熱病毒建構物之製造改良。

[0019]圖3表示直方圖之實施例，表示DENVax MVS(主種病毒)之溫度敏感度。野生型登革熱病毒及先前公開的研究級疫苗候選者病毒係包括用於與MVS級比較。

[0020]圖4表示直方圖之實施例，表示比較對照組，於C6/36細胞中DENVax MVS之病毒生長。野生型登革熱病毒及先前公開的研究級疫苗候選者病毒係包括用於與DENVax MVS比較。

[0021]圖5A-5C表示於新生小鼠的神經毒力之作圖實施例。數個實驗之匯集結果摘述野生型(wt)DENV-2 16681病毒於CDC-ICR (n=72)及塔科尼克(Taconic)-ICR (n=32)新生小鼠ic使用 10^4 pfu病毒(A)挑釀的神經毒力。DENVax MVS的神經毒力以 10^4 pfu (B)或 10^3 pfu (C)劑量於塔科尼克(Taconic)-ICR小鼠測試。指出於一個實驗(n=16)或兩個匯集實驗(n=31或32)中每組測試的動物頭數。

[0022]圖6表示直方圖之實施例，例示DENVax MVS、WVS、及BVS的溶菌斑大小。於感染後第9日測量於瓊脂上覆層下方的Vero細胞或LLC-MK₂細胞中的病毒溶菌斑之平均溶菌斑直徑 $\pm$ SD(誤差柱)。野生型登革熱病毒及先前公開的研究級疫苗候選者病毒係包括用於對照及比較。

[0023]圖7表示直方圖之實施例，例示於兩個培養溫度於C6/36細胞中DENVax MVS、WVS、及BVS之生長以證實在大規模製造之後保有此種試管內減毒標記。

[0024]圖8表示直方圖之實施例，例示於C6/36細胞中DENVax MVS、WVS、及BVS之生長受限制。感染後七日於C6/36細胞中病毒複製之平均力價 $\pm$ SD(誤差柱)。野生型登革熱病毒及先前公開的研究級疫苗候選者病毒係含括用於比較。

[0025]圖9A-9B表示DENVax MVS於新生ICR小鼠的神經毒力之資料之線圖實施例。(A) 10^4 pfu劑量之病毒的IC接種。(B) 10^3 pfu劑量之病毒的IC接種。

[0026]圖10表示一圖表實施例比較新活減毒病毒與先前生成的活減毒登革熱病毒。

【實施方式】

定義

[0027]如此處使用，「一a」或「一an」可表示一項或多於一項。

[0028]如此處使用，「一個體」或「多個體」可包括但非限制性，哺乳動物諸如人類或哺乳動物，包括馴養的或野生的，例如犬、貓、其它居家寵物(例如倉鼠、天竺鼠、小鼠、大鼠)、雪貂、兔、豬、馬、牛、土撥鼠、野生齧齒類、或動物園動物。

[0029]如此處使用，「病毒嵌合體」、「嵌合式病毒」、「黃病毒嵌合體」及「嵌合式黃病毒」等詞可表示一建構物包

含登革熱-2病毒之核苷酸序列之一部分及進一步包含非來自登革熱-2病毒之核苷酸序列或來自不同黃病毒之核苷酸序列。「登革熱嵌合體」包含至少兩個不同的登革熱病毒血清型，但非不同的黃病毒。因此，其它登革熱病毒或黃病毒之實施例包括但非限制性，得自登革熱-1病毒、登革熱-3病毒、登革熱-4病毒、西尼羅病毒、日本腦炎病毒、聖路易腦炎病毒、蜱媒腦炎病毒、黃熱病毒、及其任一種組合。

[0030]如此處使用，「核酸嵌合體」可表示本發明之一建構物包含登革熱-2病毒之核苷酸序列之一部分及進一步包含非與登革熱-2病毒之核苷酸序列相同來源的額外核苷酸序列。相對應地，此處揭示之任何嵌合式黃病毒或黃病毒嵌合體可辨識為核酸嵌合體之一實施例。

[0031]如此處使用，「活減毒病毒」可表示野生型病毒經突變或選擇用在疫苗或其它免疫原性組成物之特徵，其中有些特徵可包括毒力減低、安全性、功效、或改良生長等。

較佳實施例之詳細說明

[0032]於下列章節中，描述各種組成物及方法之實施例以詳細說明各種實施例。熟諳技藝人士顯然易知實施各種實施例並不要求採用此處摘述的全部或甚至部分特定細節，反而透過常規實驗可修正濃度、時間及其它特定細節。於某些情況下，眾所周知之方法或成分不包括於該描述中

[0033]依據本發明之實施例，可採用落入業界技巧範圍內之習知分子生物學、蛋白質化學、微生物學、及重組DNA

技術。此等技術完整解說於參考文獻(例如參考Sambrook, Fritsch & Maniatis, 分子選殖：實驗室手冊，第二版1989年，冷泉港實驗室出版社，紐約冷泉港；動物細胞培養，R.I. Freshney編輯，1986)

[0034]此處實施例係有關於個別地或同時地於個體誘生對抗一或多個登革熱病毒血清型之免疫反應之組成物、方法及用途。依據此等實施例，生成減毒登革熱病毒及核酸嵌合體及用於此處揭示之疫苗組成物。若干實施例係有關於改性或突變登革熱建構物或嵌合體。其它實施例係有關於導入突變以改性登革熱病毒之結構蛋白質之胺基酸序列，其中該突變對病毒提高了免疫原性。

[0035]已經經由於細胞培養中繼代培養野生型病毒而發展出全部四個血清型之活減毒登革熱病毒。用於對抗黃病毒及特別登革熱病毒感染及/或疾病之用於免疫接種的最有展望的活減毒疫苗候選者有若干。此等疫苗候選者已經藉其登革熱血清型之組合、其繼代培養通過的細胞系及其繼代培養次數加以標示。因此，於PDK細胞中繼代培養13次的登革熱血清型1野生型病毒標示為DEN-1 PDK-13病毒。其它疫苗候選者為DEN-2 PDK-53、DEN-3 PGMK-30/FRhL-3 (例如於一次綠猴腎細胞30次繼代培養，接著於致命性恆河猴肺細胞及DEN-4 PDK-48繼代培養三次)。此等四種候選者疫苗病毒分別係藉野生型親代DEN-1 16007、DEN-2 16681、DEN-3 16562及DEN-4 1036病毒的組織繼代培養衍生。

[0036]於某些實施例中，活減毒登革熱-2 PDK-53疫苗病毒含有病毒混合物，族群含有各種核苷酸差異。於減毒突變之基因決定特徵之後，某些減毒特性被摘取出且藉基因工程加工成為cDNA傳染性純株。RNA係從此種傳染性純株轉錄及導入Vero細胞作為新特徵化及衍生PDK-53-Vero-DEN-2-P 1病毒之繼代培養1(例如參考表1)。此種減毒病毒針對各個DEN血清型產生，但針對DEN-1、DEN-3及DEN-4，prM及E基因係經基因工程處理進入3個分開cDNA傳染性純株，如此生成四個分開PDK-53-Vero病毒(於此處分別定名為：PDK-53-Vero-DEN-2-P 1、PDK-53-Vero-DEN-1-P 1、PDK-53-Vero-DEN-3-P 1、及PDK-53-Vero-DEN-4-P 1)。此等減毒疫苗病毒種系繼代培養於Vero細胞10次(表1)，及各個分開世系群當其適應生長於Vero細胞時獲得突變(表3)。此處某些實施例係有關於衍生及用於其活減毒登革熱病毒。

[0037]先前使用此等減毒病毒之人類臨床試驗已經指出DEN-2 PDK-53於人類具有最低感染劑量(50%溶菌斑形成單位或PFU之50%最低感染劑量)，具有強力免疫原性，且未產生顯著安全性擔憂。DEN-1 PDK-13、DEN-3 PGMK-30/FRhL-3及DEN-4 PDK-48疫苗病毒候選者於人類分別具有10,000、3500、及150 PFU之較高的50%最低感染劑量。雖然使用一價DEN-2 PDK-53病毒或DEN-4 PDK-48病毒只需要一次免疫接種即可於人體達成100%血清保留率，但針對DEN-1 PDK-13及DEN-3 PGMK-30/FRhL-3病毒

需要追加接種才能達成相同的血清保留率，該等病毒具有兩個用於人類之最高感染劑量。

[0038]DEN-2 PDK-53 病毒疫苗候選者也縮寫為PDK-53具有與減毒相關的若干可量測生物標記，包括溫度敏感性、小型溶菌斑大小、於蚊C6136細胞培養中之複製減低，於完好蚊體內之複製減低，於乳小鼠之神經毒力喪失及於猴之病毒血症發生率降低。候選者PDK-53疫苗之臨床試驗已經證實其用於人類之安全性及免疫原性。此外，PDK-53疫苗於人類疫苗接種者誘生登革熱病毒專一性T細胞記憶反應。此處若干實施例描述DEN-2 PDK-53用於此處揭示的嵌合式建構物的改良。

[0039]具有登革熱-2病毒骨架及另一種登革熱病毒血清型至少一個結構蛋白質之免疫原性黃病毒嵌合體可用於製備登革熱病毒嵌合體及描述用於製造登革熱病毒嵌合體之方法。免疫原性登革熱病毒嵌合體單獨地或組合地提供於藥學上可接受之載劑作為免疫原性組成物以減少、抑制、或免疫接種個體對抗不受單獨或組合一或多個血清型諸如登革熱病毒血清型DEN-1、DEN-2、DEN-3及DEN-4的感染。當組合時，免疫原性登革熱病毒嵌合體可用作為多價疫苗(例如二價、三價及四價)而賦與同時對抗多於一個黃病毒種或種系感染的保護效果。於若干實施例中，登革熱病毒嵌合體組合於免疫原性組成物可用作為對抗已知登革熱病毒血清型之二價、三價或四價疫苗，或藉含括得自不同黃病毒之編碼一或多種蛋白質的核酸而賦予對其它病原

性黃病毒的免疫力。

[0040]於若干實施例中，此處提供無毒力免疫原性登革熱病毒嵌合體含有減毒登革熱-2病毒(例如PDK-53)之非結構蛋白質基因，或其相當物，及欲在個體內誘生免疫原性之黃病毒之結構蛋白質基因或其免疫原性部分中之一或多者。例如，若干實施例係有關於具有減低登革熱-2病毒PDK-53基因體作為病毒骨架，及編碼PDK-53基因體之衣殼、前膜/膜、或被膜之一或多個結構蛋白質基因或其組合以對欲保護對抗諸如不同黃病毒或不同登革熱病毒血清型之得自DEN-1、DEN-3或DEN-4或其它黃病毒之一或多個相對應結構蛋白質基因置換之嵌合體。依據此等實施例，此處揭示之核酸嵌合體可具有減毒登革熱-2病毒之功能性質且為無毒力，但除了其它黃病毒之外表現DEN-1、DEN-3或DEN-4之結構基因產物的抗原作用部位且為免疫原性(例如於個體誘生對基因產物的免疫反應)。然後，此等DNA建構物用以轉錄得自傳染性純株的DNA，此種DNA導入Vero細胞內再度於P1產生新子代病毒。此等新子代病毒可與PDK-53區別(例如參考P1-P10)。

[0041]於另一實施例中，核酸嵌合體可為具有但非限制性編碼得自減毒登革熱-2病毒之非結構蛋白質之第一核苷酸序列及編碼得自登革熱-4病毒之結構蛋白質之第二核苷酸序列單獨地或組合另一種黃病毒之核酸嵌合體。於其它實施例中，減毒登革熱-2病毒可為具有一或多個突變胺基酸之疫苗種系PDK-53(參考實施例)。此等額外突變賦予了

用作為活減毒登革熱-2或如此處描述用作為嵌合式建構物之期望的使用特徵。若干實施例包括第二登革熱病毒之C、prM或E蛋白中之一或多者的結構蛋白質。

[0042]其它面向包括嵌合式病毒可包括例如於對照PDK-53登革熱-2基因體中之核苷酸及胺基酸取代、刪除或插入以減少對標靶登革熱病毒基因型之免疫原性反應的干擾。此等改性可於結構蛋白質及非結構蛋白質單獨進行，或組合此處描述之改性實施例進行，且可經由減毒病毒之繼代培養，及獲得用以誘生對一或多種登革熱病毒血清型之免疫反應的改良組合生成。

[0043]此處揭示之某些實施例提出一種藉將要求的取代插入適當骨架基因體，使用重組技術製造本發明之嵌合式病毒之方法。此處其它實施例係有關於繼代培養經過確認(例如安全有效)活減毒嵌合式病毒用以獲得額外改良。於某些實施例中，此處使用之登革熱-2骨架可包括表3呈現的一或多個突變。於其它實施例中，本案之登革熱-登革熱嵌合體可包括如表3呈現的一或多個突變。於又其它實施例中，登革熱-登革熱嵌合體可包括針對Den-2/Den-1、Den-2/Den-3或Den-2/Den-4如於表3呈現針對各種嵌合體之全部突變。預期也含括包括表3之建構物表示的活減毒病毒之藥學組成物。例如，一-、二-、三-或四價組成物預期含括此處使用的如表3呈現的嵌合體及活減毒登革熱-2病毒。

[0044]於某些實施例中，此處含括之活減毒DEN-2變異體可調配成藥學組成物，其中該藥學組成物可單獨或組合

登革熱-登革熱嵌合體或登革熱-黃病毒嵌合體投予。於某些實施例中，二價、三價或四價組成物可以單次施用或多次施用投予個體。

黃病毒嵌合體

[0045]登革熱型1-4 (DEN-1至DEN-4)為蚊媒黃病毒病原。黃病毒基因體含有5'-非編碼區(5'-NC)，接著為衣殼病毒(C)編碼區，接著為前膜/膜蛋白(prM)編碼區，接著為被膜蛋白(E)編碼區，接著為非結構蛋白(NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5)之編碼區及最後為3'非編碼區(3'NC)。病毒結構蛋白質為C、prM及E，及非結構蛋白質為NS1-NS5。結構蛋白質及非結構蛋白質轉譯為單一多蛋白及由細胞及病毒蛋白酶處理。

[0046]黃病毒嵌合體可為經由融合登革熱或黃病毒科病毒種的一型或血清型之非結構蛋白質基因與蛋白質基因例如得自登革熱病毒或黃病毒科病毒種之不同型或血清型之結構蛋白質基因所形成的建構物。另外，本發明之黃病毒嵌合體為藉如下方式形成的建構物，融合得自登革熱病毒或黃病毒科病毒種之一型或血清型之非結構蛋白質基因與指導選自其它登革熱病毒血清型或其它黃病毒科病毒的多肽或蛋白質之合成的額外核苷酸序列。

[0047]於其它實施例中，此處提供之無毒力免疫原性黃病毒嵌合體含有減毒登革熱-2病毒之非結構蛋白質基因或其相當物，及欲賦予對抗該病毒之免疫原性的黃病毒之結構蛋白質基因中之一或多者或其抗原部分。適當黃病毒包

括但非限於表1列舉者。

[0048]用以建構嵌合體之其它適當登革熱病毒可為野生型毒力DEN-1 16007、DEN-2 16681、DEN-3 16562及DEN-4 1036及減毒疫苗種系DEN-1 PDK-13、DEN-2 PDK-53、DEN-3 PMK-30/FRhL-3及DEN-4 PDK-48。涵蓋DEN-1、DEN-2、DEN-3及DEN-4野生型/減毒病毒對間之基因差異與由病毒基因體編碼的胺基酸序列之變化。

[0049]DEN-2 PDK-53之序列列表相對應於DEN-2 PDK-53-V變異體，其中基因體核苷酸位置5270從A突變為T，及多蛋白之胺基酸位置1725或NS3蛋白之胺基酸位置250含有纈胺酸殘基。不含此種核苷酸突變的DEN-2 PDK-53亦即DEN-2 PDK-53-E與PDK-53-V的差異只在於此一位置。DEN-2 PDK-53-E於核苷酸位置5270具有A及於多蛋白胺基酸位置1725亦即NS3蛋白胺基酸位置250具有麩胺酸。須瞭解此處實施例包括改性PDK 53其包括於分開宿主細胞(例如Vero細胞，參考表1)之一或多個繼代培養，於該處生成此處涵蓋疫苗組成物中期望的使用特徵。

[0050]於某些實施例中，嵌合體之標示可基於DEN-2病毒專一性傳染性純株改性骨架及其它登革熱病毒或其它黃病毒之結構基因(prM-E或C-prM-E)。登革熱-2骨架之DEN-2接著為插入該結構基因之種系。一個DEN-2骨架變異體反映在數字編號後的下個字母。嵌合體可從其中建構的一個特定DEN-2骨架係以下列字母置於短橫線親代16681(P)後方，PDK-53-E(E)或PDK-53-V(V)；最末字母指示得自親代

(P)種系或其疫苗衍生物(V)之C-prM-E或得自親代(P)或其疫苗衍生物(V1)之prM-E結構基因。例如，DEN-2/1-VP表示該嵌合體包含減毒DEN-2 PDK-53V骨架包含纈胺酸於NS3-250及得自野生型DEN-1 16007之C-prM-E基因；DEN-2/1-VV表示DEN-2 PDK-53V骨架具有登革熱-1、DEN-1 PDK-13之疫苗種系；DEN-2/1-VP1表示DEN-2 PDK-53V骨架及得自野生型DEN-1 16007之prM-E基因；DEN-2/3-VP1表示DEN-2 PDK-53V骨架及得自野生型DEN-3 16562之prM-E基因；DEN-2/4VP1表示DEN-2 PDK-53V骨架及得自野生型DEN-4 1036之prM-E基因。此處揭示之其它嵌合體係以相同方式指示。

[0051]於一個實施例中，此處揭示之嵌合體含有減毒登革熱-2病毒PDK-53基因體作為病毒骨架，其中編碼PDK-53基因體之C、prM及E蛋白之結構蛋白質基因或其組合可以得自登革熱-1、登革熱-3或登革熱-4病毒之相對應結構蛋白質置換，及選擇性地另一種黃病毒欲保護對抗諸如不同黃病毒或不同登革熱病毒種系。

[0052]於非結構蛋白質區域，於非結構蛋白質NS1-53(基因體核苷酸位置2579)，發現Gly-至-Asp(野生型至PDK-53)突變；於非結構蛋白質NS2A-181(基因體核苷酸位置4018)發現Leu-至-Phe(野生型-至-PDK-53)突變；於非結構蛋白質NS3-250(基因體核苷酸位置5270)發現Glu至-Val(野生型-至-PDK-53)突變；及於非結構蛋白質NS4A-75(基因體核苷酸位置6599)發現Gly至-Ala(野生型-

至-PDK-53)突變。本發明之活減毒DEN-2病毒進一步包括如表3之活減毒登革熱病毒之任何嵌合體中呈現的突變。

[0053]PDK-53病毒種系具有於基因體核苷酸5270之混合基因型。顯著部分(約29%)病毒族群編碼存在於野生型DEN-2 16681病毒之非突變NS3-250-Glu而非NS3-250-Val突變。因兩個基因變異體皆為無毒力，故此種突變於無毒力嵌合體中可能不需要。

[0054]先前發現減毒PDK-53病毒種系之無毒力可促成於編碼非結構蛋白質之核苷酸序列中及於5'-非編碼區中的突變。例如，於NS1-53之單一突變、於NS1-53及5'NC-57之雙突變，於NS1-53及NS3-250之雙突變、及於NS1-53、5'NC-57及NS3-250之三突變，結果導致DEN-2病毒的減毒。因此，於此等基因座含有此等非保留性胺基酸取代或核苷酸取代的任何登革熱-2病毒之基因體可用作為鹼基序列用以衍生此處揭示之改性PDK-53病毒。於5'非編碼區之莖/環結構的莖中之另一突變若有所需將提供額外無毒力表現型安定性。對此等區域的突變破壞用於病毒複製重要的潛在二次結構。於DEN及委內瑞拉馬腦炎病毒兩者的此種短(長度只有6核苷酸殘基)莖結構中的單一突變破壞髮夾結構的形成。於此莖結構的進一步突變減少於此基因座反轉的可能，同時維持病毒存活能力。

[0055]此處揭示之突變可藉技藝界已知之任一種方法達成包括但非限制性，一旦於關注細胞系(例如Vero細胞)繼代培養一次具有額外特徵之天然或選擇純株。熟諳技藝

人士須瞭解如此處描述且為技藝界已知之毒力篩檢檢定分析可用以區別毒力及無毒力骨架結構。

黃病毒嵌合體之建構

[0056]此處描述之黃病毒嵌合體可藉剪接期望有免疫力的黃病毒之結構蛋白質基因中之一或多者剪接入PDK-53登革熱病毒基因體骨架製造；或藉技藝界已知之其它方法製造，使用重組基因工程去除相對應PDK-53基因及以登革熱-1、登革熱-3或登革熱-4病毒基因或業界已知之其它基因置換PDK-3基因。

[0057]另外，使用序列表中提供的序列，使用已知核酸合成技術可合成編碼黃病毒蛋白質之核酸分子及插入適當載體。因此無毒力免疫原性病毒使用熟諳技藝人士已知之重組基因工程技術製造。

[0058]標靶基因可插入骨架，其編碼針對DEN-1、DEN-3、DEN-4或其它黃病毒的關注黃病毒結構蛋白質。欲插入的黃病毒基因可為編碼C蛋白、PrM蛋白及/或E蛋白之基因。插入登革熱-2骨架之序列可編碼PrM及E結構蛋白質。插入登革熱-2骨架之序列可編碼C、prM及E結構蛋白質中之全部或中之一者。

[0059]含有編碼其它黃病毒或登革熱病毒血清型之結構蛋白質的核苷酸序列之適當嵌合體病毒或核酸嵌合體可藉篩檢其用於前述減毒表現型標記指示無毒力，及藉篩檢其免疫原性而評估作為疫苗的有用性。抗原性及免疫原性可使用熟諳技藝人士已知的例行篩檢程序，利用與黃病毒

抗體或免疫反應性血清之試管內或活體內反應性進行評估。

登革熱病毒疫苗

[0060]於某些實施例中，嵌合體病毒及核酸嵌合體可提供可作為免疫原或疫苗的活減毒病毒。若干實施例包括具有對登革熱-4病毒之免疫原性同時不會產生危險的致病或致命效應之嵌合體

[0061]為了減少個體發生DHF/DSS，需要四價疫苗來提供對全部四個病毒血清型同時的免疫力。四價疫苗係經由將本發明之活減毒登革熱-2病毒與前述登革熱-2/1、登革熱-2/3、及登革熱-2/4嵌合體於合宜藥學載劑內組合用以投予為多價疫苗。

[0062]本發明之嵌合式病毒或核酸嵌合體可包括野生型或活減毒病毒之結構基因於毒力或減毒DEN-2病毒骨架。例如，嵌合體可表現野生型DEN-4 1036病毒之結構蛋白質基因、其候選者疫苗衍生物於任一種DEN-2骨架。

[0063]此處描述之嵌合體中使用病毒可使用技藝界已知方式生長。然後進行病毒溶菌斑滴定及溶菌斑計數以便評估生長培養之存活力及表現型特性。野生型病毒可通過培養細胞系繼代培養來衍生減毒候選者起始物料。

[0064]嵌合式傳染性純株可從可用的各種登革熱血清型純株建構。若有所需也可完成病毒專一性cDNA片段之選殖。含有結構蛋白質及非結構蛋白質基因之cDNA片段藉使用各種引子從登革熱病毒RNA之反錄酶-聚合酶連鎖反應

(RT-PCR)擴增。擴增片段選殖入其它中間純株之裂解位置。然後中間嵌合式登革熱病毒純株經定序以證實所插入之登革熱病毒專一性cDNA的準確性。

[0065]藉將登革熱血清型病毒之結構蛋白質及/或非結構蛋白質基因區插入載體內建構全基因體長度嵌合式質體可使用熟諳技藝人士眾所周知的重組技術獲得。

核苷酸及胺基酸分析

[0066]於DEN-2 PDK-53疫苗病毒中的NS1-53突變對此種病毒的減毒表現型具有意義，原因在於DEN-2 16681病毒的NS1-53-Gly保留於幾乎全部至今為止已定序的黃病毒，包括蜱媒病毒。DEN-4疫苗病毒於NS1蛋白質於位置253也可含有胺基酸突變。於DEN- PDK-48疫苗病毒中之Gln至His突變的此一基因座在全部四個野生登革熱病毒基因型皆為Gln。此種Gln殘基為黃病毒屬內部登革熱病毒所獨有。NS1蛋白為從黃病毒感染細胞分泌的糖蛋白。其係存在於感染細胞表面，及NS1-專一性抗體係存在於病毒感染個體的血清中。曾經報告以NS1蛋白質免疫接種或以NS1專一性抗體被動保護動物。NS1蛋白顯然參與早期病毒RNA複製。

[0067]出現於DEN-1、-2、-3及-4減毒種系之NS2A、NS2B、NS4A及NS4B蛋白的突變本質上為保留性。DEN-2及DEN-4疫苗病毒的NS4A-75及NS4A95突變分別出現在登革熱病毒中胺基酸保留位置，但通常不出現在黃病毒

[0068]黃病毒NS3蛋白具有至少兩個已辨識功能：病毒

性蛋白酶及RNA螺旋酶/NTPase。698-aa長度(DEN-2病毒) NS3 蛋白含有以胺基為端基之絲胺酸蛋白酶領域 (NS3-51-His、-75-Asp、-135-Ser催化三聯體)接著為RNA螺旋酶 /NTPase 功能之序列部分 (NS3-196-GAGKT、-284-DEAH、-459-GRIGR)。於DEN-1、DEN-2或DEN-3病毒的NS3蛋白中之突變並無任一者出現在已辨識部分。於DEN-1 PDK-13病毒的NS-510 Tyr-至-Phe突變為保留性。因野生型DEN-2、-3及-4病毒在此位置含有Phe，故Tyr-至-Phe突變在DEN-1病毒的減毒上不可能扮演某種角色。於DEN-1 PDK-13病毒的NS3-182 Glu-至-Lys突變出現在大部分蚊媒黃病毒保留為Asp或Glu的位置，及在減毒上可扮演某種角色。此種突變係位在GAGKT螺旋酶部分上游15胺基酸殘基。如先前報告所記，於DEN-2 16681病毒中之NS3-250-Glu保留於全部蚊媒黃病毒，但黃熱病病毒除外。

[0069]核酸探針選擇性地與編碼DEN-1、DEN-3及DEN-4病毒之核酸分子或其互補序列雜交。「選擇性的」或「選擇性地」表示一序列不與其它核酸雜交以防止登革熱病毒的適當檢測。因此，於雜交核酸之設計中，選擇性將取決於存在於樣本內的其它成分。雜交核酸須具有與其雜交核酸節段之至少70%互補性。如此處用來描述核酸，「選擇性地雜交」一詞排除偶爾隨機雜交的核酸，因而具有與「專一性雜交」的相同定義。本發明之選擇性雜交核酸可具有與其雜交之序列節段至少70%、80%、85%、90%、95%、97%、98%及99%互補性，較佳85%或以上。

[0070]預期涵蓋選擇性雜交至編碼核酸或核酸之互補股、或相反股之序列、探針或引子。與核酸之專一性雜交可發生而在核酸有微小修改或取代，只要維持功能種屬專一性雜交能力即可。「探針」一詞表示可用作為與互補核酸序列選擇性雜交用於其檢測或擴增的探針或引子之核酸序列，該等探針之長度可由約5變化至100核苷酸，或較佳約10至50核苷酸，或最佳約18至24核苷酸。

[0071]若用作為引子則該組成物較佳包括至少兩個核酸分子其雜交至標靶分子的不同區，因而擴增期望區。取決於探針或引子長度，標靶區可於70%互補鹼基至完全互補之範圍，而仍然於苛刻條件下雜交。例如，為了檢測登革熱病毒存在之目的，雜交核酸(探針或引子)與其雜交序列間的互補程度為至少足夠區別與來自其它有機體的核酸之雜交。

[0072]編碼DEN-4、DEN-3或DEN-1病毒之核酸序列(例如結構元體)可插入載體內，諸如質體，及於活有機體重組表現(例如表現成登革熱-2骨架)而製造重組登革熱病毒胜肽及/或多肽及/或病毒。

核酸檢測方法

[0073]本發明提供快速基因測試，可診斷此處描述之各種疫苗病毒。本發明之此一實施例加強從發展成病毒血症的疫苗接種人類血清分離的病毒之分析，以及促進於使用候選者疫苗病毒免疫接種之非人靈長類之病毒血症之特徵化。

[0074]此等序列包括診斷性TaqMan探針，用來報告藉使用反錄酶/聚合酶連鎖反應(RT/PCR)檢測從病毒基因體RNA樣板擴增的cDNA擴增子，以及正及反擴增元體，其設計來擴增cDNA擴增子，容後詳述。於某些情況下，已經設計擴增元體中之一者含有於擴增元體3'-端之疫苗病毒專一性突變，由於在標靶位置的引子延長，有效使得該測試對疫苗種系甚至更具有專一性，結果唯有病毒RNA樣板含有該專一性突變時才出現擴增。

[0075]可使用自動化以PCR為基礎之核酸序列檢測系統，或其它已知核酸檢測技術。TaqMan檢定分析為高度專一性敏感的檢定分析，許可來自樣本核酸樣板的PCR生成的擴增子之自動化即使觀察與定量。TaqMan可決定特定序列是否存在。於本檢定分析中，正及反引子經設計而煉合標靶突變位置之上游及下游。特定檢測器探針設計具有比擴增子更高約10°C之熔點，及含有疫苗病毒專一性核苷酸突變或其補體(取決於被檢測的RT/PCR擴增子之股)，組成本檢定分析之第三引子成分。

[0076]設計來專一性檢測於疫苗病毒基因體中之一者以突變基因座之探針將含有於探針中央的疫苗專一性核苷酸。若病毒RNA樣板為疫苗病毒專一性，則此探針將導致TaqMan檢定分析中可檢測的螢光。但得自野生型DEN病毒之基因體RNA樣板將具有減低的探針雜交效率，原因在於單一核苷酸不匹配(以親代病毒DEN病毒為例)，或可能多於一個不匹配(可能發生於其它野生型DEN病毒)，且將不會導

- 致顯著螢光。DNA聚合酶比較裂解不匹配的探針而釋放通報子染料較為可能從RT/PCR擴增子樣板置換不匹配探針(TaqMan對偶基因區別檢定分析，應用生物系統公司(Applied Biosystems))。

[0077]診斷性基因測試的一種策略使用分子信標。分子信標策略也利用用於RT/PCR擴增子擴增的引子，及藉含探針通報子及淬熄劑染料於探針終端檢測擴增子內部之特定序列。於本檢定分析中，探針形成莖-環結構。分子信標檢定分析採用與TaqMan檢定分析使用者不同的淬熄劑及通報子染料。

藥學組成物

[0078]此處實施例提供以適合於活體內藥學投藥之生物可相容形式將組成物投予個體。「適合於活體內投藥之生物可相容形式」表示欲投予之活性劑形式(本實施例之藥物化學品、蛋白質、基因)，其中任何毒性效應經權衡之後皆輸給活性劑之治療效果。投予治療上活性量之治療組成物定義為就劑量及達成期望結果所需時間而言之有效量。例如，治療上活性量之化合物可依據多項因素改變，諸如個體之疾病狀態、年齡、性別、及體重，及於個體體內提引出期望反應的抗體能力。用法用量可經調整而提供最佳治療反應。

[0079]於一個實施例中，化合物(例如實施例之藥物化學品、蛋白質、胜肽等)可以習知方式投予，例如皮下、靜脈、口服、吸入、皮內、經皮施用、陰道內施用、局部施

用、鼻內或直腸投予。取決於投藥途徑，活性化合物可含於保護緩衝劑(例如FTA、F127/海藻糖/白蛋白)。於一個實施例中，可經口投予組成物。於另一個實施例中，組成物可經靜脈投予。於一個實施例中，組成物可於鼻內諸如吸入投予。於又另一個實施例中，組成物可使用無針系統(例如藥物注射器(Pharmajet))或其它皮內投予系統投予。

[0080]組成物可於適當載劑或稀釋劑與酶抑制劑共同投予或於適當載劑諸如微脂粒投予個體。如此處使用「藥學上可接受之載劑」一詞意圖包括稀釋劑諸如鹽水及水性緩衝溶液。可能需要使用防止其交互作用的材料塗覆該化合物或共同投予該化合物。活性劑也可經腸道外或經腹內投予。分散液劑可經由於甘油、液體聚乙二醇及其混合物及於油製備。於尋常儲存及使用條件下，此等製劑可含有保藏劑以防止微生物的生長或其它安定配方(例如FTA)。

[0081]適合注射用之藥學組成物可利用技藝界已知手段投予。例如無菌水性溶液(當為水溶性時)或分散液或用於臨時製備無菌注射溶液劑或分散液的無菌粉末皆可使用。於全部情況下，該組成物可為無菌且可為流體至溶液注射的程度。於製造及儲存條件下可為安定且可保藏不受微生物諸如細菌及真菌的污染。藥學上可接受之載劑可為溶劑或分散介質含有例如水、乙醇、多元醇(例如甘油、丙二醇、及液體聚乙二醇等)及其適當混合物。適當流動性例如可藉使用包衣諸如卵磷脂，或於分散液之情況下藉維持所需的粒徑及藉使用界面活性劑加以維持。微生物之預防可藉加

熱、將藥劑暴露於清潔劑、照射或添加抗菌劑或抗真菌劑達成。

[0082]無菌注射用溶液劑之製備方法，係經由將需要量之活性化合物(例如對一或多個登革熱病毒血清型誘生免疫反應之化合物)與前文列舉的成分中之一者或組合以適量摻混於適當溶劑，視需要接著過濾滅菌。

[0083]當配方時，溶液劑將以與該劑量配方可相容之方式及治療有效量投藥。配方容易以多種劑型投予，諸如前述注射溶液劑類型。預期組成物特別適合用於肌肉、皮下、皮內、鼻內及腹內投予。可追求特定比例諸如1:1、1:2或其它比例(例如給定登革熱病毒血清型之PFU)。

[0084]活性治療劑可於混合物內以預定比例配方。單劑或多劑可針對給定情況(例如旅行前、登革熱爆發時)以適當時間表投予。

[0085]於另一實施例中，鼻用溶液劑或噴灑劑、噴霧劑或吸入劑可用於遞送關注的化合物。適合用於其它投藥模式之額外配方包括栓劑及托劑。

[0086]某些配方可包括賦形劑，例如藥學等級之甘露糖醇、乳糖、澱粉、硬脂酸鎂、沙卡林鈉、纖維素、碳酸鎂等。

[0087]藥學組成物可使用保護活性成分對抗從體內快速釋放之載劑製備，諸如定時釋放配方或包衣。此等載劑包括控制釋放配方，諸如但非僅限於微膠囊遞送系統、及可生物分解生物可相容性聚合物諸如乙烯乙酸乙烯酯、聚

酐、聚乙醇酸、聚原酸酯、聚乳酸及其它為已知。

[0088]藥學組成物係以可有效抑制或緩解植體之副作用及/或減少或預防排斥的用量及頻率投予。精確之治療劑量及治療時間可使用已知測試方案或於技藝界已知之模型系統測試該等組成物且外推加以決定。劑量也可隨情況之嚴重程度改變。藥學組成物通常係經配方及投藥以發揮治療有用的效果同時減低非期望的副作用。一般而言，約 10^2 至 10^6 PFU之劑量範圍可經初始及選擇性地投予，接著視需要可在30天內或至多180天後做第二次投予。於某些實施例中，個體可接受此處揭示之一價、二價、三價或四價組成物之雙重投予，其中該組成物為單一組成混合物或具有不同登革熱病毒血清型之預定組成物。於若干實施例中，DEN2/4嵌合體可以比其它登革熱血清型諸如活減毒登革熱-1更高濃度存在。

[0089]針對任何特定個體而言，顯然可視個別需要隨著時間調整特定用法用量。

[0090]於一個實施例中，此處揭示之組成物可經皮下或皮內投予個體。

[0091]含有活減毒登革熱病毒之藥學組成物可投予個體特別為人體，例如利用皮下、肌肉、鼻內、口服、局部、經皮、腸道外、經胃腸、經支氣管及經肺泡投藥。局部投予係透過含有有效量之絲胺酸蛋白酶抑制劑局部施用乳膏劑、膠漿劑、洗劑等達成。穿皮投藥係藉施用能夠允許絲胺酸蛋白酶抑制劑穿透皮膚及進入血流之乳膏劑、洗劑、

膠漿劑等達成。此外，滲透幫浦可用於投藥。所需劑量將隨接受治療的特定病況、投藥方法及該分子從體內之清除速率而改變。

[0092]於本發明方法之某些實施例中，個體可為哺乳動物諸如人類或獸醫動物及/或家畜或牲口或野生動物。

治療方法

[0093]於本發明之一個實施例中，此處預期涵蓋使用一價、二價、三價或四價活減毒及/或嵌合式病毒組成物配方誘生對登革熱病毒血清型之免疫反應。

[0094]進一步藉下列非限制性實施例例示本發明之實施例，該等實施例絕非視為對本發明之範圍加諸限制。相反地，顯然須瞭解可訴諸多種其它實施例、修改、及其相當物，於研讀此處描述之後，不背離本發明之精髓或隨附申請專利範圍之範圍而為熟諳技藝人士顯然易知。

實施例

[0095]含括下列實施例以驗證此處呈示之某些實施例。熟諳技藝人士須瞭解下列實施例中揭示之技術表示發現明確地落入於此處揭示之實務發揮良好功能，如此可視為組成其較佳實施模式。但熟諳技藝人士鑑於本文揭示將瞭解不背離此處之精髓及範圍可於所揭示之特定實施例中做出許多變化而仍然獲得類似的或相似的結果。

實施例1

[0096]於若干實施例方法中，揭示用以產生此處所稱之「主宰種病毒(MVS)」之組成物。此等組成物可衍生自一

或多個活減毒登革熱病毒諸如DEN-1、DEN-2、DEN-3、及DEN-4。於某些方法中組成物可衍生自一或多個活減毒登革熱病毒其包括但非限制性，此處揭示之特定建構物稱作DENVax-1、DENVax-2、DENVax-3、及DENVax-4。於其它實施例方法中，使用策略以生成及特徵化此等組成物。於又其它實施例中，提供四價登革熱病毒配方及此等配方之遺傳學及表現型特徵化。

前主宰DENVax病毒之製造及分析

[0097]進行某些程序以生成前主宰登革熱種病毒，諸如登革熱病毒(例如DENVax)之一系列擴增及純化。首先，DENVax病毒經再度衍生，其方式係將從全長重組DENVax cDNA轉錄的病毒RNA轉染入製造核准細胞(例如Vero細胞)，獲得P1(繼代培養1)種病毒。得自登革熱-1至登革熱-4各自之四種P1病毒隨後經擴增及溶菌斑純化獲得候選者前主宰疫苗P7種病毒(參考表1)。進行某些測試以分析登革熱病毒之繼代培養。例如，全長基因體定序證實全部四種P2(繼代培養2)種病毒之遺傳學上皆與其同源祖先經研究衍生的研究等級候選者疫苗病毒相同。原先溶菌斑表現型也保有於P2病毒。六種溶菌斑純化病毒(P3 A-F)係針對登革熱各個血清型(例如DENVax 1-4)分離自P2種病毒，各個經分離的溶菌斑直接再進行溶菌斑純化兩次。各個病毒之第三溶菌斑純化(P5)於Vero細胞中擴增兩次(P6 A-F及P7 A-F)而製造潛在前主宰P7 DENVax種病毒(表1)。

表1 DENVax病毒於WCB-Vero細胞中之cGMP再衍生實施例

繼代培養	種病毒製造/純化	特徵化
P1	以轉錄病毒RNA轉染WCB-Vero	溶菌斑滴定
P2	擴增P1病毒	全基因體定序
P3	拾取來自P2溶菌斑檢定分析之6溶菌斑(A-F)/血清型	溶菌斑純化
P4	從P3溶菌斑檢定分析拾取溶菌斑A-F	溶菌斑純化
P5	從P4溶菌斑檢定分析拾取溶菌斑A-F	溶菌斑純化
P6	擴增P5 A-F溶菌斑	溶菌斑滴定
P7	預主宰種病毒：擴增P6 A-F	全基因體序列，TaqMAMA，溶菌斑表現型
P8*	MVS：擴增所選擇之P7種病毒	全遺傳學及表現型特徵化
P9	WVS：擴增P8主宰種病毒	全基因體序列，TaqMAMA
P10	BVS：擴增P9工作種病毒	全基因體序列，TaqMAMA
*基於遺傳學及溶菌斑分析選擇一個最佳P7種病毒(A、B、C、D、E或F)用以製造P8 MVS。		

