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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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(54)名稱

登革熱病毒血清型 4 型之建構物的組成物、方法及用途

COMPOSITIONS, METHODS AND USES FOR DENGUE VIRUS SEROTYPE-4 CONSTRUCTS

(57)摘要

在此之具體例記述登革熱 4 型(DEN-4)病毒建構物的組成物、方法及用途。一些具體例有關一種組成物，其包括，但不限於，在此所揭示之 DEN-4 病毒建構物，單獨或結合其它建構物，可用在疫苗組成物中，用以在個體中誘發免疫反應。在某些具體例中，組成物可包括超過一種登革熱病毒血清型之建構物，諸如登革熱 1 型(DEN-1)病毒、登革熱 2 型(DEN-2)病毒或登革熱 3 型(DEN-3)病毒，結合在此所揭示之 DEN-4 病毒建構物。在其它具體例中，在此所揭示之 DEN-4 建構物可於組成物中結合其它黃病毒建構物，產生抗超過一種黃病毒之疫苗。其它具體例提供 DEN-4 病毒建構物於疫苗組成物中之方法以及用途，其當投與至個體時，會在該個體中誘發抗 DEN-4 之免疫反應，其與其它疫苗組成物相比，已經過建構物修飾之改良。

Embodiments herein report compositions, methods and uses for dengue-4 (DEN-4) virus constructs. Some embodiments concern a composition that includes, but is not limited to, DEN-4 virus constructs disclosed herein that alone or in combination with other constructs can be used in a vaccine composition to induce an immune response in a subject. In certain embodiments, compositions can include constructs of more than one serotypes of dengue virus, such as dengue-1 (DEN-1) virus, dengue-2 (DEN-2) virus, or dengue-3 (DEN-3) virus in combination with DEN-4 virus constructs disclosed herein. In other embodiments, DEN-4 constructs disclosed herein can be combined in a composition with other flavivirus constructs to generate a vaccine against more than one flavivirus. Other embodiments provide methods and uses for DEN-4 virus constructs in vaccine compositions that when administered to a subject induce an

immune response in the subject against DEN-4 that is improved by modified constructs compared to other vaccine compositions.

指定代表圖：

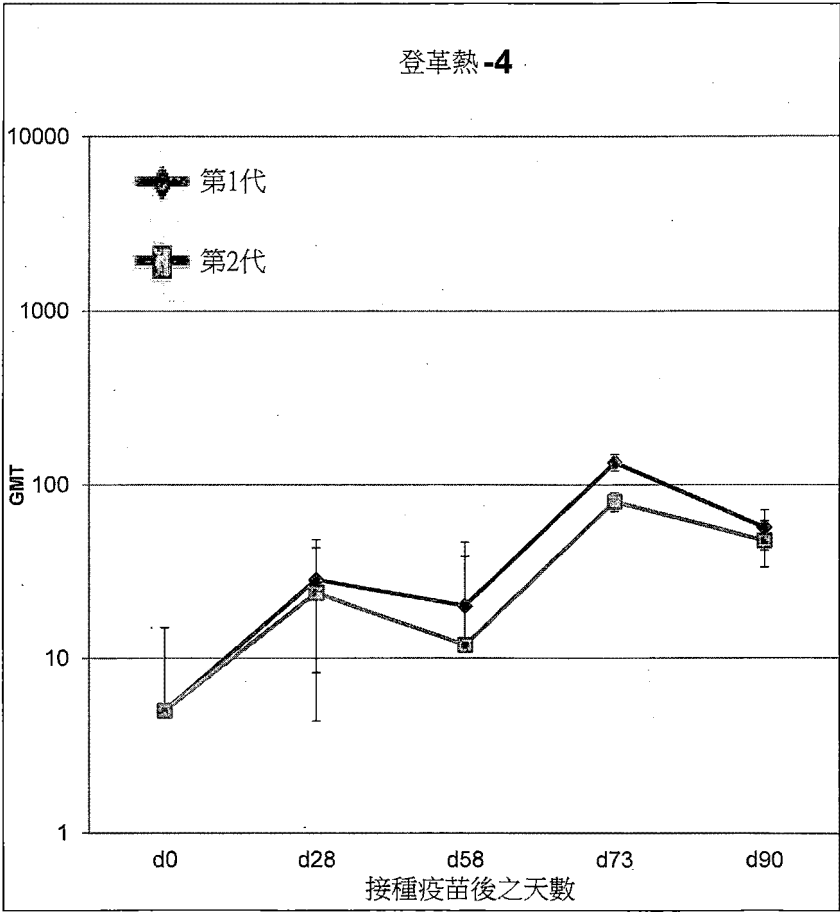


圖3

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)

登革熱病毒血清型4型之建構物的組成物、方法及用途
COMPOSITIONS, METHODS AND USES FOR DENGUE
VIRUS SEROTYPE-4 CONSTRUCTS

【技術領域】

聯邦政府資助的研究

[0001]在此揭示之一些具體例，部分由國家衛生研究院基金號碼R43 AI084291-01贊助。美國政府具有某些實施本發明之權利。

發明領域

[0002]在此之具體例記述登革熱4型(DEN-4)病毒建構物之組成物、方法以及用途。一些具體例有關一種組成物，其包括，但不限於，DEN-4病毒建構物，單獨或結合其它劑，可用在疫苗組成物中。在某些具體例中，組成物可包括超過一種登革熱病毒血清型之嵌合體建構物，諸如登革熱1型(DEN-1)病毒、登革熱2型(DEN-2)病毒或登革熱3型(DEN-3)病毒，結合DEN-4病毒嵌合體建構物，呈二、三或四價配方形式。在其它具體例中，在此所揭示之DEN-4嵌合體建構物(登革熱-登革熱嵌合體)，可結合其它黃病毒建構物。某些具體例包括具有其它登革熱血清型之組份(諸如結構元素)之DEN-4嵌合建構物。其它具體例提供DEN-4病毒嵌合體建構物於疫苗組成物中之方法以及用途，其當投與至個體時，會在該個體中誘發抗DEN-4之免

疫反應，其與其它建構物相比，已經過改良。

【先前技術】

發明背景

[0003] 感染到登革熱病毒，可能導致各種嚴重度的疼痛發熱。迄今為止，已鑑定出四種登革熱血清型：登革熱1型(DEN-1)、登革熱2型(DEN-2)或登革熱3型(DEN-3)以及登革熱4型(DEN-4)。登革熱是因為感染登革熱病毒所引起的。登革熱病毒血清型1-4型亦可引起登革熱出血熱(DHF)以及登革熱休克症候群(DSS)。最嚴重的感染結果，DHF以及DSS，可能會對生命構成威脅。登革熱病毒每年引起5千萬-1億件使人衰弱之登革熱、500,000件DHF/DSS以及超過20,000件之死亡。迄今，無有效的疫苗可提供對抗登革熱之保護，且無針對此疾病之藥物治療。蚊蟲控制之努力，在預防登革熱於流行區域之爆發方面，或預防此疾病進一步的地理擴散方面，已經無效。估計有35億人受到登革熱病毒感染的威脅。此外，登革熱病毒是旅客至流行區域，諸如亞洲、中南美洲以及加勒比海，發燒的主要原因。

[0004] 全部四種登革熱病毒血清型，在世界上各熱帶地區均有流行，對全世界熱帶地區之人類構成最嚴重的蚊媒病毒威脅。登革熱病毒主要係透過埃及斑蚊傳播至人類。被一種登革熱病毒血清型感染，終生不會重複受該血清型之感染，但無法預防其它三種登革熱病毒血清型中之一種的二次感染。事實上，之前被一種登革熱病毒血清型感染，之後在被不同血清型之二次感染時，會增加嚴重疾病

(DHF/DSS)之風險。研發有效的疫苗，對預防以及控制此全球性肆虐的疾病而言，是很重要的途徑。

【發明內容】

發明概要

[0005]在此之具體例有關DEN-4病毒嵌合體建構物之組成物、方法以及用途。在一些具體例中，組成物可包括DEN-4病毒嵌合體建構物，單獨或結合其它登革熱病毒血清型建構物，或相同或其它血清型之活減毒登革熱病毒，或其它能夠針對標的病毒(如，登革熱病毒)誘發免疫反應之黃病毒建構物。其它具體例可包括一種具有抗DEN-4之活減毒病毒建構物，以及任擇地一或多種抗DEN-1、DEN-2與DEN-3之活減毒病毒建構物之組成物。在其它具體例中，提供一種致免疫性組成物，其包括導入一個體時，會增加致免疫性之DEN-4活減毒嵌合病毒建構物。依照此等具體例，此等活減毒病毒建構物可單獨使用或結合一或多種其它DEN-1、DEN-2以及DEN-3建構物，以及藥學上可接受之賦形劑，產生抗登革熱病毒血清型之疫苗配方。在某些具體例中，產生抗一或多種登革熱病毒之單價、二價、三價或四價藥學上有效的配方。在某些具體例中，致免疫性組成物可包括DEN-1、DEN-2、DEN-3登革熱-登革熱嵌合建構物中之一或多種，結合在此所揭示之嵌合DEN-4建構物。

[0006]在某些具體例中，包括本發明之DEN-4建構物，結合DEN-1、DEN-2以及DEN-3中之一或多種之致免疫性組

成物，可用於在單一疫苗投與時，提供抗二或多種登革熱病毒血清型之同步的保護。在其它具體例中，可於一個體中投與包括DEN-1、DEN-2、DEN-3以及在此所揭示之具體例之修飾或突變的DEN-4建構物之致免疫性組成物，用以誘發抗每一種登革熱病毒血清型之改善的致免疫反應，以及在此對DEN-4之免疫反應干擾降低。

[0007]在某些具體例中，DEN-4建構物可包括一種登革熱-登革熱嵌合建構物，其在DEN-4之結構或非結構區中，具有適應的突變。在其它具體例中，DEN-4建構物可包括另一登革熱病毒血清型，DEN-1、DEN-2或DEN-3之骨架。在又其它具體例中，嵌合建構物可包括DEN-2骨架，在此DEN-4之結構或非結構區，取代DEN-2結構或非結構區。依照此等具體例，DEN-2骨架可包括任何活減毒DEN-2病毒。在其它具體例中，DEN-2骨架可包括活減毒DEN-2 PDK-53病毒作為骨架，在此該活減毒DEN-2 PDK病毒進一步包括具有DEN-4之prM (前趨膜)以及(套膜)結構蛋白中之一或多種之結構蛋白。此外，為了提高投與時，個體對DEN-4之免疫反應，DEN-2 PDK-53 骨架可包括額外的 DEN-2 PDK-53之突變或突變的回復。

[0008]在一些具體例中，為了改善病毒在試管中用於生產以及在活體內使用作為誘發對DEN-4之免疫反應之建構物二者之複製效率，修飾目前稱作DENVax-4毒株(strain)(序列辨識編號：21)之登革熱嵌合建構物，使含有DEN-2骨架之殼體/PrM接頭，以便在基因上更像DEN-4，而不是

DEN-2。目前的DENVax-4毒株具有與DEN-2一致而不是DEN-4之殼體/PrM序列，會製造與DENV-4不同之RNA次級結構。

[0009]在一些具體例中，結構蛋白基因可包含在另一登革熱病毒骨架上之DEN-4之prM以及E基因，製造登革熱-登革熱嵌合體。例如，在某些具體例中，DEN-4建構物可包括該等稱作DENVax-4c (殼體107半胱胺酸變成酪胺酸；DenVax-4b骨架、在殼體/prM接頭處有修改)、DENVax-4f或DENVax-4h (套膜417 Glu變成Lys) (見例如圖4)之建構物，在此針對某些建構物，DEN-2 PDK-53骨架具有一或多種回復成野生型DEN-2之回復(如，在非編碼區(NCR)或非結構區(NS1等))以及一或多種在DEN-4結構區(如，prM或E)中之突變，同時編碼一或多種DEN-4 (如，毒株1036)之結構蛋白。在此所揭示之修飾的DEN-4建構物可包括經修飾減毒的DEN-2 PDK-53骨架，具有一或多種DEN-4毒株1036之經修飾的結構蛋白。在一些具體例中，存在活減毒DEN-2 PDK-53病毒中之一或多種突變，可回復成對照胺基酸或另一胺基酸，用以產生在此之建構物，其可在不影響其減毒作用，但可影響DEN-4病毒之生長和/或複製之情況下，產生具有致免疫性增加之修飾的DEN-2/DENV-4建構物。在某些具體例中，該回復作用可使生長和/或複製增加。

[0010]在其它具體例中，為了產生包括經改善的免疫反應，同時維持安全性以及病毒減毒作用，修飾的DEN-4建構物可合併引入DEN-4之一或多個結構區和/或非結構區之

突變。例如，DEN-2/DEN-4之修飾的或突變的登革熱-登革熱嵌合體，可包含在DEN-2 PDK-53骨架之一或多個非結構區之突變，諸如在NS2A以及NS4A，和/或5'非編碼區(5'NCR)。在另一具體例中，修飾的DEN-4嵌合體建構物可藉由回復在PDK-53之NS2A以及NS4A處之突變(如，在NS4A處之M-L取代)，而包括DEN-2 16681之NS2A以及NS4A。一些具體例包括一種修飾的DEN-4嵌合體建構物，其係藉由回復在標的建構物之DEN-2 PDK-53骨架中相應的突變，而具有DEN-2 16681之5'NCR、NS2A以及NS4A。其它具體例可包括一種修飾的DEN-4嵌合體建構物，其係藉由回復DEN-2 PDK-53骨架中相應的突變，而具有DEN-2 16681之5'NCR。修飾的DEN-4嵌合體建構物亦可包括DEN-2 PDK-53骨架以及編碼DEN-4毒株H241之一或多個結構蛋白。任何DEN-4建構物蛋白，均可考慮用於取代登革熱血清型2型(如，PDK-53或修飾的PDK-53)之結構或非結構區。在一些具體例中，修飾的DEN-4建構物含有作為骨架之活減毒DEN-2 PDK-53，以及DEN-4結構蛋白，在此可引入突變以便修飾DEN-4(如，毒株1036)之結構區。

[0011]在其它具體例中，可於DEN-4之殼體/prM接頭胺基酸序列中引入突變，以便增加含有此突變之建構物之致免疫性。例如，DEN-4中之突變可為在DEN-4之殼體位置107處之Cys-Tyr突變。在其它具體例中，可考慮將位置107之半胱胺酸突變成任何其它具有疏水性側鏈之芳族胺基酸(見例如DEN-4e)。嵌合體建構物之其它DEN-2 PDK-53回

復，可在NS2A或NS4A中找到。又其它具體例包括DEN-4建構物，在此DEN-2骨架包含PDK-53 (MVS，序列辨識編號：21)，在此PDK-53之殼體區之胺基酸位置102-107，轉換成DEN-4對應的胺基酸，產生DENV-4b (見例如圖4)。此等骨架建構物之後可進一步包含殼體區中之半胱胺酸，在原位變成芳族胺基酸(如，酪胺酸、色胺酸等等)。在某些具體例中，此建構物以序列辨識編號：22或序列辨識編號：23表示。

[0012]在此揭示之其它 DEN-4 建構物，可包括在 DEN-4毒株之套膜位置417處，例如，1036毒株序列或其相等毒株位置，之胺基酸取代，在此提供具有DEN-4結構蛋白之登革熱-2之DK-53骨架(MVS DEN2/4，序列辨識編號：21)。具體例包括進一步突變的套膜位置417，從帶負電變成帶正電側鏈胺基酸(如，離胺酸)。預期任何帶正電側鏈均會在不會影響其安全性或減毒作用之情況下，提供DEN-4建構物增加的致免疫性。在某些具體例中，此建構物以序列辨識編號：24或序列辨識編號：25表示。

[0013]在某些具體例中，DEN-4嵌合建構物之DEN-2 PDK-53回復，具有可在DEN-2 PDK-53 MVS中找到之5' NC、NS1以及NS3突變，同時具有其它回復或突變。已證實，此等三種突變對減毒作用(如，與對照組相比，噬斑尺寸較小、生長率降低、效價較低、溫度敏感性增加以及神經毒性減少)可能很重要。

[0014]在其它具體例中，DEN-2 PDK-53基因組骨架可

用於產生DEN-1以及DEN-3之嵌合建構物，在此，DEN-2 PDK-53基因組之一或多種結構蛋白基因，可由DEN-1以及DEN-3之一或多種結構蛋白基因取代。此等建構物可在具有DEN-2 PDK-53骨架之單一嵌合體中，包括DEN-1以及DEN-3二者之組合。在一些具體例中，結構蛋白可為DEN-1和/或DEN-3之C、prM或E蛋白。在某些具體例中，結構蛋白基因包括DEN-1或DEN-3之prM以及E基因。此等雜交/嵌合病毒會表達DEN-1、DEN-3或DEN-4之表面抗原，同時保有親本DEN-2之減毒表型。在某些具體例中，此等建構物以序列辨識編號：15，DEN-2/DEN-1以及序列辨識編號：19，DEN-2/DEN-3表示，在此，此等建構物可用於在此所揭示之二、三或四價組成物。

[0015]在一些具體例中，在此所揭示之建構物可包括DEN-4、DEN-2、DEN-1以及DEN-3之嵌合建構物，其可表達DEN-1、DEN-3以及DEN-4之表面抗原，以及使用減毒DEN-2 PDK-53病毒作為骨架。

[0016]一些具體例揭示用於製造修飾的或突變的DEN-4建構物，應用於任何疫苗組成物之方法，包括，但不限於，僅具有DEN-4建構物之單一疫苗組成物；能夠誘發抗二或多種登革熱病毒血清型之免疫反應之混合單一疫苗組成物；具有在此所揭示之嵌合(以及非嵌合)建構物，結合其它能夠誘發對黃病毒以及一或多種包括DEN-4之登革熱病毒血清型之免疫反應之黃病毒建構物之混合單一疫苗組成物。

【圖式簡單說明】

[0017] 下列圖式構成本說明書之一部分，用於進一步示範說明某些具體例。單獨參考一或多個此等圖式，或結合所呈現之特別具體例之詳細說明，可更了解一些具體例。

[0018] 圖1A-1B說明(A) DEN-2 PDK-53之結構以及非結構基因之代表性概略圖，以及(B)在此所揭示之一些具體例之某些嵌合登革熱病毒建構物，分別在DEN-2 PDK-53骨架中表達不同登革熱病毒血清型之結構蛋白之示範結果。

