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(54)名稱

經修飾的病毒結構蛋白

(57)摘要

本發明提供一種包括經修飾的 S-蛋白和編碼所述經修飾的 S-蛋白的核酸的經修飾的冠狀病毒棘狀(S)-蛋白、病毒樣顆粒(VLP)。本發明還描述一種在宿主或宿主細胞中經修飾的 S-蛋白和 VLP 製造的方法。經修飾的 S-蛋白可包括含跨膜結構域(TM)或 TM 的部分、以及胞質尾(CT)或 CT 的部分，其中 CT 或 CT 的部分源自流感血球凝集素(HA)蛋白，且其中 TM 或 TM 的部分係異源性於 CT 或 CT 的部分。

Modified coronavirus spike (S)-protein, virus-like particle (VLPs) comprising the modified S protein and nucleic acids encoding modified S protein are provided. Methods for modified S-protein and VLP production in a host or host cell are also described. The modified S-protein may comprise a transmembrane domain (TM) or portion of a TM, and a cytosolic tail (CT) or portion of a CT, wherein the CT or portion of the CT is derived from an influenza hemagglutinin (HA) protein and wherein the TM or portion of the TM is heterologous to the CT or portion of the CT.

指定代表圖：

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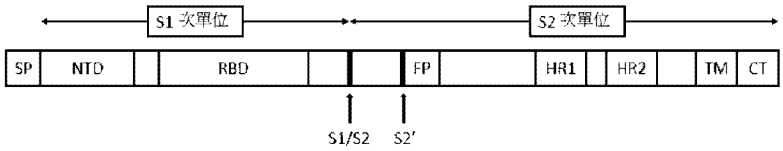


圖1

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【發明摘要】

【中文發明名稱】經修飾的病毒結構蛋白

【英文發明名稱】MODIFIED VIRAL STRUCTURAL PROTEIN

【中文】

本發明提供一種包括經修飾的S-蛋白和編碼所述經修飾的S-蛋白的核酸的經修飾的冠狀病毒棘狀(S)-蛋白、病毒樣顆粒(VLP)。本發明還描述一種在宿主或宿主細胞中經修飾的S-蛋白和VLP製造的方法。經修飾的S-蛋白可包括含跨膜結構域(TM)或TM的部分、以及胞質尾(CT)或CT的部分，其中CT或CT的部分源自流感血球凝集素(HA)蛋白，且其中TM或TM的部分係異源性於CT或CT的部分。

【英文】

Modified coronavirus spike (S)-protein, virus-like particle (VLPs) comprising the modified S protein and nucleic acids encoding modified S protein are provided. Methods for modified S-protein and VLP production in a host or host cell are also described. The modified S-protein may comprise a transmembrane domain (TM) or portion of a TM, and a cytosolic tail (CT) or portion of a CT, wherein the CT or portion of the CT is derived from an influenza hemagglutinin (HA) protein and wherein the TM or portion of the TM is heterologous to the CT or portion of the CT.

【指定代表圖】圖1。

【代表圖之符號簡單說明】

無。

【特徵化學式】

無。

【發明說明書】

【中文發明名稱】經修飾的病毒結構蛋白

【英文發明名稱】MODIFIED VIRAL STRUCTURAL PROTEIN

【技術領域】

【0001】 本發明係關於經修飾的病毒結構蛋白。本發明亦關於包含該經修飾的病毒結構蛋白的病毒樣顆粒(VLP)以及在宿主或宿主細胞中製造VLP的方法。

【先前技術】

【0002】 冠狀病毒(CoV)係歸類於尼多病毒(Nidovirales)目的最大一組病毒，其包括冠狀病毒科(Coronavirinae)、動脈炎病毒科(Arteriviridae)、洋病毒科(Mesoniviridae)和桿狀套病毒科(Roniviridae)。冠狀病毒亞科包括冠狀病毒科的兩個亞科之一個，另一個是環曲病毒亞科(Torovirinae)。冠狀病毒亞科進一步細分為四個屬，即α-冠狀病毒、β-冠狀病毒、γ-冠狀病毒和δ-冠狀病毒。α-冠狀病毒和β-冠狀病毒的成員僅在哺乳動物中發現。α-冠狀病毒屬包括兩種人病毒，HCoV-229E和HCoV-NL63。重要的動物α-冠狀病毒為豬傳染性胃腸炎病毒和貓傳染性腹膜炎病毒。

【0003】 嚴重急性呼吸症候群冠狀病毒2(SARS-CoV-2，也稱為2019-nCoV和HCoV-19)是一種新譜系B型β-冠狀病毒(Beta-CoV)並在2019年導致冠狀病毒疾病(COVID-19)，係一種具有高死亡率和發病率的呼吸系統疾病，對全世界的公共衛生造成重大影響。由於病毒的潛伏期和傳播性，SARS-CoV-2的爆發(例如2020年開始的大流行)是醫療保健系統面臨的最大挑戰。因此迫切需要針對COVID-19的治療，但對SARS-CoV-2爆發的長期管理將需要有效的疫苗。

【0004】 如最近的低溫電子斷層掃描和低溫電子顯微鏡研究所述，冠狀病毒病毒體是球形的，具有直徑約為118-140 nm。

【0005】 冠狀病毒最突出的結構特徵是從病毒體的表面發出的棒狀尖刺突起。冠狀病毒顆粒由螺旋狀核鞘結構組成，由核鞘(N)磷蛋白和病毒基因組RNA

之間的結合形成，被脂質雙層包圍，其中插入三至四種類型的結構蛋白：棘(S)蛋白、膜(M)蛋白和包膜(E)蛋白，以及僅對於某些冠狀病毒，還有血球凝集素-酯酶(HE)蛋白(Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006; 66:193-292.)

【0006】 膜(M)蛋白是病毒體中最豐富的結構蛋白。它是一種具有三個跨膜結構域的小(~25-30 kDa)蛋白，且被認為賦予病毒體的形狀。包膜(E)蛋白是一種短的，由76-109個胺基酸組成的完整膜蛋白，大小從8.4 kDa至12 kDa的範圍。一級和二級結構顯示E蛋白具有由7-12個胺基酸組成之短的親水性胺基末端，接著是由25個胺基酸組成之大的疏水性跨膜結構域(TMD)，和具有長的親水性羧基終端的末端，其包括大部分的蛋白。E蛋白參與病毒生命週期的多個態樣，諸如組裝、出芽、包膜形成和發病機制。

【0007】 棘(S)蛋白是一種醣蛋白，它是識別許多冠狀病毒的宿主受體以及病毒和宿主細胞膜的融合以供病毒進入細胞所必需的(Belouzard et al., Viruses 2012 Jun; 4(6): 1011-33)。作為病毒包膜之表面的主要醣蛋白，冠狀病毒科的S蛋白是由自然感染(包括SARS-CoV-2感染)引發的中和抗體的主要靶標，並且是靶向實驗性疫苗候選者的關鍵抗原。

【0008】 SARS-CoV-2 S蛋白(與其他冠狀病毒的S蛋白一樣)最初是作為前驅蛋白合成的。單個前驅S蛋白形成同源三聚體，並在高基氏體內進行糖化作用以及去除訊號肽的加工。S蛋白需要兩步驟蛋白酶介導的活化以促進膜融合。SARS-CoV-2 S蛋白的特徵在於S1/S2連接處的RRAR弗林蛋白酶(Furin)裂解位點可能在高基氏體區室中加工以產生兩種獨立的多肽：S1和S2多肽(或次單位)，它們在融合前的蛋白構形的同源三聚體內作為S1/S2原聚體保持非共價結合(Walls et al., Cell 2020 181(2) p281-292; Li et al., eLife 2019; 8: e51230.)。在S1/S2連接處的弗林蛋白酶裂解和融合肽上游S2'位點處的裂解發生在病毒進入細胞表面或內體期間，並可由幾種蛋白酶介導。

【0009】 此三聚體在透過受體結合結構域(RBD)表位結合至宿主細胞上的標靶受體之前係保持在融合前蛋白構形。受體結合使融合前三聚體不穩定，導致S1次單位脫落，且S2次單位通過病毒與細胞膜的融合轉變為穩定的融合後蛋白構形(Wrapp et al., Science, 13, Mar 2020, Vol. 367, Issue 6483, pp. 1260-1263)。中和來自感染有SARS-CoV-2的個體的抗體已顯示可靶向S蛋白的S1次單位的RBD (Premkumar, L., 2020 Science Immunology 11 Jun 2020: Vol. 5, Issue 48)。

【0010】 S蛋白胞外結構域在融合前蛋白構形中的穩定趨於增加重組表現產量，可能是藉由防止由於採用更穩定的融合後結構的趨勢而導致的觸發或錯誤折疊(Hsieh et al. Science 2020, 369 p.1501-1505)。

【0011】 S蛋白胞外結構域的突變已顯示促進融合前蛋白構形的穩定。WO 2018/081318及Pallesen, J等人的配套出版物(PNAS August 29, 2017 114 (35))揭露在七肽重複序列區1(HR1)與中心螺旋之間的連接處或附近的雙脯胺酸取代，這使得在融合前蛋白構形和取代中穩定MERS-CoV棘蛋白的S胞外結構域三聚體，以防止蛋白酶在S1/S2切割位點處切割和S胞外結構域的S2'切割位點的切割。在同源胺基酸殘基處用雙脯胺酸取代穩定的SARS-CoV-2 S蛋白已被使用於藉由低溫EM確定高解析度結構(Wrapp et al Science 2020 367, 1260–1263; Walls et al. Cell 2020, 181, 281-292)。此外，弗林蛋白酶識別位點的破壞被認為能使S蛋白保留在融合前蛋白構形中(Wrapp et al Science 2020 367, 1260-1263)。然而，即使有這些取代，SARS-CoV-2 S蛋白胞外結構域仍然不穩定，且難以在哺乳動物細胞中可靠地產生，阻礙了有效和高產量次單位疫苗的開發(Hsieh et al. Science 2020, 369 p.1501-1505)。

【0012】 Hsieh等人(Science 2020, 369 p.1501-1505)基於先前確定的低溫-EM結構設計並在哺乳動物細胞中表現100多種結構引導的SARS-CoV-2棘蛋白變體。這些變體在生物化學、生物物理和結構上被表徵，以確定導致產量和穩定性增加的取代。Hsieh等人報導多個脯胺酸、二硫鍵、鹽橋和空腔填充取代，其

相對於雙脯胺酸取代增加棘蛋白的表現及/或穩定性。最佳鑑定的變體HexaPro具有6個有利的脯胺酸取代，導致比其親本構建體的表現高10倍，並且能夠承受熱應激、室溫儲存和多次凍融。

【0013】 S2次單位可分為三個結構域：大胞外結構域、跨膜結構域(TM)和胞質尾(CT)。S蛋白的胞質尾先前已被證明是裝配所需的。冠狀病毒科的CT中可以發現兩種不同的保留訊號：i) 內質網回收訊號(ERRS)及/或ii) 酪胺酸依賴性定位訊號(YxxI或YxxF基序)。ERRS包括結合至外被體複合物I(COPI)的二元KxHxx基序。當與SARS膜(M)蛋白共表現時，該基序是SARS S蛋白定位至ERGIC/高基氏體區域所必需的，並且可以藉由突變KxHxx基序來破壞定位(McBride et al. J. Virol.Feb 2007, 81 (5) 2418-2428)。含有ERRS的S蛋白被募集到COPI囊泡中，並從高基氏體逆行返回到內質網(ER)。在內質網與高爾氏體之間的S蛋白的重複循環導致S蛋白細胞內滯留。α-冠狀病毒和β-冠狀病毒的S蛋白都包括ERRS(Ujike et al. Journal of General Virology (2016), 97, 1853-1864)。

【0014】 β-冠狀病毒的S蛋白，例如MERS-CoV、SARS-CoV和SARS-CoV2的S蛋白，僅具有ERRS，且不能保留在細胞內，導致S蛋白釋放到質膜中。缺乏該ERRS的突變型SARS-CoV S蛋白被運送到質膜，而原生(native)S蛋白在與M蛋白共表現時，會在出芽位點附近與M蛋白相互作用，導致S蛋白細胞內滯留，這表示ERRS SARS-CoV藉由與M蛋白相互作用促進S蛋白在後內側高爾氏體腔室中的積累，導致S蛋白引入VLP(Ujike et al. Journal of General Virology (2016), 97, 1853-1864)。最近發現移除ERRS將有助於SARS-CoV-2 S蛋白引入到慢病毒假病毒中(Ou et al., 2020 Nature Communications volume 11, Article number: 1620)。

【0015】 Yu等人(2020 Science)構建一組原型DNA疫苗，表現SARS-CoV-2 S蛋白的六種變體，具有胞質尾和跨膜結構域的各種缺失，其評估它們在恆河獼猴中對SARS-CoV-2病毒攻擊的免疫原性和保護功效。雖然SARS-CoV-2 S蛋白胞外結構域的可溶性片段引起sgmRNA水平的降低(指示病毒複製)，但全長S蛋白

免疫原實現了最佳保護。

【0016】 Broer等人(2006 J. Virol. p. 1302-1310)使用SARS-CoV S-假型逆轉錄病毒(SARSpp)研究S蛋白的跨膜和細胞質結構域在SARS-CoV的感染性和膜融合活性中的作用。SARSpp，其中S的細胞質結構域被來自水泡性口炎病毒G蛋白(VSV-G)的細胞質結構域置換，具有傳染性，高達40%的野生型。相較之下，同時含有TMD和VSV-G細胞質結構域的SARSpp的傳染性嚴重受損(<5%)。這顯示S的TMD可能參與SARS-CoV的入侵過程。

【0017】 疫苗接種藉由在感染之前誘導受試者對可能的病原體產生免疫反應來提供對抗疾病的保護。通常，這是通過使用活的減毒或完全滅活形式的傳染媒介物作為免疫原來實現的。為了避免使用完整病毒(例如滅活或減毒病毒)作為疫苗的危險，病毒蛋白或次單位或其重組形式已被用作疫苗。使用原生(native)或重組病毒蛋白作為疫苗試劑的主要障礙是確保蛋白質的構象模擬其在自然環境中的抗原。合適的佐劑，以及在胜肽的情況下，載體蛋白可被用於增強免疫反應。此外，作為疫苗的病毒蛋白或次單位可能主要引發體液反應，因此無法激發持久的免疫力。次單位疫苗可能對其中可以證明完整的滅活病毒可提供優越保護的疾病無效。

【0018】 病毒樣顆粒(VLP)可被用於免疫原性組合物中以表現具有改善的抗原呈現給免疫系統的優選構形的病毒蛋白。VLP與成熟病毒體非常相似，但它們不包含病毒基因組材料，且它們是非複制性的，這使得它們可以安全地作為疫苗投與。此外，VLP可以被設計為在VLP的表面表現病毒醣蛋白，這是它們的原生生理構形。由於VLP類似於完整的病毒體並且是多價顆粒結構，因此VLP在誘導針對醣蛋白的中和抗體方面可能比可溶性套膜蛋白抗原更有效。

【0019】 多種表現系統已被用於製造VLP，包含哺乳動物細胞系、細菌、昆蟲細胞株、酵母和植物細胞。已經在昆蟲和哺乳動物系統中產生了用於疫苗目的的30多種不同病毒的VLP(Noad, R. and Roy, P., 2003, Trends Microbiol 11:

438-44)。VLP也已經在植物中產生(參見WO2009/076778；WO2009/009876；WO 2009/076778 ； WO 2010/003225 ； WO 2010/003235 ； WO2010/006452 ； WO2011/03522；WO 2010/148511；WO2014153674和WO2012/083445)。

【0020】已經使用來自嚴重急性呼吸症候群冠狀病毒(SARS-CoV或SARS-CoV-1)的原生表面蛋白製造VLP，包含昆蟲細胞和哺乳動物細胞中的S蛋白、M蛋白、E蛋白(Liu et al., 2008, J Virol., p. 11318-11330)。SARS-CoV-2病毒樣顆粒(VLP)也已藉由在哺乳動物細胞中共表現病毒表面蛋白S、M和E來裝配(Xu et al. Front. Bioeng. Biotechnol., 30 July 2020)。研究進一步顯示，M蛋白對於病毒樣顆粒(VLP)形成是不可缺少的(Siu et al. Journal of Virology (2008) 82:11318-11330, Huang et al. Journal of Virology (2004) 78:12557-12565)。在哺乳動物細胞中，膜蛋白(M)和小封膜蛋白(E)的表現對於SARS-CoV-2 VLP的有效形成和釋放是必需的(Xu et al. Front. Bioeng. Biotechnol., 30 July 2020)。儘管如此，裝配SARS-CoV VLP的最低要求仍然存在爭議。Y. Huang等人(Journal of Virology (2004) 78:12557-12565)描述在轉染的人類細胞中VLP的形成僅需要M和N病毒蛋白的共表現，而Siu等人(Journal of Virology (2008)82:11318-11330)表明E和N蛋白都必須與M蛋白共表現才能在轉染的哺乳動物細胞中有效產生和釋放SARS-CoV VLP。

【0021】WO2012/083445揭露在植物中產生SARS CoV S蛋白，其中S蛋白的跨膜結構域和胞質尾結構域(TM/CT)被流感HA蛋白的TM/CT置換。

【0022】一些團體提出用SARS-CoV VLP進行免疫作為一種有效的疫苗策略。在這些研究中以昆蟲細胞中產生的VLP或哺乳動物細胞中產生的嵌合MHV/SARS-CoV VLP(Lokugamage et al. Vaccine 2008 Feb 6;26(6):797-808, Lu et al. 2007 Immunology 122496-5024)。

【0023】然而，有效放大和製造SARS-CoV-2 VLP在其數量可滿足全球人口廣泛接種疫苗的需要，需要有效的病毒結構蛋白和VLP製造。

【發明內容】

【0024】 本發明關於一種經修飾的病毒結構蛋白。本發明亦關於包括經修飾的病毒結構蛋白的病毒樣顆粒(VLP)以及在宿主或宿主細胞中製造VLP的方法。更具體地，本發明關於經修飾的冠狀病毒S蛋白。本發明亦關於包括經修飾的S蛋白的病毒樣顆粒(VLP)以及在宿主或宿主細胞中製造VLP的方法。

【0025】 在一個態樣中，本發明提供一種經修飾的冠狀病毒S-蛋白，依序地包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白。

【0026】 如本文所述的經修飾的S-蛋白可形成三聚體。因此，本發明亦提供一種包括如本文所述的經修飾的冠狀病毒S-蛋白的三聚體。

【0027】 在進一步態樣中，提供一種病毒樣顆粒(VLP)，包括經修飾的S-蛋白或包含如上所述的經修飾的S-蛋白的三聚體。因此，所述VLP，包括經修飾的冠狀病毒S-蛋白或包括所述經修飾的S-蛋白的三聚體，所述經修飾的S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白。

【0028】 所述VLP可進一步包括植物脂質。

【0029】 所述TM可直接融合至所述CT。所述TM可以源自冠狀病毒S-蛋白TM，且所述CT可以源自流感HA蛋白CT。再者，所述TM可以是源自所述冠狀病毒S-蛋白TM的N-端序列和源自所述流感HA蛋白TM的C-端序列的嵌合TM。所述嵌合TM可包括源自所述冠狀病毒S-蛋白TM的N-端序列，所述N-端序列包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的至少20個胺基酸；或對應於SEQ ID NO：118或164之胺基酸1-21的至少21個胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的至少22個胺基酸；及源自所述流感HA蛋白TM的C-端的一個或多於一個的胺基酸。源自所述流感HA蛋白TM的C-端的所述一個或多於一個的胺基酸可選自AGL或AGL的保留取代、MAGL或MAGL的保留取代。所述TM可包括對應於SEQ ID NO：18之胺基酸1-20的胺基酸。

【0030】 所述CT可以是源自所述冠狀病毒S-蛋白CT的N-端序列和源自所述流感HA蛋白CT的C-端序列的嵌合CT。所述嵌合CT可包括源自所述流感HA蛋白CT的C-端序列，所述C-端序列包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；及源自所述冠狀病毒S-蛋白CT的N-端的一個或多於一個的胺基酸。源自所述冠狀病毒S-蛋白CT的N-端的所述一個或多於一個的胺基酸可選自C或C的保留取代、CC或CC的保留取代、或CCM或CCM的保留取代。所述嵌合CT可包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或SEQ ID NO：127之胺基酸27-36。在一個態樣中，所述嵌合TMCT可包括嵌合TM及嵌合CT，所述嵌合TM包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的胺基酸；或對應於SEQ ID NO：118或SEQ ID NO：164之胺基酸1-21的胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的胺基酸，所述嵌合CT包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或其組合。

【0031】 所述CT或所述CT的部分可包括與具有以下序列之胺基酸80%至

100%的同一性：SEQ ID NO：15；或SEQ ID NO：6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568；或SEQ ID NO：18之胺基酸22-37；或SEQ ID NO： 19之胺基酸21-40；或SEQ ID NO：37之胺基酸21-39；或SEQ ID NO： 38之胺胺基酸25-36；或SEQ ID NO： 39之胺基酸24-34；或 SEQ ID NO：126、128、129、130或131之胺基酸22-37；或 SEQ ID NO：127之胺基酸22-36。所述TM或所述TM的部分可包括與具有SEQ ID NO： 132或133之序列80%至100%的同一性。

【0032】 所述TMCT可包括具有與SEQ ID NO：18、19、37、38、39、64、126、127、128、129、130、131、118、119、 120、123、124、125、134、135、164、165、166、169、170、171、172或173之序列約80%至約100%同一性的序列。

【0033】 所述經修飾的S蛋白可包含S1次單位和S2次單位，其中所述S2次單位包括所述嵌合TMCT。

【0034】 所述經修飾的S-蛋白可以作為前驅蛋白產生，所述前驅蛋白包括所述經修飾的S-蛋白和訊號肽。包括所述經修飾的S-蛋白和訊號肽的所述前驅蛋白可包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：1之胺基酸1-1234；或SEQ ID NO：5之胺基酸1-1234；SEQ ID NO：21之胺基酸1-1219；或SEQ ID NO：30之胺基酸1-1243；且其中所述CT的胺基酸序列包括與具有以下序列80%至100%的同一性：SEQ ID NO：15；或SEQ ID NO： 6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568。

【0035】 所述訊號肽對於所述S-蛋白可以是原生或非原生。所述非原生訊號肽可以是源自蛋白質二硫鍵異構酶(PDI)的訊號肽。所述經修飾的S-蛋白可進一步包括植物特異性N-聚醣。

【0036】 所述經修飾的S-蛋白中的所述CT或所述CT的部分可以源自流感血

球凝集素(HA)蛋白，其係源自流感B型或流感亞型H1、H2、H3、H4、H5、H6、H7 、H8、H9、H10、H11、H12、H13、H14、H15 或 H16。流感血球凝集素(HA)蛋白可以源自B型流感或流感亞型H1、H3、H5、H6、H7 或 H9。

【0037】經修飾的S-蛋白的胞外結構域可以源自SARS-CoV-2 、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，所述TM或所述TM的部分可以源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，或所述胞外結構域和所述TM或所述TM的部分兩者可以源自SARS-CoV-2、SARS- CoV-1、MERS-CoV、OC43-CoV或229E-CoV。

【0038】在進一步態樣中，與野生型冠狀病毒胺基酸序列相比時，所述經修飾的S-蛋白可包括一個或多於一個的胺基酸取代。所述一個或多個一個的取代可以將S-蛋白保持在融合前狀態。

【0039】所述一個或多於一個的胺基酸取代可包括：i) 限制在S1與S2次單位之間的切割位點處之加工的取代；ii) 一個或多於一個的胺基酸取代為一個或多於一個的脯胺酸；及iii) 限制在S1與S2次單位之間的切割位點處之加工的取代以及一個或多個的胺基酸取代為一個或多個一個的脯胺酸。

【0040】與沒有在宿主或宿主細胞中表現的一個或多於一個的取代的對應S-蛋白的產量相比時，在宿主或宿主細胞中表現時，所述一個或多於一個的胺基酸取代將S-蛋白保持在融合前狀態或製造更高產量的經修飾的S-蛋白。

【0041】與SEQ ID NO： 2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代可對應於在位置667、668、670、802、923、927、971、972處或其組合的胺基酸。

【0042】在一個態樣中，與SEQ ID NO： 2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置971和972處的胺基酸。在另一個態樣中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置802、927、971和972處的胺基酸。再者，與SEQ ID NO：2

的參考胺基酸序列相比時，所述經修飾的S-蛋白可包括一個或多於一個的胺基酸取代對應於在位置667、668、670處或其組合的胺基酸。因此，與SEQ ID NO：2的參考胺基酸序列相比時，所述經修飾的S-蛋白可包括對應於在位置667、668和670處的胺基酸的取代。

【0043】 在一個態樣中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代可對應於在位置667、668、670、971和972處的胺基酸。對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸的所述取代可以是甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO： 2之位置668處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO： 2之位置670處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置971處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代，及對應於在SEQ ID NO：2之位置972處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代。與SEQ ID NO： 2的參考胺基酸序列相比時，如上述的經修飾的S-蛋白可進一步包括對應於在位置923處的胺基酸的胺基酸取代。

【0044】 在另一個態樣中，與SEQ ID NO： 2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代可對應於在位置667、668、670、802、927、971和972處的胺基酸。對應於在SEQ ID NO： 2之位置667處的胺基酸的所述胺基酸的所述取代可以是甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO： 2之位置668處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO： 2之位置670處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代，對應於在SEQ ID NO：2之位置927處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代，對應於在SEQ ID NO：2之位置971處的胺基酸的所述胺基酸的所述取代可

以是脯胺酸或脯胺酸的保留取代，對應於在SEQ ID NO：2之位置972處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代。

【0045】在另一個態樣中，與SEQ ID NO：2之參考胺基酸序列相比時，如上所述經修飾的S-蛋白可進一步包括對應於在位置923處的胺基酸的胺基酸取代。胺基酸在經修飾的S-蛋白中的取代，對應於SEQ ID NO：2之位置667處的胺基酸的所述胺基酸的所述取代可以是甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO： 2之位置670處的胺基酸的所述胺基酸的所述取代可以是絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802、927、971和972處的胺基酸的所述胺基酸的所述取代可以是脯胺酸或脯胺酸的保留取代，及對應於在SEQ ID NO：2之位置923處的胺基酸的所述胺基酸的所述取代可以是苯丙胺酸或苯丙胺酸的保留取代。

【0046】所述經修飾的S-蛋白可包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、155、156或157之胺基酸；或SEQ ID NO： 47之胺基酸24-1259，SEQ ID NO：48之胺基酸25-1259；SEQ ID NO：49之胺基酸25-1259；SEQ ID NO：50之胺基酸25-1259；SEQ ID NO：51之胺基酸25-1259；SEQ ID NO： 52之胺基酸25-1259；SEQ ID NO：53之胺基酸25-1259；SEQ ID NO：54之胺基酸25-1259；SEQ ID NO：55之胺基酸25-1259；SEQ ID NO：56之胺基酸25-1259；SEQ ID NO：57之胺基酸25-1259；SEQ ID NO： 58之胺基酸25-1259；SEQ ID NO：59之胺基酸25-1262；SEQ ID NO：60之胺基酸25-1261；SEQ ID NO：61之胺基酸25-1258；或SEQ ID NO：62之胺基酸25-1256；SEQ ID NO： 95之胺基酸25-1243；SEQ ID NO： 96之胺基酸25-1240；SEQ ID NO：97之胺基酸25-1243；SEQ ID NO： 108之胺基酸25-1341；SEQ ID NO：109之胺基酸25-1338；SEQ ID NO：110之胺基酸

25-1341；或SEQ ID NO：144之胺基酸25-1351；SEQ ID NO：145之胺基酸25-1348；SEQ ID NO：146之胺基酸25-1351；SEQ ID NO： 55之胺基酸25-1159；SEQ ID NO：156之胺基酸25-1156；或SEQ ID NO：157之胺基酸25-1159。

【0047】在另一個態樣，本發明提供一種核酸，其包括編碼如上所述經修飾的S-蛋白的核苷酸序列。

【0048】在進一步態樣中，提供一種組合物，包括有效劑量的經修飾的S-蛋白、包含所述經修飾的S-蛋白的三聚體或包括如上所述經修飾的S-蛋白的VLP以及醫藥上可接受之載體、佐劑、媒介物或賦形劑。在又另一個態樣中，提供一種用於誘導免疫反應之疫苗。所述疫苗包括有效劑量之經修飾的S-蛋白、包括所述經修飾的S-蛋白的三聚體或包括如上所述經修飾的S-蛋白的VLP。

【0049】所述組合物進一步包括醫藥上可接受之載體、佐劑、媒介物或賦形劑。在進一步態樣中，提供一種用於誘導免疫反應的疫苗。所述疫苗包括有效劑量的VLP，所述VLP包括如上所述經修飾的冠狀病毒。所述疫苗可以是多價疫苗，包含VLP的混合物。

【0050】在又另一個態樣中，提供一種包括如上所述經修飾的S-蛋白、三聚體或VLP的(非人)宿主或宿主細胞。在又另一個態樣中，提供一種包括如上所述VLP的宿主或宿主細胞。在另一個態樣中，提供一種組合物，包括有效劑量的包含如上所述經修飾的S-蛋白的VLP。

【0051】在又另一個態樣中，提供一種S-蛋白三聚體。所述三聚體包括經修飾的S-蛋白，包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素

(HA)蛋白。如上所述，在與野生型冠狀病毒胺基酸序列相比時，三聚體中的經修飾的 S-蛋白可包括一個或多於一個的胺基酸取代。在進一步態樣中，提供一種組合物，包括有效劑量的如上述三聚體以及醫藥上可接受之載體、佐劑、媒介物或賦形劑。在另一個態樣中，亦提供一種包括如上述三聚體的病毒樣顆粒(VLP)。所述 VLP 可進一步包括植物脂質。在另一個態樣中，提供一種組合物，包括有效劑量的包含如上述三聚體的 VLP，以及提供醫藥上可接受之載體、佐劑、媒介物或賦形劑。在進一步態樣中，提供一種用於誘導免疫反應的疫苗。所述疫苗包括有效劑量的如上述三聚體。在進一步態樣中，提供一種用於誘導免疫反應的疫苗。所述疫苗包括有效劑量的包含如上述三聚體的 VLP。所述疫苗可以是多價疫苗，包括 VLP 的混合物。在又另一個態樣中，提供一種非人宿主或宿主細胞，包括三聚體或包含如上述三聚體的 VLP。

【0052】 在另一個態樣中，提供一種用於受試者中誘導對冠狀病毒感染的免疫力之方法，所述方法包括投與所述組合物或如上述疫苗。所述組合物或所述疫苗可以一次投與至受試者，或者所述組合物或所述疫苗可以多次投與至受試者。所述組合物或所述疫苗可以作為初始劑量投與，並且可以在從投與初始劑量的1天至6個月之間投與一劑或多於一劑的後續劑量。所述後續劑量可以在從投與初始劑量21天之後投與。

【0053】 在另一個態樣中，提供一種使用如上述組合物或疫苗製備之抗體或抗體片段。

【0054】 在又另一個態樣中，提供A) 一種在(非人)宿主或宿主細胞中製造病毒樣顆粒(VLP)的方法，包括：

a) 將包括編碼如上述經修飾的 S-蛋白的核苷酸序列的核酸導入至非人宿主或宿主細胞；或提供包括編碼如上述經修飾的 S-蛋白的核苷酸序列的核酸的所述非人宿主或宿主細胞；及

b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造

所述 VLP。

【0055】 在進一步步驟c) 中，可以收穫所述非人宿主或宿主細胞。

【0056】 在進一步態樣中，提供B) 一種在(非人)宿主或宿主細胞中增加冠狀病毒S-蛋白之製造的產量之方法，包括：

a) 將包括編碼如上述經修飾的 S-蛋白的核苷酸序列的核酸導入至所述非人宿主或宿主細胞；或提供包括編碼如上述經修飾的 S-蛋白的核苷酸序列的核酸的非人宿主或宿主細胞；及

b) 在允許由所述核酸編碼的所述經修飾的 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與表現未經修飾的 S-蛋白的宿主或宿主細胞相比，以更高的產量製造所述經修飾的 S-蛋白。

【0057】 在進一步步驟c) 中，可以收穫所述非人宿主或宿主細胞。

【0058】 在又另一個態樣中，提供C) 一種在(非人)宿主或宿主細胞中增加病毒樣顆粒(VLP)之製造的產量之方法，包括：

a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；

提供包括編碼經修飾的冠狀病毒 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

b) 在允許由所述核酸編碼的所述經修飾的 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與在相似或相同條件下表現未經修飾的 S-蛋白的宿主或宿主細胞相比，以更高的產量製造包括所述經修飾的 S-蛋白的 VLP。

【0059】 在進一步態樣中，提供D) 一種在(非人)宿主或宿主細胞中製造病毒樣顆粒(VLP)之方法，包括：

a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；或

提供包括編碼經修飾的 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造所述 VLP。

【0060】 在進一步態樣中，方法A)、B)、C)或D)的VLP可進一步從宿主或宿主細胞中提取和純化。宿主或宿主細胞可包括植物、植物細胞、真菌、真菌細胞、昆蟲、昆蟲細胞、動物或動物細胞。方法A)、B)、C)或D)的宿主或宿主細胞可以是植物、植物的部分或植物細胞。

【0061】 在另一個態樣中，提供一種藉由A)、B)、C)或D)的方法產生的VLP。

【0062】 此外，在又另一個態樣中，提供一種包括佐劑和病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白，且其中所述經修飾的 S-蛋白進一步包括在與 SEQ ID NO：2 之參考胺基酸序列相比時，在位置 667、668、670、971 和 972 處的取代。

【0063】 在又另一個態樣中，提供一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的S-蛋白包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白，且其中所述經修飾的 S-蛋白包括在位置 667 處的甘胺酸取代、在位置 668 處的絲胺酸取代、在位置 670 處的絲胺酸取代、在位置 971 處的脯胺酸取

代和在位置 972 處的脯胺酸取代，所述位置對應於 SEQ ID NO：2 之參考胺基酸序列。所述流感血球凝集素(HA)蛋白可以源自 B 型流感或流感亞型 H1、H3、H5、H6、H7 或 H9。所述組合物可進一步包括佐劑。

【0064】 在進一步態樣中，提供一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的S蛋白包括SEQ ID NO：21之序列。所述組合物可進一步包括佐劑。

【0065】 本發明的此概述不一定描述本發明的所有特徵。

【圖式簡單說明】

【0066】 本發明的這些和其他特徵將從以下參考圖式的描述變得更明顯。

【0067】 圖1顯示冠狀病毒S蛋白和S1/S2(aa 685/686)和S2'切割位點的位置的示意圖。SP：訊號肽(aa 1-15)；NTD：N-端結構域(aa 16-306)；RBD：受體-結合結構域(aa 335-527)；FP：融合肽(aa 816-833)；HR1：七肽重複序列1(aa 908-991)；HR2：七肽重複序列2(aa 1166-1207)；TM：跨膜結構域(aa 1214-1234)；CT：胞質尾(aa 1235-1273)。每個區域的殘基號(aa)對應於它們在SARS-CoV-2 (2019-nCoV)的S蛋白中的位置。

【0068】 圖2顯示來自示例性流感病毒株的胺基酸序列的排列比對。顯示對H1 A/California/07/2009 (SEQ ID NO：6)、H2 A/Singapore/1/1957 HA (SEQ ID NO：7)、H3A/Minnesota/41/2019 HA (SEQ ID NO：8)、H5 A/Indonesia/5/05 HA (SEQ ID NO：9)、H6 A/Teal/Hong Kong/W312/97 HA (SEQ ID NO：10)、H7 A/Guangdong/17SF003/2016 HA (SEQ ID NO：11)、H9 A/Hong Kong/1073/99 HA (SEQ ID NO：12)和B/Washington/02/2019 HA (SEQ ID NO：13)的胞外結構域的C端區、跨膜結構域(TM)和血球凝集素(HA)的胞質尾結構域(CT)。還顯示這些序列的共通序列(SEQ ID NO：14)。

【0069】 圖3A顯示在以下5'UTR的控制下，在植物中表現：具有原生(野生型)跨膜結構域和胞質尾(wtTMCT)的SARS-CoV-2 S蛋白之SARS-CoV-2 S蛋白積

累的量化倍數變化差異：nbMT78(構建體8586)、nbCSY65(構建體8589)和nbHEL40(構建體8591)；經修飾的SARS-CoV-2蛋白，其中在nbMT78(構建體8592)、nbCSY65(構建體8595)和nbHEL40(構建體8597)的控制下，原生(野生型)跨膜結構域和胞質尾(wtTMCT)已用流感H5 A/Indonesia/5/05 (H5iTMCT)的流感血球凝集素(HA)的TMCT置換；及經修飾的SARS-CoV-2蛋白，其中在nbMT78(構建體8610)、nbCSY65(構建體8611)和nbHEL40(構建體8671)的控制下，原生(野生型)胞質尾(wtCT)已用流感H5 A/Indonesia/5/05 (H5iTMCT)的流感血球凝集素(HA)的CT置換。SARS-CoV-2 S蛋白序列(稱為nCOV S (GSAS-2P))具有以下取代：相對於SEQ ID NO：2之參考序列的R667G、R668S、R670S、K971P和V972P。結果已針對自構建體8591的SARS-CoV-2 S蛋白積累進行標準化，其設置為1。圖3B顯示澄清的粗萃取物在非還原性SDS-PAGE凝膠上的蛋白質分離。以下經修飾的S蛋白在植物中表現：泳道1：在nbMT78的控制下，具有野生型跨膜和胞質尾結構域(wt TMCT)的S蛋白；泳道2：在nbCSY65的控制下，具有野生型跨膜和胞質尾結構域(wt TMCT)的S蛋白；泳道3：在nbHEL40的控制下，具有野生型跨膜和胞質尾結構域(wt TMCT)的S蛋白；泳道4：在nbMT78的控制下，具有SARS-CoV-2胞外結構域及來自H5 A/Indonesia/5/05 (H5i TMCT)之血球凝集素(HA)的跨膜和胞質尾結構域的經修飾的S蛋白；泳道5：在nbCSY65的控制下，具有SARS-CoV-2胞外結構域及來自H5 A/Indonesia/5/05 (H5i TMCT)之血球凝集素(HA)的跨膜和胞質尾結構域的經修飾的S蛋白；泳道6：在nbHEL40的控制下，具有SARS-CoV-2胞外結構域及來自H5 A/Indonesia/5/05 (H5i TMCT)之血球凝集素(HA)的跨膜和胞質尾結構域的經修飾的S蛋白；泳道7：在nbMT78的控制下，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域及來自H5 A/Indonesia/5/05 (H5i CT)之血球凝集素(HA)的胞質尾結構域(CT)的經修飾的S蛋白；泳道8：在nbCSY65的控制下，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域及來自流感H5 A/Indonesia/5/05 (H5i CT)之血球凝集素(HA)的胞質尾

結構域(CT)的經修飾的S蛋白；泳道9：在nbHEL40的控制下，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域及來自流感H5 A/Indonesia/5/05 (H5i CT)之血球凝集素(HA)的胞質尾結構域(CT)的經修飾的S蛋白。所述經修飾的S蛋白具有分子量約150kDa，且以箭頭指示。圖3C顯示在圖3B中描述的相同系列裂解物的西方墨點法分析，且泳道對應於圖3B中所描述的泳道。上圖顯示使用抗-SARS-CoV-2 S1抗體(40150-R007)進行的檢測。下圖顯示使用抗-SARS-CoV-2 S2抗體(NB100-56578)進行的檢測。SARS-CoV-2蛋白的單體(包括S1和S2次單位)具有分子量約150kDa (非還原性)。

【0070】圖4A顯示在植物中表現以下者SARS-CoV-2 S蛋白積累的量化倍數變化差異：具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H5 A/Indonesia/5/05 (H5 Indo)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H1 A/California/7/2009 (H1 California)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H3 A/Minnesota/41/2019 (H3 Minnesota)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H6 A/Teal/Hong Kong/W312/97 (H6 Hong Kong)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H7 A/Guangdong/17SF003/2016 (H7 Guangdong)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H9 A/Hong Kong/1073/99 (H9 Hong Kong)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；以及具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自B/Washington/02/2019 (B Washington)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白。結果已標準化為從編碼經修飾的SARS-CoV-2蛋白的構建體8671中積累的SARS-CoV-2 S蛋白，其中在nbHEL40 (H5 Indo)的控制下，原生(野生型)

胞質尾(wtCT)已用流感H5 A/Indonesia/5/05 (H5iCT)的流感血球凝集素(HA)的CT置換，其設置為1。圖4B顯示從表現來自以下構建體的經修飾的S蛋白的植物的粗裂解物的西方墨點法分析：泳道2，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H5 A/Indonesia/5/05 (H5 Indo)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道3，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H1 A/California/07/2009 (H1 Calif)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道4，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H3 A/Minnesota/41/2019 (H3 Minn)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道5，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H6 A/Teal/Hong Kong/W312/97 (H6 HK)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道6，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H7 A/Guangdong/17SF003/2016 (H7 Guan)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道7，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自H9 A/Hong Kong/1073/99 (H9 HK)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道8，具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜及來自B/Washington/02/2019 (B Wash)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白。泳道1是來自用模擬農桿菌浸潤(Agroinfiltration)處理的植物的粗裂解物。Sino 400150-R007抗體使用於檢測SARS-COV-2 S蛋白的S1次單位。SARS-CoV-2蛋白(包含S1和S2次單位)的單體具有分子量約150kDa(非還原性)。圖4C顯示在圖4B中描述的相同系列裂解物的西方墨點法分析，除了用NB100-56578抗體檢測SARS-COV-2 S蛋白的S2次單位。

【0071】 圖5A顯示具有以下的胺基酸序列：原生SARS-CoV-2 S蛋白的C端區(wtTM/wtCT)、流感H5血球凝集素(HA)的C端區(H5iTM/H5iCT)、具有野生型跨膜結構域(TM)和流感H5 HA胞質尾(CT)結構域(wtTM/H5iCT)的經修飾的SARS-CoV-2 S蛋白的C端區、以及具有在SARS-CoV-2跨膜(TM)結構域與H5

A/Indonesia/5/05 HA胞質尾(CT)結構域之間的可變邊緣的四個選擇性型式的經修飾的S蛋白(wtTM/H5iCT V1-V4)的C端區。冠狀病毒S蛋白的TM結構域用下劃線表示，且源自流感HA的CT結構域以粗體顯示。圖5B顯示在表現具有嵌合跨膜和胞質尾結構域(TMCT)的四種變體經修飾的S蛋白中的每一種的植物中SARS-CoV-2 S蛋白積累的量化倍數變化差異，如圖5A(wtTM/H5iCT，V1-V4)所示，相對於在表現具有嵌合TMCT(其具有野生型跨膜結構域(TM)和流感H5HA胞質尾(CT)結構域)的經修飾的SARS-CoV-2 S蛋白的植物中經修飾的SARS-CoV-2 S蛋白積累，其設置為1。

【0072】圖6A顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有野生型跨膜和胞質尾結構域(wtTMCT；構建體8591)的SARS-COV-2S蛋白。圖6B顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域和流感H5血球凝集素跨膜結構域和胞質尾結構域(H5i TMCT；構建體8597)的經修飾的S蛋白。圖6C顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感H5血球凝集素胞質尾結構域(H5i CT；構建體8671)的經修飾的S蛋白。圖6D顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域和嵌合跨膜和胞質尾結構域(TMCT)之選擇性型式的經修飾的S蛋白(H5i CT V1；構建體8980)。圖6E顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域和嵌合跨膜和胞質尾結構域(TMCT)之選擇性型式的經修飾的S蛋白(H5i CT V2；構建體8981)。圖6F顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域和嵌合跨膜和胞質尾結構域(TMCT)的SARS-CoV-2胞外結構域之選擇性型式的經修飾的S蛋白(H5i CT V3；構建體8982)。圖6G顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域和嵌合跨膜和胞質尾結構域(TMCT)之選擇性型式的經修飾的S蛋白

(H5i CT V4；構建體8983)。圖6H顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感H1血球凝集素胞質尾結構域(H1 CT；構建體7390)的經修飾的S蛋白。圖6I顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感H3血球凝集素胞質尾結構域(H3 CT；構建體7391)的經修飾的S蛋白。圖6J顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感H6血球凝集素胞質尾結構域(H6 CT；構建體7392)的經修飾的S蛋白。圖6K顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感 H7血球凝集素胞質尾結構域(H7 CT；構建體 7393)的經修飾的S蛋白。圖6L顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感 H9血球凝集素胞質尾結構域(H9 CT；構建體7394)的經修飾的S蛋白。圖6M顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有SARS-CoV-2胞外結構域、SARS-CoV-2跨膜結構域和流感HA B血球凝集素胞質尾結構域(HA B CT；構建體7395)的經修飾的S蛋白。

【0073】 圖7A顯示受體載體8501的示意圖。圖7B顯示受體載體8500的示意圖。圖7C顯示受體載體8716的示意圖。

【0074】 圖8A顯示載體8586的示意圖。圖8B顯示載體8589的示意圖。圖8C顯示載體8591的示意圖。

【0075】 圖9A顯示載體8592的示意圖。圖9B顯示載體8595的示意圖。圖9C顯示載體8597的示意圖。

【0076】 圖10A顯示載體8610的示意圖。圖10B顯示載體8611的示意圖。圖10C顯示載體8671的示意圖。

【0077】 圖11A顯示在表現具有額外取代的經修飾的SARS-CoV-2 S蛋白

(wtTM/H5iCT)的植物中積累的量化倍數變化。所述經修飾的SARS-CoV-2 S蛋白具有以下取代：“GSAS-2P”：R667G、R668S、R670S、K971P和V972P；“GSAS-4P”：R667G、R668S、R670S、K971P、V972P、F802P和A927P；以及“GSAS-6P”：R667G、R668S、R670S、K971P、V972P、F802P、A877P、A884P和A927P(相對於SEQ ID NO：2之參考序列)。結果已標準化為經修飾的SARS-CoV-2(wtTM/H5iCT)和GSAS+2P取代的積累，其設置為1。圖11B顯示在表現經修飾的SARS-CoV-2 S蛋白(wtTM/H5iCT)的植物中積累的量化倍數變化，其中每個GSAS-2P、GSAS-4P和GSAS-6P取代如圖11A所述，其係與其中每個經修飾的SARS-CoV-2 S蛋白進一步引入L923F取代之累積的量化倍數變化相比。結果已標準化為經修飾的SARS-CoV-2(wtTM/H5iCT)和GSAS+2P取代的積累，其設置為1。

【0078】圖12A顯示載體8980的示意圖。圖12B顯示載體8981的示意圖。圖12C顯示載體8982的示意圖。圖12D顯示載體8983的示意圖。

【0079】圖13A顯示載體7390的示意圖。圖13B顯示載體7391的示意圖。圖13C顯示載體7392的示意圖。圖13D顯示載體7393的示意圖。圖13E顯示載體7394的示意圖。圖13F顯示載體7395的示意圖。

【0080】圖14A顯示載體8953的示意圖。圖14B顯示載體8940的示意圖。

【0081】圖15A顯示載體8933的示意圖。圖15B顯示載體8960的示意圖。圖15C顯示載體8947的示意圖。

【0082】圖16A顯示來自表現以下構建體之經修飾的S蛋白的植物的粗裂解物的西方墨點法分析：泳道1，具有SARS-CoV-1胞外結構域、跨膜和胞質尾結構域(“wtTMCT”，構建體9231)的經修飾的S蛋白；泳道2，具有來自SARS-CoV-1的胞外結構域以及來自H5 A/Indonesia/5/05 (“H5iTMCT”，構建體9232)之血球凝集素(HA)的跨膜和胞質尾結構域(TMCT)的經修飾的S蛋白；泳道3，具有來自SARS-CoV-1的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05 (H5 Indo)

(“H5iCT”，構建體9233)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白；泳道 4，具有來自SARS-CoV-1的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05 (H5 Indo)之血球凝集素(HA)的胞質尾結構域(具有在SARS-CoV-1跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域(“H5iCT(V4)”，構建體9234)之間的可變邊緣)的經修飾的S蛋白；泳道5，具有來自SARS-CoV-1的胞外結構域和跨膜結構域以及來自H1 A/California/7/2009 (“H1cCT”，構建體9235)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白。使用於檢測的初級抗體是來自Sino Biologicals的SARS-CoV 棘S1次單位抗體(40150-MM08，1/5000)。用於檢測的二級抗體是來自JIR的山羊抗小鼠(115-035-146, 1/10 000)。所述經修飾的S蛋白具有分子量約150 kDa。

【0083】 圖16B、圖16C和圖16D顯示來自不連續碘克沙醇密度梯度的餾分F5(30%)、F6(30%)、F7(25%)、F8(25%)、F9(25%)、F10(15%)和F11(15%)的西方墨點法分析。這些餾分中之蛋白質的積累表明較高分子量結構的形成，即VLP的形成。對於來自粗裂解物之餾分的西方墨點法，用於檢測的初級抗體是來自Sino Biologicals的SARS-CoV棘S1次單位抗體，40150-MM08(1/5000)，且用於檢測的二級抗體是山羊抗小鼠，JIR，115-035-146(1/10000)。圖16B：分析來自表現具有原生TMCT結構域(wtTMCT，構建體9231)的SARS-CoV-1 S蛋白(具有2P+R667A取代)的植物的粗裂解物。圖16C：來自表現具有來自H5 A/Indonesia/5/05 HA(H5iTMCT，構建體9232)的TMCT之經修飾的SARS-CoV-1 S蛋白(具有2P+R667A取代)的植物的粗裂解物。圖 16D：來自表現具有來自H5 A/Indonesia/5/05 HA(H5iCT，構建體 9233)的胞質尾的經修飾的SARS-CoV-1 S蛋白(具有2P+R667A取代)的植物的粗裂解物。

【0084】 圖17A顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有原生TMCT結構域(wtTMCT，構建體9231)的SARS-COV-1S蛋白(具有2P+R667A取代)。圖17B顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒

(VLP)包括具有來自H5A/Indonesia/5/05 HA(H5iTMCT，構建體9232)的TMCT的經修飾的SARS-CoV-1 S蛋白(具有2P+R667A取代)。圖17C顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5A/Indonesia/5/05 HA(H5iCT，構建體9233)的胞質尾的經修飾的SARS-CoV-1 S蛋白(具有2P+R667A取代)。

【0085】圖18A顯示載體9231的示意圖。圖18B顯示載體9232的示意圖。圖18C顯示載體9233的示意圖。圖18D顯示載體9234的示意圖。圖18E顯示載體9235的示意圖。

【0086】圖19A顯示來自表現以下構建體的經修飾的S蛋白的植物的粗裂解物的西方墨點法分析：泳道1，具有MERS-CoV胞外結構域、跨膜和胞質尾結構域的經修飾的S蛋白(“wtTMCT”，構建體9246)；泳道2，具有來自MERS-CoV的胞外結構域以及來自H5 A/Indonesia/5/05之血球凝集素(HA)的跨膜和胞質尾結構域(TMCT)的經修飾的S蛋白(“H5iTMCT”，構建體9247)；泳道3，具有來自MERS-CoV的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05(H5 Indo)的血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白(“H5iCT”，構建體9249)；泳道4，具有來自MERS-CoV的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05(H5 Indo)之血球凝集素(HA)的胞質尾結構域(在MERS-CoV 跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域之間具有可變邊緣)的經修飾的S蛋白(“H5iCT(V4)”，構建體9250)；泳道5，具有來自MERS-CoV的胞外結構域和跨膜結構域以及來自H1 A/California/7/2009之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白(“H1cCT”，構建體9251)。用於檢測的初級抗體是來自Sino Biological(100208-RP02, 1/5000)的MERS-CoV棘蛋白S1抗體(N-端)。用於檢測的二級抗體是來自JIR(115-035-144, 1/10 000)的山羊抗-小鼠。所述經修飾的S蛋白具有分子量約175 kDa。圖19B顯示包括具有原生TMCT結構域之MERS-COV S蛋白(具有ASVG+2P取代) (wtTMCT，構建體9246)的病毒樣顆粒