[0098]進一步進行若干試驗以特徵化P7 DENVax種病毒，諸如分析P7種病毒之基因體序列及溶菌斑表現型且與P2種病毒比較(表2)。P7病毒之溶菌斑表現型大致類似P2種病毒。於若干實施例實驗中，監視病毒力價。大半P7種病毒之病毒力價達到超過6.0 log pfu/ml，但5病毒除外。於Vero細胞經10或以上連續繼代培養後，超過60候選者疫苗種病毒之基因體定序識別DEN-2 PDK-53基因載體之三個主要減毒決定子在NS1-53及NS3-250並無返祖事件，提示此2基因座於候選者疫苗種病毒相當穩定。此二位置從正定序及反定序生成的24候選者種系之全部序列層析圖皆為同源，但於NS1-53及NS3-250遺傳基因座並無任何微小核苷酸族群明顯。與NS1及NS3位置相反，從多個連續繼代培養研究等級疫苗病毒識別於5’NCR-57減毒基因座有不同的返祖程

度，提示此等基因座於細胞培養中經多次繼代培養後可能不如NS-1及NS3安定。因此，發展敏感性不匹配擴增檢定分析(TaqMAMA)以藉即時RT-PCR於5'NCR57基因座準確地測量返祖速率。若干研究中，全部24個P7種病毒之5'NCR57返祖位置係藉TaqMAMA測量。取決於該檢定分析中針對各個病毒之輸入病毒RNA濃度，TaqMAMA之敏感度範圍係於0.01%至0.07%返祖之範圍，比藉同位基因體序列分析可檢測的10-30%返祖敏感度極限遠更敏感。所得資料例示24個P7病毒中15個具有極少或無法檢測的返祖(<0.07%)，一個病毒(DENVax-3-D)具有幾乎100%返祖，及8個病毒(1個DENVax-1、1個DENVax-2、2個DENVax-3、及4個DENVax-4)具有於0.08%至12.85%範圍之部分返祖(表2)。針對24個P7病毒中之16個進行全長基因體定序，藉TaqMAMA測量具有低度5'NCR57返祖。全部此等已定序病毒維持另二個DENVax減毒決定子(NS1-53、NS3-250)，及全部獲得於原先基因改造重組cDNA純株所不存在的額外突變(表2)。於一個實施例標靶疫苗組成物中，選擇DENVax-1-A、DENVax-2-F、DENVax-3-F、及DENVax-4-F作為各個血清型之標靶前主宰種病毒，原因在於其基因型及溶菌斑表現型最類似原先設計的疫苗重組株。DENVax-1-A、DENVax-2-F、及DENVax-4-F具有兩個非同義突變，及DENVax-3-F有一個。證據提示於此等4個前主宰種病毒觀察得的此等額外突變不會造成該等病毒的安全性憂慮或免疫原性變更。此等前主宰種病毒進一步擴增而

生成MVS(主宰種病毒，標示為P7，表1)。

[0099]此處提供之實施例方法使用得自將選殖cDNA質體之已純化試管內轉錄病毒RNA作為純質來源以轉染疫苗核准Vero細胞而生成疫苗病毒。連續溶菌斑純化及全基因體序列分析合併入製造程序以確保所製造的疫苗種子具有最佳純度及遺傳安定性。針對DENVax之各個血清型製備六個選殖病毒作為潛在前主宰種病毒。透過基因體分析，包括TaqMAMA及完整基因體定序，以及病毒溶菌斑表現型之特徵化，前主宰種病毒經選擇進展至針對各個血清型(血清型1-4)製造主宰種病毒。選出的前主宰種病毒在5’NCR-57基因座具有無法檢測的返祖(<0.01%或<0.07%)，於其基因體帶有1或2個胺基酸取代，及保有先前觀察的小型溶菌斑表現型。

表2. 前主宰(P7)種病毒之特徵化

	純株 ^a	TaqMAMA ^b	Log ₁₀ pfu/ml	溶菌斑	於基因體識別之突變 ^d
DENVax-1	A	**	6.85	P2	NS2A-116 I-L、NS2B-92 E-D、一個無聲
	B	*	6.93	P2	nd ^e
	C	*	6.93	D	nd
	D	**	7.02	D	C-67 K-A；一個無聲
	E	0.57%	7.28	P2	nd
	F	**	7.18	P2	E473 T-M；一個無聲
DENVax-2	A	0.03%	6.33	P2	NS1-341 K-N
	B	*	6.33	P2	E-305 K-T，兩個無聲
	C	*	5.84	L	NS4A-18 T-A，四個無聲
	D	0.08%	6.20	P2	NS2B-99 I-L，一個3’NCR
	E	0.03%	6.31	P2	prM-52 K-E，NS5-412 I-V，兩個無聲
	F	**	6.15	P2	prM-52 K-E，NS5-412 I-V
DENVax-3	A	*	6.00	P2	NS5-200 K-N，一個無聲，一個3’NCR
	B	0.05%	6.27	P2	NS2A-33 I-T、NS2A-59 M-T

	C	0.30%	6.25	P2	nd
	D	100.00%	6.27	P2	nd
	E	0.31%	6.00	P2	nd
	F	**	6.30	P2	E-223 T-S，一個無聲
DENVax-4	A	0.47%	5.60	P2	E323 K-R/K、NS2B-21 L-F/L、NS2B-39 T-S，一個無聲
	B	*	5.65	D	NS2A-126 A-V；NS4A-5 N-D；NS5-383 K-R，一個無聲
	C	4.50%	5.90	P2	nd
	D	12.85%	5.97	D	nd
	E	0.52%	6.85	S	prM-85 E-D、NS2B-45 T-A、NS5-320 M-T、NS5-551 E-G，兩個無聲
	F	0.02%	6.93	S	NS2A-66 D-G、NS4A-21 A-V，四個無聲
^a選用以進一步發展MVS的選殖病毒(藉連續溶菌斑純化)標示為粗體。 ^b*：返祖率<0.07%(檢測極限)。**：返祖率<0.01%(檢測極限)。 ^c溶菌斑表現型：P2：類似P2病毒；L＝大於P2病毒，D＝類似大小，但顯然透明度與溶菌斑略有不同；S＝小於P2。 ^d與基因改造DENVax cDNA純株不同的取代。胺基酸突變係以病毒蛋白質之殘基位置及改變(wt-突變)列舉。列出各個種病毒於結構基因及非結構基因之無聲突變總數。也註明於非編碼區(NCR)之突變。 ^end＝未進行。此等純株比其它純株有更高的5'NCR-57返祖率(藉TaqMAMA)，因此從進一步序列分析中排除。					

實施例2

[0100]於若干實施例方法中，描述主宰種病毒、工作種病毒及散裝種病毒之組成物及其基因及表現型特徵化。此等組成物提供用於臨床材料及最終商業疫苗供應之製造。連續溶菌斑純化及全基因體序列分析結合於製程來確保疫苗種病毒組成物用於臨床試驗材料之製造上具有最佳安全性及遺傳安定性。

MVS、WVS、及BVS之生產及製造品質管制

[0101]於若干研究中，4種DENVax之MVS係藉將前主宰P7種病毒於核准Vero細胞擴增製造。於其它研究中，MVS用於細胞工廠製造大量WVS。進一步，DENVax之BVS備料

係從WVS擴增，及配方成用於人類臨床試驗之四價藥品混合物。產物放行之品質管制係以某些實施例方法進行包括但非限制性，測試全部MVS、WVS及BVS之身份、感染力價、無菌性、黴漿體、及於試管內及活體內之伺機性病原因子。全部種病毒使用血清型專一性RT-PCR檢定分析皆通過病毒身份測試，顯示相對應其血清型之正型擴增及相對應於非同源血清型之負型擴增(資料未顯示)。於MVS、WVS、或BVS備料中未檢測得可檢測的黴漿體或伺機性病原因子。

MVS、WVS、及BVS之遺傳分析

[0102]於某些實施例方法中，於從如上選擇之前MVS(P7)種系生成MVS後，再度定序個別病毒性RNA。全長基因體定序顯示針對DENVax-1之MVS與其前主宰種病毒相同，而WVS及隨後BVS在E-483及NS4B-108獲得2個額外取代(參考表2及3)。於E-483之Ala取代表示於MVS之基因型部分，但變成BVS中之主控基因型。DENVax-2及DENVax-3就其個別前主宰種病毒為相同(表2及3)。DENVax-2 MVS與其前主宰種病毒為相同，及WVS及BVS在NS4A-36及NS4B-111具有兩個額外突變。兩個突變於WVS皆為部分基因型，及於BVS為主要基因型。DENVax-3之MVS再度與前主宰種病毒相同，但WVS及BVS在NS4A-23含有一個額外胺基酸取代。DENVax-4 MVS於MVS製造期間(表3)在基因座NS2A-99獲得一個額外胺基酸突變(Lys至Lys/Arg混合基因型)。其WVS及BVS保有NS2A-99

Lys/Arg 混合基因型，及 BVS 具有一個額外 NS4B-238 Ser/Phe 混合基因型。同位序列結果也證實 MVS、WVS 及 BV 保有在 5'NCR-57、NS1-53、及 NS3-250 基因座之三個減毒基因決定子。藉 TaqMAMA 分析最不穩定減毒基因座證實 5'NCR-57 返祖率於 MVS 為小於 0.7% 至 0.13%，WVS 為小於 0.07%，及 BVS 為小於 0.07% 至 0.21%。於 5'NCR-57 基因座之 3% 返祖率被視為一批疫苗所能接受的最大容許返祖率 (表 3)。

表3. DENVax 種病毒之核苷酸及胺基酸取代

DENVax	核苷酸	胺基酸	前主宰	MVS ^a	WVS ^a	BVS ^a
DENVax-1	2384 G-C	E-483 Gly-Ala	-	-	Gly/Ala	Ala
	3823 A-C	NS2A-116 Ile-Leu	Leu	Leu	Leu	Leu
	4407 A-T	NS2B-92 Glu-Asp	Asp	Asp	Asp	Asp
	7148 C-T	NS4B-108 Thr-Ile	-	-	Ile	Ile
	7311 A-G	無聲	G	G	G	G
	TaqMAMA 5'NCR-57 返祖 % ^b		--	-	-	
DENVax-2	592 A-G	prM-52 Lys-Glu	Glu	Glu	Glu	Glu
	6481 G-C	NS4A-36 Ala-Pro	-	-	Ala/Pro	Pro
	7156 C-T	NS4B-111 Leu-Phe	-	-	Leu/Phe	Phe
	8803 A-G	NS5-412 Ile-Val	Val	Val	Val	Val
	TaqMAMA 5'NCR-57 返祖 % ^b		--	-	0.07%	0.21%
DENVax-3	1603 A-T	E-223 Thr-Ser	Ser	Ser	Ser	Ser
	6436 G-A	NS4A-23 Asp-Asn	-	-	Asn	Asn
	7620 A-G	無聲	G	G	G	G
	TaqMAMA 5'NCR-57 返祖 % ^b		--	-	-	-
DENVax-4	225 A-T	無聲	T	T	T	T
	3674 A-G	NS2A-66 Asp-Gly	Gly	Gly	Gly	Gly
	3773 A-A/G	NS2A-99 Lys-Lys/Arg	-	Lys/Arg	Lys/Arg	Lys/Arg
	5391 C-T	無聲	T	T	T	T

	6437 C-T	NS4A-21 Ala-Val	Val	Val	Val	Val *
	7026 T-C	無聲	T/C	T/C	T/C	T/C
	7538 C-C/T	NS4B-238 Ser-Ser/Phe	-	-	Ser/Phe	Ser/Phe
	9750 A-C	無聲	C	C	C	C
	TaqMAMA 5’NCR-57返祖 % ^b		-	0.13%	-	-
^a 粗體字：始於MVS批料之改變						
^b “-”指示返祖率<0.01%(檢測極限)， “-”指示返祖率<0.07%(檢測極限)						

[0103] 全基因體序列分析顯示於DENVax-4 MVS發展出額外胺基酸突變，而另外三批DENVax MVS保有其前主宰種病毒之同位基因體序列。總而言之，從P1種病毒衍生至前主宰(P7)種病毒，在一給定種病毒中只出現1或2個非同義突變。從P1至MVS (P8)種病毒，於任何給定DENVax種病毒識別2至7個核苷酸取代，此等取代中只有2至3者導致胺基酸改變。如此出現微小改變。RNA病毒於其基因體複製中容易發生錯誤，故於細胞繼代培養期間黃病毒基因體的基因取代並非出乎意外。於MSV之無聲突變並無任一者係在5'或3'NCR可能影響病毒突變。只有於DENVax-2之prM-52 Lys-Glu的改變及於DENVax-4之NS2A-66 Asp-Gly的取代非保留性改變。DENVax-4之NS2A-66突變係在DENV-2 PDK-53之非結構骨架部分。雖然NS2A-66基因座於DENV-2之各種種系中通常為Asp，但對DENV-4通常為Gly。可能於DENVax-4中Asp至Gly的改變係與DENVax-4匹配Vero細胞相關。DENVax-2 prM-52突變駐在prM之C端部分，從成熟病毒顆粒剪接。於某些實施例方法中，進行表現型特徵化證實於MVS種病毒中之突變皆未顯著改變疫苗的減毒表現型。

[0104] DENVax病毒驗證於製造過程之高基因安定性。位在5'NCR、NS1-53、及NS3-250之三個經界定的DENV-2 PDK-53減毒基因座於當DENVax從前主宰種系連續繼代培養至散裝疫苗製劑時於同位基因體序列維持安定。5'NCR-57基因座之高度敏感TaqMAMA驗證於登革熱病毒血清型之MVS、WVS(P9/工作)及BVS(疫苗之散裝種病毒)極少或無法檢測的返祖。DENVax BVS製劑(P10-相當)之5'NCR57返祖率顯著低於5'NCR57返祖率，出現在研究等級疫苗候選者於Vero細胞經10次連續繼代培養後(4-74%返祖)。此處提供之DENVax種病毒之大規模製造策略結果導致遺傳上安定的疫苗種病毒，於候選者疫苗病毒保有減毒標記。

DENVax MVS之溶菌斑表現型

[0105] 於一個實施例方法中，DENVax MVS之溶菌斑表現型與野生型登革熱病毒及其同源研究級嵌合式病毒於Vero細胞比較(圖2)。全部DENVax-1、-2及-3之MVS產生的溶菌斑皆顯著小於其野生型同系物，而極為類似(於0.4毫米差以內)其於Vero細胞之同源研究及病毒。DENVax-4 MVS也顯著小於野生型DENV-4，但顯著大於(0.9毫米差)原先實驗室衍生D2/4-V嵌合體。

[0106] 圖2表示實施例直方圖例示DENVax MVS比較對照組野生型病毒及研究級疫苗候選者病毒之溶菌斑大小。於Vero細胞於瓊脂糖上方覆蓋層下方的病毒溶菌斑於感染後第9日測量平均溶菌斑直徑(毫米) $\pm$ SD(誤差柱)。以黑柱

表示野生型DEN病毒及以白柱表示先前公開的研究及疫苗候選者病毒含括用作為對照組且與灰柱表示的DENVax主宰疫苗種病毒作比較。

DENVax MVS之溫度敏感度

[0107]於另一實施例方法中，於Vero細胞針對DENVax MVS測試溫度敏感度且與其同源野生型及原先研究級嵌合式疫苗病毒作比較。野生型(wt) DENV-3 16562並非溫度敏感。野生型登革熱病毒血清型1及登革熱血清型4於39°C為中等溫度敏感(於39°C之力價比37°C低約1.0 log₁₀ pfu/ml，圖3)。野生型登革熱病毒血清型-2 16681為所測試的野生型登革熱病毒中最高溫度敏感性，導致於39°C之力價降100倍。DENVax-1、2、及3與其原先同源研究級嵌合式疫苗病毒同等溫度敏感(圖2)。針對此等DENVax種系於39°C之力價降低2.0至3.0 log₁₀ pfu/ml。DENVax-4也為溫度敏感，驗證力價減低5倍。但原先研究級D2/4-V驗證力價減低約10倍。最終穩定化DENVax-4 MVS含有F127(及其它已知可穩定化此等配方的作用因子(FTA))，顯示可提升登革熱病毒之熱安定性。於DENVax-4 MVS存在有F127可能促成於Vero培養檢定分析中病毒較不明顯的溫度敏感。於分開實驗中，進一步評估於無F127存在下MVS衍生DENVax-4種系之溫度敏感度。為了從該種系去除F127，從DENVax-4散裝病毒製劑分離病毒RNA，及轉染Vero細胞。於無F127存在下於感染後(pi)第3日(圖3)此種DENVax-4病毒顯然與D2/4 V研究種系具有相等溫度敏感度(力價減低1.5 log₁₀ pfu/ml)。

[0108]圖3例示實施例直方圖例示DENVax MVS之溫度敏感度。含括野生型登革熱病毒及先前公開之研究及疫苗候選者病毒進行比較。DENVax-4 MVS含有額外F-127，可遮蓋於本檢定分析中病毒之溫度敏感性結果。也含括分開實驗分析於無F127存在下之代理DENVax-4。於37°C或39°C於Vero細胞中病毒複製之平均力價 $\pm$ SD(誤差柱)。

於蚊C6/36細胞之DENVax MVS複製

[0109]於若干實施例方法中，DENVax MVS於C6/36細胞生長以證實其於試管內減毒表現型之保留性，知曉研究級嵌合式疫苗病毒保留於此等蚊細胞的骨架DENV-2 PDK53病毒之減毒表現型。與野生型登革熱病毒比較，於感染後第6日DENVax-1、DENVax-2及DENVax-4 MVS於C6/36細胞(圖4)顯示顯著生長減低(至少3 $\log_{10}$ pfu/ml減低)。比較野生型DENVax-3 16562，DENVax-3 MSV也顯示生長減低，但減低較不顯著(1-2 $\log_{10}$ pfu/ml減低)。但DENVax-3種病毒批次之C6/36力價類似(於1 $\log_{10}$ pfu/ml差以內)原先研究級嵌合式D2/3-V疫苗病毒的C6/36力價。

[0110]圖4例示實施例直方圖作圖DENVax MVS(灰柱)於C6/36細胞之限制生長且與野生型登革熱(黑柱)及研究級疫苗病毒(白柱)作比較。感染後6日於C6/36細胞複製的病毒之平均力價 $\pm$ SD(誤差柱)。

於全蚊之病毒感染、散播、及傳播率

[0111]於若干實施例方法中，DENVax之感染率及散播率與其親代野生型登革熱病毒作比較。於某些實施例實驗

中，於埃及斑蚊(*Ae. aegypti*)進行經口感染實驗。感染血液餐經反向滴定測量病毒力價，只有親代登革熱病毒與DENVax針對各個血清型使用血液餐有類似病毒力價(小於 $1 \log_{10}$ pfu/ml差)的實驗含括用於表4之比較。DENVax-1、DENVax-2及研究級D2 PDK-53-VV45R不會經口進食感染蚊，與其親代病毒有顯著差異($p < 0.0001$)，DENV-1 16007 (44%感染)及DENV-2 16681 (43.3%感染)。因並無任何蚊受DENVax-1及-2感染，故此二疫苗病毒極少有或無散播隱憂。而DENVax-4確實經口進食感染某些蚊(55之2)，感染率顯著比其親代野生型病毒更低($p < 0.05$)，DENV-4 1036 (50之8)。兩個實驗中DENVax-3不感染任何蚊，血液餐病毒力價為 $6.0 \log_{10}$ pfu/ml(表4)，及分開實驗具有血液餐病毒力價 $6.0 \log_{10}$ pfu/ml，30隻蚊中只有一隻蚊變成感染(資料未顯示)。但野生型登革熱病毒-3 16562於 $5.2 \log_{10}$ pfu/ml也具有極低感染率(8%)，於分開實驗感染率不增高，於 $6.2 \log_{10}$ pfu/ml具有較高血液餐病毒力價(3%，30隻蚊中1隻為陽性反應，資料未顯示)。雖然野生型(wt)登革熱病毒-3及登革熱病毒-4具有比野生型登革熱病毒-1及登革熱病毒-2顯著更低的感染率，但於感染蚊之平均病毒力價相似(3.1 至 $3.9 \log_{10}$ pfu/蚊)。相反地，得自兩種感染蚊之DENVax-4力價皆為最低($0.7 \log_{10}$ pfu/蚊)，比從野生型登革熱血清型-4 1036感染蚊的力價(3.9 ± 1.5 pfu/蚊)低1,000倍。

[0112]針對該等感染蚊，藉決定病毒是否存在於腳評估。病毒從中腸擴散出。四個親代DENV結果導致36.3%至

62.5%範圍之散播率，從腳之平均病毒力價(單位 $\log_{10}$ pfu)為 0.9 ± 0.3 至 2.2 ± 0.7 (陰性樣本除外)。兩個DENVax-4感染蚊皆未導致病毒散播至腳(表4)。雖然於腳可檢測得散播病毒，但於經口感染蚊之唾液並未檢測得四個野生型登革熱病毒中之任一者，提示經口進食條件不夠敏感來測量此等DENV的傳播率。因此於其它實施例方法中，隨後進行藉直接胸內(IT)接種的高度嚴格的人工蚊感染(表4)。除了DENVax-4之外，全部病毒(野生型及DENVax)皆達成IT接種埃及斑蚊之100%感染。DENVax-4接種物具有比另外三種病毒接種物略低的病毒力價，但仍然成功的感染70%接種蚊。儘管藉IT接種達成高身體感染率，但全部四種DENVax病毒比野生型登革熱病毒(43-87%，表4)皆具有顯著較低($p < 0.005$)或無法檢測之傳播率(0-10%)。DENVax病毒於經口進食後驗證極少至無感染及散播，高度嚴格的IT結果證實此等DENVax病毒於埃及斑蚊的傳播能力極低。

表4：於全蚊體病毒感染、散播及傳播率

病毒	經口進食					IT接種				
	血液餐 ^a	感染 ^b	身體力價 ^c		散播 ^e	接種物	感染 ^b	身體力價 ^c	唾液 ^f	
	平均值 ±SD	% (P/N)	平均值 ±SD	<i>P</i> ^d	% (P/N) ^f	pfu/ 劑量	% (P/N)	平均值 ±SD	% (P/N)	<i>P</i> ^d
DENV-1 16007	6.6	44.0% (11/25)	3.6 ± 1.5		36.3% (4/11)	53.9	100% (30/30)	4.7 ± 0.48	43% (13/30)	
DENVax-1	6.9	0% (0/30)	NA	<0.0001	NA	67.8	100% (30/30)	3.4 ± 0.39	10% (3/30)	<0.005
DENV-2 16681	6.6	43.3% (13/30)	3.1 ± 1.5		38.5% (5/13)	67.8	100% (30/30)	5.2 ± 0.34	87% (26/30)	
D2 PDK53-VV45R	6.4	0% (0/30)	NA	<0.0001	NA	56.4	100% (30/30)	4.0 ± 0.20	0% (0/30)	<0.0001
DENVax-2	6.4	0% (0/30)	NA	<0.0001	NA	52.7	100% (30/30)	3.5 ± 0.27	7% (2/30)	<0.0001
DENV-3 16562	5.2	8% (2/25)	3.8 ± 0.2		50% (1/23)	34.0	100% (30/30)	4.2 ± 0.50	67% (20/30)	
DENVax-3	5.2 ± 0.02	0% (0/50)	NA	0.108	NA	37.3	100% (30/30)	3.3 ± 0.36	3% (1/30)	<0.0001
DENV-4 1036	5.8 ± 0.5	16% (8/50)	3.9 ± 1.5		62.5% (5/8)	69.4	100% (30/30)	5.2 ± 0.45	70% (21/30)	
DENVax-4	5.4 ± 0.4	3.6% (2/55)	0.7 ± 0.0	0.033	0% (0/2)	11.8	70% (21/30)	1.1 ± 0.46	0% (0/21)	<0.0001
^a 若藉反滴定得自血液餐之一個實驗(log₁₀ pfu/ml)，病毒力價或平均值±標準差。 ^b 於蚊體檢測之病毒率。P/N= 陽性/總蚊 ^c 於蚊體內平均病毒力價±標準差(log₁₀ pfu/蚊)，只含括陽性樣本用於計算 ^d 藉費雪(Fisher)正確機率，DENV與DENVax間之差之統計分析 ^e 於陽性感染蚊腳檢測之病毒率 ^f 於陽性感染蚊之唾液檢測得之病毒率。用以測量傳播效率。										

[0113]載體勝任為活減毒黃病毒疫苗病毒之重要安全性成分。先前，研究級DENV-2 PDK-53-VV45R病毒及野生型衍生物於埃及斑蚊測試，及發現NS1-53-Asp減毒突變為受損蚊複製的主要決定子。DENV-2 PDK-53疫苗之另兩個主要減毒基因座，亦即核苷酸5’NCR-57-T及NS3-250-Val，也具有於蚊複製的其它抑制效應，如此對蚊載體勝任提供額外冗餘限制。此處描述之若干實施例方法用以測試全部四種DENVax種系之蚊經口及IT感染及複製。DENVax-1、-2及-3不會經口感染任何埃及斑蚊(表4)。DENVax-4只感染3.6%經口暴露蚊，該程度顯著低於野生型DENV-4，於蚊體

的複製平均力價低於wt DENV感染蚊。出乎意外地，於感染蚊腳檢測得DENVax-4，提示DENVax-4無法於經口感染後從蚊的中腸散佈。DENVax-1、-2及-4之感染率全部顯著低於其野生型對偶部分，但DENVax-3與wt DENV-3 16562間之差異不顯著，原因在於兩種病毒之感染率低之故。比較收集自泰國美索省的埃及斑蚊體內評估DENV的其它野生種系，用於基因改造DENVax之親代野生型登革熱病毒種系顯然具有藉經口進食較低的感染率及散播率。野生型DENV-1 PUO359、DENV-2 PUO218、DENV-3 PaH881/88、及DENV-4 1288用於基因改造以黃熱病(YF) 17D疫苗為基礎的ChimeriVax-DEN疫苗具有47-77%範圍之感染率。相反地，YF 17D疫苗無法感染埃及斑蚊。雖然ChimeriVax種系含有得自此等高度傳染性wt DENV的prM-E，但ChimeriVax保有其YF 17D複製骨架的蚊減毒表現型。此處提供結果也指示DENV-2 PDK-53骨架之蚊減毒於DENVax種系中維持。此外使用野生型登革熱病毒種系具有於建構物中較低的蚊感染力者含括於此處描述之組成物提供額外安全性特徵。

[0114]經口感染結果例示DENVax具有極低蚊感染力及散播能力。此外，進行更敏感且更嚴格的IT感染實驗以進一步分析DENVax藉埃及斑蚊傳播的潛力。IT結果驗證全部四種DENVax病毒比較其野生型對偶部分皆具有無法檢測的或極低蚊傳播潛力。DENVax傳播理論上可能發生，若(1)在有足夠病毒血症力價以感染蚊的中腸的一疫苗接種人體病媒蚊進食，(2)病毒能夠於中腸上皮複製且隨後能夠散播

出中腸之外，及(3)散播病毒可於唾液腺中複製且吐出足量病毒於唾液中供傳播。需要感染蚊的人病毒血症之臨界值尚未適當建立，但人病毒血症於自然wt DENV感染後可為 10^6 - 10^8 蚊感染劑量 $_{50}$ (MID $_{50}$)/ml。此種MID $_{50}$ 係基於使用稀釋人血漿直接IT接種蚊。於非人靈長類分析DENVax指出DENVax接種後病毒血症力價極低(低於 $2.4 \log_{10}$ pfu/ml)及持續2-7日。給定DENVax之低病毒血症濃度及低蚊感染、散播、及傳播能力，此等疫苗病毒於自然界不可能藉蚊蟲傳播或造成病毒血症。

[0115]因此，提示任何血清型(P)之繼代培養中之任一者(P1-P10)可用於組成物生成對抗1、2、3或全部4個登革熱病毒血清型之有效疫苗。

於哺乳期小鼠之神經毒力

[0116]原先研究級疫苗病毒於維持於DVBD/CDC內部的新生ICR小鼠針對神經毒力高度減毒。全部此等小鼠使用 10^4 pfu各種疫苗病毒ic(腦內)挑釀皆存活。另一方面，野生型登革熱病毒血清型-2 16681病毒於各種實驗導致此等CDC-ICR小鼠之62.5%-100%死亡率。於若干實施例中，得自塔科尼克實驗室(Taconic Labs)的商用ICR小鼠(塔科尼克-ICR)用於研究於新生小鼠的神經毒力。觀察得新生塔科尼克-ICR小鼠以先前CDC-ICR小鼠對登革熱病毒血清型2感染顯著更敏感。圖5A摘述使用 10^4 pfu病毒ic挑釀，於CDC-ICR群落及塔科尼克-ICR新生小鼠之野生型登革熱病毒血清型-2 16681之神經毒力。塔科尼克-ICR小鼠(32頭小

鼠100%死亡率，平均存活時間 8.3 ± 0.5 日)比先前CDC-ICR小鼠(72頭小鼠91%死亡率，平均存活時間 14.6 ± 2.3 日)對腦內登革熱病毒血清型-2 11681挑釁更敏感。

[0117]於其它實驗方法中，為了評估DENVax MVS之神經毒力，塔科尼克-ICR小鼠最初於一項($n=16$)或兩項($n=31-32$)實驗中使用一劑量約 10^4 pfu野生型登革熱病毒血清型-2 16681、D2 PDK-53 VV45R、D2/3-V、或DENVax 1-4疫苗ic(腦內)挑釁(圖5B)。於此劑量，D2/3-V研究級病毒，以及DENVax-1、及DENVax-3 MVS具有全然減毒神經毒力表現型(未發病或致死)。如所預期，發現野生型登革熱病毒血清型-2為「致命」，平均小鼠存活時間(AST)為 8.3 ± 0.8 日。於此等登革熱病毒血清型-2-敏感塔科尼克-ICR小鼠中，D2 PDK-53-VV45R研究級病毒導致81.3%死亡率。DENVax-2 MVS及DENVax-4 MVS於塔科尼克-ICR之致命程度不一致，分別顯示 9.8 ± 1.7 、 10.2 ± 1.4 、及 11.3 ± 0.4 日之AST值。

[0118]於若干實施例方法中，於10倍低劑量(10^3 pfu，圖5C)，野生型登革熱病毒血清型-2 16681病毒之神經毒力與D2 PDK-53 VV45R、DENVax-2 MVS及DENVax-4 MVS作比較。於此較低挑釁劑量，野生型登革熱病毒血清型-2保有不一致的致命神經毒力表現型，具有 9.0 ± 1.4 日之AST。另外4種病毒具有中間神經毒力表現型，神經毒力程度為血清型專一性。D2 PDK-53-VV45R病毒及其DENVax-2 MVS同源株顯示顯著減毒(分別具有32.3%存活率帶有 13.1 ± 3.8 日AST及31.2%存活率帶有 10.5 ± 3.4 日AST)。

DENVax-4 MVS及研究級D2/4-V病毒針對神經毒力為高度減毒(分別為81.3%存活率帶有 18.8 ± 5.8 日AST及100%存活率)。結果提示DENVax-1及-3之MVS具有神經毒力的完全減毒，而DENVax-2及-4 MVS批次保有減毒表現型，密切類似其同源研究級病毒疫苗候選者。

[0119]圖5A-5C表示實施例線圖例示使用包括野生型登革熱病毒血清型-2及不同減毒登革熱病毒之各種組成物於新生小鼠測試之神經毒力。各項實驗之匯集結果摘述於CDC-ICR(n=72)及塔科尼克-ICR(n=32)新生小鼠腦內使用 10^4 pfu病毒(A)挑釀野生型登革熱病毒血清型-2 16681之神經毒力。塔科尼克-ICR小鼠使用 10^4 pfu(B)或 10^3 pfu(C)劑量測試DENVax MVS之神經毒力。一項實驗(n=16)或兩項匯集實驗(n=31或32)中指出每組測試動物頭數。

WVS及BVS之溶菌斑表現型

[0120]進行某些研究來比較WVS及BVS與MVS、野生型登革熱病毒及其同源實驗室衍生研究級嵌合體於Vero細胞之溶菌斑表現型(圖6)。平均溶菌斑大小針對各個疫苗病毒從10個溶菌斑算出，但wt DENV-1、-3、及-4之數目減少。DENVax-1、-2及-3之MVS病毒皆產生溶菌斑，顯著小於其野生型同系物，而極為類似(於0.4毫米差以內)其同源研究級病毒於Vero細胞。DENVax-4 MVS也顯著小於wt DENV-4，但略微(0.9毫米)大於原先實驗室衍生D2/4-V嵌合體。DENVax-2為例外，DENVax-1、-3、-4之WVS及BVS比較從其野生型同系物製造者保有顯著更小的溶菌斑大

小。DENVax-2 WVS及BVS產生溶菌斑，類似wt DENV-2病毒於Vero細胞產生的溶菌斑，但當於LLC-MK₂細胞測試時，全部DENVax-2製造種病毒產生溶菌斑略小於wt DENV-2 (1.4 ± 0.4)而類似實驗室衍生D2 PDK-53-VV45R (1.0 ± 0.3)(圖6)。

[0121]病毒減毒之表現型標記包括小溶菌斑表現型、溫度敏感度、於蚊細胞複製減少、藉蚊感染/散播/傳播減少、及於新生ICR小鼠神經毒力減低之評估係針對MVS備料進行評比。結果指示全部DENVax保有類似原先研究級疫苗病毒預期的減毒表現型。給定負責減毒的突變皆保留於全部MVS、WVS及BV，可預期減毒表現型保留於針對人臨床試驗製造的材料。

[0122]圖6表示範例直方圖例示DENVax MVS、WVS、及BVS之溶菌斑大小。於感染後第9日測量於瓊脂糖上方覆蓋層下方之Vero細胞或LLC-MK₂細胞中病毒溶菌斑的平均溶菌斑直徑 $\pm$ SD(誤差柱)。含括wt DENV及先前公開研究級疫苗候選者病毒用於對照及比較。

於蚊C6/36細胞之病毒複製

[0123]先前研究證實研究級以PDK-53-為主的嵌合式疫苗病毒於C6/36細胞中保留骨架DENV-2 PDK53病毒之減毒表現型。於若干實驗方法中，DENVax MSV、WVS、及BVS於C6/36細胞生長來證實於大規模製造後保留此種試管內減毒標記。比較野生型登革熱病毒，DENVax-3除外，所製造的種病毒於感染後第6日(圖7)於C6/36細胞顯示顯著

生長減慢(至少3 $\log_{10}$ pfu/ml減慢)。DENV-3種病毒比較wt DENV-3 16562也顯示生長減慢，但減慢較不顯著(1-2 $\log_{10}$ PFU/ml減慢)。但DENVax-3種病毒批料之力價係類似(於1 $\log_{10}$ PFU/ml差以內)原先研究級嵌合式D2/3-V疫苗病毒。

[0124]圖8表示DENVax MVS、WVS、及BVS於C6/36細胞之限制生長的直方圖作圖實施例。病毒於感染後7日於C6/36細胞複製之平均力價 $\pm$ SD(誤差柱)。野生型登革熱病毒及先前公開研究級疫苗候選者病毒含括供比較。

於哺乳期小鼠之神經毒力

[0125]進行額外實驗分析於新生ICR小鼠之神經毒力。於 10^4 PFU之顱內劑量，於ICR小鼠wt DENV-2 16681及D2 PDK-53-VV45R之存活率分別為0%及18.8%(圖9A)，但於CDC ICR小鼠對wt DENV-2 16681為約20%及對D2 PDK-53-VV45R為100%。於本研究中，DENVax-1及DENVax-3 MVS用於小鼠於 10^4 PFU劑量為減毒(100%存活率)，但DENVax-2及DENVax-4之MVS於超過 10^4 PFU(圖5A)之劑量造成100%死亡率。但當於 10^3 PFU病毒劑量測試時，DENVax-2(31.3%存活率)及DENVax-4(81.3%存活率)顯示相對於野生型登革熱病毒血清型-2 16681 (0%存活率)之神經毒力減低，其存活率分別係類似研究級疫苗病毒D2 PDK-53-VV45R(32.3%)及D2/4-V(100%)(圖9B)。雖然wt DENV-1、-3、或-4不含括於本研究用於比較，但先前研究工作證實藉ic途徑wt DENV-1 16007於CDC-ICR小鼠為減毒，而wt DENV-3 16562及DENV-4 1036對CDC-ICR小鼠有

高毒力(0%存活率)。可能此3種wt DENV於較為敏感的塔科尼克ICR小鼠也具有相似的或較高毒力。因此，含括此等野生型登革熱病毒用來與其同源DENVax MVS比較被視為資訊不足。本研究指出全部4種DENVax MVS及原先實驗室衍生候選者疫苗病毒相對於wt DENV-2 16681具有可相媲美的小鼠減毒表現型。

[0126]圖9A-9B表示DENVax MVS於新生ICR小鼠之神經毒力資料之線圖實施例。(A)病毒於 10^4 PFU之IC接種。(B)病毒於 10^3 PFU之IC接種。

[0127]全部DENVax種病毒批料測試其身份、無菌性及不含非期望的作用劑。全基因體序列分析顯示一個額外胺基酸突變出現在DENVax-4 MVS，而另外3個DENVax MVS保留其前主宰種病毒之同位基因體序列。於WVS批料中，相對於其前主宰種病毒，DENVax-3獲得額外胺基酸突變及另外三種血清型積聚兩個額外胺基酸取代。全部4批BVS之基因體序列皆與WVS批料相同。整體而言從P2種病毒至前主宰(P7)種病毒，於給定種病毒只出現1或2個非無聲突變。前主宰種病毒與BCS(P10)種病毒間，只觀察得1至2個核苷酸取代，全部皆出現於NS2A、4A、或4B，單一核苷酸改變例外導致保留甘胺酸及丙胺酸於殘基E-483。從P2至BVS(P10)種病毒，於任何給定DENVax種病毒識別共3至8個核苷酸取代，此等取代中只有2至4個導致胺基酸改變。於BVS之無聲突變中並無任一者係在5'-或3'-NCR區內部可能影響病毒複製。此等結果提示DENVax病毒於製造期間高度遺

傳上安定。位在5'NCR、NS1-53、及NS3-250之三個經界定的DENV-2 PDK-53減毒基因座在DENVax連續繼代培養而生成BVS批料時於同位基因體序列維持不變。高度敏感的5'-NCR-57位置之TaqMAMA顯示於DENVax之MVS、WVS、及BVS之極少或無法檢測的返祖。於DENVax-2 BVS識別0.21%之最高返祖率。P10-相當BVS之返祖率(<0.07%至0.21%)顯著低於於Vero細胞連續繼代培養後於其它疫苗候選者的返祖率(藉P10為4-74%返祖率)。如此提示DENVax種病毒之大規模製造策略就於候選者疫苗病毒維持基因穩定性及減毒標記的保留而言為成功。

[0128]因此處揭示之MVS備料將用於WVS及BVS批料之未來製造，故對全部MVS及其相當代理備料進行完整病毒減毒表現型評估，包括小溶菌斑表現型、溫度敏感度、於蚊細胞複製減少、於全蚊感染/散播/傳播減低、及於新生ICR小鼠之神經毒力減低。對WVS及BVS備料也進行溶菌斑大小、於蚊細胞之感染力以驗證其減毒。結果指出DENVax之4個血清型之全部MVS備料保有預期減毒表現型，諸如小溶菌斑、於C6/36細胞複製減少、及小鼠神經毒力減低，此點係與原先實驗室衍生疫苗病毒相似(圖6、8及9)。DENVax-4除外，如圖3及圖7顯示，DENVax之另3個MVS備料於39°C皆為TS。

[0129]針對WVS及BVS備料，分析及證實兩個減毒表現型，亦即小溶菌斑及於C6/36細胞之複製限制。由於MVS與BVS間極少有遺傳變化，預期將如同MVS保有減毒表現