[0019] 圖2是說明在非人類靈長動物中，用於分析某些包括在此所揭示之一些具體例之DEN-4嵌合建構物之疫苗之示範實驗設計之表格。

[0020] 圖3描述有關用具有在此所揭示之某些具體例之DEN-4嵌合病毒建構物之疫苗組成物，免疫動物模型所產生之DEN-4中和抗體效價之產率之實驗示範圖。

[0021] 圖4描述在此之一些具體例中所揭示之某些DEN-4嵌合體建構物，單獨或結合其它活減毒病毒建構物，用於疫苗配方之概略圖。

[0022] 圖5是說明在此所揭示之某些具體例之一些DEN-4病毒建構物之噬斑參數以及Vero細胞效價以及細胞生長之分析的一些示範數據之表格。

[0023] 圖6A-6F是提供使用某些DEN-4嵌合體建構物之示範實驗之示範ImmunoFoci結果之相片，包括DEN-4野生型(A)、DENVax-4 (B)、DENVax-4e (C)、DENVax-4h (D)、DENVax-4i (E)以及DENVax-4j (F)。

[0024]圖7是描述各種DEN-4嵌合建構物在哺乳動物細胞中之病毒效價隨著時間，稱作“感染後之天數”，推移之圖表。

[0025]圖8是各種DEN-4嵌合建構物在蚊子細胞中之病毒效價隨著時間，稱作“感染後之天數”，推移之圖表。

[0026]圖9是描述用於測試各種DEN-4嵌合建構物，在動物模型中，誘發對DEN-4之免疫反應之可接受的動物模型之流程圖。

[0027]圖10說明各種DEN-4嵌合建構物之比對，說明共同序列以及示範突變和/或回復。

[0028]圖11說明各種DEN-4嵌合建構物之比對，說明共同序列以及示範突變和/或回復。

[0029]圖12說明描述DEN-2病毒之活減毒病毒建構物之概略圖。

[0030]圖13說明在此所揭示之各種DEN-4建構物之選殖之示範概略圖。

[0031]圖14描述比較各種DEN-4建構物在細胞株中之生長的圖表。

[0032]圖15描述比較各種DEN-4建構物在蚊子細胞中之生長的圖表。

[0033]圖16描述比較在此所揭示之各種DEN-4建構物，於小鼠中之致免疫性之示範柱狀圖。

[0034]圖17描述說明於小鼠中使用各種DEN-4建構物，保護、免疫對抗登革熱之挑戰之示範圖(以存活率表示)。

[0035]圖18描述考慮用於在此之配方中之DEN-4建構物之概略圖。

[0036]圖19描述考慮用於在此之配方中之DEN-4建構物之概略圖。

[0037]圖20描述各種考慮在此使用之DEN-4建構物之圖式說明。

[0038]圖21描述各種登革熱建構物在小鼠接種疫苗後之位準，以接種疫苗後之天數表示。

[0039]圖22描述各種登革熱建構物在小鼠接種疫苗後之位準，以接種疫苗後之天數表示。

[0040]圖23描述各種登革熱建構物在小鼠接種疫苗後之位準，以接種疫苗後之天數表示。

[0041]圖24描述各種登革熱建構物在小鼠接種疫苗後之位準，以接種疫苗後之天數表示。

【實施方式】

定義

[0042]在此使用之“一”，意指一個或超過一個之項目。

[0043]在此使用“個體”之說明，可包括，但不限於，諸如人類(如，成人以及青少年)之哺乳動物，或馴養或野生的哺乳動物，例如狗、貓、其它家庭寵物(如，倉鼠、天竺鼠、小鼠、大鼠)、白鼬、兔子、豬、馬、牛、土撥鼠、野生嚙齒動物或動物園動物。

[0044]在此使用之術語“嵌合建構物”、“病毒嵌合體

"、"嵌合病毒"、"黃病毒嵌合體"以及"嵌合黃病毒"，意指包含登革熱-2病毒之一部分的核苷酸序列，且另外包含不是來自登革熱-2病毒或來自不同登革熱病毒血清型或不同的黃病毒之核苷酸序列之建構物。"登革熱嵌合體"包含至少二種不同的登革熱病毒血清型。其它登革熱病毒或黃病毒之例子包括，但不限於，來自登革熱-1病毒、登革熱-3病毒、登革熱-4病毒、西尼羅河病毒、日本腦炎病毒、聖路易(St. Louis)腦炎病毒、蜱媒腦炎病毒、黃熱病毒以及其任一組合之序列。

[0045]在此使用之"核酸嵌合體"意指在此所揭示包括核酸序列之建構物，其包含登革熱-2病毒之一部分核苷酸序列，以及另外一或多種與登革熱-2病毒之核苷酸序列來源不同之核苷酸序列。相對地，在此所揭示之任何的嵌合黃病毒、任何的登革熱嵌合體或黃病毒嵌合體，可視為核酸嵌合體之例子。

說明

[0046]為了使各具體例更詳細，在下列段落中將敘述各種示範組成物以及方法。對熟悉此技藝之人士而言，很清楚地，實施各具體例不需要使用全部或甚至一些在此所概述之具體細節，而是可透過常規的實驗修飾濃度、次數以及其它具體細節。在一些情況下，在說明書中不含已廣為人知的方法或組份。

[0047]根據本發明之具體例，有可能使用此技藝中慣用的分生、蛋白質化學、微生物以及重組DNA技術。此等

技術在文獻中有完整的解釋。參見，如，Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual*, Second Edition 1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Animal Cell Culture*, R. I. Freshney, ed., 1986)。

[0048]在此之具體例有關於個體中誘發抗DEN-4之改善的免疫反應之組成物、方法以及用途，其單獨或結合一或多種用於誘發抗其它登革熱病毒血清型或黃病毒之劑。根據此等具體例，產生DEN-4之活減毒登革熱病毒以及核酸嵌合體，且用於在此所揭示之致免疫性組成物。一些具體例有關修飾或突變的DEN-4建構物。一些具體例有關將突變和/或回復導入DEN-4嵌合建構物中，以便修飾該嵌合建構物之胺基酸序列。在某些具體例中，導入DEN-4嵌合建構物，以便修飾該嵌合建構物之胺基酸序列之突變和/或回復，可包括利用包括，但不限於，誘變技術，於已知嵌合建構物(稱作DENVax-4 (序列辨識編號：21))之C/prM斷裂位置之上游的突變。

[0049]在此之具體例有關DEN-4病毒嵌合體建構物之組成物、方法以及用途。在一些具體例中，組成物可包括單獨的DEN-4病毒嵌合體建構物，或結合其它登革熱病毒血清型建構物，或能夠誘發對標的病毒(如，登革熱病毒或其它黃病毒)之免疫反應之相同或其它血清型之活減毒登革熱病毒或其它黃病毒建構物。其它具體例可包括抗DEN-4之活減毒病毒建構物以及任擇地一或多種抗

DEN-1、DEN-2以及DEN-3之活減毒病毒建構物。在又其它具體例中，提供一種致免疫性組成物，其包括DEN-4活減毒嵌合病毒建構物，其與其它已知之建構物相比，當引入一個體時，具有增加的致免疫性。根據此等具體例，此等活減毒病毒嵌合體建構物可單獨使用，或結合一或多種其它DEN-1、DEN-2以及DEN-3建構物(如，活減毒病毒或嵌合體)，以及一藥學上可接受之賦形劑，以產生抗一或多種登革熱病毒血清型之疫苗配方。在某些具體例中，產生抗一或多種登革熱病毒之單價、二價、三價或四價藥學上有效的配方。在某些具體例中，致免疫性組成物可包括DEN-1、DEN-2、DEN-3登革熱-登革熱嵌合建構物中之一或多種，或活減毒登革熱病毒，結合在此所揭示之嵌合DEN-4建構物。

[0050]在某些具體例中，包括本發明之DEN-4建構物以及DEN-1、DEN-2以及DEN-3中之一或多種之致免疫性組成物，可用於以單一疫苗投與，提供抗二或多種登革熱病毒血清型之同步保護。在其它具體例中，可於一個體中投與一包括DEN-1、DEN-2、DEN-3以及在此所揭示之本發明之修飾或突變的DEN-4建構物之致免疫性組成物，用以誘發抗各種登革熱病毒血清型之致免疫反應，在此對DEN-4之免疫反應干擾減少。

[0051]在某些具體例中，DEN-4建構物可包括在DEN-4之結構或非結構區具有適應突變之登革熱-登革熱嵌合建構物。在其它具體例中，DEN-4建構物可包括另一登

革熱病毒血清型DEN-1、DEN-2或DEN-3之骨架。在又其它的具體例中，嵌合建構物可包括DEN-2骨架，在此DEN-4之結構或非結構區取代DEN-2之結構和/或非結構區。根據此等具體例，DEN-2骨架可包括任何具有安全且有效，同時可誘發對DEN-2之免疫反應之活減毒DEN-2病毒。在其它具體例中，DEN-2骨架可包括活減毒DEN-2 PDK-53（在原代狗腎細胞(PDK)中繼代53次)或衍生自DEN-16681毒株作為骨架，在此活減毒DEN-2 PDK-53病毒進一步包括DEN-4之prM (前趨膜)以及E (套膜)結構蛋白中一或多種之結構蛋白。此外，為了提升個體在投與時，對DEN-4之免疫反應，DEN-2 PDK-53骨架可包括DEN-2 PDK-53之額外的突變或回復。(見，例如圖4)。

[0052]在一些具體例中，結構蛋白基因可包括在另一登革熱病毒骨架上之DEN-4之prM以及E基因，製造登革熱-登革熱嵌合體。例如，在某些具體例中，DEN-4建構物可包括該等稱作DENVax-4e、DENVax-4f或DENVax-4h (見例如圖4)之建構物，在此DEN-2 PDK-53骨架具有一或多種回到野生型DEN-2胺基酸之回復(如，在非結構區(NCR)或非結構區(NS1等))以及一或多種在DEN-4結構區中之突變(如prM或E)，同時編碼DEN-4 (如，毒株1036)之一或多種結構蛋白。在此所揭示之修飾的DEN-4建構物可包括修飾減毒的DEN-2 PDK-53骨架，具有DEN-4毒株1036之一或多種修飾的結構區。在一些具體例中，一或多種存在活減毒DEN-2 PDK-53病毒中之突變，可回復成對照胺基酸或另

一胺基酸，以產生在此之建構物，其會產生修飾的DEN-2/DENV-4嵌合建構物(當與MVS序列，序列辨識編號：21相比時)，具有在不影響其減毒作用，但可影響DEN-4病毒之生長和/或複製之情況下，增加致免疫性。在某些具體例中，該回復可導致生長和/或複製增加。

[0053]在其它具體例中，修飾的DEN-4建構物可合併導入DEN-4之一或多個結構區和/或非結構區之突變，以便產生會誘發改善的免疫反應，同時保有安全性以及減毒性之建構物。例如，DEN-2/DEN-4之修飾的或突變的登革熱-登革熱嵌合體，可含有在DEN-2 PDK-53骨架之一或多個非結構區(諸如NS2A以及NS4A)處之突變，和/或在5'非編碼區(5'NCR)處之突變。在另一具體例中，修飾的DEN-4嵌合體建構物可藉由回復在PDK-53之NS2A以及NS4A處之突變(如，在NS4A處之M-L取代)，而包括DEN-2 16681之NS2A以及NS4A。一些具體例包括藉由回復標的建構物之DEN-2 PDK-53骨架中之對應的突變，而具有DEN-2 16681之5'NCR、NS2A以及NS4A之修飾的DEN-4嵌合體建構物。其它具體例可包括藉由回復DEN-2 PDK-53骨架中之對應的突變，而具有DEN-2 16681之5'NCR之修飾的DEN-4嵌合體建構物。修飾的DEN-4嵌合體建構物亦可包括DEN-2 PDK-53骨架，以及編碼DEN-4毒株H241之一或多個結構蛋白。可考慮將任何DEN-4結構蛋白，取代登革熱血清型2型(如，PDK-53或修飾的PDK-53)之結構或非結構區。在一些具體例中，修飾的DEN-4建構物含有作為骨

架之活減毒DEN-2 PDK-53，以及DEN-4結構蛋白，在此可引入突變，以便修飾DEN-4 (如，毒株1036)之結構區。在一些具體例中，可於DEN-4之殼體/prM接頭胺基酸序列中引入突變，以便增加含有此突變之建構物之致免疫性。例如，在DEN-4中之突變，可為在DEN-4之殼體位置107處之C-Y突變(見例如，DENVax-4e)。根據此等具體例中，在修飾的PDK-53骨架(DENV-4b)上，半胱胺酸可突變成芳族胺基酸(如，酪胺酸或其它)。其它突變可包括在DEN-4 1036毒株序列(見例如，DENVax-4h)中套膜位置417 (穀胺酸，E)處或在另一DEN-4中其相等位置處之胺基酸取代，在此帶負電荷之胺基酸被帶有電荷之側鏈之帶正電荷之胺基酸(如，離胺酸、精胺酸、組胺酸等)取代。嵌合建構物之其它DEN-2 PDK-53回復，可在NS2A或NS4A區中找到。

[0054]在其它具體例中，DEN-2 PDK-53基因組骨架可用於產生DEN-1以及DEN-3之嵌合登革熱病毒建構物，在此DEN-2 PDK-53基因組之一或多個結構或非結構蛋白基因，可由DEN-1以及DEN-3之一或多個結構蛋白或非結構基因取代。此等建構物可在具有DEN-2 PDK-53骨架之單一嵌合體中，包括DEN-1以及DEN-3結構或非結構基因二者之組合。在一些具體例中，結構蛋白可為DEN-1和/或DEN-3之C、prM或E部分。在某些具體例中，結構蛋白基因包括DEN-1或DEN-3之prM以及E基因，或其之組合。此等雜交/嵌合病毒可表達DEN-1、DEN-3或DEN-4之表面抗原，同時保有親本DEN-2之減毒表型。

[0055]在一些具體例中，在此所揭示之建構物可包括DEN-4、DEN-2、DEN-1以及DEN-3之嵌合建構物，其可表達DEN-1、DEN-3以及DEN-4之表面抗原，以及使用減毒DEN-2 PDK-53或活減毒DEN-2 16681病毒作為骨架。此外，為藥學組成物之部分之建構物可包括其它諸如其它活減毒病毒(如，DEN-2、其它黃病毒)之劑。另外，在此等組成物中使用之其它劑可包括其它藥學上可接受之抗病毒劑、佐劑或安定劑，以減少活減毒病毒之降解。

[0056]在此之一些具體例揭示用於製造修飾的或突變的DEN-4建構物，應用於任何抗DEN-4之疫苗組成物之方法，包括，但不限於，僅具有DEN-4建構物之單一疫苗組成物；能夠誘發抗二或多種登革熱病毒血清型之免疫反應之單一疫苗組成物之登革熱病毒建構物之混合物；在單一疫苗組成物中具有在此所揭示之嵌合(以及非嵌合)建構物，結合其它能夠誘發對不同黃病毒(如，黃熱、西尼羅河、日本腦炎等等)以及一或多種包括DEN-4之登革熱病毒血清型之免疫反應之黃病毒建構物之混合物。

[0057]在其它具體例中，可考慮與在此所揭示之DEN-4建構物一起使用之其它組合。例如，在PDK細胞中繼代13次之登革熱病毒血清型1型野生型病毒，命名為DEN-1 PDK-13病毒。其它疫苗候選者是DEN-2 PDK-53、DEN-3 PGMK-30/FRhL-3 (如，在原代綠猴腎細胞中繼代30次，接著在恆河猴胎兒肺細胞中繼代3次)以及DEN-4 PDK-48。此四個候選疫苗病毒是分別從組織繼代培養野

生型親本DEN-1 16007、DEN-2 16681、DEN-3 16562以及DEN-4 1036病毒衍生而來。此等既存之活減毒登革熱病毒中任一個，均可考慮與在此所揭示之DEN-4嵌合病毒建構物結合使用。

[0058]之前此等減毒病毒之人類臨床試驗已指出，DEN-2 PDK-53在人類中具有最低的感染劑量(5個噬斑形成單位或PFU之50%最小感染劑量)，具很強的致免疫性，且不會產生顯著的安全性問題。DEN-1 PDK-13、DEN-3 PGMK-30/FRhL-3以及DEN-4 PDK-48疫苗病毒候選者，在人類中分別具有較高的50%最小感染劑量，10,000、3500以及150 PFU。

[0059]DEN-2 PDK-53病毒疫苗候選者，之後簡稱PDK-53，具有許多與減毒相關之可測得之生物標記，包括溫度敏感性、小型噬斑、在蚊子C6136細胞培養中複製減少、在完整蚊子中之複製減少、喪失對年幼小鼠之神經毒性以及在猴子中病毒血症之發生率減少。候選者PDK-53疫苗之臨床試驗，已證實其於人類中之安全性以及致免疫性。再者，PDK-53疫苗會誘發人類疫苗接受者中之登革熱病毒專一性T細胞記憶反應。

[0060]具有登革熱-2病毒骨架以及至少一種登革熱-4病毒之結構蛋白之致免疫性黃病毒嵌合體，可用於製備登革熱病毒嵌合體，在此說明用於產生該登革熱病毒或黃病毒嵌合體之方法。提供該致免疫性黃病毒嵌合體，單獨或結合形式，於藥學上可接受之載劑中，成為致免疫性組成

物，用於使個體受一或多種登革熱病毒或黃病毒株(strain)(諸如登革熱病毒血清型DEN-4，單獨或結合DEN-2、DEN-3以及DEN-1)之感染減至最少、阻止或免疫。當結合時，該致免疫性黃病毒嵌合體可用作為多價疫苗，提供同步抗超過一種黃病毒株之保護。在某些具體例中，該黃病毒嵌合體在致免疫性組成物中係結合的，用作為抗已知登革熱病毒血清型之二價、三價或四價疫苗，或藉由包括編碼一或多種從不同黃病毒而來之蛋白之核酸，提供對其它病原黃病毒之免疫力。DEN-1、DEN-2、DEN-3以及DEN-4每一個之核酸序列，均可用於產生用於檢測生物樣本中之登革熱病毒之探針，以便，例如，評估疫苗之效率和/或登革熱病毒感染之程度。

[0061]在一些具體例中，在此提供之無致病力、致免疫性嵌合體，含有減毒登革熱-2病毒(如，PDK-53)之非結構蛋白基因或其相等物，以及一或多種黃病毒之結構蛋白基因或其致免疫性蛋白部分(在個體中可誘發抗該黃病毒之免疫性)。例如，一些具體例有關一種嵌合體，其具有減毒登革熱-2病毒PDK-53基因組作為病毒骨架，以及一或多種編碼PDK-53基因組之殼體、前趨膜/膜或膜套之結構蛋白基因，或其組合，其中該結構蛋白由從DEN-4病毒或其它欲對抗之黃病毒(諸如不同的黃病毒或不同的登革熱病毒血清型)而來之一或多種對應的結構蛋白基因取代。根據此等具體例，PDK-53骨架進一步突變或回復，以增加該建構物之致免疫性。再者，在此所揭示之核酸嵌合體

可具有減毒登革熱-2病毒之官能特性，且為非致病性的，但會表達除了其它黃病毒之外之DEN-4之結構基因產物的抗原決定位，且為致免疫性的(如，誘發對個體之基因產物之免疫反應)。突變和/或回復不會影響該嵌合建構物之減毒作用和/或安全性。