(VLP)的電子顯微照片。圖19C顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5A/Indonesia/5/05 HA之TMCT的經修飾的MERS-CoV S蛋白(具有ASVG+2P取代) (H5iTMCT，構建體9247)。圖19D顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5A/Indonesia/5/05 HA的細胞質尾的經修飾的MERS-CoV S蛋白(具有ASVG+2P取代) (H5iCT，構建體9249)。圖19E顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5 A/ Indonesia/5/05 HA的胞質尾(在MERS-CoV跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域(H5iCT (V4)，構建體 9250)之間具有可變邊緣)的經修飾的MERS-CoV S蛋白(具有ASVG+2P取代)。圖19F顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H1A/California/7/2009 HA(H1cCT，構建體9251)的胞質尾的經修飾的MERS-CoV S蛋白(具有ASVG+2P取代)。

【0087】 圖20A顯示載體9246的示意圖。圖20B顯示載體9247的示意圖。圖20C顯示載體9249的示意圖。圖20D顯示載體9250的示意圖。圖20E顯示載體9251的示意圖。

【0088】 圖21顯示受體載體7147的示意圖。

【0089】 圖22顯示移除原生訊號肽的原生SARS-CoV-2、SARS-CoV-1和MERS-CoV S蛋白序列(SEQ ID NO：2、114和115)的比對。對應於RRAR弗林蛋白酶裂解位點(667-670)和在不含訊號肽(SEQ ID NO： 2)的原生SARS-CoV-2 S蛋白中之F802P、A877P、A884P、A927P、K971P、V972P中的每一個的殘基都與來自不含訊號肽的原生SARS-CoV-1 S蛋白(SEQ ID NO： 114)和原生MERS S 蛋白(SEQ ID NO： 115)的同源殘基一起加框。

【0090】 圖23A顯示來自表現以下構建體的經修飾的S蛋白的植物的粗裂解物的西方墨點法分析：泳道3，具有OC43-CoV胞外結構域、跨膜和胞質尾結構域的經修飾的S蛋白(“wtTMCT”，構建 9269)；泳道 4，具有來自OC43-CoV的胞

外結構域以及來自H5 A/Indonesia/5/05之血球凝集素(HA)的跨膜和胞質尾結構域(TMCT)的經修飾的S蛋白(“H5iTMCT”，構建體9270)；泳道5，具有來自OC43-CoV的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05(H5 Indo)之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白(“H5iCT”，構建體 9272)；泳道6，具有來自OC43-CoV的胞外結構域和跨膜結構域以及來自H5 A/Indonesia/5/05(H5 Indo)之血球凝集素(HA)的胞質尾結構域(在OC43-CoV跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域之間具有可變邊緣)的經修飾的S蛋白(“H5iCT(V4)”，構建體9273)；泳道7，具有來自OC43-CoV的胞外結構域和跨膜結構域以及來自H1 A/California/7/2009之血球凝集素(HA)的胞質尾結構域的經修飾的S蛋白(“H1cCT”，構建體9274)。用於檢測的初級抗體是來自Antibodies-online的抗-冠狀病毒OC43棘蛋白(ABIN2754654，1/1000)。用於檢測的二級抗體是來自JIR 的山羊抗-兔(111-035-144，1/10000)。所述經修飾的S蛋白具有分子量約150 kDa。圖23B顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5A/Indonesia/5/05 HA的TMCT的經修飾的OC43-CoV S蛋白(具有GGSGS+2P取代) (H5iTMCT，構建體9270)。圖23C顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5A/Indonesia/5/05 HA的胞質尾的經修飾的OC43-CoV S蛋白(具有GGSGS+2P取代) (H5iCT，構建體9272)。圖23D顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H5 A/Indonesia/5/05 HA的胞質尾(在OC43-CoV跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域之間具有可變邊緣)的經修飾的OC43-CoV S蛋白(具有GGSGS+2P取代) (H5iCT(V4)，構建體 9273)。圖23E顯示病毒樣顆粒(VLP)的電子顯微照片，該病毒樣顆粒(VLP)包括具有來自H1A/California/7/2009 HA的胞質尾的經修飾的OC43-CoV S蛋白(具有GGSGS+2P取代) (H1cCT，構建體9274)。

【0091】 圖24A顯示載體9269的示意圖。圖24B顯示載體9270的示意圖。圖

24C顯示載體9272的示意圖。圖24D顯示載體9273的示意圖。圖24E顯示載體9274的示意圖。

【0092】 圖25A顯示包括具有原生TMCT結構域之229E-CoV S蛋白(具有R567A+2P取代) (wtTMCT，構建體9310)的病毒樣顆粒(VLP)的電子顯微照片。圖25B顯示包括具有來自H5 A/Indonesia/5/05 HA之TMCT的經修飾的229E-CoV S蛋白(具有R567A+2P取代) (H5iTMCT，構建體9311)的病毒樣顆粒(VLP)的電子顯微照片。圖25C顯示包括具有來自H5 A/Indonesia/5/05 HA之胞質尾的經修飾的229E-CoV S蛋白(具有R567A+2P取代) (H5iCT，構建體9312)的病毒樣顆粒(VLP)的電子顯微照片。圖25D顯示包括具有來自H5 A/Indonesia/5/05 HA之胞質尾的經修飾的229E-CoV S蛋白(具有R567A+2P取代) (其在229E-CoV 跨膜(TM)結構域與H5 A/Indonesia/5/05 HA胞質尾(CT)結構域之間具有可變邊緣) (H5iCT (V4)，構建體 9313)的病毒樣顆粒(VLP)的電子顯微照片。圖25E顯示具有來自H1A/California/7/2009 HA之胞質尾的經修飾的229E-CoV S蛋白(具有R567A+2P取代) (H1cCT，構建體9314)的病毒樣顆粒(VLP)的電子顯微照片。

【0093】 圖26A顯示載體9310的示意圖。圖26B顯示載體9311的示意圖。圖26C顯示載體9312的示意圖。圖26D顯示載體9313的示意圖。圖26E顯示載體9314的示意圖。

【實施方式】

【0094】 以下描述較佳實施方式。

【0095】 如本文所用，術語「包括」、「具有」、「包含」和「含有」及其文法變體都是包含性的或開放式的，並且不排除附加的、未列舉的要素及/或方法步驟。術語「基本上由……所組成」當在本文中與用途或方法結合使用時，表示可能存在額外的要素及/或方法步驟，但這些添加並不會實質上影響所述方法或使用功能的方式。術語「由……所組成」當在本文中與用途或方法結合使用時，排除附加要素及/或方法步驟的存在。在本文描述為包括某些要素及/或步

驟的用途或方法也可以在某些實施方式中基本上由那些要素及/或步驟所組成，並且在其他實施方式中由那些要素及/或步驟所組成，無論這些實施方式是否被具體提到。此外，除非另有說明，否則單數的使用包括複數，且「或」表示「及/或」。如本文所用，術語「複數個」是指多於一個，例如，兩個或更多個、三個或更多個、四個或更多個等。除非本文另有定義，否則本文使用的所有技術和科學術語與所屬技術領域中具有通常知識者通常理解的含義相同。如本文所用，術語「約」是指與給定值的大約+/-10%的變化。應當理解，這種變化始終包括在本文提供的任何給定值中，無論其是否被具體提及。術語「一(a)」或「一(an)」在本文中與術語「包括」一起使用時，可能表示「一個」，但也與「一個或多個」、「至少一個」和「一個或多個一個」的含義一致。

【0096】本描述關於經修飾的病毒結構蛋白及其在宿主或宿主細胞中的製造。經修飾的病毒結構蛋白依序地包括胞外結構域、跨膜結構域(TM)或TM的部分、及胞質尾(CT)結構域或CT的部分，其中胞外結構域及TM或TM的部分是源自冠狀病毒科，且CT或CT的部分是源自流感血球凝集素(HA)蛋白。

【0097】經修飾的病毒結構蛋白可以是經修飾的冠狀病毒結構蛋白，其中胞質尾結構域或胞質尾結構域的部分已經流感血球凝集素(HA)蛋白的胞質尾結構域或胞質尾結構域的部分置換。例如，經修飾的病毒結構蛋白可以是經修飾的冠狀病毒棘或表面(S)蛋白，其中S蛋白的胞質尾結構域或胞質尾結構域的部分已經流感血球凝集素(HA)蛋白之胞質尾結構域或該胞質尾結構域的蛋白置換。

【0098】本揭露提供一種經修飾的病毒結構蛋白，其中經修飾的病毒結構蛋白的胞外結構域及跨膜結構域可以源自冠狀病毒S蛋白的胞外結構域及跨膜結構域，且其中胞質尾結構域係源自流感血球凝集素(HA)蛋白的胞質尾結構域。

【0099】修飾的S-蛋白可以是嵌合經修飾的S-蛋白或嵌合S-蛋白。「嵌合S-蛋白」是指包括融合為單一多肽的來自兩個或多於兩個來源的胺基酸序列及/或蛋白結構域或蛋白結構域的部分的蛋白質或多肽。例如但不限於，嵌合S蛋白的

胞外結構域及跨膜結構域(TM)或TM的部分可以源自第一病毒結構蛋白，例如冠狀病毒S蛋白，且胞質尾(CT)或CT的部分可以源自第二病毒結構蛋白，例如CT可以源自流感HA。此外，胞外結構域可以源自第一病毒結構蛋白，例如第一冠狀病毒S蛋白，TM或TM的部分可以源自第二病毒結構蛋白，例如第二冠狀病毒S蛋白，且CT或CT的部分可以源自第三病毒結構蛋白，例如CT可以源自流感HA。因此，經修飾的S-蛋白或嵌合S-蛋白可包括嵌合跨膜和胞質尾結構域(TMCT)。

【0100】 經修飾的冠狀病毒S-蛋白可依序地包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 可以是嵌合 TMCT，所述嵌合 TMCT 可包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分可以是源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白。

【0101】 TM或TM的部分可直接地融合或接合至CT或CT的部分，或TM或TM的部分可藉由肽間插序列融合或接合至CT或CT的部分。

【0102】 此外，TM可以是嵌合TM，其可包括源自冠狀病毒S-蛋白TM的N末端序列和源自流感HA蛋白TM的C末端序列。CT可以是嵌合CT，其可包括源自冠狀病毒S-蛋白CT的N末端序列和源自流感HA蛋白CT的C末端序列。

【0103】 因此，嵌合TMCT可包括原生冠狀病毒S-蛋白TM、嵌合冠狀病毒S-蛋白/流感HA TM、原生流感HA CT、嵌合流感HA/冠狀病毒S-蛋白CT或其組合。嵌合冠狀病毒S-蛋白/流感HA TM包含源自冠狀病毒S-蛋白之TM的序列以及源自流感HA之TM的序列。類似地，嵌合流感HA/冠狀病毒S-蛋白CT包含源自流感HA之CT的序列以及源自冠狀病毒S-蛋白之CT的序列。

【0104】「嵌合跨膜和胞質尾結構域」或「嵌合TMCT」是指TMCT其為不是原生的冠狀病毒S蛋白TMCT。嵌合TMCT包括在自然界中沒有一起發現的序列。因此，TMCT可包括與冠狀病毒S蛋白之胞外結構域為異源性的序列。術語「異源性」是指來源自不同生物或合成來源的序列或結構域。例如，嵌合TMCT可包括源自與胞外結構域相同的冠狀病毒S-蛋白的TM或TM的部分，亦即，TM可與S蛋白之胞外結構域為同源性，或者TM或TM的部分可源自不同的病毒TM，例如來自與胞外結構域不同的冠狀病毒S蛋白的TM，亦即，TM可以與S-蛋白之胞外結構域為異源性。CT或CT的部分可以源自與經修飾的S-蛋白之胞外結構域、TM或胞外結構域和TM兩者為異源性的CT。

【0105】冠狀病毒S蛋白、經修飾的S蛋白或經修飾的冠狀病毒S蛋白之胞外結構域和跨膜結構域或跨膜結構域的部分可以源自冠狀病毒科病毒家族的任何成員。例如，冠狀病毒S-蛋白、經修飾的S-蛋白或經修飾的冠狀病毒S-蛋白之胞外結構域和跨膜結構域例如可源自冠狀病毒，諸如α-冠狀病毒(α-CoV)、β-冠狀病毒(β-CoV)、γ-冠狀病毒(γ-CoV)或δ-冠狀病毒(δ-CoV)。例如，冠狀病毒可以是α-冠狀病毒(α-CoV)或β-冠狀病毒(β-CoV)。α-冠狀病毒可以是Duvinacovirus亞屬病毒，例如HCoV-229E(229E-CoV)，或者可以是Setracovirus亞屬病毒，例如HCoV-NL63。在一較佳的實施方式中，冠狀病毒是β-冠狀病毒(β-CoV)。β冠狀病毒可以是譜系A β冠狀病毒，例如HCoV-OC43 (OC43-CoV)或HCoV-HKU1 (HKU1-CoV)，譜系 B β冠狀病毒，例如 SARS-CoV(也稱為SARS-CoV-1)或SARS-CoV-2 及其變體或譜系 C β冠狀病毒，例如MERS-CoV。

【0106】冠狀病毒S-蛋白、經修飾的S-蛋白或胞外結構域以及經修飾的冠狀病毒S-蛋白的跨膜結構域或跨膜結構域的部分可進一步源自SARS-CoV-2譜系的變體，包括但不限於B.1.1.7菌株(“α”變體) (20I/501Y.V1，MW531680.1)、B.1.351菌株(“β”變體) (20H/501Y.V2)、P.1菌株(“γ”變體) (20J/501Y.V3)、B1.617.2菌株(“δ”變體)、B.1.525菌株、B.1.429菌株(“ETA”變體)或包括在冠狀病毒S蛋白中原

生產生的突變的菌株的其他變體，或其原生存在的重組菌株。

【0107】在一個實施方式中，經修飾的病毒結構蛋白之胞外結構域和跨膜結構域或跨膜結構域的部分係源自SARS-CoV-2譜系之冠狀病毒(也稱為SARS-CoV-2變體)。在其他實施方式中，經修飾的病毒結構蛋白之胞外結構域和跨膜結構域或跨膜結構域的部分係源自SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV或其變體的棘蛋白(S)。

【0108】關於經修飾的病毒結構蛋白，如本文所用的術語「經修飾的」可以指用異源性病毒的CT或CT的部分置換來自冠狀病毒科的結構蛋白中的胞質尾結構域(CT)或CT的部分。例如，經修飾的病毒結構蛋白可以是冠狀病毒S蛋白，其中S蛋白的CT或CT的部分已用流感血球凝集素(HA)的CT或CT的部分置換。

【0109】因此，經修飾的病毒結構蛋白可以是經修飾的冠狀病毒棘(S)蛋白，其包括跨膜結構域(TM)或TM的部分、以及胞質尾(CT)或CT的部分，其中CT或CT的部分可源自流感血球凝集素(HA)蛋白，且其中TM或TM的部分與CT或CT的部分為異源性。此外，經修飾的S蛋白包括跨膜結構域(TM)或TM的部分、以及胞質尾(CT)或CT的部分，其中CT或CT的部分可源自流感血球凝集素(HA)蛋白，且其中CT或CT的部分與TM或TM的部分為異源性。

【0110】因此，在一個態樣中，提供一種經修飾的冠狀病毒棘(S)蛋白，其包括跨膜結構域(TM)或TM的部分、以及胞質尾(CT)或CT的部分，其中CT或CT的部分係源自流感血球凝集素(HA)蛋白，且其中TM或TM的部分與CT或CT的部分為異源性。經修飾的冠狀病毒棘(S)蛋白也稱為經修飾的S蛋白。

【0111】胞質尾結構域也可稱為「胞質尾」、「細胞質尾」、「細胞溶質尾端結構域」、「CT」、「CTD」、「胞質結構域」、「細胞質結構域」、「CP」、「CPD」或「C端結構域」及類似的表達。胞質尾結構域也可包括胞質尾結構域的部分。

【0112】已經發現，與野生型或未經修飾的病毒結構蛋白(例如S蛋白)相

比，經修飾的病毒結構蛋白，諸如本文所揭露的經修飾的S蛋白，具有經改善的特性。經修飾的病毒結構蛋白(例如經修飾的S蛋白)的經改善的特性之實例包括但不限於：與野生型或未經修飾的病毒結構蛋白相比，當在宿主或宿主細胞中表現時，經修飾的病毒結構蛋白之經增加的產量；與野生型或未經修飾的病毒結構蛋白相比，當在宿主或宿主細胞中表現時，病毒結構蛋白之經改善的完整性、穩定性或經改善的完整性和穩定性兩者；與包括其不包含如本文所述的修飾的病毒結構蛋白的VLP的完整性、穩定性或完整性和穩定性相比，由經修飾的病毒結構蛋白組成的病毒樣顆粒(VLP)之經改善的完整性、穩定性或經改善的完整性和穩定性兩者；與在相同或實質上相似的宿主細胞中表現的不包括經修飾的病毒結構蛋白的VLP的產量相比，當在宿主細胞中表現時，包括經修飾的病毒結構蛋白的VLP之經增加 的產量。

【0113】 此外，還描述一種在宿主或宿主細胞中製造包括經修飾的病毒結構蛋白(例如經修飾的S蛋白)的病毒樣顆粒(VLP)之方法。已經觀察到，當製造包括經修飾的病毒結構蛋白例如經修飾的S蛋白的VLP時，其中原生或野生型CT已用如本文所述的流感HA的CT置換，宿主中VLP產量增加，其係與包括以下者之病毒結構蛋白的VLP的產量相比，該病毒結構蛋白i) 包括原生CT或ii) 包括經修飾的病毒結構蛋白，其中跨膜結構域(TM)和CT已用流感HA之TM和CT置換。

【0114】 跨膜結構域也可稱為「TM」或「TMD」。跨膜和胞質尾結構域可稱為TMCT或TM/CT。

【0115】 圖3A顯示當在植物中表現經修飾的S蛋白(例如經修飾的SARS-CoV-2 S-蛋白)時，當原生跨膜和胞質尾(TMCT)用來自流感HA的TMCT(構建體8592、8595 和 8597)置換時，經修飾的S蛋白的產量或蛋白質積累(表示為倍數變化)增加大約2倍，其係與用原生TMCT(構建體8586、8589 和 8591)的S 蛋白的產量或蛋白質積累相比。此外，當經修飾的S蛋白(例如經修飾的SARS-CoV-2 S 蛋白)在植物中表現時，其中只有胞質尾(CT)用流感HA的CT(構

建體8610、8611和8671)置換，與其中TMCT已用流感HA的TMCT置換的經修飾的S蛋白的積累相比，具有流感HA的CT之經修飾的S蛋白的蛋白質積累(表示為倍數變化)進一步增加大約1.74至2.14倍之間。相應地，與具有原生跨膜和胞質尾(wtTMCT)的S蛋白的積累相比，具有流感HA的CT的經修飾的S蛋白的蛋白質積累增加大約3.57至4.40倍之間。

【0116】 圖3B顯示觀察到具有來自流感病毒HA的胞質尾(H5i CT)的經修飾的S蛋白(經修飾的SARS-CoV-2 S蛋白)具有更高的蛋白質積累，其係與具有野生型TMCT(wt TMCT)的S蛋白或具有來自植物粗萃取物之流感HA之TMCT(H5i TMCT)的經修飾的S蛋白的蛋白質積累相比。具有來自流感HA的胞質尾(H5i CT)的經修飾的S蛋白僅藉由考馬斯亮藍(Coomassie blue)染色為可見的。與具有野生型TMCT(wt TMCT)的S蛋白或具有流感HA的TMCT(H5i TMCT)的經修飾的S蛋白的條帶相比，具有來自流感HA之胞質尾(H5i CT)的經修飾的S蛋白的條帶更明顯且更厚，參見標記為S蛋白的約150 kDa的條帶。條帶的厚度對應於存在的蛋白質的量，表示H5i CT S蛋白積累更多的蛋白質。與使用的表達增強劑無關，觀察到這種更高的蛋白質積累。

【0117】 如下文更詳細進一步所討論，獲得相似的結果，其中經修飾的S-蛋白包括具有來自流感HA的胞質尾的SARS-CoV-1 S蛋白(參見圖16A)或具有來自流感HA的胞質尾的MERS CoV S蛋白(參見圖19A)。

【0118】 圖3C顯示藉由對植物粗萃取物進行西方墨點法分析的S蛋白(SARS-CoV-2 S蛋白)的積累。與具有野生型TMCT(wt TMCT)和經修飾的S蛋白的S蛋白相比，其中跨膜結構域和胞質尾(TMCT)結構域已用來自流感HA的TMCT(H5i TMCT)置換，當具有來自流感HA(H5i CT)的胞質尾的經修飾的S蛋白在植物中表現時，觀察到經修飾的S蛋白較高的積累。 圖3C中的西方墨點法分析進一步顯示，SARS CoV-2 S-蛋白包括S1結構域/次單位(上圖，用抗-SARS-CoV-2 S1抗體檢測)和S2結構域/次單位(下圖，用抗-SARS-CoV-2 S2抗體

檢測)兩者，且具有分子量約150 kDa。

【0119】 本說明書提供一種經修飾的病毒結構蛋白，其中經修飾的病毒結構蛋白可以是經修飾的冠狀病毒棘或表面蛋白(S蛋白)。經修飾的S蛋白依次地包括胞外結構域、跨膜結構域(TM)或TM的部分、以及胞質尾(CT)結構域或CT的部分，其中胞外結構域和跨膜結構域係源自冠狀病毒，且CT或CT的部分係源自流感血球凝集素(HA)蛋白的CT。TM的胞外結構域和跨膜結構域或部分可以源自相同的冠狀病毒。因此，經修飾的結構蛋白的胞外結構域和跨膜結構域或TM的部分彼此為同源性(亦即，不是異源性)，而CT或CT的部分與胞外結構域和跨膜結構域為異源性。

【0120】 此外，經修飾的S蛋白的跨膜結構域(TM)或TM的部分可以源自與胞外結構域不同的冠狀病毒。因此，在經修飾的S蛋白中的TM或TM的部分可以與經修飾的S蛋白的胞外結構域和CT結構域或CT的部分兩者為異源性(非同源性)。類似地，胞外結構域可以與TM或TM的部分以及經修飾的S蛋白的CT結構域或CT的部分為異源性(非同源性)。例如，經修飾的S蛋白的胞外結構域可以源自第一冠狀病毒，TM或TM的部分可以源自第二冠狀病毒，且CT或CT的部分可以源自流感HA。第一冠狀病毒和第二冠狀病毒可能屬於不同的冠狀病毒家族、亞群、類型、亞型、譜系或病毒株。因此，第一冠狀病毒和第二冠狀病毒可能彼此為異源性，並且也可各自與源自CT或CT的部分的病毒家族為異源性。

【0121】 例如，S蛋白胞外結構域從其衍生的第一冠狀病毒可以來自任何冠狀病毒，例如α冠狀病毒(α-CoV)或β冠狀病毒(β-CoV)。S蛋白的胞外結構域的來源的第一冠狀病毒的非限制性實例為Duvinacovirus，例如HCoV-229E；Setracovirus，例如HCoV-NL63。譜系A β冠狀病毒，例如HCoV-OC43或HCoV-HKU1，譜系B β冠狀病毒，例如SARS-CoV或SARS-CoV 2或譜系C β冠狀病毒，例如MERS-CoV。TM從其衍生的第二冠狀病毒可能屬於與胞外結構域從其衍生的第一冠狀病毒為不同的冠狀病毒家族、亞組、類型、亞型、譜系或病

毒株。例如，S蛋白TM從其衍生的第二冠狀病毒可以來自任何冠狀病毒，例如α冠狀病毒(α-CoV)或β冠狀病毒(β-CoV)，只要第二冠狀病毒與第一冠狀病毒為異源性。S蛋白的TM可以從其衍生的第二冠狀病毒的非限制性實例為Duvinacovirus，例如HCoV-229E(也稱為229E-CoV)、Setracovirus，例如HCoV-NL63(NL63-CoV)、譜系A β冠狀病毒，例如HCoV-OC43(也稱為OC43-CoV)或HCoV-HKU1(HKU1-CoV)、譜系B β冠狀病毒，例如SARS-CoV(也稱為SARS-CoV 1)或SARS-CoV 2或譜系C β冠狀病毒，例如MERS-CoV(也簡稱為「MERS」)。

【0122】冠狀病毒S蛋白中的結構域，例如SARS-CoV-1 S-蛋白、SARS-CoV-2 S-蛋白、MERS CoV S-蛋白、OC43-CoV S-蛋白或229E-CoV S-蛋白可以藉由本領域中已知的方法容易地鑑定。例如，諸如跨膜結構域的結構域可以藉由確定蛋白質的胺基酸序列的疏水性的程度來鑑定，例如使用跨膜預測程序(例如，Expert Protein Analysis System；ExPASy.org，由Swiss Institute of Bioinformatics所運營；或the Dense Alignment Surface Method, Cserzo M., et al. 1997, Prot. Eng. vol. 10, no. 6, 673-676； Lolkema J.S. 1998, FEMS Microbiol Rev. 22, no 4, 305-322)，藉由確定蛋白質的胺基酸序列的親水性輪廓(例如Kyte-Doolittle親水性輪廓)，藉由確定三維蛋白質結構並鑑定在膜中熱力學穩定的結構(例如單個α螺旋，幾個跨膜α螺旋的穩定複合物，跨膜β桶形，β螺旋或在膜中熱力學穩定的任何其他結構)。

【0123】此外，冠狀病毒S蛋白內的結構域可以藉由與已知蛋白質序列的比較例如藉由序列比對來確定。用於比較的序列比對的方法是本領域中周知的且將如下文進一步描述。

【0124】冠狀病毒S蛋白的結構域和結構域組織是眾所周知的並且已經被描述。所有冠狀病毒棘蛋白(S蛋白)在兩個次單位或結構域(名為S1的N端次單位(或結構域)，其負責受體結合以及C端S2次單位(或結構域)，其負責病毒附著、膜融

合和病毒進入)中共享相同的組織。

【0125】 圖1A顯示冠狀病毒S蛋白及其次單位和結構域以及S1/S2和S2'切割位點的位置的示意圖。S1次單位係位於病毒膜的遠端，且包含介導病毒附接至其宿主受體的受體結合結構域(RBD)。S2次單位包含融合蛋白機制，例如融合肽、兩個七肽重複序列(HR1和HR2)、融合醣蛋白的中心螺旋和跨膜結構域、以及胞質尾結構域(參見例如Kirchdoerfer等人，Nature 2016 Mar 3；531(7592)：118-2，其藉由引用併入本文)。

【0126】 跨膜結構域(TM)和胞質尾結構域(CT)位於S2次單位的C-端處。雖然這些結構域在所有冠狀病毒中都是保守的(參見圖1A和Corver等人，Virol J. 2009; 6： 230，其藉由引用併入本文)，但不同的參考文獻、團隊和作者都提到關於這些結構域的不同胺基酸編號。

【0127】 例如，胺基酸(aa)：1214-1234可以指定給TM並且aa 1235-1273可以指定給SARS-CoV-2的S蛋白中的CT(參見例如UniProtKB-P0DTC2((SPIKE_SARS2))。當將SARS-CoV-2序列(SEQ ID NO. 1)與Kirchdoerfer等人的SARS-CoV-1序列進行比對時(Nature 2016 Mar 3;531(7592):118-2)，SARS-CoV-2 TM對應於胺基酸1214-1236，而SARS-CoV-2 CT對應於胺基酸：1237-1273。

【0128】 為達本揭露之目的，當與冠狀病毒S蛋白參考序列(SEQ ID NO： 1)比對時，原生(未經修飾的)S蛋白的TM和CT對應於以下胺基酸：TM：胺基酸1214-1234和CT：胺基酸：1235-1273。

【0129】 當從S蛋白中移除包括訊號肽(SP)的15個胺基酸時，TM對應於參考序列SEQ ID NO： 2的胺基酸1199-1219，而CT對應於SEQ ID NO： 2的胺基酸1220-1258(另參見表1，用於參考序列和編號)。

【0130】 冠狀病毒S-蛋白的TM具有高度保守的N-端富含芳香族的序列，接者為疏水序列(參見圖 22和Corver等人，Virology Journal volume 6, 230 (2009))。冠狀病毒S-蛋白TM結構域的共通序列為：

WYXWLGFIAGLXAXXX{X}VXXXL (SEQ ID NO： 132)，(其中 {X}可能不存在)。

【0131】 例如，冠狀病毒S-蛋白TM結構域共通序列可以是：

WY[I/V]WLGFIAGL[V/I]A[L/I][A/V][L/M]{X}V[F/T][F/I]XL (SEQ ID NO：133)，(其中 {X} 可以是C或不存在)。

【0132】 [表1] 在經修飾的S蛋白中之TM和CT結構域的位置和參考序列中之對應胺基酸位置的非限制性實例。

S 蛋白	跨膜結構域 (TM)	胞質尾結構域 (CT)
經修飾的 S 蛋白 [1] [SARS-CoV-2 H5iCT] (SEQ ID NO：21)	1199-1219	1220-1235
SARS-CoV-2[2] (SEQ ID NO：1)	1214-1234	1235-1273
SARS-CoV-2[3] (SEQ ID NO：2)	1199-1219	1220-1258
SARS-CoV (SARS-CoV-1)[2] (SEQ ID NO：112)	1196-1216	1217-1255
SARS-CoV (SARS-CoV-1)[3] (SEQ ID NO：114)	1183-1203	1204-1242
MERS (MERS-CoV)[2] (SEQ ID NO：113)	1297-1318	1319-1353
MERS (MERS-CoV)[3] (SEQ ID NO：115)	1280-1301	1302-1336
OC43-CoV[2] (SEQ ID NO：158)	1233-1325	1326-1360
OC43-CoV[3] (SEQ ID NO：160)	1291-1311	1312-1346
229E-CoV[2] (SEQ ID NO：159)	1116-1135	1136-1173
229E-CoV[3] (SEQ ID NO：161)	1100-1119	1120-1157

[1]編號排除訊號肽，CT源自於流感HA

[2]編號包括訊號肽，CT是原生的

[3]編號排除訊號肽，CT是原生的

【0133】 雖然指定給TM和CT結構域的殘基的編號存在差異，但所屬技術領域中具有通常知識者將能夠藉由使用諸如下文所述的已知方法來確定邊界或冠狀病毒S-蛋白中的這些結構域的邊界。

【0134】 在經修飾的冠狀病毒S蛋白中，可能源自流感HA的異源性CT或CT部分可直接地融合到冠狀病毒S蛋白的TM或TM的部分的C末端，或異源性CT或CT的部分可融合到具有肽間插序列(也稱為連接子或連接子序列)的冠狀病毒S蛋白的TM或TM的部分的C末端。 因此，經修飾的S-蛋白可包括間插肽，其中該間插肽序列將CT或CT的部分融合到TM或TM的部分的C末端。

【0135】 異源性CT、CT的部分或具有異源性CT的間插肽序列可以融合到TM結構域的C-端部分中的胺基酸(例如在表1中定義的TM結構域之C端的4個胺基酸內，參考SEQ ID NO： 1、2、21、114、115、160或161)，或CT結構域的N-端部分(例如在表1中定義的CT結構域之N末端的4個胺基酸內，參考SEQ ID NO： 1、2、21、114、115、160或161)。

【0136】 例如，冠狀病毒TM可以在對應於SEQ ID NO： 1的胺基酸1230-1238中的任一個胺基酸殘基處結束。因此，冠狀病毒TM的C-端可以是胺基酸對應於SEQ ID NO： 1的胺基酸1230-1238中的任一個。在一個實例中，冠狀病毒TM可以在對應於SEQ ID NO： 1中的胺基酸1230的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1231的胺基酸殘基處結束。在進一步實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1232的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1233的胺基酸殘基處結束。在進一步實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1234的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺

基酸1235的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1236的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1237的胺基酸殘基處結束。在另一個實例中，TM可以在對應於SEQ ID NO：1中的胺基酸1238的胺基酸殘基處結束。在較佳的實施方式中，TM可以在對應於SEQ ID NO：1中的胺基酸1234的胺基酸殘基處結束。

【0137】 在另一個實例中，冠狀病毒TM或TM的部分可以在對應於SEQ ID NO：2或21的胺基酸1215-1219中的任一個胺基酸殘基處結束。因此，冠狀病毒TM或TM的部分的C末端可以是對應於SEQ ID NO：2或21的胺基酸1215-1224中的任一個的胺基酸。在一個實例中，冠狀病毒TM或TM的部分可以在對應於SEQ ID NO：2或21中的胺基酸1215的胺基酸殘基處結束。在另一個實例中，TM或TM的部分可以在對應於SEQ ID NO：2或21中的胺基酸1216的胺基酸殘基處結束。在進一步實例中，TM或TM的部分可以在對應於SEQ ID NO：2或21中的胺基酸1217的胺基酸殘基處結束。在另一個實例中，TM或TM的部分可以在對應於SEQ ID NO：2或21中的胺基酸1218的胺基酸殘基處結束。在另一個實例中，TM或TM的部分可以在對應於SEQ ID NO：2或21中的胺基酸1219的胺基酸殘基處結束。

【0138】 可以將異源性CT融合到來自冠狀病毒S蛋白的TM或TM的部分的C末端的間插肽序列可以具有0-10個胺基酸的長度。因此，間插肽序列可以具有0、1、2、3、4、5、6、7、8、9或10個胺基酸的長度。間插肽序列可以源自於冠狀病毒蛋白，例如間插肽序列可以源自於冠狀病毒S蛋白的TM的C末端或冠狀病毒S蛋白的CT的N末端或兩者。間插肽序列可進一步源自於流感HA蛋白，例如間插肽序列可以源自流感HA蛋白的TM的C末端或源自流感HA蛋白的CT的N末端， 或兩者。此外，間插肽序列可以與冠狀病毒及/或經修飾的S蛋白的HA部分為異源性，或者間插肽序列可以是人工序列。

【0139】 經修飾的S蛋白的TM/CT結構域(也稱為嵌合TMCT)的序列的非限制性實例如下所示。來自冠狀病毒S蛋白的TM結構域的序列用下劃線表示，且

源自流感HA的CT結構域以粗體顯示。斜體和粗體的序列是源自流感HA的TM的序列。斜體和下劃線的序列是源自冠狀病毒S蛋白之CT的序列。

SARS-CoV-2

- WYIWLGFIAGLIAIVMVTIML**SLWMCSNGSLQCRICI** (SEQ ID NO：18) (wtTM/H5iCT)

- WYIWLGFIAGLIAIVMVTIM***MAGL*SLWMCSNGSLQCRICI** (SEQ ID NO：19) (wtTM/H5iCT V1)

- WYIWLGFIAGLIAIVMVTIM***AGL*SLWMCSNGSLQCRICI** (SEQ ID NO：37) (wtTM/H5iCT V2)

- WYIWLGFIAGLIAIVMVTIML*CCM***CSNGSLQCRICI** (SEQ ID NO： 38) (wtTM/H5iCT V3)

- WYIWLGFIAGLIAIVMVTIML*CC***SNGSLQCRICI** (SEQ ID NO：39) (wtTM/H5iCT V4)

- WYIWLGFIAGLIAIVMVTIML**SFWMCSNGSLQCRICI** (SEQ ID NO：126)(wtTM/H1iCT)

- WYIWLGFIAGLIAIVMVTIML**MWACQKGNIRCNICI** (SEQ ID NO：127) (wtTM/H3iCT)

- WYIWLGFIAGLIAIVMVTIML**GLWMCSNGSMQCRICI** (SEQ ID NO：128) (wtTM/H6iCT)

- WYIWLGFIAGLIAIVMVTIML**VFICVKNGNMRCTICI** (SEQ ID NO：129) (wtTM/H7iCT)

- WYIWLGFIAGLIAIVMVTIML**LFWAMSNGSCRCNICI** (SEQ ID NO：

130) (wtTM/H9iCT)

- WYIWLGFIAGLIAIVMVTIML**VVYMVSRDNVSCSICL** (SEQ ID NO：131) (wtTM/BiCT)

SARS-CoV-1

- WYVWLGFIAGLIAIVMVTILL**SLWM CSNGSLQCRICI** (SEQ ID NO：118) (wtTM/H5iCT)

- WYVWLGFIAGLIAIVMVTILL*CC***SNGSLQCRICI** (SEQ ID NO：119) (wtTM/H5iCT V4)

- WYVWLGFIAGLIAIVMVTILL**SFWM CSNGSLQCRICI** (SEQ ID NO：120) (wtTM/H1cCT)

MERS-CoV

- WYIWLGFIAGLVALALCVFFIL**SLWMCSNGSLQCRICI** (SEQ ID NO：123) (wtTM/H5iCT)

- WYIWLGFIAGLVALALCVFFIL*CC***SNGSLQCRICI** (SEQ ID NO：124) (wtTM/H5iCT V4)

- WYIWLGFIAGLVALALCVFFIL**SFWMCSNGSLQCRICI** (SEQ ID NO：125) (wtTM/ H1cCT)

OC43-CoV

- WYVWLLICLAGVAMLVLLFFI**SLWMCSNGSLQCRICI** (SEQ ID NO：164) (wtTM/H5iCT)

- WYVWLLICLAGVAMLVLLFFI*CC***SNGSLQCRICI** (SEQ ID NO：165)

(wtTM/H5iCT V4)

- WYVWLLICLAGVAMLVLLFFI**SFWMCSNGSLQCRICI** (SEQ ID NO：166) (wtTM/ H1cCT)

229E-CoV

- WWVWLCISVVLIFVVSMLLL**SLWMCSNGSLQCRICI** (SEQ ID NO：169) (wtTM/H5iCT)

- WWVWLCISVVLIFVVSMLLL*CC***SNGSLQCRICI** (SEQ ID NO：170) (wtTM/H5iCT V4)

- WWVWLCISVVLIFVVSMLLL**SFWMCSNGSLQCRICI** (SEQ ID NO：171) (wtTM/ H1cCT)

【0140】經修飾的冠狀病毒S-蛋白可包括嵌合TMCT。例如，嵌合TMCT可包括源自冠狀病毒S蛋白的N端序列以及源自流感HA蛋白的C端序列，如表1B所示。TM可包括如標記為「S-蛋白TM序列」的列中所示的序列，且CT可包括如標記為「HA蛋白CT序列」的列中所示的序列。CT和TM可以藉由標記為「S-蛋白CT序列」及/或「HA蛋白TM序列」(也稱為間插序列或連接子，如下文進一步描述)的列中所示的序列來連接。

【0141】[表1B] 在經修飾的S蛋白中之TM和CT序列的非限制性實例。指示參考序列內的胺基酸位置。

SEQ ID NO：	S-蛋白 TM 序列	S-蛋白 CT 序列	HA 蛋白 TM 序列	HA 蛋白 CT 序列
18	1-21	-	-	22-37
19	1-20	-	21-24	25-40
37	1-20	-	21-23	24-39
38	1-21	22-24	-	25-36
39	1-21	22-23	-	24-34
126	1-21			22-37
127	1-21			22-36

128	1-21			22-37
129	1-21			22-37
130	1-21			22-37
131	1-21			22-37
118	1-21			22-37
119	1-21	22-23	-	24-34
120	1-21			22-37
123	1-22			23-38
124	1-22	23-24	-	25-35
125	1-22			23-38
164	1-21			22-37
165	1-21	22-23	-	24-34
166	1-21			22-37
169	1-20			21-36
170	1-20	21-22	-	23-33
171	1-20			21-36

【0142】 例如，源自冠狀病毒S-蛋白TM的N端序列可包括至少下列：

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169 或170的胺基酸1-19的至少19個胺基酸；

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169或170的胺基酸1-20的至少20個胺基酸；

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169或170的胺基酸1-21的至少21個胺基酸；

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169 或170的胺基酸1-22的至少22個胺基酸；

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169或170的胺基酸1-23的至少23個胺基酸；

對應於SEQ ID NO：18、19、37、38、39、118、119、123、124、164、165、169或170的胺基酸1-24的至少24個胺基酸。

【0143】 源自冠狀病毒S蛋白TM的N端序列可包括對應於SEQ ID NO：18或169的胺基酸1-20的至少20個胺基酸，或對應於SEQ ID NO：118或164的胺基酸1-21的至少21個胺基酸，或對應於SEQ ID NO：123的胺基酸1-22的至少22個胺

基酸；以及來自流感HA蛋白TM之C末端的一個或多於一個的胺基酸。源自冠狀病毒S蛋白TM的N端序列可包括對應於SEQ ID NO：18或169的胺基酸1-20的至少20個胺基酸，或對應於SEQ ID NO：118或169的胺基酸1-21的至少21個胺基酸，或對應於SEQ ID NO：123的胺基酸1-22的至少22個胺基酸以及來自流感HA蛋白TM之C末端的一個或多於一個的胺基酸。來自流感HA蛋白TM之C末端的一個或多於一個的胺基酸可包括0、1、2、3、4、5、6、7、8、9或10個胺基酸。例如，一個或多於一個的胺基酸可以是2、3或4個胺基酸。來自流感HA蛋白TM之C末端的一個或多於一個的胺基酸可以是A、C、G、L、S、M、W或A、C、G、L、S、M、W的保留取代或其組合。在一個實例中，來自流感HA蛋白TM之C末端的一個或多於一個的胺基酸可選自AG或AG、AGL的保留取代或AGL、MAGL的保留取代或MAGL的保留取代。

【0144】經修飾的冠狀病毒S蛋白可亦包括嵌合CT，該嵌合CT包括源自冠狀病毒S蛋白CT的N端序列以及源自流感HA蛋白CT的C端序列。

【0145】源自冠狀病毒S-蛋白CT的N-端序列可包括一個或多於一個的胺基酸。來自冠狀病毒S蛋白CT的N端的一個或多於一個的胺基酸可包括0、1、2、3、4或5個胺基酸。例如，一個或多於一個的胺基酸可以是1、2或3個胺基酸。來自冠狀病毒S蛋白CT的N端的一個或多個一個的胺基酸可以是C或M或C或M的保留取代。在一個實例中，來自冠狀病毒S蛋白的N-端的一個或多個一個的胺基酸可選自C或C的保留取代、CC或CC的保留取代、或CCM或CCM的保留取代。

【0146】源自流感HA蛋白CT的C端序列可包括，對應於SEQ ID NO：18的胺基酸27-37的至少11個胺基酸。源自流感HA蛋白CT的N-端序列可進一步包括對應於SEQ ID NO：18的胺基酸26-37的至少12個胺基酸，對應於SEQ ID NO：18的胺基酸25-37的至少13個胺基酸，對應於SEQ ID NO：18的胺基酸24-37的至少14個胺基酸，對應於SEQ ID NO：18的胺基酸23-37的至少15個胺基酸，或對應於SEQ ID NO：18的胺基酸22-37的至少16個胺基酸。

【0147】在另一個實例中，源自流感HA蛋白CT的C-端序列可包括至少下列：

- 對應於SEQ ID NO：126、127、128、129、130 或131的胺基酸27-37的至少11個胺基酸；

- 對應於SEQ ID NO： 126、127、128、129、130或131的胺基酸26-37的至少12個胺基酸；

- 對應於SEQ ID NO：126、127、128、129、130或131的胺基酸25-37的至少13個胺基酸；

- 對應於SEQ ID NO：126、127、128、129、130或131的胺基酸24-37的至少14個胺基酸；

- 對應於SEQ ID NO：126、127、128、129、130或131的胺基酸23-37的至少15個胺基酸；或

- 對應於SEQ ID NO：126、127、128、129、130或131的胺基酸22-37的至少16個胺基酸。

【0148】例如，CT可包括如表1B中所示的序列(HA蛋白CT序列)。例如，CT可包括SEQ ID NO：18、126、128、129、130、131、118、120、164或166的胺基酸22-37；或SEQ ID NO：19的胺基酸25-40；或 SEQ ID NO：37的胺基酸24-39；或SEQ ID NO：38的胺基酸25-36；或SEQ ID NO：39或119的胺基酸24-34；或 SEQ ID NO：127的胺基酸22-36；或SEQ ID NO：118或164的胺基酸22-37；或SEQ ID NO：123或125的胺基酸23-38；或SEQ ID NO：124的胺基酸25-35；或SEQ ID NO：165的胺基酸24-34；或SEQ ID NO：169的胺基酸21-36；或SEQ ID NO：170的胺基酸23-33；或SEQ ID NO：21-36的胺基酸。

【0149】流感CT或CT的部分可融合或接合至具有間插肽序列的S蛋白的TM或TM的部分。例如，間插肽序列可以源自流感CT、S-蛋白TM或其組合，或者間插肽序列可以是人工序列。間插肽序列可以為不同長度。例如，間插肽序列

可以為1、2、3、4、5、6、7、8、9或10個胺基酸長，較佳地，間插肽序列介於2個和8個胺基酸長之間。在一個實例中，間插肽序列為2個胺基酸長，且可例如包括序列LC。在另一個實例中，間插肽序列為4個胺基酸長，且可例如包括序列LCCM。在另一個實例中，間插肽序列可以為5個胺基酸長，且可例如包括序列LSLWM。在另一個實例中，間插肽序列可以為7個胺基酸長，且可例如包括序列AGLSLWM。在進一步實例中，間插肽序列可以為8個胺基酸長，且可例如包括序列MAGLSLWM。

【0150】 例如，經修飾的S-蛋白的TMCT可包括與以下序列或具有90-100%或其間任何數量的序列同一性或序列相似性的序列：

- WYIWLGFIAGLIAIVMVTIM - (X)n - CSNGSXXCXICI (SEQ ID NO：64)，

- WYVWLGFIAGLIAIVMVTIL - (X)n - CSNGSXXCXICI (SEQ ID NO：134)，或

- WYIWLGFIAGLVALALCVFFIL -(X)n – CSNGSXXCXICI (SEQ ID NO：135)，

- WYVWLLICLAGVAMLVLLFFI -(X)n – CSNGSXXCXICI (SEQ ID NO：172)，

- WWVWLCISVVLIVVVSMLLL -(X)n – CSNGSXXCXICI (SEQ ID NO：173)，

其中$(X)_n$是間插肽序列，其中間插肽序列可具有0到n個胺基酸殘基的長度，其中n可以是0-10的任意長度，例如0、1、2、3、4 、5、6、7、8、9或10個胺基酸，其中X可包括任何胺基酸，例如X可以是A、C、G、F、L、S、M、W或A、C、G、F、L、S、M、W的保留取代或其組合。

非限制性間插肽序列$(X)_n$可包括下列：

- $(X)_0$，間插肽序列為不存在；

- $(X)_1$，包括例如序列L或C，或L或C的保留取代；

- $(X)_2$，包括例如序列LC，或LC的保留取代；

- $(X)_3$，包括例如序列LCC，或LCC的保留取代；

- $(X)_4$，包括例如序列LCCM，或LCCM、SLWM的保留取代或SLWM、SFWM的保留取代或SFWM的保留取代；

- $(X)_5$，包括例如序列LSLWM，或LSLWM、LSLWM的保留取代或LSLWM、LSFWM 的保留取代或LSFWM的保留取代；

- $(X)_6$，包括例如序列GLSLWM，或GLSLWM的保留取代；

- $(X)_7$，包括例如序列AGLSLWM，或AGLSLWM的保留取代，或

- $(X)_8$，包括例如序列MAGLSLWM，或MAGLSLWM的保留取代。

【0151】 圖5B顯示具有可變邊緣(間插肽序列)的C-端區的選擇性型式的經修飾的S蛋白的蛋白積累的倍數變化，該可變邊緣介於SARS-COV-2跨膜(TM)結構域和H5A/ Indonesia/5/05 HA胞質尾(CT)結構域、wtTM/H5iCT V1(SEQ ID NO：19，構建體8980的產物)、wtTM/H5iCT V2(SEQ ID NO：37，構建體8981的產物)、wtTM/H5iCT V3(SEQ ID NO：38，構建體 #8982的產物)和wtTM/H5iCT V4(SEQ ID NO：39， 構建體8983的產物)之間，當在植物中表現時，與參考經修飾的S蛋白的蛋白積累相比，其中冠狀病毒S蛋白的胞質尾已用H5 A/Indonesia/5/05 HA wtTM/H5iCT(SEQ ID NO：18，構建體8671的產物)的冠狀病毒S蛋白置換。所有測試的經修飾的S蛋白都顯示出蛋白積累，在選擇性型式和wtTM/H5iCT參考對照之間沒有統計學上的顯著差異。

【0152】 類似地，經修飾的S蛋白包括具有TMCT的wtTM/H5iCT V4型式的SARS-CoV-1 S蛋白(圖16A)或具有TMCT的wtTM/H5iCT V4型式的MERS S蛋白(圖19A))，當在植物中表現時，與野生型S蛋白(wtTMCT)或S蛋白(其中TMCT已用H5 A/Indonesia/5/05 HA(H5iTMCT)的TMCT置換)的蛋白積累相比，顯示增加的蛋白積累。此外，與具有野生型TMCT(wtTMCT)的OC43 CoV S-蛋白的蛋白積累相比，具有TMCT的wtTM/H5iCT V4型式的OC43 CoV S-蛋白在植物中表現

時，顯示增加的蛋白積累(圖 23A)。

【0153】 因此，經修飾的S蛋白可包括TM和CT結構域(TM/CT)，其中CT或CT的部分透過間插肽序列融合至TM或TM的部分的C端，其中間插肽序列包括序列X_n。

【0154】 此外，經修飾的S蛋白可包括TM和CT結構域(TM/CT)，其包括與SEQ ID NO：18、19、37、38、39、64、126、127、128、129、130、131、118、119、120、123、124、125、134、135、164、165、166、169、170、171、172或173的序列具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99或100%或其間任何數量的序列同一性，或序列相似性的序列。

【0155】 經修飾的S蛋白可包括CT或CT的部分，其包括與SEQ ID NO：18的胺基酸22-37、SEQ ID NO：19的胺基酸21-40、SEQ ID NO：37的胺基酸21-39 、SEQ ID NO：38的胺基酸25-36或SEQ ID NO：39的胺基酸24-34、SEQ ID NO：126的胺基酸22-37、SEQ ID NO：127的胺基酸22-36、SEQ ID NO：128的胺基酸22-37、SEQ ID NO：129的胺基酸22-37、SEQ ID NO：130的胺基酸22-37或SEQ ID NO：131的胺基酸22-37具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性，或序列相似性的序列。

【0156】 經修飾的S蛋白可包括TM或TM的部分，其包括與SEQ ID NO：18的胺基酸1-20、SEQ ID NO：19的胺基酸1-20、SEQ ID NO：37的胺基酸1-20、SEQ ID NO：38的胺基酸1-24、SEQ ID NO：39的胺基酸1-23、SEQ ID NO：118的胺基酸1-21、SEQ ID NO：119的胺基酸1-23、SEQ ID NO：123的胺基酸1-22、SEQ ID NO：124的胺基酸1-24、SEQ ID NO：164的胺基酸1-21、SEQ ID NO：165的胺基酸1-23、SEQ ID NO：169的胺基酸1-20或SEQ ID NO：170的胺基酸1-22具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性，或序列相似性的序列。此外，如本文所述

的經修飾的S蛋白可包括TM或TM的部分，其包括與SEQ ID NO：132或133的序列具有80%至100%同一性。

【0157】 此外，經修飾的S-蛋白可包括與SEQ ID NO：5、59、60、61、62、95、96、97、108、109或110的序列具有70%至100%的序列同一性或序列相似性，例如經修飾的S蛋白可包括與SEQ ID NO：5、59、60、61、62、95、96、97、108、109或110的序列具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性，或序列相似性的序列。

【0158】 病毒結構蛋白例如冠狀病毒S蛋白的胞質尾結構域(CT)或CT的部分可以用來自流感血球凝集素(HA)的CT或CT的部分置換，如下所述，由此產生的蛋白被稱為經修飾的病毒結構蛋白。因此，其中原生CT或原生CT的部分已用來自HA的CT或CT的部分置換的冠狀病毒S蛋白可稱為經修飾的冠狀病毒S-蛋白或經修飾的S-蛋白。如上所述，HA CT或HA CT的部分可直接地融合到冠狀病毒TM結構域的N末端，也可透過間插肽序列融合到冠狀病毒TM或TM的部分的N末端。因此，HA CT或HA CT的部分可透過間插肽序列融合到S-蛋白TM或S-蛋白TM的部分的C末端。