型。除了本報告描述之實驗之外，已經測試所製造的DENVax於Ag129小鼠及非人靈長類之安全性及免疫原性。

[0130]此處提出範例方法驗證於cGMP下DENVax MVS、WVS、及BVS備料之製造。BVS備料用於配方目前用在人類臨床試驗評估的四價DENVax。若干實施例方法中，提供獨特的製造策略以最佳化所製造MVS之遺傳安定性及安全性。由於DENVax之主減毒基因座先前已經明確地特徵化，且為高度敏感且可量化的SNP檢定分析，故發展TaqMAMA以整合基因體序列及TaqMAMA以識別用於製造MVS之最佳前主宰種病毒。完整分析MVS之基因型及表現型特性而證實此等病毒保有期望的疫苗減毒安全性。此種可能只是活減毒病毒疫苗，從前主宰一路製造成BVS備料期間可有效分析全部主要減毒基因座。此處提供結果證實策略上設計活減毒疫苗之疫苗安全性優點。

[0131]圖10表示比較新穎活減毒疫苗與先前生成的活減毒登革熱病毒之表格實施例。指出突變，於該處與對照病毒(例如16681)或其它活減毒登革熱-2病毒不同。

材料及方法

病毒及細胞

[0132]DENV-1 16007、DENV-2 16681、DENV-3 16562、及DENV-4 1034作為野生型(wt) DENV對照組，其為四種重組DENVax疫苗候選者之親代基因型病毒。先前製備及特徵化DENVax祖先研究級病毒，標示為D2/1-V、D2 PDK-53-VV45R、D2/3-V、及D2/4-V。用於製造供疫苗製

造用的主宰細胞及工作細胞排組之Vero(非洲綠猴腎)細胞係源自於美國種型培養收集會(ATCC) CCL81細胞系，其已經藉世界衛生組織(WHO)特徵化用於疫苗製造(WCB-Vero細胞)。

從cDNA純株衍生活重組DENVax病毒

[0133] 為了於cGMP製造條件下再度衍生候選者疫苗病毒，使用先前基因改造之DENV傳染性cDNA純株，亦即pD2 PDK-53-VV45R、pD2/1-V、pD2/4-V、及試管內接合含pD2/3-V的全基因體長度病毒cDNA藉如先前描述之試管內轉錄製造新鮮病毒RNA轉錄本。簡言之，經XbaI-線性化的DENV基因體cDNA使用蛋白酶K處理，使用酚/氯仿萃取，及於乙醇沈澱而去除任何殘餘蛋白質，然後於轉錄之前懸浮於不含RNAase的Tris-EDTA緩衝液。遵照製造商推薦的方案，使用安瑟史萊(AmpliScribe) T7高產率轉錄套件(愛琵桑特技術公司(Epicentre Technologies))進行試管內轉錄。於2小時轉錄反應期間結合RNA A-cap類似物亦即m7G(5')ppp(5')A(新英格蘭生物實驗室(New England BioLabs))來添加5'-端A-cap至RNA轉錄本。然後樣本使用DNase I處理來消化樣板cDNA，接著低pH酚/氯仿萃取及乙醇沈澱而去除殘餘DNA及蛋白質。已純化之RNA轉錄本，懸浮於不含RNase之水中，分散於20微升液分內及於-80℃儲存至準備用於細胞轉染。RNA轉錄本之完整性及濃度係藉瓊脂糖凝膠電泳分析。各20微升液分估計含有足量基因體長度病毒RNA來允許藉電穿孔感染 $0.4-1 \times 10^7$ 製造核准

Vero細胞。

[0134]於山沙生物技術公司(Shantha Biotechnics)於cGMP工廠進行各個RNA轉錄本轉染WCB-Vero細胞。DENVax RNA轉錄本經解凍，混合400微升Vero細胞懸浮液(1×10^7 細胞/毫升)，及轉染預先冷凍無菌電穿孔光試管(4毫米間隙)用於藉基因帕色賽爾(Gene Pulser Xcell)整個系統(拜雷實驗室(BioRad Laboratories))進行電穿孔。各樣本以250V/ ∞ Ohms/500 μ F施加脈衝一次，於室溫培養10-15分鐘，轉移至含30毫升細胞生長培養基(含10% FBS之MEM)的75平方厘米燒瓶，及於 $36^\circ\text{C} \pm 1^\circ\text{C}$ ，5% CO_2 培養6至11日。收穫培養基，藉離心澄清、穩定化、及以小液分儲存於低於 -60°C 。從轉染所得之候選者疫苗備料(針對繼代培養層級1定名為P1)之病毒力價係於Vero細胞藉溶菌斑滴定檢定分析決定，及用於DENVax種病毒之進一步傳播

DENVax種病毒之製造

[0135]P1種病毒用於透過設計來確保製造批料之最佳遺傳安定性及安全性之策略而傳播DENVax前主宰、主宰、工作及散裝病毒批料。本策略包括三次連續溶菌斑純化，以及於各個繼代培養層級的遺傳分析而選擇用於連續種病毒製造之最佳純株病毒族群(表1)。簡言之，從轉染細胞收穫的P1種病毒以0.001之MOI感染Vero細胞擴增一次而生成P2種病毒。P2種病毒備料之液分藉溶菌斑型態學及完整病毒基因體定序評估。遺傳上證實的P2備料接種於如下溶菌斑滴定章節描述的具有疊置培養基之Vero細胞單層上而生

成明確分離的溶菌斑。使用中性紅變成可見而目測觀察後分離4個血清型疫苗病毒各自之6個個別溶菌斑(溶菌斑純株A至F)及混合入0.5毫升培養基內(繼代培養P3)。6個溶菌斑懸浮液各自接受另二回合溶菌斑純化，導致於繼代培養P4及P5之兩倍及三倍溶菌斑純化種病毒。P5病毒經由兩次連續Vero繼代培養擴增而製造P7種病毒備料。

[0136]進行使用如先前揭示的墨點定序及/或基於Taqman不匹配擴增突變檢定分析(TaqMAMA)之三個主要DENVax減毒基因座之遺傳分析，及進行溶菌斑表現型分析來篩檢全部24個P7種病毒。然後藉完整基因體定序進一步特徵化具有適當初始特性之種病毒。此等分析結果，各個DENVax血清型之6個(純株A-F) P7種病毒中之一者基於DENV-2 PDK-53減毒突變、最低基因體序列變化、及預期溶菌斑表現型之是否存在被選用為前主宰種病毒。各個選定的前主宰種病毒藉由於多個175平方厘米燒瓶之Vero細胞內以0.001 MOI進行一次病毒繼代培養擴大成為主宰種病毒(MVS或P8)。DENVax-4 MVS除外，主宰種病毒於感染後(pi) 8至10日收穫。MVS備料於感染後(pi) 6至10日收穫，藉離心澄清，藉添加蔗糖/磷酸鹽/麩胺酸鹽溶液(終濃度7.5%蔗糖，3.4 mM磷酸二氫鉀，7.2 mM磷酸氫二鉀，5.4 mM麩胺酸一鈉)及0.95至1.90% FBS(終濃度)安定化。DENVax-4 MVS以不同方式製備來最佳化其產率。簡言之，多個燒瓶之細胞於0.1% F-127波洛薩莫(poloxamer) 407存在下(其它EO-PO嵌段共聚物已經經過評估且可於此處取

代，參考核發專利案)其已經驗證可增加DENV病毒之熱安定性，以0.001之MOI感染DENVax-4前主宰種病毒。感染介質於感染後6至10日收穫，使用17% FBS(終濃度)穩定化，匯集及冷凍。全部四種DENVax MVS備料以1毫升液分儲存於低於-60℃。

[0137]於0.001之MOI，於MVS之Vero細胞培養中藉一次繼代培養製備DENVax工作種病毒(WVS)。程序係類似MVS之製造，但於多層細胞工廠(6360平方厘米)培養。WVS備料通過10 μ M及0.45 μ M過濾器過濾，使用用於MVS的相同安定劑安定化，分成多個液分置於30毫升PETG瓶或2.0毫升冷凍小瓶內，及儲存於低於-60℃。

[0138]於某些方法中，散裝種病毒(BVS)之製造係使用90毫升稀釋WVS感染融合Vero細胞之多個細胞工廠(各6360平方厘米)而達成0.001之MOI。用於稀釋MVS接種物之培養基含有0.1% F-127不含血清。經1.5小時吸附後，細胞以PBS洗3次，800毫升不含血清之DMEM培養基添加至各個細胞工廠，及細胞工廠於36($\pm$ 1)℃於5($\pm$ 0.5)% CO₂接種。接種4日後，小量培養基液分收集進行無菌測試。病毒於感染後第5日至第10日間收穫，即刻通過0.45微米孔徑過濾器過濾，各個澄清病毒匯集物1升藉添加500毫升3x FTA緩衝液安定化(終濃度15%海藻糖，1.0%普隆尼克(Pluronic) F-127波洛薩莫407、0.1%人血清USP於PBS, pH 7.4)。穩定化之病毒分散於1升PETG瓶內，於低於-60℃冷凍儲存用於隨後匯集及品質管制測試。具有病毒力價高於10⁵ PFU/ml及可

接受含量之殘餘DNA的全部安定化病毒收穫物於32℃於水浴中快速解凍，然後以無菌方式匯集及混合。全部匯集單層BVS分散於加標籤之PETG容器內及於低於-60℃儲存供進一步使用。

製造產品品質管制

[0139]MVS、WVS、及BVS種病毒接受測試身份、無菌性、及可檢測偶發作用因子。各疫苗備料之身份係藉RT-PCR使用DENVax血清型專一性引子證實。已擴增cDNA片段含有E/NS1嵌合式接合位置來允許識別各個四種DENVax血清型。各個種病毒於全部4種血清型專一性RT-PCR反應中測試以證實病毒身份及不含異源DENVax血清型之交叉污染。根據USP 71 (美國藥典章節71)進行無菌性測試。進行黴漿體測試。

[0140]下列針對病毒污染之試管內及活體內測試全部皆於種病毒製造期間使用收集未經澄清未經安定化之DENVax收穫物進行。收穫之感染性培養基首先於 $36\pm 1^{\circ}\text{C}$ 使用DENV兔多株抗血清(英維拉貞(Inviragen))中和而失活化DENV。針對試管內試驗，已中和之種病毒接種於25平方厘米燒瓶內之三種指示劑細胞系，MRC5、VERO及MA104。伊柯病毒(CPE對照)或腮腺炎病毒(血球吸附對照)分別用作為陽性CPE或血球吸附對照組。全部細胞每日監視CPE共計14日。14日結束後，移出培養上清液，以10毫升天竺鼠紅血球(RBC)溶液(3毫升0.5%天竺鼠RBC於磷酸鹽緩衝食鹽水，使用細胞培養基調整至10毫升)置換。然後燒瓶於 $5\pm 3^{\circ}\text{C}$

接種30分鐘接著於室溫接種30分鐘。單層以PBS洗滌及於10倍放大下觀察血球吸附之任何星形RBC叢簇的存在。

[0141]偶發因子之活體內測試係於哺乳期小鼠、斷乳小鼠及天竺鼠進行。哺乳期小鼠經由腹內(ip)注射接種0.1毫升或0.01毫升(各劑量組合10頭小鼠)DENV-抗血清中和種病毒樣本。同理，10頭已斷乳小鼠腹內接種0.5毫升或0.03毫升樣本。天竺鼠(每組5頭)各自腹內接種5.0毫升。每日觀察哺乳期小鼠之發病率及死亡率總計經歷接種後14日。斷乳後小鼠於接種後共觀察28日，及天竺鼠共觀察42日。若 $\geq 80\%$ 接種動物於整個觀察期維持健康，則該試驗組滿足可接受標準。

[0142]污染物之活體內測試也於雞受精卵進行。針對每種樣本，10顆母雞受精卵(9日齡)各自於35°C接種0.5毫升DENV抗血清中和樣本至尿囊液內及於35°C培養3日。從此等10顆卵收穫尿囊液，匯集，於35°C繼代培養入10顆新鮮受精卵(10-11日齡；0.5毫升/卵)之尿囊液內又經3日。同理，針對各樣本，10顆受精卵(6-7日齡)藉注射入卵囊內各自接種0.5毫升/卵(DENVax-2 一價BVS)或0.25毫升/卵(DENVax-1、DENVax-3及DENVax-4 BVS)及於35°C培養9日。得自此等10顆卵之卵囊經收穫及匯集，10%懸浮液繼代培養入10顆新鮮受精卵(6-7日齡；0.5毫升/卵)之卵囊內及於35°C又接種9日。接種於尿囊液之卵(包括初接種及繼代接種)於觀察3日後之存活率。尿囊液之兩種匯集物於4°C及25°C使用雞、天竺鼠及人O型紅血球測試血液凝集活性。卵

接種入卵囊內之卵(初次接種及繼代接種二者)觀察接種9日後之存活率。

病毒溶菌斑檢定分析及免疫焦點檢定分析

[0143]病毒力價係使用Vero細胞藉溶菌斑檢定分析或免疫焦點檢定分析測量。如先前描述於融合Vero病毒之6孔孔板內於雙瓊脂糖覆蓋中進行溶菌斑檢定分析，也用於評估DENVax種病毒之溶菌斑表現型。為了正確比較，於同一個實驗中測量全部病毒之溶菌斑大小及比較。於感染後第9日使用中性紅目測觀察後，測量各病毒多達10個明確分離溶菌斑用於計算平均溶菌斑大小。對wt DENV-1、-3、及-4測量較少溶菌斑，其溶菌斑大小較大通常不允許測量10個明確分離的溶菌斑。

[0144]因四價DENVax含有全部四個血清型，故發展DENV血清型專一性免疫焦點分析來定量於四價配方中之各種DENVax成分。個別DENVax MVS之免疫焦點檢定分析與溶菌斑檢定分析作比較以確定病毒滴定結果在兩個檢定分析間可作比較。免疫焦點檢定分析係於感染連續稀釋病毒的融合Vero細胞之6孔孔板內進行。細胞上方覆蓋含0.7%高黏度羧甲基纖維素(希格瑪公司(Sigma))之平衡鹽培養基(BSS/YE-LAH培養基)及於37°C使用5% CO₂培養7日。去除覆蓋層後，細胞薄片使用PBS洗三次，於-20°C使用冷80%丙酮固定30分鐘，使用PBS洗一次，及於37°C使用含2.5% (w/v)非脂乾乳，0.5%崔頓(Triton) X-100，0.05%吐溫(Tween)-20於PBS之封阻緩衝液封阻30分鐘。以被封阻細胞

接種以稀釋DENV血清型-專一性MAb、1F1 (DENV-1)、3H5(DENV-2)、8A-1(DENV-3)、或1H10(DENV-4)於封阻緩衝液於37°C歷時1小時或於4°C隔夜，以洗滌緩衝液(0.05%吐溫-20於PBS)洗三次，及於37°C歷時45-60分鐘接種鹼性磷酸鎂或辣根過氧化酶(HRP)-軛合親和力純質山羊抗小鼠IgG(捷克森免疫研究實驗室(Jackson Immuno Research Laboratories))。孔板於添加適當酶基質、1-步驟式NBT/BCIP加鹼性磷酸酶遏止劑(皮爾斯(Pierce))或針對HRP之載體-VIP套組(載體實驗室(Vector Labs))用於彩色展開之前洗三次。當焦點完全展開後以水清洗中止彩色展開。在光箱直接觀察及計數染色免疫焦點。

基因序列

[0145]MVS及WVS之全長基因體經定序(參見下文)。簡言之，病毒RNA藉使用葵安普(QIAamp)病毒RNA套組(葵亞真(Qiagen))從DENVax種病毒萃取，重疊cDNA片段覆蓋整個基因體，使用泰騰(Titan)一試管RT-PCR套組(羅氏應用科學公司(Roche Applied Science, Inc.))擴增。擴增cDNA片段於使用正訊息引子及反訊息引子使用大染色終結者(BigDye Terminator) v3.1循環定序套組(應用生物系統公司)定序之前接受凝膠純化。定序反應使用大染色X終結者純化套組(應用生物系統公司)清潔於DVBD/CDC之3130x1基因分析儀(應用生物系統公司)上跑。使用Lasergene SeqMan軟體(DNA星公司(DNAStar Inc.))進行基因體分析及比較。

以 Taqman 為基礎之不匹配擴增突變檢定分析

(TaqMAMA)

[0146] TaqMAMA為敏感定量單一核苷酸多形性檢定分析，發展用來更精細評估於減毒5'NC-57基因座之返祖程度，針對本研究進一步最佳化。藉TaqMAMA分析得自MVS及WVS之經萃取的病毒RNA，引子/Taqman探針二集合對野生型或疫苗5'NC-57區各自具有專一性。正訊息引子用來檢測DENV-2 wt，疫苗序列分別為D2-41-GC及D2-40-TT。各正向引子之3'-端核苷酸匹配各病毒之專一性5'NCR-57核苷酸，而各個引子之3'-端核苷酸之相鄰核苷酸與DENV-2病毒基因體序列不同以增進不匹配效應。針對野生型集合及疫苗集合之反訊息病毒、CD-207、及Taqman探針、CD-169F為相同。先前描述引子及探針序列及循環條件。於含5微升病毒RNA樣板、0.4 μ M各種引子、及0.2 μ M探針之25微升反應中，使用拜雷 (BioRad) 埃斯里普 (iScript) RT-PCR(用於探針)套組，以iQ5或CFX-95系統(拜雷)進行即時RT-PCR。針對各樣本進行各種野生型-疫苗專一性檢定分析之重複三次反應。基因體複本數目相對於針對各個病毒基因型決定的標準曲線決定，於該處RNA標準為衍生自含各種基因型專一性cDNA之nt 1-2670的質體衍生得的轉錄本。此外，檢定分析之專一性係藉使用異源基因型引子/探針集合測試各個RNA標準證實，確保於每個實驗之最低交叉反應性。結果也報告為病毒基因體顯示返祖的百分比。先前，由於較高交叉反應背景限制本檢定分析之輸入RNA濃度，原先檢測敏感度為約0.1%返祖(甄別能力)。此後，

- 檢定分析進一步使用即時PCR設備及反應套組最佳化，交叉反應性背景於遠更高的RNA樣板輸入程度(7-8 $\log_{10}$ 複本)顯著減低。此種最佳化導致檢測敏感度顯著改良，低抵0.01-0.07%返祖。

於蚊C6/36細胞之病毒複製及於哺乳動物Vero細胞之溫度敏感度

[0147]四個DENVax MVS備料及wt DENV-1、-2、-3、及-4病毒之複製野生型於C6/36蚊細胞(阿波比特氏斑蚊(*Aedes albopictus*))評估。生長於6孔孔板的C6/36細胞以0.001之MOI重複感染各個病毒，及於5% CO₂培育器內於28°C與含2% FBS之4毫升/孔DMEM培養基培養。於感染後第6日收集各種病毒之培養上清液小液分，混合含40% FBS之等量體積培養基，及於-80°C儲存至準備用於病毒溶菌斑滴定。

[0148]於6孔孔板於Vero細胞感染後5日，比較於39°C之病毒生長及於37°C之病毒生長進行溫度敏感度評估。於37°C細胞以各種病毒於0.001之MOI重複感染四次。於病毒吸附後，感染培養與4毫升/孔含2% FBS之DMEM培養基於兩個分開5% CO₂孵育器內培養，一個設定(重複孔板)於37°C及另一個設定於39°C。感染後第5日收集培養上清液液分(50微升)，混合等量體積含40% FBS之DMEM，儲存於-80°C直到準備用於病毒溶菌斑滴定。使用NIST-示蹤工廠校正溫度計(-1至51°C；爾特科(ERTCO))校準孵育器溫度。

蚊感染、散播及傳播

[0149]用於研究的埃及斑蚊係得自靠近泰國梅薩(16' N, 33' E)一村莊於2002年所建立的群落。從幼蟲蛻變之後，成蚊自由提供10%蔗糖溶液，以16:8(亮：暗)光週期維持於28°C。5至7日齡之雌蚊用於感染血液餐進食或胸內(IT)接種。收穫(未經冷凍-解凍週期)即刻使用新鮮培養DENVax及wt DENV之液分來製造用於經口感染如下指示的血液餐。其餘病毒上清液補充FBS至終濃度20%，液分儲存於-80°C用於未來病毒溶菌斑滴定及IT接種物實驗。此等實驗用之新鮮製備的DENVax種病毒於Vero細胞中從前主宰種病毒擴增，被視為DENVax MVS相當物。

[0150]於口服感染當天以1:1比例混合新鮮血液與去纖維蛋白化的雞血(科羅拉多血清公司(Colorado Serum Company))製備感染血液餐。蚊子經過糖剝奪空腹隔夜，及然後使用黑莫泰(Hemotek)膜進食系統(探索工作坊(Discovery Workshops))提供病毒：血液混合物歷時1小時。50微升液分之血液餐維持於-80°C作為病毒劑量之回滴定。完全飽食之雌蚊在冷麻木下分類及置於紙箱內，自由提供10%蔗糖溶液。紙箱置於16：8小時(亮：暗)光週期於28°C。14日後，得自各個病毒組的25至30隻蚊經由暴露於三乙基胺(福來內普(Flynap)，卡羅萊納生物供應公司(Carolina Biological Supply Company))麻醉，取一隻後腳放置於含10% FBS及5%青黴素/鏈黴素(分別為100 U/ml及100 µg/ml)的0.5毫升DMEM中。將麻醉蚊的吻插入含2.5% FBS及25%蔗糖溶液之毛細管內收集唾液。允許蚊分泌唾液至

少15分鐘及然後毛細管及蚊體置於含DMEM之分開試管內。蚊體、腳及唾液儲存於-80°C直到被磨碎及評估傳染性病毒。供IT接種用，蚊藉由冷麻木及於0.34微升接種物內接種約50 pfu病毒。接種蚊於前述相同條件下維持7日。然後蚊麻醉，如前述收集唾液及蚊體。樣本儲存於-80°C直到進一步處理。

[0151]為了處理樣本進行病毒滴定，蚊體及蚊腳樣本使用混合磨機以24週期/秒歷時4分鐘與銅包BB(克斯曼公司(Crossman Corporation)，紐約)均化，及然後於3,000 x g離心3分鐘。唾液樣本於3,000 x g離心3分鐘以從毛細管中排出流體。蚊體及蚊腳均化物及唾液樣本之10倍稀釋液藉溶菌斑檢定分析測試是否存在有傳染性病毒。從蚊體、蚊腳及唾液所得結果分別用於決定感染率、散播率及傳播率。

小鼠神經毒力

[0152]定時妊娠之雌ICR小鼠係得自塔科尼克實驗室，每日監測數次決定胎鼠的約略出生時間。於一給定實驗中，出生後約12-24小時，每種病毒使用兩窩八頭胎鼠(n=16)，使用30號針頭藉顱內(ic)接種 10^3 至 10^4 pfu病毒於20微升稀釋液挑釁。挑釁後動物每日至少監視3次，至少歷時32天。出現疾病的第一徵象(毛皮粗糙、駝背、體重減輕、活動異常、癱瘓、或嗜睡)時，動物使用異氟醚氣體藉致命性麻醉安樂死，接著斬首。安樂死的感染後日數表示動物的「至發病/生病時間」或「存活時間」。動物實驗係遵照DVBD/CDC IACUC-核准動物方案進行。

主宰種病毒之衍生

DENVax-1主宰種病毒(MVS)

[0153] 此處提供嵌合式病毒基因體之核苷酸序列及轉譯蛋白質之推定胺基酸序列。大部分prM-E基因(nt 457至-2379，下方畫線)為野生型(wt) DEN-1 16007病毒專一性；其餘基因體為DEN-2 PDK-53病毒專一性。全部基因改造取代係與野生型病毒(D1 16007或D2 16681)不同，於MVS檢測得額外突變(與基因改造cDNA純株的改變)顯著。

含括於基因體及蛋白質之取代：

[0154] D1 (prM-E)及D2骨架間之接合位置：

- a. MluI (nt 451-456)：基因改造無聲突變，nt-453 A-to-G
- b. NgoMIV (nt 2380-2385)：基因改造突變，nt-2381/2382 TG-to-CC (導致E-482 Val-to-Ala改變)

[0155] D2 PDK-53病毒骨架(與wt D2 16681改變)：全部為粗體

- a. 5'-非編碼區(NCR)-57 (nt-57 C-to-T)：主要減毒位置(紅色)
- b. NS1-53 Gly-to-Asp (nt-2579 G-to-A)：主要減毒位置(紅色)
- c. NS2A-181 Leu-to-Phe (nt-4018 C-to-T)
- d. NS3-250 Glu-to-Val (nt-5270 A-to-T)：主要減毒位置(紅色)
- e. nt-5547(NS3基因) T-to-C無聲突變
- f. NS4A-75 Gly-to-Ala (nt-6599 G-to-C)

* PDK-53之nt-8571 C-to-T無聲突變未於疫苗病毒基因改造

[0156]DEN-1 prM-E (從wt D1 16007改變)

a. 基因改造nt-1575 T-to-C無聲突變以去除天然XbaI位置

[0157]出現於疫苗種病毒之額外取代(與原先純株0.03% nt不同)

a. NS2A-116 Ile-to-Leu (nt-3823 A-to-C，粗體)

b. NS2B-92 Glu-to-Asp (nt-4407 A-to-T，粗體)

c. nt-7311 A-to-G無聲突變(粗體)

NCR-57-T, D2 PDK-53 減毒基因座										(wt D2 16681: 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AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGTTTTTTAATTAGAGAGCAGATCTCTGATGAG																				M																				N																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															

N F V C R R T F V D R G W G N G C G L F G K G S L I T C A K F K C V
1310 1320 1330 1340 1350 1360 1370 1380 1390 1400
TGACAAAAC TAGAAGGAAAGATAGTTCATATGAAAACCTAAATATTCAGTGATAGTCACCGTCCACACTGGAGATCAGCACACCGGTGGGAAATGAGAC
T K L E G K I V Q Y E N L K Y S V I V T V H T G D Q H Q V G N E T
1410 1420 1430 1440 1450 1460 1470 1480 1490 1500
TACAGAACATGGAACTGCAACCTAACACCTCAAGCTCCTACGTCCGAAATACAGCTGACCGACTACGGAACCCCTTACATTAGATTGTTACCTAGG
T E H G T T A T I T P Q A P T S E I Q L T D Y G T L T L D C S F R
1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
ACAGGGCTAGATTTTAACGAGATGGTGTGCTGACAATGAAAGAAAGATCATGGCTTGCCACAAACATGGTTCCTAGACTTACCCTGCTTGGACCT
T G L D F N E M V L L T M K E R S W L V H K Q W F L D L P L P W T S

基因改造無聲突變 (nt-1575 T-to-C): 去除天然 DEN-1 病毒專一性 xbaI 位置

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700
CTGGGGCTTCAACATCCCAAGAGACTTGGAAACAGACAAGATTACTGGTCACATTTAAGACAGCTCATGCAAGAAGCAGGAAGTGTCTACTAGGATC
G A S T S Q E T W N R Q D L L V T F K T A H A K K Q E V V V L G S
1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
ACAAAGAGGAGCAATGCACACTGCGCTGACTGGAGCGACAGAAATCCAAACGTCAGGAACGACAAACATTTTCGAGGACACCTAAATGCAGACTAAA
Q E G A M H T A L T G A T E I Q T S G T T T I F A G H L K C R L K
1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
ATGGACAATTAATTTTAAAGGGAATGTCATATGTGATGTGCACAGGCTCATTCAGTTAGAGAAAGAGTGGCTGAGACCCAGCATGGAACTGTCTGG
H D K L T L K G M S Y V M C T G S F K L E K E V A E T Q H G T V L V
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TGCAGGTTAAATATGAAGGAACAGACGCACCATGCAAGATTCCCTTTTCGACCCAGATGAGAAAGGAGCAACCCAGATGGGAGATTATTAACAGCCAA
Q V K Y E G T D A P C K I F F S T Q D E K G A T Q N G R L I T A N
2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
CCCCATAGTCACTGACAAAGAAACCACTCAATATTGAGGCAGAACCCCTTTGGTGAGAGCTACATCGTGGTAGGAGCAGGTGAAAAGCTTTGAAA
P I V T D K E K P V N I E A E P P F G E S Y I V V G A G E K A L K
2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
CTAAGCTGGTTCAAGAAAGAGCAGCATAGGAAATGTTTGAAGCAACTGCCCGAGGAGCAGAAAGGATGGCCATTCTGGGAGACACCGCATGGGACT
L S W F K K G S S I G K M F E A T A R G A R R M A I L G D T A W D F
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
TCGGTCTATAGGAGGAGTTTACGCTTATGGGAAAACCTGGTACACAGGTTTTTGGAACTGCATATGGAGTTTGTTTAGCGGAGTTTCTTGGACCAT
G S I G G V F T S M G K L V H Q V F G T A Y G V L F S G V S W T M

D1 16007 序列終點

2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
GAAATAGGAATAGGGATCTGCTGACATGGCTAGGATTTAAATTCAGGAACACGTCCTTTTCGATGATGTGCATCGCTGCGGCTTTCATTGTGACACTGTAT
K I G I G I L L T W L G L N S R N T S L S M M C I A A G I V T L Y

基因改造 NGSMIV 剪接位置, E-482 Val-to-Ala (nt-2381/2382 TG-to-CC)

>NS1
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
TTGGGAGTCATGGTGCAGGCGATAGTGGTTCGCTTGTGAGCTGGAAGAAACAAAGAACTGAAATGTGGCAGTGGGATTTTCATCAGACAACTGCACA
L G V M V Q A D S G C V V S W K N K E L K C G S G I F I T D N V H T
2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CATGGACAGAAACATAAGTTCCAACCAAGATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCCATGAAGAGGACATTGTGGAATCCGCTCAGT
W T E Q Y K F Q P E S P S K L A S A I Q K A H E E D I C G I R S V
D2 PDK-53 NS1-53-Asp 減毒基因座 (wt D2 16581: Gly, nt-2579-G)
2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
AACAGACTGGAGAACTCATGTGGAACCAATTAACACCAAGATTGAATCACATTCTATCAGAAATGAGGTGAAGTTAATATTATGACAGGAGACATC
T R L E N L M W K Q I T P E L N H I L S E N E V K L T I M T G D I
2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
AAAGGAATCATGCAGGAGGAAACGATCTCTGCGGCTCAGCCACTGAGCTGAAGTATCATGCAAAACATGGGGCAAGCAAAATGCTCTACAG
K S I M Q A G K R S L R P Q P T E L K Y S W K T W G K A K M L S T E
2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
AGTCTCATACCAAGACCTTCTCATTTGATGGCCCCGAAACAGCAGAAATGCCCCAACACAAATAGAGCTTGGAAATTCGTTGGAAGTTGAAGACTATGGCTT
S H N Q T F L I D G P E T A E C P N T N R A W N S L E V E D Y G F
2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
TGGAGTATTCACCAACATATATGGCTAAATTTGAAAGAAAAACAGGATGTATTCCTGCGACTCAAACTCATGTGACGGGCCATAAAGACAAACAGAGCC
G V F T T N I W L K L K E K Q D V F C D S K L M S A A I K D N R A

3010 3020 3030 3040 3050 3060 3070 3080 3090 3100
GTCCATGCCGATATGGGTTATTGGATAGAAAGTGCACCTCAATGACACATGGAGATAGAGAAAGCCTCTTTTCATTGAAGTTAAAACTGCCACTGGCCAA
V H A D M G Y W I E S A L N D T W K I E K A S F I E V K N C H W P K
3110 3120 3130 3140 3150 3160 3170 3180 3190 3200
AATCACACACCCCTCTGGAGCAATGGAGTGCCTAGAAAGTGAATGATAATCCAAAGATCTCGCTGGACCAAGTGTCTCAACCAACTATAGACCAGGCTA
S H T L W S N G V L E S E M I I P E N L A G P V S Q H N Y R P G Y
3210 3220 3230 3240 3250 3260 3270 3280 3290 3300
CCATACACAAATACAGGACCATGGCTCTAGGTAAGCTTGGAGTGGACTTTGATTCTGTGTGGAACAACAGTGGTAGTACTGAGGACTGCGGAAT
H T Q I T G P W H L G K L E M D F D F C D G T T V V V T E D C G N
3310 3320 3330 3340 3350 3360 3370 3380 3390 3400
AGAGSACCCCTCTTTGAGAACCAACTGCTCTGGAAAACCTATAACAGAATGGTGCTGCCGATCTTGACATTACCACCGCTAAGATACAGAGGTGAGG
R G P S L R T T T A S G K L I T E W C C R S C T L P P L R Y R G E D

>NS2A
3410 3420 3430 3440 3450 3460 3470 3480 3490 3500
ATGGGTGCTGGTACGGGATGGAAATCAGACCAATTGAAGGAGAAAGAGAAATTGGTCAACTCCTTGGTCACAGCTGGACATGGGCGGTGCGAACCTT
G C W Y G M E I R P L K E K E E N L V N S L V T A G H G Q V D N F
3510 3520 3530 3540 3550 3560 3570 3580 3590 3600
TTCACTAGGAGTCTTGGGAATGGCATTGTTCTCTGGAGGAAATGCTTAGGACCCGAGTAGGAACGAAACATGCAATCTACTAGTTGCAGTTCTTTTGTG
S L G V L G M A L F L E E M L R T R V G T K H A I L L V A V S F V

3610 3620 3630 3640 3650 3660 3670 3680 3690 3700
ACATTGATCACAGCGAAGCATGTCTTTAGAGACCTGGGAAGAGTGTGCTTATGGTAGGCGCCACTATGACGGATGACATAGGTATGGGCTGACTTATC
T L I T G N M S F R D L G R V M V M V G A T M T D D I G M G V T Y L

3710 3720 3730 3740 3750 3760 3770 3780 3790 3800
TTGCCCTACTAGCAGCTTCAAGTCAGACCACTTTTGCAGCTGGACTACTCTTGAGAAAGCTGACCTCCAAGGATTTGATGATGACTACTATAGGAAT
A L L A A F K V R P T F A A G L L L R K L T S K E L M M T T I G I

3810 3820 3830 3840 3850 3860 3870 3880 3890 3900
TGTACTCTCTCCAGAGCACCCCTACCGAGACCATCTTGTAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCTCAAAATGGTGAGAAATATGGAA
V L L S Q S T L P E T I L E L T D A L A L G M M V L K M V R N M E

於主宰及前主宰種病毒之額外 Ns2A-116 Ile-to Leu (nt3823 A-to-C)

3910 3920 3930 3940 3950 3960 3970 3980 3990 4000
AAGTATCAATTTGGCAGTGACTATCATGGCTATCTTGTGCGTCCCAACCGCAGTGATATTACAAACGCCATGGAAAGTGAAGTTGCACAAATATTGGCAGTGG
K Y Q L A V T I H A I L C V P N A V I L Q N A W K V S C T I L A V V
4010 4020 4030 4040 4050 4060 4070 4080 4090 4100
TGTCCGTTTCCCGACTGTCTTAACATCTTCACAGCAAAAACAGATTGGATACCATTAGCATTGACGATCAAAGGTCTCAATCCACAGCTATTTTCT
S V S P L F L T S S Q Q K T D W I P L A L T I K G L N P T A I F L

D2 PDK-53 專一性 NS2A-181-Phe (wt D2 16681: Leu, nt-4018-C)

>NS2B
4110 4120 4130 4140 4150 4160 4170 4180 4190 4200
AACAAACCTCTCAAGAACGACGCAAGAAAGGAGCTGGCCATTAAATGAGGCTATCATGGCAGTCGGGATGGTGAGCATTTTAGCCAGTTCTCTCTATAAA
T T L S R T S K K R S W P L N E A I M A V G M V S I L A S S L L K
4210 4220 4230 4240 4250 4260 4270 4280 4290 4300
AATGATATTTCCATGACAGGACCATTTAGTGGCTGGAGGGCTTCCTCACTGTGTGTACGTGCTCACTGGACGATCGGCCGATTGGAACTGGAGAGAGCAG
N D I P M T G P L V A G G L L T V C Y V L T G R S A D L E L E R A A
4310 4320 4330 4340 4350 4360 4370 4380 4390 4400
CCGATGTCAAAATGGGAAGACCGAGGAGATATCAGGAAGCAGTCCAATCCTGTCAATAACAATATCAGAGAGATGGTAGCATGCGATAAAAATGAAGA
D V K W E D Q A E I S G S S P I L S I T I S E D G S M S I K N E E

4410 4420 4430 4440 4450 4460 4470 4480 4490 4500
GGAGATCAAAACACTGACCACTACTATTAGAACAGGATTGCTGGTGATCTCAGGACTTTTCCTGTATCAATCAATCAACGCGACGAGCATGGTACCTG
E D Q T L T I L I R T G L L V I S G L F P V S I P I T A A A W Y L

額外 NS2B-92 Glu-to-Asp (nt-4407 A-to-T) 突變(於主宰及前主宰種病毒)

>NS3
4510 4520 4530 4540 4550 4560 4570 4580 4590 4600
TGGGAAGTGAAGAAACACGGGCGGAGATTTGTGGATGTCTTCCACCCCAACCCATGSGGAAGGCTGAACTGGAGATGGAGCCTATAGAAATTAAGC

W E V K K Q R A G V L W D V P S P P P M G K A E L E D G A Y R I K Q
4610 4620 4630 4640 4650 4660 4670 4680 4690 4700
AAAAAGGGATTCTGGATATTCCAGATCGGAGCGGAGTTTACAAAGAGGAACATTCCATACATGTGGCATGTCACACGTGGCGCTGTTCTAATGCA
K G I L G Y S Q I G A G V Y K E G T F H T M W H V T R G A V L M H
4710 4720 4730 4740 4750 4760 4770 4780 4790 4800
TAAAGGAAGAGGATTGAACCATCATGSGCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAAATGGAAGGAGGAGAA
K G K R I E P S W A D V K K D L I S Y G G G W K L E G E W K E G E
4810 4820 4830 4840 4850 4860 4870 4880 4890 4900
GAAGTCCAGGTATTGGCACTGGAGCTGGAAAAATCCAAGAGCCGTCACAAACGAAACCTGGTCTTTTCAAAACCAACCGCGGAAACATAGTGCTGTAT
E V Q V L A L E P G K N P R A V Q T K P G L F K T N A G T I G A V S
4910 4920 4930 4940 4950 4960 4970 4980 4990 5000
CTCTGGACTTTTCTCCTGGAACGTCAAGATCTCCATTATCGACAAAAAGGAAAAGTTGTGGGTCTTTATGGTAATGGTGTGTACAGGAGTGGAGC
L D F S P G T S G S P I I D K K G K V V G L Y G N G V V T R S G A
5010 5020 5030 5040 5050 5060 5070 5080 5090 5100
ATATGTGAGTGCTATAGCCAGACTGAAAAAGCATTGAAGACACCCAGAGATCGAAGATGACATTTTCCGAAAGAGAAGACTGACCATCATGGACCTC
Y V S A I A Q T E K S I E D N P E I E D D I F R K R R L T I M D L
5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
CACCCGAGAGCGGGAAGAGCAAGAGATACCTTCGGCCATGCTCAGAGAAGCTATAAAACGGGGTTTGAGAACATTAACTTTGGCCCCCACTAGAGTTG
H P G A G K T R Y L P A I V R E A I K R G L R T L I L A P T R A V V
5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
TGGCAGCTGAATGGAGGAAGCCCTTAGAGGACTTCCAATAAGATACAGACCCAGCCATCAGAGCTGTGCACACCGGGCGGAGATTGTGGACCTAAT
A A E M E E A L R G L P I R Y Q T P A I R A V H T G R E I V D L M
↓
D2 PDK-53 NS3-250-Va1 滅毒基因座 (wt D2 16681: Glu, nt-5270-A)
5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
GTGTCATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAAACTACAACTGATTATCATGGACGAAGCCCATTTCCAGACCCAGCAACT
C H A T F T M R L L S P V R V P N Y N L I I M D E A H F T D P A S
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTATGACAGCCACTCCCCGGGAAGCAGAGACCCATTTCCCTC
I A A R G Y I S T R V E M G E A A G I F M T A T P P G S R D P F P Q
5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
AGAGCAATGCACCAATCATAGATGAAGAAGAGAAATCCCTGAACGCTCGTGGAATCCGGACATGAATGGGTACGGGATTTTAAAGGGAAGACTGTTTG
S N A P I I D E E R E I P E R S W N S G H E W V T D F K G K T V W
↓
D2 PDK-53 無聲突變 nt-5547-C (wt D2 16681: T)
5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
GTTGCTTCCAAGTATAAAGCAGGAATGATATAGCAGCTTGCCCTGAGGAAAAATGGAAGAAAGTGATACAACCTCAGTAGGAAGACCTTTGATTCTGAG
F V P S I K A G N D I A A C L R K N G K K V I Q L S R K T F D S E
5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
TATGTCAAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACTGACATTTCAAGAAATGGGTGCCAATTTCAAGGCTGAGAGGGTTATAGACCCAGAC
Y V K T R T N D W D F V V T T D I S E M G A N F K A E R V I D P R R
5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
GCTGCATGAAACAGTACATACTAACAGATGGTGAAGAGCGGGTGATTCTGGCAGGACCTATGCLAGTGACCCACTCTAGTGCAGCACAAAGAGAGGGAG
C M K P V I L T D G E R V I L A G P M P V T H S S A A Q R R G R
5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AATAGGAGAGAAATCCAAAAATGAGAAATGACCAGTACATATACATGCGGGGAACTCTGGAAAAATGATGAAGACTGTGCACACTGGAAGAAAGCTAAATG
I G R N P K N E N D Q Y I Y M G E P L E N D E D C A H W K E A K M
6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
CTCTAGATAACATCAACACGCGCAGAGGAATCATTCCTAGCATGTTCGAACCAAGAGCGTGAAAAAGGTGGATGCCATTGATGGCGAATACCGCTTGAGAG
L L D N I N T P E G I I P S M F E P E R E K V D A I D G E Y R L R G
6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
GAGAAGCAAGGAAACCTTTGTAGACTTAATGAGAAAGAGGAGACCTACCACTCTGTTGGCCTACAGAGTGGCAGCTGAAGGCATCAACTACGACACAG
E A R K T F V D L M R R G D L P V W L A Y R V A A E G I N Y A D R
6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
AAGTGGTGTTTTGTAGTCAAGAACCAAAATCCTAGAGAAACCTGGAAGTTGAAATCTGGACAAAAGAGGGGAAAGGAAGTAATTGAAACCC
R W C F D G V K N N Q I L E E N V E V E I W T K E G E R K K L K P