[0062]在另一具體例中，核酸嵌合體可為具有，但不限於，編碼從減毒登革熱-2病毒而來之非結構蛋白之第一核苷酸序列，以及從登革熱-4病毒而來之結構蛋白之第二核苷酸序列，單獨或結合另一黃病毒，之核酸嵌合體。在其它具體例中，該減毒登革熱-2病毒可為疫苗株(strain)PDK-53或16681。一些具體例包括登革熱或其它黃病毒之C、prM或E中一或多種之結構蛋白。從其中可選擇出結構蛋白之黃病毒的例子包括，但不限於，DEN-1、DEN-2、DEN-3、西尼羅河病毒、日本腦炎病毒、聖路易腦炎病毒、黃熱病毒以及蜱媒腦炎病毒，以及在此所揭示之DEN-4建構物。在其它具體例中，該結構蛋白可擇自於與黃病毒非常相近之非黃病毒種類，諸如C型肝炎病毒。

[0063]在此所揭示之其它態樣包括：嵌合病毒可包括在例如DEN-2 PDK-53中之核苷酸以及胺基酸取代、刪除或插入；此等改變可降低對DEN-4病毒之致免疫性反應之干擾。此等修飾可在結構以及非結構蛋白中製造，單獨或結合在此所揭示之修飾範例。

[0064]在此之具體例包括黃病毒之結構以及非結構蛋白，其可為任何包括下列之蛋白或任何編碼下列之基因：

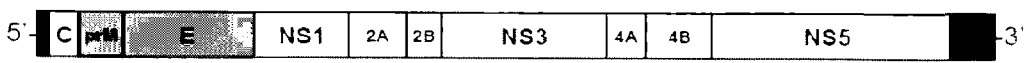
完整蛋白、該蛋白之抗原決定位，或任何包含，例如，其之五或更多個胺基酸殘基之片段之序列。

[0065]在此所揭示之某些具體例，提供使用重組技術，將所需之取代插入適當的骨架基因組中，製造本發明之嵌合病毒之方法。

黃病毒嵌合體

[0066]登革熱病毒類型1-4型(DEN-1至DEN-4)是蚊媒黃病毒病原菌。黃病毒基因組含有5'-非編碼區(5'-NC)，接著殼體蛋白(C)編碼區，接著前趨膜/膜蛋白(prM)編碼區，接著套膜蛋白(E)編碼區，接著編碼非結構蛋白(NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5)之區，以及最後3'非編碼區(3'NC) (見，例如圖1A)。病毒結構蛋白是C、prM以及E，而非結構蛋白是NS1-NS5。將結構以及非結構蛋白轉譯成單一多蛋白，然後用細胞以及病毒蛋白酶處理。

登革熱病毒基因組之結構



[0067]黃病毒嵌合體之建構物的形成，可藉由使從登革熱病毒之一類型或血清型，或黃病毒科之病毒種類而來之非結構蛋白基因，融合與蛋白基因，例如從不同的登革熱病毒類型或血清型，或黃病毒科之病毒種類而來之結構蛋白基因。選擇性地，在此所揭示之黃病毒嵌合體之建構物的形成，是藉由使從登革熱病毒之一類型或血清型，或黃病毒科之病毒種類而來之非結構蛋白基因，融合與另外

會引導擇自其它登革熱病毒血清型或其它黃病毒科之病毒之多肽或蛋白之合成之核苷酸序列。

[0068]在其它具體例中，在此提供之非致病性、致免疫性黃病毒嵌合體，含有減毒登革熱-2病毒之非結構蛋白基因或其相等物，以及欲對其產生免疫性之黃病毒的結構蛋白基因中之一或多個，或其抗原性部分。

[0069]其它適合用於建構黃病毒嵌合體之黃病毒可為野生型、毒性DEN-1 16007、DEN-2 16681、DEN-3 16562以及DEN-4 1036，以及減毒疫苗株DEN-1 PDK-13、DEN-2 PDK-53、DEN-3 PMK-30/FRhL-3以及DEN-4 PDK-48。DEN-1、DEN-2、DEN-3以及DEN-4野生型/減毒病毒對之間的基因差異，與由病毒基因組編碼之胺基酸序列之改變，可一起考慮。在此使用之任何的DEN-4毒株，均含有與考慮的和/或在此揭示的建構體同義的突變。

[0070]DEN-2 PDK-53之序列列表相當於DEN-2 PDK-53-V變異株，其中基因組核苷酸位置5270從A突變為T，而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。無此核苷酸突變之DEN-2 PDK-53變異株，DEN-2 PDK-53-E，僅在此一位置中與PDK-53-V不同。DEN-2 PDK-53-E在核苷酸位置5270處具有A，在多蛋白胺基酸位置1725、NS3蛋白胺基酸位置250處具有穀胺酸。當然，在此之具體例可包括修飾的DEN-2 PDK-53，其包括此等位置之一或多個變成天然衍生的序列之回復/突變。

[0071]DEN-3 16562之序列表，相當於其中基因組核苷酸位置1521是T，而多蛋白之胺基酸位置476或E蛋白之胺基酸位置196含有白胺酸之變異株。在DEN-3 16562培養物中出現之第二變異株，在核苷酸位置1521處具有T，而在多蛋白之胺基酸位置476或E蛋白之胺基酸位置196處含有絲胺酸。

[0072]DEN-4 PDK-48之序列表，相當於其中基因組核苷酸位置：6957是T，而多蛋白之胺基酸位置2286以及NS4B蛋白之胺基酸位置44是苯丙胺酸，7546是T，而多蛋白之胺基酸位置2366以及NS4B蛋白之胺基酸位置240是纈胺酸，以及7623是T，而多蛋白之胺基酸位置2508以及NS5蛋白之胺基酸位置21是酪胺酸之變異株。

[0073]在某些具體例中，嵌合物之命名係根據DEN-2病毒專一性感染選殖株骨架以及其它黃病毒之結構基因(prM-E或C-prM-E)插入物。DEN-2是登革熱-2骨架，接著是插入結構基因之毒株。特別的骨架變異株反映於下文中。建構該嵌合物之特別的DEN-2骨架變異株，以置於連字號後面之字母指出，親本16681 (P)、PDK-53-E (E)或PDK-53-V (V)；最後的字母指出從親本(P)毒株或其疫苗衍生物(V)而來之C-prM-E結構基因，或從該親本(P)或其疫苗衍生物(V1)而來之prM-E結構基因。例如，DEN-2/1-VP提供包含減毒DEN-2 PDK-53V骨架之嵌合體，其在NS3-250包含纈胺酸以及從野生型DEN-1 16007而來之C-prM-E基因；DEN-2/1-VV提供該DEN-2 PDK-53V骨架以

及登革熱-1、DEN-1 PDK-13之疫苗株；DEN-2/1-VP1提供DEN-2 PDK-53V骨架以及從野生型DEN-1 16007而來之prM-E基因；DEN-2/3-VP1提供DEN-2 PDK-53V骨架以及從野生型DEN-3 16562而來之prM-E基因；DEN-2/4VP1提供DEN-2 PDK-53V骨架以及從野生型DEN-4 1036而來之prM-E基因；以及DEN-2/WN-PP1提供DEN-2 16681骨架以及從西尼羅河NY99而來之prM-E基因。其它在此所揭示之嵌合體以相同之方式指出。

[0074]在一具體例中，在此所揭示之嵌合體含有減毒DEN-2病毒PDK-53基因組作為病毒骨架，其中編碼PDK-53基因組之C、prM以及E蛋白之結構蛋白基因或其組合，以從DEN-4病毒以及任擇地欲對抗保護的另一黃病毒，諸如不同的黃病毒或不同的登革熱病毒株，之相應的結構蛋白基因取代。於該DEN-2骨架中亦可併入新發現的黃病毒或黃病毒病原菌。

[0075]在非結構蛋白區域中，Gly變成Asp（野生型變成PDK-53）之突變係在非結構蛋白NS1-53處發現（基因組核苷酸位置2579）；Leu變成Phe（野生型變成PDK-53）之突變在非結構蛋白NS2A-181處發現（基因組核苷酸位置4018）；Glu變成Val（野生型變成PDK-53）之突變在非結構蛋白NS3-250處發現（基因組核苷酸位置5270）；以及Gly變成Ala之突變（野生型變成PDK-53）在非結構蛋白NS4A-75處發現（基因組核苷酸位置6599）。

[0076]減毒PDK-53病毒株在基因組nt 5270處具有混合

的基因型。大部分(大約29%)之病毒族群編碼存在野生型 DEN-2 16681 病毒中之非突變的 NS3-250-Glu，而不是 NS3-250-Val 突變。因為二者基因變異株均係非致病的，所以此突變在非致病嵌合體中並不是必需的。

[0077]之前就發現，減毒 PDK-53 病毒株之非致病性，可能歸因於編碼非結構蛋白之核苷酸序列中以及 5' 非編碼區中之突變。例如，在 NS1-53 處之單一突變、在 NS1-53 以及 5'NC-57 處之雙突變、在 NS1-53 以及 NS3-250 處之雙突變以及在 NS1-53、5'NC-57 以及 NS3-250 處之三突變，會導致 DEN-2 病毒之毒性減低。因此，任何含有在此等基因座之此非保守胺基酸取代或核苷酸取代之登革熱-2 病毒之基因組，均可用作為用於獲得在此所揭示之修飾的 PDK-53 病毒之基礎序列。若需要的話，另一在 5' 非編碼區中之莖幹/環結構中之突變，可提供額外的非致病性表型安定性。在此區之突變，會打斷對病毒複製很重要之可能的次級結構。在 DEN 以及委內瑞拉馬腦炎病毒二者中，此短(長度僅 6 個核苷酸殘基)莖幹結構中之單一突變，會破壞髮夾結構之形成。在此莖幹結構中之另外的突變，會減少在此基因座之回復，同時維持病毒生存能力之可能性。

[0078]在此所揭示之突變可用任何此技藝中已知之方法達到，包括，但不限於，定點突變、直接合成、刪除或其它使用此技藝之人士已知之技術之方法。熟悉此技藝之人士應可理解，在此所述以及此技藝中熟知之致病性篩選分析法，可用於區分致病性以及非致病性骨架結構。

黃病毒嵌合體之建構

[0079]在此所述之黃病毒嵌合體之產生，可利用剪接一或多個欲對其產生免疫力之黃病毒的結構蛋白基因，進入PDK-53登革熱病毒基因組骨架，或利用其它此技藝中已知之方法，使用重組工程，移除對應的PDK-53基因，然後用登革熱-4病毒基因或其它此技藝中已知之基因取代。

[0080]選擇性地，在此所揭示之任何建構物之核酸序列、編碼黃病毒蛋白之核酸分子，可使用任何已知的核酸合成技術合成，然後插入適當的載體中。因此，在此之具體例之非致病性、致免疫性病毒，可使用熟悉此技藝之人士已知之重組工程技術產生。

[0081]可於骨架中插入編碼DEN-4 (單獨或結合另一黃病毒)之有興趣的黃病毒結構蛋白之標的基因。欲插入之黃病毒(如，登革熱病毒)基因可為編碼C蛋白、PrM蛋白和/或E蛋白之基因。例如，插至登革熱-2骨架中之序列，可編碼PrM以及E結構蛋白二者，或僅編碼單一結構蛋白。插入登革熱-2骨架中之序列，可編碼C、prM以及E結構蛋白中之全部以及一種。

[0082]含有編碼其它黃病毒或登革熱病毒血清型之結構蛋白之核苷酸序列之適合的嵌合病毒或核酸嵌合體，可經由篩選其等顯示出非致病性之減毒表型標記，以及篩選其等之致免疫性，評估是否可用為疫苗。使用熟悉此技藝之人士已知之常規篩選程序，在試管中和/或活體內與黃

病毒抗體或免疫反應性血清之反應，可評估抗原性以及致免疫性。

登革熱病毒疫苗

[0083]在某些具體例中，嵌合病毒以及核酸嵌合體可提供可用作為免疫原或疫苗之活減毒病毒。一些具體例包括會對登革熱-4病毒展現高致免疫性，同時不會產生危險致病性或死亡作用之嵌合體。

[0084]為了降低接種僅抗一種登革熱病毒血清型之疫苗之個體中DHF/DSS之發生率，需要可提供對二至全部四種病毒血清型同時免疫之二、三或四價疫苗。四價疫苗之產生，可藉由結合活減毒登革熱-2 (如，登革熱-2 PDK-53) 與在此所述之登革熱-2/1、登革熱-2/3以及登革熱-2/4新穎嵌合體，於適合供多價疫苗方式投與，以便對抗全部四種登革熱病毒血清型之藥學載劑中。其它配方可包括以上之二價或三價配方，在此該配方包括一或多種新穎的DEN-4嵌合建構物。

[0085]在此之某些具體例中所揭示之嵌合病毒或核酸嵌合體，在致病性或減毒DEN-2病毒骨架中，可包括野生型或減毒病毒之結構基因。例如，該嵌合體可表達野生型DEN-4 1036病毒之結構蛋白以及在其各DEN-2 PDK-53背景中之候選疫苗衍生物。在某些具體例中，在此所揭示之藥學或實驗性組成物，可包括一或多種具有命名為DENVax-4c、DENVax-4g和/或DENVax-4h之建構物，單獨或結合其它黃病毒建構物。在某些範例中，此等建構物可

與一或多種在此所揭示之病毒種庫(MVS) (如, DEN-1/DEN-2)建構物一起使用。其它具體例可包括在此所揭示之DEN-4建構物以及其它黃病毒嵌合體, 諸如該等在黃熱骨架或西尼羅河骨架或其它黃病毒骨架上製得者, 在此, 此等黃病毒嵌合體能夠形成具有登革熱病毒血清型之嵌合建構物, 其當引入個體時, 可於該個體中誘發對該病毒之免疫反應。

[0086]在此所述之嵌合體中使用之病毒, 可使用此技藝中已知之技術使其生長。之後再進行病毒噬斑滴定, 並計數噬斑, 以便評估生長培養物之生存力以及表型特徵。透過培養細胞株繼代培養野生型病毒, 來衍生減毒候選初始材料。

[0087]嵌合感染選殖株可從各種可用的登革熱血清型選殖株中建構而得。若需要, 亦可完成病毒專一性cDNA片段之選殖。含有結構蛋白或非結構蛋白基因之cDNA片段, 可藉由逆轉錄酶-聚合酶鏈反應(RT-PCR), 用各種引子, 從登革熱病毒RNA中擴增出。可將擴增的片段選殖進入其它中間選殖株之斷裂位置。之後可定序中間、嵌合登革熱病毒選殖株, 以確認所插入之登革熱病毒專一性cDNA之精準度。

[0088]在某些具體例中, 使用熟悉此技藝之人士已知之重組技術, 可獲得藉由插入登革熱血清型病毒之結構蛋白或非結構蛋白進入載體而建構成之完整的基因組嵌合質體。

核苷酸以及胺基酸之分析

[0089]在某些具體例中，相對於野生型登革熱-2病毒，PDK-53在E蛋白中不含胺基酸突變；DEN-1、DEN-3以及DEN-4減毒病毒在E蛋白中可具有胺基酸突變。野生型DEN-3 16562已經證實包含少量的變異株，其在核苷酸1521處包含T，其會引導E蛋白之多蛋白位置476、胺基酸殘基位置476之白胺酸的併入。後三種病毒之每一個，在E蛋白中可具有Glu變成Lys (親本變成疫苗)之突變，然而該突變位在E蛋白中之不同的胺基酸殘基處。此取代導致從帶負電胺基酸轉變成帶正電胺基酸。DEN-4疫苗病毒之E蛋白中之Glu變成Lys之取代，是E蛋白中出現的唯一突變，而DEN-1以及DEN-3疫苗病毒之E蛋白，分別具有五以及三個胺基酸突變。

[0090]在某些具體例中，NS1-53突變發生在DEN-2 PDK-53病毒中，且對此病毒之減毒表型很重要，因為DEN-2 16681病毒之NS1-53-Gly在幾乎所有定序至今之黃病毒(包括蜱媒病毒)中係保守的。在此所揭示之DEN-4病毒建構物，在NS1蛋白之位置253處，可含有胺基酸突變。此基因座，其在DEN-4 PDK-48病毒中係Gln變成His之突變，在所有四種登革熱病毒野生血清型中係Gln。此Gln殘基在黃病毒屬內之登革熱病毒中是獨特的。NS1蛋白是一種糖蛋白，其由黃病毒感染的細胞分泌。其存在受感染之細胞的表面，而NS1專一性抗體存在被病毒感染的個體之血清中。已有用NS1蛋白或消極用NS1專一性抗體免疫來

保護動物之報導。

[0091] 某些突變係在DEN-1、-2、-3以及-4減毒毒株之NS2A、NS2B、NS4A以及NS4B蛋白中找到，其在自然中係保守的。DEN-2以及DEN-4疫苗病毒之NS4A-75以及NS4A-95突變，一般係分別發生在登革熱病毒之間之胺基酸保守位置，而不是黃病毒之間。

[0092] 黃病毒NS3蛋白具有至少二種可辨識的功能：病毒蛋白酶以及RNA解旋酶/NTP酶。698-aa長(DEN-2病毒) NS3蛋白含有胺基終端絲胺酸蛋白酶結構區(NS3-51-His、-75-Asp、-135-Ser催化三元基)，後接著RNA解旋酶/NTP酶功能(NS3-196-GAGKT)、-284-DEAH、-459-GRIGR (序列辨識編號：26)，之前出示的)之序列模體。在DEN-1、DEN-2或DEN-3病毒之NS3蛋白中，沒有突變發生在可辨識的模體內。DEN-1 PDK-13病毒中之NS3-510 Tyr變成Phe之突變係保守突變。因為野生型DEN-2、-3以及-4病毒在此位置含有Phe，Tyr變成Phe之突變不像是參與DEN-1病毒之減毒作用。在大部分蚊媒黃病毒中，DEN-1 PDK-13病毒中NS3-182 Glu變成Lys之突變，發生在保守的位置，如Asp或Glu，且其可能參與一些減毒作用。此突變位在GAGKT (序列辨識編：27)解旋酶模體之上游15個胺基酸殘基處。在某些登革熱-2病毒中，DEN-2 16681病毒中之NS3-250-Glu，除黃熱病毒除外，在全部蚊媒黃病毒中均是保守的。

[0093] 於在此之某些具體例中使用之核酸探針，會選

擇性地與編碼DEN-1、DEN-3以及DEN-4病毒或其互補序列之核酸分子雜交。"選擇性的"或"選擇性地"意指一序列，其不會與其它會干擾適當檢測登革熱病毒之核酸雜交。因此，在雜交核酸之設計上，選擇性取決於在樣本中之其它組份。雜交核酸與其欲雜交之核酸的節段，應具有至少70%的互補。在此用於描述核酸之術語"選擇性地雜交"，排除偶發隨機雜交的核酸，因此與"專一性雜交"意思相同。在此所揭示之選擇性雜交核酸，可與其欲雜交之序列片段具有至少70%、80%、85%、90%、95%、97%、98%以及99%之互補，較佳地85%或更高。