【0159】 流感「血球凝集素」或「HA」是同型三聚體膜第I型醣蛋白，通常包括訊號肽、HA1結構域和HA2結構域，其包括位於C端處的跨膜錨定位點和小的胞質尾(例如參見圖1C和圖 2)。來自各種流感病毒株的HA的胺基酸序列是本領域中所周知的。此外，編碼HA的胺基酸序列和核苷酸序列是眾所周知的且是可用的，例如，參見BioDefence Public Health base(流感病毒；參見URL：biohealthbase.org)或國家生物技術資訊中心(參見URL：ncbi. nlm.nih.gov)，兩者均藉由引用併入本文。來自不同流感病毒株的HA胞質尾結構域的示例性胺基酸序列顯示於圖2。

【0160】 雖然不同的參考文獻和團體為HA的CT給定了不同的長度，但已有顯示CT的N端序列在來自不同流感亞型和病毒株的HA中是保守的，且至少5個

殘基對於13種HA亞型中的至少10種具有序列同一性(Simpson and Lamb 1992, Journal of Virology, 790-803)。圖2顯示來自示例性流感病毒株的胺基酸序列與HA蛋白N端部分中的保守性序列的比對。流感胞質尾(CT)結構域的共通序列為：

XXWMCSNGSXXCXICI (SEQ ID NO：15) (亦參見圖 2，SEQ ID NO：14的C-端)

【0161】 對應於HA胞質尾結構域共通序列的CT序列可直接地或透過如上所述的間插肽序列(連接子序列)融合到冠狀病毒S蛋白的TM的C末端。

【0162】 此外，位於原生流感HA TM/CT邊界的N-端或C-端的胺基酸殘基亦可包括在CT序列中，該序列直接地或透過間插肽序列融合到經修飾的冠狀病毒S蛋白的TM或TM的部分。

【0163】 因此，CT或CT的部分的序列可以例如開始於對應於SEQ ID NO：14的胺基酸30-40中的任一個的胺基酸殘基。因此，CT序列的N-端可以是對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸30-40中任一個的胺基酸。在一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13 或 14中的胺基酸30的胺基酸殘基處。在另一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸31的胺基酸殘基處。在進一步實例中，CT序列可以開始於對應於SEQ ID NO： 6、7、8、9、12、13 或14的胺基酸32的胺基酸殘基處。在另一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸33的胺基酸殘基處。在進一步實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸34的胺基酸殘基處。在另一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸35的殘基處。在進一步實例中，CT序列可以開始於對應於SEQ ID NO：6-13或14的胺基酸36的胺基酸殘基處。在另一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸37的胺基酸殘基處。在進一步

實例中，CT序列可以開始於對應於SEQ ID NOs：6-13或14的胺基酸38的胺基酸殘基處。在另一個實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸39的胺基酸殘基處。在進一步實例中，CT序列可以開始於對應於SEQ ID NO：6、7、8、9、10、11、12、13或14的胺基酸40的胺基酸殘基處。

【0164】經修飾的S蛋白的胞質尾(CT)或CT的部分可以源自任何一種流感類型、亞型或病毒株的血球凝集素(HA)的CT或CT的部分。例如，CT可以源自A型流感或B型流感的HA。例如，CT可以源自流感亞型H1、H2、H3、H4、H5、H6、H7、H8、H9、 H10、H11、H12、H13、H14、H15 或 H16的HA。CT可以例如源自亞型H1、H2、H3、H5、H6、H7或H9的HA。此外，CT或CT的部分可以源自B型流感的HA。B型流感可以源自B/Yamagata或B/Victoria譜系。

【0165】例如，經修飾的S蛋白的CT或CT的部分可以源自血球凝集素(HA)流感H1、H3、H5、H6、H7、H9或B病毒株的CT。可衍生HA CT的流感病毒株的非限制性實例是流感H1 California/7/2009、H2 A/Singapore/1/1957、H3 A/Minnesota/41/2019、H5 A/Indonesia/5/05、H6 A/Teal/Hong Kong/W312/97、H7 A/Guangdong/17SF003/2016、H9 A/Hong Kong/1073/99或B/Washington/02/2019。HA CT的胺基酸序列的非限制性實例顯示於圖2中。

【0166】如圖4A所示，當SARS-CoV-2 S蛋白的原生胞質尾(CT)用來自流感HA H1 California/7/2009 (H1 Calif)、H3 A/Minnesota/41/2019 (H3 Minn)、H6 A/Teal/Hong Kong/W312/97 (H6 HK)、H7 A/Guangdong/17SF003/2016 (H7 Guan)、H9 A/Hong Kong/1073/99 (H9 HK)或B/Washington/02/2019 (B Wash)置換時，與具有來自H5 A/Indonesia/5/05 (H5 Indo)的CT的SARS-CoV-2 S相比，這些經修飾的SARS-CoV-2 S蛋白觀察到類似的蛋白積累倍數變化。西方墨點法分析證實這些觀察結果(參見圖4B和圖4C)。

【0167】當SARS-CoV-1 S蛋白的原生胞質尾(CT)、MERS S蛋白的原生CT

或OC43 CoV S蛋白的原生CT用來自流感HA H1 California/7/2009 (H1cCT)的CT置換時，獲得類似的結果(參見圖16A、圖19A和圖23A)。

【0168】 因此，胞質尾結構域(CT)或CT的部分可與具有SEQ ID NO：15的序列，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸30-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸31-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸32-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸33-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸35-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸36-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸37-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸39-50，或具有SEQ ID NO：6、7、8、9、10、12、13、14的胺基酸40-50，或具有SEQ ID NO：11的胺基酸31-49，或具有SEQ ID NO：11的胺基酸34-49，或具有SEQ ID NO：11的胺基酸32-49，或具有SEQ ID NO：11的胺基酸33-49，或具有SEQ ID NO：11的胺基酸36-49，或具有SEQ ID NO：11的胺基酸37-49，或具有SEQ ID NO：11的胺基酸38-49，或具有SEQ ID NO：11的胺基酸39-49，或具有SEQ ID NO：3的胺基酸548-568，或具有SEQ ID NO：3的胺基酸549-568，或具有SEQ ID NO：3的胺基酸550-568，或具有SEQ ID NO：3的胺基酸551-568，或具有SEQ ID NO：3的胺基酸552-568，或具有SEQ ID NO：3的胺基酸553-568，或具有SEQ ID NO：3的胺基酸554-568，或具有SEQ ID NO：3的胺基酸557-568，或具有SEQ ID NO：3的胺基酸558-568具有約70、75、80、85、86、87、88、89、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性，或序列相似性。

【0169】 此外，經修飾的S-蛋白可包括與具有SEQ ID NO：5、53、54、55、56、57或58的序列從70%至100%的序列同一性或序列相似性，例如經修飾的S蛋白可包括與具有SEQ ID NO：5、53、54、55、56、57或58的序列或具有SEQ ID NO：53的胺基酸25-1259、SEQ ID NO：54的胺基酸25-1259、SEQ ID NO：55

的胺基酸25-1259、SEQ ID NO：56的胺基酸25-1259、SEQ ID NO：57的胺基酸25-1259或SEQ ID NO：58的胺基酸25-1259具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性的序列。

【0170】在進一步實施方式中，經修飾的S蛋白胞外結構域及/或跨膜結構域可以從除了SARS-CoV-2 S白之外的冠狀病毒S蛋白獲得，例如從SARS-CoV-1 S蛋白、MERS-CoV S蛋白、OC43-CoV S蛋白、229E-CoV S蛋白等。

【0171】如圖16A所示，對於具有以下者之經修飾的SARS-CoV-1 S蛋白觀察到更高的蛋白積累：來自流感H5 HA的CT(H5iCT)、來自流感H1 HA的CT(H1cCT)或來自流感H5 HA的CT，其在SARS-CoV-1 TM和H5 HA CT之間具有可變邊緣(“H5iCT(V4)”)，當與來自植物粗萃取物的野生型 TMCT(wt TMCT)或經修飾的S蛋白與流感H5 HA的TMCT (H5i TMCT)的S-蛋白的蛋白積累相比。經修飾的S-蛋白組裝成高分子量結構(參見圖16B-16D)，其被證實是VLP(參見圖17A-17C)。儘管SARS-CoV-1蛋白與原生TMCT的蛋白積累量低於西方墨點法分析的檢測限，當SARS-CoV-1 S-蛋白與經修飾的TMCT及/或CT出現在相同凝膠上時(參見圖16A)，在凝膠上僅存在具有原生TMCT的SARS-CoV-1蛋白(參見圖16B)並且藉由電子顯微鏡觀察到VLP(參見圖17B)時，可以藉由西方墨點法分析檢測到訊號。

【0172】對於經修飾的MERS-CoV S蛋白獲得類似的結果(參見圖19A)。當與具有野生型TMCT(wt TMCT)或具有流感H5 HA的TMCT(H5i TMCT)的經修飾的S蛋白之S蛋白的蛋白積累相比時，觀察到具有來自流感H5 HA的CT(H5iCT)、來自流感H1 HA的CT(H1cCT)或來自流感H5 HA(具有在MERS-CoV TM與H5 HA CT之間具有可變邊緣)的CT(H5iCT (V4))的經修飾的MERS-CoV S蛋白更高的蛋白積累(參見蛋白質帶約175 kDa)。對於具有流感H1 HA CT(H1cCT)的精修飾的MERS-CoV觀察到最高的積累。在大約100 kDa處觀察到較小的條帶很可能是S蛋白的蛋白水解切割片段。不希望受理論束縛，咸信用流感HA CT置換原生CT

穩定MERS S-蛋白並減少S-蛋白的裂解。

【0173】 如圖23A進一步顯示，在表現具有原生OC43 CoV S-蛋白TMCT的OC43 CoV S-蛋白的植物中觀察到低蛋白產量。然而，當原生OC43 CoV S-蛋白TMCT用來自流感H5 HA的TMCT(H5iTMCT)、來自流感H5 HA的CT(H5iCT)、來自流感H1 HA的CT(H1cCT)或來自流感H5 HA(具有在OC43-CoV TM與H5 HA CT之間具有可變邊緣)的CT(H5iCT (V4))置換時，與具有原生TMCT的OC43 CoV S-蛋白相比時，觀察到更高的蛋白積累(參見在約150 kDa處的條帶。顯示在凝膠中的較大條帶被認為是蛋白質三聚體)。具有經修飾的229E-CoV S-蛋白觀察到類似的結果(數據未顯示)。

【0174】 此外，具有來自流感H5 HA的TMCT (H5iTMCT)、來自流感H5 HA的CT(H5iCT)或來自流感H1 HA的CT之MERS-CoV S-蛋白、OC43-CoV S-蛋白和229E-CoV S-蛋白觀察到形成VLP，如圖19B-19F、圖23B-23E和圖25A-25E所示。

【0175】 因此，本揭露提供「經修飾的病毒結構蛋白」、「病毒結構融合蛋白」或「嵌合病毒結構蛋白」，其中病毒結構蛋白的胞外結構域和跨膜結構域(TM)或TM的部分係源自冠狀病毒，而胞質尾(CT)或CT的部分係源自流感蛋白的CT。例如，胞外結構域和跨膜結構域可以源自冠狀病毒棘(S)蛋白，而胞質尾(CT)或CT的部分可以源自流感HA蛋白。經修飾的S蛋白可依序地包含i) 源自冠狀病毒S蛋白的胞外結構域(包括S1次單位和S2次單位的FP、HR1和HR2結構域)，ii) 冠狀病毒跨膜結構域(TM)或冠狀病毒TM的部分以及iii) 流感HA胞質尾結構域(CT)或HA CT的部分。因此，在經修飾的S蛋白中，CT或CT的部分與胞外結構域的TM是異源性的。類似地，經修飾的S蛋白的TM(和胞外結構域)與CT是異源性的。胞外結構域和跨膜結構域(TM)可能源自相同冠狀病毒(即胞外結構域和TM可彼此為同源性的)或胞外結構域可以源自第一冠狀病毒且TM可以源自第二冠狀病毒(即胞外結構域和TM 彼此為異源性的)。

【0176】 「嵌合蛋白」或「嵌合多肽」也稱為「融合蛋白」，是指包括來自

兩個或兩個以上來源的胺基酸序列的蛋白質或多肽，例如但不限於源自第一病毒結構蛋白(例如源自冠狀病毒S蛋白的胞外結構域)胞外結構域和跨膜結構域以及源自第二病毒結構蛋白(例如源自流感HA的CT)的胞質尾(CT)，其融合為單個多肽。

【0177】 經修飾的冠狀病毒S蛋白可包括跨膜和胞質尾結構域(TMCT)，其中TMCT是嵌合TMCT。嵌合TMCT可包括跨膜結構域(TM)，其中TM或TM的部分源自冠狀病毒S-蛋白和胞質尾(CT)，其中CT或CT的部分源自流感血球凝集素(HA)蛋白。此外，嵌合TMCT可包括原生冠狀病毒S-蛋白TM、嵌合冠狀病毒S-蛋白/流感HA TM、原生流感HA CT、嵌合流感HA/冠狀病毒S-蛋白 CT或其組合。例如，經修飾的冠狀病毒S-蛋白可包括具有原生流感HA CT和嵌合TM的嵌合TMCT，其中嵌合TM包括其源自冠狀病毒S-蛋白的TM的N-端序列以及其源自流感HA蛋白的TM的C-端序列。在另一個實例中，經修飾的冠狀病毒S-蛋白可包括具有原生冠狀病毒S-蛋白TM和嵌合CT的嵌合TMCT，其中嵌合CT包括源自冠狀病毒S-蛋白的N-端序列以及源自流感HA蛋白的C-端序列。在進一步實例中，經修飾的冠狀病毒S-蛋白可包括具有嵌合TM的嵌合TMCT，其中嵌合TM包括其源自冠狀病毒S-蛋白的TM的N-端序列以及其源自流感HA蛋白和嵌合CT的TM的C-端序列，其中嵌合CT包括源自冠狀病毒S-蛋白的N-端序列以及源自流感HA蛋白的C-端序列。

【0178】 當在本揭露中提及經修飾的S-蛋白或經修飾的冠狀病毒棘(S)-蛋白時，其是指經修飾的冠狀病毒棘(S)-蛋白包括跨膜結構域(TM)或S-蛋白TM的部分以及胞質尾(CT)或CT的部分，其中CT源自流感血球凝集素(HA)蛋白，且其中TM與CT為異源性的。

【0179】 經修飾的S-蛋白可包括與SEQ ID NO：5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、155、156或157之序列具有約70%至100%的序列同

一性或序列相似性，例如，經修飾的S-蛋白可包括與SEQ ID NO：5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、155、156或157之序列，或與SEQ ID NO：47之胺基酸25-1259、SEQ ID NO：48之胺基酸25-1259、SEQ ID NO：49之胺基酸25-1259、SEQ ID NO：50之胺基酸25-1259、SEQ ID NO：51之胺基酸25-1259、SEQ ID NO：52之胺基酸25-1259、SEQ ID NO：53之胺基酸25-1259、SEQ ID NO：54之胺基酸25-1259、SEQ ID NO：55之胺基酸25-1259、SEQ ID NO：56之胺基酸25-1259、SEQ ID NO：57之胺基酸25-1259、SEQ ID NO：58之胺基酸25-1259、SEQ ID NO：59之胺基酸25-1262、SEQ ID NO：60之胺基酸25-1261、SEQ ID NO：61之胺基酸 25-1258、SEQ ID NO：62之胺基酸25-1256、SEQ ID NO：95之胺基酸25-1243、SEQ ID NO：96之胺基酸25-1240、SEQ ID NO：97之胺基酸25-1243、SEQ ID NO：108之胺基酸25-1341、SEQ ID NO：109之胺基酸25-1338、SEQ ID NO：110之胺基酸25-1341、SEQ ID NO：144之胺基酸25-1351、SEQ ID NO：145之胺基酸25-1348、SEQ ID NO：146之胺基酸25-1351、SEQ ID NO：155之胺基酸25-1159、SEQ ID NO： 156之胺基酸25-1156或 SEQ ID NO：157之胺基酸25-1159具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99或100%或其間任何數量的序列同一性，或序列相似性的序列。

【0180】經修飾的S-蛋白可進一步作為經修飾的S-蛋白前體(也稱為前體S-蛋白)產生或合成，其中S-蛋白前體包括經修飾的S-蛋白和訊號肽，其中訊號肽原產於冠狀病毒(即同源性於胞外結構域)，或者訊號肽對於胞外結構域可能是非原生的或為異源性的。在非限制性實例中，原生訊號肽可以用來自蛋白質二硫鍵異構酶(protein disulfide isomerase；PDI)的訊號肽置換。

【0181】經修飾的S-蛋白前體可包括對於胞外結構域是非原生的或為異源性的訊號肽。非原生訊號肽可置換整個原生訊號肽或可置換冠狀病毒S蛋白的一部分原生訊號肽。此外，非原生或異源性訊號肽可直接地融合到經修飾的S蛋白

的N-端，或者非原生或異源性訊號肽可用間插肽融合到經修飾的S蛋白的N-端序列。

【0182】 訊號肽(也稱為訊號序列、靶向訊號、定位訊號、定位序列、轉運肽、前導序列或前導肽)是存在於大多數新合成蛋白質的 N-端處的短肽，其註定走向分泌路徑。訊號肽負責將蛋白質靶向內膜系統，包括內質網和高基氏體，於此處它被位於內質網(ER)腔內的訊號肽酶共轉譯地去除並產生成熟的蛋白質。由於用於鑑定靶向序列的實驗方法費時費力，因此發展出預測靶向訊號的不同計算方法，且在本領域中是眾所周知的。訊號肽一般具有較低的序列相似性，但會分享一些特性特徵。為了預測訊號序列及其切割位點，已經發發出許多考慮這些特性特徵的預測方法，例如SignalP(Bendtsen et al., J Mol Biol. 2004 Jul 16;340(4):783-95.; Petersen et al., Nature Methods volume 8, pages785–786(2011), Signal-CF (Chou and Shen, Biochem Biophys Res Commun. 2007 Jun 8;357(3):633-40)，及 Signal-BLAST(Frank and Sippl, Bioinformatics, 2008 Oct 1;24(19):2172-6)，在此藉由引用併入本文中。

【0183】 使用SignalP預測程式，在對應於SEQ ID NO：1之序列的序列的位置15和16之間預測出SARS-CoV-2 S蛋白的訊號肽切割位點。然而，SARS-CoV-2 S蛋白的訊號肽切割位點可被預測或出現在對應於SEQ ID NO：1之序列的序列的其他連續位置之間。例如，SARS-CoV-2 S蛋白的訊號肽切割位點也被預測或可能出現在對應於SEQ ID NO：1之序列的序列的位置13和14之間。

【0184】 原生SARS-CoV-2 S蛋白的N-端區(包括原生訊號肽序列)如下所示：

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNS (SEQ ID NO：63)

【0185】 預測的訊號肽序列(SP)加下劃線。灰色陰影的序列對應於表2中描述的序列。成熟的SARS-CoV-2 S蛋白的第一個胺基酸殘基可為纈胺酸(V)，其位置指定為1(+1)，對應於V16前體S蛋白(具有原生訊號肽的原生SARS-CoV-2 S蛋白)。成熟SARS-CoV-2 S蛋白的第一個胺基酸殘基可在SEQ ID NO：1或SEQ ID

NO：63的其他殘基處，如表2所示。例如，成熟SARS-CoV-2 S蛋白的第一個胺基酸殘基可為麩胺酸(Q)，其位置指定為14 (-2)。

[表2] 訊號肽(SP)切割位點周圍的SARS-CoV-2 S蛋白序列部分。殘基編號要不是來自包含原生信號肽的N-端(#具有SP)，就是來自位置V1處的預測切割位點(#不具有SP)，其相當於包含訊號肽的序列中的V16(前體S蛋白)。

	S	**S**	**Q**	**C**	**V**	**N**	**L**	**T**	**T**	**R**	**T**
#_具有_SP	12	13	14	15	16	17	18	19	20	21	22
#_沒有_SP*	-4	-3	-2	-1	1	2	3	4	5	6	7

*成熟蛋白質

【0186】 用於定向表現的蛋白質或多肽的位置到質外體的訊號肽或肽序列包括但不限於原生(就蛋白質而言)訊號或前導序列，或異源性訊號序列，例如但不限於，水稻澱粉酶訊號肽(McCormick 1999, Proc Natl Acad Sci USA 96:703-708)或蛋白質二硫鍵異構酶(PDI)訊號肽。因此，如本文所述，經修飾的S蛋白可作為包含經修飾的S蛋白和異源性胺基酸訊號肽序列的前體蛋白產生。例如，經修飾的S蛋白前體可包括來自蛋白質二硫鍵異構酶的訊號肽(PDI SP；登錄號Z11499的核苷酸32-103)。

【0187】 因此，本揭露亦提供包括經修飾的S-蛋白和原生或非原生訊號肽的經修飾的S蛋白的前體的蛋白、以及編碼所述蛋白的核酸。

【0188】 經修飾的病毒結構蛋白可為經修飾的S蛋白，其中經修飾的S蛋白是單體或單鏈經修飾的S蛋白。單體或單鏈經修飾的S蛋白可包括S1結構域(次單位)和S2結構域(次單位)，其中S2結構域(次單位)已經修飾以用流感HA蛋白的CT置換S蛋白的原生CT，且其中經修飾的S蛋白是單個連續的多肽鏈。單體或單鏈經修飾的S蛋白可三聚化以形成三聚體，稱為三聚體經修飾的S蛋白。三聚體是由三個通常非共價結合的蛋白質形成的大分子複合物。

【0189】 S蛋白在保留的活化切割位點被切割成2條多肽鏈，即S1次單位和S2次單位，其仍然與在同源三聚體中作為S1/S2單元體相關聯。不希望受理論束

縛，將S蛋白切割成次單位對於病毒感染性可能很重要，但對於蛋白質的三聚化可能不是必需的。

【0190】 經修飾的S蛋白可進一步包括一個或多於一個的取代、置換或突變。例如，經修飾的S蛋白可在胞外結構域中包括一個或多於一個的取代、置換或突變，以增加表現、產量、穩定性，或增加經修飾的S蛋白在合適的表現系統中的表現、產量和穩定性。

【0191】 例如，經修飾的S蛋白可包括對S1/S2及/或S2'蛋白酶切割位點的取代或突變，以防止在這些位點處的蛋白酶切割。因此，當在宿主或宿主細胞中產生時，經修飾的S蛋白不會被切割成單獨的S1次單位和S2次單位或多肽鏈。

【0192】 經修飾的病毒結構蛋白，例如經修飾的S蛋白，可進一步組裝成經修飾的病毒結構蛋白的三聚體。因此進一步提供包括如本文所述的經修飾的S蛋白的冠狀病毒蛋白三聚體。三聚體可包括單鏈經修飾的S蛋白，其中單鏈經修飾的S蛋白包括S1次單位和S2次單位，其中S2次單位的CT已用流感血球凝集素(HA)的CT置換。

【0193】 三聚體可進一步穩定在融合前構形。經修飾的病毒結構蛋白，例如經修飾的S蛋白，因此可進一步包括一個或多於一個的取代、置換或突變，以抑制S蛋白從融合前構形到融合後構形的構形變化，從而穩定融合前構形中的S蛋白或S蛋白三聚體。

【0194】 「胺基酸取代」或「取代」是指用不同的胺基酸置換蛋白質的胺基酸序列中的胺基酸。術語胺基酸、胺基酸殘基或殘基在本揭露中可互換使用。一個或多個胺基酸可在此位置處用不同於原始或野生型胺基酸的一個或多個胺基酸置換或取代，而不改變蛋白質的胺基酸序列的總長度。

【0195】 例如，經修飾的病毒結構蛋白，例如經修飾的S蛋白，可藉由脯胺酸取代、允許形成二硫鍵和鹽橋的取代及/或空腔填充取代來穩定。

【0196】 Hsieh等人(Science 2020, 369 p.1501-1505，藉由引用併入本文)在哺

乳動物細胞中設計並表現出多種SARS-CoV-2棘蛋白變體。具有六個脯胺酸取代的S蛋白變體，稱為HexaPro，與僅具有雙脯胺酸取代的變體相比，其表現量比S蛋白高9.8倍，Tm升高約5°C，並在哺乳動物細胞株中保留三聚體融合前構形。Hsieh等人認為HexaPro變體是最好的變體。

【0197】 在本揭露，用對應於SEQ ID NO：2的位置802、927、971和972(“4P”)的四個脯胺酸取代和在位置923處的額外單個胺基酸取代的組合觀察到最高的產量。此外，用對應於位置802、877、884、927、971和972(“6P”)的六個脯胺酸取代和在位置923處的額外單個胺基酸取代的組合也觀察到較高的產量。

【0198】 如本文所提供的，經修飾的S蛋白可進一步包括一個或多於一個的取代、置換或突變以增加宿主或宿主細胞中經修飾的蛋白的穩定性、產量、或穩定性和產量，例如在植物或植物細胞中。

【0199】 如本文所述的經修飾的S蛋白可在其胺基酸序列中在對應於如下所述的參考序列中的胺基酸的任一個或多個胺基酸處包括一個或多於一個的突變、修飾或取代。

【0200】 「對應胺基酸」、「對應於胺基酸」或「對應於序列」等是指胺基酸(或核苷酸)對應與參考冠狀病毒序列在序列比對中的胺基酸(或核苷酸)，如下所述。冠狀病毒序列中相應的胺基酸位置可藉由與冠狀病毒S蛋白的已知序列比對來確定。用於比較的序列比對之方法是本領域中周知的並在以下進一步描述。對應胺基酸的實例顯示在表3中。

【0201】 [表3] 冠狀病毒S蛋白中對應胺基酸/殘基位置的位置。(指定出參考序列)。

	S-蛋白中的胺基酸位置(參考指定序列)								
SARS-CoV-2[1] (SEQ ID NO： 2)	667	668	670	802	877	884	927	971	972
SARS-CoV-2[2] (SEQ ID NO： 1)	682	683	685	817	892	899	942	986	987
SARS-CoV-1[1]	651	652	654	786	861	868	911	955	956

	S-蛋白中的胺基酸位置(參考指定序列)								
(SEQ ID NO： 114)									
SARS-CoV-1[2] (SEQ ID NO： 112)	664	665	667	799	874	881	924	968	969
MERS-CoV[1] (SEQ ID NO： 115)	730	731	733	872	949	956	999	1043	1044
MERS-CoV[2] (SEQ ID NO： 113)	747	748	750	889	966	973	1016	1060	1061
OC43-CoV[1] (SEQ ID NO： 160)	748	749	751	898	N/A	976	1019	1063	1064
OC43-CoV[2] (SEQ ID NO： 158)	762	763	765	912	N/A	990	1033	1077	1078
229E-CoV[1] (SEQ ID NO： 161)	551	552	554	675	N/A	754	811	855	856
229E-CoV[2] (SEQ ID NO： 159)	567	568	570	691	N/A	770	827	871	872

1 編號排除訊號肽 (SP)

2 編號包括訊號肽 (SP)

【0202】 例如，經修飾的S蛋白可在HR1結構域與中心螺旋結構域之間的邊界處或附近具有一個或多於一個(例如兩個連續的)脯胺酸取代，其穩定融合前構形中的S胞外結構域三聚體，如(例如)WO 2018/081318中所述，其藉由引用併入本文中。此外，一個或多於一個的取代可限制及/或可防止在S1和S2次單位之間的切割位點處的加工或切割。

【0203】 經修飾的S蛋白可在如表3中所示的位置處包括一個或多於一個的取代。例如，經修飾的S蛋白可在其對應於SEQ ID NO：2的參考序列(SARS-CoV-2)中的位置667、668、670、802、877、884、923、927、971、972或其組合的位置處包括一個或多個的取代。SARS-CoV-1、MERS-CoV、OC43-CoV和229E-CoV在S蛋白中的對應位置如表3所示。其他冠狀病毒S蛋白中的對應胺基酸位置可藉由本領域中已知的方法確定。

[GSAS - 2P (971和972)]

【0204】 例如，經修飾的S蛋白可在一個或多於一個的胺基酸處具有一個或

多於一個的取代，所述胺基酸在對應於在SEQ ID NO：2的胺基酸序列的位置667、668、670、971或972處的胺基酸。

【0205】 在一個態樣中，經修飾的S蛋白可包括對應於位置667、668、670或其組合(根據SEQ ID NO：2編號)的取代、修飾或突變。例如，對應於位置667的胺基酸可為甘胺酸(G)的取代或甘胺酸(G)的保留取代，對應於位置668的胺基酸可為絲胺酸(S)的取代或絲胺酸(S)的保留取代，且對應於位置670的胺基酸可為絲胺酸(S)的取代或絲胺酸(S)的保留取代。

【0206】 經修飾的S蛋白可進一步包括對應於位置971、972或在位置971和972處(根據SEQ ID NO：2編號)的取代、修飾或突變。例如，對應於位置971及/或972的胺基酸可為脯胺酸(P)的取代或脯胺酸(P)的保留取代。

【0207】 經修飾的S蛋白可包括一個或多於一個的取代，其中該一個或多於一個的取代包括對應於在SEQ ID NO：2的位置667、668、670、971、972處的胺基酸的一個或多於一個的胺基酸的取代，或由在SEQ ID NO：2的位置667、668、670、971、972處的胺基酸的一個或多於一個的胺基酸組成。具有一個或多個一個的取代的經修飾的S蛋白可在融合前構形中穩定。此外，經修飾的S蛋白可形成在融合前構形中穩定的三聚體。

【0208】 例如，經修飾的S蛋白可包括以下取代(根據SEQ ID NO：2編號)：R667G、R668S、R670S(本文稱為“GSAS”)。經修飾的S蛋白可亦具有以下取代(依據SEQ ID NO：2編號)：K971P和V972P(本文中稱為“2P”)。此外，經修飾的S蛋白可具有以下取代(根據SEQ ID NO：2編號)：R667G、R668S、R670S、K971P和V972P(本文稱為“GSAS-2P”)。

【0209】 例如，經修飾的S蛋白可與SEQ ID NO：47序列的胺基酸序列或與SEQ ID NO：47的胺基酸 25-1259 具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的胺基酸序列，序列同一性或序列相似性，其中所述胺基酸序列在位置667處具有甘胺酸(G)或甘胺酸(G)的保

留取代、在位置668處的絲胺酸(S)或絲胺酸(S)的保留取代、在位置670處的絲胺酸(S)或絲胺酸(S)的保留取代、在位置971和972處的脯胺酸(P)或脯胺酸(P)的保留取代，其中經修飾的S蛋白，在表現時，形成VLP。

【0210】 在另一個實例中，經修飾的S蛋白可在一個或多於一個的胺基酸處具有一個或多於一個的取代，所述胺基酸對應於SEQ ID NO：114的胺基酸序列的位置654、955或956處的胺基酸或對應於SEQ ID NO：115的胺基酸序列的位置730、733、1043或1044處的胺基酸。

【0211】 例如，經修飾的S蛋白可包括以下取代：R654A(依據SEQ ID NO：114編號)或R730A及/或R733G(依據SEQ ID NO：115編號)。經修飾的S蛋白可亦具有以下取代：K955P及/或V956P(依據SEQ ID NO：114編號)或V1043P及/或L1044P(依據SEQ ID NO：115編號)。此外，經修飾的S蛋白可具有以下取代：R654A、K955P和V956P(根據SEQ ID NO：114編號)或R730A、R733G、V1043P、L1044P(根據SEQ ID NO：115編號)。

[GSAS-4P (802、927、971和972)]

【0212】 經修飾的S蛋白可進一步在對應於位置667、668和670處的胺基酸的胺基酸處具有取代，並且在對應於位置802、927、971和972(根據SEQ ID NO：2編號)的一個或多於一個的殘基處進一步具有一個或多於一個個取代。例如，對應於位置802、927、971和972處的胺基酸可為脯胺酸(P)的取代或脯胺酸(P)的保留取代。

【0213】 如圖11A所示，具有「GSAS」修飾和以下修飾的經修飾的S蛋白：F802P、A927P、K971P、V972P(稱為「GSAS-4P」，由構建體8953表現)顯示與「GSAS-2P」S 蛋白(從構建體8671表現)的產量相比，經修飾的S蛋白的產量增加2.47倍。

【0214】 因此，經修飾的S蛋白可包括一個或多於一個的取代，其中該一個或多於一個的取代包括或由對應於在SEQ ID NO：2的位置667、668、670、802、

927、971和 972處的胺基酸的胺基酸的一個或多於一個的取代組成。

【0215】 例如，經修飾的S蛋白可具有與SEQ ID NO：48的胺基酸序列或與SEQ ID NO：48的胺基酸25-1259具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量，序列同一性或序列相似性的胺基酸序列，其中該胺基酸序列在位置667處具有甘胺酸(G)或甘胺酸(G)的保留取代、在位置668處具有絲胺酸(S)或絲胺酸(S)的保留取代、在位置670處具有絲胺酸(S)或絲胺酸(S)的保留取代、在位置802、927、971和972處具有脯胺酸(P)或脯胺酸(P)的保留取代，其中該經修飾的S蛋白，在表現時，形成VLP。

【0216】 在另一個實例中，經修飾的S蛋白可在一個或多於一個的胺基酸處具有一個或多於一個的取代，該胺基酸對應於在SEQ ID NO：14的胺基酸序列的位置654、786、911、955或956處的胺基酸或對應於在SEQ ID NO：115的胺基酸序列的位置730、733、872、999、1043或1044處的胺基酸。

【0217】 例如，經修飾的S蛋白可包括以下取代：R654A(依據SEQ ID NO：114編號)或R730A及/或R733G(依據SEQ ID NO：115編號)。經修飾的S蛋白還可亦具有以下取代：F786P、S911P、K955P及/或V956P(依據SEQ ID NO：114編號)或A872P、N999P、V1043P及/或L1044P(依據SEQ ID NO：115編號)。此外，經修飾的S蛋白可具有以下取代：R654A、F786P、S911P、K955P和V956P(依據SEQ ID NO：114編號)或R730A、R733G、A872P、N999P、V1043P、L1044P(依據SEQ ID NO：1145編號)。

[GSAS-6P (802、877、884、927、971和972)]

【0218】 經修飾的S蛋白可進一步在對應於在位置667、668和670處的胺基酸的胺基酸處具有取代，並且進一步在對應於在位置802、877、884、927、971和972(依據SEQ ID NO：2編號)的一個或多於一個的殘基處具有一個或多於一個的取代。例如，對應於在位置802、877、884、927、971和972的胺基酸可為脯胺酸(P)的取代或脯胺酸(P)的保留取代(依據SEQ ID NO：2編號)。

【0219】 如圖11A所示，具有「GSAS」修飾和以下修飾的經修飾的S蛋白：F802P、A877P、A884P、A927P、K971P、V972P(稱為「GSAS-6P」，從構建體8940表現)顯示與「GSAS-2P」S 蛋白(從構建體8671表現)的產量相比，S蛋白的產量增加2.11倍。

【0220】 因此，經修飾的S蛋白可包括一個或多於一個的取代，其中該一個或多於一個的取代包括或由對應於在SEQ ID NO：2的位置667、668、670、802、877、884、927、971和972處的胺基酸的胺基酸的一個或多於一個的取代組成。

【0221】 例如，經修飾的S蛋白可具有與SEQ ID NO：49的胺基酸序列或與SEQ ID NO：48的胺基酸25-1259具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100% 或其間任何數量的序列同一性或序列相似性的胺基酸序列，其中該胺基酸序列在位置667處具有甘胺酸(G)或甘胺酸(G)的保留取代、在位置668處具有絲胺酸(S)或絲胺酸(S)的保留取代、在位置670處具有絲胺酸(S)或絲胺酸(S)的保留取代、在位置802、802、877、884、927、971 和972處具有脯胺酸(P)或脯胺酸(P)的保留取代，其中經修飾的S蛋白，在表現時，形成VLP。

【0222】 在另一個實例中，經修飾的S蛋白可在一個或多於一個的胺基酸處具有一個或多於一個的取代，該胺基酸對應於在SEQ ID NO：114的胺基酸序列的位置654、786、861、868、911、955或956處或在SEQ ID NO：115的胺基酸序列的位置730、733、872、949、956、999、1043或1044處的胺基酸。

【0223】 例如，經修飾的S蛋白可包括以下取代：R654A(依據SEQ ID NO：114編號)或R730A及/或R733G(依據SEQ ID NO：115編號)。經修飾的S蛋白可亦具有以下取代：F786P、A861P、A868P、S911P、K955P及/或V956P(依據SEQ ID NO：114編號)或A872P、S949P、A956P、N999P、V1043P及/或V1044P(依據SEQ ID NO：115編號)。此外，經修飾的S蛋白可具有以下取代：R654A、F786P、A861P、A868P、S911P、K955P和V956P(依據SEQ ID NO：114編號)或R730A、R733G、

A872P、S949P、A956P、N999P、V1043P和L1044P(依據SEQ ID NO：115編號)。

[在位置923處的取代]

【0224】 如本文所述的經修飾的S蛋白可進一步包括對應於位置923(依據SEQ ID NO：2編號)的取代、修飾或突變。例如，對應於位置923的胺基酸可為苯丙胺酸(F)的取代或苯丙胺酸(F)的保留取代。

【0225】 如圖11B所示，具有「GSAS-2P」修飾和L923F取代(從構建體8933表現)的經修飾的S蛋白顯示與沒有L923F取代(由構建體8671表現)的「GSAS-2P」S蛋白的產量相比，S蛋白的產量增加1.36倍。具有「GSAS-4P」修飾和L923F取代(從構建體8960表現)的經修飾的S蛋白顯示與沒有L923F取代(由構建體8671表現)的「GSAS-2P」S蛋白的產量相比，經修飾的S蛋白的產量增加2.88倍。具有「GSAS-6P」修飾和L923F取代(從構建體8947表現)的經修飾的S蛋白顯示與沒有L923F取代(由構建體8671表現)的「GSAS-2P」S蛋白的產量相比，增加2.47倍的產量。

【0226】 因此，經修飾的S蛋白可包括一個或多於一個的取代，其中該一個或多於一個的取代包括或由對應於在SEQ ID NO：2的位置667、668、670、927、971、972、802、877、884、923處或其組合的胺基酸的胺基酸的一個或多於一個的取代。例如，經修飾的S-蛋白可包含一個或多於一個的取代，其中該一個或多於一個的取代包括或由一個或多於一個的基酸取代組成，該胺基酸對應於SEQ ID NO：2(GSAS-2P-923)的位置667、668、670、971、972、923或其組合的胺基酸，SEQ ID NO：2(GSAS-4P-923)的位置667、668、670、927、971、972、802、923或其組合的胺基酸，或SEQ ID NO：2(GSAS-6P-923)的位置667、668、670、927、971、972、802、877、884、923或其組合的胺基酸。

【0227】 例如，經修飾的S蛋白可包括一個或多於一個的取代，其中該一個或多於一個的取代包括對應於以下位置處的胺基酸的胺基酸的一個或多於一個的取代或由其組成：

- SEQ ID NO：2 (GSAS-2P-923)的位置667、668、670、971、972和923，

- SEQ ID NO：2 (GSAS-4P-923)的位置667、668、670、927、971、972、802和923，或

- SEQ ID NO：2 (GSAS-6P-923)的位置667、668、670、927、971、972、802、877、884 和 923。

【0228】 例如，經修飾的S蛋白可具有與以下胺基酸序列具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性的胺基酸序列：SEQ ID NO：50的胺基酸序列或SEQ ID NO：50的胺基酸25-1259，其中該胺基酸序列在位置667處具有甘胺酸(G)或甘胺酸(G)的保留性取取代、在位置668和670處的絲胺酸(S)或絲胺酸(S)的保留取代、在位置971和972處的脯胺酸(P)或脯胺酸(P)的保留取代和在位置823處的苯丙胺酸(F)或苯丙胺酸(F)的保留取代；SEQ ID NO：51或SEQ ID NO：51的胺基酸25-1259，其中該胺基酸序列具有在位置667處的甘胺酸(G)或甘胺酸(G)的保留取代，在位置668和670處的絲胺酸(S)或絲胺酸(S)的保留取代，在位置927、971、972和802處的脯胺酸(P)或脯胺酸(P)的保留取代，以及在位置923處的苯丙胺酸(F)或苯丙胺酸(F)的保留取代；或SEQ ID NO：52或SEQ ID NO：52的胺基酸25-1259，其中該胺基酸序列具有在位置667處的甘胺酸(G)或甘胺酸(G)的保留取代、在位置668和670處的絲胺酸(S)或絲胺酸(S)的保留取代、在位置927、971、972、802、877和884處的脯胺酸(P)或脯胺酸(P)的保留取代，以及在位置9223處的苯丙胺酸(F)或苯丙胺酸(F)的保留取代，其中經修飾的S蛋白在表現時形成VLP。

【0229】 因此，提供一種經修飾的冠狀病毒S-蛋白，其可包括：

1. 嵌合跨膜和胞質尾結構域 (TMCT)；

2. 與對應的野生型冠狀病毒S蛋白相比，對應於在位置667、668及/或670處(依據SEQ ID NO：2編號)的胺基酸的一個或多於一個的取代；

3. 與對應的野生型冠狀病毒S蛋白相比，對應於在位置802、877、884、927、971及/或972處(依據SEQ ID NO：2編號)的胺基酸的一個或多於一個的取代；

4. 與對應的野生型冠狀病毒S蛋白相比，對應於在位置923處(依據SEQ ID NO：2編號)的取代；或

5. 如1-4所述的修飾及/或取代的組合。

【0230】 如本文所用，術語「保留取代」或「保留取代」及其語法變體是指胺基酸與參考胺基酸(取代)不同但與描述的取代或描述的殘基(亦即，非極性殘基置換非極性殘基，芳香族殘基置換芳香族殘基，極性不帶電荷的殘基置換極性不帶電荷的殘基，帶電荷的殘基置換帶電荷的殘基)屬於相同類別的胺基酸。例如，可在Sahin-Toth等人(Protein ScL, 3:240-247, 1994)、Hochuli等人(Bio/Technology, 6:1321-1325, 1988)、Henikoff S和Henikoff JG(Proc. Natl. Acad. Sci. USA 89: 109195-109, 1992)以及廣泛使用的遺傳學和分子生物學教科書中找到有關保留取代的更多資訊。

【0231】 經修飾的病毒結構蛋白可進一步經醣基化。冠狀病毒S蛋白、冠狀病毒M蛋白和冠狀病毒E蛋白係經醣基化的，同時發生N-鏈結醣基化和O-鏈結醣基化。

【0232】 經修飾的病毒結構蛋白可包括對表現經修飾的病毒結構蛋白的宿主或宿主細胞而言為獨特的醣基化型式。例如，當在植物或植物細胞中表現時，經修飾的病毒結構蛋白可包括植物特異性N-聚醣。因此，亦提供具有植物特異性N-聚醣的經修飾的病毒結構蛋白。

【0233】 如本文所述，經修飾的病毒結構蛋白的胞質尾結構域(CT)可用來自流感血球凝集素(HA)的CT置換。如上所述的病毒結構蛋白的胞外結構域和跨膜結構域(TM)融合至流感HA胞質尾結構域(CT)，使得CT相對於病毒結構蛋白(諸如S蛋白)的胞外結構域和跨膜結構域為異源性的。經修飾的S蛋白可自組裝成病毒樣顆粒(VLP)。

【0234】因此，本說明書進一步關於病毒樣顆粒(VLP)。更具體地，本說明書係關於包括經修飾的病毒結構蛋白(例如經修飾的S蛋白)的VLP、以及在宿主或宿主細胞中製造具有經修飾的病毒結構蛋白(例如經修飾的S蛋白)的VLP的方法。VLP包括經修飾的病毒結構蛋白，例如本文所述的經修飾的S-蛋白。

【0235】如圖6C、圖17A、圖17B和圖17C所示，以經修飾的S蛋白(經修飾的SARS-CoV-2或經修飾的SARS-CoV-1 S蛋白)作為示例性的經修飾的病毒結構蛋白，其中原生或野生型CT已用來自流感HA蛋白在植物中表現時自組裝成VLP的CT置換。VLP類似於在相同植物表現系統中用具有原生TM/CT序列的S蛋白(參見圖6A和圖17A)或具有H5流感TM/CT序列的經修飾的S蛋白(參見圖6B和圖17B)製造的VLP。

【0236】此外，如圖6D、圖6E、圖6F和圖6G所示，在TM與流感CT結構域之間具有可變邊緣或邊界(間插肽序列)的經修飾的S蛋白在植物中表現時亦會自組裝成 VLP。

【0237】此外，如圖6H、圖6I、圖6J、圖6K、圖6L和圖6M所示，經修飾的S蛋白，其中原生或野生型CT已用分別來自H1、H3、H6、H7、H9和B流感的流感HA蛋白的CT置換，當在植物中表現時亦會自組裝成VLP。

【0238】此外，如圖19B-19F、圖23B-23E和圖25A-25E所示，源自MERS-CoV、OC43-CoV和229E-CoV的經修飾的S-蛋白，其中經修飾的S-蛋白具有來自流感H5 HA(H5iTMCT)的TMCT、來自流感H5 HA(H5iCT)的CT或來自流感H1 HA的CT，亦形成VLP。

【0239】術語「病毒樣顆粒」(VLP)或「多個病毒樣顆粒」或「VLPs」是指病毒樣結構，其一般在形態學和抗原性上與感染中產生的病毒體相似，但缺乏足以複製的遺傳訊息，因此是非傳染性的。VLP是自組裝的結構，且包括一種或多種結構蛋白，例如經修飾的病毒結構蛋白，例如但不限於經修飾的S蛋白。因此，VLP可包括經修飾的S蛋白。VLP可進一步包括病毒結構蛋白，其中病毒結

構蛋白由經修飾的S蛋白組成。因此，在一些實施方式中，VLP可能缺乏或不含冠狀病毒M蛋白及/或冠狀病毒E蛋白。在一些實施方式中，因此，從如本文所述的經修飾的病毒結構蛋白產生的VLP不包括冠狀病毒M蛋白、冠狀病毒E蛋白或冠狀病毒M蛋白和冠狀病毒E蛋白。此外，在一些實施方式中，VLP不包括來自與冠狀病毒科或流感病毒為異源性的病毒的結構或非結構蛋白，例如VLP不包括來自非冠狀病毒科的病毒的結構和非結構蛋白。

【0240】 在另一個實施方式中，VLP可包括冠狀病毒E蛋白、冠狀病毒M蛋白和經修飾的冠狀病毒S蛋白。在另一個實施方式中，VLP可包括冠狀病毒E蛋白和經修飾的冠狀病毒S蛋白。在另一個實施方式中，VLP可包括冠狀病毒M蛋白和經修飾的冠狀病毒S蛋白。此外，VLP可包括冠狀病毒E蛋白、經修飾的冠狀病毒M蛋白和經修飾的冠狀病毒S蛋白。VLP可進一步包括經修飾的冠狀病毒E蛋白、經修飾的冠狀病毒M蛋白和經修飾的冠狀病毒S蛋白。在另一個實施方式中，VLP可包括經修飾的冠狀病毒E蛋白和經修飾的冠狀病毒S蛋白。在另一個實施方式中，VLP可包括經修飾的冠狀病毒M蛋白和經修飾的冠狀病毒S蛋白。

【0241】 VLP可在合適的宿主或宿主細胞(包含植物和植物細胞)中產生。從宿主或宿主細胞中萃取後，在合適的條件下分離和進一步純化後，VLP可作為完整結構恢復。

【0242】 可使用任何合適的方法例如化學或生物化學萃取來純化或萃取VLP。VLP對乾燥、熱、pH、界面活性劑和清潔劑相對敏感。因此，使用最大化產量、最小化細胞蛋白質對VLP餾分的污染、保持蛋白質或VLP的完整性的方法，且如果需要，相關的脂質包膜或膜，鬆散細胞壁以釋放蛋白質或VLP的方法可能是有用的。盡量減少或消除去污劑或界面活性劑的使用，例如SDS或Triton™ X-100可能有利於改善VLP萃取的產量。然後可藉由例如電子顯微鏡(參見圖 4B)或藉由粒徑篩析層析法來評估VLP的結構和尺寸。

【0243】 對於包膜病毒，例如冠狀病毒，脂質層或膜被病毒保留可能是有利

的。脂質的組成可能依系統而異(例如，植物產生的包膜病毒將在包膜中包含植物脂質或植固醇)，並且可能有助於改善免疫反應。

【0244】 因此，在宿主或宿主細胞中產生的VLP可包括來自宿主或宿主細胞的漿膜的脂質。例如，植物中產生的VLP可包括植物來源的脂質(「植物脂質」)，昆蟲細胞中產生的VLP可包含來自昆蟲細胞的漿膜的脂質(通常稱為「昆蟲脂質」)，以及哺乳動物細胞中產生的VLP可包括來自哺乳動物細胞的漿膜的脂質(通常稱為「哺乳動物脂質」)。

【0245】 植物脂質或植物來源的脂質可以呈脂質雙層的形式，並且可進一步包括包圍VLP的包膜。植物來源的脂質可包括產生VLP的植物的漿膜的脂質組分，包括磷脂、甘油三酯、甘油二酯和甘油單酯，以及脂溶性固醇或包含固醇的代謝物。實例包括卵磷脂(PC)、磷脂醯乙醇胺(PE)、磷脂酸肌醇、磷脂醯絲胺酸、醣神經鞘脂質、植固醇或其組合。植固醇的實例包括菜油固醇、豆固醇、麥角固醇(ergosterol)、蕓苔甾醇(brassicasterol)、δ-7-豆固醇、δ-7-燕麥固醇、道諾固醇(daunosterol)、麥固醇、24-甲基膽固醇、膽固醇或β-麥固醇。如本領域中具有通常知識者所理解的，漿膜的脂質組成可隨著獲得的細胞的細胞或生物體或物種的培養或生長條件而變化。通常，β-麥固醇是最豐富的植固醇。

【0246】 不希望受理論束縛，包括植物來源的脂質的植物製造的VLP可誘導比其他製造系統中製造的VLP更強的免疫反應，並且與活疫苗或減毒全病毒疫苗誘導的免疫反應相比，這些植物製造的VLP誘導的免疫反應可能更強。

【0247】 此外，除了植物脂質存在的潛在佐劑作用之外，植物N-聚醣促進由抗原呈現細胞捕獲的醣蛋白抗原的能力可能有利於植物中VLP的產生。

【0248】 在植物內產生的VLP可包括經修飾的病毒結構蛋白，其包括植物特異性N-聚醣。因此，本揭露亦提供包括具有植物特異性N-聚醣的經修飾的病毒結構蛋白的VLP。此外，提供包括植物脂質及具有植物特異性N-聚醣的經修飾的病毒結構蛋白的VLP。

【0249】亦提供在宿主或宿主細胞中製造包括經修飾的結構蛋白的病毒樣顆粒(VLP)的方法。此外，亦提供在宿主或宿主細胞中增加包括經修飾的結構蛋白的病毒樣顆粒(VLP)之製造的產量的方法。該方法包括將包含編碼經修飾的結構蛋白的序列的核酸導入宿主或宿主細胞，及在允許核酸表現的條件下培養宿主或宿主細胞，從而製造VLP。與表現未經修飾的病毒結構蛋白的宿主或宿主細胞相比，可以更高的產量製造經修飾的病毒結構蛋白。

【0250】例如，如圖3A所示，當病毒結構蛋白的胞質尾(CT)用流感HA的CT置換以製造經修飾的病毒結構蛋白時，例如經修飾的S蛋白，植物中表現的VLP的產量可能會增加。如圖11A和圖11B進一步所示，當經修飾的S蛋白進一步包括一個或多於一個的取代時，其中該一個多於一個的取代包括或由對應於SEQ ID NO：2的位置667、668、670、802、923、927、971及/或972處的胺基酸的胺基酸的一個或多於一個的取代，當在植物中表現時，可能進一步增加包括經修飾的S蛋白的VLP的產量。

【0251】在宿主或宿主細胞(例如植物或植物細胞)中製造的經修飾的病毒結構蛋白(例如經修飾的S蛋白)的產量或包括經修飾的病毒結構蛋白的VLP的產量，當與對應未經修飾的病毒結構蛋白的產量或包括對應未經修飾的病毒結構蛋白的VLP的產量相比時，可增加1.1-10倍，或其間的任何數量。例如，當在相同條件下在宿主或宿主細胞中製造時，與對應未經修飾的病毒結構蛋白的產量或其中VLP包括對應未經修飾的病毒結構蛋白的VLP的產量相比時，宿主或宿主細胞中經修飾的病毒結構蛋白(例如經修飾的S蛋白)的產量或VLP(包括經修飾的病毒結構蛋白)的產量可增加1.1、1.2、1.3、1.4、1.5、1.6、1.7、1.8、1.9、2、2.1、2.2、2.3、2.4、2.5、2.6、2.7、2.8、2.9、3、3.1、3.2、3.3、3,4、3.5、3.6、3.7、3.8、3.9、4、4.1、4.2、4.3、4.4、4.5、4.6、4.7、4.8、4.9、5.1、5.2、5.3、5.4、5.5、5.6、5.6、5.7、5.8、5.9、6、6.1、6.2、6.3、6.4、6.5、6.6、6.7、6.8、6.9、7、7.1、7.2、7.3、7.4、7.5、7.6、7.7、7.8、7.9、8、8.1、8.2、8.3、8.4、