>NS4A

6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAATTTAAGGAATTTGCAGCCGGAGAAAGTCTCTGACCCCTGAACCTAATCACAG
R W L D A R I Y S D E L A L K E F K E F A A G R K S L T L N L I T E

6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
AAATGGGTAGGCTCCCACTTCATGACTCAGAAGGCAGAGACGCACTGGACAACCTAGCAGTGTGACACGCGCTGAGGCGAGGTGGAGGGGCTACAA
M G R L P T F M T Q R A R D A L D N L A V L H T A E A G G R A Y N

6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
CCATGCTCTCAGTGAACCTGCCGGAGACCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTCACGGGAGGGATCTTTTATCTTGTGATGAGCGCA
H A L S E L P E T L E T L L L L T L L A T V T G G I F L F L M S A

D2 PDK-53 專一性 NS4A-75-11a (wt D2 16681: Gly, nt-6599-G)

6610 6620 6630 6640 6650 6660 6670 6680 6690 6700
AGGGGCATAGGGAGATGACCCCTGGGAATGTGCTGCATAATCACGGCTAGCATCTCTCTATGGTACGACAAATACAGCCACACTGGATAGCAGCTTCAA
R G I G K M T L G M C C I I T A S I L L W Y A Q I Q P H W I A A S I

6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TAATACTGAGTGTCTTTCATAGTTTTCCTTATTCAGAACCTGAAAAACAGAGAACACCCCAAGACAACCACTGACCTACGTTGTGATAGCCATCCT
I L E F F L I V L L I P E P E K Q R T P Q D N Q L T Y V V I A I L

>NS4B

6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
CACAGTCTGGGCGGCAACCATGGCAACGAGATGGGTTTCCTAGAAAAACGAGAAAGATCTCGGATTGGGAAGCATGCAACCCAGCAACCCGAGAGC
T V V A A T M A N E M G F L E K T K K D L G L G S I A T Q Q P E S

6910 6920 6930 6940 6950 6960 6970 6980 6990 7000
AACATCCTGGACATAGATCTAGCTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCACACATTTGTACACCAATGTTGAGACATAGCATGAAAATT
N I L D I D L R P A S A W T L Y A V A T T F V T P M L R H S I E N S

7010 7020 7030 7040 7050 7060 7070 7080 7090 7100
CCTCAGTGAATGTGTCTTAAACAGCTATAGCCAAACAGCCACAGTGTAAATGGTCTCGGGAAAGGATGGCCATTGTCAAAAGATGGACATCGGAGTCC
S V N V S L T A I A N Q A T V L M G L G K G W P L S K M D I G V P

7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
CCTTCTCGCCATTGGATGCTACTCACAAGTCAACCCCATACCTCTCACAGAGCTCTTTTCTTATTGGTAGCATTATGCCATCATAGGGCCAGGACTC
L L A I G C Y S Q V N P I T L T A A L F L L V A H Y A I I G P G L

7210 7220 7230 7240 7250 7260 7270 7280 7290 7300
CAAGCAAAAGCAACAGAGAGCTCAGAAAAGAGCAGCGCGGCATCATGAAAAACCAACTGTGATGGGAATTAACAGTGAATGACATGATCCATATC
Q A K A T R E A Q K R A A A G I M K N P T V D G I T V I D L D P I P

7310 7320 7330 7340 7350 7360 7370 7380 7390 7400
CTTATGATCCGAGTTTGAAAGCAGTGGGACAAAGTAATGCTCCTAGTCTCTGCTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
Y D P K F E K Q L G Q V M L L V L C V T Q V L M M R T T W A L C E

額外無聲突變 (nt-7311 A-to-G, 於主宰及前主宰種病毒)

7410 7420 7430 7440 7450 7460 7470 7480 7490 7500
GGCTTTAACCCTTAGCTACCGGSCCATCTCCACATTGTGGGAAGGAATCCAGGGAGGTTTGGAACTACTACCTTGGCGGTGTCAATGGCTAACATTTT
A L T L A T G P I S T L W E G N P G R F W N T T I A V S M A N I F

> NS5

7510 7520 7530 7540 7550 7560 7570 7580 7590 7600
AGAGGGAGTTACTTGGCCGAGCTGGACTTCTCTTTCTATTATGAAGAACACACCAACACAAAGAGGGGAAGTGGCAACATAGGAGAGACGCTTGGAG
R G S Y L A G A G L L F S I M K N T T N T R R G T G N I G E T L G E

7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
AGAAATGGAAAAGCCGATTGAACGCATTGGGAAAAAGTGAATCCAGATCTACAAGAAAAGTGGAAATCCAGGAAGTGGATAGAACCTTAGCAAAAAGAGG
K W K S R L N A L G K S E F Q I Y K K S G I Q E V D R T L A K E G

7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
CATTAAPAGAGGAGAAACCGACCATCACGCTGTGTGCGAGGCTCAGCAAACTGAGATGGTTCGTTGAGAGAACATGGTCACACAGAGGGGAAGTAA
I K R G E T D H H A V S R G S A K L R W F V E R N M V T P E G K V

7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
GTGGACCTCGGTTGTGGCAGAGGAGCTGTCATACTATTGTGGAGGACTAAAGATGTAAGAGAAATCAAGGCCTAACAAAAGGAGGACAGGACAG
V D L G C G R G G W S Y Y C G G L K N V R E V K G L T K G G P G H E

7910 7920 7930 7940 7950 7960 7970 7980 7990 8000
AAGAACCCTCCCATGTCAACATATGGGTGGAATCTAGTGGCTTTCAAGTGGAGTTGACGTTTCTTTCATCCCGCCAGAAAAGTGTGACACATTATT
E P I P M S T Y G W N L V R L Q S G V D V F F I P P E K C D T L L

8010 8020 8030 8040 8050 8060 8070 8080 8090 8100
GTGTGACATAGGGGAGTCAACACCAATCCACAGTGGAGCAGGACGAACACTCAGAGTCCTTAACCTTAGTAGAAAATGGTTGAACACCAACACTCAA
C D I G E S S P N P T V E A G R T L R V L N L V E N W L N N N T Q

8110 8120 8130 8140 8150 8160 8170 8180 8190 8200
TTTTCATATAAGGTTCTCAACCCATATATGCCCTCAGTCATAGAAAAATGGAAGCACTACAAAGGAATATGGAGGAGCCTTAGTGTAGGAATCCACTCT
F C I K V L N P Y M P S V I E K M E A L Q R K Y G G A L V R N P L S

8210 8220 8230 8240 8250 8260 8270 8280 8290 8300
CACGAAACTCCACACATGAGATGTACTGGGTATCCAAATGCTTCCGGGAACATAGTGTCAATCAGTGAACATGATTTCAGGGATGTTGATCAACAGATTTAC
R N S T H E M Y W V S N A S G N I V S S V N M I S R M L I N R F T

8310 8320 8330 8340 8350 8360 8370 8380 8390 8400
AATGAGATACAAGAAAGCCACTTACGAGCCGGATGTTGACCTCGGAAGCCGACCCCTAACATCGGGATTGAAAGTGAGATACCAAACTAGATATAATT
M R Y K K A T Y E P D V D L G S G T R N I G I E S E I P N L D I I

8410 8420 8430 8440 8450 8460 8470 8480 8490 8500
GGGAAAGAGTAAAGAAATAAAGCAAGAGCATGAACATCATGGCACTATGACCAAGACCACCCATACAAACCGTGGGCATACCATGTTAGCTATGAAA
G K R I E K I K Q E H E T S W H Y D Q D H P Y K T W A Y H G S Y E T

8510 8520 8530 8540 8550 8560 8570 8580 8590 8600
CAAAACAGACTGGATCACCATCATCCATGGTCAACGGAGTGGTCAAGGCTGCTGACAAACCTTGGGACGTCGTCCTCCCATGCTGACACAGATGGCAATGAC
K Q T G S A S S M V N G V V R L L T K P W D V V P M V T Q M A M T

8610 8620 8630 8640 8650 8660 8670 8680 8690 8700
AGACACGACTCCATTGGGACACAGCGCGTTTTTAAAGAGAAAGTGACACGAGAACCCAAAGAACCGAAAGAGGCACGAGAAATCAATGAAAATAACA
D T T F F G Q R V F K E K V D T R T Q E P K E G T K K L K I T

8710 8720 8730 8740 8750 8760 8770 8780 8790 8800
GCAGAGTGGCTTTGGAAGAAATTAGGGAAGAAAGACACCCAGGATGTGACCCAGAGAAGAAATTCACAGAAAGGTGAGAAGCAATGCAAGCCTTGGGG
A E W L N K E L G K K K T P R M C T R E E F T R K V R S N A A L G A

8810 8820 8830 8840 8850 8860 8870 8880 8890 8900
CCATATTCACTGATGAGAAACAAAGTGGAAAGTCGGCACGTGAGGCTGTTGAAGATAGTAGGTTTGGGAGCTGGTTGACAAAGGAAGGAATCTCCATCTTGA
I F T D E N K W K S A R E A V E D S R F W E L V D K E R N L H L E

8910 8920 8930 8940 8950 8960 8970 8980 8990 9000
AGGAAGTGTGAACATGTGTGTACACATGATGGGAAAAGAGAGAGCTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGCCATATGTTACATG
G K C E T C Y N M M G K R E K K L G E F G K A K G S R A I W Y M

9010 9020 9030 9040 9050 9060 9070 9080 9090 9100
TGGCTTGGGACACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGAGGTGGAAGGAGAG
W L G A R F L E F E A L G F L N E D H W F S R E N S L S G V E G E G

9110 9120 9130 9140 9150 9160 9170 9180 9190 9200
GGCTGCACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGAGGAGCAATGTATGCCGATGACACCCGAGGATGGGATACAAAGATCACACT
L H K L G Y I L R D V S K K E G G A M Y A D D T A G W D T R I T L

9210 9220 9230 9240 9250 9260 9270 9280 9290 9300
AGAAGACTAAAANATGAAGAAATGGTACAAACACATGGAAGGAGAAACACAGAAACTAGCCGAGGCCATTTTCAAACTAACGTACCAAAACAAAGGTG
E D L K N E E M V T N H M E G E H K K L A E A I F K L T Y Q N K V

9310 9320 9330 9340 9350 9360 9370 9380 9390 9400
GTGCGTGTGCAAGACCAACCAAGAGGCACAGTAATGGACATCATATCGAGAGAGAACCAAGAGGTAGTGGACACAGTGGCCCTATGGACTCAATA
V R V Q R P T P R G T V M D I I S R R D Q R G S G Q V G T Y G L N T

9410 9420 9430 9440 9450 9460 9470 9480 9490 9500
CTTTCACCAATATGGAAGCCCAACTAATCAGACAGATGGAGGGAGAGGAGTCTTAAAGCATTCAGCACCTAACCAATCACAGPAGAAATCCGTGTGCA
F T N M E A Q L I R Q M E G E G V F K S I Q H L T I T E E I A V Q

9510 9520 9530 9540 9550 9560 9570 9580 9590 9600
AAACTGGTTAGCAAGAGTGGGGCGGAAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTTGTGTTGTGAAACCTTTAGATGACAGGTTTCGCAAGCGCT
N W L A R V G R E R L S R M A I S G D D C V V K P L D D R F A S A

9610 9620 9630 9640 9650 9660 9670 9680 9690 9700
TTAACAGCTCTAATGACATGGGAAGATTAGGAAAGACATACACAAATGGGACCTTCAAGAGGATGGAATGATTGGACACAGTGCCTTCTGTTTAC
L T A L N D M G K I R K D I Q Q W E P S R G W N D W T Q V P F C S H

9710 9720 9730 9740 9750 9760 9770 9780 9790 9800
ACCATTTCCATGAGTAAATGAAAGACGGTCGCGTACTCGTTGTTCCATGTAGAAACCAAGATGAACTGATTGGCAGAGCCCGAATCTCCCAAGGAGC
H F H E L I M K D G R V L V V P C R N Q D E L I G R A R I S Q G A

9810 9820 9830 9840 9850 9860 9870 9880 9890 9900
AGGGTGGTCTTTGCGGGAGACGGCTGTTTGGGGAAGTCTTACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGSCAAAT
G W S L R E T A C L G K S Y A Q M W S L M Y F H R R D L R L A A N

9910 9920 9930 9940 9950 9960 9970 9980 9990 10000
GCTATTGCTCGGCAGTACCATCACATTGGGTTCACCAAGTCCGAACACCTGGTCCATACATGCTAAACATGAATGGATGACACGGAAGACATGCTGA
A I C S A V F S H W V P T S R T T W S I H A K H E W M T T E D M L T

10010 10020 10030 10040 10050 10060 10070 10080 10090 10100

CAGCTGCGAACAGGGTGTGGATTCAAGAAAAACCCATGGATTGGAAGACAAACTCCAGTGGGAATCATGGGAGGAAATCCCATACTGGGGAAAAAGAGAAGA
 V W N R V W I Q E N P W M E D K T P V E S W E E I P Y L G K R E D
 10110 10120 10130 10140 10150 10160 10170 10180 10190 10200
 CCAATGGTGGCGGCTCATTTGATTGGGTAAACAAGCAGGGCCACCTGGGCAAGAAGAACTCCAAGCAGCAATAAATCAAGTTAGATCCCTTAGATAGGCAATGAA
 Q W C G G S L I G L T S R A T W A K N I Q A A I N Q V R S L I G N E
 10210 10220 10230 10240 10250 10260 10270 10280 10290 10300
 GAATACACAGATTACATGCCATCCATGAAAAGATTCAAGAGAGAAGCAGGAGAAGCAGGAGTTCTTGTTGGTAGAAGCAAACAACTAACATGAAACAAGGCTA
 E Y T D Y M P S M K R F R R E E E E A G V L W *
 10310 10320 10330 10340 10350 10360 10370 10380 10390 10400
 GAAGTCAGGTCGGATTAAAGCCATAGTACGGAAAAAATCTATGCTACCTTGAGCCCCCTCCAAGGACGTTAAAGAAAGTACAGGCCATCATAAATGCCATAG
 10410 10420 10430 10440 10450 10460 10470 10480 10490 10500
 CTTGAGTAAACTATGACGCCCTGTAGCTCCACCTGAGRAGGTGTAAAAAATCCGGAGGAGCCACAAACCRITGGAAGCTGTACGCATGGCGTAGTGGACTAGC
 10510 10520 10530 10540 10550 10560 10570 10580 10590 10600
 GGTAGAGGAGAGCCCTCCCTTACAAATTCGACAGCAACAATGGGGGCCCAAGGCCAGATGAAGCTGTAGTCTCGCTGGAAGGACTAGAGGGTTAGAGGAGAC
 10610 10620 10630 10640 10650 10660 10670 10680 10690 10700
 CCCCCCGAAACAAAAACAGCATATTGACGCTGGGAAAGACCGAGATCTGCTGTCTCCTCAGCATCATTCAGGCACAGAACGCCAGAAATGSAATG
 10710 10720
 GTGCTGTTGAATCAACAGGTTCT

DENVax-2主宰種病毒(MVS)

[0158] 此處提供重組病毒基因體之核苷酸序列及轉譯蛋白質之推定胺基酸序列。基因改造病毒係基於D2 PDK-53病毒。標示出與野生型DEN-2 16681病毒(也是PDK-53之親代病毒)不同的全部基因改造取代，以及於MVS檢測得的額外突變(從基因改造cDNA純株改變)。

含括於基因體及蛋白質之取代：

[0159] D2 PDK-53病毒骨架(從wt D2 16681改變): 全部皆粗體

a. 5'-非編碼區(NCR)-57 (nt-57 C-to-T): 主要減毒基因座(紅色)

b. prM-29 Asp-to-Val (nt-524 A-to-T)

c. nt-2055 C-to-T (E基因)無聲突變

d. NS1-53 Gly-to-Asp (nt-2579 G-to-A) : 主要減毒基因座(紅色)

e. NS2A-181 Leu-to-Phe (nt-4018 C-to-T)

f. NS3-250 Glu-to-Val (nt-5270 A-to-T): 主要減毒基因座(紅色)

g. nt-5547 (NS3基因) T-to-C無聲突變

h. NS4A-75 Gly-to-Ala (nt-6599 G-to-C)

*於疫苗病毒中PDK-53之nt-8571 C-to-T無聲突變係未經基因改造。

[0160] 基因改造純株標記(無聲突變):

a. nt-900 T-to-C無聲突變：感染純株標記

[0161] 出現於疫苗種病毒之額外取代(與原先純株差異0.02% nt)

a. prM-52 Lys-to-Glu (nt-592 A-to-G), 粗體

b. NS5-412 Ile-to-Val (nt-8803 A-to-G), 粗體

nt-57-n, D2 PDK-53 滅毒基因座 (nt-2 16681: C)

D2 PDK-53 專一性 p21-29 Val (nt-2 16681 Asp, nt-524-A) 額外 p21-52 Lys-to-Glu 突變 (nt-592 A-to-G)

基因改造無聲純株標記 :: nt-900 T-to-C 無聲突變

D2 PDK-53 nt-2055-T 無聲突變 (D2 16681: C)

CGGGAGATTTGGACCTAATGTGTGCTGTCCACATTTCACCATAGGAGCTGTCTATACCCAGTTTASAGTGTCCCAAACTAGACCTTGATATCATGAGACGAGGUCCTATTCACGAGACCCAGCAAGT

5410 5420 5430 5440 5450 5460 5470 5480 5490 5500 5510 5520
ATAGCGGCTACAGAGCATACATCTCCATCTGCAGTCGGAGGTGACGAGCAGCTGGGGAATTATTATGCAACCTTCTCCCCGGGGAACGACAGAGACCACCTTCCTCAGAGCAATGCCACCAATCATATA

5530 5540 5550 5560 5570 5580 5590 5600 5610 5620 5630 5640
GATGAAAGAAAGAGAAATCCCTGACGCCTGTCGGAATTCGCGACATGAATGGGCTACCGGATTTTAAAGGAGAGACTGTTTGGTTCGTTTCAAGATGAAGACAGGAAATGATATAGCGCGCT
D E E R E I P E R S W N S G H E V V T D F K G K T V M F V F P S I K A G N D I A A

D2 PDK-53 無聲突變 nt-5547-C (D2 16681: T)

3650 3660 3670 3680 3690 3700 3710 3720 3730 3740 3750 3760
TGCCTGACAAATATGGAAGAAAGTGATACACTCAGTAGGAGACCTTTGATTCTTGAGTGTCTCAASACTAGAACCAATGATTGGGACTTCGTGGTATCAACTGCAATTCAGGATATG
C L R K N G G K V I O L S R K T P D S E Y V K C K T R T N D W D F V V T T T D I S E M

5770 5780 5790 5800 5810 5820 5830 5840 5850 5860 5870 5880
G G T G C C A T T T C A G A C G G T A T T A G A C C C A A G C G T G C A T G A A C C A C T C A T C T A C A G A T T G G T G A A G A C C G G G T A T T C G R C A G A G C A T A T G C T G C T G G C C C A C T C T A G T
G A N P K A E R V I D F R M C N K R V I L T D G E E R V I L A S P M P V T H S S

5890 5900 5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
GCATCCAGAGGATAGAGGAGAAATGAGAGAGAAATCCAAATATGAGATGACACGATCATATACATGGGAGACCTCTGAGAAATGTCGAGACTGTGACACTGGAACAGAGCTATTAATG
A A O R G R I T R N P K E N D O V Y I Y M G E P L E N D E C A H E E A K M

6010 6020 6030 6040 6050 6060 6070 6080 6090 6100 6110 6120
CTCTTGGATACATCACTCGCTCAGAGGGAATCTCTCCATGCTTTCGAACACGAGCGGTAAAGGCTGTGATGCCCTTGATGGCGGATACCGCTTGAGGAGGAGGAACGAGGAAACCTTT
L D N I N T P E G I L P S M P E F E R E K V D A I D G B Y L R L R G E A R K T F

6130 6140 6150 6160 6170 6180 6190 6200 6210 6220 6230 6240
GTAGATCTTAATGAGAGACGAGACCTACCAAGTCGTGGTCTTGACCTACAGATGGCAGCTGAGGACCTATCACATCCAGACAGAGGCTGTGTCTTGTATGGATCAAGAGAACCAACCTCTTA
V D L M R R K G D L S P V W L L A Y R V A A E G T I N Y A D R R N C F D G V K N N Q I L

6250 6260 6270 6280 6290 6300 6310 6320 6330 6340 6350 6360
GUAAGAAGCTGGTGAATCTGGACAAAAGAGAGGGGAGAGAAATTGGAACCCAGATGTTGGATGCTAAGATCTATTCTGACCCACTGGCGCTAAAGAAATTAAAGCAATT
E E N V S V R I N T K E G E R K L K P R W L D A R I Y S D P L A L K E F K E P

7NS 4A

5370 5380 5390 5400 5410 5420 5430 5440 5450 5460 5470 5480
GCAAGCCGGAGAAAGAGTCTGACGCTGAACCTTAATCAGACAGAAAGGAGTAGGCTCCGACCTTCATGACTCAGAGGCGAAGAGACCGCACTGGACAACTTATGACGTGTGCGACATGGCTGAG
A A G R K S L T L N L I T E N G R L P T F M T Q K A R D A L D N L A V L L H T A E

4490 4500 4510 4520 4530 4540 4550 4560 4570 4580 4590
 GCAGGTGGAAAGCGCTACCAACTATGCTCTCAGTGAACATGCCGGAACGCTGAGACATTCTCTTACTGACACTTCTGGCGTACAGCTACAGCGGAAAGGATCTTTTATCTTCTCATGAGCGCA
 A G G G A Y A Y N H A L S E L F E T L E T L L L T L L A T V T G G I F L F L F L M S A

D2 PDK-53 專一性 NS4A-75-A1a (wt D2 16681: Gly, nt-6599-G

6619 6620 6630 6640 6650 6660 6670 6680 6690 6700 6710 6720
AGGGGCAATAGGAGCAATGACCCCTGGGGAATGTGCTGCATAATCAAGGCTACACATCTCTCTATAGGCAACAAATACGGACACTGGGATAGCAGCTTCGAATCAATCACTGGAGTTTTCCTTC
R G I G K M T L G M C C I I T A S I L L K Y A Q I Q P H W I A A S I I L E F F L

6730 6740 6750 6760 6770 6780 6790 6800 6810 6820 6830 6840
 ATAGTTTTCGTTATTCAGAGACCTGAAAAACAGAGAACGCGCCACAGACACCACTGACCTAGTTTGTCTAAGCAATCCYCACATGGTGCGCCACAGCTGGCAACAGAGATGGTTTC

6850 6860 6870 6880 6890 6900 6910 6920 6930 6940 6950 6960
CTAGAGAAACGAGAGAAAGATCTGGGATCTGGGAGCAT7GCAACCCACGACACCCGAGAGCAGACATCTTGGACATAGATCTACGCTCTGATCAGCATGGACGCTGTATCCCGTGGCCAGA

6970 6980 6990 7000 7010 7020 7030 7040 7050 7060 7070 7080
ACATTGTTACACGAAAGTTTGACATAGCATTGAATTCCTCATGTGAATGTGTCCTTACACGCTATAGCCACCCAAAGCCACAGTGTGTAATGGGTTCGGGAAAGGATGCCCCATTGCA

7093 7100 7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
 AAGATGGACATCGGAGATTCCCTTCTCGCCATTGGATGCTACTACAGAGTCAACCCCACTACTCTCAGCAGCAGCTCTTTTCTCTATTGGTATCACAATTATGCCATCATAGGGCCAGAGACTC

7210 7220 7230 7240 7250 7260 7270 7280 7290 7300 7310 7320
CAAGCAAAACCAACCAAGCAAGCTCAGAAAGACAGCGCGCGCGGCATCATGAAACCCCAACTGCTGCAATGCAATACACGATTGACCTAGATCCAACTCCITATGATTCAAAGTITGAA

7330 7340 7350 7360 7370 7380 7390 7400 7410 7420 7430 7440
AAGCAGTATGGGACAACTAATCTCTCTGATCTCTGCTGACTCAGATATATGATGATGAGACTACATGAGGCTCTGTGTGAGAGCTTTAACTCTTAGCTACCGGGCCCTCTCTCCACTGTGG

7180 7460 7470 7480 7490 7500 7510 7520 7530 7540 7550 7560
GAGGGAATTCGAGGAGGCTTTGGAACTACCACTGCGGTGTCACTGGCTAACCTTTTAGAGGAGGTACTGTCGCGGAGCTGGACTTCCTCTTTCTATATGGAAGAACACACCAAC

>NS5

7570	7580	7590	7600	7610	7620	7630	7640	7650	7660	7670	7680
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[illegible]

DENVax-3主宰種病毒(MVS)

[0162] 此處提供嵌合式病毒基因體之核苷酸序列及轉譯蛋白質之推定胺基酸序列。大部分prM-E基因(nt-457至-2373，下方畫線)為野生型(wt) DEN-3 16562病毒專一性；其餘核苷酸序列為DEN-2 PDK-53病毒專一性。DEN-3病毒之E蛋白具有比DEN-2 E蛋白更少兩個胺基酸。因此，始於NgoMIV之nt位置係比原先DEN-2 PDK-53 nt位置少6 nt。標記出與野生型病毒(DEN-3 16562或DEN-2 16681)不同的全部基因改造取代以及額外突變(從基因改造cDNA純株改變)。

含括於基因體及蛋白質之取代：

[0163] 接合位置：

- a. MluI (nt 451-456)：基因改造無聲突變，nt-453 A-to-G
- b. NgoMIV (nt 2374-2379)：基因改造突變，nt-2375/2376

TG-to-CC (導致E-480 Val-to-Ala改變)

[0164] D2 PDK-53病毒骨架(從wt D2 16681改變)：粗體

- a. 5'-非編碼區(NCR)-57 (nt-57 C-to-T)：主要減毒基因座(紅色)
- b. NS1-53 Gly-to-Asp (nt-2573 G-to-A)：主要減毒基因座(紅色)
- c. NS2A-181 Leu-to-Phe (nt-4012 C-to-T)
- d. NS3-250 Glu-to-Val (nt-5264 A-to-T)：主要減毒基因座(紅色)
- e. nt-5541 (NS3基因) T-to-C無聲突變
- f. NS4A-75 Gly-to-Ala (nt-6593 G-to-C)

*於疫苗病毒中PDK-53之nt-8565 C-to-T無聲突變係未經基因改造

[0165] 於DEN-3 prM-E之基因改造突變(從wt D3 16562改變)

- a. 基因改造nt-552 C-to-T無聲突變：純株標記
- b. 基因改造E-345 His-to-Leu (nt-1970 A-to-T)用於培養中有效複製

[0166] 出現於疫苗種病毒之額外取代(與原先純株差異0.02% nt)

- a. E-223 Thr-to-Ser突變(nt1603 A-to-T，粗體)
- b. nt-7620 A-to-G無聲突變(粗體)

MCR-57-T, D2 PDK-53。減毒基因座 (wt D2 16681:C)

> 5'-非編碼區

10 20 30 40 50 60 70 80 90 100

AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGTTTTTTAATTAGAGAGCAGATCTCTGATGA

M N

110 120 130 140 150 160 170 180 190 200

ATAACCAACGGAAAAAGGCGAAAAACACGCGTTTCAATATGCTGAACGCGAGAGAAACCGCGTGTGCAACAGCTGACAAAGAGATTCTCACT

N Q R K K A K N T P F N M L K R E R N R V S T V Q Q L T K R F S L

210 220 230 240 250 260 270 280 290 300

TGGAATGCTGCAGGACGAGGACCATTAACCTGTCATGGCCCTGGTGGCGTTCCTTCGTTTCTAACATCCACGACAGCAGGGATATTGAAGAGA

G M L Q G R G F L K L F M A L V A F L R F L T I P P T A G I L K R

310 320 330 340 350 360 370 380 390 400

TGGGAAACATTAATAAATCAAAAGCTATTAAATGTTTGGAGGGGTTCAGGAAAGAGATTGGAAGGATGCTGAACATCTTGAATAGGAGACGCGATCTG

N G T I K K S K A I N V L R G F R K E I G R M L N I L N R R R S A

> prM

410 420 430 440 450 460 470 480 490 500

CAGGCTAGTCAATTATGCTGATTCCCAACAGTGTATGGCGTTCCATTAAACACGCGTGTGAGAGCGCGCATGATTGTGGGGAAGAATGAAGAGGAAA

G M I I M L I P T V M A F H L T T R D G E F R M I V G K N E R G K

基因改造, 剪接位置 (nt-453 A-to-G 無聲突變)

510 520 530 540 550 560 570 580 590 600

ATCCCTACTTTTCAAGACACGCGTCTGGAAATCAACATGTGCACACTGATAGCTATGGATCTGGGAGAGATGTGTGATGACACCGGTCACTTACAAATGCCCC

S L L F K T A S G I N M C T L I A M D L G E M C D D T V T Y K C P

無聲 C-to-T nt 突變為純株標記

610 620 630 640 650 660 670 680 690 700

CACATTACCGAAGTGGAGCGTGAAGACATTGACTGCTGGTGCACCTTACATCGACATGGGTGACTTATGGAACATGCAATCAAGCTGGAGGACATAGAC

H I T E V E F E D I D C W C N L T S T W V T Y G T C N Q A G E H R R

> M

710 720 730 740 750 760 770 780 790 800

GCGATAAGAGATCACTGGCGTTAGCTCCCATCTTGGCATGGGACTGGACACACGCACTCAAACTGGATGTGGGCTGAAGGACTTGGAGCAAGTCGA

D K R S V A L A P H V G M G L D T R T Q T W M S A E G A W R Q V E

810 820 830 840 850 860 870 880 890 900

GAAGGTAGAGACATGGGCGCTTAGGCACCCAGGGTTTACCATACTAGCCCTATTCTTCTGCCATTACATAGGCACTTCTCTGACCCAGAAAGTGGTTATT

K V E T W A L R H P G F T I L A L F L A H Y I G T S L T Q K V V I

> E

910 920 930 940 950 960 970 980 990 1000

TTTTACTATTAACTGCTGCTTACCCCATCCATGACATGAGATGTGTAGGAGTAGGAAACAGASATTTTGTGGAAGGCCATATCGGGAGCTACGTGGGTG

F I L L M L V T P S M T M R C V G V G N R D F V E G L S G A T W V D

1010 1020 1030 1040 1050 1060 1070 1080 1090 1100

ACGTGGTGTCTGAGCACGCTGGGTGTGTGACTACCATGGCTAAGAACACAGCCACGCTGGACATAGAGCTTACAGAGACCGAGGCCACCCACCTGGCGAC

V V L E H G G C V T T M A K N R P T L D I E L Q K T E A T Q L A T

1110 1120 1130 1140 1150 1160 1170 1180 1190 1200

CCTAAGGAAGCTATGCATTGAGGGAAATTAACACATATACACCGACTCAAGATGTCCACCCAGGSGGAGCGATTTTACCTTGAGGACGAGGACGAG

L R K L C T I E G K I F N I T T D S R C P T Q G E A I L P E E Q D Q

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300

AACTACGTGTGTAAAGCATACATACGTGGACAGAGCTGGGGAACGGTTGTGTTTGTGTCAGGGAAGCTTGGTGACATGCGCGAAATTTCAATGTT

N Y V C K H T Y V D R G W G N G C G L F G K G S L V T C A K F Q C L

1310 1320 1330 1340 1350 1360 1370 1380 1390 1400

TAGAATCAATGAGGGAAAGTGGTGCACATGAGAACCTCAAATACACCGTCAATCATCAGTGCACACAGGAGACCAACACCGGTGGGAAATGAAC

E S I E G K V V Q H E N L K Y T V I I T V H T G D Q H Q V G N E T

1410 1420 1430 1440 1450 1460 1470 1480 1490 1500

GCAGGGATCACGGCTGAGATAACACCCAGGCATCAACCGCTGAAGCCATTTTACCTGAAATATGGACCCCTCGGGCTAGAATGCTCACCACGGACAGGT

Q G V T A E I T P Q A S T A E A I L P E Y G T L G L E C S P R T G

1510 1520 1530 1540 1550 1560 1570 1580 1590 1600

TTGGATTTCAATGAATGATCTCATTGACAAATGAAGACAAAGCATGGATGGTACATAGACAAATGGTTCCTTGAATTAACCCCTACCATGACATCAGGAG

L D F N E M I S L T M K N K A W M V H R Q W F F D L P L P W T S G A

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700

CTTACGAGAAACACCAACTTGGAAACAGGAAGAGCTTCTTGTGACATTAAAAATGCACATGCACAAAGCAAGAGTAGTTGTTCTTGGATCACAAGA

S A E T P T W N R K E L L V T F K N A H A K K Q E V V V L G S Q E

於主率及前主率種病毒之額外 E-233 Thr-to-Ser 突變(wt D3 16562: nt-1603 A)

1710 1720 1730 1740 1750 1760 1770 1780 1790 1800

GGGAGCAATGCATACAGCACTGACAGGAGCTACAGAGATCCAAACCTCAGGAGGSCAAGATATCTTTGCGGGGCACTTAAATGTAGACTCAAGATGGAC

G A M H T A L T G A T E I Q T S G S T S I F A G H L K C R L K M D

1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
AAATTGGAACTCAAGGGGATGAGCTATGCAATGTGCTTGGTGTGTTGAAAGAAAGATCTCCGAAACGACGATGGGACAATACTCATTAGGG
K L E L K G M S Y A M C L S S F V L K K E V S E T Q H G T I L I K V

1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TTGAGTACAAGGGGAGATGCACCTGCAAGATTCCTTTCTCCACGGGAGGATGGACACAGGAAAAGCTCTCAATGGCAGAGCTGATCACAGCCCAATCCAGT
E Y K G E D A P C K I P F S T E D G Q G K A L N G R L I T A N P V

基因改造 E-345 His-to-Leu (wt D3 16562: nt-1970-A) 用於有效生長

2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
GGTGACCAAGAGAGGAGCCCTGTCAACATTGAGGCTGAACTCCTTTTGGAGAAAGTAACATAGTAATTGGAAATTGGAGACAAAGCCCTGAAATCAAC
V T K K E E P V N I E A E P P F G E S N I V I G I G D K A L K I N

2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
TGGTACACAGAGGGAGCTCGATTGGGAAGATGTTTCGAGGCCACTGCCAGAGGTGCGAGGCGCATGGCCATCTTGGGAGACACAGCTTGGGACTTTGGAT
W Y K K G S S I G K M F E A T A R G A R R M A I L G D T A W D F G S

2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
CAGTGGGTGGTGTTTGAATTCATTAGGGAAAATGGTCCACCAATATTTGGGAGTGCTTACACAGCCCTATTTGGTGGAGTCTCTCGATGATGAAAT
V G G V L N S L G K M V H Q I F G S A Y T A L F G G V S W M M K I

D3 16562 序列之終點

2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
TGGAAATAGGTTCCTCTTAACCTGGATAGGGTTGAACTCAAAAATACCTTCTATGTCATTTTCATGCAATCGCGCCGCGCATTTGTGACACTGTATTTGGGA
G I G V L L T W I G L N S K N T S M S F S C I A A G I V T L Y L G

基因改造 NS1-53 剪接位置, E-480 Val-to-Ala (nt-2375/2376 TG-to-CC)

> NS1

2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
GTCATGGTGCAGGCCGATAGTGGTTGCGTTGTGAGCTGGAAAAACAAGAACTGAATGTGGCAGTGGGATTTTCATCACAGACACGTCACACATGGA
V M V Q A D S G C V V S W K N K E L K C G S G I F I T D N V H T W T

2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CAGAACATACAGTTTCCAACCAAGATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCCATGGAAGAGGACATTTGTGGGAATCCGCTCAGTAACAAG
E Q Y K F Q P E S P S K L A S A I Q K A H E E D I C G I R S V T R

D2 PDX-53 NS1-53-Rsp 減毒基因座 (wt D2 16681: Gly, nt-2573-G)

2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
ACTGGAGAACTCTGATGTGAAACAATAACACCAGATTTGAATCACATCTATCAGAAAATGAGGTGAAGTTAACTATTATGACAGGAGACATCAAGGA
L E N L M W K Q I T P E L N H I L S E N E V K L T I M T G D I K G

2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
ATCATGCGAGGCAGGAACGATCTCTGCGGCTCAGGCCACTGAGCTGAAGTATTCATGGAACATGGGGCAAGCAAAATGCTCTACAGAGTCTC
I M Q A G K R S L R P Q P T E L K Y S W K T W G R A K M L S T E S H

2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
ATAACCAAGACCTTTCTCATTGATGGGCCGAAACAGCAGAAATGCCCAACACAAATAGAGCTTGGAAATTCGTTGGAGTTGAAGACTATGSCCTTTGGAGT
N Q T F L I D G P E T A E C P N T N R A W N S L E V E D Y G F G V

2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
ATTCAACCAATATATATGGCTAAATTTGAAGAAAACAGGATGATTTCTGCGACTCAAACTCATGTACGCGGCCATAAAGACAACAGAGCCGTCAT
F T T N I W L K L K E K Q D V F C D S K L M S A A I K D N R A V H

3010 3020 3030 3040 3050 3060 3070 3080 3090 3100
GCCGATATGGSTTATTTGATAGAAAGTGCACTCAATGACACATGGAAGATAGAGAAAGCCTCTTTCATTGAAGTTAAAACTGCCACTGGCCAAATCAC
A D M G Y W I E S A L N D T W K I E K A S F I E V K N C H W P K S H

3110 3120 3130 3140 3150 3160 3170 3180 3190 3200
ACACCCCTCTGAGCAATGGAGTGTAGAAAGTGAGATGATTAATCCAAAGAAATCTCGCTGGACCCAGTGTCTCAACACAACTATAGACCCAGGTACCATAC
T L W S N G V L E S E M I I P K N L A G P V S Q H N Y R P G Y H T

3210 3220 3230 3240 3250 3260 3270 3280 3290 3300
ACAAATACAGGACCATGGCATCTAGGTAAGCTTGAGATGGACTTTGATTTCTGTGATGGAACAACAGTGTGTAGTACTGAGGACTGCGGAAATAGAGGA
Q I T S P W H L G K L E M D F D F C D G T T V V V T E D C G N R G

3310 3320 3330 3340 3350 3360 3370 3380 3390 3400
CCCTCTTTGAGAACACCACTGCTCTGGAAAACATACAGAAATGGTGGCGGATCTTGACATTACCCCGCTAAGATACAGAGGTGAGGATGGGT
P S L R T T T A S G K L I T E W C C R S C T L P P L R Y R G E D G C