[0094]會選擇性地雜交至編碼核酸或該核酸之互補或相反鏈之序列、探針以及引子之考慮。只要能維持功能種類-專一性雜交能力，核酸中具有些微修飾或取代，亦可發生核酸之專一性雜交。"探針"意指一核酸序列，其可用作為與互補核酸序列選擇性雜交之探針或引子，用於其等之檢測或擴增，探針之長度變化可從約5個至100個核苷酸，或較佳地從約10個至50個核苷酸，或最佳地約18-24個核苷酸。

[0095]假如使用作為引子，該組成物較佳地包括至少二個會雜交至該標的分子之不同的區之核酸分子，以便擴增所欲的區。視探針以及引子之長度而定，標的區之範圍可介於70%互補鹼基以及全部互補之間，且仍可在嚴苛條件下雜交。例如，為檢測登革熱病毒之存在之目的，雜交核酸(探針或引子)與其欲雜交之序列之間，互補的程度為

至少足夠區分與核酸之雜交以及其它有機體。

[0096]可將編碼DEN-4、DEN-3或DEN-1病毒之核酸序列插入諸如質體之載體中，然後於活有機體中重組表達，以產生重組登革熱病毒胜肽和/或多肽。

核酸檢測方法

[0097]本發明提供用於診斷在此所述之疫苗病毒中每一個之快速基因試驗。本發明之此具體例提高了從進展成病毒血症之接種疫苗的人類血清中分離出之病毒的分析，以及提高以候選疫苗病毒免疫之非人類靈長類中，病毒血症之特徵化。

[0098]此等序列包括一診斷TaqMan探針，其用於報告檢測使用逆轉錄酶/聚合酶鏈反應(RT/PCR)，從病毒基因組RNA樣版擴增之cDNA擴增子；以及一設計用於擴增cDNA擴增子之正向以及反向擴增引子，如下所述。在某些情況下，其中一擴增引子設計成，在該擴增引子之3'終端處含有疫苗病毒專一性突變，其能有效地使對疫苗株之測試更專一，因為在標的位置引子之延伸，所以擴增反應僅發生在該病毒RNA樣版含有該專一性突變時。

[0099]可使用基於PCR之自動核酸序列檢測系統，其漸漸廣泛地用於診斷實驗室。TaqMan分析係高度專一以及靈敏的分析法，其容許自動即時可視化以及定量從樣本核酸樣版而來之PCR產生的擴增子。TaqMan可測定專一性序列之存在與否。在此分析中，正向以及反向引子設計成分別黏合標的突變位置之上游以及下游。專一性檢測探

針，其設計成具有熔點溫度約高於各擴增引子 10°C ，以及含有疫苗病毒專一性核苷酸突變或其互補物(視欲檢測之RT/PCR擴增子之鏈而定)，構成此分析法之第三引子組份。設計成用以專一性地檢測在嵌合建構物之一者中之突變基因座之探針，可含有供檢測任何突變之專一性核苷酸改變。

[0100] 一用於診斷基因檢測之策略係使用分子信標。分子信標策略亦利用用於RT/PCR擴增擴增子之引子，以及利用探針終端含有報導子以及淬滅染料之探針，檢測該擴增子內之專一性序列。在此分析中，該探針形成莖環結構。5'-以及3'-終端報導染料以及淬滅染料，分別地位在短莖結構之終端，其將淬滅染料帶至報導染料之附近位置。該莖環結構在RT/PCR分析法之變性步驟期間熔化。假如標的病毒RNA含有該標的序列，且被正向以及反向擴增引子擴增，則該探針之開口環會在循環之黏合步驟期間雜交至該標的序列。當該探針黏合至該擴增子樣版之每一鏈時，淬滅以及報告染料會分開，而可檢測到該報告染料之螢光。此是即時鑑定以及定量分析法，其與TaqMan分析法非常相似。分子信標分析法使用與該等在TaqMan分析法中所使用不同的淬滅以及報告染料。

藥學配方

[0101] 任何疫苗技藝中已知之藥學配方，在此均會考慮。在某些具體例中，配方可單獨含有DEN-4建構物，或含有各種比率之DEN-4建構物以及一或多種額外的DEN血

清型(或其它黃病毒組成物)，以及在此所揭示之DEN-4結構物，其取決於流行區域中，預期曝露或存在之登革熱病毒亞型。配方可考慮含有其它用來接種個體之劑，包括，但不限於，熟悉此技藝之人士已知之其它活性或非活性成份或組成物。在某些具體例中，於在此所揭示之配方中可包括佐劑。

[0102] 本發明之其它態樣，可包括調節疫苗於個體中抗登革熱病毒之免疫反應。抗登革熱病毒之疫苗可包括一種組成物，其包含一定比率之登革熱病毒、活減毒登革熱病毒或其片段，諸如從登革熱病毒血清型衍生或獲得之蛋白或核酸。各種血清型之比率可為相等的，或某些血清型存在之比率高於其它，此取決於對病毒的需求或曝露或可能的曝露。根據此等具體例，針對血清型1、2、3中任一個與在此所揭示之DEN-4建構物之比率，可為1：2、1：3、1：4、1：10、1：20；1：1：1、1：2：2、1：2：1、1：1：1：1、1：2：1：2；1：3：1：3、2：3：3：3、5：4：5：5、4：4：4：5、1：2：2、4：4：5：5、4：4：5：6或任何比率，此取決於，例如，存在於配方中之血清型的數量、預定的反應以及所欲的效果。最後數字代表配方中DEN-4之數量。各數字代表10的倍率($6=10^6$ PFU)。任何登革熱病毒血清型配方，均可考慮用於產生用於投與至需要的個體中之疫苗(如，減毒病毒等等)。

[0103] 在此之具體例提供適合活體內投藥之生物相容的形式，投與組成物於個體中。"適合活體內投與之生物相

容的形式"意指欲投與之活性劑之形式(如，具體例之藥用蛋白、胜肽或基因等等)，其中該活性劑之治療作用勝過任何的毒性作用。投與治療活性數量之治療組成物，界定為在劑量以及需要達到所欲結果之時間下之有效數量。例如，化合物之治療活性數量，可隨著諸如下列之因素改變：個體之疾病狀態、年齡、性別以及體重，以及抗體在個體中引起所欲的反應之能力。給藥方案可調整至可提供最適的治療反應。

[0104] 在一具體例中，該化合物(如，具體例之藥用蛋白、胜肽等等)可以慣用之方法投與，諸如皮下、靜脈、皮內、口服投與、吸入、經皮給藥、皮內、陰道給藥、局部給藥、鼻內或直腸投藥。取決於投藥途徑，可於活性化合物上包覆材料，防止該化合物因受到酵素、酸以及其它會導致該化合物無活性之天然條件而降解。在一具體例中，該化合物可經鼻內投與，諸如吸入。

[0105] 化合物可在適當的載劑或稀釋劑中，與酵素抑制劑共同投與至個體，或在諸如微脂粒子之適當的載劑中投與至個體。在此使用之術語"藥學上可接受之載劑"，意指包括諸如食鹽水以及水性緩衝溶液之稀釋液。可能需要於化合物上包覆材料，或使該化合物與材料共同投與，以防止其失去活性。活性劑亦可經非腸道或腹膜內投與。亦可製備於甘油、液態聚乙二醇及其混合物，以及油中之分散劑。在一般的貯存以及使用條件下，此等製品可含有防止微生物生長之防腐劑。

[0106] 適合注射用途之藥學組成物可以此技藝中已知之方法投與。例如，可使用無菌水溶液(在此係水可溶性的)，或用於臨時製備無菌注射溶液或分散液之分散劑以及無菌粉末。在所有的情況下，該組成物是無菌的，且流動程度可易於注射。在製造以及貯存之條件下應該為安定的，且可保持對抗諸如細菌以及真菌之微生物之污染。藥學上可接受之載劑可為溶劑或含，例如，水、乙醇、聚醇(例如，甘油、丙二醇以及液態聚乙二醇等等)之分散介質，以及其適合的混合物。例如，利用諸如卵磷脂之塗層；在分散劑之情況下，維持所需之粒徑；以及使用界面活性劑，可保持適當的流動性。微生物之預防，可藉由加熱、使該劑曝露於清潔劑、輻射或添加各種抗細菌或抗真菌劑而達到。

[0107] 需要時，製備無菌注射溶液時，可合併所需數量之活性劑以及以上所述之成分之一或組合。

[0108] 水性組成物可包括有效數量之治療化合物、胜肽、抗原決定位核心區、刺激劑、抑制劑等等，溶於或分散於藥學上可接受之載劑或水性介質中。在此所揭示之化合物以及生物材料可用業界已知之方法純化。

[0109] 配製時，溶液應以可與劑型配方相容，且以治療有效數量之方式投與。配方可很容易地以不同劑型投與，諸如以上所述之注射溶液類型。亦可考慮使用低釋出膠囊、定時釋出微粒等等。此等特別的水溶液特別適合靜脈、肌肉、皮下以及腹膜內投與。

[0110] 該活性治療劑可配製於混合物中，以便包含約 10^2 至約 5×10^6 PFU 之在此所考慮之各建構物。亦可以在預定條件下，以適當的時程，投與單一劑量或多劑量。在某些具體例中，為了誘發干擾較少的免疫反應或不同的淋巴結，在第0天，於單一解剖或多個解剖位置投與雙劑量。在某些具體例中，可於個體中投與登革熱病毒建構物之單-、二-、三-或四價配方。此等配方中之任一個，可以單一或多劑量方式提供給個體。在某些具體例中，可投與一個劑量，一段時間之後再追加。

[0111] 在另一具體例中，可使用鼻溶液或噴霧劑、氣霧劑或吸入劑來傳送有興趣的化合物。適合其它模式投與之額外的配方包括栓劑以及子宮托。亦可使用直腸子宮托或栓劑。一般就栓劑而言，傳統的結合劑以及載劑可包括，例如，聚二醇或三酸甘油酯；此等栓劑可由含有範圍從0.5%至10%，較佳地1%、2%之活性成份之混合物形成。

[0112] 含有 $\alpha 1$ -抗胰蛋白酶、其類似物或絲胺酸蛋白酶活性之抑制劑或其功能衍生物之藥學組成物，可以，例如，皮下、肌肉、鼻內、口服、局部、經皮、非腸道、胃腸道、經支氣管以及經肺泡之方法，投與該至個體，特別是人類。

[0113] 在本發明之方法之某些具體例中，該個體可為諸如人類或脊椎動物和/或豢養動物之哺乳動物。

[0114] 本發明之一具體例方法，提供正準備旅遊至有登革熱病毒之國家之個體接種疫苗。在其它具體例，個體

可為在流行區域內之居民。可考慮在第0天於個體身上打一針或打二針，接著在少於30天、2個月、3個月、6個月或差不多1年之後追加。

套組

[0115] 其它具體例有關使用在此所揭示之方法(如，施用或投與疫苗之方法)以及組成物之套組。一些具體例有關具有用於預防或治療具有、曝露或可能曝露於一或多種登革熱病毒之個體之疫苗組成物之套組。在某些具體例中，套組可含有一種或超過一種預定比率之登革熱病毒血清型之配方(如，減毒疫苗)。套組可為可攜式的，例如，能夠運送至諸如軍事基地或偏遠村莊之偏遠地區，且可在該地方使用。其它套組可在衛生機構使用，治療已曝露於一或多種登革熱病毒或可能曝露於登革熱病毒之風險之個體。

[0116] 套組亦可包括適合的容器，例如，小藥瓶、藥管、迷你-或微離心管、試管、長頸瓶、藥瓶、針筒或其它容器。當提供額外的組份或劑時，該套組可含有一或多種額外的容器，供用於容納此劑或組份。在此之套組典型地亦可包括用於緊密限制容納該劑、組成物以及任何其它試劑容器，供商業販售之構件。此等容器可包括射出或吹塑成型之塑膠容器，於其中可保存所欲之小藥瓶。任擇地，一或多種諸如致免疫劑或其它抗病毒劑、抗真菌劑或抗細菌劑之額外之劑，可能為所述之組成物所需的，例如，用作為對抗一或多種額外微生物之疫苗之組成物。

[0117] 下列非限制性範例將更進一步地說明本發明之

具體例，任何情況下，其等不應被解釋範疇之限制。熟悉此技藝之人士應了解，在範例中所揭示之技術係因發現其是可於在此所揭示之實例中運作良好之技術，因此可視為構成此實務之較佳模式。然而，根據本揭示內容，熟悉此技藝之人士應能理解，在所揭示之特定具體例中可有許多的變化，且仍可在不逸離在此之技術思想以及範疇之情況下，獲得相同或相似的結果。

範例

範例1

[0118] 在某些示範例方法中，DEN-4嵌合體建構物係配製成藥學上可接受之組成物。

[0119] 圖1A描述在此所揭示之一些具體例之示範病毒的骨架，稱作 DEN-2 PDK-53 基因組 (之前揭示在 PCT/US01/05142 中，美國專利申請案第 10/204,252 號，各案之各種目的之全部內容均在此併入本案以為參考)，其可用於產生修飾的 DENV-4 建構物 (亦指第二代)。如圖 1A 所示，已經鑑定出在非結構區，諸如 NS1-G53D、NS3-E250V 之專一性胺基酸取代突變，以及在 5' 非編碼區，在 DEN-2 PDK-53 基因組中之 C57T，中之核苷酸取代突變。原始 DENV-1、3 以及 4 建構物 (亦指第一代) 之產生，係利用分別的血清型之結構編碼序列，取代 DENV-2 骨架中之 prM 以及 E 之編碼序列 (圖 1B)。為產生可加強修飾的 DENVax-4 建構物在試管中以及活體內之複製效率，以及改善於宿主中之致免疫性，可於該原始 DENVax-4 建構物之非編碼區、結構蛋白編碼區

和/或非結構區引入點突變。例如，可在目前的DENVax-4 C/prM斷裂位置之胺基酸序列上游製造修飾，模擬與登革熱-2相反之野生型登革熱-4 (該DENVax-4目前含有的)。

[0120] 表1中提供在某些示範DENV-4建構物中之一些額外的修飾。以下說明的是某些修飾的DENVax-4建構物 (DENVax-4b、DENVax-4c以及DENVax-4d)中，與DENV-2、DENV-1以及原始DENVax-4野生型序列對齊之序列。在此等序列中選擇的改變以黑體以及下標方式標示：

	C-100	殼體 -- prM	
DENV-2：	NILNRRRRSAGMIIMLIPTVMA	FHLTTRN	序列辨識編號：1
DENV-4 WT：	NILN GRKRSTITLL CLIPTVMA	FHL STRD	序列辨識編號：2
DENVax-4ori：	NILNRRRR SS AGMIIMLIPTVMA	FHL TTRD	序列辨識編號：3
DENVax-4b：	NILNRRRR SS TITLL CLIPTVMA	FHL STRD	序列辨識編號：4
DENVax-4c：	NILN GRKRSTITLL CLIPTVMA	FHL STRD	序列辨識編號：5
DENVax-4d：	*ILN GRKRSTITLL CLIPTVMA	FHL STRD	序列辨識編號：6

[0121] 圖4表示一種原始以及修飾的DENV-4建構物之概略圖。DENVax-4e是使用DENVax-4b序列作為骨架，然後在殼體蛋白之胺基酸107處，併入C變成Y之突變所產生的。DENVax4f、DENVax4g以及DENVax4j係建立在DENVax-4a骨架上，但含有在圖4中所指出之PDK-53序列之減毒突變之野生型回復：DENVax-4f含有野生型(DEN-2 16681) NS2A以及NS4A；DENVax-4g含有野生型5’NCR、NS2A以及NS4A；以及DENVax-4j含有野生型5’NCR。DENVax4h在DENV4 1036序列中之套膜417處具有E變成K之取代。DENVax4i在NS4A處具有M變成L之取代。DENVax4k具有從代替1036毒株之DENV-4 H241而來之

PrM/E基因(表1)。在DENVax4e、h以及i中建構之突變，係以從DENVax4以及DENVax-4b於Vero細胞中連續繼代而來之序列資料為基礎。

[0122] DENVax-4b 含有 7 個全部的胺基酸改變，DENVax-4c 含有 9 個全部的胺基酸改變，以及 DENVax-4d 含有一胺基酸刪除，導致該序列之框架移動。將 RNA 轉錄以及電穿孔進入 Vero 細胞，以供擴增以及病毒復活。測試 DENVax-4b 以及 DENVax-4c 在 Vero 以及 C6/36 細胞中，在生長時程實驗方面之生長效率，以 DENVax4-P2、DENVax4-P8 以及 DENVax2-P2 作為對照組。DENVax-4-P2 以及 DENVax-2-P2 是沒有經過病毒噬斑純化之基因選擇之病毒樣本，方法是其中從 DENVax 感染的 Vero 細胞單層挑選之個別病毒噬斑，然後在上面放置一層含有中性紅之瓊脂凝膠，以便顯視出單一噬斑。DENVax-4-P8 已經過噬斑純化，獲得具選殖的 DENVax-4 基因型之病毒貯存株。進行此程序以產生不具有回復減毒突變之種原病毒(MVS)。DENVax-4c 在 Vero 細胞中生長後，不會達到足夠的波峰效價，且具有比 DENVax-4 或 DENVax-4b 慢的起始生長率。在 DENVax-4 以及 DENVax-4b 於 Vero 細胞中之生長曲線的波峰效價之間，沒有顯著差異，且二者具有相似的起始生長速率。在 C6/36 蚊子細胞之分析中，DENVax-4b 以及 DENVax-4c 之生長二者均達到顯著地小於野生型 DENV-4 之波峰效價，確定其等之減毒性。

表1 示範DEN-4嵌合建構物：與先前揭示之DEN-4/DEN-2 PDK-53相比之建構物差異

示範DENV-4 建構物	修飾
DENVax-4e	DENVax-4b骨架之殼體107 C突變成Y，位置416 G突變成A
DENVax-4f	NS2以及NS4中之減毒突變，回復成登革熱病毒株16681之對應的序列
DENVax-4g	5' NCR、NS2以及NS4中之減毒突變，回復成登革熱病毒血清型2型毒株16681之對應的序列
DENVax-4h	DENVax-4b骨架之套膜417 E突變成K，位置2185 G突變成A
DENVax-4i	DENVax-4b骨架之NS4A 17 M突變成L，位置6424 A突變成T
DENVax-4j	5' NCR中之減毒突變，回復成登革熱病毒血清型2型毒株16681之對應的序列
DENVax-4k	DENV-2骨架之prM以及E之編碼序列被登革熱病毒血清型4型毒株H241之結構編序列取代