8.5、8.6、8.7、8.8、8.9、9、9.1、9.2、9.3、9.4、9.5、9.6、9.7、9.8、9.9、10倍或其間任何的數量。

【0252】本文描述的經修飾的病毒結構蛋白包括具有胺基酸序列的經修飾的S蛋白，該胺基酸序列與SEQ ID NO：1、 2、 5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、112、113、114、115、144、145、146、155、 156、157、158、159、160或161，或與SEQ ID NO：47的胺基酸25-1259、SEQ ID NO：48的胺基酸25-1259、SEQ ID NO：49的胺基酸25-1259、SEQ ID NO：50的胺基酸25-1259、SEQ ID NO：51的胺基酸 25-1259、SEQ ID NO： 52的胺基酸25-1259、SEQ ID NO： 53的胺基酸25-1259、SEQ ID NO：54的胺基酸25-1259、SEQ ID NO：55的胺基酸25-1259、SEQ ID NO：56的胺基酸25-1259、 SEQ ID NO：57的胺基酸25-1259、SEQ ID NO：58的胺基酸25-1259、SEQ ID NO： 59的胺基酸25-1262、SEQ ID NO： 60的胺基酸25-1261、SEQ ID NO：61的胺基酸125-1258、SEQ ID NO：62的胺基酸25-1256、SEQ ID NO：95的胺基酸25-1243、SEQ ID NO：96的胺基酸25-1240、SEQ ID NO：97的胺基酸25-1243、SEQ ID NO： 108的胺基酸25-1341、SEQ ID NO： 109 的胺基酸25-1338、SEQ ID NO： 110的胺基酸25-1341、SEQ ID NO： 144 的胺基酸25-1351、SEQ ID NO：145的胺基酸25-1348、SEQ ID NO：146的胺基酸25-1351、SEQ ID NO： 155的胺基酸25-1159、SEQ ID NO： 156的胺基酸25-1156或SEQ ID NO： 157的胺基酸25-1159具有約 70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性，且其中該經修飾的S蛋白當在宿主或宿主細胞中表現時形成VLP。經修飾的S蛋白的胞外結構域和跨膜結構域的胺基酸序列具有與SEQ ID NO： 1的胺基酸1-1234、與SEQ ID NO： 2的胺基酸1-1219、與SEQ ID NO： 5的胺基酸1-1234、與SEQ ID NO： 21的胺基酸1-1219、與SEQ ID NO： 30的胺基酸1-1243、與SEQ ID NO： 47的胺基酸25-1243、與SEQ ID NO： 48的胺基酸25-1243、與SEQ ID NO： 49的胺

基酸25-1243、與SEQ ID NO：50的胺基酸25-1243、與SEQ ID NO：51的胺基酸25-1243、與SEQ ID NO：52的胺基酸25-1243、與SEQ ID NO：53的胺基酸25-1243、與SEQ ID NO：54的胺基酸25-1243、與SEQ ID NO：55的胺基酸25-1243、與SEQ ID NO：56的胺基酸125-1243、SEQ ID NO：57的胺基酸25-1243、SEQ ID NO：58的胺基酸25-1243、與SEQ ID NO：59的胺基酸25-1242、與SEQ ID NO：60的胺基酸25-1242、與SEQ ID NO：61的胺基酸25-1246、或與SEQ ID NO：62 的胺基酸25-1245、SEQ ID NO：95的胺基酸25-1227、SEQ ID NO：96 的胺基酸25-1227、SEQ ID NO：97的胺基酸25-1227、SEQ ID NO：108的胺基酸25-1325、SEQ ID NO：109的胺基酸25-1325、SEQ ID NO：110的胺基酸25-1325、SEQ ID NO：144的胺基酸25-1335、SEQ ID NO：145的胺基酸25-1335、SEQ ID NO：146的胺基酸25-1335、SEQ ID NO：155的胺基酸25-1143、SEQ ID NO：156的胺基酸25-1143、或SEQ ID NO：156的胺基酸25-1143、SEQ ID NO：157的胺基酸25-1143具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性，且經修飾的S蛋白的胞質尾結構域(CT)的胺基酸序列具有與SEQ ID NO：15的序列或與SEQ ID NO：6、8、7、9、10、12、13、14的胺基酸35-50或與SEQ ID NO：11的胺基酸34-49，或SEQ ID NO：3的胺基酸553-568約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性，其中經修飾的S蛋白當在宿主或宿主細胞中表現時形成VLP。

【0253】 此外，經修飾的病毒結構蛋白可由核苷酸序列編碼，該核苷酸序列與根據SEQ ID NO：22、26、29、70、71、72、73、74、75、76、77、78、79、90、91、92、95、96、97、103、104、105、139、140、141、150、151或152的核苷酸序列具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性，且其中該核苷酸序列編碼在宿主或宿主細胞中表現時形成VLP的經修飾的S蛋白。

【0254】進一步提供編碼經修飾的S蛋白的核苷酸序列，其胺基酸序列與SEQ ID NO：1、2、5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、155、156或157具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間任何數量的序列同一性或序列相似性，且其中經修飾的S蛋白當在宿主或宿主細胞中表現時形成VLP。該核苷酸序列可編碼經修飾的S蛋白的胞外結構域和跨膜結構域的胺基酸序列，其與SEQ ID NO：1的胺基酸1-1234、與SEQ ID NO：2的胺基酸1-1219、與SEQ ID NO：5的胺基酸1-1234、與SEQ ID NO：21的胺基酸1-1219或與SEQ ID NO：30的胺基酸1-1243、與SEQ ID NO：47的胺基酸25-1243、與SEQ ID NO：48的胺基酸25-1243、與SEQ ID NO：49的胺基酸25-1243、與SEQ ID NO：50的胺基酸25-1243、與SEQ ID NO：51的胺基酸25-1243、與SEQ ID NO：52的胺基酸25-1243、與SEQ ID NO：53的胺基酸25-1243、與SEQ ID NO：54的胺基酸25-1243、與SEQ ID NO：55的胺基酸25-1243、與SEQ ID NO：56的胺基酸25-1243、與SEQ ID NO：57的胺基酸25-1243、與SEQ ID NO：58的胺基酸25-1243、與SEQ ID NO：59的胺基酸25-1242、與SEQ ID NO：60的胺基酸25-1242、與SEQ ID NO：61的胺基酸25-1246、與SEQ ID NO：62的胺基酸25-1245、與SEQ ID NO：95的胺基酸25-1227、與SEQ ID NO：96的胺基酸25-1227、與SEQ ID NO：97的胺基酸25-1227、與SEQ ID NO：108的胺基酸25-1325、與SEQ ID NO：109的胺基酸25-1325、與SEQ ID NO：110的胺基酸25-1325、與SEQ ID NO：144的胺基酸25-1335、與SEQ ID NO：145的胺基酸25-1335、與SEQ ID NO：146的胺基酸25-1335、與SEQ ID NO：155的胺基酸25-1143、與SEQ ID NO：156的胺基酸25-1143、與SEQ ID NO：157的胺基酸25-1143具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間的任何數量的序列同一性或序列相似性，且經修飾的S蛋白的胞質尾結構域的胺基酸序列與SEQ ID NO：

15的序列，或與SEQ ID NO：6、8、7、9、10、12、13、14的胺基酸35-50，或與SEQ ID NO：11的胺基酸34-49，或與SEQ ID NO：3的胺基酸553-568具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、 99、100%或其間的任何數量的序列同一性或序列相似性，且其中經修飾的S蛋白當在宿主或宿主細胞中表現時形成VLP。

【0255】 進一步提供編碼經修飾的S蛋白的核苷酸序列，其胺基酸序列與SEQ ID NO：5、21、30或47-62的胺基酸序列，或與SEQ ID NO：47的胺基酸24-1259，SEQ ID NO：48的胺基酸25-1259，SEQ ID NO：49的胺基酸25-1259，SEQ ID NO：50的胺基酸25-1259，SEQ ID NO：51的胺基酸25-1259，SEQ ID NO：52的胺基酸25-1259，SEQ ID NO：53的胺基酸25-1259，SEQ ID NO：54的胺基酸25-1259，SEQ ID NO：55的胺基酸25-1259，SEQ ID NO：56的胺基酸25-1259，SEQ ID NO：57的胺基酸25-1259，SEQ ID NO：58的胺基酸25-1259，SEQ ID NO：59的胺基酸25-1262 ，SEQ ID NO：60的胺基酸25-1261，SEQ ID NO：61的胺基酸25-1258，SEQ ID NO：62的胺基酸25-1256，SEQ ID NO：95的胺基酸25-1243，SEQ ID NO：96的胺基酸25-1240，SEQ ID NO：97的胺基酸25-1243，SEQ ID NO：108的胺基酸25-1341，SEQ ID NO：109的胺基酸25-1338，SEQ ID NO：110的胺基酸25-1341，SEQ ID NO：144的胺基酸25-1351，SEQ ID NO：145的胺基酸25-1348，SEQ ID NO：146的胺基酸25-1351，SEQ ID NO：155的胺基酸25-1159，SEQ ID NO：156的胺基酸25-1156，SEQ ID NO：157的胺基酸25-1159具有約70、75、80、85、87、90、91、92、93、94、95、96、97、98、99、100%或其間的任何數量的序列同一性或序列相似性，且其中經修飾的S蛋白當在宿主或宿主細胞中表現時形成VLP。

【0256】 術語「百分比相似性」、「序列相似性」、「百分比同一性」或「序列同一性」，當提及特定序列時，例如，如威斯康星大學GCG軟體程式中的規定使用，或藉由手動比對和目視檢查(參見，例如，Current Protocols in Molecular

Biology, Ausubel et al., eds. 1995補充)。用於比較的序列比對方法是本領域中周知的。可進行用於比較的序列的最佳比對，使用例如Smith & Waterman (1981, Adv. Appl. Math. 2:482)的演算法，藉由Needleman & Wunsch (1970, J. Mol. Biol. 48:443)的比對演算法，藉由Pearson & Lipman (1988, Proc. Natl. Acad. Sci. USA 85:2444)的搜索相似性方法，藉由這些演算法(例如：Wisconsin遺傳學軟體包中的GAP、BESTFIT、FASTA和TFASTA，Genetics Computer Group (GCG), 575 Science Dr., Madison, Wis.)的電腦化實現

【0257】 適用於確定百分比序列同一性和序列相似性的演算法的一個實例是BLAST和BLAST2.0演算法，其分別描述於Altschul等人(1977, Nuc. Acids Res. 25:3389-3402)和Altschul等人(1990, J. Mol. Biol. 215:403-410)。BLAST和BLAST 2.0與本文所述的參數一起用於確定本揭露的核酸和蛋白質的百分比序列同一性。例如，BLASTN程式(用於核苷酸序列)可用於預設值字長(W)為11，期望值(E)為10，M=5，N=-4和兩條鏈的比較。對於胺基酸序列，BLASTP程式可用於預設值字長為3，期望值(E)為10，BLOSUM62評分矩陣(參見Henikoff & Henikoff, 1989, Proc. Natl. Acad. Sci. USA 89:10915)比對(B)為 50，期望值(E)為 10，M=5，N=-4，和兩條鏈的比較。用於執行BLAST分析的軟體可透過國家生物技術資訊中心公開獲得(參見URL: ncbi.nlm.nih.gov/)。

【0258】 本揭露中提及的核酸序列或核苷酸序列可為「實質上同源性」、「實質上相似」或「實質上相同」於序列，或序列的互補，如果核酸序列或核苷酸序列在嚴格雜交條件下與本文定義的一種或多於一種核苷酸序列或核酸序列或核苷酸序列的互補序列雜交。序列為「實質上同源性」、「實質上相似」或「實質上相同」，當至少約70%，或70%至100%之間，或其間的任何數量，例如70、72、74、76、78、80、82、84、86、88、90、92、94、96、98、100%或其間的任何數量的核苷酸在核苷酸序列的定義長度上匹配，限制條件為此類同源性序列呈現如本文所述的序列或編碼產物的一個或多於一個特性。

【0259】許多生物體表現出偏移使用特定密碼子來編碼特定胺基酸在生長肽鏈中的插入。密碼子偏好或密碼子偏移(生物體之間密碼子使用的差異)是由遺傳密碼的簡併性提供的，且在許多生物體當中都有很好的記錄。密碼子偏移通常與傳訊RNA(mRNA)的轉譯效率相關，而其又被認為是取決於被轉譯的密碼子的特性和特定傳遞RNA(tRNA)分子的可用性等。選定的tRNA在細胞中的優勢一般反映肽合成中最常用的密碼子。因此，基於密碼子最佳化，可定制基因以在給定生物體中進行最佳基因表現。最佳化編碼異源性表現蛋白的核苷酸序列的過程可能是改善表現產量的重要步驟。最佳化要求可能包括改善宿主生產外源蛋白質之能力的步驟。

【0260】本領域中已知有不同的密碼子最佳化技術用於改善轉譯低效的蛋白質編碼區的轉譯動力學。這些技術主要依賴於識別某些宿主生物體的密碼子使用。如果某種基因或序列應在此生物體中表現，則此類基因和序列的編碼序列將被修飾，這樣人們將用宿主生物體的更常用的密碼子置換感興趣的序列的密碼子。

【0261】「密碼子最佳化」定義為藉由用密碼子置換原生序列的至少一個、多於一個或大量的密碼子來修飾核酸序列以增強在感興趣的宿主或宿主細胞中的表現，該密碼子可能更頻繁地或最頻繁地用於另一個生物體或物種的基因中。多種物種對某些胺基酸的某些密碼子呈現出特定的偏移。

【0262】本揭露包括已經密碼子最佳化的合成多核苷酸序列，例如已經針對人類密碼子使用或植物密碼子使用進行最佳化的序列。然後可在宿主例如植物中表現密碼子最佳化的多核苷酸序列。更具體地，針對人類密碼子使用或植物密碼子使用最佳化的序列可在植物中表現。不希望受理論束縛，咸信當植物用作宿主時，針對人類密碼子最佳化的序列增加序列的鳥嘌呤-胞嘧啶含量(GC含量)並改善表現產量。

【0263】如本文所用術語「構建體」、「載體」或「表達載體」是指用於將

外源性核苷酸序列(例如編碼如本文所述經修飾的病毒結構蛋白的核苷酸序列)轉移到宿主細胞(例如植物細胞)並引導外源性核酸序列在宿主細胞中的表現。「表現卡匣」是指包含感興趣核苷酸序列的核酸，其在合適的啟動子或其他調控元件的控制下並且可操作的(或可操作地)連接至用於在宿主細胞中轉錄感興趣的核酸。本領域中具有通常知識者將理解，表現卡匣可包括終止(終止子)序列，該序列是對宿主細胞(例如植物宿主)有活性的任何序列。例如，在植物中，終止序列可以源自二分RNA病毒的RNA-2基因組片段，例如comovirus，終止序列可以是NOS終止子，或者終止子序列可以是從苜蓿色素體藍素基因的3'UTR中獲得。

【0264】 如本文所述，包括編碼經修飾的病毒結構蛋白的核苷酸序列的核酸可進一步包括增強病毒結構蛋白在宿主、宿主的部分或宿主細胞中的表現的序列。增強表現的序列可包括5' UTR增強子元件，或植物來源的表現增強子，可操作地關聯於編碼經修飾的病毒結構蛋白的核酸。亦可最佳化編碼經修飾的病毒結構蛋白的序列，藉由例如最佳化人類密碼子使用、增加的GC含量或其組合以增加表現。

【0265】 「調控區域」、「調控元件」或「啟動子」是指核酸的部分，典型但不總是在基因的蛋白質編碼區的上游，其可由DNA或RNA組成，或由DNA和RNA兩者組成。當調控區域是有活性的，且與感興趣的核苷酸序列可操作地關聯或可操作地鏈接時，這可能會導致感興趣的核苷酸序列的表現。調控元件可能能夠介導器官特異性，或控制發育或時間基因活化。「調控區域」包括啟動子元件、呈現基礎啟動子活性的核心啟動子元件、反應外部刺激可誘導型元件、介導啟動子活性的元件，例如負調控元件或轉錄增強子。如本文所用「調控區域」亦包括在轉錄後有活性的元件，例如調控基因表現的調控元件，例如翻譯和轉錄增強子、轉譯和轉錄抑制子、上游活性序列和mRNA不穩定性決定子。這些後面元件中的幾個可能位於編碼區的近端。

【0266】 在本揭露的上下文中，術語「調控元件」或「調控區域」典型是指DNA的序列，通常但不總是在結構基因的編碼序列的上游(5')，其藉由提供對RNA聚合酶及/或轉錄在特定位點處開始所需的其他因子的識別來控制編碼區的表現。然而，應理解位於內含子內或序列3'端的其他核苷酸序列也可能有助於感興趣編碼區表現的調控。提供識別RNA聚合酶或其他轉錄因子以確保在特定位點處起始的調控元件的實例是啟動子元件。大多數(但不是全部)真核啟動子元件包含TATA盒，保守核酸序列，由腺苷和胸苷核苷酸鹼基對組成，通常位於轉錄起始位點上游約25個鹼基對處。啟動子元件可包括負責轉錄起始的基礎啟動子元件、以及修飾基因表現的其他調控元件。

【0267】 有幾種類型的調控區域，包括彼等受發育調控的、可誘導型或組成型。在器官或組織發育前間的特定時間下，在某些器官或器官的組織內，在發育上受調控或控制其控制下基因的分化表現的調控區域被活化。然而，一些受發育調控的調控區域在特定發育階段下可能偏好在某些器官或組織內活化，它們也可以發育調控的方式活化，或在植物內的其他器官或組織中也處於基礎水平。組織特異性調控區域的實例，例如參見特異性調控區域，包括油菜籽啟動子和十字花科植物啟動子(Rask et al., 1998, J. Plant Physiol. 152: 595-599; Bilodeau et al., 1994, Plant Cell 14: 125-130)。葉-特異性啟動子的實例包括色素體藍素啟動子(參見US 7,125,978，其藉由引用併入本文)。

【0268】 可誘導型調控區域是能夠反應誘導子直接或間接活化一個或多個DNA序列或基因的轉錄的調控區域。在沒有誘導子的情況下，DNA序列或基因將不會被轉錄。典型地，特異性結合到可誘導型調控區域以活化轉錄的蛋白因子可以非活性形式存在，然後藉由誘導子直接或間接轉化成為活性形式。然而，蛋白因子也可能不存在。誘導子可以是化學試劑，例如蛋白質、代謝物、生長調節劑、除草劑或酚類化合物，或由熱、冷、鹽或有毒元素直接施加或透過病原體或疾病病原(諸如病毒)的作用間接施加的生理應力。可藉由將誘導子外部應

用於細胞或植物，例如藉由噴灑、澆水、加熱或類似方法，將含有誘導型調控區域的植物細胞暴露於誘導子。可誘導型調控元件可源自植物或非植物基因(例如Gatz, C. and Lenk, I.R.P., 1998, Trends Plant Sci. 3, 352-358)。潛在可誘導型啟動子的實例包括但不限於四環素可誘導型啟動子(Gatz, C.,1997, Ann. Rev. Plant Physiol. Plant Mol. Biol. 48, 89-108)、類固醇可誘導型啟動子(Aoyama, T. and Chua, N.H.,1997, Plant J. 2, 397-404)和乙醇可誘導型啟動子(Salter, M.G., et al, 1998, Plant Journal 16, 127-132; Caddick, M.X., et al,1998, Nature Biotech. 16, 177-180)、細胞分裂素可誘導型IB6和CKI1基因(Brandstatter, I. and Kieber, J.J.,1998, Plant Cell 10, 1009-1019; Kakimoto, T., 1996, Science 274, 982-985)、和生長素可誘導元件DR5(Ulmasov, T., et al., 1997, Plant Cell 9, 1963-1971)。

【0269】 組成型調控區域引導基因在整個植物的多個部分並在整個植物發育過程中的持續表現。已知組成型調控元件的實例包括與CaMV 35S轉錄本相關的啟動子(p35S; Odell et al., 1985, Nature, 313: 810-812，其併入本文作為參考)，水稻肌動蛋白1(Zhang et al, 1991, Plant Cell, 3: 1155-1165)，肌動蛋白2(An et al., 1996, Plant J., 10: 107-121)，或tms 2(US 5,428,147)，以及磷酸丙糖異構酶1(Xu et. al., 1994, Plant Physiol. 106: 459-467)基因，玉米泛素1基因(Cornejo et al, 1993, Plant Mol. Biol. 29: 637-646)，阿拉伯芥泛素1和6基因(Holtorf et al, 1995, Plant Mol. Biol. 29: 637-646)，煙草轉譯起始因子4A基因(Mandel et al, 1995 Plant Mol. Biol. 29: 995-1004)，木薯靜脈花葉病毒啟動子，pCAS(Verdaguer et al., 1996)，核酮糖雙磷酸羧化酶的小次單位的啟動子，pRbcS：(Outchkourov et al., 2003)，pUbi(用於單子葉植物和雙子葉植物)。

【0270】 如本文所用，術語「組成型」不一定表示在組成型調控區域的控制下的核苷酸序列在所有細胞類型中以相同水平表現，而是該序列在廣範圍的細胞類型中表現，即使經常觀察到豐度的變化。

【0271】 根據需要，本揭露的一種或多種遺傳構建體可亦包括進一步的增強

子，轉譯或轉錄增強子。增強子可位於被轉錄序列的5’或3’。增強子區是所屬技術領域中具有通常知識者所周知的，可包括ATG起始密碼子、相鄰序列等。起始密碼子，如果存在，可與編碼序列的閱讀框(“框內”)同相，以提供轉錄序列的正確轉譯。

【0272】術語「5’UTR」或「5’非轉譯區」、「5’前導序列」或「5’UTR增強子元件」是指沒有轉譯的mRNA的區域。5’UTR典型從轉錄起始位點開始，並在轉譯起始位點或編碼區的起始密碼子之前結束。5’UTR可調控mRNA轉錄本的穩定性及/或轉譯。

【0273】如本文所用，術語「植物來源的表現增強子」是指從植物獲得的核苷酸序列，該核苷酸序列編碼5’UTR。植物來源的表現增強子的實例描述於美國臨時專利申請號62/643,053(2018年3月14日提交)和國際申請號PCT/CA2019/050319(2019年3月14日提交)中；其併入本文作為參考)或Diamos A.G等人文獻(2016, Front Plt Sci. 7:1-15；其藉由引用併入本文)。植物來源的表現增強子可選自nbEPI42、nbSNS46、nbCSY65、nbHEL40、nbSEP44、nbMT78、nbATL75、nbDJ46、nbCHP79、nbEN42、atHSP69、atGRP62、atPK65、atRP46、nb30S72、nbGT61、nbPV55、nbPPI43、nbPM64和nbH2A86，如US 62/643,053和PCT/CA2019/050319中所描述。植物來源的表現增強子可用於植物表現系統內，該系統包括與植物來源的表現增強子序列和感興趣的核苷酸序列(例如編碼經修飾的S蛋白的核苷酸序列)可操作地連接的調控區域。

【0274】RNA的穩定性及/或轉譯效率可藉由包括3’非轉譯區(3’UTR)來進一步改善。本發明的一種或多種遺傳構建體因此可進一步包括3’UTR。

【0275】3’非轉譯區可包含聚腺苷酸化訊號及能夠影響mRNA加工或基因表現的任何其他調控信訊。聚腺苷酸化訊號的特徵通常在於將聚腺苷酸軌跡添加到mRNA前驅物體的3’端。聚腺苷酸化訊號通常藉由同源性於規範形式5’AATAAA-3’ (儘管變異並不少見)的存在來識別。合適的3’區的非限制性實例

是3’轉錄的非轉譯區，含有農桿菌腫瘤誘導(Ti)質體基因(例如胭脂鹼合成酶(Nos基因))和植物基因(例如大豆儲藏蛋白基因)的多聚腺苷酸化訊號；核酮糖-1,5-雙磷酸羧化酶基因的小次單位(ssRUBISCO；US 4,962,028；其藉由引用併入本文)；用於調控色素體藍素表現的啟動子，描述於US 7,125,978(其藉由引用併入本文)；源自Arracacha病毒B分離基因(AvB)的3’UTR(SEQ ID NO：40)；源自甜菜壞死性黃脈病毒(trBNYVV)的3’UTR(SEQ ID NO：41)；源自南方豆花葉病毒(SBMV)的3’UTR(SEQ ID NO：42)；源自蕪菁輪點病毒(TuRSV)的3’UTR(SEQ ID NO：43)；源自豇豆花葉病毒(CPMV)的3’UTR(SEQ ID NO：44)；源自蠶豆真花葉病毒(BBTMV)的3’UTR(SEQ ID NO：45)或源自歐爾密甜瓜病毒(trOUMV)的3’UTR(SEQ ID NO：46)。3’UTR可能與源自異源性序列的5’UTR結合使用以調節表現水平。

【0276】 因此，提供「構建體」、「載體」、「表現載體」或「表現卡匣」，其包括核酸，包括在3’UTR的控制下和可操作的(或可操作地)連接到3’UTR的感興趣的核苷酸序列(例如經修飾的病毒結構蛋白)。此外，核酸可包括可操作的(或可操作地)連接到感興趣的核苷酸序列(例如經修飾的病毒結構蛋白)的3’UTR。

【0277】 經修飾的病毒結構蛋白可靶向宿主細胞(例如所欲的植物或植物細胞)的宿主的任何細胞內或細胞外空間、細胞器或組織。為了將表現的蛋白質定位到特定位置，編碼蛋白質的核酸可連接到編碼訊號肽或前導序列的核酸序列。訊號肽也可稱為轉運肽、訊號序列、前導序列、靶向訊號、定位訊號、定位序列、轉運肽或前導肽。

【0278】 本發明的一個或多於一個經修飾的遺傳構建體可在任何合適的宿主或宿主細胞中表現，該宿主或宿主細胞由本揭露的核酸，或核苷酸序列，或構建體或載體轉形。宿主或宿主細胞可來自任何來源，包括植物、真菌、細菌、昆蟲和動物例如哺乳動物。因此，宿主或宿主細胞可選自植物或植物細胞、真菌或真菌細胞、細菌或細菌細胞、昆蟲或昆蟲細胞以及動物或動物細胞。哺乳

動物或動物可能不是人類。在一個較佳的實施方式中，宿主或宿主細胞是植物、植物的部分或植物細胞。

【0279】 如本文所用，術語「植物」、「植物的部分」、「植物部分」、「植物物質」、「植物生物質」、「植物材料」、「植物萃取物」或「植物葉」可包括完整植物、組織、細胞或其任何部分、細胞內植物組分、細胞外植物組分、植物的液體或固體萃取物、或其組合，其能夠提供轉錄、轉譯和翻譯後機制，用於表現一種或多於一種本文所述的核酸，及/或可從中萃取和純化表現的蛋白質或VLP。植物可包括但不限於草本植物。草本植物可以是一年生、二年生或多年生植物。植物可進一步包括但不限於農作物，包括例如芥花、蔓苔屬植物、玉米、菸草屬植物(菸草)例如圓葉菸草(*Nicotiana benthamiana*)、黃花菸草(*Nicotiana rustica*)、菸草(*Nicotiana, tabacum*)、翼柄菸草(*Nicotiana alata*)、阿拉伯芥(*Arabidopsis thaliana*)、苜蓿、馬鈴薯、甘藷(*Ipomoea batatus*)、人參、豌豆、燕麥、大米、大豆、小麥、大麥、向日葵、棉花、玉米、黑麥(*Secale creame*)、高粱(*Sorghum bicolor*、*Sorghum vulgare*)、紅花(*Carthamus tinctorius*)。

【0280】 如本文所用，術語「植物部分」是指植物的任何部分，包括但不限於葉；莖；根；花；果實；從葉、莖、根、花、果實獲得的植物細胞；從葉、莖、根、花、果實獲得的植物萃取物或其組合。在一個實施方式中，植物部分是指植物的地上部分，例如葉、莖、花和果實。如本文所用，術語「植物提取物」是指在物理地(例如藉由冷凍然後在合適的緩衝液中萃取)、機械地(例如藉由研磨或均質植物或植物的部分，然後藉由在合適的緩衝液中萃取)、酶促地(例如使用細胞壁降解酶)、化學地(例如使用一種或多種螯合劑或緩衝液)或其組合來處理植物、植物的部分、植物細胞或其組合後獲得的植物衍生產品。可進一步加工植物萃取物以去除不需要的植物組分，例如細胞壁碎片。可獲得植物萃取物以幫助從植物、植物的部分或植物細胞中回收一種或多種組分，例如來自植物、植物的部分或植物細胞的蛋白質(包括蛋白質複合物、蛋白質超結構及/

或VLP)、核酸、脂質、碳水化合物或其組合。如果植物萃取物包括蛋白質，則它可被稱為蛋白質萃取物。蛋白質萃取物可以是粗植物萃取物、部分純化的植物或蛋白質萃取物、或純化產物，其包含來自植物組織的一種或多種蛋白質、蛋白質複合物，例如蛋白質三聚體、蛋白質超結構及/或VLP。如果需要，可使用所屬技術領域中具有通常知識者已知的技術部分地純化蛋白質萃取物或植物萃取物，例如，可對萃取物進行鹽或pH沉澱、離心、梯度密度離心、過濾、色層分析、例如粒徑篩析層析、離子交換層析、親和層析或其組合。亦可使用所屬技術領域中具有通常知識者已知的技術來純化蛋白質萃取物。

【0281】本揭露的構建體可使用Ti質體、Ri質體、植物病毒載體、直接DNA轉化、顯微注射、電穿孔等引入植物細胞中。關於此類技術的綜述參見例如Weissbach和Weissbach，Methods for Plant Molecular Biology, Academy Press, New York VIII, pp. 421-463 (1988)；Geierson and Corey, Plant Molecular Biology, 2d Ed. (1988)；和Miki and Iyer, Fundamentals of Gene Transfer in Plants. In Plant Metabolism, 2d Ed. DT. Dennis, DH Turpin, DD Lefebvre, DB Layzell (eds), Addison Wesly, Langmans Ltd. London, pp. 561-579 (1997)。其他方法包括直接DNA攝取、脂質體的使用、電穿孔，例如使用原生質體、顯微注射、微撞擊或鬚晶，以及真空滲透。例如，參見Bilang等人(Gene 100: 247-250 (1991), Scheid et al. (Mol. Gen. Genet. 228: 104-112, 1991)，Guerche等人(Plant Science 52: 111-116, 1987)，Neuhause等人(Theor. Appl Genet. 75: 30-36, 1987)，Klein等人，Nature 327: 70-73 (1987)；Howell等人(Science 208: 1265, 1980)，Horsch等人(Science 227: 1229-1231, 1985)，DeBlock等人，Plant Physiology 91: 694-701, 1989)，Methods for Plant Molecular Biology(Weissbach and Weissbach, eds., Academic Press Inc., 1988)，Methods in Plant Molecular Biology (Schuler and Zielinski, eds., Academic Press Inc., 1989)，Liu and Lomonossoff (J Virol Meth, 105:343-348, 2002,)，美國專利申請案第4,945,050號；第5,036,006號；和第5,100,792號，美國專利申請案第08/438,666

號(1955年5月10日申請)，和第07/951,715號(1992年9月25日申請) (所有文獻藉由引用併入本文)。

【0282】 如下文所述，瞬時表現方法可用於表現本揭露的構建體(參見Liu和Lomonossoff，2002，Journal of Virological Methods，105：343-348；其藉由引用併入本文)。或者，可以使用基於真空的瞬態表現方法，如 Kapila等人，1997所述，該方法藉由引用併入本文。這些方法可包括，例如但不限於，農桿菌接種或農桿菌浸潤、注射器浸潤的方法，然而，也可使用如上所述的其他瞬時方法。以農桿菌接種、農桿菌浸潤或注射器浸潤，包含所欲核酸的農桿菌的混合物進入組織的細胞間隙，例如植物的葉、地上部分(包括莖、葉和花)，植物的其他部分(莖、根、花)或整株植物。穿過表皮之後，農桿菌感染並將t-DNA複製轉移到細胞中。t-DNA被附加地轉錄且mRNA被轉譯，導致在受感染細胞中產生感興趣的蛋白質，然而，t-DNA在細胞核內的通道是短暫的。

【0283】 為了幫助識別轉化的植物細胞，可進一步操作本揭露的構建體以包括植物可選的標記物。有用的可選的標記物包括提供對化學品例如抗生素(例如建他黴素、潮黴素、康黴素)或除草劑(例如草銨膦、草甘膦、氯磺隆)等的抗性的酶。類似地，可使用用於產生可藉由顏色變化可識別的化合物的酶，例如GUS(β-尿苷酸酶)，或螢光，例如螢光素酶或GFP。

【0284】 也被認為是本揭露的部分的是含有本揭露的基因構建體的轉基因植物、植物細胞或種子，其可用作適合於本文所述之瞬時蛋白質表現的平台植物。從植物細胞再生完整植物的方法也是本領域中周知的(例如參見Guerineau and Mullineaux (1993, Plant transformation and expression vectors. In: Plant Molecular Biology Labfax (Croy RRD ed) Oxford, BIOS Scientific Publishers, pp 121-148)。一般而言，轉化的植物細胞在適當的培養基中培養，其中可能含有選擇劑，諸如抗生素，其中可選的標記物用於促進轉化植物細胞的識別。一旦癒傷組織形成，可根據已知方法藉由利用適當的植物激素來促進枝條形成，並且

將枝條轉移到生根培養基中用於植物的再生。然後可使用植物從種子或使用營養繁殖技術建立重複世代。不需使用組織培養也可以產生轉基因植物。穩定轉化和再生這些生物體的方法是本領域建立的且是所屬技術領域中具有通常知識者已知的。Vasil等人(Cell Culture and Somatic Cell Genetics of Plants, VoI I, Il and III, Laboratory Procedures and Their Applications, Academic Press, 1984) 和 Weissbach(Methods for Plant Molecular Biology, Academic Press, 1989)綜述可用的技術。獲得轉化和再生植物的方法對本揭露不是關鍵的。

【0285】 如果植物、植物部分或植物細胞要被兩種或更多種核酸構建體轉化或共轉化，則可在單個轉染事件中將核酸構建體引入農桿菌中，使得匯集核酸，和轉染的細菌細胞。或者，可以依序地引入構建體。在這種情況下，如所述將第一構建體引入農桿菌中，細胞在選擇性條件(例如在抗生素的存在)下生長，其中只有單一轉化的細菌可以生長。在此第一選擇步驟之後，如所述將第二核酸構建體引入農桿菌中，並且細胞在雙選擇性條件下生長，其中只有雙轉化細菌可以生長。然後雙轉化的細菌可用於轉化本文所述的植物、植物的部分或植物細胞，或可進行進一步的轉化步驟以容納第三核酸構建體。

【0286】 或者，如果植物、植物部分或植物細胞要被兩種或更多種核酸構建體轉化或共轉化，則核酸構建體可藉由將農桿菌細胞的混合物與植物、植物部分或植物細胞共浸潤而引入植物中，每個農桿菌細胞可包含待引入植物內的一種或多種構建體。為了改變構建體內感興趣的核苷酸序列在植物、植物部分或植物細胞內的相對表現水平，在浸潤步驟期間，可以改變包含所需構建體的各種農桿菌種群的濃度。

【0287】 經修飾的病毒表面蛋白或包含如本文所述經修飾的病毒表面蛋白的VLP可用於在受試者中引發免疫反應。

【0288】 「免疫反應」一般是指受試者的適應性免疫系統的反應。適應性免疫系統一般包括體液反應及細胞介導的反應。體液反應是免疫的態樣，由B淋巴

細胞譜系(B細胞)的細胞中產生的分泌型抗體所介導。分泌型抗體結合至入侵微生物(諸如病毒或細菌)的表面上的抗原，標記它們以進行破壞。體液免疫一般用於指抗體產生及其伴隨的過程，以及抗體的效應功能，包括Th2細胞活化及細胞介素產生、記憶細胞產生、調理素促進吞噬作用、病原體清除等。術語「調變」或「調控」等類似術語是指特定反應或參數的增加或減少，如藉由一般已知或使用的幾種測定法中的任一種所測定的，其中一些在本文中舉例說明。

【0289】 細胞介導的反應是一種免疫反應，其不涉及抗體，而是涉及巨噬細胞、自然殺手細胞((NK)、抗原特異性細胞毒性T淋巴細胞的活化，以及反應於抗原而釋放多種細胞介素。細胞介導的免疫一般用於指某些Th細胞活化、Tc細胞活化及T細胞介導的反應。細胞介導的免疫在反應於病毒感染方面可能特別重要。

【0290】 例如，抗原特異性CD8陽性T淋巴細胞的誘導可使用ELISPOT測定法來測量；CD4陽性T淋巴細胞的刺激可使用增殖測定法來測量。抗冠狀病毒抗體滴度可使用ELISA測定法來量化;抗原特異性或交叉反應性抗體的同型亦可使用抗-同型抗體(例如抗-IgG、IgA、IgE或IgM)來測量。進行此類測定法的方法及技術是本領域中周知的。

【0291】 細胞介素的存在或水平亦可被量化。例如，T輔助細胞反應(Th1/Th2)將就由使用ELISA(例如BD Biosciences OptEIA套組)測量IFN-γ及IL-4分泌細胞來表徵。可以培養從受試者獲得的外周血單核細胞(PBMC)或脾細胞，並分析上清液。T淋巴細胞亦可藉由螢光活化細胞分選(FACS)，使用標記特異性螢光標記及本領域中周知的方法進行量化。

【0292】 亦可進行微量中和測定法來表徵受試者的免疫反應，例如參見Rowe等人，1973年的方法。病毒中和滴度可以多種方式進行量化，包括：1) 在細胞的晶體紫固定/著色後計數裂解溶菌斑(溶菌斑測定法)；體外培養細胞裂解的顯微觀察；及 2) 冠狀病毒的ELISA和分光光度法檢測。

【0293】 如本文所用，術語「表位」或「多個表位」是指抗體特異性結合的抗原的結構部分。

【0294】 提供一種製造抗體或抗體片段的方法，該方法包括將經修飾的病毒結構蛋白、三聚體或三聚體的經修飾的病毒結構蛋白或包括如本文所述經修飾的病毒結構蛋白的VLP投與至受試者，或宿主動物，從而製造抗體或抗體片段。亦提供一種藉由該方法製造的抗體或抗體片段。

【0295】 本揭露因此亦提供一種如本文所述的病毒結構蛋白或包括經修飾的病毒結構蛋白的VLP用途，用於誘導受試者對冠狀病毒感染的免疫力。本文亦揭露一種抗體或抗體片段，藉由將經修飾的病毒結構蛋白或包括該修飾的病毒結構蛋白的VLP投與至受試者或宿主動物所製備的。

【0296】 進一步提供一種組合物，包括有效劑量之經修飾的病毒結構蛋白或包括該經修飾的病毒結構蛋白的VLP(如本文所述)；以及醫藥上可接受之載體、佐劑、媒介物或賦形劑，用於誘導受試者的免疫反應。亦提供一種用於在受試者中再次誘導冠狀病毒免疫反應的疫苗，其中該疫苗包括有效劑量之經修飾的病毒結構蛋白或包括經修飾的病毒結構蛋白的VLP。

【0297】 進一步提供一種組合物，其可包括VLP的混合物，其限制條件為組合物內的至少一種VLP包含如本文所述經修飾的冠狀病毒S蛋白。例如，可以表現來自一種或一種以上冠狀病毒家族、亞組、類型、亞型、譜系或品系中的每一種的包括一種或多種經修飾的S蛋白的每個冠狀病毒S蛋白並且純化相應的VLP。從兩種或多於兩種冠狀病毒家族、亞群、類型、亞型、譜系或品系(例如，兩種、三種、四種、五種、六種、七種、八種、九種、十種或更多種冠狀病毒家族、亞組、類型、亞型、譜系或品系)獲得的病毒樣顆粒可根據需要組合以製造VLP的混合物，其限制條件是VLP的混合物中的一種或多於一種VLP包括如本文所述經修飾的S蛋白。VLP可以所欲的比率(例如大約等值比)組合或製造，或可以一種冠狀病毒家族、亞組、類型、亞型、譜系或品系包括組合物中大部分

VLP的方式組合。進一步提供一種VLP的組合物，該VLP包括具有胞外結構域及/或TM或TM的部分(衍生自一種或多於一種冠狀病毒家族、亞組、類型、亞型、譜系或品系的每一種)的一種或多於一種經修飾的S蛋白，使得如本揭露中提供的不同經修飾的S蛋白的混合物可以存在於組合物的任何個體VLP中。

【0298】 組合物或疫苗可包括VLP，該VLP包括經修飾的病毒結構蛋白，該經修飾的病毒結構蛋白例如來自一種類型的冠狀病毒家族、亞群、類型、亞型、譜系或品系的經修飾的S蛋白，或者組合物或疫苗可包括多種VLP類型，其中每種VLP類型包括經修飾的S蛋白，其中相同VLP中之經修飾的S蛋白源自於一種類型的冠狀病毒家族、亞群、類型、亞型、譜系或品系，亦即，組合物或疫苗可包括不同冠狀病毒VLP的混合物，其中每種VLP可包括來自相同冠狀病毒家族、亞組、類型、亞型、譜系或品系之經修飾的S蛋白。例如，組合物或疫苗可包括第一VLP，其包括來自第一冠狀病毒家族、亞組、類型、亞型、譜系或品系的第一經修飾的S蛋白；以及第二VLP，其包括來自第二冠狀病毒家族、亞組、類型、亞型、譜系或品系的第二經修飾的S蛋白。此外，組合物或疫苗亦可包括第三VLP，其包括來自第三冠狀病毒家族、亞組、類型、亞型、譜系或品系的第三經修飾的S蛋白及/或組合物或疫苗可包括第四VLP，其包括來自第四冠狀病毒家族、亞組、類型、亞型、譜系或品系的第四經修飾的S蛋白。因此，本說明書亦提供一種組合物或疫苗，其為單價(單價的)或多價(多價的)。單價組合物或疫苗可使受試者免疫於單一類型的冠狀病毒品系，而多價組合物或疫苗可使受試者免疫於多於一種冠狀病毒品系。例如，組合物或疫苗可以是二價組合物或疫苗，其在投與後可使受試者免疫於兩種不同類型的冠狀病毒家族、亞群、類型、亞型、譜系或品系。此外，組合物或疫苗可以是三價組合物，或者疫苗或組合物可以是四價的或四價組合物或疫苗。

【0299】 此外，多價組合物可包括VLP，其包括具有不同HA胞質尾的一種或多於一種經修飾的S蛋白。例如，多價組合物可包括VLP或包含兩個或更多個

經修飾的S蛋白的VLP，每一個包括S蛋白胞外結構域、S蛋白跨膜結構域及和胞質尾，衍生自流感H1、H3、H5、H6、H7、H9或B菌株品系的HA。流感病毒株的非限制性實例為例如H1 California/7/2009、H3 A/Minnesota/41/2019、H5 A/Indonesia/5/05、H6 A/Teal/Hong Kong/W312/97、H7 A/Guangdong/17SF003/2016、H9 A/Hong Kong/1073/99或B/Washington/02/2019。

【0300】具有多種類型VLP的多價組合物或疫苗可進一步包括醫藥上可接受之載體、佐劑、媒介物或賦形劑，用於誘導受試者的免疫反應。

【0301】用於增強受試者對疫苗抗原的免疫反應的佐劑系統是眾所周知的且可以與如本文所述的疫苗或醫藥組合物結合使用。可使用多種類型的佐劑。人類使用的常見佐劑為氫氧化鋁、磷酸鋁及磷酸鈣。還有許多基於油乳劑的佐劑(水包油或油包水乳劑，例如弗氏不完全佐劑(FIA)、Montanide™、佐劑65及Lipovant™)、來自細菌的產品(或其合成衍生物)、內毒素、脂肪酸、石蠟油或植物油、膽固醇及脂肪胺或原生有機化合物，例如角鯊烯。可以使用的非限制性佐劑包括例如角鯊烯油的水包油乳劑(例如MF-59或AS03)、由整合至穩定乳劑(SE)中的合成TLR4促效劑葡萄呱喃糖苷脂質A(GLA)組成的佐劑(GLA-SE)或CpG 1018(是一種toll樣受體(TLR9)促效劑佐劑)。

【0302】因此，疫苗或醫藥組合物可包括一種或多於一種佐劑。例如，疫苗或醫藥組合物可包括氫氧化鋁、磷酸鋁、磷酸鈣、水包油或油包水乳劑、包括角鯊烯的乳劑(例如MF-59或AS03)、包括GLA-SE的乳劑，或CpG 1018佐劑。

【0303】本說明書中的醫藥組合物、疫苗或調配物可以其本身已知的方式製備，例如藉由常規混合、溶解、製粒、糖衣錠製造、研磨、乳化、包囊、包埋或壓片製程。

【0304】醫藥組合物、疫苗或調配物可以藉由在投藥之前混合或預混合任何組成成分來製造，例如藉由手動或機械輔助混合兩種或更多種疫苗懸浮液、醫藥上可接受之載體、佐劑、媒介物或賦形劑，作為在投與最終調配物、疫苗或

醫藥組合物之前進行的步驟。

【0305】 醫藥組合物、疫苗或調配物可以口服、皮內、鼻內、肌肉內、腹膜內、靜脈內或皮下投與至受試者。

【0306】 注射劑可以常規形式製備，作為液體溶液或懸浮液，適合於注射之前溶解或懸浮在液體中的固體形式，或作為乳劑。合適的賦形劑為例如水、鹽水、葡萄糖、甘露醇、乳糖、卵磷脂、白蛋白、麩酸鈉、半胱胺酸鹽酸鹽等。此外，若需要，可注射的醫藥組合物可包括少量無毒輔助物質，例如潤濕劑、pH緩衝劑等。生理可相容的緩衝劑包括但不限於漢克斯溶液(Hank's solution)、林格氏溶液(Ringer's solution)或生理鹽水緩衝劑。若需要，可以利用吸收增強製劑(例如脂質體)。

【0307】 組合物或疫苗可以一次(單劑量)投與至受試者。此外，疫苗或組合物可以多次(多劑量)投與至受試者。因此，組合物、調配物或疫苗可以單劑量投與至受試者來引發免疫反應，或者組合物、調配物或疫苗可以多次(多劑量)投與。例如，組合物或疫苗的劑量可以2、3、4或5次投與。因此，組合物或疫苗可以初始劑量投與至受試者，隨後可以一或多於一次劑量投與至受試者。劑量的投與可以在時間上彼此分開。例如，在投與初始劑量之後，可以在1天、2天、3天、4天、5天、6天、1週、2週、3週、1個月、2個月、3個月、4個月、5個月或6個月或從投與初始劑量之間的任何時間投與一或多於一次的後續劑量。此外，組合物或疫苗可以每年投與一次。例如，組合物或疫苗可以作為季節性疫苗投與。

【0308】 本揭露進一步提供以下序列。

[表4] SEQ ID NO和序列描述。

SEQ ID NO:	序列描述
1	原生 SARS-CoV-2 S 蛋白 wtTM/CT AA (P0DTC2)
2	原生 SARS-CoV-2 S 蛋白 wtTM/CT AA (P0DTC2) 不含訊號肽 (SP)
3	H5 A/Indonesia/5/05 血液凝集素(HA) AA (A5A5L7)
4	H5 A/Indonesia/5/05 血液凝集素 (HA) 病毒 cDNA (EF541394.1)

SEQ ID NO:	序列描述
5	經修飾的 SARS-CoV-2，具有 H5 A/Indonesia/5/05 (H5i) 血液凝集素 CT AA
6	H1 California/7/2009 血液凝集素 TM/CT 區 AA
7	H2 A/Singapore/1/1957 HA 血液凝集素 TM/CT 區 AA
8	H3 A/Minnesota/41/2019 血液凝集素 TM/CT 區 AA
9	H5 A/Indonesia/5/05 血液凝集素 TM/CT 區 AA
10	H6 A/Teal/Hong Kong/W312/97 血液凝集素 TM/CT 區 AA
11	H7 A/Guangdong/17SF003/2016 血液凝集素 TM/CT 區 AA
12	H9 A/Hong Kong/1073/99 血液凝集素 TM/CT 區 AA
13	B/Washington/02/2019 血液凝集素 TM/CT 區 AA
14	流感血液凝集素 TM/CT 區的 C-終端區的共通序列
15	流感血液凝集素的 CT 結構域的共通序列
16	原生 SARS-CoV-2 S 蛋白 (wtTM/CT)的 TM/CT 區
17	H5 A/Indonesia/5/05 血液凝集素 (H5iTM/CT)的 TM/CT
18	具有 H5i 血液凝集素 CT 之經修飾的 SARS-CoV-2 S 蛋白的 TM/CT 區
19	具有 H5i 血液凝集素 CT 之經修飾的 S 蛋白的 TM/CT 區(變異 1)
20	(無 SP) SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT AA
21	(無 SP) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血液凝集素 CT AA
22	PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-DNA
23	PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-AA (構建體 8591 製造)
24	IF(PDI)-CoV(opt2).c
25	IF(AVB)-CoV(opt2).r
26	PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP H5iTM/CT-DNA
27	PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP H5iTM/CT-AA (構建體 8597 製造)
28	IF(Avb)-H5I.r
29	PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP wtTM/H5iCT-DNA
30	PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP wtTM/H5iCT-AA (構建體 8671 製造)
31	選殖載體 8501 從左到右 T-DNA
32	構建體 8586 從 2X35S(+C) prom 至 NOS term
33	選殖載體 8500 從左到右 T-DNA]
34	構建體 8589 從 2X35S(+C) prom 至 NOS term
35	選殖載體 8716 從左到右 T-DNA
36	構建體 8591 從 2X35S(+C) prom 至 NOS term
37	具有 H5i 血液凝集素 CT 之經修飾的 S 蛋白的 C-終端區(選擇性 2)
38	具有 H5i 血液凝集素 CT 之經修飾的 S 蛋白的 C-終端區(選擇性 3)
39	具有 H5i 血液凝集素 CT 之經修飾的 S 蛋白的 C-終端區(選擇性 4)
40	3'UTR AvB (Arracacha 病毒 B 分離)
41	3'UTR trBNYVV (甜菜壞死性黃脈病毒)
42	3' UTR SBMV (南方豆花葉病毒)
43	3' UTR TuRSV (蕪菁輪點病毒)
44	3' UTR CPMV (豇豆花葉病毒)
45	3' BBTMV (蠶豆真花葉病毒)
46	3' UTR trOUMV (歐爾密甜瓜病毒)