> NS2A

3410 3420 3430 3440 3450 3460 3470 3480 3490 3500

GCTGGTACGGGATGGAATCAGACCATTGAAGGAGAAAGAGAATTGGTCAACTCCTGGGTCACAGCTGGACATGGGCAGTTCGACAACCTTTTCACT
W Y G M E I R P L K E K E E N L V N S L V T A G H G Q V D N F S L

3510 3520 3530 3540 3550 3560 3570 3580 3590 3600
AGGAGTCTTGGGAATGSCATTGTCTCGGAGGAAATGCTTAGGACCCGAGTAGGAAACGAACATGCAATACTACTAGTTGCAGTTTCTTTGTGACATTG
G V L G M A L F L E E M L R T R V G T K H A I L L V A V S F V T L

3610 3620 3630 3640 3650 3660 3670 3680 3690 3700
ATCACAGGGAACATGTCTTTAGAGACCTGGGAAGAGTGATGGTTATGGTAGCCGCCACTATGACGGATGACATAGGTATGGCGTGACTTATCTTGCCCC
I T G N M S F R D L G R V M V M V G A T M T D D I G M G V T Y L A L

3710 3720 3730 3740 3750 3760 3770 3780 3790 3800
TACTAGCAGCCTTCAAGTCAGACCAACTTTGCGAGCTGGACTACTCTTGAGAAAGCTGACCTCCAGGAATTGATGATGACTACTATAGGAATTGTACT
L A A F K V R P T F A A G L L L R K L T S K E L M M T T I G I V L

3810 3820 3830 3840 3850 3860 3870 3880 3890 3900
CCTCTCCAGAGCACCATACAGAGACCAITCTTGAGTTGACTGATGCGTTAGCCTTAGGCATGATGGTCTCAAAATGGTGAGAAATATGGAAAGATAT
L S Q S T I P E T I L E L T D A L A L G M M V L K M V R N M E K Y

3910 3920 3930 3940 3950 3960 3970 3980 3990 4000
CAATTGGCAGTGACTATCTGGCTATCTTGTGCGTCCCAACCGCAGTGATATTACAAAACGCAATGGAAGTGAGTTGCACAATATTGGCAGTGGTGTCGG
Q L A V T I M A I L C V P N A V I L Q N A W K V S C T I L A V V S V

4010 4020 4030 4040 4050 4060 4070 4080 4090 4100
TTTCCCACTGTTCTTAACATCCTFCACAGCAAAAACAGATTGGATACCATTTAGCATTTGACGATCAAAAGGTCTCAATCCAACAGCTATTTTCTAACAC
S P L F L T S S Q Q K T D W I P L A L T I K G L N P T A I F L T T

D2 PDK-53 專一性 NS2A-181-Phe (wt D2 16681: Leu, nt-4012-C)

> NS2B

4110 4120 4130 4140 4150 4160 4170 4180 4190 4200
CCTCTCAAGAACCCAGCAAGAAAGGAGCTGGCCATTAAATGAGGCTATCATGSCAGTCGGGATGGTGAGCATTTTGGCCAGTTCTCTCTTAAAAATGAT
L S R T S K K R S W P L N E A I N A V G M V S I L A S S L L K N D

4210 4220 4230 4240 4250 4260 4270 4280 4290 4300
ATTCCCACTCAGCAGGACATTAGTGGCTGGAGGCTCCTCACTGCTGCTACGTCGCTGACGATCGGCCGATTGGAACTGGAGAGACAGCCGATG
I P M T G P L V A G G L L T V C Y V L T G R S A D L E L E R A A D V

4310 4320 4330 4340 4350 4360 4370 4380 4390 4400
TCAAATGGGAAGACCGGCAGAGATATCAGGAAGCAGTCCCAATCCTGTCAATAACAATATCAGAAGATGGTAGCATGTCGATAAAAAATGAAGAGGAAGA
K W E D Q A E I S G S S P I L S I T I S E D G S M S I K N E E E

4410 4420 4430 4440 4450 4460 4470 4480 4490 4500
ACAAACACTGACCTACTCATTAGAACAGGATTGCTGGTGATCTCAGGATTTTTCTGTATCAATACCAATCACGGCAGCAGCATGGTACCTGTGGGAA
Q T L T I L I R T G L L V I S G L F P V S I P I T A A A W Y L N E

> NS3

4510 4520 4530 4540 4550 4560 4570 4580 4590 4600
GTGAAGAACAACGGCCGCGAGTATTGTGGGATGTTCTTCAACCCACCCATGGGAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAGCAAAAG
V K K Q R A G V L W D V P S P P P M G K A E L E D G A Y R I K Q R G

4610 4620 4630 4640 4650 4660 4670 4680 4690 4700
GSATTCTTGGATATTCCAGATCGGAGCCGGAGTTTACAAAGAAGGAACATTCCATACAATGTGCGATGTACACGTTGGCGCTGTTCTAATGCATAAAGG
I L G Y S Q I G A G V Y K E G T F H T M W H V T R G A V L M H K G

4710 4720 4730 4740 4750 4760 4770 4780 4790 4800
AAAGAGGATTGAACCATCATGGCGGACGTCBAGAAAGACCTATATCATATGGAGGAGGCTGGAAATTAGAAGGAGAATGGAAGGAAGGAGAAGTGC
K R I E P S W A D V K K D L I S Y G G G W K L E G E W K E G E E V

4810 4820 4830 4840 4850 4860 4870 4880 4890 4900
CAGGTATTGGCACTGGAGCCTGGAAAAATCCAAGAGCCGTCCAAACGAAACCTGGTCTTTTCAAAACCAACGCCGGAACAATAGTGTCTGTATCTCTGG
Q V L A L E P G K N P R A V Q T K P G L F K T N A G T I G A V S L D

4910 4920 4930 4940 4950 4960 4970 4980 4990 5000
ACTTTTCTCTGGAGCTCAGCATCTCCATTATCGACAAAAAGGAAAGTTGTGGGTCTTTATGTTAATGGTGTGTTACAAGGAGTGGAGCATATGT
F S P G T S G S P I I D K K G K V V G L Y G N G V V T R S G A Y V

5010 5020 5030 5040 5050 5060 5070 5080 5090 5100
GAGTGTATAGCCCACTGAAAAAGCATTGAAGACAACCCAGAGATCGAAGATGACATTTTCCGAAGAGAAAGTGGACCATATGGACCTTCCACCCA
S A I A Q T E K S I E D N P E I E D D I F R K R R L T I M D L H F

5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
GGAGCGGAAAGACGAGAGATACCTTCGGGCCATAGTCAGAGAAGCTATAAACGGGTTTGAGAACATTAATCTTGGCCCCCACTAGAGTTTGGCGAG
G A G K T K R Y L P A I V R E A I K R G L R T L I L A P T R V V A A

5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
CTGAAATGGAGGAGCCCTTAGAGGACTTCCAATAAGATACCGAGACCCAGCCATCAGAGCTGTGCACACCGGGCGGGAGATTGTGGACCTAATGTGTCA
E M E E A L R G L P I R Y Q T P A I R A V H T G R E I V D L M C H
|
D2 PDK-53 NS3-250-Val 減毒基因座 (D2 16681: Glu, nt-5270-A)
5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
TGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCTAACTACAACTGATTATCATGGACGAAGCCCATTTACACAGACCCAGCAAGTATAGCA
A T F T M R L L S F V R V P N Y N L I I M D E A H F T D P A S I A
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
GCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCGAGCTGGGATTTTATGACAGCCACTCCCCGGGAGGAGAGACCCATTTCTCAGAGCA
A R G Y I S T R V E M G E A A G I F M T A T P P G S R D P F P Q S N
5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
ATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAAATTCGGACATGAATGGGTACGGATTTTAAAGGGAAGACTGTTGGTTCGT
A P I I D E E R E I P E R S W N S G H E W V T D F K G K T V W F V
|
D2 PDK-53 無聲突變 nt-5541-C (D2 16681: T)
5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
TCCAAGTATAAAGCAGGAAATGATATAGCAGCTTGCTGAGGAAATGGAAAGAAAGTGATACAACCTCAGTAGGAAGACCTTTGATTCTGAGTATGTC
P S I K A G N D I A A C L R K N G K K V I Q L S R K T F D S E Y V
5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
AAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACTGACATTTTCAAGGCTGAGAGGTTATAGACCCAGAGCGCTGCA
K T R T N D W D F V V T T D I S E M G A N F K A E R V I D P R R C M
5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
TGAACCAAGTCATACATAGAGAGCGGTGATTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGCAGCACAAGAGAGAGGAGAAATAGG
K P V I L T D G E E R V I L A G P M P V T H S S A A Q R R G R I G
5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AAGAAATCCAAAAATGAGAATGACCATATACATGGGGGAACCTCTGGAAATGATGAAGACTGTGCACACTGGAAAGAGCTAAATGCTCCTA
R N P K N E N D Q Y I Y M G E P L E N D E D C A H W K E A K M L L
6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
GATAACATCAACGCGCAGAGGAATCATTCCTAGCATGTTTGAACAGAGCGTGAAAGGTGGATGCCATTGATGGCSAATACCGCTTGAGAGGAGAG
D N I N T P E G I I P S M F E P E R E K V D A I D G E Y R L R G E A
6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
CAAGGAAACCTTTGTAGACTTAATGAGAGAGGAGACCTACCACTCTGGTTGGCTTACAGAGTGGCAGCTGAAGGCATCAACTACGCAGACAGAAAGGTG
R K T F V D L M R R G D L P V W L A Y R V A A E G I N Y A D R R W
6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
GGTGTTTGATGGAGTCAAGAACCAACATCCTAGAAAGAAACGTGGAAATCTGGACAAAAGAGGGGAAAGAAATGAAACCCAGATGG
C F D G V K N N Q I L E E N V E V E I W T K E G E R K K L K P R W
|
> NS4A
6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
TTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAGAAATTTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCTGAACCTAATCAGAGAAATGG
L D A R I Y S D P L A L K E F K E F A A G R K S L T L N L I T E M G
6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
GTAGGCTCCCAACCTTCATGACTCAGAGGCAAGAGACGCTGGACAACCTTAGCAGTGTGACACAGGCTGAGGCAGTGGAGGGCGTACAACCATGC
R L P T F M T Q K A R D A L D N L A V L H T A E A G G R A Y N H A
6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
TCTCAGTGAATGCGGAGACCTGGAGACATTGCTTTTACTGACACTTCTGGCTACAGTACAGGGAGGGATCTTTTATCTTGTATGAGCGCAAGGGGC
L S E L P E T L E T L L L L A T V T G G I F L F L M S A R G
|
D2 PDK-53 專一性 NS4A-75-A1a (wt D2 16681: Gly, nt-6599-G)
6610 6620 6630 6640 6650 6660 6670 6680 6690 6700
ATAGGGAAGATGACCCCTGGGAATGTGCTGCATAATCAGCGCTAGCATCCTCCTATGGTACGCACAAATACAGCCACACTGGATAGCAGCTTCATAATAC
I G K M T L G M C C I I T A S I L L W Y A Q I Q P H W I A A S I I L
6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TGGAGTTFTTCTCATAGTTFGTCTTATTCAGAACCTGAAAAACAGAGAACACCCCAAGACAACCACTGACCTACGTTGTCATGCCATCCTCAGACT
E F F L I V L L I P E P E K Q R T P Q D N Q L T Y V V I A I L T V
|
> NS4B
6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
GGTGGCCGCAACCATGSCAAACGAGATGGGTTTCTAGAAAAACGAAGAAAGATCTCGGATTGGGAAGCATTTGCAACCCAGCAACCCGAGAGCAACATC
V A A T M A N E M G F L E K T K K D L G L G S I A T Q Q P E S N I
6910 6920 6930 6940 6950 6960 6970 6980 6990 7000

CTGGACATAGATCTACGTCCTGCATCAGCATGGACGCTGTATGCCGTGGCCACACATTTGTTACACCAATGTTGAGACATAGCATTGAAATTCCTCAG
L D I D L R P A S A W T L Y A V A T T F V T F M L R H S I E N S S V

7010 7020 7030 7040 7050 7060 7070 7080 7090 7100
TGATTTGTGTCCTTAACAGCTATAGCCAAACCAAGCCACAGTGTATATGGGCTCGGGAAAGGATGGCCATTGTCAAGATGGACATCGGAGTTCCCTTCT
N V S L T A I A N Q A T V L M G L G K G W P L S K M D I G V P L L

7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
CGCCATTGGATGCTACTCACAAGTCAACCCCAATACTCTCAGCAGCTCTTTCTTATTGGTAGCACATTATGCCATCATAGGGCCAGSACTCCAAGCA
A I G C Y S Q V N P I T L T A A L F L L V A H Y A I I G P G L Q A

7210 7220 7230 7240 7250 7260 7270 7280 7290 7300
AAAGCAACCCAGAGAAGCTCAGAAAAGAGCAGCGCGGGCATCATGAAAACCCAACTGTGGATGGAAATAACAGTGATTGACCTAGATCCAATACCTEATG
K A T R E A Q K R A A A G I M K N P T V D G I T V I D L D P I P Y D

7310 7320 7330 7340 7350 7360 7370 7380 7390 7400
ATCCAAAGTTTGAAGCAGTTGGGACAAGTAATGCTCCTAGTCCCTGCGTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGAGGCTTT
P K F E K Q L G Q V M L L V L C V T Q V L M M R T T W A L C E A L

7410 7420 7430 7440 7450 7460 7470 7480 7490 7500
AACCTTAGCTACCGGGCCCATCTCCACATTGTGGGAAGGAATCCAGGGAGGTTTGGAACTACCATTTGCCGTTGTCATGGCTAACATTTTAGAGGG
T L A T G P I S T L W E G N P G R F W N T T I A V S M A N I F R G

> NS5

7510 7520 7530 7540 7550 7560 7570 7580 7590 7600
AGTTACTTTGGCCGAGCTGGACTTCTCTTTCTATTATGAAGAACCAACCAACAAGAAGGGGAACTGGCAACATAGGAGAGACGCTTGGAGAGAAAT
S Y L A G A G L L F S I M K N T T N T R R G T G N I G E T L G E K W

7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
GGAAAGCCGATTGAGCGCTTGGGAAAGTGAATCCAGATCTACAAGAAAGTGGAAATCCAGGAAGTGATAGAACCTTAGCAAAAGAGCATTA
K S R L N A L G K S E F Q I Y K K S G I Q E V D R T L A K E G I K

於主宰及前主宰種病毒之額外 nt-7260 A-to-G 無聲突變

7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
AAGAGCAGAAACCGACCATCACGCTGTGTCCGAGGCTCAGCAAACTGAGATGGTTGCTTGGAGAGAACATGGTCAACACAGAGGGAAGTAGTGGAC
R G E T D H H A V S R G S A K L R W F V E R N M V T P E G K V V D

7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
CTCGGTTGTGGCAGAGGAGCTGGTCACTATTGTGGAGACTAAAGAAATGTAAGAGAAGTCAAGGCCCTAACAAAGGAGGACGAGACACGAAAGAC
L G C G R G W S Y Y C G G L K N V R E V K G L T K G G P G H E E P

7910 7920 7930 7940 7950 7960 7970 7980 7990 8000
CCATCCCCATGTCAACATATGGGTGGAATCTAGTGGCTCTCAAGTGGAGTTGACGTTTCTTCATCCCCCAGAAAAGTGTACACATTATTTGTGTGA
I F M S T Y G W N L V R L Q S G V D V F F I P P E K C D T L L C D

8010 8020 8030 8040 8050 8060 8070 8080 8090 8100
CATAGGGGAGTATCACCACATCCACAGTGGGAAGCAGGACGAACACTCAGAGTCTTAACTTAGTAGAAAAATGGTTGAACAACACACTCAATTTTGC
I G E S S P N P T V E A G R T L R V L N L V E N W L N N N T Q F C

8110 8120 8130 8140 8150 8160 8170 8180 8190 8200
ATAAAGGTTCTCAACCATATATGCCCTCAGTCATGAAAAAATGGAAGCACTACAAAGGAAATATGGAGGAGCCTTAGTGAGGAATCCACTCTCACGAA
I K V L N P Y M P S V I E K M E A L Q R K Y G G A L V R N P L S R N

8210 8220 8230 8240 8250 8260 8270 8280 8290 8300
ACTCCACACATGAGATGTACTGGGTATCCAATGCTTCCGGGAACATAGTGTCTCAGTGAACATGATTTCAAGGATGTTGATCAACAGATTACAAATGAG
S T H E M Y W V S N A S G N I V S S V N M I S R M L I N R F T M R

8310 8320 8330 8340 8350 8360 8370 8380 8390 8400
ATACAAGAAAGCCACTTACGAGCCGATGTTGACCTCGGAAGCGGAACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATATTTGGGAAA
Y K K A T Y E P D V D L G S G T R N I G I E S E I P N L D I I G K

8410 8420 8430 8440 8450 8460 8470 8480 8490 8500
AGATAGAAAAATAAGCAAGAGCATGAACATCATGGCACTATGACCAAGACCCCATACAAACGTTGGGCATACCATGGTATGAACAAAC
R I E K I K Q E H E T S W H Y D Q D H P Y K T W A Y H G S Y E T K Q

8510 8520 8530 8540 8550 8560 8570 8580 8590 8600
AGACTGGATCAGCATCATCCATGGTCAACGCGAGTGGCTGCTGACAAAACCTTGGGACGTGCTCCCATGGTGACACAGATGGCAATGACAGACAC
T G S A S S M V N G V V R L L T K P W D V V P M V T Q M A E T D T

8610 8620 8630 8640 8650 8660 8670 8680 8690 8700
GACTCCATTTGGACAACAGCGCGTTTTTAAGAGAAAGTGGACACGAGAACCCAGAACCGAAAGGACGAGGAAACTAATGAAATTAACAGCAGNG
T P F G Q Q R V F K E K V D T R T Q E P K E G T K K L M K I T A E

8710 8720 8730 8740 8750 8760 8770 8780 8790 8800
TGGCTTTGGAAAGAAATTAGGGAAGAAAGACACCCAGGATGTGCCACAGAGAAATTCACAGAAAGGTGAGAGCAATGCAGCCTTGGGGGCCATAT
W L W K E L G K K K T P R M C T R E E F T R K V R S N A A L G A I F

8810 8820 8830 8840 8850 8860 8870 8880 8890 8900
TCACTGATGAGAACAGTGGGAAGTCGGCACGTGAGGCTGTTGAAGATAGTAGSTTTGGGAGCTGGTTGACAAAGGAAGGAATCCATCTTGAAGGAAA
T D E N K W K S A R E A V E D S R F W E L V D K E R N L H L E G K

8910 8920 8930 8940 8950 8960 8970 8980 8990 9000
GTGTGAAACATGTGTGTACACATGATGGGAAAAAGAGAGAAGAGCTAGGGGAATTCGGCAAGGCAAAAGGCGAGGACCATATGGTACATGTGGCTT
C E T C V Y N H M G K R E K K L G E F G K A K G S R A I W Y M W L

9010 9020 9030 9040 9050 9060 9070 9080 9090 9100
GGAGCACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAAATGAAGATCACTGGTCTCCAGAGAGAACTCCCTGAGTGGAGTGGAAAGGAGAAAGGCTGC
G A R F L E F E A L G F L N E D H W F S R E N S L S G V E G E G L H

9110 9120 9130 9140 9150 9160 9170 9180 9190 9200
ACAAGCTAGGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGGAGCAATGTATGCCGATGACACCGCAGGATGGGATACAGAAATCACACTAGAGAA
K L G Y I L R D V S K K E G G A M Y A D D T A G W D T R I T L E D

9210 9220 9230 9240 9250 9260 9270 9280 9290 9300
CCTAAAAAATGAAGAAATGGTAACAAACCATGGAAGGAGAAACAAAGAACTAGCCGAGGCCATTTTCAARCTAACGTACCAAAACAGGTGGTGGCT
L K N E E M V T N H M E G E H K K L A E A I F K L T Y Q N K V V R

9310 9320 9330 9340 9350 9360 9370 9380 9390 9400
GTGCAAGAGCAACACCAAGAGGCACAGTAATGGACATCATATCGAGAGAGAGACCAAGAGGTAGTGGACAAATGGCACCTATGGACTCAATACTTCA
V Q R P T P R G T V M D I I S R R D Q R G S G Q V G T Y G L N T F T

9410 9420 9430 9440 9450 9460 9470 9480 9490 9500
CCAATATGGAAGCCCACTAATCAGACAGATGGAGGGAGAGGAGTCTTTAAAGCATTGACACCTAACATCAGAGAAATCGCTGTGCAAACTG
N M E A Q L I R Q M E G E G V F K S I Q H L T I T E E I A V Q N W

9510 9520 9530 9540 9550 9560 9570 9580 9590 9600
GTTAGCAAGAGTGGGCGCGAAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTGTGTTGTGAAACCTTTAGATGACAGGTTCGCAAGCGCTTTAAAC
L A R V G R E R L S R M A I S G D D C V V K P L D D R F A S A L T

9610 9620 9630 9640 9650 9660 9670 9680 9690 9700
GCTCTAATGACATGGGAAAGATTAGGAAAGACATACAACATGGGAACCTTCAGAGGATGGAAATGATTGGACACAAGTGGCCCTCTGTTCACACCAT
A L N D M G K I R K D I O Q W E P S R G W N D W T Q V P F C S H H F

9710 9720 9730 9740 9750 9760 9770 9780 9790 9800
TCCATGAGTTAATCATGAAAGACGGTTCGCTACTCGTTGTTCCATGTAGAAACCAAGATGAATGATTGGCAGAGCCCAATCTCCCAAGGAGCAGGSGT
H E L I M K D G R V L V V P C R N Q D E L I G R A R I S Q G A G W

9810 9820 9830 9840 9850 9860 9870 9880 9890 9900
GTCTTTGCGGGAGACGGCTGTTGGGGAGTCTTACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGCGGCAATGCTATT
S L R E T A C L G K S Y A Q M W S L M Y F H R R D L R L A A N A I

9910 9920 9930 9940 9950 9960 9970 9980 9990 10000
TGCTCGGCACTACCATTCAGTTGGGTTCCAACAAGTCGAACACCTGGTCCATACATGCTAAACATGAATGATGACACGGAAGACATGCTGACAGTCT
C S A V P S H W V P T S R T T W S I H A K H E W M T T E D M L T V W

10010 10020 10030 10040 10050 10060 10070 10080 10090 10100
GGAACAGGCTGTGGATTCAAGAAAACCCATGGATGGAAGACAAAACCTCCAGTGGAAATCATGGGAGGAAATCCCATACTTGGGGAAGAGAGACCAATG
N R V W I Q E N F W M E D K T P V E S W E E I P Y L G K R E D Q W

10110 10120 10130 10140 10150 10160 10170 10180 10190 10200
GTGCGGCTCATTGATTGGGTTAAACAAGCAGGGCCACCTGGGCAAGAACATCCAAGCAGCAATAAATCAAGTTAGATCCCTTATAGGCAATGAAGAATAC
C G S L I G L T S R A T W A K N I Q A A I N Q V R S L I G N E E Y

10210 10220 10230 10240 10250 10260 10270 10280 10290 10300
ACAGATTACATGCCATCCATGAAAAGATTCAAGAGAGAAGAGGAAGAGCAGGAGTCTGTGGTAGAAGCAAACTAACATGAAACAGGCTAGAAATC
T D Y M P S M K R F R R E E E A G V L W *

10310 10320 10330 10340 10350 10360 10370 10380 10390 10400
AGGTCGGATTAAAGCATAGTACGGAAAAAATATGCTACCTGTGAGCCCGTCCAAAGGACGTTAAAGAAAGTCAGGCCATCATAAATGCCATAGCTTGAG
10410 10420 10430 10440 10450 10460 10470 10480 10490 10500
TAAACTATGCAGCCTGTAGCTCCACCTGAGAAGGTGTAATAAATCCGGGAGGCCAATAACCATGGAAGCTGTACGCAATGGCGTAGTGGACTAGCGGTTAG

10510 10520 10530 10540 10550 10560 10570 10580 10590 10600
AGGAGACCCCTCCCTTACAAATCGCAGCAACATGGGGCCCAAGCGGAGATGAAGCTGTAGTCTGCTGGAAGGACTAGAGGTTAGAGGAGACCCCCCC

10610 10620 10630 10640 10650 10660 10670 10680 10690 10700
GAAACAAAAACAGCATATTGACGCTGGGAAAGACAGAGATCCTGCTGCTCCTCAGCATCATTCAGGGCACAGAACCCAGAAATGGAATGGTGTCTG

10710

DENVax-4主宰種病毒(MVS)

[0167]嵌合式病毒基因體之核苷酸序列及轉譯蛋白質之推定胺基酸序列。大部分prM-E基因(nt-457至-2379，下方畫線)為野生型(wt) DEN-4 1036病毒專一性；其餘核苷酸序列為DEN-2 PDK-53病毒專一性。標記出與野生型病毒(DEN-3 16562或DEN-2 16681)不同的全部基因改造取代，以及額外突變(從基因改造cDNA純株改變)。

含括於基因體及蛋白質之取代：

[0168]接合位置：

a. MluI (nt 451-456): 基因改造無聲突變，nt-453 A-to-G

b. NgoMIV (nt 2380-2385): 基因改造突變，nt-2381/2382 TG-to-CC (導致E-482 Val-to-Ala改變)

[0169]D2 PDK-53病毒骨架(從wt D2 16681)改變

a. 5'-非編碼區(NCR)-57 (nt-57 C-to-T)：主要減毒基因座(紅色)

b. NS1-53 Gly-to-Asp (nt-2579 G-to-A)：主要減毒基因座(紅色)

c. NS2A-181 Leu-to-Phe (nt-4018 C-to-T，粗體)

d. NS3-250 Glu-to-Val (nt-5270 A-to-T)：主要減毒基因座(紅色)

e. nt-5547 (NS3基因) T-to-C無聲突變(粗體)

f. NS4A-75 Gly-to-Ala (nt-6599 G-to-C，粗體)

*PDK-53之nt-8571 C-to-T無聲突變於疫苗病毒中係未

經基因改造

[0170]於cDNA純株之基因改造取代

a.基因改造C-100 Arg-to-Ser (nt-396 A-to-C)：可改善於培養中的病毒複製

b.基因改造nt-1401 A-to-G無聲突變

c.基因改造E-364 Ala-to-Val (nt-2027 C-to-T)：可改善於培養中的病毒複製

d.基因改造E-447 Met-to-Leu (nt-2275 A-to-C)：可改善於培養中的病毒複製

[0171]於疫苗種病毒出現的額外取代(與原先純株差異0.06% nt)

a. nt-225 (C基因) A-to-T無聲突變(粗體)

b. NS2A-66 Asp-to-Gly (nt-3674 A-to-G)突變(粗體)

c. NS2A-99 Lys-to-Lys/Arg mix (nt-3773 A-to-A/G混合，粗體)

d. nt-5391 C-to-T (NS3基因)無聲突變(粗體)

e. NS4A-21 Ala-to-Val (nt-6437 C-to-T，粗體)

f. nt-7026 T-to-C/T混合無聲突變(粗體)

g. nt-9750 A-to-C無聲突變(粗體)

NCR-57-T, D2 PDK-53 滅毒基因座 : (wt D2 16681: C)

> 5'-非編碼區

10 20 30 40 50 60 70 80 90 100

AGTTGTTAGTCTACGTGGACCGACAAAGACAGATTCTTTGAGGGAGCTAAGCTCAATGTAGTTCTAACAGITTTTATATTAGAGAGCAGATCTCTGATGA

M N

110 120 130 140 150 160 170 180 190 200

ATAACCAACGGAAGGCGAAACACGCTTTCAATATGCTGAAACSCGAGAGAAACCGCGTGTGCACTGTGCAACAGCTGACAAAGAGATTCTCACT

N Q R K K A K N T P F N M L K R E R N R V S T V Q Q L T K R F S L

210 220 230 240 250 260 270 280 290 300

TGGAATGCTGACGGGACGAGGACCTTTAAACTGTTTCATGGCCCTGGTGGCGTTCCTTCGTTTCTAACCAATCCACCAACAGCAGGGATATTGAAGAGA

G M L Q G R G P L K L F M A L V A F L R F L T I P P T A G I L K R

於主宰及前主宰種病毒之額外 nt-225 A-to-T 無聲突變

310 320 330 340 350 360 370 380 390 400

TGGGGAACAATTAATAATCAAAAGCTATTATGTTTGGAGAGGGTTCAGGAAAGAGATTGGAAGGATGCTGAACATCTTGAATAGGAGACGACGCTCTG

W G T I K K S K A I N V L R G F R K E I G R M L N I L N R R R S S A

基因改造 C-100 Arg-to-Ser (nt 396 A-to-C)

> p-M D4 1036 序列之起點

410 420 430 440 450 460 470 480 490 500

CAGGCATGATGATTATGCTGATTCCAACAGTGATGGCGTTCATTAAACCTTCGCTGATGGCGAACCCCTCATGATAGTGGCAAAACATGAAAGGGCGAG

G M I I M L I P T V M A F H L T T R D G E P L M I V A K H E R G R

基因改造 M111 剪接位置 (nt-453 A-to-G 無聲 :)

510 520 530 540 550 560 570 580 590 600

ACCTCTCTTGTTTAAGACACAGAGGGGATCAACAAATGCACCTCTCATTTGCCATGGACTTGGGTGAATGTGTGAGGACACTGTCCACTATAAATGCCCC

P L L F K T T E G I N K C T L I A M D L G E M C E D T V T Y K C P

610 620 630 640 650 660 670 680 690 700

TTACTGGTCAATACCGAACTGAAGACATTGATTGCTGGTGGCAATCTCACGTTCTACCTGGGTCATGTATGGGACATGCACCCAGAGCGGAGAACGGAGAC

L L V N T E P E D I D C W C N L T S T W V M Y G T C T Q S G E R R R

> M

710 720 730 740 750 760 770 780 790 800

GAGAGAGCGCTCAGTAGTTTAACACCACTTACGAATGGGATTGGAAACAAGAGCTGAGACATGGATGTCATCGGAACGGGCTTGGAGACATCGGTCG

E K R S V A L T P H S G M G L E T R A E T W M S S E G A W K H A Q

810 820 830 840 850 860 870 880 890 900

GAGACTAGAGAGCTGGATACTCAGAAACCCAGGATTTCGCSCTCTTGGCAGGATTTATGGCTTATATGATTGGGCAACAGGAATCCAGCGAACTGTCTTC

R V E S W I L R N P G F A L L A G F M A Y M I G Q T G I Q R T V F

> E

910 920 930 940 950 960 970 980 990 1000

TTTCTCTTAATGATGCTGGTCCGCCCATCTTACGGATGCGATGCGTAGGAGTAGGAACACAGAGACTTTGTGGAAGGAGTCTCAGGTGGAGCATGGGTGC

F V L M M L V A P S Y G M R C V G V G N R D F V E G V S G G A W V D

1010 1020 1030 1040 1050 1060 1070 1080 1090 1100

ATCTGGTCTTGAACATGGAGGATGCGTCCACACCAATGGCCAGGAAACCAACCTTGGATTTTGAACCTGACTAAGACAACAGCAAGGAAGTGGCTCT

L V L E H G G C V T T M A Q G K P T L D F E L T R K T T A K E V A L

1110 1120 1130 1140 1150 1160 1170 1180 1190 1200

GTTAAGACCTATTCATTTGAAGCTCAATATCAACATTAACACCGCAACAAGATGTCACGCAAGGAGAGCCCTTATCTAAAGAGGAAACAGACCAA

L R T Y C I E A S I S N I T T A T R C P T Q G E P Y L K E E Q D Q

1210 1220 1230 1240 1250 1260 1270 1280 1290 1300

CAGTACATTTGCCGAGAGATGTGGTAGACAGAGGGTGGGCAATGGCTGTGGCTTGTGTTGAAAAGGAGGAGTTGTGACATGTGGAAGTTTTCATGTT

Q Y I C R R D V V D R G W G N G C G L F G K G G V V T C A K F S C S

1310 1320 1330 1340 1350 1360 1370 1380 1390 1400

CGGGGAAGATAACAGGCAATTGGTCCAAATTGAGPACCTTGAATACACAGTGGTTGTAACAGTCCACATGGAGACACCCATGCAATAGGAAATGACAC

G K I T G N L V Q I E N L E Y T V V V T V H N G D T H A V G N D T

1410 1420 1430 1440 1450 1460 1470 1480 1490 1500

GTCCATCATGGATTTACAGCCACGATAACCTCCAGTCCACCATCGGTGGAAGTCAATTTGCCGACTATGGAGAACTAACACTCGATTGTGAACCCAGG

S N H G V T A T I T F R S P S V E V K L P D Y G E L T L D C E P R

於基因改造純株之無聲 nt 1401 A-to-G 突變

1510 1520 1530 1540 1550 1560 1570 1580 1590 1600

TCTGGAATTGACTTTAATGAGATGATTCTGATGAAATGAAAAAGAAAACATGGCTTGTGCATAGCAATGTTTTTGGATCTACCTTACCATGGACAG

S G I D F N E M I L M K M K K K T W L V H R Q W F L D L P L P W T A

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700

CAGGAGCAGACATCAGAGGTTCACTTGAATTACAAAGAGAGATGTTGACATTTAAGGTTTCTCATGCCAAGAGACAGGATGTGACAGTGTGGGATC

G A D T S E V H W N Y K E R M V T F K V P H A K R Q D V T V L G S

1710 1720 1730 1740 1750 1760 1770 1780 1790 1800

TCAGGAAGAGCCATGCAATTTGCCCTCGCTGGAGCCACAGAATGGACTCCGCTGATGGAATCAGATGTTTTCAGGACATCTCAAGTGCAAGATCCGT

Q E G A M H S A L A G A T E V D S G D G N H M F A G H L K C K V R

1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
ATCGAGAAATTGAGAAATCAAGGGAATGTCTATACACGATGTGTTTCAAGGAAAGTTCTCAATTGACAAAGAGATGGCAGAAAACACAGCATGGGACACAGTGG
M E K L R I K G M S Y T M C S G K F S I D K E M A E T Q H G T T V V
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000
TGAAGTCAAGTATGAAGTCTCTGGAGCTCCGTGTAAAGTCCCATAGAGATAAGAGATGTGAAACAGGAAAAAGTGGTTGGCGGTATCATCTCATCCAC
K V K Y E G A G A P C K V P I E I R D V N K E K V V G R I I S S T
2010 2020 2030 2040 2050 2060 2070 2080 2090 2100
CCCTTTGGCTGAGAAATACCAACAGTGTAAACCAACATAGAGTTAGAACCCCCCTTTGGGGACAGCTACATAGTGATAGGTGTGGAAACAGTGCATTAAACA
P L A E N T N S V T N I E L E P P F G D S Y I V I G V G N S A L T

基因改造 E-364 Ala-to-Val (nt-2027 C-to-T) 以改善培養中之病毒生長

2110 2120 2130 2140 2150 2160 2170 2180 2190 2200
CTCCATTGGTTTCAGGAAAGGAGTTCCATTGGCAAGATGTTTGAGTCCACATACAGAGGTGCAAAACGAATGGCCATTCTAGTGAACACAGCTTGGGATT
L H W F R K G S S I G K M F E S T Y R G A K R M A I L G E T A W D F
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
TTGGTTCCGTTGGTGGACTGTTTCACATCATTTGGGAAAGGCTGTGCACCCAGGTTTTTGGAAAGTGTGTATACAACCCCTGTTTGGAGGAGTCTCATGGATGAT
G S V G G L F T S L G K A V H Q V F G S V Y T T L F G G V S W M I

基因改造 E-447 Met-to-Leu (nt-2275 A-to-C) 突變

D4 1036 序列之終點

2310 2320 2330 2340 2350 2360 2370 2380 2390 2400
TAGAATCCTAATTGGGTTCCCTAGTGTGTTGGATTGGCAGCACTCAAGGAACACTTCAATGGCTATGACGTGCATAGCTGCCGSCATTGTGACACTGTAT
R I L I G F L V L W I G T N S R N T S M A M T C I A A G I V T L Y

基因改造 NcoMIV 剪接位置, E-482 Val-to-Ala (nt-2381/2382 TC-to-CC)

> NS1
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500
TTGGGGTTCATGGTGCAGGCCGATAGTGGTTGCGTTGTGAGCTGGGAAACAAAGAACTGAAATGTGGCAGTGGGATTTCATCAGACAACTGTGCACA
L G V M V Q A D S G C V V S W K N K E L K C G S G I F I T D N V H T
2510 2520 2530 2540 2550 2560 2570 2580 2590 2600
CATGACACAGAACATACAGTTCACACCAAGATCCCTTCAAACTAGCTTCAGCTATCCAGAAAGCCATGAAGAGGACATTTGTGGAATCCGCTCAGT
W T E Q Y K F Q P E S P S K L A S A I Q K A H E E D I C G I R S V

D2 EDK-53 NS1-53-Asp 減毒基因座 (wt D2 16681: Gly, nt-2579-G)

2610 2620 2630 2640 2650 2660 2670 2680 2690 2700
AACAAAGCTGGGAAATTCATGTGGAAACAAATAACACCAAGATTAATACATTCATACAGAAATGAGGTGAAGTTAACTATTATGACAGGAGACATC
T R L E N L M W K Q I T P E L N H I L S E N E V K L T I M T G D I
2710 2720 2730 2740 2750 2760 2770 2780 2790 2800
AAAGGAATCATGACGAGGAGAAACAGATCTCTCGGGCTCAGCCCACTGAGCTGAGGTATTCATGGAAACATGGGGCAAAGCAAAATGCTCTCTACAG
K G I M Q A G K R S L R P Q P T E L K Y S W K T W G K A K M L S T E
2810 2820 2830 2840 2850 2860 2870 2880 2890 2900
AGTCTCATTAACAGACCTTTCTCATGTATGGCCCCGAAACAGCAGAAATGCCCAACACAAATAGAGCTTGGAAATCGTTGGAAAGTTGAAGACTATGGCTT
S H N Q T F L I D G P E T A E C P N T N R A W N S L E V E D Y G F
2910 2920 2930 2940 2950 2960 2970 2980 2990 3000
TGGAGTATTACACCAATATATGGCTAAAATTGAAGAAACAGGATGTATTCTGCGACTCAAACTCATGTACGCGGCCATAAAGACAACAGAGGCC
G V F T T N I W L K L K E K Q D V F C D S K L M S A A I K D N R A
3010 3020 3030 3040 3050 3060 3070 3080 3090 3100
GTCCATCCGATATGGGTTATTGGATAGAAAGTGCACCTCAATGACACATGGAAGATAGAGAAAGGCTCTTTCATTGAAGTTAAAAGTGGCACTGGCCAA
V H A D M G Y W I E S A L N D T W K I E K A S F I E V K N C H W P K
3110 3120 3130 3140 3150 3160 3170 3180 3190 3200
AATCACACACCCCTCTGGAGCAATGGAGTGTCTAGAAAGTGAAGATGAATTCCAAAGAACTCTCGCTGGACCACTGTCTCAACACAACTATAGACCAGGCTA
S H T L W S N G V L E S E M I I P K N L A G F V S Q H N Y R P G Y
3210 3220 3230 3240 3250 3260 3270 3280 3290 3300
CCATACACAAATACAGACCATGGCATCTAGGTAAAGTTGAGATGGACTTTGATTTCTGTGATGGAACACAGTGGTAGTGACTGAGGACTGCGGAAAT
H T Q I T G P W H L G K L E M D F D F C D G T T V V V T E D C G N
3310 3320 3330 3340 3350 3360 3370 3380 3390 3400
AGAGGACCCCTTTTGAAGAACCACTGCTCTGGAAACTCATACAGAAATGGTGTGCGGATCTTGCACATTACCAACCGCTAGATACAGAGGTGAGG
R G P S L R T T T A S G K L I T E W C C R S C T L P P L R Y R G E D

> NS2A

3410 3420 3430 3440 3450 3460 3470 3480 3490 3500

ATGGGGTCTGGTACGGGATGGAAATCAGACCATTTGAAGGAGAAAGAGAAATTTGGTCAACTCCTTGGTCACAGCTGGACATGGGCAGGTGCGAACCTT
G C W Y G M E I R P L K E K E N L V N S L V T A G H G Q V D N F