範例2

整段感染性cDNA選殖株之產生

[0123] 為產生含有修飾的DENVax-4建構物序列之整段感染性cDNA選殖株，使用多步驟消化/連接計劃。其具有下列步驟：1)將包括修飾的核酸序列或修飾的結構蛋白編碼序列(例如，b、c或d，或以上建構物中之任一個)之AgeI/MluI合成片段，插至pD2/3-PP1-5'中，產生pD2/4i-b、c或d；2)消化pDENVax-4整段cDNA選殖株，萃取MluI/NgoMIV片段，然後將其插入pD2/4i-b、c或d中對應的位置，獲得pD2/4i-b、c或d；3)消化pDENVax-4整段cDNA選殖株，萃取NgoMIV/XbaI片段，然後將其插入pD2/4i-b、c或d之對應的位置中，產生該含有修飾的序列之整段感染

性選殖株。利用序列分析，確認該最後整段的感染性選殖株之序列。

病毒世代

[0124] 將各修飾的建構物之cDNA選殖株轉錄進入基因組病毒RNA中。利用電穿孔，將RNA轉形進入Vero細胞中。令病毒生長12天，同時監測CPE，然後收集。電穿孔後第一次收集的稱作P1 (繼代1)。之後的擴增以及繼代稱作P2、P3等等。原始的DENVax-4以及DENVax-4b以及c具有限的CPE，然而DENVax-4d不會產生任何顯而易見的CPE。與在試管中生長之其它病毒不同，當在Vero細胞中生長時，登革熱病毒不會產生非常多的CPE。雖然DENVax-4d病毒在試管中不會產生任何CPE，但其與其它毒株一起同時擴增。擴增的P1病毒(例如，DENVax-4b、c、d P1)產生夠高的效價來進行序列分析以及生長曲線實驗。DENVax-4d沒有顯示出效價，因此在電穿孔後沒有製造出病毒。

[0125] DENVax-4b 以及 -4c 病毒已經完全定序。DENVax-4b-P2 病毒具有二個突變。核苷酸416位在DENVax-4b病毒之殼體(接近C/prM接頭)中經基因工程修飾之位置處。因為此為混合族群，所以nt 416回復成“A”核苷酸，而不是基因工程的“G”核苷酸，導致預期的胺基酸精胺酸被取代為絲胺酸。在DENVax-4b-P2中找到之第二突變係位在核苷酸8769處。此導致胺基酸改變從預期的麩醯胺酸變成脯胺酸。此突變在感染性選殖株之NS5基因區中。DENVax-4c-P2病毒具有四個突變。其等皆完全回復，與具

有混合族群之DENVax-4b不同。在基因組之殼體區中之核苷酸400處之突變，導致C/prM接頭處之基因工程修飾。此導致在該位置預期的胺基酸為脯胺酸，而不是蘇胺酸。其它三個突變位在非結構基因中，其等中之二個引起胺基酸改變，而一個為沈默突變。

病毒之表型以及基因特徵化

[0126] 病毒之表型特徵化係於Vero細胞以及C6/36 (白線斑蚊)細胞中進行。圖5-6表示由修飾的DENVax-4建構物產生之病毒變異株之示範表面特徵。噬斑尺寸是重要的減毒標記，且可用於分析每一個病毒變異株。如圖5所示，該DENVax-4b病毒之噬斑直徑大約為0.3cm。DENVax-4c病毒之噬斑直徑為約0.1cm。DENVax-4h病毒之噬斑直徑為約0.3cm。DENVax-4i病毒之噬斑直徑為約0.1 cm。DENVax-4c病毒之噬斑直徑為約0.2 cm。每一個尺寸代表5-10個噬斑之平均值。b以及c候選病毒中之噬斑，特別是DENVax-4c不是均勻的。有一些小型以及一些大型噬斑之病毒的混合族群。可描述此等小型以及大型噬斑之序列變異性之可能的核苷酸改變，其可能會有助於試管中之減毒以及適應。若需要，可將此等突變經基因工程進入另外的DENVax-4變異株中。圖6A-6F表示野生型DENV-4病毒(A)以及DENVax-4b-f病毒變異株每一個(B-F)之示範結果。

[0127] 在一些示範方法中，測定DENV-4建構物產生的病毒之生長曲線。用各種DEN-4建構物組成物(例如，DENVax-4b-j以及DENVax-4P1)，以0.001之MOI感染單層

Vero細胞。在一些示範實驗中，到第13天，每隔一天採樣，以及滴定一試樣量。DENVax-2-P2病毒較快地達到波峰效價。DENVax-4b病毒之波峰效價以及生長速率與DENVax-4-P2以及P8病毒相似。DENVax-4c病毒一開始具較慢的生長速率，但最後達到相似的波峰效價。DENVax-4b以及DENVax-4c病毒之效率以及波峰效價比得上原始DENVax-4。在其它示範實驗中，從第2天至第12天，每隔一天採取樣本。在第7、9以及11天保留以及安定化獲得的培養基供進一步研究。用IFA滴定從第2天至第12天之樣本。DENVax-4e-4h病毒顯示與對照DENVax-相似的波峰效價(圖7)。

[0128] 為證明減毒作用，每一個疫苗病毒在C6/36蚊子細胞中之複製效率，與野生型病毒相比，應會減少。此表型係DENVax疫苗病毒基本上安全的特徵，用以確保沒有傳播天然減毒嵌合病毒之可能性。在一些示範方法中，進行在C6/36蚊子細胞中之生長，以便比較DENVax4b以及DENVax-4c病毒，與野生型登革熱4病毒(毒株1036)之生長特徵。在其它示範實驗中，進行DENVax4c-4j以及原始DENVax4之間之比較。用每一種P2病毒(-b、-c以及野生型)，以0.001之MOI感染一式二份瓶的C6/36細胞，然後生長14天。登革熱4野生型病毒(WT D4 1036)複製最有效率，且效價最高。DENVax-4b病毒在C6/36細胞中複製得非常好，在第14天達到波峰效價 2.7×10^6 pfu/mL。DENVax4c病毒生長得非常慢，直到第6天之後，加速生長至第14天，達

到波峰效價為 2.2×10^4 pfu/mL。第6天時，DENVax-4b以及DENVax4c二者與野生型於C6/36細胞中相比，生長均同樣地降低，且具有與原始DENVax-4相似的效價。在其它示範實驗中，在此之某些具體例之嵌合登革熱病毒係在C6/36蚊子細胞中生長。比較在蚊子細胞中生長之DENVax4e - 4j與對照DENVax4。用MOI為0.001之各個P2病毒感染一式二瓶的C6/36細胞，然後生長12天。從第2天至第12天均收集樣本。比較在蚊子細胞中之生長以及在Vero細胞中之生長。在第7天、第9天以及第11天取培養基並安定化。用IFA滴定從第2天至第12天之樣本，然後分析病毒之產率。與對照DENVax4比較病毒效價以及建構物之生長(見圖8)。

[0129] 圖7-8表示說明各種DENV4建構物之病毒，在Vero細胞(圖7)以及C6/36蚊子細胞(圖8)中之生長曲線的示範圖。許多在此某些具體例之新穎的DENVax4建構物，在Vero細胞中會產生比對照DENVax4高的效價(圖7)，而在蚊子細胞中會產生比對照DENVax4低的效價(圖8)，就如在動物模型中進一步之評估所欲的(見表2)。

病毒變異株在小鼠中之安全性以及效率

[0130] 進行研究以分析DENVax-4b、c或其它變異株病毒之致免疫性。表2提出一示範研究設計。於一群10個AG129之小鼠身上，皮下(在掌墊中)接種 10^4 PFU之各個原始DENVax-4以及不同的變異株。對照群注射僅具賦形劑之溶液。此等小鼠在42天後接受追加劑量。在第一次接種後第42天以及第56天採取供血清分析之血清樣本，以及用

PRNT分析血清轉化現象。使用第二代DENVax-4b以及c變異株作為免疫原時，DENVax-4之致免疫性沒有顯著的改善。

表2 小鼠研究設計之簡介

群組		劑量	免疫接種之數量	動物之數量
1	DENVax-4	10 ⁴ PFU	2	10
2	DENVax-4b	10 ⁴ PFU	2	10
3	DENVax-4c	10 ⁴ PFU	2	10
4	TFA	NA	2	10

[0131] 為進一步修飾以及擴大DENVax-4b之致免疫性，使此病毒從在試管中適應在Vero細胞之生長。此之進行是在Vero細胞中進行10代盲傳，理論是，在哺乳動物細胞培養中之適應，會加強病毒之複製能力，因此加強其致免疫性。此“新的”第二代DENVax-4稱作DENVax-4b-P10 (繼代-10)。

[0132] 進行另一個評估包括三個不同的DEN4病毒之登革熱病毒疫苗之不同的四價配方之研究；第一代、第二代(4b建構物)以及同源野生型DEN4 1036。皮下注射6隻小鼠之群組，含有10⁴ PFU DENVax-1、10³ PFU DENVax-2、10⁴ PFU DENVax-3以及10⁵ PFU DENVax 4 (4 : 3 : 4 : 5)，容積50μL之四價疫苗配方。對照小鼠以相同途徑注射10⁵ PFU之第1代、第2代或野生型1036單價DENV4。僅注射稀釋液之小鼠群組作為對照組。所有的小鼠在第42天接受相應疫苗配方之追加注射，以及在第一次接種後第0天、第21天、第41天以及第56天採血，評估抗全部四種DENV血清型之中和

抗體是否出現。在第56天，用DENV-2 (NGC毒株)挑戰群組4、5以及6之小鼠，評估生存率(現在沒有小鼠適應致命DENV4毒株供有效的分析使用)。如表3所述，第1代以及第2代DENVax-4疫苗單獨投與時，具有比得上之致免疫性量變曲線。然而，當其等以四價登革熱病毒疫苗提供時，對DENV-4之免疫反應僅因第2代DENVax-4之干擾，而會有所減低。野生型DENV4係高度致免疫性的，且在四價登革熱病毒疫苗之情況下，其會干擾以及抑制由其它三種登革熱病毒疫苗所誘發之中和抗體的反應。野生型DENV4、第1代以及第2代DENVax-4，提供抗異源DENV-2挑戰部分的保護。

第2代DENVax在NHP中之安全性以及效率

表3 小鼠研究#2之研究設計以及PRNT結果

	群組	劑量	DENV1	DENV2	DENV3	DENV4
1	DENVax (第1代DENVax-4)	4:3:4:5	1280 (320)	640 (320)	>1280 (320)	640 (160)
2	DENVax (以野生型DENV-4 取代DENV-4)	4:3:4:5	160 (320)	160 (160)	320 (160)	640 (640)
3	DENVax (以第2代 DENVax-4取代DE NVax-4)	4:3:4:5	>1280 (640)	640 (320)	>1280 (640)	80 (80)
4	DENVax-4 (第2代)	10 ⁵	X	X	X	320 (80)
5	野生型DENV-4	10 ⁵	X	X	X	640 (320)
6	DENVax-4 (第1代)	10 ⁵	X	X	X	320 (80)

[0133] 在皮下注射每一個 0.5ml 注射容積之四價DENVax配方後，評估DENVax在四個食蟹猴(Cynomologus macaques)之群組中之致免疫性(表4以及圖2)。此研究之目

的是評估重要的第2代 DENVax-4 建構物，與第1代 DENVax-4之比較。額外地，探索不同的方法，以改善由 DENVax誘起之對DENV-4的中和抗體反應。此等包括測試如之前使用之含有10X劑量的DENVax-4之配方(稱作“新配方”)，以及降低四價混合物之DENVax-2組份，因為此疫苗是四種疫苗病毒株中最具致免疫性的。測試不同的投藥天數，比較在相同天接種以及追加(第0天)，與第0天接種而第60天追加。在第0天、第28天、第58天、第73天以及第90天採取供血清學之樣本。抗DENV-4變異株病毒以及原始病毒之中和抗體效價的動力學示於圖3中，作為範例，在此可觀察到類似的位準。

表4 NHP研究設計：

群組	疫苗來源	配方	治療
1	DENVax配方 (臨床貯存株)	2e4、5e4、1e5、3e5	2劑(第0天)
2	DENVax配方(4b-P10)	2e4、5e4、1e5、3e5(4b)	2劑(第0天)
3	DENVax配方 (臨床貯存株) w/10x DENVax-4	2e4、5e4、1e5、3e6	2劑(第0天)
4	DENVax配方 (臨床貯存株) w/10x DENVax-4	2e4、5e4、1e5、3e6	2劑(0，60)
5	DENVax新配方	2e4、1e4、1e5、3e6	2劑(0，60)

[0134] 供NHP研究之疫苗配方係整批配製的。群組1接受cGMP製造且與目前欲在人類臨床試驗中測試之疫苗一致的疫苗。提供給NHP疫苗，之後反滴定以決定實際的劑量。此等結果呈現於以下表5中。

[0135] 表5 疫苗貯存株-反滴定結果：

	iFFU/劑量	所欲劑量		所欲劑量		所欲劑量	
DENVax	GP1	GP2	反滴定	GP3以及4	反滴定	GP5	反滴定
D1	2.00E+04	2.00E+04	1.90E+04	2.00E+04	1.80E+04	2.00E+04	1.80E+04
D2	5.00E+04	5.00E+04	2.60E+04	5.00E+04	2.40E+04	1.00E+04	3.60E+03
D3	1.00E+05	1.00E+05	1.80E+05	1.00E+05	1.40E+05	1.00E+05	1.70E+05
D4	3.00E+05	300000 (4b)	2.10E+05	3.00E+06	2.90E+06	3.00E+06	3.00E+06

[0136] 在第一劑之後，採取第-11 (基準線)、3、5、7、9、11、13、15、17、21、28、58、62以及66之樣本供病毒血症研究。從血清樣本中萃取出RNA，然後利用tetraplex qRT-PCR分析法測定病毒效價。提供任何可測得之病毒血症之唯一病毒是DENVax-2，且此在第一次接種疫苗後第21天解決。在投與疫苗追加劑量後，沒有測得病毒。

[0137] 血清學之評估係使用在96孔培養皿之高通量PRNT分析法。第1代以及第2代DENVax-4之比較(群組1與群組2比較)，在此等二種病毒之致免疫性方面，沒有顯示出顯著差異(表6)。

表6 NHP研究之幾何平均效價

群組	DEN	d0	d28	d58	d73	d90	d128	d149	d181	d210
1	1	5	226.3	134.5	160.0	95.1	67.3	95.1	226.3	226.3
5455a	2	5	1810.2	1280.0	905.1	905.1	761.1	761.1	761.1	380.5
0,0	3	5	226.3	190.3	320.0	226.3	95.1	134.5	226.3	160.0
	4	5	28.3	20.0	134.5	56.6	23.8	33.6	113.1	67.3
2	1	5	33.6	16.8	47.6	40.0	23.8	23.8	20.0	67.3
5455b	2	5	1076.3	1280.0	905.1	1076.3	1076.3	1280.0	640.0	640.0
0,0	3	5	67.3	33.6	226.3	80.0	23.8	28.3	28.3	33.6
	4	5	23.8	11.9	80.0	47.6	23.8	33.6	23.8	20.0
3	1	5	80.0	47.6	56.6	67.3	40.0	33.6	134.5	134.5
5456	2	5	380.5	320.0	538.2	538.2	190.3	508.0	269.1	269.1
0,0	3	5	95.1	80.0	134.5	95.1	40.0	40.0	160.0	113.1
	4	5	95.1	134.5	160.0	160.0	134.5	134.5	320.0	226.3
4	1	5	16.8	16.8	80.0	56.6	23.8	23.8	16.8	20.0
5456	2	5	134.5	134.5	269.1	320.0	134.5	134.5	95.1	80.0
0,60	3	5	23.8	23.8	134.5	95.1	23.8	20.0	28.3	28.3
	4	5	23.8	20.0	134.5	113.1	56.6	80.0	28.3	28.3
5	1	5	20.0	11.9	134.5	134.5	33.6	20.0	28.3	14.1
5356	2	5	28.3	8.4	95.1	80.0	10.0	5.9	5.0	5.0
0,60	3	5	23.8	11.9	190.3	190.3	23.8	28.3	33.6	28.3
	4	5	33.6	33.6	269.1	134.5	113.1	56.6	80.0	67.3

[0138] 評估較高劑量的DENVax-4 (群組3)顯示出，在DENV-4中和抗體反應之動力學方面，可獲得顯著的差異。比較二種不同疫苗配方時，波峰效價保持大約相等(在2倍稀釋範圍內)，但對DENV-4所獲得之波峰效價之速率，遠早於用較高劑量DENVax-4進行免疫作用之速率。此外，當在配方中DENVax-2之數量降低(群組5)時，在此四價DENVax疫苗中之血清反應方面，DENV-4之動力學以及波峰效價沒有明顯的差異。

[0139] 圖9表示一用於測試在此所揭示之病毒建構物，於動物模型中之安全性以及效率之示範程序之流程圖。例如，可在動物模型，如AG129，中，測試包括一或多種用作為疫苗之嵌合登革熱病毒之組成物，諸如DENVax4e、DENVax4f或DENVax4h或其它嵌合建構物之組成物，或對照組成物。第1天，在動物身上接種疫苗，然後在第30天或

第42天或其它適當的時間，或之前，用相同或不同登革熱病毒疫苗組成物追加。然後，藉由曝露於一或多種登革熱病毒血清型挑戰該等動物，評估對該挑戰所誘發之免疫反應。在例如第0天、第30天、第41天、第48天、第52天或第84天或其它適當的日子，收集血液樣本，以便測試中和抗體，以及在諸如第5天以及第47天之其它天測試病毒血症(或針對所選之組成物以及投與操作程序而言認為適當的)。病毒選殖以及回復至P1

[0140] 使用質體突變生成，來製造用於在此所揭示之疫苗組成物之新的DEN-4嵌合選殖株。合成編碼用於點突變之引子，然後用於擴增完整新的感染性選殖株。用DpnI消化樣版，然後定序之後的質體。轉錄RNA，並電穿孔進入Vero細胞中，製造繼代程度0之病毒(P0)，之後利用Vero細胞中之單一繼代(P1)擴增。

[0141] DENVax-4b選殖株中之殼體/PrM接頭處之修飾，在NHP研究中，看來不會引起DEN-4之致免疫性增加。使用從DEN-4以及DENVax-4b之盲系列繼代而來之資料，鑑定出3個可增加Vero細胞適應之點突變。此外，一些減毒突變回復成野生型序列，增加於小鼠中之致免疫性。如圖6所示，DENVax-4e以及DENVax-4h之較大的IFU尺寸以及促使細胞溶解的表型，說明了此等選殖株之任一個，在小鼠中均可顯示出致免疫性增加。進行用於分析新DENVax-4選殖株中每一個之生長動力學之實驗，以便測定是否所插入的修飾會增加Vero細胞之適應作用。亦於A129小鼠中進行測