SEQ ID NO:	序列描述
	具有取代基之經修飾的 S 蛋白
47	PDI-S 蛋白 GSAS-2P (構建體 8671 製造)
48	PDI-S 蛋白 GSAS-4P (構建體 8953 製造)
49	PDI-S 蛋白 GSAS-6P (構建體 8940 製造)
50	PDI-S 蛋白 GSAS-2P-923 (構建體 8933 製造)
51	PDI-S 蛋白 GSAS-4P-923 (構建體 8960 製造)
52	PDI-S 蛋白 GSAS-6P-923 (構建體 8947 製造)
	經修飾的 S 蛋白，具有來自不同 HA 品系的 CT
53	PDI-S-蛋白+H1 Cal (構建體 7390 製造)
54	PDI-S-蛋白+H3 Minn (構建體 7391 製造)
55	PDI-S-蛋白+H6 HK (構建體 7392 製造)
56	PDI-S-蛋白+H7 Guangdong (構建體 7393 製造)
57	PDI-S-蛋白+H9 HK (構建體 7394 製造)
58	PDI-S-蛋白+ B/ Wash (構建體 7395 製造)
	經修飾的 S 蛋白 C-終端變異
59	PDI-經修飾的 S 蛋白 ，具有 H5i 血液凝集素 CT (V1) (構建體 8980 製造)
60	PDI-經修飾的 S 蛋白 ，具有 H5i 血液凝集素 CT (V2) (構建體 8981 製造)
61	PDI-經修飾的 S 蛋白 ，具有 H5i 血液凝集素 CT (V3) (構建體 8982 製造)
62	PDI-經修飾的 S 蛋白 ，具有 H5i 血液凝集素 CT (V4) (構建體 8983 製造)
	N-終端區
63	原生 SARS-CoV-2 蛋白 (包含然訊號肽)的 N-終端區
64	經修飾的 SARS-CoV-2 S 蛋白的 TM/CT 區，具有間插肽序列 X_n
	經修飾的 S 蛋白，具有取代基 (DNA)
65	PDI-S 蛋白 GSAS+4P-DNA
66	PDI-S 蛋白 GSAS+6P-DNA
67	PDI-S 蛋白 GSAS+2P+L923F-DNA
68	PDI-S 蛋白 GSAS+4P+L923F-DNA
69	PDI-S 蛋白 GSAS+6P+L923F-DNA
	經修飾的 S 蛋白 C-終端變異(DNA)
70	PDI-經修飾的 S 蛋白，具有 H5i 血液凝集素 CT (V1) DNA
71	PDI-經修飾的 S 蛋白，具有 H5i 血液凝集素 CT (V2) DNA
72	PDI-經修飾的 S 蛋白，具有 H5i 血液凝集素 CT (V3) DNA
73	PDI-經修飾的 S 蛋白，具有 H5i 血液凝集素 CT (V4) DNA
	經修飾的 S 蛋白，具有來自不同 HA 品系 (DNA)和蛋白的 CT
74	PDI-S-蛋白+H1 Cal DNA
75	PDI-S-蛋白+H3 Minn DNA
76	PDI-S-蛋白+H6 HK DNA
77	PDI-S-蛋白+H7 Guangdong DNA
78	PDI-S-蛋白+H9 HK DNA
79	PDI-S-蛋白+ B/ Wash DNA
80	IF-H1HawaiiCT.r
81	IF-H3MinnesotaCT.r
82	IF-HongKongCT.r

SEQ ID NO:	序列描述
83	IF-GuangdongCT.r
84	IF-H9HKCT.r
85	IF-BWashCT.r
	經修飾的 SARS-COV-1 S 蛋白 (DNA)和引子
86	IF(nbHEL40)-PDI.c
87	IF(AvB+wtCT).r
88	PDI-SARS-COV-1 wtTMCT-DNA
89	PDI-SARS-COV-1 H5iTMCT-DNA
90	PDI-SARS-COV-1 H5iCT-DNA
91	PDI-SARS-COV-1 H5iCT(V4)-DNA
92	PDI-SARS-COV-1 H1cCT-DNA
	經修飾的 SARS-COV-1 S 蛋白 (AA)
93	PDI-SARS-COV-1 wtTMCT-AA
94	PDI-SARS-COV-1 H5iTMCT-AA
95	PDI-SARS-COV-1 H5iCT-AA
96	PDI-SARS-COV-1 H5iCT(V4)-AA
97	PDI-SARS-COV-1 H1cCT-AA
	經修飾的 MERS S 蛋白 (DNA) 和引子
98	IF(AvB+wtCT-MERS).r
99	IF(H1cCT-wtTM).r
100	IF(H5ITMCT).r
101	PDI-MERS-wtTMCT-DNA
102	PDI-MERS-H5iTMCT-DNA
103	PDI-MERS-H5iCT-DNA
104	PDI-MERS-H5iCT(V4)-DNA
105	PDI-MERS-H1cCT-DNA
	經修飾的 SARS-COV-1 S 蛋白 (AA)
106	PDI-MERS-wtTMCT-AA
107	PDI-MERS-H5iTMCT-AA
108	PDI-MERS-H5iCT-AA
109	PDI-MERS-H5iCT(V4)-AA
110	PDI-MERS-H1cCT-AA
	其他序列
111	選殖載體 7147 從左到右 T-DNA
112	原生 SARS-CoV-1 S 蛋白 wtTM/CT AA (P59594)
113	原生 MERS S 蛋白 wtTM/CT AA (AFY13307)
114	原生 SARS-CoV-1 S 蛋白 wtTM/CT AA (P59594) 不含訊號肽
115	原生 MERS S 蛋白 wtTM/CT AA (AFY13307) 不含訊號肽
116	經修飾的 PDI-SARS-COV-1 wtTMCT-AA 的 TMCT 區
117	經修飾的 PDI-SARS-COV-1 H5iTMCT-AA 的 TMCT 區
118	經修飾的 PDI-SARS-COV-1 H5iCT-AA 的 TMCT 區
119	經修飾的 PDI-SARS-COV-1 H5iCT(V4)-AA 的 TMCT 區
120	經修飾的 PDI-SARS-COV-1 H1cCT-AA 的 TMCT 區
121	經修飾的 PDI-MERS-wtTMCT-AA 的 TMCT 區
122	經修飾的 PDI-MERS-H5iTMCT-AA 的 TMCT 區
123	經修飾的 PDI-MERS-H5iCT-AA 的 TMCT 區

SEQ ID NO:	序列描述
124	經修飾的 PDI-MERS-H5iCT(V4)-AA 的 TMCT 區
125	經修飾的 PDI-MERS-H1cCT-AA 的 TMCT 區
126	經修飾的 PDI-S-蛋白+H1 Cal 的 TMCT 區
127	經修飾的 PDI-S-蛋白+H3 Minn 的 TMCT 區
128	經修飾的 PDI-S-蛋白+H6 HK 的 TMCT 區
129	經修飾的 PDI-S-蛋白+H7 Guangdong 的 TMCT 區
130	經修飾的 PDI-S-蛋白+H9 HK 的 TMCT 區
131	經修飾的 PDI-S-蛋白+ B/ Wash 的 TMCT 區
132	冠狀病毒 S-蛋白 的 TM 結構域的共通序列
133	冠狀病毒 S-蛋白的 TM 結構域的共通序列
134	具有間插肽序列 X_n 之經修飾的 SARS-CoV-1 S 蛋白的 TM/CT 區
135	具有間插肽序列 X_n 之經修飾的 MERS S 蛋白的 TM/CT 區
	經修飾的 OC43-CoV S 蛋白 (DNA)和引子
136	IF(AvB+wtCT-OC43).r
137	PDI-OC43-wtTMCT-DNA
138	PDI-OC43-H5iTMCT-DNA
139	PDI-OC43-H5iCT-DNA
140	PDI-OC43-H5iCT(V4)-DNA
141	PDI-OC43-H1cCT-DNA
	經修飾的 OC43-CoV S 蛋白 (AA)
142	PDI-OC43-wtTMCT-AA
143	PDI-OC43-H5iTMCT-AA
144	PDI-OC43-H5iCT-AA
145	PDI-OC43-H5iCT(V4)-AA
146	PDI-OC43-H1cCT-AA
	經修飾的 229E-CoV S 蛋白 (DNA) 和引子
147	IF(CoV229EwtCT).r
148	PDI-229E -wtTMCT-DNA
149	PDI-229E -H5iTMCT-DNA
150	PDI-229E -H5iCT-DNA
151	PDI-229E -H5iCT(V4)-DNA
152	PDI-229E -H1cCT-DNA
	經修飾的 229E-CoV S 蛋白 (AA)
153	PDI-229E -wtTMCT-AA
154	PDI-229E -H5iTMCT-AA
155	PDI-229E -H5iCT-AA
156	PDI-229E -H5iCT(V4)-AA
157	PDI-229E-H1cCT-AA
	其他序列
158	原生 OC43-CoV S 蛋白 wtTM/CT AA (AVR40344)
159	原生 229E S 蛋白 wtTM/CT AA (P15423)
160	原生 OC43-CoV S 蛋白 wtTM/CT AA (AVR40344) 不含訊號肽
161	原生 229E S 蛋白 wtTM/CT AA (P15423) 不含訊號肽
162	經修飾的 PDI-OC43-COV wtTMCT-AA 的 TMCT 區
163	經修飾的 PDI-OC43-COV H5iTMCT-AA 的 TMCT 區

SEQ ID NO:	序列描述
164	經修飾的 PDI-OC43-COV H5iCT-AA 的 TMCT 區
165	經修飾的 PDI-OC43-COV H5iCT(V4)-AA 的 TMCT 區
166	經修飾的 PDI-OC43-COV H1cCT-AA 的 TMCT 區
167	經修飾的 PDI-229E-wtTMCT-AA 的 TMCT 區
168	經修飾的 PDI-229E-H5iTMCT-AA 的 TMCT 區
169	經修飾的 PDI-229E-H5iCT-AA 的 TMCT 區
170	經修飾的 PDI-229E-H5iCT(V4)-AA 的 TMCT 區
171	經修飾的 PDI-229E-H1cCT-AA 的 TMCT 區的 TMCT 區
172	具有間插肽序列 X_n 之經修飾的 OC43-CoV S 蛋白的 TM/CT 區
173	具有間插肽序列 X_n 之經修飾的 229E-CoV S 蛋白的 TM/CT 區

【0309】 本發明將在以下實施例中進一步說明。

[實施例]

[實施例1] 經修飾的結構蛋白構建體的製備

【0310】 SARS-CoV-2 S蛋白構建體是使用本領域中眾所周知的技術製造。例如，如下所述選殖具有wtTMCT的SARS-COV-2棘蛋白(構建體編號8586、8589、8591，參見圖8A至圖8C)。具有H5iTMCT的SARS-COV-2棘蛋白的構建體(構建體編號8592、8595、8597，參見圖9A至圖9C)和具有H5iCT的SARS-COV-2棘蛋白的構建體(構建體編號8610、8611、8671，參見圖10A至10C)係使用類似技術獲得，且序列引子、模板和產物在表 5中描述。

具有wtTMCT的SARS-COV-2棘蛋白(構建體編號8586、8589、8591)

【0311】 編碼成熟SARS-CoV-2 棘(S)蛋白2的序列(SEQ ID NO：23) (具有GSAS+K971P+V972P胞外結構域突變及來自SARS-CoV-2的原生跨膜結構域和原生胞質尾(wtTMCT)，融合到苜蓿PDI分泌訊號肽(PDISP))係使用以下基於PCR的方法選殖到三個不同的表現系統中。含有SARS-COV-2棘蛋白(wtTMCT)編碼序列的片段係使用引子IF(PDI)-CoV(opt2).c (SEQ ID NO： 24) 和IF(AVB)-CoV(opt2).r (SEQ ID NO：25)，使用具有wtTMCT基因序列(SEQ ID NO：22)的PDISP-SARS-COV-2棘蛋白作為模板。PCR產物係使用In-Fusion選殖系統(Clontech, Mountain View, CA) 選殖到三個不同的表現系統。

【0312】 對於第一表現系統，構建體編號8501(圖7A)係用AatII和StuI限制酶

水解，且線性化的質體用於第一In-Fusion組裝反應。構建體編號8501是一種受體質體，用於在基於2X35S(+C)/nbMT78/PDI/AvB/NOS的表達卡匣中「In-Fusion」選殖感興趣的基因。此受體質體亦引入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制因子的共表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：31中呈現。所得構建體給定編號8586(SEQ ID NO：32)。來自融合至苜蓿PDI分泌訊號肽(PDISP)的SARS-COV-2的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：23 中。質體8586的表示呈現在圖8A中。

【0313】 對於第二表現系統，構建體編號8500(圖7B)也用AatII和StuI限制酶水解，且線性化質粒用於第二In-Fusion組裝反應。構建體編號8500是一種受體質體，用於在基於2X35S(+C)/nbCSY65/PDI/AvB/NOS的表現卡匣中「In-Fusion」選殖感興趣的基因。此受體質體亦引入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制因子的共表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：33中呈現。所得構建體給定編號8589(SEQ ID NO：34)。來自融合至苜蓿PDI分泌訊號肽(PDISP)的SARS-COV-2的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：23中。質體8589的表示呈現在圖8B中。

【0314】 對於第三表現系統，構建體編號8716(圖7C)也用AatII和StuI限制酶水解，且線性化質體用於第三In-Fusion組裝反應。構建體編號8716是一種受體質體，用於在基於2X35S(+C)/nbHEL40/PDI/AvB/NOS的表現卡匣中「In-Fusion」選殖感興趣的基因。此受體質體亦引入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制因子的共表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：35中呈現。所得構建給定編號8591(SEQ ID NO：36)。來自融合至苜蓿PDI分泌訊號肽(PDISP)的SARS-COV-2的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：23中。質體8591的表示呈現在圖

8C中。

具有H5iTMCT的SARS-COV-2棘蛋白(構建體編號8592、8595、8597)

【0315】編碼來自具有GSAS+K971P+V972P胞外結構域突變及具有來自H5A/Indonesia/5/05 HA的跨膜結構域和胞質尾(H5iTMCT)的SARS-CoV-2 (SEQ ID NO： 27)的成熟棘(S)蛋白的序列係融合至苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到上述相同的三個表現系統中(引子參見表5，所用序列參見實施例3)。構建體編號8592(圖9A)源自受體構建體8501，構建體編號8595(圖9B)源自受體構建體8500，構建體編號8597(圖9C)源自受體構建體8716，使用與上述類似的技術，且引子 、模板和產物在下表5中提供。

具有H5iCT的SARS-COV-2棘蛋白(構建體編號8610、8611、8671)

【0316】編碼來自具有GSAS+K971P+V972P胞外結構域突變及來自H5A/Indonesia/5/05 HA的胞質尾(H5iCT)的SARS-CoV-2(SEQ ID NO：30)的成熟棘(S)蛋白的序列，係融合至苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到上述相同的三個表現系統中(引子參見表 5，所用序列參見實施例3)。構建體編號8610(圖10A)源自受體構建體8501，構建體編號8611(圖10B)源自受體構建體8500，且構建體編號8671(圖10C)源自受體構建體8716，使用與上述類似的技術，且引子、模板和產物在下表5中提供。

具有選擇性TM CT融合序列的SARS-COV-2棘蛋白(構建體編號8980、8981、8982、8983)

【0317】編碼來自具有GSAS+K971P+V972P胞外結構域突變及來自H5A/Indonesia/5/05 HA的胞質尾(H5iCT)的SARS-CoV-2的成熟棘(S)蛋白的序列(如SEQ ID NO：19所示)係融合至苜蓿PDI分泌訊號肽(PDISP)，並選殖到與構建體8671所述相同的表現系統中，產生構建體8980(圖12A)。類似的構建體係創建用於編碼來自具有GSAS+K971P+V972P胞外結構域突變，及來自H5A/Indonesia/5/05 HA的胞質尾(H5iCT)的SARS-CoV-2的成熟棘(S)蛋白的，如SEQ

ID NO：37所示(構建體8981，圖12B)、SEQ ID NO：38(構建體8982，圖12C)和SEQ ID NO：39(構建體8983，圖12D)。

具有來自其他HA品系的CT的SARS-COV-2棘蛋白(構建體編號7390、7391、7392、7393、7394和7395)

【0318】編碼來自具有GSAS+K971P+V972P胞外結構域突變及來自H1 A/California/7/2009 HA的胞質尾(H1CT)的SARS-CoV-2的成熟棘(S)蛋白的序列係融合到苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到與上述構建體8671相同的表現系統中(引子參見表5，且所用序列參見實施例3)。所得構建體7390因此編碼包含H1A/California/7/2009 HA胞質尾(H1CT)之經修飾的S蛋白(圖13A)。類似的構建體係創建用於H3 A/Minnesota/41/2019(構建體7391，H3 CT) (圖13B)、H6 A/Teal/Hong Kong/W312/97 (構建體7392，H6 CT) (圖13C)、H7 A/Guangdong/17SF003/2016 (構建體7393，H7 CT) (圖13D)、H9 A/Hong Kong/1073/99 (構建體7394，H9h CT) (圖13E)或B/Washington/02/2019 (構建體7395，HA B CT) (圖13F)。

具有取代基的SARS-COV-2棘蛋白(構建體編號8933、8960、8947)

【0319】包括S蛋白中突變(例如R667G、R668S、R670S、F802P、A877P、A884P、A927P、K971P、V972P和L923F)之組合之經修飾的SARS-CoV-2 S蛋白構建體係使用本領域中眾所周知的技術製造且基本上如上所述。構建體具有以下取代基：構建體8933：R667G、R668S、R670S、K971P、V972P和L923F(「GSAS-2P-923」)；構建體8960：R667G、R668S、R670S、F802P、A927P、K971P、V972P和L923F(「GSAS-4P-923」)和構建體8947：R667G、R668S、R670S、F802P、A877P、A884P、A927P、K971P、V972P和L923F(「GSAS-6P-923」)。

具有wtTMCT和經修飾的TMCT的SARS-COV-1棘蛋白(構建體編號9231、9232、9233、9234、9235)

【0320】編碼具有R654A+K955P+V956P胞外結構域突變及具有來自

SARS-CoV-1的原生跨膜結構域和原生胞質尾(wtTMCT)的成熟SARS-CoV-1棘(S)蛋白的序列(SEQ ID NO： 88) (融合至苜蓿PDI分泌訊號肽(PDISP))係藉由基於PCR的方法選殖到以下表現系統中。含有PDISP-SARS-COV-1棘蛋白(wtTMCT)編碼序列的片段係使用引子IF(nbHEL40)-PDI.c (SEQ ID NO：86)和IF(AvB+wtCT).r (SEQ ID NO：87)，使用具有wtTMCT基因序列(SEQ ID NO：88)的PDISP-SARS-COV-1棘蛋白作為模板來擴增。PCR產物係使用In-Fusion選殖系統(Clontech, Mountain View, CA)選殖到以下表現系統中。

【0321】 構建體編號7147(圖21)以AatII和StuI限制酶水解，且線性化質體係用於第一In-Fusion組裝反應。構建體編號7147是一種受體質體，用於在基於2X35S(+C)/nbHEL40/AvB/NOS的表現卡匣中「In Fusion」選殖感興趣的基因。此受體質體亦引入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制因子的共表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：111 中呈現。所得構建體給定編號9231。來自融合至苜蓿PDI分泌訊號肽(PDISP)的SARS-COV-1的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：93中。質體9231的表示呈現在圖18A中。

【0322】 編碼來自具有R654A+K955P+V956P胞外結構域突變及i)來自H5A/Indonesia/5/05 HA的跨膜結構域和胞質尾(H5iTMCT)， ii)來自H5 A/Indonesia/5/05 HA的胞質尾(H5iCT和變異H5iCT(V4))， 或iii)來自H1 A/California/7/2009 HA的胞質尾(H1cCT)的SARS-CoV-1的成熟棘(S)蛋白的序列係融合至苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到與上述構建體9231相同的表現系統中(引子參見表5，且所用序列參見實施例3)。所得構建體9232、9233、9234、9235因此編碼包含H5 A/Indonesia/5/05 TMCT (H5iTMCT)之經修飾的S蛋白(圖18B，SEQ ID NO： 94)、包含H5 A/Indonesia/5/05 CT (H5iCT)之經修飾的SARS-COV-1 S蛋白(圖18C， SEQ ID NO： 95)、包含H5 A/Indonesia/5/05 CT變體(H5iCT(V4))之經修飾的S蛋白(圖18D， SEQ ID NO：

96)，或包含H1 A/California/7/2009 CT(H1cCT)之經修飾的S蛋白(圖18E，SEQ ID NO：97)。

具有wtTMCT和經修飾的TMCT的MERS-CoV棘蛋白(構建體編號9246、9247、9249、9250、9251)

【0323】 編碼具有R730A+R733G+V1043P+L1044P胞外結構域突變和具有來自MERS-CoV的原生跨膜結構域和原生胞質尾(wtTMCT)的成熟MERS-CoV棘(S)蛋白(SEQ ID NO：101)的序列(融合至苜蓿PDI分泌訊號肽(PDISP))係藉由基於PCR的方法選殖到以下表現系統中。含有PDISP-MERS-COV棘蛋白(wtTMCT)編碼序列的片段係使用引子IF(nbHEL40)-PDI.c(SEQ ID NO：86)和IF(AvB+wtCT-MERS).r (SEQ ID NO：98)，使用具有wtTMCT基因序列(SEQ ID NO：101)的PDISP-MERS-COV棘蛋白作為模板來擴增。PCR產物係使用In-Fusion選殖系統(Clontech, Mountain View, CA)選殖到以下表現系統中。

【0324】 構建體編號7147(圖21)以AatII和StuI限制酶水解，且線性化質體係用於第一In-Fusion組裝反應。構建體編號7147是一種受體質體，用於在基於2X35S(+C)/nbHEL40/AvB/NOS的表現卡匣中「In Fusion」選殖感興趣的基因。此受體質體亦併入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制子的共表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO： 111中呈現。所得構建體給定編號9246。來自融合至苜蓿PDI分泌訊號肽(PDISP)的MERS-COV的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：106中。質體9246的表示呈現在圖20A中。

【0325】 編碼來自MERS-CoV的成熟棘(S)蛋白的序列，具有R730A+R733G+V1043P+L1044P胞外結構域突變，以及i)來自H5 A/Indonesia/5/05 HA的跨膜結構域和胞質尾(H5iTMCT)，ii)來自H5 A/Indonesia/5/05 HA的胞質尾(H5iCT和變異H5iCT(V4))，或iii)來自H1 A/California/7/2009 HA的胞質尾(H1cCT)係融合至苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到如上述構建體9246

相同的表現系統中(引子參見表5，且所用序列參見實施例3)。所得構建體9247、9249、9250、9251因此編碼包含H5 A/Indonesia/5/05 TMCT (H5iTMCT)之經修飾的MERS-COV S蛋白(圖20B，SEQ ID NO：107)，包含H5A/Indonesia/5/05 CT (H5iCT)之經修飾的S蛋白(圖20C，SEQ ID NO：108)，包含H5 A/Indonesia/5/05 CT變體(H5iCT(V4))之經修飾的S蛋白(圖 20D，SEQ ID NO：109)，或包含H1 A/California/7/2009 CT(H1cCT)之經修飾的S蛋白(圖20E，SEQ ID NO：110)。

具有wtTMCT和經修飾的TMCT的OC43-CoV棘蛋白(構建體編號9269、9270、9272、9273 和 9274)

【0326】編碼成熟OC43-CoV棘(S)蛋白的序列(SEQ ID NO：137)，具有R761G+R762G+R764G+R765S+A1077P+L1078P 胞外結構域突變和來自OC43-Co的原生跨膜結構域和原生胞質尾(wtTMCT) (融合至苜蓿PDI分泌訊號肽(PDISP))係藉由基於PCR的方法選殖到以下表現系統中。含有PDISP-OC43-COV 棘蛋白(wtTMCT)編碼序列的片段係使用引子IF(nbHEL40)-PDI.c (SEQ ID NO：86)和IF(AvB+wtCT-OC43).r (SEQ ID NO：136)，使用具有wtTMCT基因序列(SEQ ID NO：137)的PDISP-OC43-COV棘蛋白作為模板來擴增。PCR產物係使用In-Fusion選殖系統(Clontech, Mountain View, CA)選殖到以下表現系統中。

【0327】構建體編號7147(圖21)以AatII和StuI限制酶水解，且線性化質體係用於第一In-Fusion組裝反應。構建體編號7147是一種受體質體，用於在基於2X35S(+C)/nbHEL40/AvB/NOS的表現卡匣中「In Fusion」選殖感興趣的基因。此受體質體亦併入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制子的表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：111中呈現。所得構建體給定編號9269。來自融合至苜蓿PDI分泌訊號肽(PDISP)的OC43-COV的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：142中。質體9269的表示呈現在圖24A中。

【0328】編碼來自OC43-CoV的成熟棘(S)蛋白的序列，具有R761G+R762G+R764G+R765S+A1077P+L1078P胞外結構域突變，以及i)來自H5 A/Indonesia/5/05 HA的跨膜結構域和胞質尾(H5iTMCT)、ii)來自H5 A/Indonesia/5/05 HA(H5iCT和變異H5iCT(V4))的胞質尾，或iii)來自H1 A/California/7/2009 HA的胞質尾(H1cCT)係融合至苜蓿PDI分泌訊號肽(PDISP)且藉由類似基於PCR的方法選殖到如上述構建體9269相同的表現系統中(引子參見表5，且所用序列參見實施例3)。所得構建體9270、9272、9273和9274因此編碼包含H5A/Indonesia/5/05 TMCT(H5iTMCT)之修飾的OC43-COV S蛋白(圖24B，SEQ ID NO：143)，包含H5 A/Indonesia/5/05 CT(H5iCT)之經修飾的S蛋白(圖24C，SEQ ID NO：144)，包含H5 A/Indonesia/5/05 CT變體(H5iCT(V4))之經修飾的S蛋白(圖24D，SEQ ID NO：145)，或包含H1 A/California/7/2009 CT(H1cCT)之經修飾的S蛋白(圖24E，SEQ ID NO：146)。

具有wtTMCT和經修飾的TMCT之229E-CoV棘蛋白(構建體編號9310、9311、9312、9313和9314)

【0329】編碼成熟229E-CoV棘(S)蛋白的序列(SEQ ID NO：148)，具有R567A+T871P+I872P胞外結構域突變以及來自229E-CoV的原生跨膜結構域和原生胞質尾(wtTMCT) (融合到苜蓿分泌訊號肽(PDISP))係藉由基於PCR的方法選殖到以下表現系統中。含有PDISP-229E-COV棘蛋白(wtTMCT)編碼序列的片段係使用引子IF(nbHEL40)-PDI.c(SEQ ID NO：86)和IF(CoV229EwtCT).r (SEQ ID NO：147)，使用具有wtTMCT基因序列(SEQ ID NO：148)的PDISP-COV棘蛋白作為模板來擴增。PCR產物係使用In-Fusion選殖系統(Clontech, Mountain View, CA)選殖到以下表現系統中。

【0330】構建體編號7147(圖21)以AatII和StuI限制酶水解，且線性化質體係用於第一In-Fusion組裝反應。構建體編號7147是一種受體質體，用於在基於2X35S(+C)/nbHEL40/AvB/NOS的表現卡匣中「In Fusion」選殖感興趣的基因。

此受體質體亦併入基因構建體，用於在苜蓿色素體藍素基因啟動子和終止子下沉默TBSV P19抑制子的表現。骨架是pCAMBIA二元質體，從左到右t-DNA邊緣的序列在SEQ ID NO：111中呈現。所得構建體給定編號9310。來自融合至苜蓿PDI分泌訊號肽(PDISP)的229E-COV的成熟棘蛋白的胺基酸序列呈現在SEQ ID NO：153中。質體9310的表示呈現在圖26A中。

【0331】編碼來自229E-CoV的成熟棘(S)蛋白的序列，具有R567A+T871P+I872P胞外結構域突變，以及i)來自H5 A/Indonesia/5/05 HA的跨膜結構域和胞質尾(H5iTMCT)，ii)來自H5 A/Indonesia/5/05 HA的胞質尾(H5iCT和變異H5iCT(V4))，或iii)來自H1 A/California/7/2009 HA的胞質尾(H1cCT)係融合至苜蓿PDI分泌訊號肽(PDISP)，並藉由類似基於PCR的方法選殖到如上述構建體9310相同的表現系統中(引子參見表5，且所用序列參見實施例3)。所得構建體9311、9312、9313和9314因此編碼包含H5 A/Indonesia/5/05 TMCT(H5iTMCT)之經修飾的229E-COV S蛋白(圖26B，SEQ ID NO：154)，包含H5 A/Indonesia/5/05 CT(H5iCT)之經修飾的S蛋白(圖26C，SEQ ID NO：155)，包含H5 A/Indonesia/5/05 CT變體(H5iCT(V4))之經修飾的S蛋白(圖26D，SEQ ID NO：156)，或包含H1 A/California/7/2009 CT(H1cCT)之經修飾的S蛋白(圖26E，SEQ ID NO：157)。

[表5]

構建體 #	5' UTR	感興趣的基因 (GOI)	TMCT 區	引子 1 (片段 1 之前置引子)	引子 2 (片段 1 之反置引子)	第一次 PCR 的模板/ 所得基因	所得蛋白	受體質體
8586	nbMT78	SARS-CoV-2 S	wt TMCT	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 22	SEQ ID NO: 23	SEQ ID NO: 31
8589	nbCSY65	SARS-CoV-2 S	wt TMCT	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 22	SEQ ID NO: 23	SEQ ID NO: 33
8591	nbHEL40	SARS-CoV-2 S	wt TMCT	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 22	SEQ ID NO: 23	SEQ ID NO: 35
8592	nbMT78	SARS-CoV-2 S	H5iTMCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 26	SEQ ID NO: 27	SEQ ID NO: 31
8595	nbCSY65	SARS-CoV-2 S	H5iTMCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 26	SEQ ID NO: 27	SEQ ID NO: 33
8597	nbHEL40	SARS-CoV-2 S	H5iTMCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 26	SEQ ID NO: 27	SEQ ID NO: 35
8610	nbMT78	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 31
8611	nbCSY65	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 33
8671	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 35
8953	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 65	SEQ ID NO: 48	SEQ ID NO: 35
8940	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 66	SEQ ID NO: 49	SEQ ID NO: 35
8933	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 67	SEQ ID NO: 50	SEQ ID NO: 35
8960	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 68	SEQ ID NO: 51	SEQ ID NO: 35
8947	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 69	SEQ ID NO: 52	SEQ ID NO: 35
8980	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT (V1)	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 70	SEQ ID NO: 59	SEQ ID NO: 35
8981	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT (V2)	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 71	SEQ ID NO: 60	SEQ ID NO: 35
8982	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT (V3)	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 72	SEQ ID NO: 61	SEQ ID NO: 35
8983	nbHEL40	SARS-CoV-2 S	wtTM/H5iCT (V4)	SEQ ID NO: 24	SEQ ID NO: 28	SEQ ID NO: 73	SEQ ID NO: 62	SEQ ID NO: 35
7390	nbHEL40	SARS-CoV-2 S	wtTM/H1cCT	SEQ ID NO: 24	SEQ ID NO: 80	SEQ ID NO: 74	SEQ ID NO: 53	SEQ ID NO: 35
7391	nbHEL40	SARS-CoV-2 S	wtTM/H3mCT	SEQ ID NO: 24	SEQ ID NO: 81	SEQ ID NO: 75	SEQ ID NO: 54	SEQ ID NO: 35
7392	nbHEL40	SARS-CoV-2 S	wtTM/H6hkCT	SEQ ID NO: 24	SEQ ID NO: 82	SEQ ID NO: 76	SEQ ID NO: 55	SEQ ID NO: 35
7393	nbHEL40	SARS-CoV-2 S	wtTM/H7gCT	SEQ ID NO: 24	SEQ ID NO: 83	SEQ ID NO: 77	SEQ ID NO: 56	SEQ ID NO: 35
7394	nbHEL40	SARS-CoV-2 S	wtTM/H9hkCT	SEQ ID NO: 24	SEQ ID NO: 84	SEQ ID NO: 78	SEQ ID NO: 57	SEQ ID NO: 35
7395	nbHEL40	SARS-CoV-2 S	wtTM/BwCT	SEQ ID NO: 24	SEQ ID NO: 85	SEQ ID NO: 79	SEQ ID NO: 58	SEQ ID NO: 35
9231	nbHEL40	SARS-COV-1 S	wtTMCT	SEQ ID NO: 86	SEQ ID NO: 87	SEQ ID NO: 88	SEQ ID NO: 93	SEQ ID NO: 111
9232	nbHEL40	SARS-COV-1 S	H5iTMCT	SEQ ID NO: 86	SEQ ID NO: 28	SEQ ID NO: 89	SEQ ID NO: 94	SEQ ID NO: 111
9233	nbHEL40	SARS-COV-1 S	wtTM/H5iCT	SEQ ID NO: 86	SEQ ID NO: 28	SEQ ID NO: 90	SEQ ID NO: 95	SEQ ID NO: 111

構建體 #	5' UTR	感興趣的基因 (GOI)	TMCT 區	引子 1 (片段 1 之前置引子)	引子 2 (片段 1 之反置引子)	第一次 PCR 的模板/ 所得基因	所得蛋白	受體質體
9234	nbHEL40	SARS-COV-1 S	wtTM/H5iCT (V4)	SEQ ID NO: 86	SEQ ID NO: 28	SEQ ID NO: 91	SEQ ID NO: 96	SEQ ID NO: 111
9235	nbHEL40	SARS-COV-1 S	wtTM/H1cCT	SEQ ID NO: 86	SEQ ID NO: 80	SEQ ID NO: 92	SEQ ID NO: 97	SEQ ID NO: 111
9246	nbHEL40	MERS S	wtTMCT	SEQ ID NO: 86	SEQ ID NO: 98	SEQ ID NO: 101	SEQ ID NO: 106	SEQ ID NO: 111
9247	nbHEL40	MERS S	H5iTMCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 102	SEQ ID NO: 107	SEQ ID NO: 111
9249	nbHEL40	MERS S	wtTM/H5iCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 103	SEQ ID NO: 108	SEQ ID NO: 111
9250	nbHEL40	MERS S	wtTM/H5iCT (V4)	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 104	SEQ ID NO: 109	SEQ ID NO: 111
9251	nbHEL40	MERS S	wtTM/H1cCT	SEQ ID NO: 86	SEQ ID NO: 99	SEQ ID NO: 105	SEQ ID NO: 110	SEQ ID NO: 111
9269	nbHEL40	OC43 S	wtTMCT	SEQ ID NO: 86	SEQ ID NO: 136	SEQ ID NO: 137	SEQ ID NO: 142	SEQ ID NO: 111
9270	nbHEL40	OC43 S	H5iTMCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 138	SEQ ID NO: 143	SEQ ID NO: 111
9272	nbHEL40	OC43 S	wtTM/H5iCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 139	SEQ ID NO: 144	SEQ ID NO: 111
9273	nbHEL40	OC43 S	wtTM/H5iCT (V4)	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 140	SEQ ID NO: 145	SEQ ID NO: 111
9274	nbHEL40	OC43 S	wtTM/H1cCT	SEQ ID NO: 86	SEQ ID NO: 99	SEQ ID NO: 141	SEQ ID NO: 146	SEQ ID NO: 111
9310	nbHEL40	229E S	wtTMCT	SEQ ID NO: 86	SEQ ID NO: 147	SEQ ID NO: 148	SEQ ID NO: 153	SEQ ID NO: 111
9311	nbHEL40	229E S	H5iTMCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 149	SEQ ID NO: 154	SEQ ID NO: 111
9312	nbHEL40	229E S	wtTM/H5iCT	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 150	SEQ ID NO: 155	SEQ ID NO: 111
9313	nbHEL40	229E S	wtTM/H5iCT (V4)	SEQ ID NO: 86	SEQ ID NO: 100	SEQ ID NO: 151	SEQ ID NO: 156	SEQ ID NO: 111
9314	nbHEL40	229E S	wtTM/H1cCT	SEQ ID NO: 86	SEQ ID NO: 99	SEQ ID NO: 152	SEQ ID NO: 157	SEQ ID NO: 111

[實施例2] 方法

[農桿菌轉染]

【0332】 使用D'Aoust 等人，2008(Plant Biotech. J. 6:930-40)描述的方法藉由

電穿孔法用SARS-CoV-2經修飾的S蛋白表現載體轉染農桿菌菌株AGL1。經轉染的農桿菌在補充有10 mM 2-(N-嗎啉基)乙磺酸(MES)、20 μM乙醯丁香酮、50 μg/ml卡本西林(carbenicillin)和 25 μg/ml羧苄青黴素pH5.6的YEB培養基中生長至OD_{600}介於0.6和16之間。農桿菌懸浮液在使用之前離心，並重新懸浮在浸潤培養基(10 mM $MgCl_2$和10 mM MES pH 5.6)中。

[植物生物質的製備、接種和農桿菌浸潤]

【0333】 圓葉菸草(*N. benthamiana*)植物在填充有商業泥炭苔蘚基質的平地中由種子生長。允許植物在溫室中在16/8光週期和25°C白天/20°C夜晚的溫度狀態下生長。播種之後三週，挑出單個小植株，移植到盆中，並在相同環境條件下在溫室中再生長三週。

【0334】 用每種表現載體轉染的農桿菌在補充有10 mM 2-(N-嗎啉基)乙磺酸(MES)、20 μM乙醯丁香酮、50 μg/ml卡本西林和25 μg/ml pH 5.6羧苄青黴素的YEB培養基中生長，直到它們達到OD_{600}介於0.6和16之間。農桿菌懸浮液在使用之前離心，並重新懸浮在浸潤培養基(10 mM $MgCl_2$和10 mM MES pH 5.6)中，並在4°C下儲存過夜。在浸潤當天，將培養批次稀釋為2.5培養體積並在使用之前使其加溫。在 20-40 Torr的真空下，將圓葉菸草的全株倒置在氣密不鏽鋼罐中的細菌懸浮液中2分鐘。將植物送回溫室進行6或9天的培養期直至收穫。

[葉收穫和總蛋白質和VLP萃取]

【0335】 培養之後，收穫植物的地上部分，在-80°C下冷凍並壓碎。藉由在2體積的冷50 mM Tris緩衝液(pH 8.0 + 500 mM NaCl，0.4 μg/ml偏亞硫酸鹽和1 mM苯甲磺醯氟)中機械均質化(Polytron)每個冷凍壓碎的植物材料的樣品來萃取總可溶性蛋白質。均質化之後，將漿液在4°C下以10,000 g離心10分鐘，並將這些澄清的粗萃取物(上清液)保留用於分析。

【0336】 澄清的粗萃取物的總蛋白質含量係藉由布拉德福測定法(Bio-Rad，Hercules，California)使用牛血清白蛋白作為參考標準來確定。在還原

條件下使用Criterion™ TGX Stain-Free™預製凝膠(Bio-Rad Laboratories, Hercules, CA)藉由SDS-PAGE分離蛋白質。藉由用考馬斯亮藍染色凝膠來顯現蛋白質。或者，用Gel Doc™ EZ成像系統(Bio-Rad Laboratories，Hercules，CA)對蛋白質進行可視化並電轉移到聚偏二氟乙烯(PVDF)膜(Roche Diagnostics Corporation，Indianapolis，Indiana)上進行免疫檢測。在進行免疫墨點法之前，將膜在4°C下用5%脫脂牛奶和0.1%Tween-20的Tris緩衝鹽水(TBS-T)封閉16-18小時。

【0337】 對於VLP純化，使用具有兩體積萃取緩衝液(pH7.0下的50mM Tris緩衝液+500mM NaCl)的混合器藉由機械萃取從冷凍生物質中萃取蛋白質，並使用0.5M檸檬酸將pH降低至6.1。將漿液通過大孔尼龍過濾器過濾以去除大碎片並在4°C下5000g離心5分鐘。收集上清液並再次以5000 g離心30分鐘(4°C)以去除額外的碎片並通過澄清過濾器。然後將上清液加載到不連續的碘克沙醇密度梯度上。分析密度梯度離心係如以下進行：製備含有Tris緩衝液中不連續碘克沙醇密度梯度的38 mL試管(3 ml 35%、3 ml 30%、3 ml 25%、3 ml 15% 和5 ml 10%碘克沙醇)並以22毫升含有病毒樣顆粒的萃取物覆蓋。梯度以120,000 g離心2小時(4°C)。離心之後，從底到頂收集1 mL餾分，並藉由SDS-PAGE結合蛋白質染色或西方墨點法分析餾分。使用Amicon離心裝置將級分6至9合併並進行緩衝液交換。蛋白質含量藉由布拉德福測定法測定。

[蛋白質分析和免疫墨點法]

【0338】 免疫墨點法是以TBS-Tween 20 0.1%中的2%脫脂牛奶稀釋的初級mAb（抗-S1, Sino Biological, cat#40150-R007 或抗-S2, Novus biological, cat#NB100-56578)進行第一次培育。過氧化物酶偶聯的山羊抗-兔(Jackson Immunoresearch, cat #115-035-144)作為二級抗體在TBS-Tween 20 0.1%中的2%脫脂牛奶進行化學發光檢測。免疫反應性複合物係藉由使用發光胺作為基底的化學發光檢測(Roche Diagnostics Corporation)。辣根過氧化物酶-酵素結合人IgG抗體係藉由使用EZ-Link Plus® 活化過氧化物酶結合套組(Pierce, Rockford, IL)進

行。

【0339】 在澄清的粗萃取物中評估植物產量，並使用基於毛細管的電泳方法(Protein Simple，BioTechne)技術和WES分析系統進行分析。簡言之，粗萃取物中的可溶性蛋白質在毛細管中按分子量分離並固定到基質上。使用純化的VLP的標準曲線用於確定S蛋白數量，並根據製造商的說明使用抗-S2抗體(Novus bio，cat#NB100-56578)進行檢測。然後使用設置為1的比較器構造對產量進行標準化。

【0340】 用於檢測SARS-CoV S蛋白的初級抗體是來自Sino Biologicals的SARS-CoV棘S1次單位抗體，40150-MM08(1/5000)，且用於檢測的二級抗體是山羊抗-小鼠，JIR，115-035-146(1/10000)。用於檢測MERS CoV S蛋白的初級抗體是來自Sino Biological，(100208-RP02，1/5000)的MERS-CoV棘蛋白S1抗體(N-端)。用於檢測的二級抗體是來自JIR(115-035-144, 1/10000)的山羊抗-小鼠。用於檢測的初級抗體是來自Antibodies-online的抗-冠狀病毒OC43棘蛋白(ABIN2754654, 1/1000)。用於檢測的二級抗體是來自JIR的山羊抗-兔(111-035-144, 1/10000)。

[電子顯微鏡]

【0341】 為了確定表現的S蛋白是否組裝成VLP，對純化的VLP進行免疫捕獲顆粒的穿透式電子顯微鏡(TEM)。將輝光放電的碳/銅網格(10s，0.3mbar)放置於20μL純化的VLP(100μg/mL)上5分鐘，然後用無菌蒸餾水洗滌4次。將網格漂浮在20μL之2%乙酸氧鈾(uranyl acetate)上1分鐘，然後藉由接觸濕濾紙移除過量溶液，並允許在濾紙上乾燥24小時，然後在TEM(Tecnai顯微鏡)下觀察。

[實施例3]

【0342】 在上述實施例中使用以下序列。

原生SARS-CoV-2 S蛋白wtTM/CT AA(P0DTC2) (SEQ ID NO：1)

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHS

TQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNII
RGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKS
WMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGY
FKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGD
SSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT
LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAW
NRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIR
GDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYL
YRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGV
GYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVL
TESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNT
SNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGA
EHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENS
VAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY
GSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILP
DPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGL
TVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNG
IGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQA
LNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVT
QQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPH
GVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQR
NFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKN
HTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQY
IKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDED
DSEPVLKGVKLHYT

原生SARS-CoV-2 S蛋白wtTM/CT AA (P0DTC2)，不含訊號肽(SP) (SEQ ID NO：：2)

VNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWF
HAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQS
LLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANN
CTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDL
PQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYV
GYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNF
RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLY
NSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIAD
YNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDIS
TEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH
APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDI
ADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEV
PVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGIC
ASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVT
TEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQ
DKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV
TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSA
LLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIAN
QFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISS
VLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAA
TKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKN
FTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGN
CDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASV

VNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAI

VMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

H5 A/Indonesia/5/05 血球凝集素 (HA) AA (A5A5L7) (SEQ ID NO：3)

MEKIVLLLAIVSLVKSDQICIGYHANNSTEQVDTIMEKNVTVTHAQDILEK

THNGKLCDLDGVKPLILRDCSVAGWLLGNPMCDEFINVPEWSYIVEKAN

PTNDLCYPGSFNDYEELKHLLSRINHFEKIQIIPKSSWSDHEASSGVSSACP

YLGSPSFFRNVVWLIKKNSTYPTIKKSYNNTNQEDLLVLWGIHHPNDAAE

QTRLYQNPTTYISIGTSTLNQRLVPKIATRSKVNGQSGRMEFFWTILKPND

AINFESNGNFIAPEYAYKIVKKGDSAIMKSELEYGNCNTKCQTPMGAINSS

MPFHNIHPLTIGECPKYVKSNRLVLATGLRNSPQRESRRKKRGLFGAIAGF

IEGGWQGMVDGWYGYHHSNEQGSGYAADKESTQKAIDGVTNKVNSIID

KMNTQFEAVGREFNNLERRIENLNKKMEDGFLDVWTYNAELLVLMENE

RTLDFHDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNECMESIRN

GTYNYPQYSEEARLKREEISGVKLESIGTYQILSIYSTVASSLALAIMMAG

LSLWMCSNGSLQCRICI

H5 A/Indonesia/5/05血球凝集素(HA)病毒cDNA(EF541394.1) (SEQ ID NO：4)

CTGTAAAAATGGAGAAAATAGTGCTTCTTCTTGCAATAGTCAGTCTTG

TTAAAAGTGATCAGATTTGCATTGGTTACCATGCAAACAATTCAACAG

AGCAGGTTGACACAATCATGGAAAAGAACGTTACTGTTACACATGCC

CAAGACATACTGGAAAAGACACACAACGGGAAGCTCTGCGATCTAGA

TGGAGTGAAGCCTCTAATTTTAAGAGATTGTAGTGTAGCTGGATGGCT

CCTCGGGAACCCAATGTGTGACGAATTCATCAATGTACCGGAATGGTC

TTACATAGTGGAGAAGGCCAATCCAACCAATGACCTCTGTTACCCAGG

GAGTTTCAACGACTATGAAGAACTGAAACACCTATTGAGCAGAATAA

ACCATTTTGAGAAAATTCAAATCATCCCCAAAAGTTCTTGGTCCGATC

ATGAAGCCTCATCAGGAGTGAGCTCAGCATGTCCATACCTGGGAAGTC

CCTCCTTTTTTAGAAATGTGGTATGGCTTATCAAAAAGAACAGTACAT

ACCCAACAATAAAGAAAAGCTACAATAATACCAACCAAGAAGATCTT

TTGGTACTGTGGGGAATTCACCATCCTAATGATGCGGCAGAGCAGACA

AGGCTATATCAAAACCCAACCACCTATATTTCCATTGGGACATCAACA

CTAAACCAGAGATTGGTACCAAAAATAGCTACTAGATCCAAAGTAAA

CGGGCAAAGTGGAAGGATGGAGTTCTTCTGGACAATTTTAAAACCTA

ATGATGCAATCAACTTCGAGAGTAATGGAAATTTCATTGCTCCAGAAT

ATGCATACAAAATTGTCAAGAAAGGGGACTCAGCAATTATGAAAAGT

GAATTGGAATATGGTAACTGCAACACCAAGTGTCAAACTCCAATGGG

GGCGATAAACTCTAGTATGCCATTCCACAACATACACCCTCTCACCAT

CGGGGAATGCCCCAAATATGTGAAATCAAACAGATTAGTCCTTGCAA

CAGGGCTCAGAAATAGCCCTCAAAGAGAGAGCAGAAGAAAAAAGAG

AGGACTATTTGGAGCTATAGCAGGTTTTATAGAGGGAGGATGGCAGG

GAATGGTAGATGGTTGGTATGGGTACCACCATAGCAATGAGCAGGGG

AGTGGGTACGCTGCAGACAAAGAATCCACTCAAAAGGCAATAGATGG

AGTCACCAATAAGGTCAACTCAATCATTGACAAAATGAACACTCAGTT

TGAGGCCGTTGGAAGGGAATTTAATAACTTAGAAAGGAGAATAGAGA

ATTTAAACAAGAAGATGGAAGACGGGTTTCTAGATGTCTGGACTTATA

ATGCCGAACTTCTGGTTCTCATGGAAAATGAGAGAACTCTAGACTTTC

ATGACTCAAATGTTAAGAACCTCTACGACAAGGTCCGACTACAGCTTA

GGGATAATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTCTATCACA

AATGTGATAATGAATGTATGGAAAGTATAAGAAACGGAACGTACAAC

TATCCGCAGTATTCAGAAGAAGCAAGATTAAAAAGAGAGGAAATAAG

TGGGGTAAAATTGGAATCAATAGGAACTTACCAAATACTGTCAATTTA

TTCAACAGTGGCGAGTTCCCTAGCACTGGCAATCATGATGGCTGGTCT
ATCTTTATGGATGTGCTCCAATGGATCGTTACAATGCAGAATTTGCAT
TTAAATTTGTGAGTTCAG

經修飾的SARS-CoV-2，具有H5 A/Indonesia/5/05血球凝集素CT AA (SEQ ID NO：5)

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHS
TQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNII
RGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKS
WMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGY
FKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGD
SSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCT
LKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAW
NRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIR
GDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYL
YRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGV
GYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVL
TESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNT
SNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGA
EHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENS
VAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY
GSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILP
DPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGL
TVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNG
IGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQA
LNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVT

QQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPH

GVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQR

NFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKN

HTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQY

IKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

H1 A/California/7/2009 血球凝集素TM/CT AA (SEQ ID NO：6)

IDGVKLESTRIYQILAIYSTVASSLVLVVSLGAISFWMCSNGSLQCRICI

H2 A/Singapore/1/1957 血球凝集素 TM/CT AA (SEQ ID NO：7)

IKGVKLSSMGVYQILAIYATVAGSLSLAIMMAGISFWMCSNGSLQCRICI

H3 A/Minnesota/41/2019 血球凝集素 TM/CT AA (SEQ ID NO：8)

IKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

H5 A/Indonesia/5/05 血球凝集素 TM/CT AA (SEQ ID NO：9)

ISGVKLESIGTYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

H6 A/Teal/Hong Kong/W312/97 血球凝集素 TM/CT AA (SEQ ID NO：10)

IESVKLENLGVYQILAIYSTVSSSLVLVGLIMAMGLWMCSNGSMQCRICI

H7 A/Guangdong/17SF003/2016 血球凝集素 TM/CT AA (SEQ ID NO：11)

IDPVKLSSGYKDVILWFSFGASCFILLAIVMGLVFICVKNGNMRCTICI

H9 A/Hong Kong/1073/99 血球凝集素 TM/CT AA (SEQ ID NO：12)

IEGVKLESEGTYKILTIYSTVASSLVLAMGFAAFLFWAMSNGSCRCNICI

B/Washington/02/2019 血球凝集素 TM/CT AA (SEQ ID NO：13)

AASLNDDGLDNHTILLYYSTAASSLAVTLMIAIFVVYMVSRDNVSCSICL

流感血球凝集素之C-端區的共通序列(SEQ ID NO：14)

IXGVKLXSXGXYXILXIYSTVASSLXLXXXXXXXXXWMCSNGSXXCXICI

流感血球凝集素之CT結構域的共通序列(SEQ ID NO：15)

XXWMCSNGSXXCXICI

原生SARS-CoV-2 S蛋白的C-端區 wtTM/CT (SEQ ID NO：16)

WYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCC

KFDEDDSEPVLKGVKLHYT

H5 A/Indonesia/5/05 血球凝集素的C-端區 (SEQ ID NO：17)

ISGVKLESIGTYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

具有H5i血球凝集素CT之經修飾的SARS-CoV-2 S蛋白的C-端區 (SEQ ID NO：18)

WYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

具有H5i血球凝集素CT之經修飾的 SARS-CoV-2 S蛋白的C-端區，變體 1 (SEQ ID NO：19)

WYIWLGFIAGLIAIVMVTIMMAGLSLWMCSNGSLQCRICI

(無SP) SARS-CoV-2 S蛋白GSAS+PP wtTM/CT AA (SEQ ID NO：20)

VNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWF

HAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQS

LLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANN

CTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDL

PQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYV

GYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNF

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLY

NSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIAD

YNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDIS

TEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH

APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDI

ADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEV

PVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGIC

ASYQTQTNSPGSASSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVT

TEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQ

DKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV

TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSA

LLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIAN

QFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISS

VLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAAT

KMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNF

TTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGN

CDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASV

VNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAI

VMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

(無SP) 經修飾的SARS-CoV-2 S 蛋白 GSAS+PP，具有H5i血球凝集素CT AA (SEQ ID NO：21)

VNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWF

HAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQS

LLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANN

CTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDL

PQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYV

GYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNF

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLY

NSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIAD

YNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDIS

TEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH

APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDI

ADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEV

PVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGIC

ASYQTQTNSPGSASSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVT

TEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQ

DKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV

TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSA

LLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIAN

QFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISS

VLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAAT

KMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNF

TTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGN

CDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASV

VNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAI

VMVTIMLSLWMCSNGSLQCRICI

PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-DNA (SEQ ID NO：22)