3510 3520 3530 3540 3550 3560 3570 3580 3590 3600
TTCACCTAGGAGTCTTGGGAATGGCATTTGTCTCTGGAGGAAATGCTTAGGACCCGAGTAGGABCGAAACATGCAATCTACTAGTTGCAGTTTCTTTTGTG
S L G V L G M A L F L E E M L R T R V G T K H A I L L V A V S F V

3610 3620 3630 3640 3650 3660 3670 3680 3690 3700
ACATTGATCACAGGGAACATGTCTTTAGAGACCTGGGAGAGATGATGGTTATGGTAGGCGCCACTATGACGGGTGACATAGGTATGGGCGTGACTTATC
T L I T G N M S F R D L G R V M V M V G A T M T G D I G M G V T Y L

於主宰及前主宰種病毒之額外 NS2A-66 Asp-to-Gly (nt-3674 A-to-G 突變)

3710 3720 3730 3740 3750 3760 3770 3780 3790 3800
TTGCCCTACTAGCAGCTTCAAAGTCAGACCACTTTTGLAGCTGGACTACTCTTGAGAAAGCTGACCTCCAGGGAATTTGATGATGACTACTATAGGAAT
A L L A A F K V R P T F A A G L L L R K L T S K E L M M T T I G I

於主宰種病毒之額外 NS2A-99 K to R/K(混合) (nt-3773 A-to-G/A 突變)

3810 3820 3830 3840 3850 3860 3870 3880 3890 3900
TGTACTCTCTCCAGAGCACCATACCAGAGCCATTCTTGAGTTGACTGATCGGTTAGGCTTAGGCATGATGGTCTCAAATGGTGAGAAATATGGAA
V L L S Q S T I P E T I L E L T D A L A L G N M V L K M V R N M E

3910 3920 3930 3940 3950 3960 3970 3980 3990 4000
AAGTATCAATTGGCAGTGACTATCATGGCTATCTTGCGCTCCCAACCGCAGTGATATTACAAACCGCATGGAAGTGAGTTGCACATATTGGCAGTGG
R Y Q L A V T I M A I L C V P N A V I L Q N A W K V S C T I L A V V

4010 4020 4030 4040 4050 4060 4070 4080 4090 4100
TGTCCTTTCCCACTGTTCTTAACATCTTCACAGCAAAACAGATTGGATACCATTTAGCATTGACGATCAAGGTCTCAATCCACAGCTATTTTTCT
S V S P L F L T S S Q K T D W I P L A L T I K G L N P T A I F L

D2 PDK-53 專一性: NS2A-181-Phe (wt D2 16681: Leu, nt-4018-C)

> NS2B

4110 4120 4130 4140 4150 4160 4170 4180 4190 4200
AACAACTCTCTCAAGAACAGCAAGAAAGGAGCTGGCCATTAAATGAGCCTATCATGGCAGTCGGGATGGTGAGCATTTAGCCAGTTCTCTCTCAAAA
T T L S R T S K K R S W F L N E A I M A V G M V S I L A S S L K

4210 4220 4230 4240 4250 4260 4270 4280 4290 4300
AATGATATTTCCCATGACAGGACCATTAGTGGCTGGAGGGCTCCTCACTGTGTGCTACGTGCTCACTGGACGATCGGCCGATTGGAACTGGGAGAGAGCAG
N D I P M T G P L V A G G L L T V C Y V L T G R S A D L E L E R A A

4310 4320 4330 4340 4350 4360 4370 4380 4390 4400
CCGATGTCAAATGGGAAGACCGAGGATATCAGGAAGCAGTCCAAATCCTGTCAATAACATATCAGAAGATGGTAGCATGCGATAAAAAATGAAGA
D V K W E D Q A E I S G S S P I L S I T I S E D G S M S I K N E E

4410 4420 4430 4440 4450 4460 4470 4480 4490 4500
CGAAGAACAACTACTGACCATCTCATTTAGAACAGGATTGCTGGTATCTCAGGACTTTTTCCTGTATCAATACCAATCACGGCAGCAGCATGGTACCTG
E E Q T L T I L I R T G L L V I S G L F P V S I P I T A A A W Y L

> NS3

4510 4520 4530 4540 4550 4560 4570 4580 4590 4600
TGGGAAGTGAAGAAACAACCGGCCGGAGTATTGTGGGATGTTCTTCCACCCCAACCCATGGGAAGGCTGAACTGGAAGATGGAGCCTATAGAATTAAAGC
W E V K K Q R A G V L W D V P S P P P M G K A E L E D G A Y R I K Q

4610 4620 4630 4640 4650 4660 4670 4680 4690 4700
AAAAAGGGATICTTGGATATTCCAGATCGGAGCCGGAGTTTACAAAGAGGAACATTCCATACATGTGGCATGTACACAGTGGCGCTGTICTAATGCA
K G I L G Y S Q I G A G V Y K E G T F H T M W H V T R G A V L M H

4710 4720 4730 4740 4750 4760 4770 4780 4790 4800
TAAAGGAAAGAGGATTGAACCATCATGGSCGGACGTCAAGAAAGACCTAATATCATATGGAGGAGGCTGGAAGTTAGAAGGAGAATGGAAGGAAGGAGAA
K G K R I E P S W A D V K K D L I S Y G G G W K L E G E W K E G E

4810 4820 4830 4840 4850 4860 4870 4880 4890 4900
GAAGTCCAGGTATTGGCACTGGAGCCTGGAAAAAATCCAGAGCCGTCCAAACGAAACCTGGTCTTTTCAAACCAACGCCGGAACAAATAGGIGCTGTAT
E V Q V L A L E P G K N P R A V Q T K P G L F K T N A G T I G A V S

4910 4920 4930 4940 4950 4960 4970 4980 4990 5000
CTCTGGACTTTTCTCTGGAACGTCCAGGATCTCCAATTATCGACAAAAAAGGAAAGTTGTGGGTCTTTATGGTAATGGTGTGTACAAAGGAGTGGAGC
L D F S P G T S G S P I I D K K G K V V G L Y G N G V V T R S G A

5010 5020 5030 5040 5050 5060 5070 5080 5090 5100
ATATGTGAGTGCTATAGCCCACTGAAAAGCATTGAAGACACCCAGAGATCGAAGATGACATTTCCGAAAGAGAAAGACTGACCATCATGGACCTC
Y V S A I A Q T E K S I E D N P E I E D D I F R K R R L T I M D L

5110 5120 5130 5140 5150 5160 5170 5180 5190 5200
CACCAGGAGCGGGAGAGACGAAGAGATACCTTCGGCCATAGTCAGAGAAAGCTATAAAACGGGGTTTGAGAACATTATCTTGCCCCCCTAGAGTTG
H P G A G K T K R Y L P A I V R E A I K R G L R T L I L A P T R V V
5210 5220 5230 5240 5250 5260 5270 5280 5290 5300
TGGCAGCTGAATGAGAGAGCCCTTAGAGGACTTCCAATAAGATACAGACCCAGCCATCAGAGCTGTGCACACCGGGCGGAGATTGTGAGCCTAAT
A A E M E E A L R G L P I R Y Q T P A I R A V H T G R E I V D L M

D2 PDK-53 NS3-250-Val 減毒基因座 (D2 16681: Glu, nt-5270-A)

5310 5320 5330 5340 5350 5360 5370 5380 5390 5400
GTGTCATGCCACATTTACCATGAGGCTGCTATCACCAGTTAGAGTGCCAACTACAACCTGATTATCATGGACGAGGCCATTTCCAGATCCAGCAAGT
C H A T F T M R L L S P V R V P N Y N L I I M D E A H F T D P A S

於主率及前主率種病毒之額外 nt-5391 C-to-T 無聲突變

5410 5420 5430 5440 5450 5460 5470 5480 5490 5500
ATAGCAGCTAGAGGATACATCTCAACTCGAGTGGAGATGGGTGAGGCAGCTGGGATTTTATGACAGCCACTCCCCCGGGAAGCAGAGACCCATTTCCCTC
I A A R G Y I S T R V E M G E A A G I F M T A T P P G S R D P F P Q

5510 5520 5530 5540 5550 5560 5570 5580 5590 5600
AGAGCAATGCACCAATCATAGATGAAGAAAGAGAAATCCCTGAACGCTCGTGGAAATCCGGACATGAATGGGTACGCGATTTTAAAGGGAAGACTGTTTG
S N A P I I D E E R E I P E R S W N S G H E W V T D F K G K T V W

D2 PDK-53 專一性無聲突變 nt-5547-C (D2 16681: T)

5610 5620 5630 5640 5650 5660 5670 5680 5690 5700
GTTCGTTCCAAGTATAAAAGCAGGAATGATATAGCAGCTTGCCCTGAGGAAAAATGGAAGGAAGTGATCACTCAGTAGGAGACCTTTGATTCTGAG
F V P S I K A G N D I A A C L R K N G K K V I Q L S R K T F D S E

5710 5720 5730 5740 5750 5760 5770 5780 5790 5800
TATGTCAGACTAGAACCAATGATTGGGACTTCGTGGTTACAACCTGACATTTAGAAATGGGTGCCAATTTCAAGSCTGAGAGGGTTATAGACCCAGAC
Y V K T R T N D W D F V V T T D I S E M G A N F K A E R V I D P R R

5810 5820 5830 5840 5850 5860 5870 5880 5890 5900
GCTGCATGAAACCACTCATACTAACAGATGGTGAAGAGCGGGTGATTTCTGGCAGGACCTATGCCAGTGACCCACTCTAGTGACGACAAAGAGAGGGAG
C M K P V I L T D G E E R V I L A G P M P V T H S S A A Q R R G R

5910 5920 5930 5940 5950 5960 5970 5980 5990 6000
AATAGGAAGAAATCCAAAAATGAGAATGACCACTATACATGSGGGAACCTCTGGAAATGATGAAGACTGTGCACACTGGAAAGAGCTAATAATG
I G R N P K N E N D Q Y I Y M G E P L E N D E D C A H W K E A K M

6010 6020 6030 6040 6050 6060 6070 6080 6090 6100
CTCCTAGATAACATCAACACGCCAGGAATCATTCCTAGCATGTTTCCGAACAGAGCGTGAAAGGTGGATGCCATTGATGGGGAATACCGCTTGAGAG
L L D N I N T P E G I I P S M F E P E R E K V D A I D G E Y R L R G

6110 6120 6130 6140 6150 6160 6170 6180 6190 6200
GAGAAGCAAGGAAACCTTTGTAGACTTAATGAGAAGAGGAGACCTACCACTCTGGTGGCCTACAGAGTGGCAGCTGAAGGCATCAGTACGCAGACAG
E A R K T F V D L M R R G D L P V W L A Y R V A A E G I N Y A D R

6210 6220 6230 6240 6250 6260 6270 6280 6290 6300
AAGGTGGTGTGTTTGTATGGAGTCAAGAACAAACCAATCCTAGAAAGAAACGTTGAAATCTGGACAAAAGAGGGGAAAGGAATTTGAAACCC
R W C F D G V K N N Q I L E E N V E V E I W T K E G E R K K L K P

> NS4A

6310 6320 6330 6340 6350 6360 6370 6380 6390 6400
AGATGGTTGGATGCTAGGATCTATTCTGACCCACTGGCGCTAAAAGAAATTAAGGAATTTGCAGCCGGAAGAAAGTCTCTGACCCCTGAACCTAATACAG
R W L D A R I Y S D P L A L K E F K E F A A G R K S L T L N L I T E

6410 6420 6430 6440 6450 6460 6470 6480 6490 6500
AARTGGGTAGGCTCCCAACCTTCATGACTCAGAGGTAAGAGACGCACTGGACAACTAGCAGTGTGCACACGGCTGAGGCAGGTGAAGGGCGCTACAA
M G R L P T F M T Q K V R D A L D N L A V L H T A E A G G R A Y N

於主率及前主率種病毒之額外 NS4A-21 Ala-to-Val (nt-6437 C-to-T)突變

6510 6520 6530 6540 6550 6560 6570 6580 6590 6600
CCATGCTCTCAGTGAACCTGCCGGAGACCTGAGAGACATTGCTTTTACTGACACTCTGGCTACAGTCACGGGAGGGATCTTTTATTCTTGATGAGCGCA
H A L S E L P E T L E T L L L T L L A T V T G S I F L F L M S A

D2 PDK-53 專一性 NS4A-75-Ala (wt D2 16681: Gly, nt-6599-G)

6610 6620 6630 6640 6650 6660 6670 6680 6690 6700
AGGGGCATAGGGAAGATGACCCCTGGGAATGTGCTGCATAATCACGCTAGCATCCTCTATGTTACGCACAAAACACGCCACACTGGATAGCAGCTCAA
R G I G K M T L G M C C I I T A S I L L W Y A Q I Q P H W I A A S I

6710 6720 6730 6740 6750 6760 6770 6780 6790 6800
TAATACTGGGTTTTTCTCATAGTTTGTCTTATTCAGAACCTGAAAAACAGAGAACACCCCAAGACCAACCACTGACCTACGTTGTCTATAGCCATCTCT

I L E F F L I V L L I P E P E K Q R T P Q D N Q L T Y V V I A I L

> NS4B

6810 6820 6830 6840 6850 6860 6870 6880 6890 6900
CACAGTGGTGGCCGCAACCATGGCAACGAGATGGGTTTCCTAGAAAAACGAAGAAGATCTCGGATTGGGAGCATTGCAACCCGCAACCCGAGAGC
T V V A A T M A N E M G F L E K T K K D L G L G S I A T Q Q P E S

6910 6920 6930 6940 6950 6960 6970 6980 6990 7000
AACATCCTGGACATAGATCTACGTCTCGATCAGCATGGACGCTGTATGCCGTGGCCACACACATTGTTACACCAATGTTGAGACATAGCATTGAAATT
N I L D I D L R P A S A W T L Y A V A T T F V T P M L R H S I E N S

7010 7020 7030 7040 7050 7060 7070 7080 7090 7100
CCTCAGTGAATGTGTCCCTAACAGCCATAGCCACCAAGCCACAGTGTAAATGGGTCTCGGGAAGGATGGCCATTGTCAAGATGGACATCGGAGTTCC
S V N V S L T A I A N Q A T V L M G L G K G W P L S K M D I G V P

I

於主宰及前主宰種病毒之額外 nt-7026 T-to-C/T 混合無聲突變

7110 7120 7130 7140 7150 7160 7170 7180 7190 7200
CCTTCTCGCCATTGGATGCTACTCACAAGTCAACCCCATAACTCTCAGCAGCTCTTTTCTTATTGGTAGCATTATGCCATCATAGGGCGAGGACTC
L L A I G C Y S Q V N P I T L T A A L F L L V A H Y A I I G P G L

7210 7220 7230 7240 7250 7260 7270 7280 7290 7300
CAAGCAAAAGCAACAGAGAGCTCAGAAAAGACGAGCGGGCGGCATCATGAAAAACCACTGTCGATGGGAATAACAGTGATTGACCTAGATCCCAATAC
Q A K A T R E A Q K R A A A G I M K N P T V D G I T V I D L D P I P

7310 7320 7330 7340 7350 7360 7370 7380 7390 7400
CTTATGATCCAAAGTTGAAAAGCACTTGGGACAAAGTAATGTCTCTAGTCCCTGCTGACTCAAGTATTGATGATGAGGACTACATGGGCTCTGTGTGA
Y D P K F E K Q L G Q V M L L V L C V T Q V L M M R T T W A L C E

7410 7420 7430 7440 7450 7460 7470 7480 7490 7500
GGCTTTAACCTTAGCTACCGGGCCCATCTCCACATTGTGSSAAGGAAATCCAGGAGGTTTTGGAACTACTACCATTCGCGTGTCAATGGCTACATTTT
A L T L A T G P I S T L W E G N P G R F W N T T I A V S M A N I F

> NS5

7510 7520 7530 7540 7550 7560 7570 7580 7590 7600
AGAGGGAGTTACTTGGCCGAGAGTGGACTTCTCTTTTCATTATGAAGACACAAACCAAGAGGGGAAGTGGCAACATAGGAGAGCGTTGGAG
R G S Y L A G A G L L F S I M K N T T N T R R G T G N I G E T L G E

7610 7620 7630 7640 7650 7660 7670 7680 7690 7700
AGAAATGGAAGCCGATTGAACGCAATTGGGAAAAAGTGAATTCAGATCTACAAGAAAAGTGGAAATCCAGGAAGTGGATAGAACCTTAGCAAAAGAGG
K W K S R L N A L G K S E F Q I Y K K S G I Q E V D R T L A K E G

7710 7720 7730 7740 7750 7760 7770 7780 7790 7800
CATTAAAGAGGAGAAACGGACCATCACGCTGTGTGCGGAGGCTCAGCAAACTGAGATGGTTCGTTGAGAGAAACATGGTCACACCAGAGGGGAAAGTA
I K R G E T D H H A V S R G S A K L R W F V E R N M V T P E G K V

7810 7820 7830 7840 7850 7860 7870 7880 7890 7900
GTGGAGCTCGGTGTGGCAGAGGAGGCTGTCTACTATTGTGGAGGACTAAAGAAATGTAAGAGAGATCAAGGCCCTAACAAAAGGAGGACAGGACAG
V D L G C G R G G W S Y Y C G G L K N V R E V K G L T K G G P G H E

7910 7920 7930 7940 7950 7960 7970 7980 7990 8000
AAGAACCCTCCCATGTCAACATATGGGTGGAATCTAGTGGCTCTCAAAGTGGAGTTGACGTTTCTTCATCCCGCCAGAAAAGTGTGACACATPATP
E P I P M S T Y G W N L V R L Q S G V D V F F I P P E K C D T L L

8010 8020 8030 8040 8050 8060 8070 8080 8090 8100
GTGTGACATAGGGGAGTCATCACCAATCCACAGTGGAGCGAGGACGACACTCAGAGTCCCTTAAGTCTAGTAGAAATTTGGTTGAACCAACACCTCAA
C D I G E S S P N P T V E A G R T L R V L N L V E N W L N N N T Q

8110 8120 8130 8140 8150 8160 8170 8180 8190 8200
TTTTCATAAAGGTTCTCAACCATATATGCCCTCAGTCATAGAAAAATGGAAGCACTACAAAGGAATATGGAGGAGCCTTAGTGAGGAAATCCACTCT
F C I K V L N P Y M P S V I E K M E A L Q R K Y G G A L V R N P L S

8210 8220 8230 8240 8250 8260 8270 8280 8290 8300
CACGAACTCCACATGAGATGTACTGGGTATCCAAATGCTTCGGGGAACATAGTGTATCAGTGAACATGATTTCAGGATGTGTATCAACAGATTAC
R N S T H E M Y W V S N A S G N I V S S V N M I S R M L I N R F T

8310 8320 8330 8340 8350 8360 8370 8380 8390 8400
AATGACATACAAGAAAGCCACTTACGAGCCGATGTTGACCTCGGAAGCGGACCCGTAACATCGGGATTGAAAGTGAGATACCAACCTAGATATAATT
M R Y K K A T Y E P D V D L G S G T R N I G I E S E I P N L D I I

8410 8420 8430 8440 8450 8460 8470 8480 8490 8500
GGGAAAGAAATAGAAAAATAAGCAAGAGCATGAACATCATGGCACTATGACCAAGACCCCATACAAAACGTGGGCATACCATGGTAGCTATGAAA
G K R I E K I K Q E H E T S W H Y D Q D H P Y K T W A Y H G S Y E T

8510 8520 8530 8540 8550 8560 8570 8580 8590 8600
CAAAACAGACTGGATCAGCATCATCCATGGTCAACGGAGTGGTCAGGCTGTGACAAAACCTTGGGACGTCGTCCTCCCATGGTGACACAGATGGCAATGAC
K Q T G S A S S M V N G V V R L L T K P W D V V F M V T Q M A M T

8610 8620 8630 8640 8650 8660 8670 8680 8690 8700
AGACACGACTCCATTGGACACACGCGCTTTTAAAGAGAAAGTGGACACGAGAACCCAGAACGAGGACGAGAACTAATGAAATTAACA
D T T P F G Q R V F K E K V D T R T Q E P K E G T K K L M K I T

8710 8720 8730 8740 8750 8760 8770 8780 8790 8800
GCAGAGTGGCTTTGGAAGAAATTAGGGAAGAAAAGACACCCAGGATGTGCACGAGAGAATTCACAGAAAGGTGAGAGCAATGCAGCCTTGGGG
A E W L W K Z L G K K K T P R M C T R E E F T R K V R S N A A L G A

8810 8820 8830 8840 8850 8860 8870 8880 8890 8900
CCATATTCACTGATGAGAACAGTGGAGTGGGACGTGAGGCTGTTGAAGATAGTAGGTTTGGGAGCTGGTTGACAAGGAAAGGAATCTCCATCTTGA
I F T D E N K W K S A R E A V E D S R F W E L V D K E R N L H L E

8910 8920 8930 8940 8950 8960 8970 8980 8990 9000
AGGAAAGTGTGAAACATGTGTACACATGATGGGAAAAGAGAGAAGAACTAGGGGAATTCGGCAAGGCAAAAGGCAGCAGAGCCATATGGTACATG
G K C E T C V Y N M M G K R E K K L G E F G K A K G S R A I W Y M

9010 9020 9030 9040 9050 9060 9070 9080 9090 9100
TGGCTTGGGACACGCTTCTTAGAGTTTGAAGCCCTAGGATTCTTAATAGAGATCACTGGTTCTCCAGAGAGAACTCCCTGAGTGGAGTGGAGAGAAAG
W L G A R F L E F E A L G F L N E D H W F S R E N S L S G V E G E G

9110 9120 9130 9140 9150 9160 9170 9180 9190 9200
GGCTGCACAAGCTAGTTACATTCTAAGAGACGTGAGCAAGAAAGAGGGAGCAATGTATGCCGATGACACCGCAGGATGGGATACAGAATCACACT
L H K L G Y I L R D V S K K E G G A M Y A D D T A G W D T R I T L

9210 9220 9230 9240 9250 9260 9270 9280 9290 9300
AGAAGACCTAAATAATGAAGAAATGGTAACCAACCATGGGAAGGAGACACAAGAACTAGCCGAGGCCATTTCAACTACGTACCAAAACAAGGTG
E D L K N E E M V T N H M E G E H K K L A E A I F K L T Y Q N K V

9310 9320 9330 9340 9350 9360 9370 9380 9390 9400
GTGCGTGTGCAAGACCAACACCAAGAGGCACAGTAATGGACATCATATCGAAGAGACCAAGAGGTAGTGGACAAAGTTGGACCTATGGATCAATA
V R V Q R P T P R G T V M D I I S R R D Q R G S G Q V G T Y G L N T

9410 9420 9430 9440 9450 9460 9470 9480 9490 9500
CTTTCACCAATATGGGAAGCCCACTAATCAGACAGATGGAGGGAGAAGGAGTCTTTAAAGCATTCAGCACCTAAACAATCACAGAAGAAATCGCTGTGCA
F T N M E A Q L I R Q M E G E G V F K S I Q H L T I T E E I A V Q

9510 9520 9530 9540 9550 9560 9570 9580 9590 9600
AAACTGGTTAGCAAGAGTGGGGCCGCAAGGTTATCAAGAATGGCCATCAGTGGAGATGATTGTGTTGTGAACCTTTAGATGACAGGTTCGCAAGCGCT
N W L A R V G R E R L S R M A I S G D D C V V K P L D D R F A S A

9610 9620 9630 9640 9650 9660 9670 9680 9690 9700
TTAAGAGCTTAAATGACATGGGAAGATTAGGAAGACATACACCAATGGGAACCTTCAAGAGGATGGAATGATTGGACACAAGTSCCTTCTGTTCAC
L T A L N D M G K I R K D I Q Q W E P S R G W N D W T Q V P F C S H

9710 9720 9730 9740 9750 9760 9770 9780 9790 9800
ACCATTTCATGAGTTATCATGAAGACGCTCGCTACTCCTGTTCCCTGTGAAACCAAGATGAAGTGAATGGCAGAGCCCGAATCTCCCAAGGAGC
H F H E L I M K D G R V L V V P C R N Q D E L I G R A R I S Q G A

於主率及前主率種病毒之額外 nt-9750 A-to-C 無聲突變

9810 9820 9830 9840 9850 9860 9870 9880 9890 9900
AGGGTGGTCTTTGGGGAGACGGCTGTTTGGGAAGTCTTACGCCCAATGTGGAGCTTGATGTACTTCCACAGACGCGACCTCAGGCTGGGGGCAAT
G W S L R E T A C L G K S Y A Q M W S L M Y F H R R D L R L A A N

9910 9920 9930 9940 9950 9960 9970 9980 9990 10000
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【符號說明】

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【序列表】

<110> 武田疫苗股份有限公司 (TAKEDA VACCINES, INC.)
<110> 美國政府，由衛生及公共服務部部長代表 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES)

<120> 用於疫苗中之登革熱病毒嵌合式建構物的組成物及方法

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Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
260 265 270

Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
275 280 285

Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
290 295 300

Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
305 310 315 320

Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
325 330 335

Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
340 345 350

Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
355 360 365

Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
370 375 380

Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
385 390 395 400

Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys
405 410 415

Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
420 425 430

Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
435 440 445

Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
450 455 460

Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
465 470 475 480

Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
485 490 495

Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn
500 505 510

Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
515 520 525

Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
530 535 540

Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala
545 550 555 560

Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
565 570 575

Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
580 585 590

Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
595 600 605

Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
610 615 620

Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
625 630 635 640

Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser
645 650 655

Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
660 665 670

Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
675 680 685

Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
690 695 700

Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
705 710 715 720

Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
725 730 735

Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
740 745 750

Thr Ser Leu Ser Met Met Cys Ile Ala Ala Ala Ile Val Thr Leu Tyr
755 760 765

Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
770 775 780

Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
785 790 795 800

His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
805 810 815

Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
820 825 830

Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
835 840 845

Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
850 855 860

Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
865 870 875 880

Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
885 890 895

Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
915 920 925

Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
930 935 940

Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
945 950 955 960

Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
965 970 975

Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
980 985 990

Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
995 1000 1005

Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
1010 1015 1020

Gly	Pro	Val	Ser	Gln	His	Asn	Tyr	Arg	Pro	Gly	Tyr	His	Thr	Gln
	1025					1030					1035			
Ile	Thr	Gly	Pro	Trp	His	Leu	Gly	Lys	Leu	Glu	Met	Asp	Phe	Asp
	1040					1045					1050			
Phe	Cys	Asp	Gly	Thr	Thr	Val	Val	Val	Thr	Glu	Asp	Cys	Gly	Asn
	1055					1060					1065			
Arg	Gly	Pro	Ser	Leu	Arg	Thr	Thr	Thr	Ala	Ser	Gly	Lys	Leu	Ile
	1070					1075					1080			
Thr	Glu	Trp	Cys	Cys	Arg	Ser	Cys	Thr	Leu	Pro	Pro	Leu	Arg	Tyr
	1085					1090					1095			
Arg	Gly	Glu	Asp	Gly	Cys	Trp	Tyr	Gly	Met	Glu	Ile	Arg	Pro	Leu
	1100					1105					1110			
Lys	Glu	Lys	Glu	Glu	Asn	Leu	Val	Asn	Ser	Leu	Val	Thr	Ala	Gly
	1115					1120					1125			
His	Gly	Gln	Val	Asp	Asn	Phe	Ser	Leu	Gly	Val	Leu	Gly	Met	Ala
	1130					1135					1140			
Leu	Phe	Leu	Glu	Glu	Met	Leu	Arg	Thr	Arg	Val	Gly	Thr	Lys	His
	1145					1150					1155			
Ala	Ile	Leu	Leu	Val	Ala	Val	Ser	Phe	Val	Thr	Leu	Ile	Thr	Gly
	1160					1165					1170			
Asn	Met	Ser	Phe	Arg	Asp	Leu	Gly	Arg	Val	Met	Val	Met	Val	Gly
	1175					1180					1185			
Ala	Thr	Met	Thr	Asp	Asp	Ile	Gly	Met	Gly	Val	Thr	Tyr	Leu	Ala
	1190					1195					1200			
Leu	Leu	Ala	Ala	Phe	Lys	Val	Arg	Pro	Thr	Phe	Ala	Ala	Gly	Leu
	1205					1210					1215			
Leu	Leu	Arg	Lys	Leu	Thr	Ser	Lys	Glu	Leu	Met	Met	Thr	Thr	Ile
	1220					1225					1230			
Gly	Ile	Val	Leu	Leu	Ser	Gln	Ser	Thr	Leu	Pro	Glu	Thr	Ile	Leu
	1235					1240					1245			

Glu	Leu	Thr	Asp	Ala	Leu	Ala	Leu	Gly	Met	Met	Val	Leu	Lys	Met
1250						1255					1260			
Val	Arg	Asn	Met	Glu	Lys	Tyr	Gln	Leu	Ala	Val	Thr	Ile	Met	Ala
1265						1270					1275			
Ile	Leu	Cys	Val	Pro	Asn	Ala	Val	Ile	Leu	Gln	Asn	Ala	Trp	Lys
1280						1285					1290			
Val	Ser	Cys	Thr	Ile	Leu	Ala	Val	Val	Ser	Val	Ser	Pro	Leu	Phe
1295						1300					1305			
Leu	Thr	Ser	Ser	Gln	Gln	Lys	Thr	Asp	Trp	Ile	Pro	Leu	Ala	Leu
1310						1315					1320			
Thr	Ile	Lys	Gly	Leu	Asn	Pro	Thr	Ala	Ile	Phe	Leu	Thr	Thr	Leu
1325						1330					1335			
Ser	Arg	Thr	Ser	Lys	Lys	Arg	Ser	Trp	Pro	Leu	Asn	Glu	Ala	Ile
1340						1345					1350			
Met	Ala	Val	Gly	Met	Val	Ser	Ile	Leu	Ala	Ser	Ser	Leu	Leu	Lys
1355						1360					1365			
Asn	Asp	Ile	Pro	Met	Thr	Gly	Pro	Leu	Val	Ala	Gly	Gly	Leu	Leu
1370						1375					1380			
Thr	Val	Cys	Tyr	Val	Leu	Thr	Gly	Arg	Ser	Ala	Asp	Leu	Glu	Leu
1385						1390					1395			
Glu	Arg	Ala	Ala	Asp	Val	Lys	Trp	Glu	Asp	Gln	Ala	Glu	Ile	Ser
1400						1405					1410			
Gly	Ser	Ser	Pro	Ile	Leu	Ser	Ile	Thr	Ile	Ser	Glu	Asp	Gly	Ser
1415						1420					1425			
Met	Ser	Ile	Lys	Asn	Glu	Glu	Glu	Asp	Gln	Thr	Leu	Thr	Ile	Leu
1430						1435					1440			
Ile	Arg	Thr	Gly	Leu	Leu	Val	Ile	Ser	Gly	Leu	Phe	Pro	Val	Ser
1445						1450					1455			
Ile	Pro	Ile	Thr	Ala	Ala	Ala	Trp	Tyr	Leu	Trp	Glu	Val	Lys	Lys
1460						1465					1470			

Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met
1475 1480 1485

Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys
1490 1495 1500

Gly Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu
1505 1510 1515

Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu
1520 1525 1530

Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys
1535 1540 1545

Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu
1550 1555 1560

Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly
1565 1570 1575

Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr
1580 1585 1590

Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly
1595 1600 1605

Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly
1610 1615 1620

Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser
1625 1630 1635

Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile
1640 1645 1650

Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu
1655 1660 1665

His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val
1670 1675 1680

Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro
1685 1690 1695

Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Glu	Glu	Ala	Leu	Arg	Gly	Leu
1700						1705					1710			
Pro	Ile	Arg	Tyr	Gln	Thr	Pro	Ala	Ile	Arg	Ala	Val	His	Thr	Gly
1715						1720					1725			
Arg	Glu	Ile	Val	Asp	Leu	Met	Cys	His	Ala	Thr	Phe	Thr	Met	Arg
1730						1735					1740			
Leu	Leu	Ser	Pro	Val	Arg	Val	Pro	Asn	Tyr	Asn	Leu	Ile	Ile	Met
1745						1750					1755			
Asp	Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser	Ile	Ala	Ala	Arg	Gly
1760						1765					1770			
Tyr	Ile	Ser	Thr	Arg	Val	Glu	Met	Gly	Glu	Ala	Ala	Gly	Ile	Phe
1775						1780					1785			
Met	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Arg	Asp	Pro	Phe	Pro	Gln	Ser
1790						1795					1800			
Asn	Ala	Pro	Ile	Ile	Asp	Glu	Glu	Arg	Glu	Ile	Pro	Glu	Arg	Ser
1805						1810					1815			
Trp	Asn	Ser	Gly	His	Glu	Trp	Val	Thr	Asp	Phe	Lys	Gly	Lys	Thr
1820						1825					1830			
Val	Trp	Phe	Val	Pro	Ser	Ile	Lys	Ala	Gly	Asn	Asp	Ile	Ala	Ala
1835						1840					1845			
Cys	Leu	Arg	Lys	Asn	Gly	Lys	Lys	Val	Ile	Gln	Leu	Ser	Arg	Lys
1850						1855					1860			
Thr	Phe	Asp	Ser	Glu	Tyr	Val	Lys	Thr	Arg	Thr	Asn	Asp	Trp	Asp
1865						1870					1875			
Phe	Val	Val	Thr	Thr	Asp	Ile	Ser	Glu	Met	Gly	Ala	Asn	Phe	Lys
1880						1885					1890			
Ala	Glu	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Met	Lys	Pro	Val	Ile
1895						1900					1905			
Leu	Thr	Asp	Gly	Glu	Glu	Arg	Val	Ile	Leu	Ala	Gly	Pro	Met	Pro
1910						1915					1920			

Val	Thr	His	Ser	Ser	Ala	Ala	Gln	Arg	Arg	Gly	Arg	Ile	Gly	Arg
1925						1930					1935			
Asn	Pro	Lys	Asn	Glu	Asn	Asp	Gln	Tyr	Ile	Tyr	Met	Gly	Glu	Pro
1940						1945					1950			
Leu	Glu	Asn	Asp	Glu	Asp	Cys	Ala	His	Trp	Lys	Glu	Ala	Lys	Met
1955						1960					1965			
Leu	Leu	Asp	Asn	Ile	Asn	Thr	Pro	Glu	Gly	Ile	Ile	Pro	Ser	Met
1970						1975					1980			
Phe	Glu	Pro	Glu	Arg	Glu	Lys	Val	Asp	Ala	Ile	Asp	Gly	Glu	Tyr
1985						1990					1995			
Arg	Leu	Arg	Gly	Glu	Ala	Arg	Lys	Thr	Phe	Val	Asp	Leu	Met	Arg
2000						2005					2010			
Arg	Gly	Asp	Leu	Pro	Val	Trp	Leu	Ala	Tyr	Arg	Val	Ala	Ala	Glu
2015						2020					2025			
Gly	Ile	Asn	Tyr	Ala	Asp	Arg	Arg	Trp	Cys	Phe	Asp	Gly	Val	Lys
2030						2035					2040			
Asn	Asn	Gln	Ile	Leu	Glu	Glu	Asn	Val	Glu	Val	Glu	Ile	Trp	Thr
2045						2050					2055			
Lys	Glu	Gly	Glu	Arg	Lys	Lys	Leu	Lys	Pro	Arg	Trp	Leu	Asp	Ala
2060						2065					2070			
Arg	Ile	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Glu	Phe
2075						2080					2085			
Ala	Ala	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met
2090						2095					2100			
Gly	Arg	Leu	Pro	Thr	Phe	Met	Thr	Gln	Lys	Ala	Arg	Asp	Ala	Leu
2105						2110					2115			
Asp	Asn	Leu	Ala	Val	Leu	His	Thr	Ala	Glu	Ala	Gly	Gly	Arg	Ala
2120						2125					2130			
Tyr	Asn	His	Ala	Leu	Ser	Glu	Leu	Pro	Glu	Thr	Leu	Glu	Thr	Leu
2135						2140					2145			

Leu	Leu	Leu	Thr	Leu	Leu	Ala	Thr	Val	Thr	Gly	Gly	Ile	Phe	Leu
2150						2155					2160			
Phe	Leu	Met	Ser	Ala	Arg	Gly	Ile	Gly	Lys	Met	Thr	Leu	Gly	Met
2165						2170					2175			
Cys	Cys	Ile	Ile	Thr	Ala	Ser	Ile	Leu	Leu	Trp	Tyr	Ala	Gln	Ile
2180						2185					2190			
Gln	Pro	His	Trp	Ile	Ala	Ala	Ser	Ile	Ile	Leu	Glu	Phe	Phe	Leu
2195						2200					2205			
Ile	Val	Leu	Leu	Ile	Pro	Glu	Pro	Glu	Lys	Gln	Arg	Thr	Pro	Gln
2210						2215					2220			
Asp	Asn	Gln	Leu	Thr	Tyr	Val	Val	Ile	Ala	Ile	Leu	Thr	Val	Val
2225						2230					2235			
Ala	Ala	Thr	Met	Ala	Asn	Glu	Met	Gly	Phe	Leu	Glu	Lys	Thr	Lys
2240						2245					2250			
Lys	Asp	Leu	Gly	Leu	Gly	Ser	Ile	Ala	Thr	Gln	Gln	Pro	Glu	Ser
2255						2260					2265			
Asn	Ile	Leu	Asp	Ile	Asp	Leu	Arg	Pro	Ala	Ser	Ala	Trp	Thr	Leu
2270						2275					2280			
Tyr	Ala	Val	Ala	Thr	Thr	Phe	Val	Thr	Pro	Met	Leu	Arg	His	Ser
2285						2290					2295			
Ile	Glu	Asn	Ser	Ser	Val	Asn	Val	Ser	Leu	Thr	Ala	Ile	Ala	Asn
2300						2305					2310			
Gln	Ala	Thr	Val	Leu	Met	Gly	Leu	Gly	Lys	Gly	Trp	Pro	Leu	Ser
2315						2320					2325			
Lys	Met	Asp	Ile	Gly	Val	Pro	Leu	Leu	Ala	Ile	Gly	Cys	Tyr	Ser
2330						2335					2340			
Gln	Val	Asn	Pro	Ile	Thr	Leu	Ile	Ala	Ala	Leu	Phe	Leu	Leu	Val
2345						2350					2355			
Ala	His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	Lys	Ala	Thr
2360						2365					2370			

Arg	Glu	Ala	Gln	Lys	Arg	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro	
2375						2380				2385				
Thr	Val	Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Asp	Pro	Ile	Pro	Tyr
2390						2395					2400			
Asp	Pro	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val
2405						2410					2415			
Leu	Cys	Val	Thr	Gln	Val	Leu	Met	Met	Arg	Thr	Thr	Trp	Ala	Leu
2420						2425					2430			
Cys	Glu	Ala	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Ser	Thr	Leu	Trp
2435						2440					2445			
Glu	Gly	Asn	Pro	Gly	Arg	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser
2450						2455					2460			
Met	Ala	Asn	Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu
2465						2470					2475			
Leu	Phe	Ser	Ile	Met	Lys	Asn	Thr	Thr	Asn	Thr	Arg	Arg	Gly	Thr
2480						2485					2490			
Gly	Asn	Ile	Gly	Glu	Thr	Leu	Gly	Glu	Lys	Trp	Lys	Ser	Arg	Leu
2495						2500					2505			
Asn	Ala	Leu	Gly	Lys	Ser	Glu	Phe	Gln	Ile	Tyr	Lys	Lys	Ser	Gly
2510						2515					2520			
Ile	Gln	Glu	Val	Asp	Arg	Thr	Leu	Ala	Lys	Glu	Gly	Ile	Lys	Arg
2525						2530					2535			
Gly	Glu	Thr	Asp	His	His	Ala	Val	Ser	Arg	Gly	Ser	Ala	Lys	Leu
2540						2545					2550			
Arg	Trp	Phe	Val	Glu	Arg	Asn	Met	Val	Thr	Pro	Glu	Gly	Lys	Val
2555						2560					2565			
Val	Asp	Leu	Gly	Cys	Gly	Arg	Gly	Gly	Trp	Ser	Tyr	Tyr	Cys	Gly
2570						2575					2580			
Gly	Leu	Lys	Asn	Val	Arg	Glu	Val	Lys	Gly	Leu	Thr	Lys	Gly	Gly
2585						2590					2595			