試，分析致免疫性。

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[0142] 登革熱疫苗株於Vero細胞中之系列繼代，係一種用於選擇較適合於試管中生長之毒株之典型的方法。在此等示範生長實驗中，DENVax-2 (圖1)作為對照組，在第2天出現最高的起始效價，接著是DENVax-4b-P10、DENVax-4以及DENVax-4b-P1。在生長期間結束時(第12天)，DENVax-2具有最高的波峰效價，接著是DENVax-4b-P10、DENVax-4b-P1以及DENVax-4。

序列中之胺基酸改變

[0143] DENVax4-P10基因組定序顯示出對應於胺基酸 E-417 E-K (Glu-Lys) 以及 NS4A-17 M-L 之突變。DENVax4b-P10序列顯示出對應於胺基酸 C-107 C-Y之突變。E-417 E-K突變會改變胺基酸殘基，如此胺基團(NH₂)取代羧基羥基基團。然而，R基團仍帶電，且保持親水性。NS4A-17 M-L突變導致從R基團中移除硫酸根，但保持產生疏水性胺基酸之非極性。C-107 C-Y突變導致R基團劇烈的改變。半胱胺酸具有SH基團，其能夠形成雙硫鍵，然而酪胺酸具有含羥基基團之碳苯環。此引起胺基酸殘基變成親水性，而不是疏水性，影響其與其它胺基酸R基團之交互反應。

[0144] 圖20是表示DENVax-4建構物於生長動力學實驗期間之效價圖。採取每一樣本之日子繪在x軸上，而效價繪在y軸上。

接種DENVax之NHP中之中和抗體

[0145] 在某些方法中，用更大型的測試致免疫性方案之研究，進行DEN-4嵌合建構物之評估。測試DENVax-4b與DENVax-4a相比之致免疫性。第0天，在群組1以及2上接種2劑，且沒有追加接種。在所有劑量中使用相等效價之DENVax-4 (菱形)或DENVax-4b (方形)。在包括DENV-4之任一個血清型之間，發現中和抗體之幾何平均效價(GMT)沒有顯著差異。此顯示出，於四價DENVa劑量中使用DENVax-4b，不會影響或增加抗DENV-4之中和抗體反應。圖21：群組1 (DENVax-4，菱形)以及群組2 (DENVax-4b，方形)之GMT值的比較。GMT值是由噬斑減少中和技術而來之中和抗體值之測量值。

[0146] 比較於群組1以及群組3中之中和抗體反應，決定增加四價DENVax中之DENVax-4的劑量，是否會增加抗DENV-4之致免疫性。結果顯示出，與用傳統四價DENVax免疫的相比，用較高劑量之DENVax-4免疫之靈長類動物，顯示出在第一個60天中檢測之初級中和抗體之GMT增加。在其它DENV血清型之間，在GMT方面沒有顯著的差異(圖22)。此顯示出，較高劑量的DENVax-4會改善抗DENV-4之中和抗體反應。

[0147] 比較群組1 (菱形)以及4 (方形)中之中和抗體反應，以便測試致免疫程序在致免疫性上之影響(圖23)。圖23說明GMT值，證明疫苗程序在中和抗體反應上之影響。此指出，在第0天2個劑量且沒有追加，與在第0天1劑然後第

60天1劑相比，沒有顯著影響。最後，比較從群組4 (菱形) 以及群組5 (方形)而來之數據，看是否減少DENVax-2的劑量，會影響DENVax-4之致免疫結果。結果顯示，在抗DENV-4之GMT中，沒有顯著的差異，但在抗DENV-2之GMT中，群組5顯著地降低。此指出，由DENVax-2誘起之抗體反應，在由DENVax-4誘起之抗體反應上，不具有嚴重的影響(圖24)。圖24表示群組4 (菱形)以及群組5 (方形)對全部DENV血清型之GMT值。使用噬斑減少中和技術測量結果。

[0148] 此等實驗之結果支持，在此所揭示之建構物會改善DENV-4中和抗體反應。在配方中，DENVax-4劑量增加，確實顯示出中和抗體產物顯著的增加。DENVax-2確實亦似乎不會對DENVax-4之中和抗體反應產生衝擊。在首劑接種2劑之方法以及首劑與追加接種方法之間，在抗體產生方面，僅有些微差異至無差異。產生足夠抗DENV-4 1036 (其為目前使用於DENVax-4中之毒株)之中和抗體效價。成功的DENV-4疫苗，應能夠適當地中和多種野生型DENV-4之毒株，包括具基因組修飾、不同基因型以及不同表型之新演變的毒株。

[0149] 定序期間，在二個建構中之繼代1以及繼代10之間，均鑑定出三個點突變。如之前討論的，此等突變位於DENVax-4b之殼體區中，以及位在DENVax-4之prM與套膜基因中。將此等突變併入該建構物中，可藉由減少病毒之減毒作用，提供於Vero細胞中之生長增加，其可改善致免疫性。如在此所揭示的，DENVax-4h在中和抗體效價方面，

具有2倍的增加，而DENVax-4e在中和抗體效價方面具有1.5倍的增加。在其它方法中，測試增加的DEN-4之致免疫性，然後與其它二價、三價以及四價建構物組成物相比。

材料以及方法

細胞培養

[0150] Vero細胞係一種由美國綠猴腎衍生而來之哺乳動物細胞。Vero細胞株應用於試管中之實驗。Vero細胞可在37°C下，Dulbecco氏之修飾的Eagle's培養基(DMEM，Mediatech Inc., Manassas VA)，補充有10%胎牛血清(FBS，Hyclone, Logan UT)、2% L-麩醯胺酸(Hyclone)以及1%盤尼西林-鏈黴素(Pen-Strep，Hyclone)中生長。為繼代培養該細胞，使用Tryple Express溶液(Life Technologies, Grand Island NY)從瓶表面移除細胞。

病毒感染Vero單層

[0151] 在感染之前約48個小時，將Vero細胞種在T-75 cm²瓶中。使用補充有10% FBS、2% L-麩醯胺酸以及1%盤尼西林-鏈黴素之DMEM作為細胞生長培養基。細胞匯合時，使用4 mL以1：5於PBS中稀釋之0.25%胰蛋白酶溶液，胰酶化1瓶。計數細胞，建立MOI。剩下的二瓶，在預定MOI下，於1mL具DENVax-4-P2（第1代DENVax-4）或DENVax-4b-P3或其它建構物，且稀釋於BA-1稀釋液(牛血清蛋白1X M199、0.05M Tris-HCL、1X L-麩醯胺酸、7.5%碳酸氫鈉、1X Pen-strep、1X Fungizone)中感染。利用每10分鐘振動，避免細胞單層乾燥，使病毒吸收至Vero細胞上，

歷時90分鐘。在吸收後，於每一瓶中加入20 mL補充有5% FBS之DMEM。在37°C下培育該等瓶7天。

病毒收集以及之後的感染：盲繼代

[0152] 在預定的期間後，在每一瓶上觀察CPE，然後收集病毒上清液，且在20% FBS中安定化，供用於在-80°C下貯存。用1 mL從前述瓶中獲得之病毒上清液，感染之前接種匯合T-75 cm²之Vero瓶。利用每10分鐘振動，使病毒吸收90分鐘。在病毒吸收後，於每一瓶中加入20 mL之DMEM 5% FBS。每7天，將新無感染的對照瓶劃在培養皿上。每7天重覆此方法，歷時10個禮拜，每個病毒產生10個繼代，提供DENVax-4-P2-P1至P10或DENVax-4b-P3-P1至P10，或各種建構物之其它指示的稱呼。

病毒之噬斑滴定

[0153] 進行在第1、5以及10周從DENVax-4-P2以及DENVax-4b-P3以及其它嵌合建構物採取之樣本之噬斑滴定，以測量效價。依序將病毒樣本在BA-1稀釋液中稀釋成 1×10^{-1} 至 1×10^{-6} 。樣本之噬斑滴定一式三份，利用每8分鐘振動，使100 uL每一稀釋液吸附至預接種Vero細胞之6孔培養皿，歷時90分鐘。吸附後，孔上覆蓋4 mL之BSS/瓊脂(NaCl、KCl、NaH₂PO₄-H₂O、葡萄糖、CaCl₂-2H₂O、MgSO₄-7H₂O)溶液，然後在37°C下培育4天。在第4天時，在孔上覆蓋2 mL BSS/瓊脂/中性紅溶液，然後在37°C下培育一整夜。在第5天、第6天以及第7天計數噬斑。

生長曲線分析

[0154] 建製在Vero細胞上之生長曲線，分析適應的毒株之生長動力學。如之前所述，接種Vero瓶。在第0天，計數Vero細胞匯合瓶，以便計算在0.001 MOI下，感染該瓶所需之病毒PFU。用1 mL之DENVax-4、DENVax-4b-P1、DENVax-4b-P10或DENVax-2或其它合建構物(如，DENVax-4e、4h等等)感染該等瓶。藉由每8分鐘振動，歷時90分鐘，使病毒吸附至單層上。吸附後，於每一瓶中加入10 mL沒有補充有1% F-127之FBS之cDMEM，然後令樣本在37°C，5% CO₂下培育。在第2天以及第4-12天，從每一瓶之上清液中收集樣本。在第4天以及第6-12天收集瓶中全部的上清液收取疫苗，然後用新配製的cDMEM-F127取代生長培養基。在換培養基期間，用PBS清洗3次。使樣本在1x FTA (FTA:15%海藻糖、1% F-127、0.1%人類血清白蛋白，PBS)中安定，然後以之前所述之方法進行噬斑滴定，以便測定效價。

[0155] 在DENVax-4以及DENVax-4b均在Vero細胞中盲繼代10次後，對每一繼代進行定序，鑑定P1與P10之間之突變。在CDC進行DENVax-4-P2-P1與P10以及DENVax-4b-P3-P1與P10之定序反應。使用QIAmp病毒RNA套組，從病毒貯存株中分離出病毒RNA。使用逆轉錄酶PCR(RT-PCR)，使用之前由CDC設計之引子，將RNA轉錄成DNA。引子係從DENV-2 16681以及DENV-4 1036之序列設計而得的。利用RT-PCR，從每一建構物擴增出大約7-9個PCR片段。之後利用Beckman Coulter，使用自動定序反應

定出DNA片段之序列，然後對齊以供比對。

定序

[0156] 在各種建構物在Vero細胞中繼代10次或更多次之後，對每一繼代定序，以便鑑定突變。在每一樣本上進行定序反應，使用QIAmp病毒RNA套組，從病毒貯存株中分離出病毒RNA。使用逆轉錄酶PCR (RT-PCR)，使用之前由CDC設計之引子，將RNA轉錄成DNA。引子係從DENV-2 16681以及DENV-4 1036之序列設計而得的。利用RT-PCR，從每一建構物擴增大約7-9個PCR片段。之後利用Beckman Coulter，使用自動定序反應定出DNA片段之序列，然後對齊以供比對。

非人類靈長動物之研究

[0157] 將食蟹猴安排在不同的研究群組，用具有各種DEN-4建構物之四價DENVax之劑接種疫苗。每群組測試一種配方。配方1可含有高劑量之帶有DENVax-4第1代之DENVax，而群組1中之靈長動物在第0天給予2個劑量之首劑，沒有追加。配方2含有高劑量之帶有DEN-4建構物之DENVax，以及群組2中之靈長動物在第0天給予2個劑量之首劑，沒有追加。疫苗接種可經由皮下或ID，或利用其它方法，使用針頭或無針系統與針筒。可在第0、28、58、73、90、128天或其它適合的時間點，採取供血清學分析之樣本。利用噬斑減少中和技術，測量血清中之中和抗體反應。

噬斑減少中和技術

[0158] 為測試血清樣本中之中和抗體產率，可使用噬斑

減少中和分析法。在接種疫苗之前2天，先接種Vero 6孔培養皿，以確保單層匯合。依序在96孔培養皿中之BA-1稀釋液中，稀釋血清樣本2倍，然後在，4°C下培育登革熱病毒大約20個小時。培育後，用製備好的病毒/血清稀釋液接種Vero細胞。使樣本在每8分鐘振動下歷時90分鐘進行吸附，防止單層乾燥。吸附後，於孔上覆蓋1：1之BSS以及瓊脂溶液，然後在37°C下培育4天。第4天，在細胞上覆蓋1：1比率之補充有中性紅溶液之BSS與瓊脂。在第5天、第6天以及第7天計數孔上可見之噬斑。GMT值意指可中和50%之病毒之血清的平均稀釋。此之測量是藉由測定在無血清之情況下形成之噬斑的數目，除以2 (考慮到稀釋)，然後注意那一個稀釋的血清引起等於或少於該數目之噬斑形成。

[0159] 與DENVax-4e (殼體突變)相比，DENVax-4h (套膜突變)之較高的致免疫性，暗示DENVax-4套膜蛋白可能是最佳化的。套膜蛋白提供用於產生中和抗體之抗原決定位，以及修飾用於最佳化能誘起強抗體反應之抗原決定位之序列，可增加抗體效價。DENVax-4h之位置417處之套膜突變，是莖幹區中之保守部分。與其它黃病毒相比，DENV-4在此位置具有不同的胺基酸。莖幹區位在E蛋白之結構域III中，最強之中和抗原決定位位於此。結合以及中和此位置之抗體，會防止該莖幹區在內吞作用後，與核內體膜融合。事實上，在包括DENV-1、-2、-3以及WNV之黃病毒家族之中，位置417是保守的。從E回復成K可改變次結構，以利更強健的免疫反應。如在其它黃病毒中可見到的，進一步

的突變可回復成保守帶電天門冬胺酸(D)。

[0160] 本發明之前面的討論係用以例示說明之目的。該前述之內容不意圖用於限制本發明至在此所揭示之形式。雖然本發明之說明書包括一或多個具體例以及某些變化以及修飾，但其它變化以及修飾均落在本發明之範疇內，如，落在此技藝之人士，於了解本揭示內容後之技術以及理解之範圍內。本發明意圖獲得包括選擇性具體例至該等所請求所容許之範圍，包括替換、可互換和/或相等之結構、功能、範圍或步驟，不管此等替換、可互換和/或相等結構、功能、範圍或步驟在此是否揭示，以及無意圖公開地獻出任何可專利之標的。

【符號說明】

(無)

【序列表】

<110> 武田疫苗股份有限公司
美國政府，由衛生及公共服務部部長代表

<120> 登革熱病毒血清型 4 型之建構物的組成物、方法及用途

<130> PI-56921-D1-GE

<150> 61/724,190
<151> 2012-11-08

<150> 61/788,536
<151> 2013-03-15

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<170> PatentIn version 3.5

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

Lys Arg Lys Lys Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr
100 105 110

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

Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ala Ser Gly
130 135 140

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

Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr Glu Val Glu Pro Glu
165 170 175

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

Thr Cys Asn Gln Ala Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
195 200 205

Leu Ala Pro His Val Gly Met Gly Leu Asp Thr Arg Thr Gln Thr Trp
210 215 220

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

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

Tyr Ile Gly Thr Ser Leu Thr Gln Lys Val Val Ile Phe Ile Leu Leu
260 265 270

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

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

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

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

Asn Tyr Val Cys Lys His Thr Tyr Val Asp Arg Gly Trp Gly Asn Gly
370 375 380

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

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

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

Asn Glu Thr Gln Gly Val Thr Ala Glu Ile Thr Pro Gln Ala Ser Thr
435 440 445

Ala Glu Ala Ile Leu Pro Glu Tyr Gly Thr Leu Gly Leu Glu Cys Ser
450 455 460

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

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

Pro Trp Thr Ser Gly Ala Thr Ala Glu Thr Pro Thr Trp Asn Arg Lys
500 505 510

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

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

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

Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Glu Leu Lys Gly Met Ser
565 570 575

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

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

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

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

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

Val Ile Gly Ile Gly Asp Lys Ala Leu Lys Ile Asn Trp Tyr Lys Lys
660 665 670

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

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

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

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

Ile Gly Val Leu Leu Thr Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser
740 745 750

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

Ala Val Val Gln Ala Asp Met Gly Cys Val Ile Asn Trp Lys Gly Lys
770 775 780

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

Trp Thr Glu Gln Tyr Lys Phe Gln Ala Asp Ser Pro Lys Arg Leu Ala
805 810 815

Thr Ala Ile Ala Gly Ala Trp Glu Asn Gly Val Cys Gly Ile Arg Ser
820 825 830

Thr Thr Arg Met Glu Asn Leu Leu Trp Lys Gln Ile Ala Asn Glu Leu
835 840 845

Asn Tyr Ile Leu Trp Glu Asn Asn Ile Lys Leu Thr Val Val Val Gly
850 855 860

Asp Ile Thr Gly Val Leu Glu Gln Gly Lys Arg Thr Leu Thr Pro Gln
865 870 875 880

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

Val Thr Ala Glu Thr Gln Asn Ser Ser Phe Ile Ile Asp Gly Pro Ser
900 905 910

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

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

Arg Glu Val Tyr Thr Gln Leu Cys Asp His Arg Leu Met Ser Ala Ala
945 950 955 960

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

Ser Gln Lys Asn Gly Ser Trp Lys Leu Glu Lys Ala Ser Phe Ile Glu
980 985 990

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

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

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

Gly Pro Trp His Leu Gly Lys Leu Glu Leu Asp Phe Asn Tyr Cys
1040 1045 1050

Glu Gly Thr Thr Val Val Ile Ser Glu Asn Cys Gly Thr Arg Gly
1055 1060 1065

Pro Ser Leu Arg Thr Thr Thr Val Ser Gly Lys Leu Ile His Glu
1070 1075 1080

Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Met Gly
1085 1090 1095

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

Lys Glu Glu Asn Met Val Lys Ser Leu Ala Ser Ala Gly Ser Gly
1115 1120 1125

Lys Val Asp Asn Phe Thr Met Gly Val Leu Cys Leu Ala Ile Leu
1130 1135 1140

Phe Glu Glu Val Met Arg Gly Lys Phe Gly Lys Lys His Met Ile
1145 1150 1155

Ala Gly Val Leu Phe Thr Phe Val Leu Leu Leu Ser Gly Gln Ile
1160 1165 1170

Thr Trp Arg Asp Met Ala His Thr Leu Ile Met Ile Gly Ser Asn
1175 1180 1185

Ala Ser Asp Arg Met Gly Met Gly Val Thr Tyr Leu Ala Leu Ile
1190 1195 1200

Ala Thr	Phe Lys Ile Gln	Pro	Phe Leu Ala Leu Gly	Phe Phe Leu
1205		1210	1215	
Arg Lys	Leu Thr Ser Arg	Glu	Asn Leu Leu Leu Gly	Val Gly Leu
1220		1225	1230	
Ala Met	Ala Ala Thr Leu	Arg	Leu Pro Glu Asp Ile	Glu Gln Met
1235		1240	1245	
Ala Asn	Gly Ile Ala Leu	Gly	Leu Met Ala Leu Lys	Leu Ile Thr
1250		1255	1260	
Gln Phe	Glu Thr Tyr Gln	Leu	Trp Thr Ala Leu Val	Ser Leu Thr
1265		1270	1275	
Cys Ser	Asn Thr Ile Phe	Thr	Leu Thr Val Ala Trp	Arg Thr Ala
1280		1285	1290	
Thr Leu	Ile Leu Ala Gly	Ile	Ser Leu Leu Pro Val	Cys Gln Ser
1295		1300	1305	
Ser Ser	Met Arg Lys Thr	Asp	Trp Leu Pro Met Thr	Val Ala Ala
1310		1315	1320	
Met Gly	Ala Gln Pro Leu	Pro	Leu Phe Ile Phe Ser	Leu Lys Asp
1325		1330	1335	
Thr Leu	Lys Arg Arg Ser	Trp	Pro Leu Asn Glu Gly	Val Met Ala
1340		1345	1350	
Val Gly	Leu Val Ser Ile	Leu	Ala Ser Ser Leu Leu	Arg Asn Asp
1355		1360	1365	
Val Pro	Met Ala Gly Pro	Leu	Val Ala Gly Gly Leu	Leu Ile Ala
1370		1375	1380	
Cys Tyr	Val Ile Thr Gly	Thr	Ser Ala Asp Leu Thr	Val Glu Lys
1385		1390	1395	
Ala Ala	Asp Val Thr Trp	Glu	Glu Glu Ala Glu Gln	Thr Gly Val
1400		1405	1410	
Ser His	Asn Leu Met Val	Thr	Val Asp Asp Asp Gly	Thr Met Arg
1415		1420	1425	