ATGGCGAAAAACGTTGCGATTTTCGGCTTATTGTTTTCTCTTCTTGTGT

TGGTTCCTTCTCAGATCTTCGCGGTGAATCTTACGACGCGAACACAGT

TACCACCCGCATATACAAATAGCTTCACTCGGGGTGTTTATTACCCCG

ACAAAGTGTTCAGGTCCTCCGTGCTCCACTCAACACAGGACCTCTTTC

TTCCTTTCTTTTCTAACGTGACATGGTTTCATGCCATTCATGTATCCGG

CACTAACGGTACTAAGAGGTTCGATAATCCTGTGCTCCCTTTCAATGA

CGGCGTTTACTTTGCAAGCACAGAGAAGAGTAACATCATCCGAGGTTG

GATCTTTGGCACTACCCTCGATTCAAAGACGCAGAGCCTCCTCATTGT

GAACAATGCCACTAACGTGGTGATCAAAGTTTGCGAGTTTCAGTTCTG

CAATGACCCTTTCTTGGGGGTGTACTATCATAAGAACAACAAGTCTTG

GATGGAATCTGAATTCCGCGTCTATAGCAGCGCCAACAACTGCACCTT

TGAATACGTGTCCCAGCCCTTCCTTATGGACCTGGAGGGAAAGCAGGG

AAACTTTAAGAATCTGAGAGAGTTCGTGTTTAAAAATATCGACGGCTA

TTTTAAGATCTATTCTAAGCACACGCCTATTAATCTCGTGCGCGATCTT

CCACAAGGCTTCAGCGCCCTGGAACCACTCGTGGACCTCCCAATTGGT

ATCAACATCACTAGATTTCAGACTCTGCTTGCCCTCCACCGATCCTATC

TGACACCCGGAGACTCCTCTAGCGGCTGGACTGCCGGCGCTGCCGCTT

ATTACGTTGGTTATCTTCAGCCACGCACGTTCCTGCTGAAGTATAACG

AGAATGGTACTATTACCGATGCCGTGGATTGTGCCCTTGACCCCCTGT

CCGAAACTAAGTGCACACTCAAGTCATTCACTGTGGAAAAAGGAATC

TACCAGACAAGCAATTTTCGGGTCCAGCCTACTGAGAGCATTGTGCGC

TTTCCTAACATCACAAATCTTTGCCCCTTCGGAGAGGTTTTCAATGCTA

CACGGTTTGCCTCCGTGTATGCCTGGAACCGCAAGAGAATTTCCAATT

GCGTGGCCGATTACTCCGTGCTCTACAATAGTGCAAGCTTTAGCACCT

TTAAGTGCTATGGCGTATCCCCTACTAAGCTTAACGACTTGTGTTTCAC

AAACGTGTATGCCGACTCCTTTGTGATACGGGGCGACGAAGTTAGACA

GATAGCACCAGGACAGACGGGAAAGATAGCTGACTACAACTATAAGC

TTCCTGATGACTTCACTGGCTGCGTTATCGCGTGGAATTCTAACAACCT

GGACTCAAAAGTCGGCGGCAACTATAACTATCTCTATCGGCTGTTCCG

CAAGAGTAACCTTAAGCCCTTTGAGAGAGATATAAGCACTGAAATCT

ACCAGGCTGGCAGTACGCCCTGTAATGGCGTGGAAGGCTTTAATTGTT

ATTTTCCACTGCAATCCTATGGTTTTCAGCCAACCAATGGCGTGGGCT

ACCAACCATACCGCGTCGTGGTGCTCTCCTTTGAACTGCTCCACGCTC

CCGCGACTGTCTGCGGCCCCAAGAAGTCCACGAACCTTGTGAAGAAT

AAGTGCGTTAATTTTAATTTCAACGGCCTCACTGGAACAGGAGTGCTC

ACTGAGAGTAACAAGAAGTTCCTGCCATTTCAACAATTTGGCAGAGAC

ATAGCCGATACTACTGACGCCGTTAGGGACCCCCAGACCCTCGAGATT

CTCGATATAACGCCCTGCTCCTTCGGTGGAGTTTCCGTGATCACGCCA

GGCACCAATACCAGTAACCAGGTCGCCGTGCTGTATCAGGATGTCAAC

TGTACTGAGGTGCCCGTAGCCATCCATGCGGATCAGCTCACACCAACT

TGGAGGGTGTACAGCACCGGCTCCAATGTATTCCAGACTCGGGCCGG

ATGCCTTATTGGCGCCGAACACGTGAACAATAGTTACGAATGCGATAT

TCCAATTGGCGCCGGAATCTGTGCTAGCTACCAGACTCAGACGAACTC

CCCAGGCAGCGCCAGCAGCGTTGCCAGCCAGTCAATCATCGCTTATAC

AATGTCACTTGGAGCCGAAAACTCCGTGGCTTACTCAAACAACAGCAT

CGCCATCCCCACAAACTTCACCATATCCGTGACAACTGAGATTCTGCC

AGTGTCCATGACTAAGACGTCCGTAGATTGCACTATGTACATATGCGG

CGACAGCACAGAATGTTCTAATCTGCTGCTGCAATATGGAAGCTTCTG

CACTCAACTGAACAGAGCGCTCACAGGCATCGCCGTGGAGCAGGATA

AGAATACCCAGGAGGTGTTCGCCCAAGTTAAGCAGATCTACAAGACC

CCACCCATAAAGGATTTCGGTGGATTCAATTTTAGTCAGATACTCCCA

GACCCATCTAAGCCATCCAAGAGGAGCTTTATCGAGGATCTTTTGTTT

AACAAAGTTACTCTGGCCGACGCCGGTTTCATCAAGCAGTACGGAGAT

TGCCTCGGCGACATCGCTGCTCGTGACCTCATCTGTGCGCAAAAGTTT

AACGGTCTGACGGTGCTGCCTCCCCTCCTTACTGATGAAATGATCGCC

CAGTATACCAGCGCACTCCTCGCTGGCACCATAACATCCGGTTGGACA

TTCGGCGCTGGTGCAGCACTGCAGATACCATTCGCCATGCAAATGGCA

TATCGTTTCAACGGTATCGGTGTCACACAGAATGTCCTATATGAGAAC

CAGAAGCTGATCGCAAATCAGTTCAATAGTGCCATCGGAAAAATCCA

GGATAGCCTTAGCAGCACAGCCTCAGCCCTTGGCAAACTCCAGGATGT

CGTGAACCAGAATGCCCAGGCTCTCAATACCCTCGTGAAGCAGCTCTC
ATCTAATTTCGGCGCAATTTCCAGTGTCCTCAACGACATCCTCAGCCG
CCTCGACCCCCCCGAGGCCGAAGTGCAGATTGACAGACTGATTACAG
GTCGACTCCAGAGCCTCCAGACTTACGTGACTCAGCAGCTGATAAGAG
CCGCCGAGATAAGGGCCAGCGCTAACCTGGCTGCCACAAAGATGTCT
GAGTGCGTGCTGGGCCAGTCCAAGAGAGTAGACTTCTGTGGCAAAGG
CTACCATCTGATGAGCTTCCCACAATCCGCACCTCACGGCGTAGTGTT
CCTCCACGTGACATATGTACCGGCTCAGGAGAAGAATTTCACTACCGC
TCCTGCTATATGCCATGATGGAAAGGCTCACTTCCCCCGGGAGGGGGT
GTTCGTGTCCAACGGCACCCATTGGTTTGTGACTCAGCGGAATTTCTA
CGAACCCCAGATCATAACCACTGACAACACATTTGTGTCCGGAAATTG
TGACGTGGTCATTGGAATAGTGAACAACACTGTTTATGATCCACTGCA
GCCAGAACTTGACAGCTTTAAGGAGGAGCTCGACAAGTACTTCAAGA
ATCATACGTCACCAGATGTGGACCTCGGAGATATTAGCGGTATCAATG
CCAGTGTTGTCAATATTCAGAAGGAAATAGACCGCCTTAATGAGGTCG
CCAAAAATCTGAACGAGAGCCTCATCGATCTTCAGGAGCTGGGCAAA
TATGAGCAGTACATCAAGTGGCCTTGGTATATTTGGCTTGGCTTCATC
GCCGGCCTGATCGCCATAGTAATGGTCACAATTATGCTCTGCTGCATG
ACCTCTTGCTGCTCCTGTCTGAAAGGCTGCTGCTCTTGCGGATCCTGCT
GCAAATTTGATGAGGATGACAGTGAACCAGTCCTGAAGGGCGTGAAG
CTGCACTATACTTAG

PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-AA (SEQ ID NO：23)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV

YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSC
GSCCKFDEDDSEPVLKGVKLHYT

IF(PDI)-CoV(opt2).c (SEQ ID NO：24)

TCTCAGATCTTCGCGGTGAATCTTACGACGCGAACACAGTTACCACCC

GCAT

IF(AVB)-CoV(opt2).r (SEQ ID NO：25)

ACGACACGACTAAGGCCTCTAAGTATAGTGCAGCTTCACGCCCTTCAG

GAC

PDI-經修飾的SARS-CoV-2 S蛋白GSAS+PP H5iTM/CT-DNA (SEQ ID NO：

26)

ATGGCGAAAAACGTTGCGATTTTCGGCTTATTGTTTTCTCTTCTTGTGT

TGGTTCCTTCTCAGATCTTCGCGGTGAATCTTACGACGCGAACACAGT

TACCACCCGCATATACAAATAGCTTCACTCGGGGTGTTTATTACCCCG

ACAAAGTGTTCAGGTCCTCCGTGCTCCACTCAACACAGGACCTCTTTC

TTCCTTTCTTTTCTAACGTGACATGGTTTCATGCCATTCATGTATCCGG

CACTAACGGTACTAAGAGGTTCGATAATCCTGTGCTCCCTTTCAATGA

CGGCGTTTACTTTGCAAGCACAGAGAAGAGTAACATCATCCGAGGTTG

GATCTTTGGCACTACCCTCGATTCAAAGACGCAGAGCCTCCTCATTGT

GAACAATGCCACTAACGTGGTGATCAAAGTTTGCGAGTTTCAGTTCTG

CAATGACCCTTTCTTGGGGGTGTACTATCATAAGAACAACAAGTCTTG

GATGGAATCTGAATTCCGCGTCTATAGCAGCGCCAACAACTGCACCTT

TGAATACGTGTCCCAGCCCTTCCTTATGGACCTGGAGGGAAAGCAGGG

AAACTTTAAGAATCTGAGAGAGTTCGTGTTTAAAAATATCGACGGCTA

TTTTAAGATCTATTCTAAGCACACGCCTATTAATCTCGTGCGCGATCTT

CCACAAGGCTTCAGCGCCCTGGAACCACTCGTGGACCTCCCAATTGGT

ATCAACATCACTAGATTTCAGACTCTGCTTGCCCTCCACCGATCCTATC

TGACACCCGGAGACTCCTCTAGCGGCTGGACTGCCGGCGCTGCCGCTT

ATTACGTTGGTTATCTTCAGCCACGCACGTTCCTGCTGAAGTATAACG

AGAATGGTACTATTACCGATGCCGTGGATTGTGCCCTTGACCCCCTGT

CCGAAACTAAGTGCACACTCAAGTCATTCACTGTGGAAAAAGGAATC

TACCAGACAAGCAATTTTCGGGTCCAGCCTACTGAGAGCATTGTGCGC

TTTCCTAACATCACAAATCTTTGCCCCTTCGGAGAGGTTTTCAATGCTA

CACGGTTTGCCTCCGTGTATGCCTGGAACCGCAAGAGAATTTCCAATT

GCGTGGCCGATTACTCCGTGCTCTACAATAGTGCAAGCTTTAGCACCT

TTAAGTGCTATGGCGTATCCCCTACTAAGCTTAACGACTTGTGTTTCAC

AAACGTGTATGCCGACTCCTTTGTGATACGGGGCGACGAAGTTAGACA

GATAGCACCAGGACAGACGGGAAAGATAGCTGACTACAACTATAAGC

TTCCTGATGACTTCACTGGCTGCGTTATCGCGTGGAATTCTAACAACCT

GGACTCAAAAGTCGGCGGCAACTATAACTATCTCTATCGGCTGTTCCG

CAAGAGTAACCTTAAGCCCTTTGAGAGAGATATAAGCACTGAAATCT

ACCAGGCTGGCAGTACGCCCTGTAATGGCGTGGAAGGCTTTAATTGTT

ATTTTCCACTGCAATCCTATGGTTTTCAGCCAACCAATGGCGTGGGCT

ACCAACCATACCGCGTCGTGGTGCTCTCCTTTGAACTGCTCCACGCTC

CCGCGACTGTCTGCGGCCCCAAGAAGTCCACGAACCTTGTGAAGAAT

AAGTGCGTTAATTTTAATTTCAACGGCCTCACTGGAACAGGAGTGCTC

ACTGAGAGTAACAAGAAGTTCCTGCCATTTCAACAATTTGGCAGAGAC

ATAGCCGATACTACTGACGCCGTTAGGGACCCCCAGACCCTCGAGATT

CTCGATATAACGCCCTGCTCCTTCGGTGGAGTTTCCGTGATCACGCCA

GGCACCAATACCAGTAACCAGGTCGCCGTGCTGTATCAGGATGTCAAC

TGTACTGAGGTGCCCGTAGCCATCCATGCGGATCAGCTCACACCAACT

TGGAGGGTGTACAGCACCGGCTCCAATGTATTCCAGACTCGGGCCGG

ATGCCTTATTGGCGCCGAACACGTGAACAATAGTTACGAATGCGATAT

TCCAATTGGCGCCGGAATCTGTGCTAGCTACCAGACTCAGACGAACTC

CCCAGGCAGCGCCAGCAGCGTTGCCAGCCAGTCAATCATCGCTTATAC

AATGTCACTTGGAGCCGAAAACTCCGTGGCTTACTCAAACAACAGCAT

CGCCATCCCCACAAACTTCACCATATCCGTGACAACTGAGATTCTGCC

AGTGTCCATGACTAAGACGTCCGTAGATTGCACTATGTACATATGCGG

CGACAGCACAGAATGTTCTAATCTGCTGCTGCAATATGGAAGCTTCTG

CACTCAACTGAACAGAGCGCTCACAGGCATCGCCGTGGAGCAGGATA

AGAATACCCAGGAGGTGTTCGCCCAAGTTAAGCAGATCTACAAGACC

CCACCCATAAAGGATTTCGGTGGATTCAATTTTAGTCAGATACTCCCA

GACCCATCTAAGCCATCCAAGAGGAGCTTTATCGAGGATCTTTTGTTT

AACAAAGTTACTCTGGCCGACGCCGGTTTCATCAAGCAGTACGGAGAT

TGCCTCGGCGACATCGCTGCTCGTGACCTCATCTGTGCGCAAAAGTTT

AACGGTCTGACGGTGCTGCCTCCCCTCCTTACTGATGAAATGATCGCC

CAGTATACCAGCGCACTCCTCGCTGGCACCATAACATCCGGTTGGACA

TTCGGCGCTGGTGCAGCACTGCAGATACCATTCGCCATGCAAATGGCA

TATCGTTTCAACGGTATCGGTGTCACACAGAATGTCCTATATGAGAAC

CAGAAGCTGATCGCAAATCAGTTCAATAGTGCCATCGGAAAAATCCA

GGATAGCCTTAGCAGCACAGCCTCAGCCCTTGGCAAACTCCAGGATGT

CGTGAACCAGAATGCCCAGGCTCTCAATACCCTCGTGAAGCAGCTCTC

ATCTAATTTCGGCGCAATTTCCAGTGTCCTCAACGACATCCTCAGCCG

CCTCGACCCCCCCGAGGCCGAAGTGCAGATTGACAGACTGATTACAG

GTCGACTCCAGAGCCTCCAGACTTACGTGACTCAGCAGCTGATAAGAG

CCGCCGAGATAAGGGCCAGCGCTAACCTGGCTGCCACAAAGATGTCT

GAGTGCGTGCTGGGCCAGTCCAAGAGAGTAGACTTCTGTGGCAAAGG

CTACCATCTGATGAGCTTCCCACAATCCGCACCTCACGGCGTAGTGTT

CCTCCACGTGACATATGTACCGGCTCAGGAGAAGAATTTCACTACCGC

TCCTGCTATATGCCATGATGGAAAGGCTCACTTCCCCCGGGAGGGGGT

GTTCGTGTCCAACGGCACCCATTGGTTTGTGACTCAGCGGAATTTCTA
CGAACCCCAGATCATAACCACTGACAACACATTTGTGTCCGGAAATTG
TGACGTGGTCATTGGAATAGTGAACAACACTGTTTATGATCCACTGCA
GCCAGAACTTGACAGCTTTAAGGAGGAGCTCGACAAGTACTTCAAGA
ATCATACGTCACCAGATGTGGACCTCGGAGATATTAGCGGTATCAATG
CCAGTGTTGTCAATATTCAGAAGGAAATAGACCGCCTTAATGAGGTCG
CCAAAAATCTGAACGAGAGCCTCATCGATCTTCAGGAGCTGGGCAAA
TATGAGCAGTACATCAAGTGGCCTTGGTATCAAATACTGTCAATTTAT
TCAACAGTGGCGAGTTCCCTAGCACTGGCAATCATGATGGCTGGTCTA
TCTTTATGGATGTGCTCCAATGGATCGTTACAATGCAGAATTTGCATTT
AA

PDI-經修飾的SARS-CoV-2 S蛋白GSAS+PP H5iTM/CT-AA (SEQ ID NO：27)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF

QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQC
RICI

IF(Avb)-H5I.r (SEQ ID NO：28)

ACGACACGACTAAGGCCTTTAAATGCAAATTCTGCATTGTAACGATCC

PDI-經修飾的SARS-CoV-2 S蛋白GSAS+PP wtTM/H5iCT-DNA (SEQ ID NO：29)

ATGGCGAAAAACGTTGCGATTTTCGGCTTATTGTTTTCTCTTCTTGTGT
TGGTTCCTTCTCAGATCTTCGCGGTGAATCTTACGACGCGAACACAGT
TACCACCCGCATATACAAATAGCTTCACTCGGGGTGTTTATTACCCCG
ACAAAGTGTTCAGGTCCTCCGTGCTCCACTCAACACAGGACCTCTTTC
TTCCTTTCTTTTCTAACGTGACATGGTTTCATGCCATTCATGTATCCGG
CACTAACGGTACTAAGAGGTTCGATAATCCTGTGCTCCCTTTCAATGA
CGGCGTTTACTTTGCAAGCACAGAGAAGAGTAACATCATCCGAGGTTG
GATCTTTGGCACTACCCTCGATTCAAAGACGCAGAGCCTCCTCATTGT

GAACAATGCCACTAACGTGGTGATCAAAGTTTGCGAGTTTCAGTTCTG

CAATGACCCTTTCTTGGGGGTGTACTATCATAAGAACAACAAGTCTTG

GATGGAATCTGAATTCCGCGTCTATAGCAGCGCCAACAACTGCACCTT

TGAATACGTGTCCCAGCCCTTCCTTATGGACCTGGAGGGAAAGCAGGG

AAACTTTAAGAATCTGAGAGAGTTCGTGTTTAAAAATATCGACGGCTA

TTTTAAGATCTATTCTAAGCACACGCCTATTAATCTCGTGCGCGATCTT

CCACAAGGCTTCAGCGCCCTGGAACCACTCGTGGACCTCCCAATTGGT

ATCAACATCACTAGATTTCAGACTCTGCTTGCCCTCCACCGATCCTATC

TGACACCCGGAGACTCCTCTAGCGGCTGGACTGCCGGCGCTGCCGCTT

ATTACGTTGGTTATCTTCAGCCACGCACGTTCCTGCTGAAGTATAACG

AGAATGGTACTATTACCGATGCCGTGGATTGTGCCCTTGACCCCCTGT

CCGAAACTAAGTGCACACTCAAGTCATTCACTGTGGAAAAAGGAATC

TACCAGACAAGCAATTTTCGGGTCCAGCCTACTGAGAGCATTGTGCGC

TTTCCTAACATCACAAATCTTTGCCCCTTCGGAGAGGTTTTCAATGCTA

CACGGTTTGCCTCCGTGTATGCCTGGAACCGCAAGAGAATTTCCAATT

GCGTGGCCGATTACTCCGTGCTCTACAATAGTGCAAGCTTTAGCACCT

TTAAGTGCTATGGCGTATCCCCTACTAAGCTTAACGACTTGTGTTTCAC

AAACGTGTATGCCGACTCCTTTGTGATACGGGGCGACGAAGTTAGACA

GATAGCACCAGGACAGACGGGAAAGATAGCTGACTACAACTATAAGC

TTCCTGATGACTTCACTGGCTGCGTTATCGCGTGGAATTCTAACAACCT

GGACTCAAAAGTCGGCGGCAACTATAACTATCTCTATCGGCTGTTCCG

CAAGAGTAACCTTAAGCCCTTTGAGAGAGATATAAGCACTGAAATCT

ACCAGGCTGGCAGTACGCCCTGTAATGGCGTGGAAGGCTTTAATTGTT

ATTTTCCACTGCAATCCTATGGTTTTCAGCCAACCAATGGCGTGGGCT

ACCAACCATACCGCGTCGTGGTGCTCTCCTTTGAACTGCTCCACGCTC

CCGCGACTGTCTGCGGCCCCAAGAAGTCCACGAACCTTGTGAAGAAT

AAGTGCGTTAATTTTAATTTCAACGGCCTCACTGGAACAGGAGTGCTC

ACTGAGAGTAACAAGAAGTTCCTGCCATTTCAACAATTTGGCAGAGAC

ATAGCCGATACTACTGACGCCGTTAGGGACCCCCAGACCCTCGAGATT

CTCGATATAACGCCCTGCTCCTTCGGTGGAGTTTCCGTGATCACGCCA

GGCACCAATACCAGTAACCAGGTCGCCGTGCTGTATCAGGATGTCAAC

TGTACTGAGGTGCCCGTAGCCATCCATGCGGATCAGCTCACACCAACT

TGGAGGGTGTACAGCACCGGCTCCAATGTATTCCAGACTCGGGCCGG

ATGCCTTATTGGCGCCGAACACGTGAACAATAGTTACGAATGCGATAT

TCCAATTGGCGCCGGAATCTGTGCTAGCTACCAGACTCAGACGAACTC

CCCAGGCAGCGCCAGCAGCGTTGCCAGCCAGTCAATCATCGCTTATAC

AATGTCACTTGGAGCCGAAAACTCCGTGGCTTACTCAAACAACAGCAT

CGCCATCCCCACAAACTTCACCATATCCGTGACAACTGAGATTCTGCC

AGTGTCCATGACTAAGACGTCCGTAGATTGCACTATGTACATATGCGG

CGACAGCACAGAATGTTCTAATCTGCTGCTGCAATATGGAAGCTTCTG

CACTCAACTGAACAGAGCGCTCACAGGCATCGCCGTGGAGCAGGATA

AGAATACCCAGGAGGTGTTCGCCCAAGTTAAGCAGATCTACAAGACC

CCACCCATAAAGGATTTCGGTGGATTCAATTTTAGTCAGATACTCCCA

GACCCATCTAAGCCATCCAAGAGGAGCTTTATCGAGGATCTTTTGTTT

AACAAAGTTACTCTGGCCGACGCCGGTTTCATCAAGCAGTACGGAGAT

TGCCTCGGCGACATCGCTGCTCGTGACCTCATCTGTGCGCAAAAGTTT

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PDI-經修飾的SARS-CoV-2 S蛋白GSAS+PP wtTM/H5iCT-AA (SEQ ID NO：30)

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選殖載體8501，從左到右T-DNA (SEQ ID NO：31)

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選殖載體 8500，從左到右T-DNA (SEQ ID NO：33)

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TGCATGACGTTATTTATGAGATGGGTTTTTATGATTAGAGTCCCGCAA

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GGATAAATTATCGCGCGCGGTGTCATCTATGTTACTAGATCTCTAGAG

TCTCAAGCTTGGCGCGCCCACGTGACTAGTGGCACTGGCCGTCGTTTT

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TGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCG

CACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGCTA

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ACTATCAGTGTTTGACAGGATATATTGGCGGGTAAACCTAAGAGAAA

AGAGCGTTTA

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ACATTTAATACGCGATAGAAAACAAAATATAGCGCGCAAACTAGGAT

AAATTATCGCGCGCGGTGTCATCTATGTTACTAGAT

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TAACACATTGCGGACGTTTTTAATGTACTGAATTAACGCCGAATCCCG

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CGCAGCCTGAATGGCGAATGCTAGAGCAGCTTGAGCTTGGATCAGATT

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CTTTATTGTGAAGATAGTGGAAAAGGAAGGTGGCTCCTACAAATGCC

ATCATTGCGATAAAGGAAAGGCCATCGTTGAAGATGCCTCTGCCGAC

AGTGGTCCCAAAGATGGACCCCCACCCACGAGGAGCATCGTGGAAAA

AGAAGACGTTCCAACCACGTCTTCAAAGCAAGTGGATTGATGTGATA

ACATGGTGGAGCACGACACACTTGTCTACTCCAAAAATATCAAAGAT

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TTGCGATAAAGGAAAGGCCATCGTTGAAGATGCCTCTGCCGACAGTG

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ACTGACGTAAGGGATGACGCACAATCCCACTATCCTTCGCAAGACCCT

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TCCTGTTGCCGGTCTTGCGATGATTATCATATAATTTCTGTTGAATTAC

GTTAAGCATGTAATAATTAACATGTAATGCATGACGTTATTTATGAGA

TGGGTTTTTATGATTAGAGTCCCGCAATTATACATTTAATACGCGATA

GAAAACAAAATATAGCGCGCAAACTAGGATAAATTATCGCGCGCGGT

GTCATCTATGTTACTAGAT

具有H5i血球凝集素CT之經修飾的SARS-CoV-2 S蛋白的C-端區，變體2 (SEQ ID NO：37)

WYIWLGFIAGLIAIVMVTIMAGLSLWMCSNGSLQCRICI

具有H5i血球凝集素CT之經修飾的SARS-CoV-2 S蛋白的C-端區，變體3 (SEQ ID NO：38)

WYIWLGFIAGLIAIVMVTIMLCCMCSNGSLQCRICI

具有H5i血球凝集素CT之經修飾的SARS-CoV-2 S蛋白的C-端區，變體4 (SEQ ID NO：39)

WYIWLGFIAGLIAIVMVTIMLCCSNGSLQCRICI

3'UTR AvB (Arracacha病毒B) (SEQ ID NO：40)

TAGTCGTGTCGTTTTTCAAATAATATAATCCTTTTAGGGTTTTAGTTAG

TTTAAATTTTCTGTTGCTCCTGTTTAGCAGGTCGTGCCTTCAGCAAGCA

CACAAAAACAGAGTGTTTATTTTAAGTTGTTTGTTTAGTGATTCAAAA

AAAAA

3'UTR trBNYVV (甜菜壞死性黃脈病毒) (SEQ ID NO： 41)

CCTATCTTGATGAAGGTTGTTGTGGTTTTCTCATTACTGTTTTATTATTG

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CTAATTGTTTGTTGGGTTGTAATGTACTGACTGGGTGTGAATTGTACCA

GTCGTTAAAGGGTTTACTATCAGTATATTGATAT

3' UTR SBMV (南方豆花葉病毒) (SEQ ID NO： 42)

TGAGGAGTTGTATAATAATACCTGCACCCTTCTCTTTGGCAGGGAGGG

TGTTTCGTTTTCACAATGCCACGCGCTTGAGGGAGAATGCACGTTAAT

CATCCCTCCGCTAGTGATGGAGCGTAATCCAAAAGT

3’ UTR TuRSV (蕪菁輪點病毒) (SEQ ID NO： 43)

TGATTTATAATAGCCATAGATTAAGTTTAAATGTATTACGTTTGTATTT

TATTCTCTTTTTTAAGTTTCCTATGTTGTTTTAAATTAAATATCTGTATA

ATTAGTAGATGTAAATCTGCTTTGTGCGTTTGACAGTCTGTGGAAACG

CACTGGTTCATGAGATAGGACCACCTAGGAGGTAGGACTCTGGGTTTT

AATTATCTCATTTCTTAGTTATACCGTATTATATATATGATTTAGTAGT

AATTGTTTTCTCTTGATATGTATTATTACTTTTTTATT

3’ UTR CPMV (豇豆花葉病毒) (SEQ ID NO： 44)

ATTTTCTTTAGTTTGAATTTACTGTTATTCGGTGTGCATTTCTATGTTTG

GTGAGCGGTTTTCTGTGCTCAGAGTGTGTTTATTTTATGTAATTTAATT

TCTTTGTGAGCTCCTGTTTAGCAGGTCGTCCCTTCAGCAAGGACACAA

AAAGATTTTAATTTTATT

3’ UTR BBTMV (蠶豆真花葉病毒) (SEQ ID NO： 45)

TAGTTTTCTTCCGCTTTTCTTTTGTAGTGTGTGGTTTTCTTTGTTTCTTCT

TTTCTTTTCTCTTTCCTTTTCTCTTACTCCTGCCTGGCAGGTCGTGCCTT

CAGTAAGCACAACAAAAATATGCATTTATTAGAGTATTTCTTTCTTCTT

TAGCATAAAGGTATTGAAGACCTATAAACTTCGTCCGGGTTGGGGAA

AGTACCAGCTTAGCATATCTTTAGAAAACTATATAGAGCTCTTTACCT

TGAGTTGTTTCCTAAAGTTTATGCAAAAAA

3’ UTR trOUMV (歐爾密甜瓜病毒) (SEQ ID NO： 46)

CTCACGTCTGGGGTGAGCCCTAGCCAAATAGGAAAACGATAAGCGCT

TTGCATGCAAAATGAGTTGGGCCACAAGTGCCACTCGCAGCGAAGGC

GGTCTGAGGTTTCCCCCTGGCGGTTACTTCCATATCTTTGGGAGATAA

CTGGG

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H5i血球凝集素CT AA (SEQ ID NO：47)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN

GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+4P，具有H5i血球凝集素CT AA (SEQ ID NO：48)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSPIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTPSALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR

LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL

MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN

GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK

EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL

QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+6P，具有H5i血球凝集素CT AA (SEQ ID NO：49)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK

VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY

FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV

YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE

FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL

HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL

DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT

RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN

VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK

VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS

YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF

NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG

VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF

QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY

TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST

ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF

GGFNFSQILPDPSKPSKRSPIEDLLFNKVTLADAGFIKQYGDCLGDIAARD

LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGPALQIPFP

MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTPSALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP+923，具有H5i血球凝集素CT AA (SEQ ID NO：50)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF

GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSFSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+4P+923，具有H5i血球凝集素CT AA (SEQ ID NO：51)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY

TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST

ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF

GGFNFSQILPDPSKPSKRSPIEDLLFNKVTLADAGFIKQYGDCLGDIAARD

LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA

MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSFSSTPSALGKLQ

DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR

LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL

MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN

GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK

EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL

QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+6P+923，具有H5i血球凝集素CT AA (SEQ ID NO：52)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK

VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY

FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV

YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE

FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL

HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL

DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT

RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN

VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK

VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS

YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF

NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG

VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSPIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGPALQIPFP
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSFSSTPSALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSLWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H1 Cal血球凝集素CT AA (SEQ ID NO：53)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS

YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLSFWMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H3 Minn血球凝集素 CT AA (SEQ ID NO：54)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN

VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLMWACQKGNIRCNICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H6 HK血球凝集素CT AA (SEQ ID NO：55)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL

DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLGLWMCSNGSMQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H7 Guangdong血球凝集素CT AA (SEQ ID NO：56)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE

FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLVFICVKNGNMRCTICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有 H9 HK血球凝集素 CT AA (SEQ ID NO：57)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY

FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLLFWAMSNGSCRCNICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有 B/Wash 血球凝集素 CT AA (SEQ ID NO：58)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLVVYMVSRDNVSCSICL

(PDI)經修飾的SARS-CoV-2 S 蛋白GSAS+PP，具有H5i 血球凝集素 CT (選擇性 1) AA (SEQ ID NO：59)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD
LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK

EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL

QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMMAGLSLWMCSNGSLQC

RICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H5i血球凝集素 CT (選擇性 2) AA (SEQ ID NO：60)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK

VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY

FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV

YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE

FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL

HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL

DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT

RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN

VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK

VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS

YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF

NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG

VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF

QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY

TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST

ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF

GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD

LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA

MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ

DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR

LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMAGLSLWMCSNGSLQCRI
CI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H5i血球凝集素 CT (選擇性 3) AA (SEQ ID NO：61)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST
ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF
GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD

LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA
MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ
DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR
LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL
MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN
GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK
EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL
QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMCSNGSLQCRICI

(PDI)經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H5i 血球凝集素 CT (選擇性 4) AA (SEQ ID NO：62)

MAKNVAIFGLLFSLLVLVPSQIFAVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVY
FASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGV
YYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRE
FVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL
DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQS
YGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNF
NGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGG
VSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVF
QTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQSIIAY
TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDST

ECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDF

GGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARD

LICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA

MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ

DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGR

LQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHL

MSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSN

GTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFK

EELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL

QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCSNGSLQCRICI

原生SARS-CoV-2 S蛋白的N-端區 (下劃線的原生訊號肽序列) (SEQ ID NO：63)

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNS

經修飾的 TMCT，具有 肽間插序列 $(X)_n$ (SEQ ID NO： 64)

WYIWLGFIAGLIAIVMVTIM$(X)_n$CSNGSXXCXICI

PDI-S 蛋白 GSAS+4P-DNA (SEQ ID NO： 65)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcggtgaatcttacg

acgcgaacacagttaccacccgcatatacaaatagcttcactcggggtgtttattaccccgacaaagtgttcaggtcct

ccgtgctccactcaacacaggacctctttcttcctttctttttctaacgtgacatggtttcatgccattcatgtatccggcact

aacggtactaagaggttcgataatcctgtgctccctttcaatgacggcgtttactttgcaagcacagagaagagtaaca

tcatccgaggttggatctttggcactaccctcgattcaaagacgcagagcctcctcattgtgaacaatgccactaacgt

ggtgatcaaagtttgcgagtttcagttctgcaatgacccttttcttgggggtgtactatcataagaacaacaagtcttggat

ggaatctgaattccgcgtctatagcagcgccaacaactgcacctttgaatacgtgtcccagcccttccttatggacctg

gagggaaagcagggaaactttaagaatctgagagagttcgtgtttaaaaatatcgacggctattttaagatctattctaa

gcacacgcctattaatctcgtgcgcgatcttccacaaggcttcagcgccctggaaccactcgtggacctcccaattgg

tatcaacatcactagatttcagactctgcttgccctccaccgatcctatctgacacccggagactcctctagcggctgg

actgccggcgctgccgcttattacgttggttatcttcagccacgcacgttcctgctgaagtataacgagaatggtactat

taccgatgccgtggattgtgcccttgacccccctgtccgaaactaagtgcacactcaagtcattcactgtggaaaaagg

aatctaccagacaagcaattttcgggtccagcctactgagagcattgtgcgctttcctaacatcacaaatctttgcccctt

cggagaggttttcaatgctacacggtttgcctccgtgtatgcctggaaccgcaagagaatttccaattgcgtggccgat

tactccgtgctctacaatagtgcaagctttagcacctttaagtgctatggcgtatcccctactaagcttaacgacttgtgtt

tcacaaacgtgtatgccgactcctttgtgatacggggcgacgaagttagacagatagcaccaggacagacgggaaa

gatagctgactacaactataagcttcctgatgacttcactggctgcgttatcgcgtggaattctaacaacctggactcaa

aagtcggcggcaactataactatctctatcggctgttccgcaagagtaaccttaagccctttgagagagatataagcac

tgaaatctaccaggctggcagtacgccctgtaatggcgtggaaggctttaattgttattttccactgcaatcctatggtttt

cagccaaccaatggcgtgggctaccaaccataccgcgtcgtggtgctctcctttgaactgctccacgctcccgcgac

tgtctgcggccccaagaagtccacgaaccttgtgaagaataagtgcgttaattttaatttcaacggcctcactggaaca

ggagtgctcactgagagtaacaagaagttcctgccatttcaacaatttggcagagacatagccgatactactgacgcc

gttagggacccccagaccctcgagattctcgatataacgccctgctccttcggtggagtttccgtgatcacgccaggc

accaataccagtaaccaggtcgccgtgctgtatcaggatgtcaactgtactgaggtgcccgtagccatccatgcggat

cagctcacaccaacttggagggtgtacagcaccggctccaatgtattccagactcgggccggatgccttattggcgc

cgaacacgtgaacaatagttacgaatgcgatattccaattggcgccggaatctgtgctagctaccagactcagacga

actccccaggcagcgccagcagcgttgccagccagtcaatcatcgcttatacaatgtcacttggagccgaaaactcc

gtggcttactcaaacaacagcatcgccatccccacaaacttcaccatatccgtgacaactgagattctgccagtgtcca

tgactaagacgtccgtagattgcactatgtacatatgcggcgacagcacagaatgttctaatctgctgctgcaatatgg

aagcttctgcactcaactgaacagagcgctcacaggcatcgccgtggagcaggataagaatacccaggaggtgttc

gcccaagttaagcagatctacaagaccccacccataaaggatttcggtggattcaattttagtcagatactcccagacc

catctaagccatccaagaggagccccatcgaggatcttttgtttaacaaagttactctggccgacgccggtttcatcaa

gcagtacggagattgcctcggcgacatcgctgctcgtgacctcatctgtgcgcaaaagtttaacggtctgacggtgct

gcctcccctccttactgatgaaatgatcgcccagtataccagcgcactcctcgctggcaccataacatccggttggac

attcggcgctggtgcagcactgcagataccattcgccatgcaaatggcatatcgtttcaacggtatcggtgtcacaca
gaatgtcctatatgagaaccagaagctgatcgcaaatcagttcaatagtgccatcggaaaaatccaggatagccttag
cagcacaccctcagcccttggcaaactccaggatgtcgtgaaccagaatgcccaggctctcaataccctcgtgaagc
agctctcatctaatttcggcgcaatttccagtgtcctcaacgacatcctcagccgcctcgaccccccgaggccgaag
tgcagattgacagactgattacaggtcgactccagagcctccagacttacgtgactcagcagctgataagagccgcc
gagataagggccagcgctaacctggctgccacaaagatgtctgagtgcgtgctgggccagtccaagagagtagac
ttctgtggcaaaggctaccatctgatgagcttcccacaatccgcacctcacggcgtagtgttcctccacgtgacatatg
taccggctcaggagaagaatttcactaccgctcctgctatatgccatgatggaaaggctcacttcccccgggagggg
gtgttcgtgtccaacggcacccattggtttgtgactcagcggaatttctacgaaccccagatcataaccactgacaaca
catttgtgtccggaaattgtgacgtggtcattggaatagtgaacaacactgtttatgatccactgcagccagaacttgac
agctttaaggaggagctcgacaagtacttcaagaatcatacgtcaccagatgtggacctcggagatattagcggtatc
aatgccagtgttgtcaatattcagaaggaaatagaccgccttaatgaggtcgccaaaaatctgaacgagagcctcatc
gatcttcaggagctgggcaaatatgagcagtacatcaagtggccttggtatatttggcttggcttcatcgccggcctga
tcgccatagtaatggtcacaattatgctctctttatggatgtgctccaatggatcgttacaatgcagaatttgcatttaa

PDI-S 蛋白 GSAS+6P-DNA (SEQ ID NO： 66)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcggtgaatcttacg
acgcgaacacagttaccacccgcatatacaaatagcttcactcggggtgtttattaccccgacaaagtgttcaggtcct
ccgtgctccactcaacacaggacctctttcttcctttctttttctaacgtgacatggtttcatgccattcatgtatccggcact
aacggtactaagaggttcgataatcctgtgctccctttcaatgacggcgtttactttgcaagcacagagaagagtaaca
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tcgccatagtaatggtcacaattatgatggccggcctctctttatggatgtgctccaatggatcgttacaatgcagaattt
gcatttaa

PDI-經修飾的 S 蛋白 具有 H5i 血球凝集素 CT (V2) DNA (SEQ ID NO： 71)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcggtgaatcttacg
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tttaa

PDI-經修飾的S蛋白，具有 H5i 血球凝集素 CT (V3) DNA (SEQ ID NO： 72)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcggtgaatcttacg
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tcgccatagtaatggtcacaattatgctctgctgcatgtgctccaatggatcgttacaatgcagaatttgcatttaa

PDI-經修飾的S蛋白，具有 H5i 血球凝集素 CT (V4) DNA (SEQ ID NO： 73)

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PDI-S-蛋白+ B/ Wash DNA (SEQ ID NO： 79)

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IF-H3MinnesotaCT.r (SEQ ID NO： 81)

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IF-GuangdongCT.r (SEQ ID NO： 83)

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IF-H9HKCT.r (SEQ ID NO： 84)

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IF-BWashCT.r (SEQ ID NO： 85)

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IF(nbHEL40)-PDI.c (SEQ ID NO： 86)

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IF(AvB+wtCT).r (SEQ ID NO： 87)

ACGACACGACTAAGGCCTTTAGGTATAATGGAGTTTCACCCCCTTCAG

AA

PDI-SARS-COV-1 wtTMCT-DNA (SEQ ID NO： 88)

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PDI-SARS-COV-1 H5iTMCT-DNA (SEQ ID NO： 89)

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PDI-SARS-COV-1 H5iCT-DNA (SEQ ID NO： 90)

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PDI-SARS-COV-1 H5iCT(V4)-DNA (SEQ ID NO： 91)

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PDI-SARS-COV-1 H1cCT-DNA (SEQ ID NO： 92)

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PDI-SARS-COV-1 wtTMCT-AA (SEQ ID NO： 93)

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KLHYT

PDI-SARS-COV-1 H5iTMCT-AA (SEQ ID NO： 94)

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PDI-SARS-COV-1 H5iCT-AA (SEQ ID NO： 95)

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LGFIAGLIAIVMVTILLSLWMCSNGSLQCRICI
PDI-SARS-COV-1 H5iCT(V4)-AA (SEQ ID NO： 96)
MAKNVAIFGLLFSLLVLVPSQIFASDLDRCTTFDDVQAPNYTQHTSSMRG
VYYPDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDGIYFAA
TEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFELCDNPFFAVS
KPMGTQTHTMIFDNAFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKD
GFLYVYKGYQPIDVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSPAQDI
WGTSAAAYFVGYLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSF
EIDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKK
ISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDV
RQIAPGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRY

LRHGKLRPFERDISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQP

YRVVVLSFELLNAPATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSK

RFQPFQQFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSEVA

VLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAGCLIGAEHVDT

SYECDIPIGAGICASYHTVSLLASTSQKSIVAYTMSLGADSSIAYSNNTIAIP

TNFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSFCTQLNR

ALSGIAAEQDRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKR

SFIEDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLL

TDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQ

NVLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLV

KQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRA

AEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLH

VTYVPSQERNFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIIT

TDNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG

DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYVW

LGFIAGLIAIVMVTILLCCSNGSLQCRICI

PDI-SARS-COV-1 H1cCT-AA (SEQ ID NO： 97)

MAKNVAIFGLLFSLLVLVPSQIFASDLDRCTTFDDVQAPNYTQHTSSMRG

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TEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFELCDNPFFAVS

KPMGTQTHTMIFDNAFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKD

GFLYVYKGYQPIDVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSPAQDI

WGTSAAAYFVGYLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSF

EIDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKK

ISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDV

RQIAPGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRY
LRHGKLRPFERDISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQP
YRVVVLSFELLNAPATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSK
RFQPFQQFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSEVA
VLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAGCLIGAEHVDT
SYECDIPIGAGICASYHTVSLLASTSQKSIVAYTMSLGADSSIAYSNNTIAIP
TNFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSFCTQLNR
ALSGIAAEQDRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKR
SFIEDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLL
TDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQ
NVLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLV
KQLSSNFGAISSVLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRA
AEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLH
VTYVPSQERNFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIIT
TDNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG
DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYVW
LGFIAGLIAIVMVTILLSFWMCSNGSLQCRICI

IF(AvB+wtCT-MERS).r (SEQ ID NO： 98)

ACGACACGACTAAGGCCTTCAGTGAACGTGGACCTTGTGAGGCTCAA
GGTCATACTCCTC

IF(H1cCT-wtTM).r (SEQ ID NO： 99)

ACGACACGACTAAGGCCTTCAAATACATATTCTACACTGTAGAGACCC
A

IF(H5ITMCT).r (SEQ ID NO： 100)

ACGACACGACTAAGGCCTTCAAATGCAAATTCTGCATTGTAACGATCC

PDI-MERS-wtTMCT-DNA (SEQ ID NO： 101)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcgTATGTCG
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AGGCCGACGGCATTATCTACCCCCAAGGTCGGACATATTCCAACATAA
CTATCACCTATCAGGGGCTATTCCCTTATCAGGGCGACCATGGGGACA
TGTACGTTTACAGCGCTGGTCACGCTACAGGGACGACCCCCCAGAAGC
TCTTCGTGGCGAACTATAGTCAGGACGTGAAACAGTTTGCCAACGGTT
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TCAGCCCTTCCACGAGTGCCACAATTCGAAAGATCTATCCGGCCTTCA
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TCTTCAACCACACGCTTGTGCTGCTTCCCGATGGGTGCGGTACTTTGCT
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CGCCGGGAACTCGTATACTTCCTTTGCCACTTATCATACTCCAGCCAC
GGATTGTAGCGATGGGAACTACAATAGGAACGCCAGTTTGAATTCCTT
TAAAGAGTACTTCAACTTGCGGAATTGTACCTTCATGTATACATATAA
CATTACTGAGGACGAAATTCTCGAATGGTTCGGAATCACTCAAACAGC
CCAGGGAGTGCACCTCTTTAGTTCTCGCTATGTGGACTTATATGGAGG
CAATATGTTTCAATTCGCCACCTTACCCGTCTACGATACGATCAAGTA
TTACTCGATCATACCCCACTCCATTAGGTCCATTCAGAGCGATCGCAA
GGCATGGGCCGCATTCTATGTGTATAAGCTCCAGCCCCTGACCTTCCT
CTTGGATTTCTCCGTGGACGGCTACATCAGAAGGGCTATCGATTGCGG
GTTCAACGACCTCAGCCAGCTGCATTGTTCTTATGAGAGCTTTGACGT
GGAAAGCGGAGTTTACTCAGTCTCTTCCTTTGAGGCTAAACCTTCAGG
TAGCGTCGTAGAGCAAGCAGAGGGTGTGGAGTGCGATTTCTCACCACT

GCTCAGCGGAACCCCACCCCAGGTCTACAACTTTAAGCGGCTCGTGTT

CACAAACTGTAACTATAACTTGACTAAGTTGCTGTCACTCTTTTCCGTG

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TTTGTGACGCAGCAAACCCTACTAACTGTATCGCGCCAGTTAATGGCT

ACTTTATTAAAACAAATAACACACGCATTGTGGATGAATGGAGTTACA

CAGGGTCCAGCTTCTACGCTCCAGAGCCTATCACCTCTCTGAACACAA
AGTATGTGGCACCTCAGGTCACATATCAGAACATCTCGACAAACCTGC
CCCCCCCACTCTTGGGCAACTCCACAGGGATCGACTTCCAGGACGAGC
TTGACGAATTCTTCAAGAACGTGTCCACCAGTATCCCTAATTTTGGTTC
GCTGACCCAAATTAACACAACCCTGCTCGATCTGACATATGAAATGCT
TTCACTACAGCAGGTGGTCAAAGCGTTGAACGAGTCGTATATCGACCT
GAAAGAGTTAGGGAATTACACATACTATAACAAATGGCCCTGGTATA
TTTGGTTAGGATTCATTGCCGGGCTGGTGGCCCTTGCCTTGTGCGTATT
TTTCATCTTGTGCTGTACCGGTTGCGGTACGAATTGCATGGGAAAACT
GAAATGTAATCGGTGCTGCGATCGCTATGAGGAGTATGACCTTGAGCC
TCACAAGGTCCACGTTCACTGA

PDI-MERS-H5iTMCT-DNA (SEQ ID NO： 102)

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AGCAGACCTTCTTCGATAAGACTTGGCCTCGGCCAATTGATGTGTCCA
AGGCCGACGGCATTATCTACCCCCAAGGTCGGACATATTCCAACATAA
CTATCACCTATCAGGGGCTATTCCCTTATCAGGGCGACCATGGGGACA
TGTACGTTTACAGCGCTGGTCACGCTACAGGGACGACCCCCCAGAAGC
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TGCTAGGATCCTCTGTGGGCAATTTTAGCGACGGTAAGATGGGTCGGT
TCTTCAACCACACGCTTGTGCTGCTTCCCGATGGGTGCGGTACTTTGCT
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CGCCGGGAACTCGTATACTTCCTTTGCCACTTATCATACTCCAGCCAC

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PDI-MERS-H5iCT-DNA (SEQ ID NO： 103)

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PDI-MERS-H5iCT(V4)-DNA (SEQ ID NO： 104)

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AGGCCGACGGCATTATCTACCCCCAAGGTCGGACATATTCCAACATAA

CTATCACCTATCAGGGGCTATTCCCTTATCAGGGCGACCATGGGGACA

TGTACGTTTACAGCGCTGGTCACGCTACAGGGACGACCCCCCAGAAGC

TCTTCGTGGCGAACTATAGTCAGGACGTGAAACAGTTTGCCAACGGTT

TTGTAGTGCGCATCGGGGCAGCCGCTAACTCCACTGGTACTGTTATTA

TCAGCCCTTCCACGAGTGCCACAATTCGAAAGATCTATCCGGCCTTCA

TGCTAGGATCCTCTGTGGGCAATTTTAGCGACGGTAAGATGGGTCGGT

TCTTCAACCACACGCTTGTGCTGCTTCCCGATGGGTGCGGTACTTTGCT

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CGCCTCCCAGTTGGGAAATTGTGTTGAATATTCCCTGTACGGAGTGTC

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CAGTGCCCGTTCCGCCATCGAGGATCTGCTCTTCGACAAAGTAACTAT

TGCAGATCCCGGATACATGCAGGGGTATGACGACTGCATGCAGCAGG

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ACAAAGTGTTGCCTCCTCTCATGGACGTGAACATGGAAGCGGCCTATA

CCTCCTCACTTCTAGGCTCCATAGCGGGCGTGGGATGGACCGCAGGGC

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AATAACGCACAAGCCCTGTCAAAGCTGGCTTCAGAGCTCTCAAATACA

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TTTGGTTAGGATTCATTGCCGGGCTGGTGGCCCTTGCCTTGTGCGTATT

TTTCATCTTGtgctgctccaatggatcgttacaatgcagaatttgcattTGA

PDI-MERS-H1cCT-DNA (SEQ ID NO： 105)

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AGGCCGACGGCATTATCTACCCCCAAGGTCGGACATATTCCAACATAA

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TCTTCGTGGCGAACTATAGTCAGGACGTGAAACAGTTTGCCAACGGTT

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TCAGCCCTTCCACGAGTGCCACAATTCGAAAGATCTATCCGGCCTTCA

TGCTAGGATCCTCTGTGGGCAATTTTAGCGACGGTAAGATGGGTCGGT

TCTTCAACCACACGCTTGTGCTGCTTCCCGATGGGTGCGGTACTTTGCT

GAGGGCCTTTTACTGTATCCTAGAGCCCCGATCCGGCAACCACTGCCC

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CTTGGATTTCTCCGTGGACGGCTACATCAGAAGGGCTATCGATTGCGG

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GGAGGATTGTAAGCTGCCCCTTGGTCAAAGCTTATGCGCACTGCCCGA

TACGCCCAGCACACTTACACCAGCTTCAGTGGGGTCCGTCCCCGGGGA

AATGAGATTGGCCTCGATCGCTTTCAACCACCCCATACAGGTGGATCA

GCTCAACTCGTCATACTTCAAGCTAAGCATCCCTACTAATTTCTCCTTT

GGTGTGACTCAGGAGTACATTCAGACCACAATTCAAAAGGTGACCGTT

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AATAACGCACAAGCCCTGTCAAAGCTGGCTTCAGAGCTCTCAAATACA

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PDI-MERS-wtTMCT-AA (SEQ ID NO： 106)