Pro	Gly	His	Glu	Glu	Pro	Ile	Pro	Met	Ser	Thr	Tyr	Gly	Trp	Asn
	2600					2605					2610			
Leu	Val	Arg	Leu	Gln	Ser	Gly	Val	Asp	Val	Phe	Phe	Ile	Pro	Pro
	2615					2620					2625			
Glu	Lys	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser	Ser	Pro
	2630					2635					2640			
Asn	Pro	Thr	Val	Glu	Ala	Gly	Arg	Thr	Leu	Arg	Val	Leu	Asn	Leu
	2645					2650					2655			
Val	Glu	Asn	Trp	Leu	Asn	Asn	Asn	Thr	Gln	Phe	Cys	Ile	Lys	Val
	2660					2665					2670			
Leu	Asn	Pro	Tyr	Met	Pro	Ser	Val	Ile	Glu	Lys	Met	Glu	Ala	Leu
	2675					2680					2685			
Gln	Arg	Lys	Tyr	Gly	Gly	Ala	Leu	Val	Arg	Asn	Pro	Leu	Ser	Arg
	2690					2695					2700			
Asn	Ser	Thr	His	Glu	Met	Tyr	Trp	Val	Ser	Asn	Ala	Ser	Gly	Asn
	2705					2710					2715			
Ile	Val	Ser	Ser	Val	Asn	Met	Ile	Ser	Arg	Met	Leu	Ile	Asn	Arg
	2720					2725					2730			
Phe	Thr	Met	Arg	Tyr	Lys	Lys	Ala	Thr	Tyr	Glu	Pro	Asp	Val	Asp
	2735					2740					2745			
Leu	Gly	Ser	Gly	Thr	Arg	Asn	Ile	Gly	Ile	Glu	Ser	Glu	Ile	Pro
	2750					2755					2760			
Asn	Leu	Asp	Ile	Ile	Gly	Lys	Arg	Ile	Glu	Lys	Ile	Lys	Gln	Glu
	2765					2770					2775			
His	Glu	Thr	Ser	Trp	His	Tyr	Asp	Gln	Asp	His	Pro	Tyr	Lys	Thr
	2780					2785					2790			
Trp	Ala	Tyr	His	Gly	Ser	Tyr	Glu	Thr	Lys	Gln	Thr	Gly	Ser	Ala
	2795					2800					2805			
Ser	Ser	Met	Val	Asn	Gly	Val	Val	Arg	Leu	Leu	Thr	Lys	Pro	Trp
	2810					2815					2820			

Asp	Val	Val	Pro	Met	Val	Thr	Gln	Met	Ala	Met	Thr	Asp	Thr	Thr
2825						2830					2835			
Pro	Phe	Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	Asp	Thr	Arg
2840						2845					2850			
Thr	Gln	Glu	Pro	Lys	Glu	Gly	Thr	Lys	Lys	Leu	Met	Lys	Ile	Thr
2855						2860					2865			
Ala	Glu	Trp	Leu	Trp	Lys	Glu	Leu	Gly	Lys	Lys	Lys	Thr	Pro	Arg
2870						2875					2880			
Met	Cys	Thr	Arg	Glu	Glu	Phe	Thr	Arg	Lys	Val	Arg	Ser	Asn	Ala
2885						2890					2895			
Ala	Leu	Gly	Ala	Ile	Phe	Thr	Asp	Glu	Asn	Lys	Trp	Lys	Ser	Ala
2900						2905					2910			
Arg	Glu	Ala	Val	Glu	Asp	Ser	Arg	Phe	Trp	Glu	Leu	Val	Asp	Lys
2915						2920					2925			
Glu	Arg	Asn	Leu	His	Leu	Glu	Gly	Lys	Cys	Glu	Thr	Cys	Val	Tyr
2930						2935					2940			
Asn	Met	Met	Gly	Lys	Arg	Glu	Lys	Lys	Leu	Gly	Glu	Phe	Gly	Lys
2945						2950					2955			
Ala	Lys	Gly	Ser	Arg	Ala	Ile	Trp	Tyr	Met	Trp	Leu	Gly	Ala	Arg
2960						2965					2970			
Phe	Leu	Glu	Phe	Glu	Ala	Leu	Gly	Phe	Leu	Asn	Glu	Asp	His	Trp
2975						2980					2985			
Phe	Ser	Arg	Glu	Asn	Ser	Leu	Ser	Gly	Val	Glu	Gly	Glu	Gly	Leu
2990						2995					3000			
His	Lys	Leu	Gly	Tyr	Ile	Leu	Arg	Asp	Val	Ser	Lys	Lys	Glu	Gly
3005						3010					3015			
Gly	Ala	Met	Tyr	Ala	Asp	Asp	Thr	Ala	Gly	Trp	Asp	Thr	Arg	Ile
3020						3025					3030			
Thr	Leu	Glu	Asp	Leu	Lys	Asn	Glu	Glu	Met	Val	Thr	Asn	His	Met
3035						3040					3045			

Glu	Gly	Glu	His	Lys	Lys	Leu	Ala	Glu	Ala	Ile	Phe	Lys	Leu	Thr
	3050					3055					3060			
Tyr	Gln	Asn	Lys	Val	Val	Arg	Val	Gln	Arg	Pro	Thr	Pro	Arg	Gly
	3065					3070					3075			
Thr	Val	Met	Asp	Ile	Ile	Ser	Arg	Arg	Asp	Gln	Arg	Gly	Ser	Gly
	3080					3085					3090			
Gln	Val	Gly	Thr	Tyr	Gly	Leu	Asn	Thr	Phe	Thr	Asn	Met	Glu	Ala
	3095					3100					3105			
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Gln	Trp	Glu	Pro	Ser	Arg	Gly	Trp	Asn	Asp	Trp	Thr	Gln	Val	Pro
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Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile
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His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr Val
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Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys
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Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala
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Arg Phe Arg Arg Glu Glu Glu Glu Ala Gly Val Leu Trp Lys Ala
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Lys Ser Gly His His Lys Cys His Ser Leu Ser Lys Leu Cys Ser
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35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65 70 75 80

Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
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Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
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Met Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
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Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
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Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
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Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
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Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
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Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
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Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
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Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
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Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
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Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
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Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
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Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
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Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
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Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
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Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
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Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
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Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
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Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
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Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys
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Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
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Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
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Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
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Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
 465 470 475 480
 Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn
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 Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
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 Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
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 Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
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 Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
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 Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
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 Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
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 Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
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 Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
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Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
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Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
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Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
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Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
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His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
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Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
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Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
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Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
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Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
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Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
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Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
915 920 925

Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
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Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
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 Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu
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 Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly
 1115 1120 1125
 His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala
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 Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala
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 Gly Ile Val Leu Leu Ser Gln Ser Thr Leu Pro Glu Thr Ile Leu
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 Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile
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 Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys
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 Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu
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1595						1600					1605			
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Leu	Tyr	Gly	Asn	Gly	Val	Val	Thr	Arg	Ser	Gly	Ala	Tyr	Val	Ser
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1640						1645					1650			
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1655						1660					1665			
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1670						1675					1680			
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1685						1690					1695			
Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Glu	Glu	Ala	Leu	Arg	Gly	Leu
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Tyr	Asn	His	Ala	Leu	Ser	Glu	Leu	Pro	Glu	Thr	Leu	Glu	Thr	Leu
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Phe	Leu	Met	Ser	Ala	Arg	Gly	Ile	Gly	Lys	Met	Thr	Leu	Gly	Met
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tgtaaaaaat ccgggaggcc acaaaccatg gaagctgtac gcatggcgta gtggactagc	10500

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<400> 5

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Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
20 25 30

Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65 70 75 80

Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
85 90 95

Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
100 105 110

Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu Pro His Met Ile Val
115 120 125

Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe Lys Thr Glu Val Gly
130 135 140

Val Asn Met Cys Thr Leu Met Ala Met Asp Leu Gly Glu Leu Cys Glu
145 150 155 160

Asp Thr Ile Thr Tyr Glu Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu
165 170 175

Asp Ile Asp Cys Trp Cys Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly
180 185 190

Thr Cys Thr Thr Met Gly Glu His Arg Arg Glu Lys Arg Ser Val Ala
195 200 205

Leu Val Pro His Val Gly Met Gly Leu Glu Thr Arg Thr Glu Thr Trp
210 215 220

Met Ser Ser Glu Gly Ala Trp Lys His Val Gln Arg Ile Glu Thr Trp
225 230 235 240

Ile Leu Arg His Pro Gly Phe Thr Met Met Ala Ala Ile Leu Ala Tyr
245 250 255

Thr Ile Gly Thr Thr His Phe Gln Arg Ala Leu Ile Phe Ile Leu Leu
260 265 270

Thr Ala Val Thr Pro Ser Met Thr Met Arg Cys Ile Gly Met Ser Asn
275 280 285

Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ser Trp Val Asp Ile Val
290 295 300

Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
305 310 315 320

Leu Asp Phe Glu Leu Ile Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu
325 330 335

Arg Lys Tyr Cys Ile Glu Ala Lys Leu Thr Asn Thr Thr Thr Glu Ser
340 345 350

Arg Cys Pro Thr Gln Gly Glu Pro Ser Leu Asn Glu Glu Gln Asp Lys
355 360 365

Arg Phe Val Cys Lys His Ser Met Val Asp Arg Gly Trp Gly Asn Gly
370 375 380

Cys Gly Leu Phe Gly Lys Gly Gly Ile Val Thr Cys Ala Met Phe Arg
385 390 395 400

Cys Lys Lys Asn Met Glu Gly Lys Val Val Gln Pro Glu Asn Leu Glu
405 410 415

Tyr Thr Ile Val Ile Thr Pro His Ser Gly Glu Glu His Ala Val Gly
420 425 430

Asn Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser
435 440 445

Ser Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu
450 455 460

Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln
465 470 475 480

Met Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu
485 490 495

Pro Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile
500 505 510

Gln Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln
515 520 525

Asp Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
530 535 540

Thr Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr
545 550 555 560

Gly His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly
565 570 575

Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile
580 585 590

Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly
595 600 605

Asp Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys
610 615 620

Arg His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu
625 630 635 640

Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser
645 650 655

Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe
660 665 670

Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly
675 680 685

Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
690 695 700

Leu Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe
705 710 715 720

Gly Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys
725 730 735

Ile Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser
740 745 750

Thr Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr
755 760 765

Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
770 775 780

Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
785 790 795 800

His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
805 810 815

Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
820 825 830

Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
835 840 845

Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
850 855 860

Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
865 870 875 880

Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
885 890 895

Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
915 920 925

Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
930 935 940

Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
945 950 955 960

Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
965 970 975

Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
980 985 990

Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
995 1000 1005

Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
1010 1015 1020

Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln
1025 1030 1035

Ile Thr Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp
1040 1045 1050

Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn
1055 1060 1065

Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile
1070 1075 1080

Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr
1085 1090 1095

Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu
1100 1105 1110

Lys	Glu	Lys	Glu	Glu	Asn	Leu	Val	Asn	Ser	Leu	Val	Thr	Ala	Gly
1115						1120					1125			
His	Gly	Gln	Val	Asp	Asn	Phe	Ser	Leu	Gly	Val	Leu	Gly	Met	Ala
1130						1135					1140			
Leu	Phe	Leu	Glu	Glu	Met	Leu	Arg	Thr	Arg	Val	Gly	Thr	Lys	His
1145						1150					1155			
Ala	Ile	Leu	Leu	Val	Ala	Val	Ser	Phe	Val	Thr	Leu	Ile	Thr	Gly
1160						1165					1170			
Asn	Met	Ser	Phe	Arg	Asp	Leu	Gly	Arg	Val	Met	Val	Met	Val	Gly
1175						1180					1185			
Ala	Thr	Met	Thr	Asp	Asp	Ile	Gly	Met	Gly	Val	Thr	Tyr	Leu	Ala
1190						1195					1200			
Leu	Leu	Ala	Ala	Phe	Lys	Val	Arg	Pro	Thr	Phe	Ala	Ala	Gly	Leu
1205						1210					1215			
Leu	Leu	Arg	Lys	Leu	Thr	Ser	Lys	Glu	Leu	Met	Met	Thr	Thr	Ile
1220						1225					1230			
Gly	Ile	Val	Leu	Leu	Ser	Gln	Ser	Thr	Ile	Pro	Glu	Thr	Ile	Leu
1235						1240					1245			
Glu	Leu	Thr	Asp	Ala	Leu	Ala	Leu	Gly	Met	Met	Val	Leu	Lys	Met
1250						1255					1260			
Val	Arg	Asn	Met	Glu	Lys	Tyr	Gln	Leu	Ala	Val	Thr	Ile	Met	Ala
1265						1270					1275			
Ile	Leu	Cys	Val	Pro	Asn	Ala	Val	Ile	Leu	Gln	Asn	Ala	Trp	Lys
1280						1285					1290			
Val	Ser	Cys	Thr	Ile	Leu	Ala	Val	Val	Ser	Val	Ser	Pro	Leu	Phe
1295						1300					1305			
Leu	Thr	Ser	Ser	Gln	Gln	Lys	Thr	Asp	Trp	Ile	Pro	Leu	Ala	Leu
1310						1315					1320			
Thr	Ile	Lys	Gly	Leu	Asn	Pro	Thr	Ala	Ile	Phe	Leu	Thr	Thr	Leu
1325						1330					1335			

Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile
1340 1345 1350

Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys
1355 1360 1365

Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu
1370 1375 1380

Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu
1385 1390 1395

Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser
1400 1405 1410

Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser
1415 1420 1425

Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu
1430 1435 1440

Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser
1445 1450 1455

Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys
1460 1465 1470

Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met
1475 1480 1485

Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys
1490 1495 1500

Gly Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu
1505 1510 1515

Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu
1520 1525 1530

Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys
1535 1540 1545

Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu
1550 1555 1560

Trp	Lys	Glu	Gly	Glu	Glu	Val	Gln	Val	Leu	Ala	Leu	Glu	Pro	Gly
	1565					1570					1575			
Lys	Asn	Pro	Arg	Ala	Val	Gln	Thr	Lys	Pro	Gly	Leu	Phe	Lys	Thr
	1580					1585					1590			
Asn	Ala	Gly	Thr	Ile	Gly	Ala	Val	Ser	Leu	Asp	Phe	Ser	Pro	Gly
	1595					1600					1605			
Thr	Ser	Gly	Ser	Pro	Ile	Ile	Asp	Lys	Lys	Gly	Lys	Val	Val	Gly
	1610					1615					1620			
Leu	Tyr	Gly	Asn	Gly	Val	Val	Thr	Arg	Ser	Gly	Ala	Tyr	Val	Ser
	1625					1630					1635			
Ala	Ile	Ala	Gln	Thr	Glu	Lys	Ser	Ile	Glu	Asp	Asn	Pro	Glu	Ile
	1640					1645					1650			
Glu	Asp	Asp	Ile	Phe	Arg	Lys	Arg	Arg	Leu	Thr	Ile	Met	Asp	Leu
	1655					1660					1665			
His	Pro	Gly	Ala	Gly	Lys	Thr	Lys	Arg	Tyr	Leu	Pro	Ala	Ile	Val
	1670					1675					1680			
Arg	Glu	Ala	Ile	Lys	Arg	Gly	Leu	Arg	Thr	Leu	Ile	Leu	Ala	Pro
	1685					1690					1695			
Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Glu	Glu	Ala	Leu	Arg	Gly	Leu
	1700					1705					1710			
Pro	Ile	Arg	Tyr	Gln	Thr	Pro	Ala	Ile	Arg	Ala	Val	His	Thr	Gly
	1715					1720					1725			
Arg	Glu	Ile	Val	Asp	Leu	Met	Cys	His	Ala	Thr	Phe	Thr	Met	Arg
	1730					1735					1740			
Leu	Leu	Ser	Pro	Val	Arg	Val	Pro	Asn	Tyr	Asn	Leu	Ile	Ile	Met
	1745					1750					1755			
Asp	Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser	Ile	Ala	Ala	Arg	Gly
	1760					1765					1770			
Tyr	Ile	Ser	Thr	Arg	Val	Glu	Met	Gly	Glu	Ala	Ala	Gly	Ile	Phe
	1775					1780					1785			

Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser
1790 1795 1800

Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser
1805 1810 1815

Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys Thr
1820 1825 1830

Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala
1835 1840 1845

Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys
1850 1855 1860

Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp
1865 1870 1875

Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys
1880 1885 1890

Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile
1895 1900 1905

Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro
1910 1915 1920

Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg
1925 1930 1935

Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro
1940 1945 1950

Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
1955 1960 1965

Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met
1970 1975 1980

Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr
1985 1990 1995

Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg
2000 2005 2010

Arg	Gly	Asp	Leu	Pro	Val	Trp	Leu	Ala	Tyr	Arg	Val	Ala	Ala	Glu
	2015					2020					2025			
Gly	Ile	Asn	Tyr	Ala	Asp	Arg	Arg	Trp	Cys	Phe	Asp	Gly	Val	Lys
	2030					2035					2040			
Asn	Asn	Gln	Ile	Leu	Glu	Glu	Asn	Val	Glu	Val	Glu	Ile	Trp	Thr
	2045					2050					2055			
Lys	Glu	Gly	Glu	Arg	Lys	Lys	Leu	Lys	Pro	Arg	Trp	Leu	Asp	Ala
	2060					2065					2070			
Arg	Ile	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Glu	Phe
	2075					2080					2085			
Ala	Ala	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met
	2090					2095					2100			
Gly	Arg	Leu	Pro	Thr	Phe	Met	Thr	Gln	Lys	Ala	Arg	Asp	Ala	Leu
	2105					2110					2115			
Asp	Asn	Leu	Ala	Val	Leu	His	Thr	Ala	Glu	Pro	Gly	Gly	Arg	Ala
	2120					2125					2130			
Tyr	Asn	His	Ala	Leu	Ser	Glu	Leu	Pro	Glu	Thr	Leu	Glu	Thr	Leu
	2135					2140					2145			
Leu	Leu	Leu	Thr	Leu	Leu	Ala	Thr	Val	Thr	Gly	Gly	Ile	Phe	Leu
	2150					2155					2160			
Phe	Leu	Met	Ser	Ala	Arg	Gly	Ile	Gly	Lys	Met	Thr	Leu	Gly	Met
	2165					2170					2175			
Cys	Cys	Ile	Ile	Thr	Ala	Ser	Ile	Leu	Leu	Trp	Tyr	Ala	Gln	Ile
	2180					2185					2190			
Gln	Pro	His	Trp	Ile	Ala	Ala	Ser	Ile	Ile	Leu	Glu	Phe	Phe	Leu
	2195					2200					2205			
Ile	Val	Leu	Leu	Ile	Pro	Glu	Pro	Glu	Lys	Gln	Arg	Thr	Pro	Gln
	2210					2215					2220			
Asp	Asn	Gln	Leu	Thr	Tyr	Val	Val	Ile	Ala	Ile	Leu	Thr	Val	Val
	2225					2230					2235			

Ala	Ala	Thr	Met	Ala	Asn	Glu	Met	Gly	Phe	Leu	Glu	Lys	Thr	Lys
2240						2245					2250			
Lys	Asp	Leu	Gly	Leu	Gly	Ser	Ile	Ala	Thr	Gln	Gln	Pro	Glu	Ser
2255						2260					2265			
Asn	Ile	Leu	Asp	Ile	Asp	Leu	Arg	Pro	Ala	Ser	Ala	Trp	Thr	Leu
2270						2275					2280			
Tyr	Ala	Val	Ala	Thr	Thr	Phe	Val	Thr	Pro	Met	Leu	Arg	His	Ser
2285						2290					2295			
Ile	Glu	Asn	Ser	Ser	Val	Asn	Val	Ser	Leu	Thr	Ala	Ile	Ala	Asn
2300						2305					2310			
Gln	Ala	Thr	Val	Leu	Met	Gly	Leu	Gly	Lys	Gly	Trp	Pro	Leu	Ser
2315						2320					2325			
Lys	Met	Asp	Ile	Gly	Val	Pro	Leu	Leu	Ala	Ile	Gly	Cys	Tyr	Ser
2330						2335					2340			
Gln	Val	Asn	Pro	Ile	Thr	Leu	Thr	Ala	Ala	Phe	Phe	Leu	Leu	Val
2345						2350					2355			
Ala	His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	Lys	Ala	Thr
2360						2365					2370			
Arg	Glu	Ala	Gln	Lys	Arg	Ala	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro
2375						2380					2385			
Thr	Val	Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Asp	Pro	Ile	Pro	Tyr
2390						2395					2400			
Asp	Pro	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val
2405						2410					2415			
Leu	Cys	Val	Thr	Gln	Val	Leu	Met	Met	Arg	Thr	Thr	Trp	Ala	Leu
2420						2425					2430			
Cys	Glu	Ala	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Ser	Thr	Leu	Trp
2435						2440					2445			
Glu	Gly	Asn	Pro	Gly	Arg	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser
2450						2455					2460			

Met	Ala	Asn	Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu
	2465					2470					2475			
Leu	Phe	Ser	Ile	Met	Lys	Asn	Thr	Thr	Asn	Thr	Arg	Arg	Gly	Thr
	2480					2485					2490			
Gly	Asn	Ile	Gly	Glu	Thr	Leu	Gly	Glu	Lys	Trp	Lys	Ser	Arg	Leu
	2495					2500					2505			
Asn	Ala	Leu	Gly	Lys	Ser	Glu	Phe	Gln	Ile	Tyr	Lys	Lys	Ser	Gly
	2510					2515					2520			
Ile	Gln	Glu	Val	Asp	Arg	Thr	Leu	Ala	Lys	Glu	Gly	Ile	Lys	Arg
	2525					2530					2535			
Gly	Glu	Thr	Asp	His	His	Ala	Val	Ser	Arg	Gly	Ser	Ala	Lys	Leu
	2540					2545					2550			
Arg	Trp	Phe	Val	Glu	Arg	Asn	Met	Val	Thr	Pro	Glu	Gly	Lys	Val
	2555					2560					2565			
Val	Asp	Leu	Gly	Cys	Gly	Arg	Gly	Gly	Trp	Ser	Tyr	Tyr	Cys	Gly
	2570					2575					2580			
Gly	Leu	Lys	Asn	Val	Arg	Glu	Val	Lys	Gly	Leu	Thr	Lys	Gly	Gly
	2585					2590					2595			
Pro	Gly	His	Glu	Glu	Pro	Ile	Pro	Met	Ser	Thr	Tyr	Gly	Trp	Asn
	2600					2605					2610			
Leu	Val	Arg	Leu	Gln	Ser	Gly	Val	Asp	Val	Phe	Phe	Ile	Pro	Pro
	2615					2620					2625			
Glu	Lys	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser	Ser	Pro
	2630					2635					2640			
Asn	Pro	Thr	Val	Glu	Ala	Gly	Arg	Thr	Leu	Arg	Val	Leu	Asn	Leu
	2645					2650					2655			
Val	Glu	Asn	Trp	Leu	Asn	Asn	Asn	Thr	Gln	Phe	Cys	Ile	Lys	Val
	2660					2665					2670			
Leu	Asn	Pro	Tyr	Met	Pro	Ser	Val	Ile	Glu	Lys	Met	Glu	Ala	Leu
	2675					2680					2685			

Gln	Arg	Lys	Tyr	Gly	Gly	Ala	Leu	Val	Arg	Asn	Pro	Leu	Ser	Arg
2690						2695					2700			
Asn	Ser	Thr	His	Glu	Met	Tyr	Trp	Val	Ser	Asn	Ala	Ser	Gly	Asn
2705						2710					2715			
Ile	Val	Ser	Ser	Val	Asn	Met	Ile	Ser	Arg	Met	Leu	Ile	Asn	Arg
2720						2725					2730			
Phe	Thr	Met	Arg	Tyr	Lys	Lys	Ala	Thr	Tyr	Glu	Pro	Asp	Val	Asp
2735						2740					2745			
Leu	Gly	Ser	Gly	Thr	Arg	Asn	Ile	Gly	Ile	Glu	Ser	Glu	Ile	Pro
2750						2755					2760			
Asn	Leu	Asp	Ile	Ile	Gly	Lys	Arg	Ile	Glu	Lys	Ile	Lys	Gln	Glu
2765						2770					2775			
His	Glu	Thr	Ser	Trp	His	Tyr	Asp	Gln	Asp	His	Pro	Tyr	Lys	Thr
2780						2785					2790			
Trp	Ala	Tyr	His	Gly	Ser	Tyr	Glu	Thr	Lys	Gln	Thr	Gly	Ser	Ala
2795						2800					2805			
Ser	Ser	Met	Val	Asn	Gly	Val	Val	Arg	Leu	Leu	Thr	Lys	Pro	Trp
2810						2815					2820			
Asp	Val	Val	Pro	Met	Val	Thr	Gln	Met	Ala	Met	Thr	Asp	Thr	Thr
2825						2830					2835			
Pro	Phe	Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	Asp	Thr	Arg
2840						2845					2850			
Thr	Gln	Glu	Pro	Lys	Glu	Gly	Thr	Lys	Lys	Leu	Met	Lys	Ile	Thr
2855						2860					2865			
Ala	Glu	Trp	Leu	Trp	Lys	Glu	Leu	Gly	Lys	Lys	Lys	Thr	Pro	Arg
2870						2875					2880			
Met	Cys	Thr	Arg	Glu	Glu	Phe	Thr	Arg	Lys	Val	Arg	Ser	Asn	Ala
2885						2890					2895			
Ala	Leu	Gly	Ala	Val	Phe	Thr	Asp	Glu	Asn	Lys	Trp	Lys	Ser	Ala
2900						2905					2910			

Arg	Glu	Ala	Val	Glu	Asp	Ser	Arg	Phe	Trp	Glu	Leu	Val	Asp	Lys
	2915					2920					2925			
Glu	Arg	Asn	Leu	His	Leu	Glu	Gly	Lys	Cys	Glu	Thr	Cys	Val	Tyr
	2930					2935					2940			
Asn	Met	Met	Gly	Lys	Arg	Glu	Lys	Lys	Leu	Gly	Glu	Phe	Gly	Lys
	2945					2950					2955			
Ala	Lys	Gly	Ser	Arg	Ala	Ile	Trp	Tyr	Met	Trp	Leu	Gly	Ala	Arg
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Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65 70 75 80

Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
85 90 95

Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
100 105 110

Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu Pro His Met Ile Val
115 120 125

Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe Lys Thr Glu Val Gly
130 135 140

Val Asn Met Cys Thr Leu Met Ala Met Asp Leu Gly Glu Leu Cys Glu
145 150 155 160

Asp Thr Ile Thr Tyr Glu Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu
165 170 175

Asp Ile Asp Cys Trp Cys Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly
180 185 190

Thr Cys Thr Thr Met Gly Glu His Arg Arg Glu Lys Arg Ser Val Ala
195 200 205

Leu Val Pro His Val Gly Met Gly Leu Glu Thr Arg Thr Glu Thr Trp
210 215 220

Met Ser Ser Glu Gly Ala Trp Lys His Val Gln Arg Ile Glu Thr Trp
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Ile Leu Arg His Pro Gly Phe Thr Met Met Ala Ala Ile Leu Ala Tyr
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Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ser Trp Val Asp Ile Val
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Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
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Arg Phe Val Cys Lys His Ser Met Val Asp Arg Gly Trp Gly Asn Gly
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Cys Gly Leu Phe Gly Lys Gly Gly Ile Val Thr Cys Ala Met Phe Arg
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Cys Lys Lys Asn Met Glu Gly Lys Val Val Gln Pro Glu Asn Leu Glu
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Tyr Thr Ile Val Ile Thr Pro His Ser Gly Glu Glu His Ala Val Gly
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Asn Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser
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Ser Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu
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Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln
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Met Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu
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Pro Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile
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Gln Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln
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Asp Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
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Thr Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr
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Gly His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly
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Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile
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Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly
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Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser
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 Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe
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 Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly
 675 680 685
 Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
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 Gly Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys
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 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
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Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
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Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
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Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
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Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
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Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
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Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
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Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
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Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
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Gly Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln
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Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn
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Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile
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Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Leu
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35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65 70 75 80

Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
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Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
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Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Thr Tyr Gly
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Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65 70 75 80

Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
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Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Thr Tyr Gly
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Asn Glu Thr Gln Gly Val Thr Ala Glu Ile Thr Pro Gln Ala Ser Thr
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Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met
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Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu
900 905 910

Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val
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Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu
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Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly
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Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile	Leu	Lys	Arg	Trp	Gly	Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val	65	70	75	80
Leu	Arg	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	85	90	95	
Arg	Arg	Arg	Ser	Ser	Ala	Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	100	105	110	
Met	Ala	Phe	His	Leu	Thr	Thr	Arg	Asp	Gly	Glu	Pro	Leu	Met	Ile	Val	115	120	125	
Ala	Lys	His	Glu	Arg	Gly	Arg	Pro	Leu	Leu	Phe	Lys	Thr	Thr	Glu	Gly	130	135	140	
Ile	Asn	Lys	Cys	Thr	Leu	Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Glu	145	150	155	160
Asp	Thr	Val	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Val	Asn	Thr	Glu	Pro	Glu	165	170	175	
Asp	Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Met	Tyr	Gly	180	185	190	
Thr	Cys	Thr	Gln	Ser	Gly	Glu	Arg	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala	195	200	205	
Leu	Thr	Pro	His	Ser	Gly	Met	Gly	Leu	Glu	Thr	Arg	Ala	Glu	Thr	Trp	210	215	220	
Met	Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Ala	Gln	Arg	Val	Glu	Ser	Trp	225	230	235	240
Ile	Leu	Arg	Asn	Pro	Gly	Phe	Ala	Leu	Leu	Ala	Gly	Phe	Met	Ala	Tyr	245	250	255	
Met	Ile	Gly	Gln	Thr	Gly	Ile	Gln	Arg	Thr	Val	Phe	Phe	Val	Leu	Met	260	265	270	
Met	Leu	Val	Ala	Pro	Ser	Tyr	Gly	Met	Arg	Cys	Val	Gly	Val	Gly	Asn	275	280	285	
Arg	Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ala	Trp	Val	Asp	Leu	Val	290	295	300	

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Leu Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu
325 330 335

Arg Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr
340 345 350

Arg Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln
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Gln Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly
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Cys Gly Leu Phe Gly Lys Gly Gly Val Val Thr Cys Ala Lys Phe Ser
385 390 395 400

Cys Ser Gly Lys Ile Thr Gly Asn Leu Val Gln Ile Glu Asn Leu Glu
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Tyr Thr Val Val Val Thr Val His Asn Gly Asp Thr His Ala Val Gly
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Asn Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser
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Pro Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp
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Cys Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys
465 470 475 480

Met Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
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Pro Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn
500 505 510

Tyr Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln
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Asp Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu
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Ala Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala
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Gly His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly
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Ala Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly
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Tyr Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe
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Arg Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly
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Ala Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser
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Val Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe
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Gly Ser Val Tyr Thr Thr Leu Phe Gly Gly Val Ser Trp Met Ile Arg
725 730 735

Ile Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn
740 745 750

Thr Ser Met Ala Met Thr Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr
755 760 765

Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
770 775 780

Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
785 790 795 800

His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
805 810 815

Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
820 825 830

Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
835 840 845

Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
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Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
865 870 875 880

Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
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Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
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Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
930 935 940

Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
945 950 955 960

Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
965 970 975

Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
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Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
995 1000 1005

Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
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1055						1060					1065			
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1070						1075					1080			
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1100						1105					1110			
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His	Gly	Gln	Val	Asp	Asn	Phe	Ser	Leu	Gly	Val	Leu	Gly	Met	Ala
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1160						1165					1170			
Asn	Met	Ser	Phe	Arg	Asp	Leu	Gly	Arg	Val	Met	Val	Met	Val	Gly
1175						1180					1185			
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1190						1195					1200			
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Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met
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Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu
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Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala Ile
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Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys
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Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu
1385 1390 1395

Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser
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Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser
1415 1420 1425

Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu
1430 1435 1440

Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser
1445 1450 1455

Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys
1460 1465 1470

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Glu	Asp	Asp	Ile	Phe	Arg	Lys	Arg	Arg	Leu	Thr	Ile	Met	Asp	Leu
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Leu	Leu	Asp	Asn	Ile	Asn	Thr	Pro	Glu	Gly	Ile	Ile	Pro	Ser	Met
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Phe	Glu	Pro	Glu	Arg	Glu	Lys	Val	Asp	Ala	Ile	Asp	Gly	Glu	Tyr
1985						1990					1995			
Arg	Leu	Arg	Gly	Glu	Ala	Arg	Lys	Thr	Phe	Val	Asp	Leu	Met	Arg
2000						2005					2010			
Arg	Gly	Asp	Leu	Pro	Val	Trp	Leu	Ala	Tyr	Arg	Val	Ala	Ala	Glu
2015						2020					2025			
Gly	Ile	Asn	Tyr	Ala	Asp	Arg	Arg	Trp	Cys	Phe	Asp	Gly	Val	Lys
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Asn	Asn	Gln	Ile	Leu	Glu	Glu	Asn	Val	Glu	Val	Glu	Ile	Trp	Thr
2045						2050					2055			
Lys	Glu	Gly	Glu	Arg	Lys	Lys	Leu	Lys	Pro	Arg	Trp	Leu	Asp	Ala
2060						2065					2070			
Arg	Ile	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Glu	Phe
2075						2080					2085			
Ala	Ala	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met
2090						2095					2100			
Gly	Arg	Leu	Pro	Thr	Phe	Met	Thr	Gln	Lys	Val	Arg	Asp	Ala	Leu
2105						2110					2115			
Asp	Asn	Leu	Ala	Val	Leu	His	Thr	Ala	Glu	Ala	Gly	Gly	Arg	Ala
2120						2125					2130			
Tyr	Asn	His	Ala	Leu	Ser	Glu	Leu	Pro	Glu	Thr	Leu	Glu	Thr	Leu
2135						2140					2145			

Leu 2150	Leu	Leu	Thr	Leu	Leu	Ala 2155	Thr	Val	Thr	Gly	Gly 2160	Ile	Phe	Leu
Phe 2165	Leu	Met	Ser	Ala	Arg	Gly 2170	Ile	Gly	Lys	Met	Thr 2175	Leu	Gly	Met
Cys 2180	Cys	Ile	Ile	Thr	Ala	Ser 2185	Ile	Leu	Leu	Trp	Tyr 2190	Ala	Gln	Ile
Gln 2195	Pro	His	Trp	Ile	Ala	Ala 2200	Ser	Ile	Ile	Leu	Glu 2205	Phe	Phe	Leu
Ile 2210	Val	Leu	Leu	Ile	Pro	Glu 2215	Pro	Glu	Lys	Gln	Arg 2220	Thr	Pro	Gln
Asp 2225	Asn	Gln	Leu	Thr	Tyr	Val 2230	Val	Ile	Ala	Ile	Leu 2235	Thr	Val	Val
Ala 2240	Ala	Thr	Met	Ala	Asn	Glu 2245	Met	Gly	Phe	Leu	Glu 2250	Lys	Thr	Lys
Lys 2255	Asp	Leu	Gly	Leu	Gly	Ser 2260	Ile	Ala	Thr	Gln	Gln 2265	Pro	Glu	Ser
Asn 2270	Ile	Leu	Asp	Ile	Asp	Leu 2275	Arg	Pro	Ala	Ser	Ala 2280	Trp	Thr	Leu
Tyr 2285	Ala	Val	Ala	Thr	Thr	Phe 2290	Val	Thr	Pro	Met	Leu 2295	Arg	His	Ser
Ile 2300	Glu	Asn	Ser	Ser	Val	Asn 2305	Val	Ser	Leu	Thr	Ala 2310	Ile	Ala	Asn
Gln 2315	Ala	Thr	Val	Leu	Met	Gly 2320	Leu	Gly	Lys	Gly	Trp 2325	Pro	Leu	Ser
Lys 2330	Met	Asp	Ile	Gly	Val	Pro 2335	Leu	Leu	Ala	Ile	Gly 2340	Cys	Tyr	Ser
Gln 2345	Val	Asn	Pro	Ile	Thr	Leu 2350	Thr	Ala	Ala	Leu	Phe 2355	Leu	Leu	Val
Ala 2360	His	Tyr	Ala	Ile	Ile	Gly 2365	Pro	Gly	Leu	Gln	Ala 2370	Lys	Ala	Thr

Arg	Glu	Ala	Gln	Lys	Arg	Ala	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro
2375						2380					2385			
Thr	Val	Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Asp	Pro	Ile	Pro	Tyr
2390						2395					2400			
Asp	Pro	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val
2405						2410					2415			
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2420						2425					2430			
Cys	Glu	Ala	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Ser	Thr	Leu	Trp
2435						2440					2445			
Glu	Gly	Asn	Pro	Gly	Arg	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser
2450						2455					2460			
Met	Ala	Asn	Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu
2465						2470					2475			
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2480						2485					2490			
Gly	Asn	Ile	Gly	Glu	Thr	Leu	Gly	Glu	Lys	Trp	Lys	Ser	Arg	Leu
2495						2500					2505			
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2510						2515					2520			
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2525						2530					2535			
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2540						2545					2550			
Arg	Trp	Phe	Val	Glu	Arg	Asn	Met	Val	Thr	Pro	Glu	Gly	Lys	Val
2555						2560					2565			
Val	Asp	Leu	Gly	Cys	Gly	Arg	Gly	Gly	Trp	Ser	Tyr	Tyr	Cys	Gly
2570						2575					2580			
Gly	Leu	Lys	Asn	Val	Arg	Glu	Val	Lys	Gly	Leu	Thr	Lys	Gly	Gly
2585						2590					2595			

Pro	Gly	His	Glu	Glu	Pro	Ile	Pro	Met	Ser	Thr	Tyr	Gly	Trp	Asn
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Leu	Val	Arg	Leu	Gln	Ser	Gly	Val	Asp	Val	Phe	Phe	Ile	Pro	Pro
	2615					2620					2625			
Glu	Lys	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser	Ser	Pro
	2630					2635					2640			
Asn	Pro	Thr	Val	Glu	Ala	Gly	Arg	Thr	Leu	Arg	Val	Leu	Asn	Leu
	2645					2650					2655			
Val	Glu	Asn	Trp	Leu	Asn	Asn	Asn	Thr	Gln	Phe	Cys	Ile	Lys	Val
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Asn	Ser	Thr	His	Glu	Met	Tyr	Trp	Val	Ser	Asn	Ala	Ser	Gly	Asn
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Ile	Val	Ser	Ser	Val	Asn	Met	Ile	Ser	Arg	Met	Leu	Ile	Asn	Arg
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Phe	Thr	Met	Arg	Tyr	Lys	Lys	Ala	Thr	Tyr	Glu	Pro	Asp	Val	Asp
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Asn	Leu	Asp	Ile	Ile	Gly	Lys	Arg	Ile	Glu	Lys	Ile	Lys	Gln	Glu
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His	Glu	Thr	Ser	Trp	His	Tyr	Asp	Gln	Asp	His	Pro	Tyr	Lys	Thr
	2780					2785					2790			
Trp	Ala	Tyr	His	Gly	Ser	Tyr	Glu	Thr	Lys	Gln	Thr	Gly	Ser	Ala
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Ser	Ser	Met	Val	Asn	Gly	Val	Val	Arg	Leu	Leu	Thr	Lys	Pro	Trp
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Asp	Val	Val	Pro	Met	Val	Thr	Gln	Met	Ala	Met	Thr	Asp	Thr	Thr
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Pro	Phe	Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	Asp	Thr	Arg
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	2855					2860					2865			
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Thr	Leu	Glu	Asp	Leu	Lys	Asn	Glu	Glu	Met	Val	Thr	Asn	His	Met
	3035					3040					3045			

Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr
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Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly
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Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly
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Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala
3095 3100 3105

Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile
3110 3115 3120

Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu
3125 3130 3135

Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly
3140 3145 3150

Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala
3155 3160 3165

Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln
3170 3175 3180

Gln Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro
3185 3190 3195

Phe Cys Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg
3200 3205 3210

Val Leu Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg
3215 3220 3225

Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala
3230 3235 3240

Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe
3245 3250 3255

His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile Cys Ser Ala
3260 3265 3270

Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile
3275 3280 3285

His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr Val
3290 3295 3300

Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys
3305 3310 3315

Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg
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Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala
3335 3340 3345

Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser
3350 3355 3360

Leu Ile Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys
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Arg Phe Arg Arg Glu Glu Glu Glu Ala Gly Val Leu Trp
3380 3385 3390

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Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
20 25 30

Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
35 40 45

Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
50 55 60

Ile	Leu	Lys	Arg	Trp	Gly	Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val	65	70	75	80
Leu	Arg	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	85	90	95	
Arg	Arg	Arg	Ser	Ser	Ala	Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	100	105	110	
Met	Ala	Phe	His	Leu	Thr	Thr	Arg	Asp	Gly	Glu	Pro	Leu	Met	Ile	Val	115	120	125	
Ala	Lys	His	Glu	Arg	Gly	Arg	Pro	Leu	Leu	Phe	Lys	Thr	Thr	Glu	Gly	130	135	140	
Ile	Asn	Lys	Cys	Thr	Leu	Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Glu	145	150	155	160
Asp	Thr	Val	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Val	Asn	Thr	Glu	Pro	Glu	165	170	175	
Asp	Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Met	Tyr	Gly	180	185	190	
Thr	Cys	Thr	Gln	Ser	Gly	Glu	Arg	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala	195	200	205	
Leu	Thr	Pro	His	Ser	Gly	Met	Gly	Leu	Glu	Thr	Arg	Ala	Glu	Thr	Trp	210	215	220	
Met	Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Ala	Gln	Arg	Val	Glu	Ser	Trp	225	230	235	240
Ile	Leu	Arg	Asn	Pro	Gly	Phe	Ala	Leu	Leu	Ala	Gly	Phe	Met	Ala	Tyr	245	250	255	
Met	Ile	Gly	Gln	Thr	Gly	Ile	Gln	Arg	Thr	Val	Phe	Phe	Val	Leu	Met	260	265	270	
Met	Leu	Val	Ala	Pro	Ser	Tyr	Gly	Met	Arg	Cys	Val	Gly	Val	Gly	Asn	275	280	285	
Arg	Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ala	Trp	Val	Asp	Leu	Val	290	295	300	

Leu Glu His Gly Gly Cys Val Thr Thr Met Ala Gln Gly Lys Pro Thr
305 310 315 320

Leu Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu
325 330 335

Arg Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr
340 345 350

Arg Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln
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Gln Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly
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Cys Gly Leu Phe Gly Lys Gly Gly Val Val Thr Cys Ala Lys Phe Ser
385 390 395 400

Cys Ser Gly Lys Ile Thr Gly Asn Leu Val Gln Ile Glu Asn Leu Glu
405 410 415

Tyr Thr Val Val Val Thr Val His Asn Gly Asp Thr His Ala Val Gly
420 425 430

Asn Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser
435 440 445

Pro Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp
450 455 460

Cys Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys
465 470 475 480

Met Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
485 490 495

Pro Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn
500 505 510

Tyr Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln
515 520 525

Asp Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu
530 535 540

Ala Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala
545 550 555 560

Gly His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly
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Met Ser Tyr Thr Met Cys Ser Gly Lys Phe Ser Ile Asp Lys Glu Met
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Ala Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly
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Ala Gly Ala Pro Cys Lys Val Pro Ile Glu Ile Arg Asp Val Asn Lys
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Glu Lys Val Val Gly Arg Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn
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Thr Asn Ser Val Thr Asn Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser
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Tyr Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe
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Arg Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly
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Ala Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser
690 695 700

Val Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe
705 710 715 720

Gly Ser Val Tyr Thr Thr Leu Phe Gly Gly Val Ser Trp Met Ile Arg
725 730 735

Ile Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn
740 745 750

Thr Ser Met Ala Met Thr Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr
755 760 765

Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
770 775 780

Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
785 790 795 800

His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
805 810 815

Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
820 825 830

Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
835 840 845

Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
850 855 860

Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
865 870 875 880

Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
885 890 895

Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
900 905 910

Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
915 920 925

Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
930 935 940

Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
945 950 955 960

Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
965 970 975

Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
980 985 990

Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
995 1000 1005

Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala
1010 1015 1020

Gly	Pro	Val	Ser	Gln	His	Asn	Tyr	Arg	Pro	Gly	Tyr	His	Thr	Gln
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1040						1045					1050			
Phe	Cys	Asp	Gly	Thr	Thr	Val	Val	Val	Thr	Glu	Asp	Cys	Gly	Asn
1055						1060					1065			
Arg	Gly	Pro	Ser	Leu	Arg	Thr	Thr	Thr	Ala	Ser	Gly	Lys	Leu	Ile
1070						1075					1080			
Thr	Glu	Trp	Cys	Cys	Arg	Ser	Cys	Thr	Leu	Pro	Pro	Leu	Arg	Tyr
1085						1090					1095			
Arg	Gly	Glu	Asp	Gly	Cys	Trp	Tyr	Gly	Met	Glu	Ile	Arg	Pro	Leu
1100						1105					1110			
Lys	Glu	Lys	Glu	Glu	Asn	Leu	Val	Asn	Ser	Leu	Val	Thr	Ala	Gly
1115						1120					1125			
His	Gly	Gln	Val	Asp	Asn	Phe	Ser	Leu	Gly	Val	Leu	Gly	Met	Ala
1130						1135					1140			
Leu	Phe	Leu	Glu	Glu	Met	Leu	Arg	Thr	Arg	Val	Gly	Thr	Lys	His
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Ala	Ile	Leu	Leu	Val	Ala	Val	Ser	Phe	Val	Thr	Leu	Ile	Thr	Gly
1160						1165					1170			
Asn	Met	Ser	Phe	Arg	Asp	Leu	Gly	Arg	Val	Met	Val	Met	Val	Gly
1175						1180					1185			
Ala	Thr	Met	Thr	Gly	Asp	Ile	Gly	Met	Gly	Val	Thr	Tyr	Leu	Ala
1190						1195					1200			
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1205						1210					1215			
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1220						1225					1230			
Gly	Ile	Val	Leu	Leu	Ser	Gln	Ser	Thr	Ile	Pro	Glu	Thr	Ile	Leu
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Glu	Leu	Thr	Asp	Ala	Leu	Ala	Leu	Gly	Met	Met	Val	Leu	Lys	Met
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	1310					1315					1320			
Thr	Ile	Lys	Gly	Leu	Asn	Pro	Thr	Ala	Ile	Phe	Leu	Thr	Thr	Leu
	1325					1330					1335			
Ser	Arg	Thr	Ser	Lys	Lys	Arg	Ser	Trp	Pro	Leu	Asn	Glu	Ala	Ile
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Met	Ala	Val	Gly	Met	Val	Ser	Ile	Leu	Ala	Ser	Ser	Leu	Leu	Lys
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	1370					1375					1380			
Thr	Val	Cys	Tyr	Val	Leu	Thr	Gly	Arg	Ser	Ala	Asp	Leu	Glu	Leu
	1385					1390					1395			
Glu	Arg	Ala	Ala	Asp	Val	Lys	Trp	Glu	Asp	Gln	Ala	Glu	Ile	Ser
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Met	Ser	Ile	Lys	Asn	Glu	Glu	Glu	Glu	Gln	Thr	Leu	Thr	Ile	Leu
	1430					1435					1440			
Ile	Arg	Thr	Gly	Leu	Leu	Val	Ile	Ser	Gly	Leu	Phe	Pro	Val	Ser
	1445					1450					1455			
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	1460					1465					1470			

Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met
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Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys
1490 1495 1500

Gly Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu
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Gly Thr Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu
1520 1525 1530

Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys
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Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu
1550 1555 1560

Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu Pro Gly
1565 1570 1575

Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys Thr
1580 1585 1590

Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly
1595 1600 1605

Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly
1610 1615 1620

Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser
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Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile
1640 1645 1650

Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu
1655 1660 1665

His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val
1670 1675 1680

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發明摘要

※ 申請案號：108114540

※ 申請日：103.3.14

※ I P C 分類：

【發明名稱】(中文/英文)

用於疫苗中之登革熱病毒嵌合式建構物的組成物及方法

COMPOSITIONS AND METHODS FOR DENGUE VIRUS CHIMERIC
CONSTRUCTS IN VACCINES

【中文】

此處實施例實證登革熱病毒建構物及活減毒登革熱病毒之組成物、用途及製造。若干實施例係有關於一種組成物包括但非限制性，四價登革熱病毒組成物。於某些實施例中，組成物可包括一或多個登革熱病毒血清型之建構物，諸如登革熱-1(DEN-1)病毒、登革熱-2(DEN-2)病毒、登革熱-3(DEN-3)病毒、及登革熱-4(DEN-4)病毒建構物。於其它實施例中，如此處揭示的建構物可組合於一組成物以產生對抗多於一種或多種登革熱病毒建構物之疫苗，該建構物可以或可不接續地於哺乳動物細胞內繼代培養。

【英文】

Embodiments herein report compositions, uses and manufacturing of dengue virus constructs and live attenuated dengue viruses. Some embodiments concern a composition that includes, but is not limited to, a tetravalent dengue virus composition. In certain embodiments, compositions can include constructs of one or more serotypes of dengue virus, such as dengue-1 (DEN-1) virus, dengue-2 (DEN-2) virus, dengue-3 (DEN-3) or dengue-4 (DEN-4) virus constructs. In other embodiments, constructs disclosed herein can be combined in a composition to generate a vaccine against more one or more dengue virus constructs that may or may not be subsequently passaged in mammalian cells.

【代表圖】

【本案指定代表圖】：第（ ）圖。（無）

【本代表圖之符號簡單說明】：

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：

（無）

申請專利範圍

1. 一種編碼登革熱-1/登革熱-2多肽嵌合體的聚核苷酸分子，該聚核苷酸包含一第一核苷酸序列及一第二核苷酸序列，該第一核苷酸序列編碼來自改性活減毒登革熱-2病毒株PDK 53的非結構蛋白質，且該第二核苷酸序列編碼來自登革熱-1的至少一結構蛋白質，其中該聚核苷酸包含至少一突變，其中該至少一突變包含下列一或多者：

在位置3823之腺嘌呤至胞嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置1243之異白胺酸的白胺酸，其對應至NS2A 116；

在位置4407之腺嘌呤至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置1437之麩胺酸的天冬胺酸，其對應至NS2B-92；以及

在位置7311之腺嘌呤至鳥嘌呤的突變。

2. 如請求項1之聚核苷酸分子，其進一步包含下列之至少一額外突變：

在位置7148之胞嘧啶至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置2351之蘇胺酸的異白胺酸，其對應至NS4B-108；以及

在位置2384之鳥嘌呤至胞嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置763之甘胺酸的丙胺酸，其對應至E-483。

3. 如請求項2之聚核苷酸分子，其包含由SEQ ID NO: 1所表示之聚核苷酸。
4. 如請求項1之聚核苷酸分子，其編碼登革熱-1/登革熱-2多肽嵌合體，其中該多肽是由SEQ ID NO: 3所表示。
5. 一種由如請求項1至4中任一項之聚核苷酸分子所編碼的多肽分子。
6. 一種登革熱-1/登革熱-2嵌合體，其包含一或多種如請求項5之多肽分子。
7. 一種藥學組成物，其包含如請求項1至4中任一項之聚核苷酸分子、如請求項5之多肽分子或如請求項6之登革熱-1/登革熱-2嵌合體，及藥學上可接受之賦形劑。
8. 一種藥學可接受量之如請求項7之組成物於製備藥物的用途，該藥物是用於在個體內誘發免疫反應，其中該組成物在個體內誘發對登革熱病毒的免疫反應。
9. 一種載體，其編碼如請求項1-4中任一項之聚核苷酸分子。
10. 一種細胞，其包含如請求項1-4中任一項的聚核苷酸分子或如請求項9之載體。
11. 一種編碼改性活減毒登革熱-2病毒株PDK-53多肽分子的聚核苷酸分子，其中該聚核苷酸包含至少一突變，其中該至少一突變包含：

在位置592之腺嘌呤至鳥嘌呤的突變，其編碼代替在該多肽分子之胺基酸位置166之離胺酸的麩胺酸，其對應至prM-52；以及

在位置8803之腺嘌呤至鳥嘌呤的突變，其編碼代替在該多肽分子之胺基酸位置2903之異白胺酸的纈胺酸，其對應至NS5-412。

12. 如請求項11之聚核苷酸分子，其進一步包含下列之至少一額外突變：

在位置6481之鳥嘌呤至胞嘧啶的突變，其編碼代替在該多肽分子之胺基酸位置2129之丙胺酸的脯胺酸，其對應至NS4A-36；以及

在位置7156之胞嘧啶至胸腺嘧啶的突變，其編碼代替在該多肽分子之胺基酸位置2354之白胺酸的苯丙胺酸，其對應至NS4B-111。

13. 如請求項12之聚核苷酸分子，其包含由SEQ ID NO: 4所表示之聚核苷酸。
14. 如請求項11之聚核苷酸分子，其編碼改性活減毒登革熱-2病毒株PDK-53，其中該多肽是由SEQ ID NO: 6所表示。
15. 一種由如請求項11至14中任一項之聚核苷酸分子所編碼的多肽分子。
16. 一種改性活減毒登革熱-2病毒株PDK-53，其包含一或多種如請求項15之多肽分子。
17. 一種藥學組成物，其包含如請求項11至14中任一項之聚核苷酸分子、如請求項15之多肽分子或如請求項16之登革熱-2病毒，及藥學上可接受之賦形劑。

18. 一種藥學可接受量之如請求項17之組成物於製備藥物的用途，該藥物是用於在個體內誘發免疫反應，其中該組成物在個體內誘發對登革熱病毒的免疫反應。
19. 一種載體，其編碼如請求項11至14中任一項之聚核苷酸分子。
20. 一種細胞，其包含如請求項11至14中任一項的聚核苷酸分子或如請求項19之載體。
21. 一種編碼登革熱-3/登革熱-2多肽嵌合體的聚核苷酸分子，該聚核苷酸包含一第一核苷酸序列及一第二核苷酸序列，該第一核苷酸序列編碼來自改性活減毒登革熱-2病毒株PDK-53的非結構蛋白質，且該第二核苷酸序列編碼來自登革熱-3的至少一結構蛋白質，其中該聚核苷酸包含至少一突變，其中該至少一突變包含：

在位置1603之腺嘌呤至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置503之蘇胺酸的絲胺酸，其對應至E-223；以及

在位置7620之腺嘌呤至鳥嘌呤的突變。
22. 如請求項21之聚核苷酸分子，其進一步包含在位置6436之腺嘌呤至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置1243之天冬胺酸的天冬醯胺酸，其對應至N42A-23。
23. 如請求項22之聚核苷酸分子，其包含由SEQ ID NO: 7所表示之聚核苷酸。

24. 如請求項21之聚核苷酸分子，其編碼登革熱-3/登革熱-2多肽嵌合體，其中該多肽是由SEQ ID NO: 9所表示。
25. 一種由如請求項21至24中任一項之聚核苷酸所編碼的多肽分子。
26. 一種登革熱-3/登革熱-2多肽嵌合體，其包含一或多種如請求項25之多肽分子。
27. 一種藥學組成物，其包含如請求項21至24中任一項之聚核苷酸分子、如請求項25之多肽分子或如請求項26之登革熱-3/登革熱-2嵌合體，及藥學上可接受之賦形劑。
28. 一種藥學可接受量之如請求項27之組成物於製備藥物的用途，該藥物是用於在個體內誘發免疫反應，其中該組成物在個體內誘發對登革熱病毒的免疫反應。
29. 一種載體，其編碼如請求項21至24中任一項之聚核苷酸分子。
30. 一種細胞，其包含如請求項21至24中任一項的聚核苷酸分子或如請求項29之載體。
31. 一種編碼登革熱-4/登革熱-2多肽嵌合體的聚核苷酸分子，該聚核苷酸包含一第一核苷酸序列及一第二核苷酸序列，該第一核苷酸序列編碼來自改性活減毒登革熱-2病毒株PDK-53的非結構蛋白質，且該第二核苷酸序列編碼來自登革熱-4的至少一結構蛋白質，其中該聚核苷酸包含至少一突變，其中該至少一突變包含：

在位置225之腺嘌呤至胸腺嘧啶的突變；

- 在位置3674之腺嘌呤至鳥嘌呤的突變，其編碼代替在該嵌合體之胺基酸位置1193之天冬胺酸的甘胺酸，其對應至NS2A-66；
 - 在位置5391之胞嘧啶至胸腺嘧啶的突變；
 - 在位置6437之胞嘧啶至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置2114之丙胺酸的纈胺酸，其對應至NS4A-21；
 - 在位置7026之胸腺嘧啶至胞嘧啶的突變；以及
 - 在位置9750之腺嘌呤至胞嘧啶的突變。
32. 如請求項31之聚核苷酸分子，其進一步包含在位置3773之腺嘌呤至鳥嘌呤的突變，其編碼代替在該嵌合體之胺基酸位置1226之離胺酸的精胺酸，其對應至NS2A-99。
33. 如請求項31或32之聚核苷酸分子，其進一步包含在位置7538之胞嘧啶至胸腺嘧啶的突變，其編碼代替在該嵌合體之胺基酸位置2481之絲胺酸的苯丙胺酸，其對應至NS4B-238。
34. 如請求項33之聚核苷酸分子，其包含由SEQ ID NO: 10所表示之聚核苷酸。
35. 如請求項31或32之聚核苷酸分子，其編碼登革熱-4/登革熱-2多肽嵌合體，其中該多肽是由SEQ ID NO: 12所表示。
36. 一種由如請求項31至35中任一項之聚核苷酸所編碼的多肽分子。

37. 一種登革熱-4/登革熱-2多肽嵌合體，其包含一或多種如請求項36之多肽分子。
38. 一種藥學組成物，其包含如請求項31至35中任一項之聚核苷酸分子、如請求項36之多肽分子或如請求項37之登革熱-4/登革熱-2嵌合體，及藥學上可接受之賦形劑。
39. 一種藥學可接受量之如請求項38之組成物於製備藥物的用途，該藥物是用於在個體內誘發免疫反應，其中該組成物在個體內誘發對登革熱病毒的免疫反應。
40. 一種載體，其編碼如請求項31至35中任一項之聚核苷酸分子。
41. 一種細胞，其包含如請求項31至35中任一項的聚核苷酸分子或如請求項40之載體。
42. 一種免疫原性組成物，其包含至少一如請求項1至4、11至14、21至24或31至35中任一項之聚核苷酸分子以及藥學上可接受之載劑。
43. 如請求項42之組成物，其中該組成物含有全部四種登革熱病毒血清型，為四價組成物。
44. 如請求項43之組成物，其進一步包含用於黃病毒之免疫原性組成物，該黃病毒是選自由下列所構成之群組：黃熱病毒、蜱媒腦炎病毒、日本腦炎病毒、西尼羅病毒、C型肝炎病毒、及其中二或多者的組合。
45. 一種套組，其包含至少一如請求項1至4、11至14、21至24或31至35中任一項之聚核苷酸分子；或至少一如請求項7、17、27、38或42至45中任一項之組成物及容器

46. 一種組成物，其包含一或多種如請求項6、16、26及37之活減毒病毒，及藥學上可接受之載劑。
47. 如請求項46之組成物，其中該組成物包含能夠在個體內誘發免疫反應對抗全部四種登革熱病毒血清型的四價登革熱病毒組成物。
48. 如請求項9、19、29及40中任一項之載體，其中該載體為質體載體。
49. 如請求項9、19、29及40中任一項之載體，其中該載體為cDNA傳染性純株。

D2/4嵌合體比較wt D2 16681及D4-1036間之遺傳變異

基因	D2		接合	D4		接合	D2									
	NCR	C		prM	E		NS1	NS2A			NS3		NS4A		NS4B	NS5
突變型*	PDK-53	種	Eng	MuJ	種	種	PDK-53	種	種	PDK-53	PDK-53	種	PDK-53	種	PDK-53	種
基礎型WT位點 蛋白質-AA位點	CS7T NCR	A225T C-無變	A396C C-1100S	A453G prM-全變	C647G/C prM-T75R/T E-無變	A1401G C2027T A2275C E-V482A E-A3264V E-M4447L	TGZ380/1CC G2579A NS1-G53D	A3674G NS2A-D66G	A3773A/G NS2A-K99K/R NS2A-L191F	C4018T	A5270T NS3-E250V NS3-全變	C5391T NS3-無變	T5547C	C6437T NS4A-A21V NS4A-G75A	G6599C NS4B-無變	T7026C/T NS5-全變 NS5-無變
D2-16681	C	A	A [R]	A			G [G]	A [D]	A [G]	C [L]	A [G]	C	T	C [A]	G [G]	C
D2-PDK-53	T	-	-				A [D]	-	-	T [F]	T [V]	-	c	-	C [A]	t
D4-1036					G [T]	A	C [A]	A [M]								
遺傳D2/4-VI (pD2/4-VPI)	T	-	C [G]	g	-	g	T [V]	C [L]	CC [A]	A [D]	-	-	T [F]	T [V]	-	c
DEWvar-4 (MVS)	T	t	C [G]	g	-	g	T [V]	C [L]	CC [A]	A [D]	G [G]	A/G [K/R]	T [F]	T [V]	t	c

*、^ 同wt D2 16681或D4 1036；小寫字母：於釋放病毒區之無變突變
* PDK-53: D2-PDK-53唯一性基因型(相似於16681)；紅：主要病毒PDK-53基因型；藍：突變只出現在特定病毒毒株而不位於先鋒株；Eng：D2/4病毒之基因改造突變；MuJ及NpoMIV：D2/4嵌合基因改造位點；
**、C8571T (PDK-53 無變突變)不含於大部分D2/4嵌合式病毒

圖1

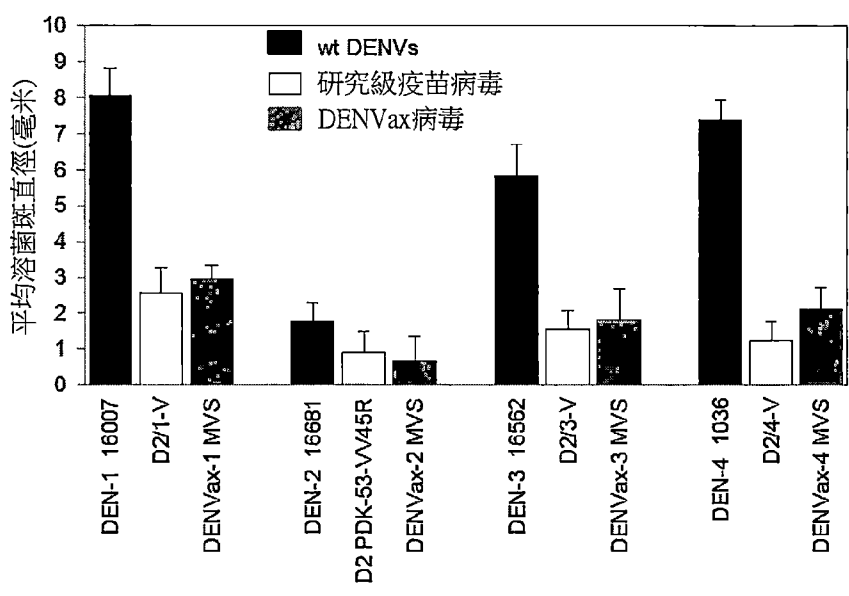


圖2

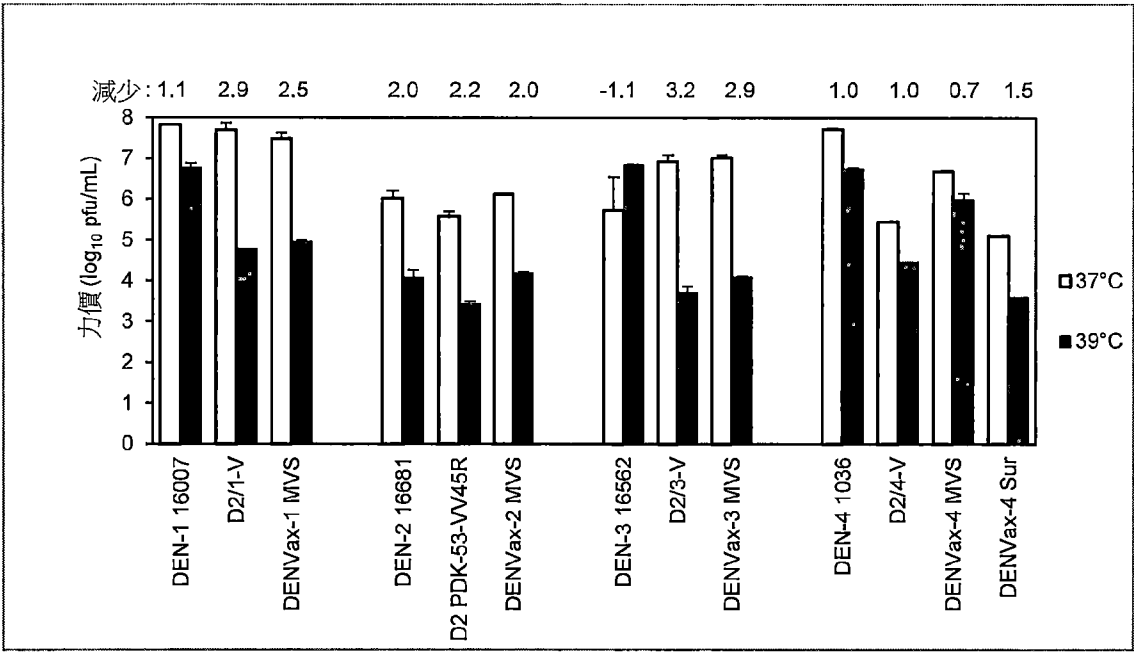


圖3

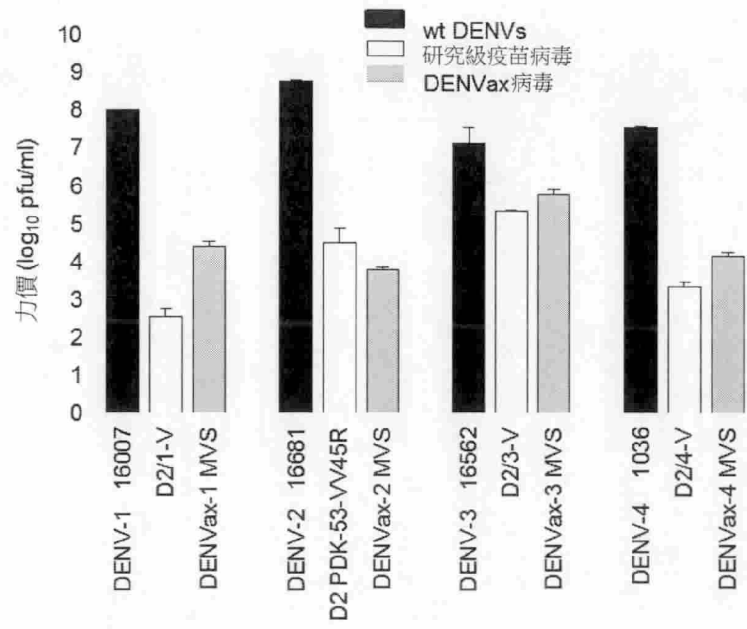


圖4

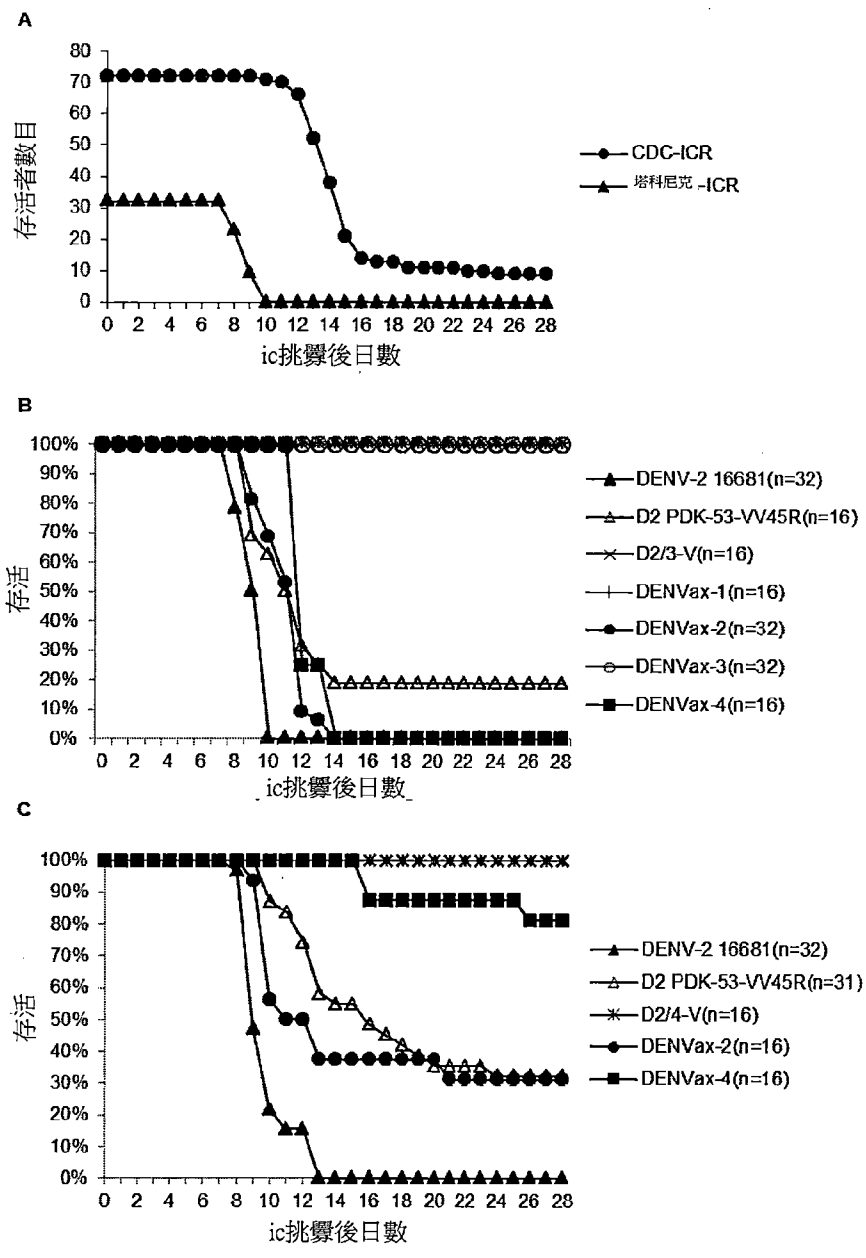


圖5

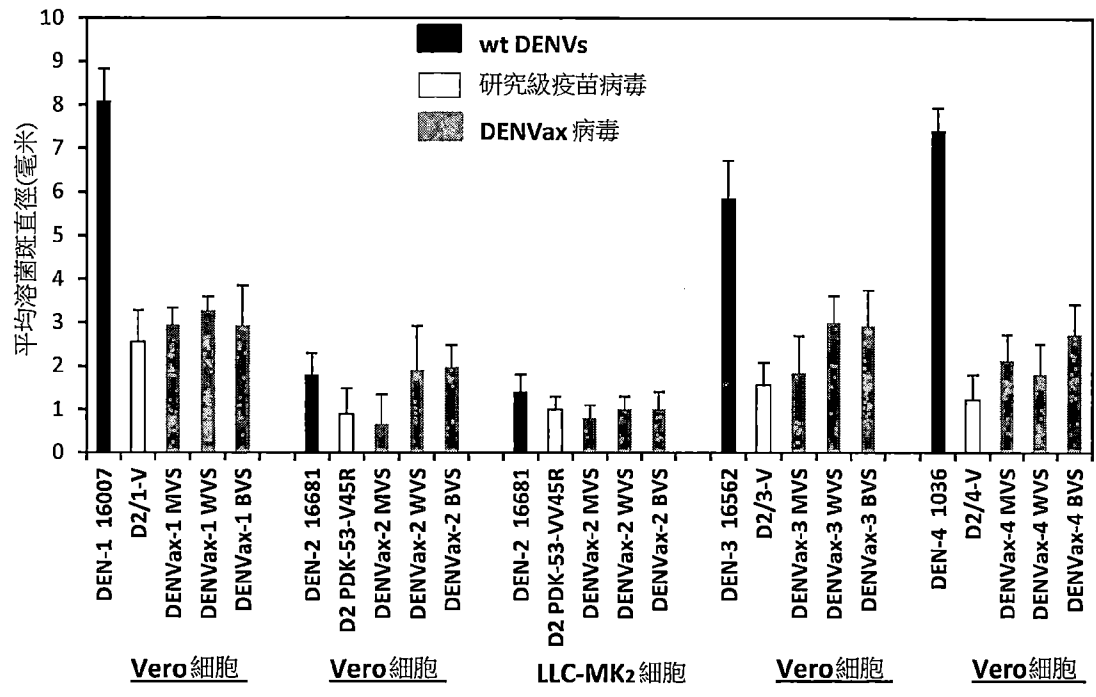


圖6

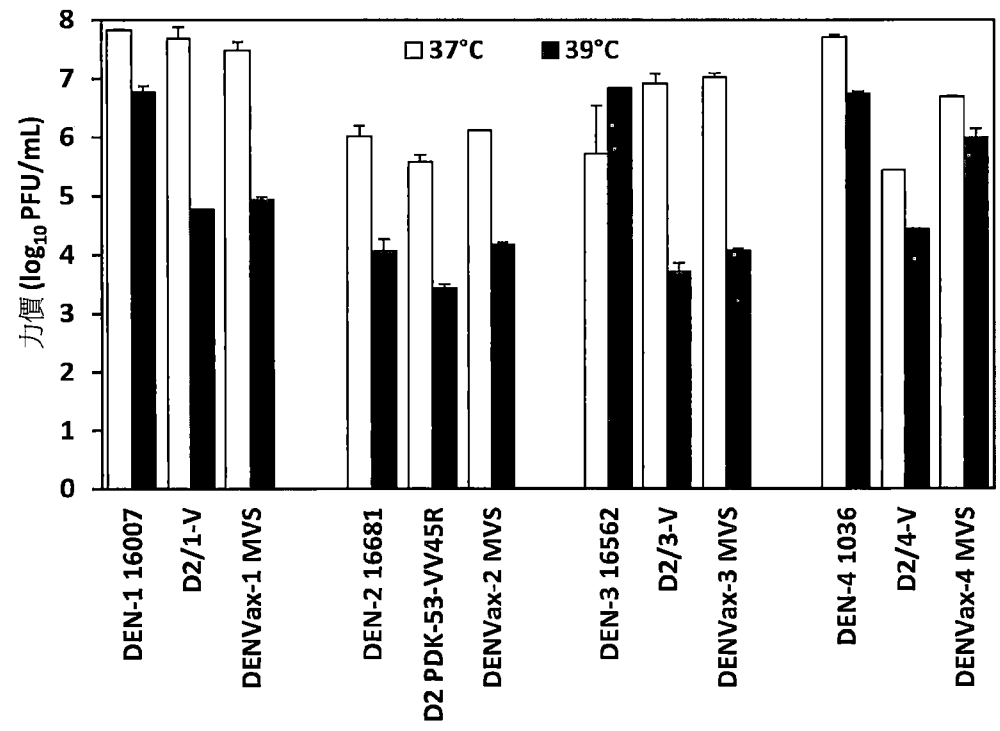


圖 7

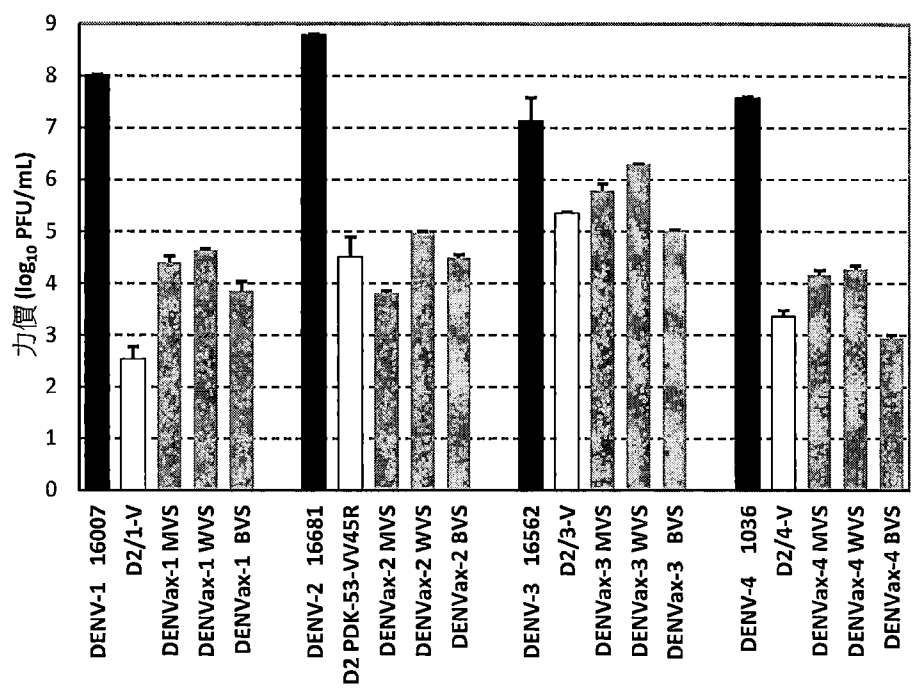
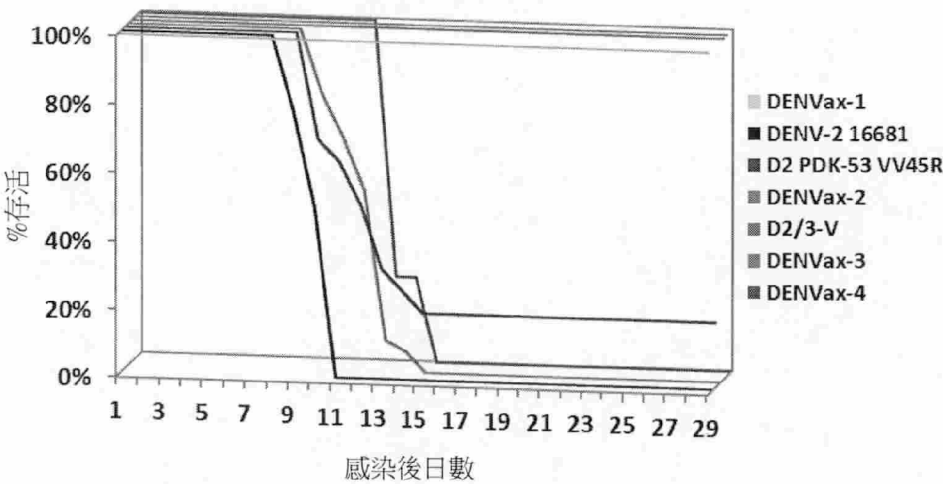


圖 8

A



B

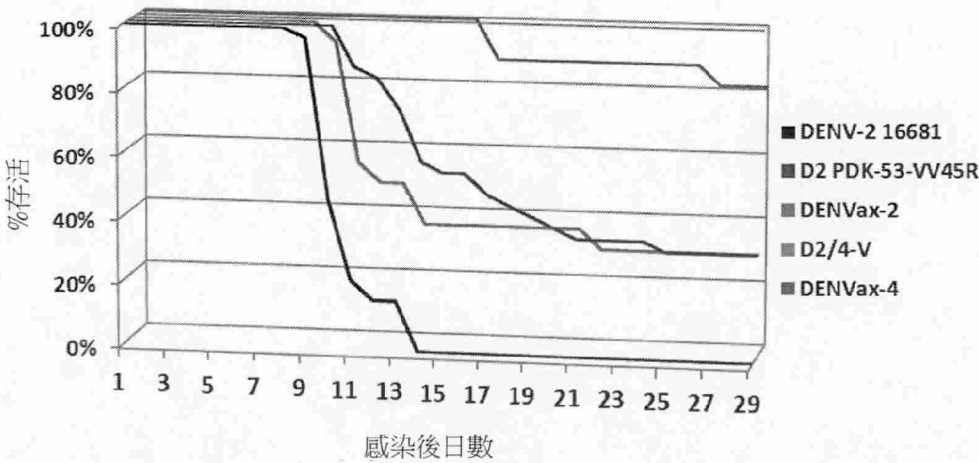


圖9

血清型	種系	病毒來源	C57T	A524T	T900C ^a	C2055T	G2579A	C4018T	A5270T	T5547C	G6599C	C8571T
			5'NCR	prM-D29V	M (無聲)	E (無聲)	NS1-G53D	NS2A-L181	NS3-E250V	NS3(無聲)	NS4A-G75A	NS5(無聲)
DENV-2	16681	從人體分離	C	A	T	C	G	C	A	T	G	C
	PDK-53	16681之PDK細胞繼代	T	T	-	t	A	T	T/A mix	c	C	t
	PDK53-V(VV45R)	重組PDK-53-V	T	T	c	t	A	T	T	c	C	C
	PDK53-E(V648R)	重組PDK-53-E	T	T	c	t	A	T	A	c	C	C

下方畫線突變：PDK-53之三個最重要滅毒基因座
紅字：PDK-53專一性序列(從16681改變)
粗體字：PDK-53與純株衍生V或E病毒間之不同核苷酸序列
^a基因改造無聲純株標記以區別原先PDK-53與重組(純株衍生)病毒

圖10