Ile Lys	Asp Asp	Glu Thr	Glu Asn	Ile Leu	Thr Val	Leu Leu	Lys
1430			1435		1440		
Thr Ala	Leu Leu	Ile Val	Ser Gly	Ile Phe	Pro Tyr	Ser Ile	Pro
1445			1450		1455		
Ala Thr	Leu Leu	Val Trp	His Thr	Trp Gln	Lys Gln	Thr Gln	Arg
1460			1465		1470		
Ser Gly	Val Leu	Trp Asp	Val Pro	Ser Pro	Pro Glu	Thr Gln	Lys
1475			1480		1485		
Ala Glu	Leu Glu	Glu Gly	Val Tyr	Arg Ile	Lys Gln	Gln Gly	Ile
1490			1495		1500		
Phe Gly	Lys Thr	Gln Val	Gly Val	Gly Val	Gln Lys	Glu Gly	Val
1505			1510		1515		
Phe His	Thr Met	Trp His	Val Thr	Arg Gly	Ala Val	Leu Thr	His
1520			1525		1530		
Asn Gly	Lys Arg	Leu Glu	Pro Asn	Trp Ala	Ser Val	Lys Lys	Asp
1535			1540		1545		
Leu Ile	Ser Tyr	Gly Gly	Gly Trp	Arg Leu	Ser Ala	Gln Trp	Gln
1550			1555		1560		
Lys Gly	Glu Glu	Val Gln	Val Ile	Ala Val	Glu Pro	Gly Lys	Asn
1565			1570		1575		
Pro Lys	Asn Phe	Gln Thr	Met Pro	Gly Ile	Phe Gln	Thr Thr	Thr
1580			1585		1590		
Gly Glu	Ile Gly	Ala Ile	Ala Leu	Asp Phe	Lys Pro	Gly Thr	Ser
1595			1600		1605		
Gly Ser	Pro Ile	Ile Asn	Arg Glu	Gly Lys	Val Val	Gly Leu	Tyr
1610			1615		1620		
Gly Asn	Gly Val	Val Thr	Lys Asn	Gly Gly	Tyr Val	Ser Gly	Ile
1625			1630		1635		

Ala	Gln	Thr	Asn	Ala	Glu	Pro	Asp	Gly	Pro	Thr	Pro	Glu	Leu	Glu
1640						1645					1650			
Glu	Glu	Met	Phe	Lys	Lys	Arg	Asn	Leu	Thr	Ile	Met	Asp	Leu	His
1655						1660					1665			
Pro	Gly	Ser	Gly	Lys	Thr	Arg	Lys	Tyr	Leu	Pro	Ala	Ile	Val	Arg
1670						1675					1680			
Glu	Ala	Ile	Lys	Arg	Arg	Leu	Arg	Thr	Leu	Ile	Leu	Ala	Pro	Thr
1685						1690					1695			
Arg	Val	Val	Ala	Ala	Glu	Met	Glu	Glu	Ala	Leu	Lys	Gly	Leu	Pro
1700						1705					1710			
Ile	Arg	Tyr	Gln	Thr	Thr	Ala	Thr	Lys	Ser	Glu	His	Thr	Gly	Arg
1715						1720					1725			
Glu	Ile	Val	Asp	Leu	Met	Cys	His	Ala	Thr	Phe	Thr	Met	Arg	Leu
1730						1735					1740			
Leu	Ser	Pro	Val	Arg	Val	Pro	Asn	Tyr	Asn	Leu	Ile	Ile	Met	Asp
1745						1750					1755			
Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser	Ile	Ala	Ala	Arg	Gly	Tyr
1760						1765					1770			
Ile	Ser	Thr	Arg	Val	Gly	Met	Gly	Glu	Ala	Ala	Ala	Ile	Phe	Met
1775						1780					1785			
Thr	Ala	Thr	Pro	Pro	Gly	Thr	Ala	Asp	Ala	Phe	Pro	Gln	Ser	Asn
1790						1795					1800			
Ala	Pro	Ile	Gln	Asp	Glu	Glu	Arg	Asp	Ile	Pro	Glu	Arg	Ser	Trp
1805						1810					1815			
Asn	Ser	Gly	Asn	Glu	Trp	Ile	Thr	Asp	Phe	Val	Gly	Lys	Thr	Val
1820						1825					1830			
Trp	Phe	Val	Pro	Ser	Ile	Lys	Ala	Gly	Asn	Asp	Ile	Ala	Asn	Cys
1835						1840					1845			
Leu	Arg	Lys	Asn	Gly	Lys	Lys	Val	Ile	Gln	Leu	Ser	Arg	Lys	Thr
1850						1855					1860			

Phe	Asp	Thr	Glu	Tyr	Gln	Lys	Thr	Lys	Leu	Asn	Asp	Trp	Asp	Phe
1865						1870					1875			
Val	Val	Thr	Thr	Asp	Ile	Ser	Glu	Met	Gly	Ala	Asn	Phe	Lys	Ala
1880						1885					1890			
Asp	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Leu	Lys	Pro	Val	Ile	Leu
1895						1900					1905			
Thr	Asp	Gly	Pro	Glu	Arg	Val	Ile	Leu	Ala	Gly	Pro	Met	Pro	Val
1910						1915					1920			
Thr	Val	Ala	Ser	Ala	Ala	Gln	Arg	Arg	Gly	Arg	Val	Gly	Arg	Asn
1925						1930					1935			
Pro	Gln	Lys	Glu	Asn	Asp	Gln	Tyr	Ile	Phe	Met	Gly	Gln	Pro	Leu
1940						1945					1950			
Asn	Asn	Asp	Glu	Asp	His	Ala	His	Trp	Thr	Glu	Ala	Lys	Met	Leu
1955						1960					1965			
Leu	Asp	Asn	Ile	Asn	Thr	Pro	Glu	Gly	Ile	Ile	Pro	Ala	Leu	Phe
1970						1975					1980			
Glu	Pro	Glu	Arg	Glu	Lys	Ser	Ala	Ala	Ile	Asp	Gly	Glu	Tyr	Arg
1985						1990					1995			
Leu	Lys	Gly	Glu	Ser	Arg	Lys	Thr	Phe	Val	Glu	Leu	Met	Arg	Arg
2000						2005					2010			
Gly	Asp	Leu	Pro	Val	Trp	Leu	Ala	His	Lys	Val	Ala	Ser	Glu	Gly
2015						2020					2025			
Ile	Lys	Tyr	Thr	Asp	Arg	Lys	Trp	Cys	Phe	Asp	Gly	Glu	Arg	Asn
2030						2035					2040			
Asn	Gln	Ile	Leu	Glu	Glu	Asn	Met	Asp	Val	Glu	Ile	Trp	Thr	Lys
2045						2050					2055			
Glu	Gly	Glu	Lys	Lys	Lys	Leu	Arg	Pro	Arg	Trp	Leu	Asp	Ala	Arg
2060						2065					2070			

Thr	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Asp	Phe	Ala
2075						2080					2085			
Ala	Gly	Arg	Lys	Ser	Ile	Ala	Leu	Asp	Leu	Val	Thr	Glu	Ile	Gly
2090						2095					2100			
Arg	Val	Pro	Ser	His	Leu	Ala	His	Arg	Thr	Arg	Asn	Ala	Leu	Asp
2105						2110					2115			
Asn	Leu	Val	Met	Leu	His	Thr	Ser	Glu	His	Gly	Gly	Arg	Ala	Tyr
2120						2125					2130			
Arg	His	Ala	Val	Glu	Glu	Leu	Pro	Glu	Thr	Met	Glu	Thr	Leu	Leu
2135						2140					2145			
Leu	Leu	Gly	Leu	Met	Ile	Leu	Leu	Thr	Gly	Gly	Ala	Met	Leu	Phe
2150						2155					2160			
Leu	Ile	Ser	Gly	Lys	Gly	Ile	Gly	Lys	Thr	Ser	Ile	Gly	Leu	Ile
2165						2170					2175			
Cys	Val	Ile	Ala	Ser	Ser	Gly	Met	Leu	Trp	Met	Ala	Asp	Val	Pro
2180						2185					2190			
Leu	Gln	Trp	Ile	Ala	Ser	Ala	Ile	Val	Leu	Glu	Phe	Phe	Met	Met
2195						2200					2205			
Val	Leu	Leu	Ile	Pro	Glu	Pro	Glu	Lys	Gln	Arg	Thr	Pro	Gln	Asp
2210						2215					2220			
Asn	Gln	Leu	Ala	Tyr	Val	Val	Ile	Gly	Ile	Leu	Thr	Leu	Ala	Ala
2225						2230					2235			
Ile	Val	Ala	Ala	Asn	Glu	Met	Gly	Leu	Leu	Glu	Thr	Thr	Lys	Arg
2240						2245					2250			
Asp	Leu	Gly	Met	Ser	Lys	Glu	Pro	Gly	Val	Val	Ser	Pro	Thr	Ser
2255						2260					2265			
Tyr	Leu	Asp	Val	Asp	Leu	His	Pro	Ala	Ser	Ala	Trp	Thr	Leu	Tyr
2270						2275					2280			
Ala	Val	Ala	Thr	Thr	Val	Ile	Thr	Pro	Met	Leu	Arg	His	Thr	Ile
2285						2290					2295			

Glu	Asn	Ser	Thr	Ala	Asn	Val	Ser	Leu	Ala	Ala	Ile	Ala	Asn	Gln
2300						2305					2310			
Ala	Val	Val	Leu	Met	Gly	Leu	Asp	Lys	Gly	Trp	Pro	Ile	Ser	Lys
2315						2320					2325			
Met	Asp	Leu	Gly	Val	Pro	Leu	Leu	Ala	Leu	Gly	Cys	Tyr	Ser	Gln
2330						2335					2340			
Val	Asn	Pro	Leu	Thr	Leu	Ala	Ala	Ala	Val	Leu	Leu	Leu	Val	Thr
2345						2350					2355			
His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	Lys	Ala	Thr	Arg
2360						2365					2370			
Glu	Ala	Gln	Lys	Arg	Thr	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro	Thr
2375						2380					2385			
Val	Asp	Gly	Ile	Met	Thr	Ile	Asp	Leu	Asp	Pro	Val	Ile	Tyr	Asp
2390						2395					2400			
Ser	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val	Leu
2405						2410					2415			
Cys	Ala	Val	Gln	Leu	Leu	Leu	Met	Arg	Thr	Ser	Trp	Ala	Leu	Cys
2420						2425					2430			
Glu	Val	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Thr	Thr	Leu	Trp	Glu
2435						2440					2445			
Gly	Ser	Pro	Gly	Lys	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser	Met
2450						2455					2460			
Ala	Asn	Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu	Ala
2465						2470					2475			
Phe	Ser	Ile	Met	Lys	Ser	Val	Gly	Thr	Gly	Lys	Arg	Gly	Thr	Gly
2480						2485					2490			
Ser	Gln	Gly	Glu	Thr	Leu	Gly	Glu	Lys	Trp	Lys	Lys	Lys	Leu	Asn
2495						2500					2505			

Gln	Leu	Ser	Arg	Lys	Glu	Phe	Asp	Leu	Tyr	Lys	Lys	Ser	Gly	Ile
2510						2515					2520			
Thr	Glu	Val	Asp	Arg	Thr	Glu	Ala	Lys	Glu	Gly	Leu	Lys	Arg	Gly
2525						2530					2535			
Glu	Ile	Thr	His	His	Ala	Val	Ser	Arg	Gly	Ser	Ala	Lys	Leu	Gln
2540						2545					2550			
Trp	Phe	Val	Glu	Arg	Asn	Met	Val	Ile	Pro	Glu	Gly	Arg	Val	Ile
2555						2560					2565			
Asp	Leu	Gly	Cys	Gly	Arg	Gly	Gly	Trp	Ser	Tyr	Tyr	Cys	Ala	Gly
2570						2575					2580			
Leu	Lys	Lys	Val	Thr	Glu	Val	Arg	Gly	Tyr	Thr	Lys	Gly	Gly	Pro
2585						2590					2595			
Gly	His	Glu	Glu	Pro	Val	Pro	Met	Ser	Thr	Tyr	Gly	Trp	Asn	Ile
2600						2605					2610			
Val	Lys	Leu	Met	Ser	Gly	Lys	Asp	Val	Phe	Tyr	Leu	Pro	Pro	Glu
2615						2620					2625			
Lys	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser	Ser	Pro	Ser
2630						2635					2640			
Pro	Thr	Val	Glu	Glu	Ser	Arg	Thr	Ile	Arg	Val	Leu	Lys	Met	Val
2645						2650					2655			
Glu	Pro	Trp	Leu	Lys	Asn	Asn	Gln	Phe	Cys	Ile	Lys	Val	Leu	Asn
2660						2665					2670			
Pro	Tyr	Met	Pro	Thr	Val	Ile	Glu	His	Leu	Glu	Arg	Leu	Gln	Arg
2675						2680					2685			
Lys	His	Gly	Gly	Met	Leu	Val	Arg	Asn	Pro	Leu	Ser	Arg	Asn	Ser
2690						2695					2700			
Thr	His	Glu	Met	Tyr	Trp	Ile	Ser	Asn	Gly	Thr	Gly	Asn	Ile	Val
2705						2710					2715			
Ser	Ser	Val	Asn	Met	Val	Ser	Arg	Leu	Leu	Leu	Asn	Arg	Phe	Thr
2720						2725					2730			

Met	Thr	His	Arg	Arg	Pro	Thr	Ile	Glu	Lys	Asp	Val	Asp	Leu	Gly
2735						2740					2745			
Ala	Gly	Thr	Arg	His	Val	Asn	Ala	Glu	Pro	Glu	Thr	Pro	Asn	Met
2750						2755					2760			
Asp	Val	Ile	Gly	Glu	Arg	Ile	Lys	Arg	Ile	Lys	Glu	Glu	His	Ser
2765						2770					2775			
Ser	Thr	Trp	His	Tyr	Asp	Asp	Glu	Asn	Pro	Tyr	Lys	Thr	Trp	Ala
2780						2785					2790			
Tyr	His	Gly	Ser	Tyr	Glu	Val	Lys	Ala	Thr	Gly	Ser	Ala	Ser	Ser
2795						2800					2805			
Met	Ile	Asn	Gly	Val	Val	Lys	Leu	Leu	Thr	Lys	Pro	Trp	Asp	Val
2810						2815					2820			
Val	Pro	Met	Val	Thr	Gln	Met	Ala	Met	Thr	Asp	Thr	Thr	Pro	Phe
2825						2830					2835			
Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	Asp	Thr	Arg	Thr	Pro
2840						2845					2850			
Arg	Pro	Met	Pro	Gly	Thr	Arg	Lys	Val	Met	Glu	Ile	Thr	Ala	Glu
2855						2860					2865			
Trp	Leu	Trp	Arg	Thr	Leu	Gly	Arg	Asn	Lys	Arg	Pro	Arg	Leu	Cys
2870						2875					2880			
Thr	Arg	Glu	Glu	Phe	Thr	Lys	Lys	Val	Arg	Thr	Asn	Ala	Ala	Met
2885						2890					2895			
Gly	Ala	Val	Phe	Thr	Glu	Glu	Asn	Gln	Trp	Asp	Ser	Ala	Arg	Ala
2900						2905					2910			
Ala	Val	Glu	Asp	Glu	Glu	Phe	Trp	Lys	Leu	Val	Asp	Arg	Glu	Arg
2915						2920					2925			
Glu	Leu	His	Lys	Leu	Gly	Lys	Cys	Gly	Ser	Cys	Val	Tyr	Asn	Met
2930						2935					2940			

Met	Gly	Lys	Arg	Glu	Lys	Lys	Leu	Gly	Glu	Phe	Gly	Lys	Ala	Lys
	2945					2950					2955			
Gly	Ser	Arg	Ala	Ile	Trp	Tyr	Met	Trp	Leu	Gly	Ala	Arg	Tyr	Leu
	2960					2965					2970			
Glu	Phe	Glu	Ala	Leu	Gly	Phe	Leu	Asn	Glu	Asp	His	Trp	Phe	Ser
	2975					2980					2985			
Arg	Glu	Asn	Ser	Tyr	Ser	Gly	Val	Glu	Gly	Glu	Gly	Leu	His	Lys
	2990					2995					3000			
Leu	Gly	Tyr	Ile	Leu	Arg	Asp	Ile	Ser	Lys	Ile	Pro	Gly	Gly	Ala
	3005					3010					3015			
Met	Tyr	Ala	Asp	Asp	Thr	Ala	Gly	Trp	Asp	Thr	Arg	Ile	Thr	Glu
	3020					3025					3030			
Asp	Asp	Leu	His	Asn	Glu	Glu	Lys	Ile	Thr	Gln	Gln	Met	Asp	Pro
	3035					3040					3045			
Glu	His	Arg	Gln	Leu	Ala	Asn	Ala	Ile	Phe	Lys	Leu	Thr	Tyr	Gln
	3050					3055					3060			
Asn	Lys	Val	Val	Lys	Val	Gln	Arg	Pro	Thr	Pro	Lys	Gly	Thr	Val
	3065					3070					3075			
Met	Asp	Ile	Ile	Ser	Arg	Lys	Asp	Gln	Arg	Gly	Ser	Gly	Gln	Val
	3080					3085					3090			
Gly	Thr	Tyr	Gly	Leu	Asn	Thr	Phe	Thr	Asn	Met	Glu	Ala	Gln	Leu
	3095					3100					3105			
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<223> 多肽，衍生自登革熱病毒血清型 2 型/登革熱病毒血清型 1 型，MVS