MAKNVAIFGLLFSLLVLVPSQIFAYVDVGPDSVKSACIEVDIQQTFFDKTW

PRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYVYSAGHATG

TTPQKLFVANYSQDVKQFANGFVVRIGAAANSTGTVIISPSTSATIRKIYPA
FMLGSSVGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCP
AGNSYTSFATYHTPATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNIT
EDEILEWFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSIIP
HSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDCGFNDLSQLH
CSYESFDVESGVYSVSSFEAKPSGSVVEQAEGVECDFSPLLSGTPPQVYNF
KRLVFTNCNYNLTKLLSLFSVNDFTCSQISPAAIASNCYSSLILDYFSYPLS
MKSDLSVSSAGPISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKC
SRFLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGG
WLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLG
NCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNY
YCLRACVSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTRSMLK
RRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPAS
VGSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQK
VTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLF
ASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADP
GYMQGYDDCMQQGPASARDLICAQYVAGYKVLPPLMDVNMEAAYTSS
LLGSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKF
NQALGAMQTGFTTTNEAFHKVQDAVNNNAQALSKLASELSNTFGAISAS
IGDIIQRLDPPEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLAKD
KVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVV
SAYGLCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLN
TKYVAPQVTYQNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLT
QINTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG
FIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKVH

VH

PDI-MERS-H5iTMCT-AA (SEQ ID NO： 107)

MAKNVAIFGLLFSLLVLVPSQIFAYVDVGPDSVKSACIEVDIQQTFFDKTW
PRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYVYSAGHATG
TTPQKLFVANYSQDVKQFANGFVVRIGAAANSTGTVIISPSTSATIRKIYPA
FMLGSSVGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCP
AGNSYTSFATYHTPATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNIT
EDEILEWFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSIIP
HSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDCGFNDLSQLH
CSYESFDVESGVYSVSSFEAKPSGSVVEQAEGVECDFSPLLSGTPPQVYNF
KRLVFTNCNYNLTKLLSLFSVNDFTCSQISPAAIASNCYSSLILDYFSYPLS
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SRFLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGG
WLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLG
NCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNY
YCLRACVSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTRSMLK
RRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPAS
VGSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQK
VTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLF
ASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADP
GYMQGYDDCMQQGPASARDLICAQYVAGYKVLPPLMDVNMEAAYTSS
LLGSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKF
NQALGAMQTGFTTTNEAFHKVQDAVNNNAQALSKLASELSNTFGAISAS
IGDIIQRLDPPEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLAKD
KVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVV

SAYGLCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLN

TKYVAPQVTYQNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLT

QINTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYQILSI

YSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

PDI-MERS-H5iCT-AA (SEQ ID NO： 108)

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PRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYVYSAGHATG

TTPQKLFVANYSQDVKQFANGFVVRIGAAANSTGTVIISPSTSATIRKIYPA

FMLGSSVGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCP

AGNSYTSFATYHTPATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNIT

EDEILEWFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSIIP

HSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDCGFNDLSQLH

CSYESFDVESGVYSVSSFEAKPSGSVVEQAEGVECDFSPLLSGTPPQVYNF

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MKSDLSVSSAGPISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKC

SRFLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGG

WLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLG

NCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNY

YCLRACVSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTRSMLK

RRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPAS

VGSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQK

VTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLF

ASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADP

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LLGSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKF

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IGDIIQRLDPPEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLAKD

KVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVV

SAYGLCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLN

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QINTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG

FIAGLVALALCVFFILSLWMCSNGSLQCRICI

PDI-MERS-H5iCT(V4)-AA (SEQ ID NO： 109)

MAKNVAIFGLLFSLLVLVPSQIFAYVDVGPDSVKSACIEVDIQQTFFDKTW

PRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYVYSAGHATG

TTPQKLFVANYSQDVKQFANGFVVRIGAAANSTGTVIISPSTSATIRKIYPA

FMLGSSVGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCP

AGNSYTSFATYHTPATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNIT

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MKSDLSVSSAGPISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKC

SRFLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGG

WLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLG

NCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNY

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RRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPAS

VGSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQK

VTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLF

ASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADP

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LLGSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKF

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KVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVV

SAYGLCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLN

TKYVAPQVTYQNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLT

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PDI-MERS-H1cCT-AA (SEQ ID NO： 110)

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FMLGSSVGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCP

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SRFLSDDRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGG

WLVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLG

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YCLRACVSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTRSMLK

RRDSTYGPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPAS
VGSVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQK
VTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLF
ASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADP
GYMQGYDDCMQQGPASARDLICAQYVAGYKVLPPLMDVNMEAAYTSS
LLGSIAGVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKF
NQALGAMQTGFTTTNEAFHKVQDAVNNNAQALSKLASELSNTFGAISAS
IGDIIQRLDPPEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLAKD
KVNECVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVV
SAYGLCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLN
TKYVAPQVTYQNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLT
QINTTLLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLG
FIAGLVALALCVFFILSFWMCSNGSLQCRICI

選殖載體 7147，從左到右T-DNA (SEQ ID NO： 111)

tggcaggatatattgtggtgtaaacaaattgacgcttagacaacttaataacacattgcggacgtttttaatgtactgaatt
aacgccgaatcccgggctggtatatttatatgttgtcaaataactcaaaaaccataaaagtttaagttagcaagtgtgta
cattttacttgaacaaaaatattcacctactactgttataaatcattattaaacattagagtaaagaaatatggatgataag
aacaagagtagtgatattttgacaacaattttgttgcaacatttgagaaaattttgttgttctctcttttcattggtcaaaaac
aatagagagagaaaaaggaagagggagaataaaaacataatgtgagtatgagagagaaagttgtacaaaagttgta
ccaaaatagttgtacaaatatcattgaggaatttgacaaaagctacacaaataagggttaattgctgtaaataaataagg
atgacgcattagagagatgtaccattagagaatttttggcaagtcattaaaaagaaagaataaattatttttaaaattaaa
agttgagtcatttgattaaacatgtgattatttaatgaattgatgaaagagttggattaaagttgtattagtaattagaatttg
gtgtcaaatttaatttgacatttgatcttttcctatatattgccccatagagtcagttaactcatttttatatttcatagatcaaat
aagagaaataacggtatattaatccctccaaaaaaaaaaaacggtatatttactaaaaaatctaagccacgtaggagg
ataacaggatccccgtaggaggataacatccaatccaaccaatcacaacaatcctgatgagataacccactttaagcc

cacgcatctgtggcacatctacattatctaaatcacacattcttccacacatctgagccacacaaaaaccaatccacatc

tttatcacccattctataaaaaatcacactttgtgagtctacactttgattcccttcaaacacatacaaagagaagagacta

attaattaattaatcatcttgagagaaaatggaacgagctatacaaggaaacgacgctagggaacaagctaacagtga

acgttgggatggaggatcaggaggtaccacttctcccttcaaacttcctgacgaaagtccgagttggactgagtggc

ggctacataacgatgagacgaattcgaatcaagataatccccttggtttcaaggaaagctggggtttcgggaaagttg

tatttaagagatatctcagatacgacaggacggaagcttcactgcacagagtccttggatcttggacgggagattcgg

ttaactatgcagcatctcgatttttcggtttcgaccagatcggatgtacctatagtattcggtttcgaggagttagtatcac

cgtttctggagggtcgcgaactcttcagcatctctgtgagatggcaattcggtctaagcaagaactgctacagcttgcc

ccaatcgaagtggaaagtaatgtatcaagaggatgccctgaaggtactcaaaccttcgaaaaagaaagcgagtaagt

taaaatgcttcttcgtctcctatttataatatggtttgttattgttaattttgttcttgtagaagagcttaattaatcgttgttgttat

gaaatactatttgtatgagatgaactggtgtaatgtaattcatttacataagtggagtcagaatcagaatgtttcctccata

actaactagacatgaagacctgccgcgtacaattgtcttatatttgaacaactaaaattgaacatcttttgccacaacttta

taagtggttaatatagctcaaatatatggtcaagttcaatagattaataatggaaatatcagttatcgaaattcattaacaat

caacttaacgttattaactactaattttatatcatccccttttgataaatgatagtacaccaattaggaaggagcatgctcgc

ctaggagattgtcgtttcccgccttcagtttgcaagctgctctagccgtgtagccaatacgcaaaccgcctctccccgc

gcgttgggaattactagcgcgtgtcgacaagcttgcatgccggtcaacatggtggagcacgacacacttgtctactcc

aaaaatatcaaagatacagtctcagaagaccaaagggcaattgagacttttcaacaaagggtaatatccggaaacctc

ctcggattccattgcccagctatctgtcactttattgtgaagatagtggaaaaggaaggtggctcctacaaatgccatca

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tcctacaaatgccatcattgcgataaaggaaaggccatcgttgaagatgcctctgccgacagtggtcccaaagatgg

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atctccactgacgtaagggatgacgcacaatcccactatccttcgcaagacccttcctctatataaggaagttcatttca

tttggagaggcactccatttgaatctatcaaaccaaaacacattgagacgtcacgtactcctcagccaaaacgacacc

cccatctgtctatccactggcccctggatctgctgcccaaactaactccatggtgaccctgggatgcctggtcaaggg

ctatttccctgagccagtgacagtgacctggaactctggatccctgtccagcggtgtgcacaccttcccagctgtcctg

cagtctgacctctacactctgagcagctcagtgactgtcccctccagcacctggcccagcgagaccgtcacctgcaa

cgttgcccacccggccagcagcaccaaggtggacaagaaaattgtgcccagggattgtggttgtaagccttgcatat

gtacagtcccagaagtatcatctgtcttcatcttccccccaaagcccaaggatgtgctcaccattactctgactcctaag

gtcacgtgtgttgtggtagacatcagcaaggatgatcccgaggtccagttcagctggtttgtagatgatgtggaggtg

cacacagctcagacgcaaccccgggaggagcagttcaacagcactttccgctcagtcagtgaacttcccatcatgca

ccaggactggctcaatggcaaggagacgtccagattttggcgatctattcaactgtcgccagttcattggtactggtag

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gtcgtttttcaaataatataatccttttagggttttagttagtttaaattttctgttgctcctgtttagcaggtcgtgccttcagc

aagcacacaaaaacagagtgtttatttttaagttgtttgtttagtgattcaaaaaaaaaatcgttcaaacatttggcaataaa

gtttcttaagattgaatcctgttgccggtcttgcgatgattatcatataatttctgttgaattacgttaagcatgtaataattaa

catgtaatgcatgacgttatttatgagatgggtttttatgattagagtcccgcaattatacatttaatacgcgatagaaaac

aaaatatagcgcgcaaactaggataaattatcgcgcgcggtgtcatctatgttactagatctctagagtctcaagcttgg

cgcgcccacgtgactagtggcactggccgtcgttttacaacgtcgtgactgggaaaaccctggcgttacccaacttaa

tcgccttgcagcacatccccctttcgccagctggcgtaatagcgaagaggcccgcaccgatcgcccttcccaacagt

tgcgcagcctgaatggcgaatgctagagcagcttgagcttggatcagattgtcgtttcccgccttcagtttaaactatca

gtgtttgacaggatatattggcgggtaaacctaagagaaaagagcgttta

原生 SARS-CoV-1 S 蛋白 wtTM/CT AA P59594 (SEQ ID NO： 112)

MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYYPDEIFRSDT

LYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDGIYFAATEKSNVVRGWV

FGSTMNNKSQSVIIINNSTNVVIRACNFELCDNPFFAVSKPMGTQTHTMIF

DNAFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKDGFLYVYKGYQPI

DVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVG

YLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGIYQTSNFR
VVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVLY
NSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDVRQIAPGQTGVIA
DYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRYLRHGKLRPFERD
ISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLN
APATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDV
SDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSEVAVLYQDVNCTDVS
TAIHADQLTPAWRIYSTGNNVFQTQAGCLIGAEHVDTSYECDIPIGAGICA
SYHTVSLLRSTSQKSIVAYTMSLGADSSIAYSNNTIAIPTNFSISITTEVMPV
SMAKTSVDCNMYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQDRNT
REVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLA
DAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYTAALV
SGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQIANQ
FNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVL
NDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATK
MSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTT
APAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGNCDV
VIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQ
KEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMV
TILLCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT

原生 MERS S 蛋白 wtTM/CT AA AFY13307 (SEQ ID NO： 113)

MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKTWPRPIDVS
KADGIIYPQGRTYSNITITYQGLFPYQGDHGDMYVYSAGHATGTTPQKLF
VANYSQDVKQFANGFVVRIGAAANSTGTVIISPSTSATIRKIYPAFMLGSS
VGNFSDGKMGRFFNHTLVLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYT

SFATYHTPATDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILE
WFGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSIIPHSIRSIQ
SDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDCGFNDLSQLHCSYESF
DVESGVYSVSSFEAKPSGSVVEQAEGVECDFSPLLSGTPPQVYNFKRLVF
TNCNYNLTKLLSLFSVNDFTCSQISPAAIASNCYSSLILDYFSYPLSMKSDL
SVSSAGPISQFNYKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRFLSD
DRTEVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGWLVASG
STVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDTKIASQLGNCVEYS
LYGVSGRGVFQNCTAVGVRQQRFVYDAYQNLVGYYSDDGNYYCLRAC
VSVPVSVIYDKETKTHATLFGSVACEHISSTMSQYSRSTRSMLKRRDSTY
GPLQTPVGCVLGLVNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPG
EMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTVDCK
QYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDSVRNLFASVKSS
QSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAIEDLLFDKVTIADPGYMQG
YDDCMQQGPASARDLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIA
GVGWTAGLSSFAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQALG
AMQTGFTTTNEAFHKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQ
RLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLAKDKVNE
CVKAQSKRSGFCGQGTHIVSFVVNAPNGLYFMHVGYYPSNHIEVVSAYG
LCDAANPTNCIAPVNGYFIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYV
APQVTYQNISTNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTT
LLDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPWYIWLGFIAGL
VALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKVHVH

原生 SARS-CoV-1 S 蛋白 wtTM/CT AA P59594，不具有 訊號肽(SEQ ID NO：114)

SDLDRCTTFDDVQAPNYTQHTSSMRGVYYPDEIFRSDTLYLTQDLFLPFY
SNVTGFHTINHTFGNPVIPFKDGIYFAATEKSNVVRGWVFGSTMNNKSQS
VIIINNSTNVVIRACNFELCDNPFFAVSKPMGTQTHTMIFDNAFNCTFEYIS
DAFSLDVSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGFNT
LKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVGYLKPTTFMLKYD
ENGTITDAVDCSQNPLAELKCSVKSFEIDKGIYQTSNFRVVPSGDVVRFPN
ITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVLYNSTFFSTFKCYG
VSATKLNDLCFSNVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFM
GCVLAWNTRNIDATSTGNYNYKYRYLRHGKLRPFERDISNVPFSPDGKPC
TPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLNAPATVCGPKLST
DLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDVSDFTDSVRDPKT
SEILDISPCSFGGVSVITPGTNASSEVAVLYQDVNCTDVSTAIHADQLTPA
WRIYSTGNNVFQTQAGCLIGAEHVDTSYECDIPIGAGICASYHTVSLLRST
SQKSIVAYTMSLGADSSIAYSNNTIAIPTNFSISITTEVMPVSMAKTSVDCN
MYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQDRNTREVFAQVKQM
YKTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAGFMKQYGE
CLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYTAALVSGTATAGWTFG
AGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQIANQFNKAISQIQESLT
TTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEA
EVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKR
VDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAICHEGKAY
FPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGNCDVVIGIINNTVYDP
LQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAK
NLNESLIDLQELGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLCCMTSCC
SCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT

原生 MERS S 蛋白 wtTM/CT AA AFY13307，不具有 訊號肽(SEQ ID NO：115)

YVDVGPDSVKSACIEVDIQQTFFDKTWPRPIDVSKADGIIYPQGRTYSNITI
TYQGLFPYQGDHGDMYVYSAGHATGTTPQKLFVANYSQDVKQFANGFV
VRIGAAANSTGTVIISPSTSATIRKIYPAFMLGSSVGNFSDGKMGRFFNHTL
VLLPDGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPATDCSDGNY
NRNASLNSFKEYFNLRNCTFMYTYNITEDEILEWFGITQTAQGVHLFSSRY
VDLYGGNMFQFATLPVYDTIKYYSIIPHSIRSIQSDRKAWAAFYVYKLQPL
TFLLDFSVDGYIRRAIDCGFNDLSQLHCSYESFDVESGVYSVSSFEAKPSG
SVVEQAEGVECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVND
FTCSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFNYKQSFSN
PTCLILATVPHNLTTITKPLKYSYINKCSRFLSDDRTEVPQLVNANQYSPC
VSIVPSTVWEDGDYYRKQLSPLEGGGWLVASGSTVAMTEQLQMGFGITV
QYGTDTNSVCPKLEFANDTKIASQLGNCVEYSLYGVSGRGVFQNCTAVG
VRQQRFVYDAYQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHAT
LFGSVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGLVNSSLF
VEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLASIAFNHPIQVDQLN
SSYFKLSIPTNFSFGVTQEYIQTTIQKVTVDCKQYVCNGFQKCEQLLREYG
QFCSKINQALHGANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEP
VSISTGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASARDLICA
QYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIPFAQSI
FYRLNGVGITQQVLSENQKLIANKFNQALGAMQTGFTTTNEAFHKVQDA
VNNNAQALSKLASELSNTFGAISASIGDIIQRLDVLEQDAQIDRLINGRLTT
LNAFVAQQLVRSESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSF
VVNAPNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGYFIKT
NNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNISTNLPPPLLGNS

TGIDFQDELDEFFKNVSTSIPNFGSLTQINTTLLDLTYEMLSLQQVVKALN
ESYIDLKELGNYTYYNKWPWYIWLGFIAGLVALALCVFFILCCTGCGTNC
MGKLKCNRCCDRYEEYDLEPHKVHVH

經修飾的 PDI-SARS-COV-1 wtTMCT-AA的TMCT區域(SEQ ID NO： 116)

WYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGSCCKFDEDDSEP
VLKGVKLHYT

經修飾的PDI-SARS-COV-1 H5iTMCT-AA的TMCT區域 (SEQ ID NO：117)

WYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

經修飾的PDI-SARS-COV-1 H5iCT-AA的TMCT區域 (SEQ ID NO： 118)

WYVWLGFIAGLIAIVMVTILLSLWMCSNGSLQCRICI

經修飾的PDI-SARS-COV-1 H5iCT(V4)-AA的TMCT區域 (SEQ ID NO： 119)

WYVWLGFIAGLIAIVMVTILLCCSNGSLQCRICI

經修飾的PDI-SARS-COV-1 H1cCT-AA的TMCT區域 (SEQ ID NO： 120)

WYVWLGFIAGLIAIVMVTILLSFWMCSNGSLQCRICI

經修飾的PDI-MERS-wtTMCT-AA的TMCT區域 (SEQ ID NO： 121)

WYIWLGFIAGLVALALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDL
EPHKVHVH

經修飾的PDI-MERS-H5iTMCT-AA的TMCT區域 (SEQ ID NO： 122)

WYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

經修飾的 PDI-MERS-H5iCT-AA的TMCT區域 (SEQ ID NO： 123)

WYIWLGFIAGLVALALCVFFILSLWMCSNGSLQCRICI

經修飾的PDI-MERS-H5iCT(V4)-AA的TMCT區域 (SEQ ID NO： 124)

WYIWLGFIAGLVALALCVFFILCCSNGSLQCRICI

經修飾的PDI-MERS-H1cCT-AA的TMCT 區域 (SEQ ID NO： 125)

WYIWLGFIAGLVALALCVFFILSFWMCSNGSLQCRICI

經修飾的PDI-S-蛋白+H1 Cal 的TMCT區域 (SEQ ID NO： 126)

WYIWLGFIAGLIAIVMVTIMLSFWMCSNGSLQCRICI

經修飾的 PDI-S-蛋白+H3 Minn的TMCT區域 (SEQ ID NO： 127)

WYIWLGFIAGLIAIVMVTIMLMWACQKGNIRCNICI

經修飾的 PDI-S-蛋白+H6 HK的TMCT區域 (SEQ ID NO： 128)

WYIWLGFIAGLIAIVMVTIMLGLWMCSNGSMQCRICI

經修飾的 PDI-S-蛋白+H7 Guangdong的TMCT 區域 (SEQ ID NO： 129)

WYIWLGFIAGLIAIVMVTIMLVFICVKNGNMRCTICI

經修飾的 PDI-S-蛋白+H9 HK 的TMCT 區域 (SEQ ID NO： 130)

WYIWLGFIAGLIAIVMVTIMLLFWAMSNGSCRCNICI

經修飾的 PDI-S-蛋白+ B/ Wash 的TMCT 區域(SEQ ID NO： 131)

WYIWLGFIAGLIAIVMVTIMLVVYMVSRDNVSCSICL

冠狀病毒 S-蛋白之TM 結構域的共通序列(SEQ ID NO： 132)

WYXWLGFIAGLXAXXX{X}VXXXL ({X} may be absent)

冠狀病毒 S-蛋白之TM 結構域 的共通序列(SEQ ID NO： 133)

WY[I/V]WLGFIAGL[V/I]A[L/I][A/V][L/M]{X}V[F/T][F/I]XL (其中 {X} 可為C或不存在)

具有肽間插序列 X_n之經修飾的 SARS-CoV-1 S 蛋白的TM/CT 區域 (SEQ ID NO： 134)

WYVWLGFIAGLIAIVMVTIL - (X)n - CSNGSXXCXICI

具有肽間插序列 X_n之經修飾的 MERS S 蛋白的TM/CT 區域 (SEQ ID NO： 135)

WYIWLGFIAGLVALALCVFFIL -(X)n – CSNGSXXCXICI

IF(AvB+wtCT-OC43).r (SEQ ID NO： 136)

ACGACACGACTAAGGCCTTCAGTCGTCATGCGAGGTCTTAATGACAAG

C

PDI-OC43-wtTMCT-DNA (SEQ ID NO： 137)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcgGTGATCG

GCGATCTGAATTGTACCCTGGATCCCCGCCTGAAAGGGAGCTTTAACA

ACCGAGATACAGGACCCCCGTCTATATCCATAGATACAGTGGATGTTA

CGAACGGGCTCGGCACCTACTATGTGCTAGACCGAGTTTATTTGAACA

CCACCTTATTCCTCAATGGATACTACCCAACTTCAGGTAGTACTTACA

GAAACATGGCGCTGAAGGGTACGGATCTGCTGAGCACCCTATGGTTTA

AACCTCCCTTCCTCTCGGACTTTATTAATGGCATCTTCGCTAAGGTGAA

AAACACGAAGGTTTTCAAAGATGGAGTGATGTATTCAGAGTTCCCTGC

GATCACCATTGGAAGTACCTTCGTGAATACTTCCTATAGCGTGGTGGT

TCAACCACGGACAATCAACTCCACCCAGGACGGCGTCAACAAGCTCC

AGGGATTGCTGGAGGTGTCAGTCTGTCAATATAACATGTGTGAGTACC

CACACACTATCTGTCACCCTAATCTAGGCAACCACTTTAAGGAACTGT

GGCACTACGATACGGGGGTGGTAAGTTGCTTATATAAGAGAAATTTCA

CCTATGATGTTAATGCAACGTACCTGTACTTTCACTTCTATCAAGAAG

GAGGAACTTTCTACGCATATTTCACAGATACCGGCTTTGTGACGAAAT

TCTTATTCAACGTTTACCTCGGAATGGCATTAAGCCATTATTACGTGAT

GCCTCTCACTTGCATCAGACGCCCTAAGGATGGTTTTTCTCTGGAGTA

CTGGGTCACTCCCCTGACACCACGGCAGTACCTGCTTGCTTTTAACCA

GGACGGTATCATTTTTAATGCCGTCGATTGTATGAGCGATTTTATGAG

CGAGATAAAGTGCAAGACCCAATCTATTGCTCCGCCCACGGGGGTGT

ACGAACTGAATGGTTACACCGTCCAGCCCGTTGCCGATGTATATAGAC

GGAAACCAGACCTGCCCAATTGCAACATCGAAGCTTGGTTAAACGAT

AAGTCAGTGCCCTCCCCCCTCAATTGGGAGAGGAAGACTTTCTCCAAC

TGTAATTTCAACATGTCAAGCCTGATGTCTTTCATTCAAGCCGATTCGT

TCACTTGTAATAATATAGATGCAGCAAAGATCTATGGTATGTGCTTCA

GTTCCATCACAATAGATAAGTTTGCAATACCAAACCGTCGCAAGGTGG

ACCTTCAGCTCGGCAACCTGGGCTATCTGCAGTCCAGCAATTATAGAA

TAGACACCACCGCCACATCATGTCAGCTGTACTATAACCTCCCAGCAG

CGAACGTCAGTGTTAGTAGGTTCAATCCTTCTACCTGGAATAAAAGGT

TTGGATTCATCGAAGATAGTGTGTTCGTACCTCAGCCAACAGGAGTGT

TCACCAATCACAGCGTGGTCTACGCCCAACATTGCTTCAAGGCACCCA

AAAATTTCTGCCCATGTAGCAGTTGCTCCTGCCCGGGTAAGAACAATG

GGATCGGCACCTGCCCAGCAGGCACCAATTCACTTACATGCGATAATC

TGTGTACACTGGATCCTATTACACTTAAGGCCCCTGATACCTACAAAT

GCCCCCAGAGCAAGAGCCTGGTCGGTATCGGAGAACACTGTTCCGGA

CTTGCAGTAAAAAGCGACTATTGTGGAAATAACTCTTGCACTTGTCAG

CCACAAGCCTTCCTCGGTTGGTCCGCTGACTCTTGTTTACAAGGGGAT

AAGTGTAACATCTTCGCAAATTTCATCTTACACGATGTGAATAACGGC

TTAACATGCAGCACAGATCTCCAGAAGGCAAACACAGAGATCGAATT

AGGAGTCTGCGTTAATTACGATCTCTACGGGATCTCTGGCCAGGGCAT

CTTCGTGGAGGTTAATGCTACCTACTACAATAGTTGGCAAAATCTGCT

CTACGATAGCAATGGCAACCTCTATGGATTCAGAGACTATATTACTAA

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PDI-OC43-H5iTMCT-DNA (SEQ ID NO： 138)

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PDI-OC43-H5iCT-DNA (SEQ ID NO： 139)

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PDI-OC43-H5iCT(V4)-DNA (SEQ ID NO： 140)

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PDI-OC43-H1cCT-DNA (SEQ ID NO： 141)

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AAGTGTAACATCTTCGCAAATTTCATCTTACACGATGTGAATAACGGC

TTAACATGCAGCACAGATCTCCAGAAGGCAAACACAGAGATCGAATT

AGGAGTCTGCGTTAATTACGATCTCTACGGGATCTCTGGCCAGGGCAT

CTTCGTGGAGGTTAATGCTACCTACTACAATAGTTGGCAAAATCTGCT

CTACGATAGCAATGGCAACCTCTATGGATTCAGAGACTATATTACTAA

CAGGACGTTCATGATTCACTCGTGCTATTCCGGGCGGGTGTCAGCAGC

TTATCACGCAAATTCTTCAGAGCCAGCTCTGCTATTCCGAAACATAAA

ATGTAATTACGTGTTCAATAATTCACTGACTCGGCAGCTGCAGCCGAT

TAATTACAGCTTCGACAGCTACCTTGGTTGCGTTGTTAACGCCTACAA

CTCCACTGCCATATCAGTTCAGACCTGCGACCTTACTGTGGGCTCTGG

CTATTGTGTCGATTATTCAAAGAACGGGGGGAGCGGGTCCGCAATAA

CAACTGGCTATAGGTTCACCAATTTTGAGCCTTTCACCGTGAATAGTG

TCAACGATAGCCTGGAGCCTGTCGGAGGTCTTTATGAGATACAAATCC

CCTCCGAGTTCACAATTGGCAACATGGAAGAGTTCATCCAGACGAGTT

CCCCAAAGGTGACGATCGATTGCGCGGCTTTCGTCTGCGGCGACTACG

CCGCATGCAAGTTACAACTCGTTGAGTATGGAAGTTTTTGCGATAATA

TAAACGCAATTCTGACTGAAGTGAACGAACTGCTGGACACCACTCAGT

TGCAGGTGGCAAATTCGCTCATGAACGGCGTGACACTGTCAACCAAA

CTGAAGGACGGTGTCAATTTCAATGTGGATGACATTAACTTCAGCCCC

GTACTGGGCTGTTTGGGTAGTGAGTGTTCTAAGGCTAGCAGCCGCTCC

GCCATTGAGGACTTGTTGTTTGATAAAGTTAAGCTGAGTGACGTTGGA

TTTGTTGAGGCGTATAATAACTGTACCGGTGGTGCAGAGATAAGGGAT

CTGATCTGTGTCCAGAGTTATAAGGGGATTAAGGTTCTCCCCCCGCTA

CTCTCGGAGAATCAGATATCAGGATACACCCTGGCCGCTACCTCAGCC

TCGCTGTTTCCCCCTTGGACCGCTGCCGCCGGTGTCCCATTTTATTTGA

ATGTGCAGTATCGGATCAACGGTCTGGGAGTGACAATGGACGTGCTGT

CTCAGAACCAGAAACTGATCGCCAATGCATTCAACAATGCTCTGCACG

CCATCCAGCAAGGGTTTGACGCTACAAATTCTGCCCTCGTAAAAATCC

AGGCCGTGGTGAATGCTAACGCCGAAGCCCTTAATAATCTGCTCCAGC

AGCTTTCTAACCGCTTTGGAGCTATTTCTGCCTCACTGCAGGAAATTCT

ATCCAGACTGGATCCCCCTGAGGCAGAAGCCCAAATCGACCGTCTCAT

AAACGGCAGACTCACTGCTCTTAACGCCTACGTTAGTCAACAATTGAG

CGATTCGACCTTGGTGAAATTCAGCGCAGCTCAGGCTATGGAGAAGGT

GAACGAGTGCGTGAAGTCACAGAGCTCCAGAATCAATTTCTGTGGCA

ATGGGAACCATATCATCTCCTTGGTTCAGAATGCTCCCTACGGCCTGT

ATTTCATCCACTTCAACTACGTGCCCACGAAGTACGTTACAGCCAAAG

TGTCCCCCGGACTGTGCATCGCTGGTAACAGGGGCATTGCACCAAAAT

CCGGCTACTTCGTCAATGTCAACAACACATGGATGTATACTGGGAGTG

GTTATTATTACCCTGAACCTATAACAGAGAACAATGTAGTAGTCATGT

CCACATGCGCCGTCAATTATACTAAGGCCCCCTATGTTATGCTCAACA

CTTCAATTCCCAATCTCCCGGATTTCAAAGAAGAGCTGGATCAGTGGT

TTAAGAATCAGACATCCGTGGCCCCTGACTTAAGCTTGGATTATATCA

ATGTGACTTTTTTAGACTTACAGGTCGAGATGAACCGACTCCAGGAAG

CTATAAAAGTACTGAACCACTCCTATATCAATCTGAAAGATATCGGTA

CATACGAATATTACGTAAAATGGCCTTGGTATGTGTGGCTACTAATTT

GCCTTGCGGGCGTGGCTATGCTGGTCCTGCTGTTCTTCATTagcttctggatgt

gctctaatgggtctctacagtgtagaatatgtattTGA

PDI-OC43-wtTMCT-AA (SEQ ID NO： 142)

MAKNVAIFGLLFSLLVLVPSQIFAVIGDLNCTLDPRLKGSFNNRDTGPPSIS

IDTVDVTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLL

STLWFKPPFLSDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSV

VVQPRTINSTQDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKEL

WHYDTGVVSCLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTK

FLFNVYLGMALSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQ

DGIIFNAVDCMSDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKP

DLPNCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNN

IDAAKIYGMCFSSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQ

LYYNLPAANVSVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQH

CFKAPKNFCPCSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDT

YKCPQSKSLVGIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQG

DKCNIFANFILHDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFV

EVNATYYNSWQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHA

NSSEPALLFRNIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISV

QTCDLTVGSGYCVDYSKNGGSGSAITTGYRFTNFEPFTVNSVNDSLEPVG

GLYEIQIPSEFTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSF

CDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFS

PVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLI

CVQSYKGIKVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQY

RINGLGVTMDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVN

ANAEALNNLLQQLSNRFGAISASLQEILSRLDPPEAEAQIDRLINGRLTAL
NAYVSQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQ
NAPYGLYFIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTW
MYTGSGYYYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEE
LDQWFKNQTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLK
DIGTYEYYVKWPWYVWLLICLAGVAMLVLLFFICCCTGCGTSCFKKCGG
CCDDYTGYQELVIKTSHDD

PDI-OC43-H5iTMCT-AA (SEQ ID NO： 143)

MAKNVAIFGLLFSLLVLVPSQIFAVIGDLNCTLDPRLKGSFNNRDTGPPSIS
IDTVDVTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLL
STLWFKPPFLSDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSV
VVQPRTINSTQDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKEL
WHYDTGVVSCLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTK
FLFNVYLGMALSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQ
DGIIFNAVDCMSDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKP
DLPNCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNN
IDAAKIYGMCFSSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQ
LYYNLPAANVSVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQH
CFKAPKNFCPCSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDT
YKCPQSKSLVGIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQG
DKCNIFANFILHDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFV
EVNATYYNSWQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHA
NSSEPALLFRNIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISV
QTCDLTVGSGYCVDYSKNGGSGSAITTGYRFTNFEPFTVNSVNDSLEPVG
GLYEIQIPSEFTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSF

CDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFS
PVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLI
CVQSYKGIKVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQY
RINGLGVTMDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVN
ANAEALNNLLQQLSNRFGAISASLQEILSRLDPPEAEAQIDRLINGRLTAL
NAYVSQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQ
NAPYGLYFIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTW
MYTGSGYYYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEE
LDQWFKNQTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLK
DIGTYEYYVKWPWYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRI
CI

PDI-OC43-H5iCT-AA (SEQ ID NO： 144)

MAKNVAIFGLLFSLLVLVPSQIFAVIGDLNCTLDPRLKGSFNNRDTGPPSIS
IDTVDVTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLL
STLWFKPPFLSDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSV
VVQPRTINSTQDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKEL
WHYDTGVVSCLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTK
FLFNVYLGMALSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQ
DGIIFNAVDCMSDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKP
DLPNCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNN
IDAAKIYGMCFSSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQ
LYYNLPAANVSVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQH
CFKAPKNFCPCSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDT
YKCPQSKSLVGIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQG
DKCNIFANFILHDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFV

EVNATYYNSWQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHA
NSSEPALLFRNIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISV
QTCDLTVGSGYCVDYSKNGGSGSAITTGYRFTNFEPFTVNSVNDSLEPVG
GLYEIQIPSEFTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSF
CDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFS
PVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLI
CVQSYKGIKVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQY
RINGLGVTMDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVN
ANAEALNNLLQQLSNRFGAISASLQEILSRLDPPEAEAQIDRLINGRLTAL
NAYVSQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQ
NAPYGLYFIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTW
MYTGSGYYYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEE
LDQWFKNQTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLK
DIGTYEYYVKWPWYVWLLICLAGVAMLVLLFFISLWMCSNGSLQCRICI

PDI-OC43-H5iCT(V4)-AA (SEQ ID NO： 145)

MAKNVAIFGLLFSLLVLVPSQIFAVIGDLNCTLDPRLKGSFNNRDTGPPSIS
IDTVDVTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLL
STLWFKPPFLSDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSV
VVQPRTINSTQDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKEL
WHYDTGVVSCLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTK
FLFNVYLGMALSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQ
DGIIFNAVDCMSDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKP
DLPNCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNN
IDAAKIYGMCFSSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQ
LYYNLPAANVSVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQH

CFKAPKNFCPCSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDT
YKCPQSKSLVGIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQG
DKCNIFANFILHDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFV
EVNATYYNSWQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHA
NSSEPALLFRNIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISV
QTCDLTVGSGYCVDYSKNGGSGSAITTGYRFTNFEPFTVNSVNDSLEPVG
GLYEIQIPSEFTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSF
CDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFS
PVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLI
CVQSYKGIKVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQY
RINGLGVTMDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVN
ANAEALNNLLQQLSNRFGAISASLQEILSRLDPPEAEAQIDRLINGRLTAL
NAYVSQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQ
NAPYGLYFIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTW
MYTGSGYYYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEE
LDQWFKNQTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLK
DIGTYEYYVKWPWYVWLLICLAGVAMLVLLFFICCSNGSLQCRICI

PDI-OC43-H1cCT-AA (SEQ ID NO： 146)

MAKNVAIFGLLFSLLVLVPSQIFAVIGDLNCTLDPRLKGSFNNRDTGPPSIS
IDTVDVTNGLGTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLL
STLWFKPPFLSDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSV
VVQPRTINSTQDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKEL
WHYDTGVVSCLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTK
FLFNVYLGMALSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQ
DGIIFNAVDCMSDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKP

DLPNCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNN

IDAAKIYGMCFSSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQ

LYYNLPAANVSVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQH

CFKAPKNFCPCSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDT

YKCPQSKSLVGIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQG

DKCNIFANFILHDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFV

EVNATYYNSWQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHA

NSSEPALLFRNIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISV

QTCDLTVGSGYCVDYSKNGGSGSAITTGYRFTNFEPFTVNSVNDSLEPVG

GLYEIQIPSEFTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSF

CDNINAILTEVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFS

PVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLI

CVQSYKGIKVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQY

RINGLGVTMDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVN

ANAEALNNLLQQLSNRFGAISASLQEILSRLDPPEAEAQIDRLINGRLTAL

NAYVSQQLSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQ

NAPYGLYFIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTW

MYTGSGYYYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEE

LDQWFKNQTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLK

DIGTYEYYVKWPWYVWLLICLAGVAMLVLLFFISFWMCSNGSLQCRICI

IF(CoV229EwtCT).r (SEQ ID NO： 147)

ACGACACGACTAAGGCCTTCACTGTATGTGGATCTTTTCGACATCGTA

PDI-229E -wtTMCT-DNA (SEQ ID NO： 148)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcgCAAACGA

CTAATGGGCTGAACACCAGTTACAGCGTCTGTAACGGCTGCGTCGGAT

ATAGCGAGAACGTGTTCGCAGTGGAAAGTGGGGGGTACATTCCTTCC

GACTTCGCTTTCAATAACTGGTTTCTCCTGACTAACACAAGCTCCGTCG

TGGATGGCGTGGTCAGGTCCTTTCAGCCTCTTCTCCTGAATTGCCTGTG

GTCTGTGTCCGGGTTAAGATTCACTACAGGCTTCGTATACTTCAACGG

GACGGGCCGGGGGGATTGCAAGGGCTTCTCCTCCGACGTGCTGTCAG

ATGTGATCCGTTACAATCTGAACTTCGAAGAGAACTTACGGCGGGGG

ACAATCCTGTTCAAAACATCATATGGCGTAGTCGTATTTTACTGCACC

AATAATACCCTGGTGAGTGGGGACGCCCATATTCCCTTCGGAACAGTG

CTGGGTAACTTTTACTGTTTTGTCAACACTACGATCGGAAACGAAACC

ACTAGCGCCTTTGTCGGAGCTCTGCCAAAAACAGTTAGGGAGTTCGTG

ATCTCTCGGACCGGTCACTTCTATATCAACGGCTACCGTTATTTTACTT

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AATGTAAGTCAAACGTCAATTGCCAACATCATCTATTGTAACTCAGTA

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TTCTATTCCACGAGCCCGATTCAGAGCGTGGAACTGCCAGTTTCCATC

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CTAACGTCGGCAGGTGGTCAGCGTCCATTAACACAGGCAATTGCCCGT

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TATACGATGTGAGTGGAGTGGGCGTTATACGCGTGTCTAACGACACCT

TTCTAAACGGCATAACCTACACAAGCACGTCAGGCAATCTGTTAGGTT

TTAAAGACGTCACTAAAGGCACTATATATAGCATCACCCCATGCAACC

CACCTGATCAATTAGTCGTATATCAGCAAGCTGTTGTGGGTGCTATGC

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CAGCCAACTTGTCGATTCCCTCTAACTGGACAACGTCTGTCCAAGTCG

AATATCTGCAGATCACCTCAACCCCCATAGTAGTCGATTGCTCAACCT

ACGTCTGCAACGGTAATGTCAGATGTGTCGAGCTGCTCAAGCAGTACA

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GTAATCCCTAGCTTGCCCACATCCGGCTCTCGGGTGGCGGGGCGGAGC

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CGGGATTGCGTTGGGCGGCCTGACGTCCGCTGTCTCCATCCCTTTCTCT

CTGGCTATACAAGCCCGACTGAATTATGTGGCCCTGCAGACTGATGTC

CTGCAAGAAAATCAGAAGATTCTTGCCGCCAGCTTCAACAAGGCCAT

GACTAATATTGTGGATGCGTTTACCGGAGTGAATGACGCCATCACCCA

AACGTCCCAAGCCCTGCAGACAGTCGCCACGGCGTTAAACAAAATCC

AGGATGTAGTGAATCAGCAAGGGAACAGCTTGAATCACCTGACGTCC

CAGTTAAGACAGAACTTTCAGGCAATCAGTAGCTCAATCCAGGCTATC

TACGATCGATTAGATCCTCCTCAGGCAGATCAGCAGGTGGATCGGCTC

ATCACCGGCCGCCTCGCGGCATTGAATGTTTTCGTAAGTCATACCTTG

ACCAAGTACACGGAGGTGAGGGCCAGTCGCCAGCTGGCTCAGCAAAA

AGTGAATGAGTGTGTGAAATCACAGAGCAAACGGTACGGGTTTTGTG

GAAATGGGACGCACATCTTTAGCATCGTTAATGCTGCCCCCGAAGGGT

TAGTCTTCCTGCACACTGTGCTCCTTCCTACCCAGTATAAAGATGTCGA

AGCATGGTCTGGGCTCTGTGTCGATGGAACTAACGGTTATGTCCTTCG

ACAGCCAAACCTCGCTCTCTATAAAGAAGGGAATTACTATAGGATCAC

CTCAAGAATCATGTTCGAGCCCAGGATACCAACAATGGCCGATTTTGT

GCAGATTGAAAATTGTAACGTGACCTTTGTGAATATCAGTCGATCCGA

GCTTCAAACGATTGTTCCTGAGTACATCGACGTGAATAAAACTCTACA

AGAGCTGTCCTATAAACTGCCTAATTATACCGTGCCTGACCTTGTAGT

CGAGCAATACAACCAGACTATTCTGAACCTGACATCGGAAATCTCTAC

ATTGGAGAATAAAAGCGCCGAGCTCAATTACACAGTGCAGAAGCTGC

AGACCCTGATCGACAATATTAACAGCACTCTTGTGGACTTAAAGTGGC

TGAACCGTGTGGAGACTTACATCAAGTGGCCCTGGTGGGTGTGGCTCT

GTATTTCCGTGGTCCTTATATTTGTTGTAAGTATGCTGCTCCTGTGCTG

TTGCTCAACCGGGTGCTGCGGTTTTTTCTCCTGTTTCGCCTCATCCATC

CGTGGCTGTTGTGAGAGCACTAAACTGCCATATTACGATGTCGAAAAG

ATCCACATACAGTGA

PDI-229E -H5iTMCT-DNA (SEQ ID NO： 149)

atggcgaaaaacgttgcgattttcggcttattgttttctcttcttgtgttggttccttctcagatcttcgcgCAAACGA

CTAATGGGCTGAACACCAGTTACAGCGTCTGTAACGGCTGCGTCGGAT

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TGGATGGCGTGGTCAGGTCCTTTCAGCCTCTTCTCCTGAATTGCCTGTG

GTCTGTGTCCGGGTTAAGATTCACTACAGGCTTCGTATACTTCAACGG

GACGGGCCGGGGGGATTGCAAGGGCTTCTCCTCCGACGTGCTGTCAG

ATGTGATCCGTTACAATCTGAACTTCGAAGAGAACTTACGGCGGGGG

ACAATCCTGTTCAAAACATCATATGGCGTAGTCGTATTTTACTGCACC

AATAATACCCTGGTGAGTGGGGACGCCCATATTCCCTTCGGAACAGTG

CTGGGTAACTTTTACTGTTTTGTCAACACTACGATCGGAAACGAAACC

ACTAGCGCCTTTGTCGGAGCTCTGCCAAAAACAGTTAGGGAGTTCGTG

ATCTCTCGGACCGGTCACTTCTATATCAACGGCTACCGTTATTTTACTT

TGGGCAACGTCGAAGCCGTCAATTTTAATGTGACAACTGCAGAGACA

ACTGACTTTTGCACTGTGGCTCTCGCCAGTTATGCCGATGTGCTGGTG

AATGTAAGTCAAACGTCAATTGCCAACATCATCTATTGTAACTCAGTA

ATCAACCGGCTCCGCTGTGACCAACTCTCATTCGACGTCCCCGACGGA

TTCTATTCCACGAGCCCGATTCAGAGCGTGGAACTGCCAGTTTCCATC

GTATCCCTCCCAGTTTACCACAAGCACACTTTTATCGTTCTCTACGTAG

ATTTTAAACCCCAGTCAGGAGGAGGGAAATGCTTCAACTGCTACCCGG

CTGGCGTGAACATCACCTTGGCCAATTTTAATGAAACTAAAGGGCCCC

TTTGCGTGGATACGTCACACTTTACCACAAAGTATGTTGCAGTCTATG

CTAACGTCGGCAGGTGGTCAGCGTCCATTAACACAGGCAATTGCCCGT

TCTCTTTCGGGAAAGTGAACAACTTCGTGAAGTTTGGAAGTGTGTGCT

TCAGTTTGAAAGACATTCCGGGCGGCTGCGCCATGCCTATTGTGGCTA

ATTGGGCTTATTCCAAGTACTACACCATTGGCTCTCTCTACGTTAGCTG

GAGCGACGGTGACGGTATAACGGGCGTACCACAACCGGTGGAAGGGG

TCAGCTCTTTCATGAATGTCACTCTGGACAAGTGTACCAAATATAATA

TATACGATGTGAGTGGAGTGGGCGTTATACGCGTGTCTAACGACACCT

TTCTAAACGGCATAACCTACACAAGCACGTCAGGCAATCTGTTAGGTT

TTAAAGACGTCACTAAAGGCACTATATATAGCATCACCCCATGCAACC

CACCTGATCAATTAGTCGTATATCAGCAAGCTGTTGTGGGTGCTATGC

TGTCAGAAAACTTCACCAGCTACGGGTTCTCCAATGTGGTGGAACTGC

CCAAATTCTTTTACGCTAGCAATGGCACATATAACTGTACTGACGCCG

TCTTGACTTACAGTTCATTCGGAGTGTGCGCGGACGGCAGCATTATCG

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PDI-229E -H5iCT-DNA (SEQ ID NO： 150)

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PDI-229E -H5iTMCT-AA (SEQ ID NO： 154)

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VSEMLTFDKKAFTLANVSSFGDYNLSSVIPSLPTSGSRVAGRSAIEDILFSK
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YTGSLIGGIALGGLTSAVSIPFSLAIQARLNYVALQTDVLQENQKILAASFN
KAMTNIVDAFTGVNDAITQTSQALQTVATALNKIQDVVNQQGNSLNHLT
SQLRQNFQAISSSIQAIYDRLDPPQADQQVDRLITGRLAALNVFVSHTLTK
YTEVRASRQLAQQKVNECVKSQSKRYGFCGNGTHIFSIVNAAPEGLVFLH
TVLLPTQYKDVEAWSGLCVDGTNGYVLRQPNLALYKEGNYYRITSRIMF
EPRIPTMADFVQIENCNVTFVNISRSELQTIVPEYIDVNKTLQELSYKLPNY
TVPDLVVEQYNQTILNLTSEISTLENKSAELNYTVQKLQTLIDNINSTLVD
LKWLNRVETYIKWPWWVWLCISVVLIFVVSMLLLSLWMCSNGSLQCRIC
I

PDI-229E -H5iCT(V4)-AA (SEQ ID NO： 156)

MAKNVAIFGLLFSLLVLVPSQIFAQTTNGLNTSYSVCNGCVGYSENVFAV
ESGGYIPSDFAFNNWFLLTNTSSVVDGVVRSFQPLLLNCLWSVSGLRFTT
GFVYFNGTGRGDCKGFSSDVLSDVIRYNLNFEENLRRGTILFKTSYGVVV
FYCTNNTLVSGDAHIPFGTVLGNFYCFVNTTIGNETTSAFVGALPKTVREF
VISRTGHFYINGYRYFTLGNVEAVNFNVTTAETTDFCTVALASYADVLVN
VSQTSIANIIYCNSVINRLRCDQLSFDVPDGFYSTSPIQSVELPVSIVSLPVY
HKHTFIVLYVDFKPQSGGGKCFNCYPAGVNITLANFNETKGPLCVDTSHF
TTKYVAVYANVGRWSASINTGNCPFSFGKVNNFVKFGSVCFSLKDIPGGC
AMPIVANWAYSKYYTIGSLYVSWSDGDGITGVPQPVEGVSSFMNVTLDK

CTKYNIYDVSGVGVIRVSNDTFLNGITYTSTSGNLLGFKDVTKGTIYSITPC
NPPDQLVVYQQAVVGAMLSENFTSYGFSNVVELPKFFYASNGTYNCTDA
VLTYSSFGVCADGSIIAVQPANVSYDSVSAIVTANLSIPSNWTTSVQVEYL
QITSTPIVVDCSTYVCNGNVRCVELLKQYTSACKTIEDALRNSARLESAD
VSEMLTFDKKAFTLANVSSFGDYNLSSVIPSLPTSGSRVAGRSAIEDILFSK
LVTSGLGTVDADYKKCTKGLSIADLACAQYYNGIMVLPGVADAERMAM
YTGSLIGGIALGGLTSAVSIPFSLAIQARLNYVALQTDVLQENQKILAASFN
KAMTNIVDAFTGVNDAITQTSQALQTVATALNKIQDVVNQQGNSLNHLT
SQLRQNFQAISSSIQAIYDRLDPPQADQQVDRLITGRLAALNVFVSHTLTK
YTEVRASRQLAQQKVNECVKSQSKRYGFCGNGTHIFSIVNAAPEGLVFLH
TVLLPTQYKDVEAWSGLCVDGTNGYVLRQPNLALYKEGNYYRITSRIMF
EPRIPTMADFVQIENCNVTFVNISRSELQTIVPEYIDVNKTLQELSYKLPNY
TVPDLVVEQYNQTILNLTSEISTLENKSAELNYTVQKLQTLIDNINSTLVD
LKWLNRVETYIKWPWWVWLCISVVLIFVVSMLLLCCSNGSLQCRICI

PDI-229E-H1cCT-AA (SEQ ID NO： 157)

MAKNVAIFGLLFSLLVLVPSQIFAQTTNGLNTSYSVCNGCVGYSENVFAV
ESGGYIPSDFAFNNWFLLTNTSSVVDGVVRSFQPLLLNCLWSVSGLRFTT
GFVYFNGTGRGDCKGFSSDVLSDVIRYNLNFEENLRRGTILFKTSYGVVV
FYCTNNTLVSGDAHIPFGTVLGNFYCFVNTTIGNETTSAFVGALPKTVREF
VISRTGHFYINGYRYFTLGNVEAVNFNVTTAETTDFCTVALASYADVLVN
VSQTSIANIIYCNSVINRLRCDQLSFDVPDGFYSTSPIQSVELPVSIVSLPVY
HKHTFIVLYVDFKPQSGGGKCFNCYPAGVNITLANFNETKGPLCVDTSHF
TTKYVAVYANVGRWSASINTGNCPFSFGKVNNFVKFGSVCFSLKDIPGGC
AMPIVANWAYSKYYTIGSLYVSWSDGDGITGVPQPVEGVSSFMNVTLDK
CTKYNIYDVSGVGVIRVSNDTFLNGITYTSTSGNLLGFKDVTKGTIYSITPC