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

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	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	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	
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	
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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 1175	Ser Phe Arg Asp	Leu Gly Arg Val Met Val 1180 1185	Met Val Gly
Ala Thr 1190	Met Thr Asp Asp	Ile Gly Met Gly Val Thr 1195 1200	Tyr Leu Ala
Leu Leu 1205	Ala Ala Phe Lys	Val Arg Pro Thr Phe Ala 1210 1215	Ala Gly Leu
Leu Leu 1220	Arg Lys Leu Thr	Ser Lys Glu Leu Met Met 1225 1230	Thr Thr Ile
Gly Ile 1235	Val Leu Leu Ser	Gln Ser Thr Ile Pro Glu 1240 1245	Thr Ile Leu
Glu Leu 1250	Thr Asp Ala Leu	Ala Leu Gly Met Met Val 1255 1260	Leu Lys Met
Val Arg 1265	Asn Met Glu Lys	Tyr Gln Leu Ala Val Thr 1270 1275	Ile Met Ala
Ile Leu 1280	Cys Val Pro Asn	Ala Val Ile Leu Gln Asn 1285 1290	Ala Trp Lys
Val Ser 1295	Cys Thr Ile Leu	Ala Val Val Ser Val Ser 1300 1305	Pro Leu Phe
Leu Thr 1310	Ser Ser Gln Gln	Lys Thr Asp Trp Ile Pro 1315 1320	Leu Ala Leu
Thr Ile 1325	Lys Gly Leu Asn	Pro Thr Ala Ile Phe Leu 1330 1335	Thr Thr Leu
Ser Arg 1340	Thr Ser Lys Lys	Arg Ser Trp Pro Leu Asn 1345 1350	Glu Ala Ile
Met Ala 1355	Val Gly Met Val	Ser Ile Leu Ala Ser Ser 1360 1365	Leu Leu Lys
Asn Asp 1370	Ile Pro Met Thr	Gly Pro Leu Val Ala Gly 1375 1380	Gly Leu Leu
Thr Val 1385	Cys Tyr Val Leu	Thr Gly Arg Ser Ala Asp 1390 1395	Leu Glu Leu

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			
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			

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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
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Cys	Leu	Arg	Lys	Asn	Gly	Lys	Lys	Val	Ile	Gln	Leu	Ser	Arg	Lys
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Phe	Val	Val	Thr	Thr	Asp	Ile	Ser	Glu	Met	Gly	Ala	Asn	Phe	Lys
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Ala	Glu	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Met	Lys	Pro	Val	Ile
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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
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Arg	Ile	Tyr	Ser	Asp	Pro	Leu	Ala	Leu	Lys	Glu	Phe	Lys	Glu	Phe
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Ala	Ala	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met
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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
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Gln	Ala	Thr	Val	Leu	Met	Gly	Leu	Gly	Lys	Gly	Trp	Pro	Leu	Ser
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	2345					2350					2355			
Ala	His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	Lys	Ala	Thr
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	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			
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2495						2500					2505			
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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			
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2645						2650					2655			
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2660						2665					2670			
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2675						2680					2685			
Gln	Arg	Lys	Tyr	Gly	Gly	Ala	Leu	Val	Arg	Asn	Pro	Leu	Ser	Arg
2690						2695					2700			

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Pro	Phe	Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	Asp	Thr	Arg
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2885						2890					2895			
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2990						2995					3000			
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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
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Phe	Cys	Ser	His	His	Phe	His	Glu	Leu	Ile	Met	Lys	Asp	Gly	Arg
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Cys	Leu	Gly	Lys	Ser	Tyr	Ala	Gln	Met	Trp	Ser	Leu	Met	Tyr	Phe
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His	Arg	Arg	Asp	Leu	Arg	Leu	Ala	Ala	Asn	Ala	Ile	Cys	Ser	Ala
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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
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Trp	Asn	Arg	Val	Trp	Ile	Gln	Glu	Asn	Pro	Trp	Met	Glu	Asp	Lys
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Thr	Pro	Val	Glu	Ser	Trp	Glu	Glu	Ile	Pro	Tyr	Leu	Gly	Lys	Arg
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Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser
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<223> 衍生自登革熱病毒血清型 2 型/登革熱病毒血清型 3 型，MVS
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Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
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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 Asp Gly Glu Pro Arg Met Ile Val
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Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ala Ser Gly
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Ile Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Asp
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Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr Glu Val Glu Pro Glu
165 170 175

Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Thr Tyr Gly
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Thr Cys Asn Gln Ala Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
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Leu Ala Pro His Val Gly Met Gly Leu Asp Thr Arg Thr Gln Thr Trp
210 215 220

Met Ser Ala Glu Gly Ala Trp Arg Gln Val Glu Lys Val Glu Thr Trp
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Tyr Ile Gly Thr Ser Leu Thr Gln Lys Val Val Ile Phe Ile Leu Leu
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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 Asp Ile Glu Leu Gln Lys Thr Glu Ala Thr Gln Leu Ala Thr Leu
325 330 335

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340 345 350

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

Asn Tyr Val Cys Lys His Thr Tyr Val Asp Arg Gly Trp Gly Asn Gly
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Tyr Thr Val Ile Ile Thr Val His Thr Gly Asp Gln His Gln Val Gly
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Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys
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Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly
850 855 860

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

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

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

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

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

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

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

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

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

Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala Leu Phe
1130 1135 1140

Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His Ala Ile
1145 1150 1155

Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn Met
1160 1165 1170

Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr
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Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu
1190 1195 1200

Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu
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Thr	Asp	Ala	Leu	Ala	Leu	Gly	Met	Met	Val	Leu	Lys	Met	Val	Arg
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Asn	Met	Glu	Lys	Tyr	Gln	Leu	Ala	Val	Thr	Ile	Met	Ala	Ile	Leu
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Cys	Val	Pro	Asn	Ala	Val	Ile	Leu	Gln	Asn	Ala	Trp	Lys	Val	Ser
	1280					1285					1290			
Cys	Thr	Ile	Leu	Ala	Val	Val	Ser	Val	Ser	Pro	Leu	Phe	Leu	Thr
	1295					1300					1305			
Ser	Ser	Gln	Gln	Lys	Thr	Asp	Trp	Ile	Pro	Leu	Ala	Leu	Thr	Ile
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Lys	Gly	Leu	Asn	Pro	Thr	Ala	Ile	Phe	Leu	Thr	Thr	Leu	Ser	Arg
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Thr	Ser	Lys	Lys	Arg	Ser	Trp	Pro	Leu	Asn	Glu	Ala	Ile	Met	Ala
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Val	Gly	Met	Val	Ser	Ile	Leu	Ala	Ser	Ser	Leu	Leu	Lys	Asn	Asp
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Ile	Pro	Met	Thr	Gly	Pro	Leu	Val	Ala	Gly	Gly	Leu	Leu	Thr	Val
	1370					1375					1380			
Cys	Tyr	Val	Leu	Thr	Gly	Arg	Ser	Ala	Asp	Leu	Glu	Leu	Glu	Arg
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Ala	Gln	Thr	Glu	Lys	Ser	Ile	Glu	Asp	Asn	Pro	Glu	Ile	Glu	Asp
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Asp	Ile	Phe	Arg	Lys	Arg	Arg	Leu	Thr	Ile	Met	Asp	Leu	His	Pro
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Ala	Ile	Lys	Arg	Gly	Leu	Arg	Thr	Leu	Ile	Leu	Ala	Pro	Thr	Arg
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Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp Phe Val
1865 1870 1875

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

Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr
1895 1900 1905

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

His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro
1925 1930 1935

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

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

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

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

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

Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile
2015 2020 2025

Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn
2030 2035 2040

Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu
2045 2050 2055

Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile
2060 2065 2070

Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala
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Val	Ala	Thr	Thr	Phe	Val	Thr	Pro	Met	Leu	Arg	His	Ser	Ile	Glu
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Ala	Gln	Lys	Arg	Ala	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro	Thr	Val
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Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Asp	Pro	Ile	Pro	Tyr	Asp	Pro
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Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val	Leu	Cys
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Val	Thr	Gln	Val	Leu	Met	Met	Arg	Thr	Thr	Trp	Ala	Leu	Cys	Glu
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Ala	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Ser	Thr	Leu	Trp	Glu	Gly
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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			
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Glu	Leu	Thr	Asp	Ala	Leu	Ala	Leu	Gly	Met	Met	Val	Leu	Lys	Met
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1265						1270					1275			
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1280						1285					1290			
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1295						1300					1305			
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Gln	Arg	Ala	Gly	Val	Leu	Trp	Asp	Val	Pro	Ser	Pro	Pro	Pro	Met
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1490						1495					1500			
Gly	Ile	Leu	Gly	Tyr	Ser	Gln	Ile	Gly	Ala	Gly	Val	Tyr	Lys	Glu
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Val Thr 1925	His Ser Ser Ala Ala 1930	Gln Arg Arg Gly Arg 1935	Ile Gly Arg
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Leu Glu 1955	Asn Asp Glu Asp Cys 1960	Ala His Trp Lys Glu 1965	Ala Lys Met
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Phe Glu 1985	Pro Glu Arg Glu Lys 1990	Val Asp Ala Ile Asp 1995	Gly Glu Tyr
Arg Leu 2000	Arg Gly Glu Ala Arg 2005	Lys Thr Phe Val Asp 2010	Leu Met Arg
Arg Gly 2015	Asp Leu Pro Val Trp 2020	Leu Ala Tyr Arg Val 2025	Ala Ala Glu
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Lys Glu 2060	Gly Glu Arg Lys Lys 2065	Leu Lys Pro Arg Trp 2070	Leu Asp Ala
Arg Ile 2075	Tyr Ser Asp Pro Leu 2080	Ala Leu Lys Glu Phe 2085	Lys Glu Phe
Ala Ala 2090	Gly Arg Lys Ser Leu 2095	Thr Leu Asn Leu Ile 2100	Thr Glu Met
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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
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Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile
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Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys
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DENV-4e

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Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile
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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			
Ile	Pro	Ile	Thr	Ala	Ala	Ala	Trp	Tyr	Leu	Trp	Glu	Val	Lys	Lys
1460						1465					1470			
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1475						1480					1485			
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1490						1495					1500			
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1505						1510					1515			
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1520						1525					1530			
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1535						1540					1545			

Lys	Asp	Leu	Ile	Ser	Tyr	Gly	Gly	Gly	Trp	Lys	Leu	Glu	Gly	Glu
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Asp	Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser	Ile	Ala	Ala	Arg	Gly
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Trp	Asn	Ser	Gly	His	Glu	Trp	Val	Thr	Asp	Phe	Lys	Gly	Lys	Thr
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Val	Trp	Phe	Val	Pro	Ser	Ile	Lys	Ala	Gly	Asn	Asp	Ile	Ala	Ala
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Cys	Leu	Arg	Lys	Asn	Gly	Lys	Lys	Val	Ile	Gln	Leu	Ser	Arg	Lys
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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
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Ala	Glu	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Met	Lys	Pro	Val	Ile
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Phe	Glu	Pro	Glu	Arg	Glu	Lys	Val	Asp	Ala	Ile	Asp	Gly	Glu	Tyr
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Arg	Leu	Arg	Gly	Glu	Ala	Arg	Lys	Thr	Phe	Val	Asp	Leu	Met	Arg
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Asn	Asn	Gln	Ile	Leu	Glu	Glu	Asn	Val	Glu	Val	Glu	Ile	Trp	Thr
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Lys	Glu	Gly	Glu	Arg	Lys	Lys	Leu	Lys	Pro	Arg	Trp	Leu	Asp	Ala
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Ala	Ala	Gly	Arg	Lys	Ser	Leu	Thr	Leu	Asn	Leu	Ile	Thr	Glu	Met
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Gly	Arg	Leu	Pro	Thr	Phe	Met	Thr	Gln	Lys	Ala	Arg	Asp	Ala	Leu
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Tyr	Asn	His	Ala	Leu	Ser	Glu	Leu	Pro	Glu	Thr	Leu	Glu	Thr	Leu
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2150						2155					2160			
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Cys	Cys	Ile	Ile	Thr	Ala	Ser	Ile	Leu	Leu	Trp	Tyr	Ala	Gln	Ile
2180						2185					2190			

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

※ 申請案號：

※ 申請日：

※IPC 分類：

【發明名稱】(中文/英文)

登革熱病毒血清型4型之建構物的組成物、方法及用途
COMPOSITIONS, METHODS AND USES FOR DENGUE VIRUS
SEROTYPE-4 CONSTRUCTS

【中文】

在此之具體例記述登革熱4型(DEN-4)病毒建構物的組成物、方法及用途。一些具體例有關一種組成物，其包括，但不限於，在此所揭示之DEN-4病毒建構物，單獨或結合其它建構物，可用在疫苗組成物中，用以在個體中誘發免疫反應。在某些具體例中，組成物可包括超過一種登革熱病毒血清型之建構物，諸如登革熱1型(DEN-1)病毒、登革熱2型(DEN-2)病毒或登革熱3型(DEN-3)病毒，結合在此所揭示之DEN-4病毒建構物。在其它具體例中，在此所揭示之DEN-4建構物可於組成物中結合其它黃病毒建構物，產生抗超過一種黃病毒之疫苗。其它具體例提供DEN-4病毒建構物於疫苗組成物中之方法以及用途，其當投與至個體時，會在該個體中誘發抗DEN-4之免疫反應，其與其它疫苗組成物相比，已經過建構物修飾之改良。

【英文】

Embodiments herein report compositions, methods and uses for dengue-4 (DEN-4) virus constructs. Some embodiments concern a composition that includes, but is not limited to, DEN-4 virus constructs disclosed herein that alone or in combination with other constructs can be used in a vaccine composition to induce an immune response in a subject. In certain embodiments, compositions can include constructs of more than one serotypes of dengue virus, such as dengue-1 (DEN-1) virus, dengue-2 (DEN-2) virus, or dengue-3 (DEN-3) virus in combination with DEN-4 virus constructs disclosed herein. In other embodiments, DEN-4 constructs disclosed herein can be combined in a composition with other flavivirus constructs to generate a vaccine against more than one flavivirus. Other embodiments provide methods and uses for DEN-4 virus constructs in vaccine compositions that when administered to a subject induce an immune response in the subject against DEN-4 that is improved by modified constructs compared to other vaccine compositions.

【代表圖】

【本案指定代表圖】：第（ 3 ）圖。

【本代表圖之符號簡單說明】：

(無)

【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. 一種核酸分子，其包含一嵌合黃病毒建構物，該建構物包含編碼從活減毒(live, attenuated)登革熱-2病毒而來之非結構蛋白及一或多種結構蛋白之核酸序列，以及至少編碼一或多種從第二黃病毒而來之結構蛋白之核酸序列，該第二黃病毒係選自登革熱-1、登革熱-3或登革熱-4病毒，其中該嵌合建構物進一步包含一或多個突變，該突變包含：

於套膜(E)蛋白中的突變，當該E蛋白係從該第二黃病毒而來，該突變係在與登革熱-4之胺基酸位置417同義之位置處，其中該在與胺基酸位置417同義之位置處之E蛋白中的該突變係將穀胺酸改變為一帶正電殘基；

於殼體(C)蛋白中的突變，該突變係在與該活減毒登革熱-2病毒之胺基酸位置107同義之胺基酸位置處，其中該在與胺基酸位置107同義之胺基酸位置處之該C蛋白中的該突變係於該活減毒登革熱-2中改變為一芳族胺基酸殘基；以及

於NS4A中的突變，該突變係在與該活減毒登革熱-2病毒之胺基酸位置17同義之胺基酸位置處。

2. 如請求項1之核酸分子，其中該第二黃病毒係登革熱-4。
3. 如請求項2之核酸分子，其中減毒登革熱-2之胺基酸位置102-106係經登革熱-4病毒於該等位置處的同義胺基酸所取代。

4. 如請求項2之核酸分子，其中該登革熱-4係來自毒株 (strain)1036。
5. 如請求項1之核酸分子，其中與417同義之該位置處係離胺酸而非於該第二黃病毒中的穀胺酸。
6. 如請求項1之核酸分子，其中該在與胺基酸107同義之該位置處的該芳族胺基酸係酪胺酸。
7. 如請求項1之核酸分子，其中該於NS4A蛋白中與胺基酸17同義之該位置處的該突變係將甲硫胺酸改變為一鹼性胺基酸。
8. 如請求項1之核酸分子，其中該於NS4A蛋白中與胺基酸17同義之該位置處的該突變係將甲硫胺酸改變為白胺酸。
9. 如請求項1之核酸分子，其中該活減毒登革熱-2含有於5'NCR中57位置處之突變、於NS1之53位置處之突變、以及於NS3之250位置處之突變。
10. 如請求項1之核酸分子，其中該活減毒登革熱-2含有於NS1之53位置處之突變以及於NS3之250位置處之突變。
11. 如請求項1之核酸分子，其進一步包含從第三不同黃病毒而來之結構蛋白。
12. 如請求項11之核酸分子，其中該第三不同黃病毒係擇自於由下列所構成之群組：西尼羅河病毒、日本腦炎病毒、聖路易(St. Louis)腦炎病毒、蜱媒腦炎病毒以及黃熱病毒。
13. 如請求項1之核酸分子，其中該活減毒登革熱-2病毒包

含經突變之登革熱-2 PDK-53骨架。

14. 一種組成物，其包含一或多個如請求項1之核酸分子，以及一藥學上可接受之載劑。
15. 如請求項14之組成物，其中該組成物進一步包含額外的登革熱-登革熱嵌合體。
16. 如請求項14之組成物，其中該組成物係二價、三價或四價登革熱病毒組成物之一部分。
17. 如請求項14之組成物，其中該組成物進一步包含其他活減毒黃病毒。
18. 一種組成物，其包含一或多個由一或多個如請求項1之核酸分子所編碼之多肽，以及一藥學上可接受之載劑。
19. 一種使用如請求項14之組成物於製造一藥物之用途，該藥物係用於在個體中誘發對登革熱病毒之免疫反應。
20. 如請求項19之用途，其中於該個體中會誘發對登革熱-1、登革熱-2、登革熱-3以及登革熱-4之至少一者的免疫反應。
21. 一種套組，其包含一或多個如請求項14之組成物，以及一容器。
22. 一種活減毒病毒，其包含如請求項1之核酸分子。
23. 一種活減毒登革熱-4嵌合體，其包含序列辨識編號：22 (DENVax4e)、序列辨識編號：9 (DENVax4i)或序列辨識編號：24 (DENVax4h)所示之聚核苷酸序列。
24. 一種組成物，其包含一或多個如請求項23之活減毒登革熱-4嵌合體，以及一藥學上可接受之載劑。

25. 一種使用如請求項24之組成物於製造一藥物之用途，該藥物係用於在個體中誘發對登革熱病毒之免疫反應。