NPPDQLVVYQQAVVGAMLSENFTSYGFSNVVELPKFFYASNGTYNCTDA
VLTYSSFGVCADGSIIAVQPANVSYDSVSAIVTANLSIPSNWTTSVQVEYL
QITSTPIVVDCSTYVCNGNVRCVELLKQYTSACKTIEDALRNSARLESAD
VSEMLTFDKKAFTLANVSSFGDYNLSSVIPSLPTSGSRVAGRSAIEDILFSK
LVTSGLGTVDADYKKCTKGLSIADLACAQYYNGIMVLPGVADAERMAM
YTGSLIGGIALGGLTSAVSIPFSLAIQARLNYVALQTDVLQENQKILAASFN
KAMTNIVDAFTGVNDAITQTSQALQTVATALNKIQDVVNQQGNSLNHLT
SQLRQNFQAISSSIQAIYDRLDPPQADQQVDRLITGRLAALNVFVSHTLTK
YTEVRASRQLAQQKVNECVKSQSKRYGFCGNGTHIFSIVNAAPEGLVFLH
TVLLPTQYKDVEAWSGLCVDGTNGYVLRQPNLALYKEGNYYRITSRIMF
EPRIPTMADFVQIENCNVTFVNISRSELQTIVPEYIDVNKTLQELSYKLPNY
TVPDLVVEQYNQTILNLTSEISTLENKSAELNYTVQKLQTLIDNINSTLVD
LKWLNRVETYIKWPWWVWLCISVVLIFVVSMLLLSFWMCSNGSLQCRIC
I

原生 OC43-CoV S 蛋白 wtTM/CT AA (AVR40344) (SEQ ID NO： 158)

MFLILLISLPTAFAVIGDLNCTLDPRLKGSFNNRDTGPPSISIDTVDVTNGL
GTYYVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGTDLLSTLWFKPPFL
SDFINGIFAKVKNTKVFKDGVMYSEFPAITIGSTFVNTSYSVVVQPRTINST
QDGVNKLQGLLEVSVCQYNMCEYPHTICHPNLGNHFKELWHYDTGVVS
CLYKRNFTYDVNATYLYFHFYQEGGTFYAYFTDTGFVTKFLFNVYLGMA
LSHYYVMPLTCIRRPKDGFSLEYWVTPLTPRQYLLAFNQDGIIFNAVDCM
SDFMSEIKCKTQSIAPPTGVYELNGYTVQPVADVYRRKPDLPNCNIEAWL
NDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADSFTCNNIDAAKIYGMCF
SSITIDKFAIPNRRKVDLQLGNLGYLQSSNYRIDTTATSCQLYYNLPAANV
SVSRFNPSTWNKRFGFIEDSVFVPQPTGVFTNHSVVYAQHCFKAPKNFCP

CSSCSCPGKNNGIGTCPAGTNSLTCDNLCTLDPITLKAPDTYKCPQSKSLV
GIGEHCSGLAVKSDYCGNNSCTCQPQAFLGWSADSCLQGDKCNIFANFIL
HDVNNGLTCSTDLQKANTEIELGVCVNYDLYGISGQGIFVEVNATYYNS
WQNLLYDSNGNLYGFRDYITNRTFMIHSCYSGRVSAAYHANSSEPALLFR
NIKCNYVFNNSLTRQLQPINYSFDSYLGCVVNAYNSTAISVQTCDLTVGS
GYCVDYSKNRRSRRAITTGYRFTNFEPFTVNSVNDSLEPVGGLYEIQIPSE
FTIGNMEEFIQTSSPKVTIDCAAFVCGDYAACKLQLVEYGSFCDNINAILT
EVNELLDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFSPVLGCLGS
ECSKASSRSAIEDLLFDKVKLSDVGFVEAYNNCTGGAEIRDLICVQSYKGI
KVLPPLLSENQISGYTLAATSASLFPPWTAAAGVPFYLNVQYRINGLGVT
MDVLSQNQKLIANAFNNALHAIQQGFDATNSALVKIQAVVNANAEALN
NLLQQLSNRFGAISASLQEILSRLDALEAEAQIDRLINGRLTALNAYVSQQ
LSDSTLVKFSAAQAMEKVNECVKSQSSRINFCGNGNHIISLVQNAPYGLY
FIHFNYVPTKYVTAKVSPGLCIAGNRGIAPKSGYFVNVNNTWMYTGSGY
YYPEPITENNVVVMSTCAVNYTKAPYVMLNTSIPNLPDFKEELDQWFKN
QTSVAPDLSLDYINVTFLDLQVEMNRLQEAIKVLNHSYINLKDIGTYEYY
VKWPWYVWLLICLAGVAMLVLLFFICCCTGCGTSCFKKCGGCCDDYTG
YQELVIKTSHDD

原生 229E S 蛋白 wtTM/CT AA (P15423) (SEQ ID NO： 159)

MFVLLVAYALLHIAGCQTTNGLNTSYSVCNGCVGYSENVFAVESGGYIPS
DFAFNNWFLLTNTSSVVDGVVRSFQPLLLNCLWSVSGLRFTTGFVYFNGT
GRGDCKGFSSDVLSDVIRYNLNFEENLRRGTILFKTSYGVVVFYCTNNTL
VSGDAHIPFGTVLGNFYCFVNTTIGNETTSAFVGALPKTVREFVISRTGHF
YINGYRYFTLGNVEAVNFNVTTAETTDFCTVALASYADVLVNVSQTSIAN
IIYCNSVINRLRCDQLSFDVPDGFYSTSPIQSVELPVSIVSLPVYHKHTFIVL

YVDFKPQSGGGKCFNCYPAGVNITLANFNETKGPLCVDTSHFTTKYVAV
YANVGRWSASINTGNCPFSFGKVNNFVKFGSVCFSLKDIPGGCAMPIVAN
WAYSKYYTIGSLYVSWSDGDGITGVPQPVEGVSSFMNVTLDKCTKYNIY
DVSGVGVIRVSNDTFLNGITYTSTSGNLLGFKDVTKGTIYSITPCNPPDQL
VVYQQAVVGAMLSENFTSYGFSNVVELPKFFYASNGTYNCTDAVLTYSS
FGVCADGSIIAVQPRNVSYDSVSAIVTANLSIPSNWTTSVQVEYLQITSTPI
VVDCSTYVCNGNVRCVELLKQYTSACKTIEDALRNSARLESADVSEMLT
FDKKAFTLANVSSFGDYNLSSVIPSLPTSGSRVAGRSAIEDILFSKLVTSGL
GTVDADYKKCTKGLSIADLACAQYYNGIMVLPGVADAERMAMYTGSLI
GGIALGGLTSAVSIPFSLAIQARLNYVALQTDVLQENQKILAASFNKAMT
NIVDAFTGVNDAITQTSQALQTVATALNKIQDVVNQQGNSLNHLTSQLR
QNFQAISSSIQAIYDRLDTIQADQQVDRLITGRLAALNVFVSHTLTKYTEV
RASRQLAQQKVNECVKSQSKRYGFCGNGTHIFSIVNAAPEGLVFLHTVLL
PTQYKDVEAWSGLCVDGTNGYVLRQPNLALYKEGNYYRITSRIMFEPRIP
TMADFVQIENCNVTFVNISRSELQTIVPEYIDVNKTLQELSYKLPNYTVPD
LVVEQYNQTILNLTSEISTLENKSAELNYTVQKLQTLIDNINSTLVDLKWL
NRVETYIKWPWWVWLCISVVLIFVVSMLLLCCCSTGCCGFFSCFASSIRG
CCESTKLPYYDVEKIHIQ

原生 OC43-CoV S 蛋白 wtTM/CT AA (AVR40344)，不具有訊號肽(SEQ ID NO： 160)

VIGDLNCTLDPRLKGSFNNRDTGPPSISIDTVDVTNGLGTYYVLDRVYLN
TTLFLNGYYPTSGSTYRNMALKGTDLLSTLWFKPPFLSDFINGIFAKVKNT
KVFKDGVMYSEFPAITIGSTFVNTSYSVVVQPRTINSTQDGVNKLQGLLE
VSVCQYNMCEYPHTICHPNLGNHFKELWHYDTGVVSCLYKRNFTYDVN
ATYLYFHFYQEGGTFYAYFTDTGFVTKFLFNVYLGMALSHYYVMPLTCI

RRPKDGFSLEYWVTPLTPRQYLLAFNQDGIIFNAVDCMSDFMSEIKCKTQ

SIAPPTGVYELNGYTVQPVADVYRRKPDLPNCNIEAWLNDKSVPSPLNW

ERKTFSNCNFNMSSLMSFIQADSFTCNNIDAAKIYGMCFSSITIDKFAIPNR

RKVDLQLGNLGYLQSSNYRIDTTATSCQLYYNLPAANVSVSRFNPSTWN

KRFGFIEDSVFVPQPTGVFTNHSVVYAQHCFKAPKNFCPCSSCSCPGKNN

GIGTCPAGTNSLTCDNLCTLDPITLKAPDTYKCPQSKSLVGIGEHCSGLAV

KSDYCGNNSCTCQPQAFLGWSADSCLQGDKCNIFANFILHDVNNGLTCS

TDLQKANTEIELGVCVNYDLYGISGQGIFVEVNATYYNSWQNLLYDSNG

NLYGFRDYITNRTFMIHSCYSGRVSAAYHANSSEPALLFRNIKCNYVFNN

SLTRQLQPINYSFDSYLGCVVNAYNSTAISVQTCDLTVGSGYCVDYSKNR

RSRRAITTGYRFTNFEPFTVNSVNDSLEPVGGLYEIQIPSEFTIGNMEEFIQT

SSPKVTIDCAAFVCGDYAACKLQLVEYGSFCDNINAILTEVNELLDTTQL

QVANSLMNGVTLSTKLKDGVNFNVDDINFSPVLGCLGSECSKASSRSAIE

DLLFDKVKLSDVGFVEAYNNCTGGAEIRDLICVQSYKGIKVLPPLLSENQI

SGYTLAATSASLFPPWTAAAGVPFYLNVQYRINGLGVTMDVLSQNQKLI

ANAFNNALHAIQQGFDATNSALVKIQAVVNANAEALNNLLQQLSNRFGA

ISASLQEILSRLDALEAEAQIDRLINGRLTALNAYVSQQLSDSTLVKFSAA

QAMEKVNECVKSQSSRINFCGNGNHIISLVQNAPYGLYFIHFNYVPTKYV

TAKVSPGLCIAGNRGIAPKSGYFVNVNNTWMYTGSGYYYPEPITENNVV

VMSTCAVNYTKAPYVMLNTSIPNLPDFKEELDQWFKNQTSVAPDLSLDY

INVTFLDLQVEMNRLQEAIKVLNHSYINLKDIGTYEYYVKWPWYVWLLI

CLAGVAMLVLLFFICCCTGCGTSCFKKCGGCCDDYTGYQELVIKTSHDD

原生 229E S 蛋白 wtTM/CT AA (P15423)，不具有訊號肽(SEQ ID NO： 161)

QTTNGLNTSYSVCNGCVGYSENVFAVESGGYIPSDFAFNNWFLLTNTSSV

VDGVVRSFQPLLLNCLWSVSGLRFTTGFVYFNGTGRGDCKGFSSDVLSD

VIRYNLNFEENLRRGTILFKTSYGVVVFYCTNNTLVSGDAHIPFGTVLGNF
YCFVNTTIGNETTSAFVGALPKTVREFVISRTGHFYINGYRYFTLGNVEAV
NFNVTTAETTDFCTVALASYADVLVNVSQTSIANIIYCNSVINRLRCDQLS
FDVPDGFYSTSPIQSVELPVSIVSLPVYHKHTFIVLYVDFKPQSGGGKCFN
CYPAGVNITLANFNETKGPLCVDTSHFTTKYVAVYANVGRWSASINTGN
CPFSFGKVNNFVKFGSVCFSLKDIPGGCAMPIVANWAYSKYYTIGSLYVS
WSDGDGITGVPQPVEGVSSFMNVTLDKCTKYNIYDVSGVGVIRVSNDTF
LNGITYTSTSGNLLGFKDVTKGTIYSITPCNPPDQLVVYQQAVVGAMLSE
NFTSYGFSNVVELPKFFYASNGTYNCTDAVLTYSSFGVCADGSIIAVQPR
NVSYDSVSAIVTANLSIPSNWTTSVQVEYLQITSTPIVVDCSTYVCNGNVR
CVELLKQYTSACKTIEDALRNSARLESADVSEMLTFDKKAFTLANVSSFG
DYNLSSVIPSLPTSGSRVAGRSAIEDILFSKLVTSGLGTVDADYKKCTKGL
SIADLACAQYYNGIMVLPGVADAERMAMYTGSLIGGIALGGLTSAVSIPF
SLAIQARLNYVALQTDVLQENQKILAASFNKAMTNIVDAFTGVNDAITQT
SQALQTVATALNKIQDVVNQQGNSLNHLTSQLRQNFQAISSSIQAIYDRL
DTIQADQQVDRLITGRLAALNVFVSHTLTKYTEVRASRQLAQQKVNECV
KSQSKRYGFCGNGTHIFSIVNAAPEGLVFLHTVLLPTQYKDVEAWSGLCV
DGTNGYVLRQPNLALYKEGNYYRITSRIMFEPRIPTMADFVQIENCNVTF
VNISRSELQTIVPEYIDVNKTLQELSYKLPNYTVPDLVVEQYNQTILNLTSE
ISTLENKSAELNYTVQKLQTLIDNINSTLVDLKWLNRVETYIKWPWWVW
LCISVVLIFVVSMLLLCCCSTGCCGFFSCFASSIRGCCESTKLPYYDVEKIHI
Q

經修飾的 PDI-OC43-COV wtTMCT-AA的TMCT 區域 (SEQ ID NO： 162)

WYVWLLICLAGVAMLVLLFFICCCTGCGTSCFKKCGGCCDDYTGYQELV
IKTSHDD

經修飾的 PDI-OC43-COV H5iTMCT-AA 的TMCT 區域(SEQ ID NO： 163)

WYQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

經修飾的 PDI-OC43-COV H5iCT-AA的TMCT 區域 (SEQ ID NO： 164)

WYVWLLICLAGVAMLVLLFFISLWMCSNGSLQCRICI

經修飾的 PDI-OC43-COV H5iCT(V4)-AA的TMCT 區域 (SEQ ID NO： 165)

WYVWLLICLAGVAMLVLLFFICCSNGSLQCRICI

經修飾的 PDI-OC43-COV H1cCT-AA的TMCT 區域 (SEQ ID NO： 166)

WYVWLLICLAGVAMLVLLFFISFWMCSNGSLQCRICI

經修飾的 PDI-229E-wtTMCT-AA的TMCT 區域 (SEQ ID NO： 167)

WWVWLCISVVLIFVVSMLLLCCCSTGCCGFFSCFASSIRGCCESTKLPYY DVEKIHIQ

經修飾的 PDI-229E-H5iTMCT-AA的TMCT 區域 (SEQ ID NO： 168)

WWQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

經修飾的 PDI-229E-H5iCT-AA的TMCT 區域 (SEQ ID NO： 169)

WWVWLCISVVLIFVVSMLLLSLWMCSNGSLQCRICI

經修飾的 PDI-229E-H5iCT(V4)-AA的TMCT 區域 (SEQ ID NO： 170)

WWVWLCISVVLIFVVSMLLLCCSNGSLQCRICI

經修飾的 PDI-229E-H1cCT-AA的TMCT 區域 (SEQ ID NO： 171)

WWVWLCISVVLIFVVSMLLLSFWMCSNGSLQCRICI

具有肽間插序列X_n之經修飾的OC43-CoV S蛋白的TM/CT區域 (SEQ ID NO： 172)

WYVWLLICLAGVAMLVLLFFI -(X)n – CSNGSXXCXICI

具有肽間插序列X_n之經修飾的OC43-CoV S蛋白的TM/CT 區域 (SEQ ID NO： 173)

WWVWLCISVVLIFVVSMLLL -(X)n – CSNGSXXCXICI

【0343】所有引用文獻藉由引用併入本文。

【0344】已經描述關於本發明一個或多個具體實施方式。然而，對於本領域中具有通常知識者來說顯而易見的是，在不脫離如申請專利範圍所限定的本發明的範圍的情況下，可以進行多種變化和修飾。

【符號說明】

無。

【序列表】

<110> 加拿大商苜蓿股份有限公司
(Medicago Inc.)

<120> 經修飾的病毒結構蛋白

<130> 110P001517TW

<140> 110132402
<141> 2021-09-01

<150> US 63/073,327
<151> 2020-09-01

<150> US 63/211,716
<151> 2021-06-17

<160> 173

<170> PatentIn version 3.5

<210> 1
<211> 1273
<212> PRT
<213> SARS-CoV-2

<400> 1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
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Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
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Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

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

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

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

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1250 1255 1260

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

<210> 2
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<212> PRT
<213> SARS-CoV-2

<400> 2

Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser
1 5 10 15

Phe Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val
20 25 30

Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr
35 40 45

Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe
50 55 60

Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr
65 70 75 80

Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp
85 90 95

Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val
100 105 110

Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val
115 120 125

Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val
130 135 140

Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe
145 150 155 160

Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu
165 170 175

Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His
180 185 190

Thr Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu
195 200 205

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

Thr Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser

225 230 235 240

Ser Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln
245 250 255

Pro Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp
260 265 270

Ala Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu
275 280 285

Lys Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg
290 295 300

Val Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu
305 310 315 320

Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr
325 330 335

Ala Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val
340 345 350

Leu Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser
355 360 365

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

Phe Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr
385 390 395 400

Gly Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly
405 410 415

Cys Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly
420 425 430

Asn Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro
435 440 445

Phe Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro
450 455 460

Cys Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr
465 470 475 480

Gly Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val
485 490 495

Val Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro
500 505 510

Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe
515 520 525

Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe

530 535 540

Leu Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala
545 550 555 560

Val Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser
565 570 575

Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln
580 585 590

Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala
595 600 605

Ile His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly
610 615 620

Ser Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His
625 630 635 640

Val Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys
645 650 655

Ala Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val
660 665 670

Ala Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn
675 680 685

Ser Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr
690 695 700

Ile Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser
705 710 715 720

Val Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn
725 730 735

Leu Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu
740 745 750

Thr Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala
755 760 765

Gln Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly
770 775 780

Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg
785 790 795 800

Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala
805 810 815

Gly Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg
820 825 830

Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro

835 840 845

Leu Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala
850 855 860

Gly Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln
865 870 875 880

Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val
885 890 895

Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe
900 905 910

Asn Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser
915 920 925

Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu
930 935 940

Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser
945 950 955 960

Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val
965 970 975

Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr
980 985 990

Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
995 1000 1005

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1010 1015 1020

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1025 1030 1035

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1040 1045 1050

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1055 1060 1065

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1070 1075 1080

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1085 1090 1095

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1100 1105 1110

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1115 1120 1125

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn

1130 1135 1140

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1145 1150 1155

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1160 1165 1170

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

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1190 1195 1200

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1205 1210 1215

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1220 1225 1230

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1235 1240 1245

Val Leu Lys Gly Val Lys Leu His Tyr Thr
1250 1255

<210> 3
<211> 568
<212> PRT

<213> 流感

<400> 3

Met Glu Lys Ile Val Leu Leu Leu Ala Ile Val Ser Leu Val Lys Ser
1 5 10 15

Asp Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Gln Val
20 25 30

Asp Thr Ile Met Glu Lys Asn Val Thr Val Thr His Ala Gln Asp Ile
35 40 45

Leu Glu Lys Thr His Asn Gly Lys Leu Cys Asp Leu Asp Gly Val Lys
50 55 60

Pro Leu Ile Leu Arg Asp Cys Ser Val Ala Gly Trp Leu Leu Gly Asn
65 70 75 80

Pro Met Cys Asp Glu Phe Ile Asn Val Pro Glu Trp Ser Tyr Ile Val
85 90 95

Glu Lys Ala Asn Pro Thr Asn Asp Leu Cys Tyr Pro Gly Ser Phe Asn
100 105 110

Asp Tyr Glu Glu Leu Lys His Leu Leu Ser Arg Ile Asn His Phe Glu
115 120 125

Lys Ile Gln Ile Ile Pro Lys Ser Ser Trp Ser Asp His Glu Ala Ser
130 135 140

Ser Gly Val Ser Ser Ala Cys Pro Tyr Leu Gly Ser Pro Ser Phe Phe
145 150 155 160

Arg Asn Val Val Trp Leu Ile Lys Lys Asn Ser Thr Tyr Pro Thr Ile
165 170 175

Lys Lys Ser Tyr Asn Asn Thr Asn Gln Glu Asp Leu Leu Val Leu Trp
180 185 190

Gly Ile His His Pro Asn Asp Ala Ala Glu Gln Thr Arg Leu Tyr Gln
195 200 205

Asn Pro Thr Thr Tyr Ile Ser Ile Gly Thr Ser Thr Leu Asn Gln Arg
210 215 220

Leu Val Pro Lys Ile Ala Thr Arg Ser Lys Val Asn Gly Gln Ser Gly
225 230 235 240

Arg Met Glu Phe Phe Trp Thr Ile Leu Lys Pro Asn Asp Ala Ile Asn
245 250 255

Phe Glu Ser Asn Gly Asn Phe Ile Ala Pro Glu Tyr Ala Tyr Lys Ile
260 265 270

Val Lys Lys Gly Asp Ser Ala Ile Met Lys Ser Glu Leu Glu Tyr Gly
275 280 285

Asn Cys Asn Thr Lys Cys Gln Thr Pro Met Gly Ala Ile Asn Ser Ser
290 295 300

Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys
305 310 315 320

Tyr Val Lys Ser Asn Arg Leu Val Leu Ala Thr Gly Leu Arg Asn Ser
325 330 335

Pro Gln Arg Glu Ser Arg Arg Lys Lys Arg Gly Leu Phe Gly Ala Ile
340 345 350

Ala Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr
355 360 365

Gly Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys
370 375 380

Glu Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser
385 390 395 400

Ile Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe
405 410 415

Asn Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp
420 425 430

Gly Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met
435 440 445

Glu Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu
450 455 460

Tyr Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly
465 470 475 480

Asn Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu
485 490 495

Ser Ile Arg Asn Gly Thr Tyr Asn Tyr Pro Gln Tyr Ser Glu Glu Ala
500 505 510

Arg Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly
515 520 525

Thr Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
530 535 540

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
545 550 555 560

Ser Leu Gln Cys Arg Ile Cys Ile
565

<210> 4
<211> 1729
<212> DNA
<213> 流感

<400> 4

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agatttgcat tggttaccat gcaaacaatt caacagagca ggttgacaca atcatggaaa 120

agaacgttac tgttacacat gcccaagaca tactggaaaa gacacacaac gggaagctct 180

gcgatctaga tggagtgaag cctctaattt taagagattg tagtgtagct ggatggctcc 240

tcgggaaccc aatgtgtgac gaattcatca atgtaccgga atggtcttac atagtggaga 300

aggccaatcc aaccaatgac ctctgttacc cagggagttt caacgactat gaagaactga 360

aacacctatt gagcagaata aaccattttg agaaaattca aatcatcccc aaaagttctt 420

ggtccgatca tgaagcctca tcaggagtga gctcagcatg tccatacctg ggaagtccct 480

ccttttttag aaatgtggta tggcttatca aaaagaacag tacataccca acaataaaga 540

aaagctacaa taataccaac caagaagatc ttttggtact gtggggaatt caccatccta 600

atgatgcggc agagcagaca aggctatatc aaaacccaac cacctatatt tccattggga 660

catcaacact aaaccagaga ttggtaccaa aaatagctac tagatccaaa gtaaacgggc 720

aaagtggaag gatggagttc ttctggacaa ttttaaaacc taatgatgca atcaacttcg 780

agagtaatgg aaatttcatt gctccagaat atgcatacaa aattgtcaag aaaggggact 840

cagcaattat gaaaagtgaa ttggaatatg gtaactgcaa caccaagtgt caaactccaa 900

tgggggcgat aaactctagt atgccattcc acaacataca ccctctcacc atcggggaat 960

gccccaaata tgtgaaatca aacagattag tccttgcaac agggctcaga aatagccctc 1020

aaagagagag cagaagaaaa aagagaggac tatttggagc tatagcaggt tttatagagg 1080

gaggatggca gggaatggta gatggttggt atgggtacca ccatagcaat gagcagggga 1140

gtgggtacgc tgcagacaaa gaatccactc aaaaggcaat agatggagtc accaataagg 1200

tcaactcaat cattgacaaa atgaacactc agtttgaggc cgttggaagg gaatttaata 1260

acttagaaag gagaatagag aatttaaaca agaagatgga agacgggttt ctagatgtct 1320

ggacttataa tgccgaactt ctggttctca tggaaaatga gagaactcta gactttcatg 1380

actcaaatgt taagaacctc tacgacaagg tccgactaca gcttagggat aatgcaaagg 1440

agctgggtaa cggttgtttc gagttctatc acaaatgtga taatgaatgt atggaaagta 1500

taagaaacgg aacgtacaac tatccgcagt attcagaaga agcaagatta aaaagagagg 1560

aaataagtgg ggtaaaattg gaatcaatag gaacttacca aatactgtca atttattcaa 1620

cagtggcgag ttccctagca ctggcaatca tgatggctgg tctatcttta tggatgtgct 1680

ccaatggatc gttacaatgc agaatttgca tttaaatttg tgagttcag 1729

<210> 5
<211> 1250
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 SARS-CoV-2，具有 H5 A/Indonesia/5/05 血球凝集素 CT AA

<400> 5

Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
1 5 10 15

Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe

20 25 30

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

325 330 335

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser

625 630 635 640

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala

930 935 940

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu
1190 1195 1200

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

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met

1220 1225 1230

Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
1235 1240 1245

Cys Ile
1250

<210> 6
<211> 50
<212> PRT
<213> 流感

<400> 6

Ile Asp Gly Val Lys Leu Glu Ser Thr Arg Ile Tyr Gln Ile Leu Ala
1 5 10 15

Ile Tyr Ser Thr Val Ala Ser Ser Leu Val Leu Val Val Ser Leu Gly
20 25 30

Ala Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
35 40 45

Cys Ile
50

<210> 7
<211> 50
<212> PRT
<213> 流感

<400> 7

Ile Lys Gly Val Lys Leu Ser Ser Met Gly Val Tyr Gln Ile Leu Ala
1 5 10 15

Ile Tyr Ala Thr Val Ala Gly Ser Leu Ser Leu Ala Ile Met Met Ala
20 25 30

Gly Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
35 40 45

Cys Ile
50

<210> 8
<211> 49
<212> PRT
<213> 流感

<400> 8

Ile Lys Gly Val Glu Leu Lys Ser Gly Tyr Lys Asp Trp Ile Leu Trp
1 5 10 15

Ile Ser Phe Ala Ile Ser Cys Phe Leu Leu Cys Val Ala Leu Leu Gly
20 25 30

Phe Ile Met Trp Ala Cys Gln Lys Gly Asn Ile Arg Cys Asn Ile Cys
35 40 45

Ile

<210> 9
<211> 50
<212> PRT
<213> 流感

<400> 9

Ile Ser Gly Val Lys Leu Glu Ser Ile Gly Thr Tyr Gln Ile Leu Ser
1 5 10 15

Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala Leu Ala Ile Met Met Ala
20 25 30

Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
35 40 45

Cys Ile
50

<210> 10
<211> 50
<212> PRT
<213> 流感

<400> 10

Ile Glu Ser Val Lys Leu Glu Asn Leu Gly Val Tyr Gln Ile Leu Ala
1 5 10 15

Ile Tyr Ser Thr Val Ser Ser Ser Leu Val Leu Val Gly Leu Ile Met
20 25 30

Ala Met Gly Leu Trp Met Cys Ser Asn Gly Ser Met Gln Cys Arg Ile
35 40 45

Cys Ile
50

<210> 11
<211> 49
<212> PRT
<213> 流感

<400> 11

Ile Asp Pro Val Lys Leu Ser Ser Gly Tyr Lys Asp Val Ile Leu Trp
1 5 10 15

Phe Ser Phe Gly Ala Ser Cys Phe Ile Leu Leu Ala Ile Val Met Gly
20 25 30

Leu Val Phe Ile Cys Val Lys Asn Gly Asn Met Arg Cys Thr Ile Cys
35 40 45

Ile

<210> 12
<211> 50
<212> PRT

<213> 流感

<400> 12

Ile Glu Gly Val Lys Leu Glu Ser Glu Gly Thr Tyr Lys Ile Leu Thr
1 5 10 15

Ile Tyr Ser Thr Val Ala Ser Ser Leu Val Leu Ala Met Gly Phe Ala
20 25 30

Ala Phe Leu Phe Trp Ala Met Ser Asn Gly Ser Cys Arg Cys Asn Ile
35 40 45

Cys Ile
50

<210> 13
<211> 50
<212> PRT
<213> 流感

<400> 13

Ala Ala Ser Leu Asn Asp Asp Gly Leu Asp Asn His Thr Ile Leu Leu
1 5 10 15

Tyr Tyr Ser Thr Ala Ala Ser Ser Leu Ala Val Thr Leu Met Ile Ala
20 25 30

Ile Phe Val Val Tyr Met Val Ser Arg Asp Asn Val Ser Cys Ser Ile
35 40 45

Cys Leu
50

<210> 14
<211> 50
<212> PRT
<213> 人工序列

<220>
<223> 流感血球凝集素的 C-端區的共通序列

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (7)..(7)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (13)..(13)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (16)..(16)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (26)..(26)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (28)..(36)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (44)..(45)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (47)..(47)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 14

Ile Xaa Gly Val Lys Leu Xaa Ser Xaa Gly Xaa Tyr Xaa Ile Leu Xaa
1 5 10 15

Ile Tyr Ser Thr Val Ala Ser Ser Leu Xaa Leu Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Xaa Trp Met Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile
35 40 45

Cys Ile
50

<210> 15
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 流感血球凝集素的 CT 結構域的共通序列

<220>
<221> misc_feature
<222> (1)..(2)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (10)..(11)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (13)..(13)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 15

Xaa Xaa Trp Met Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile Cys Ile
1 5 10 15

<210> 16
<211> 69

<212> PRT
<213> SARS-CoV-2

<400> 16

Trp Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe
1 5 10 15

Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys
20 25 30

Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys Ser Cys Gly Ser
35 40 45

Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys Gly Val
50 55 60

Lys Leu His Tyr Thr
65

<210> 17
<211> 50
<212> PRT
<213> 流感

<400> 17

Ile Ser Gly Val Lys Leu Glu Ser Ile Gly Thr Tyr Gln Ile Leu Ser
1 5 10 15

Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala Leu Ala Ile Met Met Ala
20 25 30

Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
35 40 45

Cys Ile
50

<210> 18
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 SARS-CoV-2 S 蛋白的 C-端區，具有 H5i 血球凝集素 CT

<400> 18

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 19
<211> 40
<212> PRT
<213> 人工序列

<220>

<223> 經修飾的 SARS-CoV-2 S 蛋白的 C-端區，具有 H5i 血球凝集素 CT, 變異 1

<400> 19

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
20 25 30

Ser Leu Gln Cys Arg Ile Cys Ile
35 40

<210> 20
<211> 1258
<212> PRT
<213> 人工序列

<220>
<223> (無 SP) SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT AA

<400> 20

Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser
1 5 10 15

Phe Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val
20 25 30

Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr
35 40 45

Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe
50 55 60

Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr
65 70 75 80

Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp
85 90 95

Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val
100 105 110

Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val
115 120 125

Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val
130 135 140

Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe
145 150 155 160

Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu
165 170 175

Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His
180 185 190

Thr Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu
195 200 205

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

Thr Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser
225 230 235 240

Ser Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln
245 250 255

Pro Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp
260 265 270

Ala Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu
275 280 285

Lys Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg
290 295 300

Val Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu
305 310 315 320

Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr
325 330 335

Ala Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val
340 345 350

Leu Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser
355 360 365

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

Phe Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr
385 390 395 400

Gly Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly
405 410 415

Cys Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly
420 425 430

Asn Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro
435 440 445

Phe Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro
450 455 460

Cys Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr
465 470 475 480

Gly Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val
485 490 495

Val Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro
500 505 510

Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe
515 520 525

Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe
530 535 540

Leu Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala
545 550 555 560

Val Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser
565 570 575

Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln
580 585 590

Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala
595 600 605

Ile His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly
610 615 620

Ser Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His
625 630 635 640

Val Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys
645 650 655

Ala Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gly Ser Ala Ser Ser Val
660 665 670

Ala Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn
675 680 685

Ser Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr
690 695 700

Ile Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser
705 710 715 720

Val Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn
725 730 735

Leu Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu
740 745 750

Thr Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala
755 760 765

Gln Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly
770 775 780

Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg
785 790 795 800

Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala
805 810 815

Gly Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg
820 825 830

Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro
835 840 845

Leu Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala
850 855 860

Gly Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln
865 870 875 880

Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val
885 890 895

Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe
900 905 910

Asn Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser
915 920 925

Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu
930 935 940

Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser
945 950 955 960

Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val
965 970 975

Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr
980 985 990

Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
995 1000 1005

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1010 1015 1020

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1025 1030 1035

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1040 1045 1050

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1055 1060 1065

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1070 1075 1080

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1085 1090 1095

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1100 1105 1110

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1115 1120 1125

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1130 1135 1140

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1145 1150 1155

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1160 1165 1170

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

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1190 1195 1200

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1205 1210 1215

Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1220 1225 1230

Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro
1235 1240 1245

Val Leu Lys Gly Val Lys Leu His Tyr Thr
1250 1255

<210> 21
<211> 1235
<212> PRT
<213> 人工序列

<220>
<223> (無 SP) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血球凝集素 CT AA

<400> 21

Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser
1 5 10 15

Phe Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val
20 25 30

Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr
35 40 45

Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe
50 55 60

Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr
65 70 75 80

Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp
85 90 95

Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val
100 105 110

Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val
115 120 125

Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val
130 135 140

Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe
145 150 155 160

Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu
165 170 175

Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His
180 185 190

Thr Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu
195 200 205

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

Thr Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser
225 230 235 240

Ser Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln
245 250 255

Pro Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp
260 265 270

Ala Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu
275 280 285

Lys Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg
290 295 300

Val Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu
305 310 315 320

Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr
325 330 335

Ala Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val
340 345 350

Leu Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser
355 360 365

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

Phe Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr
385 390 395 400

Gly Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly
405 410 415

Cys Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly
420 425 430

Asn Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro
435 440 445

Phe Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro
450 455 460

Cys Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr
465 470 475 480

Gly Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val
485 490 495

Val Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro
500 505 510

Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe
515 520 525

Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe
530 535 540

Leu Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala
545 550 555 560

Val Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser
565 570 575

Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln
580 585 590

Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala
595 600 605

Ile His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly
610 615 620

Ser Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His
625 630 635 640

Val Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys
645 650 655

Ala Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gly Ser Ala Ser Ser Val
660 665 670

Ala Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn
675 680 685

Ser Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr
690 695 700

Ile Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser
705 710 715 720

Val Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn
725 730 735

Leu Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu
740 745 750

Thr Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala
755 760 765

Gln Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly
770 775 780

Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg
785 790 795 800

Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala
805 810 815

Gly Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg
820 825 830

Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro
835 840 845

Leu Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala
850 855 860

Gly Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln
865 870 875 880

Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val
885 890 895

Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe
900 905 910

Asn Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser
915 920 925

Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu
930 935 940

Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser
945 950 955 960

Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val
965 970 975

Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr
980 985 990

Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn
995 1000 1005

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys
1010 1015 1020

Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro
1025 1030 1035

Gln Ser Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val
1040 1045 1050

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His
1055 1060 1065

Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn
1070 1075 1080

Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln
1085 1090 1095

Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val
1100 1105 1110

Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro
1115 1120 1125

Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn
1130 1135 1140

His Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn
1145 1150 1155

Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu
1160 1165 1170

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

Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile Trp Leu
1190 1195 1200

Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Met
1205 1210 1215

Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
1220 1225 1230

Cys Ile
1235

<210> 22
<211> 3849
<212> DNA
<213> 人工序列

<220>
<223> PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-DNA

<400> 22
atggcgaaaa acgttgcgat tttcggctta ttgttttctc ttcttgtgtt ggttccttct 60

cagatcttcg cggtgaatct tacgacgcga acacagttac cacccgcata tacaaatagc 120

ttcactcggg gtgtttatta ccccgacaaa gtgttcaggt cctccgtgct ccactcaaca 180

caggacctct ttcttccttt cttttctaac gtgacatggt ttcatgccat tcatgtatcc 240

ggcactaacg gtactaagag gttcgataat cctgtgctcc ctttcaatga cggcgtttac 300

tttgcaagca cagagaagag taacatcatc cgaggttgga tctttggcac taccctcgat 360

tcaaagacgc agagcctcct cattgtgaac aatgccacta acgtggtgat caaagtttgc 420

gagtttcagt tctgcaatga ccctttcttg ggggtgtact atcataagaa caacaagtct 480

tggatggaat ctgaattccg cgtctatagc agcgccaaca actgcacctt tgaatacgtg 540

tcccagccct tccttatgga cctggaggga aagcagggaa actttaagaa tctgagagag 600

ttcgtgttta aaaatatcga cggctatttt aagatctatt ctaagcacac gcctattaat 660

ctcgtgcgcg atcttccaca aggcttcagc gccctggaac cactcgtgga cctcccaatt 720

ggtatcaaca tcactagatt tcagactctg cttgccctcc accgatccta tctgacaccc 780

ggagactcct ctagcggctg gactgccggc gctgccgctt attacgttgg ttatcttcag 840

ccacgcacgt tcctgctgaa gtataacgag aatggtacta ttaccgatgc cgtggattgt 900

gcccttgacc ccctgtccga aactaagtgc acactcaagt cattcactgt ggaaaaagga 960

atctaccaga caagcaattt tcgggtccag cctactgaga gcattgtgcg ctttcctaac 1020

atcacaaatc tttgcccctt cggagaggtt ttcaatgcta cacggtttgc ctccgtgtat 1080

gcctggaacc gcaagagaat ttccaattgc gtggccgatt actccgtgct ctacaatagt 1140

gcaagcttta gcacctttaa gtgctatggc gtatccccta ctaagcttaa cgacttgtgt 1200

ttcacaaacg tgtatgccga ctcctttgtg atacggggcg acgaagttag acagatagca 1260

ccaggacaga cgggaaagat agctgactac aactataagc ttcctgatga cttcactggc 1320

tgcgttatcg cgtggaattc taacaacctg gactcaaaag tcggcggcaa ctataactat 1380

ctctatcggc tgttccgcaa gagtaacctt aagccctttg agagagatat aagcactgaa 1440

atctaccagg ctggcagtac gccctgtaat ggcgtggaag gctttaattg ttattttcca 1500

ctgcaatcct atggttttca gccaaccaat ggcgtgggct accaaccata ccgcgtcgtg 1560

gtgctctcct ttgaactgct ccacgctccc gcgactgtct gcggccccaa gaagtccacg 1620

aaccttgtga agaataagtg cgttaatttt aatttcaacg gcctcactgg aacaggagtg 1680

ctcactgaga gtaacaagaa gttcctgcca tttcaacaat ttggcagaga catagccgat 1740

actactgacg ccgttaggga cccccagacc ctcgagattc tcgatataac gccctgctcc 1800

ttcggtggag tttccgtgat cacgccaggc accaatacca gtaaccaggt cgccgtgctg 1860

tatcaggatg tcaactgtac tgaggtgccc gtagccatcc atgcggatca gctcacacca 1920

acttggaggg tgtacagcac cggctccaat gtattccaga ctcgggccgg atgccttatt 1980

ggcgccgaac acgtgaacaa tagttacgaa tgcgatattc caattggcgc cggaatctgt 2040

gctagctacc agactcagac gaactcccca ggcagcgcca gcagcgttgc cagccagtca 2100

atcatcgctt atacaatgtc acttggagcc gaaaactccg tggcttactc aaacaacagc 2160

atcgccatcc ccacaaactt caccatatcc gtgacaactg agattctgcc agtgtccatg 2220

actaagacgt ccgtagattg cactatgtac atatgcggcg acagcacaga atgttctaat 2280

ctgctgctgc aatatggaag cttctgcact caactgaaca gagcgctcac aggcatcgcc 2340

gtggagcagg ataagaatac ccaggaggtg ttcgcccaag ttaagcagat ctacaagacc 2400

ccacccataa aggatttcgg tggattcaat tttagtcaga tactcccaga cccatctaag 2460

ccatccaaga ggagctttat cgaggatctt ttgtttaaca aagttactct ggccgacgcc 2520

ggtttcatca agcagtacgg agattgcctc ggcgacatcg ctgctcgtga cctcatctgt 2580

gcgcaaaagt ttaacggtct gacggtgctg cctcccctcc ttactgatga aatgatcgcc 2640

cagtatacca gcgcactcct cgctggcacc ataacatccg gttggacatt cggcgctggt 2700

gcagcactgc agataccatt cgccatgcaa atggcatatc gtttcaacgg tatcggtgtc 2760

acacagaatg tcctatatga gaaccagaag ctgatcgcaa atcagttcaa tagtgccatc 2820

ggaaaaatcc aggatagcct tagcagcaca gcctcagccc ttggcaaact ccaggatgtc 2880

gtgaaccaga atgcccaggc tctcaatacc ctcgtgaagc agctctcatc taatttcggc 2940

gcaatttcca gtgtcctcaa cgacatcctc agccgcctcg acccccccga ggccgaagtg 3000

cagattgaca gactgattac aggtcgactc cagagcctcc agacttacgt gactcagcag 3060

ctgataagag ccgccgagat aagggccagc gctaacctgg ctgccacaaa gatgtctgag 3120

tgcgtgctgg gccagtccaa gagagtagac ttctgtggca aaggctacca tctgatgagc 3180

ttcccacaat ccgcacctca cggcgtagtg ttcctccacg tgacatatgt accggctcag 3240

gagaagaatt tcactaccgc tcctgctata tgccatgatg gaaaggctca cttcccccgg 3300

gagggggtgt tcgtgtccaa cggcacccat tggtttgtga ctcagcggaa tttctacgaa 3360

ccccagatca taaccactga caacacattt gtgtccggaa attgtgacgt ggtcattgga 3420

atagtgaaca acactgttta tgatccactg cagccagaac ttgacagctt taaggaggag 3480

ctcgacaagt acttcaagaa tcatacgtca ccagatgtgg acctcggaga tattagcggt 3540

atcaatgcca gtgttgtcaa tattcagaag gaaatagacc gccttaatga ggtcgccaaa 3600

aatctgaacg agagcctcat cgatcttcag gagctgggca aatatgagca gtacatcaag 3660

tggccttggt atatttggct tggcttcatc gccggcctga tcgccatagt aatggtcaca 3720

attatgctct gctgcatgac ctcttgctgc tcctgtctga aaggctgctg ctcttgcgga 3780

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tatacttag 3849

<210> 23
<211> 1282
<212> PRT
<213> 人工序列

<220>
<223> PDI-SARS-CoV-2 S 蛋白 GSAS+PP wtTM/CT-AA

<400> 23

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
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Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys Met Thr Ser
1235 1240 1245

Cys Cys Ser Cys Leu Lys Gly Cys Cys Ser Cys Gly Ser Cys Cys
1250 1255 1260

Lys Phe Asp Glu Asp Asp Ser Glu Pro Val Leu Lys Gly Val Lys
1265 1270 1275

Leu His Tyr Thr
1280

<210> 24
<211> 52
<212> DNA
<213> 人工序列

<220>
<223> IF(PDI)-CoV(opt2).c

<400> 24
tctcagatct tcgcggtgaa tcttacgacg cgaacacagt taccacccgc at 52

<210> 25
<211> 51
<212> DNA
<213> 人工序列

<220>
<223> IF(AVB)-CoV(opt2).r

<400> 25
acgacacgac taaggcctct aagtatagtg cagcttcacg cccttcagga c 51

<210> 26
<211> 3789
<212> DNA
<213> 人工序列

<220>
<223> PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP H5iTM/CT-DNA

<400> 26
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ttcactcggg gtgtttatta ccccgacaaa gtgttcaggt cctccgtgct ccactcaaca 180

caggacctct ttcttccttt cttttctaac gtgacatggt ttcatgccat tcatgtatcc 240

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tttgcaagca cagagaagag taacatcatc cgaggttgga tctttggcac taccctcgat 360

tcaaagacgc agagcctcct cattgtgaac aatgccacta acgtggtgat caaagtttgc 420

gagtttcagt tctgcaatga ccctttcttg ggggtgtact atcataagaa caacaagtct 480

tggatggaat ctgaattccg cgtctatagc agcgccaaca actgcacctt tgaatacgtg 540

tcccagccct tccttatgga cctggaggga aagcagggaa actttaagaa tctgagagag 600

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ctcgtgcgcg atcttccaca aggcttcagc gccctggaac cactcgtgga cctcccaatt 720

ggtatcaaca tcactagatt tcagactctg cttgccctcc accgatccta tctgacaccc 780

ggagactcct ctagcggctg gactgccggc gctgccgctt attacgttgg ttatcttcag 840

ccacgcacgt tcctgctgaa gtataacgag aatggtacta ttaccgatgc cgtggattgt 900

gcccttgacc ccctgtccga aactaagtgc acactcaagt cattcactgt ggaaaaagga 960

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atcacaaatc tttgcccctt cggagaggtt ttcaatgcta cacggtttgc ctccgtgtat 1080

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ccacccataa aggatttcgg tggattcaat tttagtcaga tactcccaga cccatctaag 2460

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gcgcaaaagt ttaacggtct gacggtgctg cctcccctcc ttactgatga aatgatcgcc 2640

cagtatacca gcgcactcct cgctggcacc ataacatccg gttggacatt cggcgctggt 2700

gcagcactgc agataccatt cgccatgcaa atggcatatc gtttcaacgg tatcggtgtc 2760

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gtgaaccaga atgcccaggc tctcaatacc ctcgtgaagc agctctcatc taatttcggc 2940

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cagattgaca gactgattac aggtcgactc cagagcctcc agacttacgt gactcagcag 3060

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tgcgtgctgg gccagtccaa gagagtagac ttctgtggca aaggctacca tctgatgagc 3180

ttcccacaat ccgcacctca cggcgtagtg ttcctccacg tgacatatgt accggctcag 3240

gagaagaatt tcactaccgc tcctgctata tgccatgatg gaaaggctca cttcccccgg 3300

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ctcgacaagt acttcaagaa tcatacgtca ccagatgtgg acctcggaga tattagcggt 3540

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aatctgaacg agagcctcat cgatcttcag gagctgggca aatatgagca gtacatcaag 3660

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tgcatttaa 3789

<210> 27
<211> 1262
<212> PRT
<213> 人工序列

<220>
<223> PDI-經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP H5iTM/CT-AA

<400> 27

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
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Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val
1220 1225 1230

Ala Ser Ser Leu Ala Leu Ala Ile Met Met Ala Gly Leu Ser Leu
1235 1240 1245

Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255 1260

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<211> 48
<212> DNA
<213> 人工序列

<220>
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Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
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Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
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Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
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Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
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Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
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Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
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225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
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Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
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Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
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Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
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Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
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Thr Phe Lys Cys Tyr Gly Val Ser Pro Thr Lys Leu Asn Asp Leu Cys
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Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
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Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
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Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
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Phe Arg Lys Ser Asn Leu Lys Pro Phe Glu Arg Asp Ile Ser Thr Glu
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Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
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Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
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Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
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Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
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Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
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Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
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Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
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Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
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Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

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755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

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Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

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Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr Ser Gly Trp Thr
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Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
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Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
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Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
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Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
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Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
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<210> 35
<211> 4436
<212> DNA
<213> 人工序列

<220>
<223> 選殖載體 8716 從左到右 T-DNA

<400> 35
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aataactcaa aaaccataaa agtttaagtt agcaagtgtg tacattttta cttgaacaaa 180

aatattcacc tactactgtt ataaatcatt attaaacatt agagtaaaga aatatggatg 240

ataagaacaa gagtagtgat attttgacaa caattttgtt gcaacatttg agaaaatttt 300

gttgttctct cttttcattg gtcaaaaaca atagagagag aaaaaggaag agggagaata 360

aaaacataat gtgagtatga gagagaaagt tgtacaaaag ttgtaccaaa atagttgtac 420

aaatatcatt gaggaatttg acaaaagcta cacaaataag ggttaattgc tgtaaataaa 480

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aagaataaat tatttttaaa attaaaagtt gagtcatttg attaaacatg tgattattta 600

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gtatatttac taaaaaatct aagccacgta ggaggataac aggatccccg taggaggata 840

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<223> 構建體 8591 從 2X35S prom 至 NOS term

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tccaaaaata tcaaagatac agtctcagaa gaccaaaggg caattgagac ttttcaacaa 420

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tccactgacg taagggatga cgcacaatcc cactatcctt cgcaagaccc ttcctctata 720

taaggaagtt catttcattt ggagaggcac tccatttgaa tctatcaaac caaaacacat 780

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<210> 37
<211> 39
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 SARS-CoV-2 S 蛋白的 C-端區，具有 H5i 血球凝集素 CT, 變異 2

<400> 37

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser
20 25 30

Leu Gln Cys Arg Ile Cys Ile
35

<210> 38
<211> 36
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 SARS-CoV-2 S 蛋白的 C-端區，具有 H5i 血球凝集素 CT, 變異 3

<400> 38

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Cys Cys Met Cys Ser Asn Gly Ser Leu Gln Cys
20 25 30

Arg Ile Cys Ile
35

<210> 39
<211> 34
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 SARS-CoV-2 S 蛋白的 C-端區，具有 H5i 血球凝集素 CT, 變異 4

<400> 39

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1 5 10 15

Val Thr Ile Met Leu Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
20 25 30

Cys Ile

<210> 40
<211> 151
<212> DNA
<213> Arracacha 病毒 B

<400> 40
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taagttgttt gtttagtgat tcaaaaaaaa a 151

<210> 41
<211> 182
<212> DNA
<213> 甜菜壞死性黃脈病毒

<400> 41
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ttatgtcggt tcttgattat gtggtgcata attattgaac taattgtttg ttgggttgta 120

atgtactgac tgggtgtgaa ttgtaccagt cgttaaaggg tttactatca gtatattgat 180

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<210> 42
<211> 132
<212> DNA
<213> 南方豆花葉病毒

<400> 42
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acaatgccac gcgcttgagg gagaatgcac gttaatcatc cctccgctag tgatggagcg 120

taatccaaaa gt 132

<210> 43
<211> 282
<212> DNA
<213> 蕪菁輪點病毒

<400> 43
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ttaagtttcc tatgttgttt taaattaaat atctgtataa ttagtagatg taaatctgct 120

ttgtgcgttt gacagtctgt ggaaacgcac tggttcatga gataggacca cctaggaggt 180

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tagtaattgt tttctcttga tatgtattat tacttttta tt 282

<210> 44
<211> 165
<212> DNA
<213> 豇豆花葉病毒

<400> 44

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caggtcgtcc cttcagcaag gacacaaaaa gattttaatt ttatt 165

<210> 45
<211> 275
<212> DNA
<213> 蠶豆真花葉病毒

<400> 45
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atgcatttat tagagtattt ctttcttctt tagcataaag gtattgaaga cctataaact 180

tcgtccgggt tggggaaagt accagcttag catatcttta gaaaactata tagagctctt 240

taccttgagt tgtttcctaa agtttatgca aaaaa 275

<210> 46
<211> 147
<212> DNA
<213> 歐爾密甜瓜病毒

<400> 46
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gagttgggcc acaagtgcca ctcgcagcga aggcggtctg aggtttcccc ctggcggtta 120

cttccatatc tttgggagat aactggg 147

<210> 47

<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血球凝集素 CT AA

<400> 47

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1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile

115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr

420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu

725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met

1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 48
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+4P，具有 H5i 血球凝集素 CT AA

<400> 48

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr

165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

Phe Arg Lys Ser Asn Leu Lys Pro Phe Glu Arg Asp Ile Ser Thr Glu

465 470 475 480

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp

770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Pro Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Pro Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn

1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 49
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+6P，具有 H5i 血球凝集素 CT AA

<400> 49

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp

210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His

515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Pro Ile Glu Asp Leu Leu Phe

820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Pro Ala Leu Gln Ile Pro Phe Pro Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Pro Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn

1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 50
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP+923，具有 H5i 血球凝集素 CT AA

<400> 50

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala

260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg

565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala

865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Phe Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val

1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 51
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+4P+923，具有 H5i 血球凝集素 CT AA

<400> 51

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val

1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly

305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val

610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Pro Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn

915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Phe Ser Ser Thr Pro Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr

1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 52
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+6P+923，具有 H5i 血球凝集素 CT AA

<400> 52

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe

50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser

355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp

660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Pro Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Pro Ala Leu Gln Ile Pro Phe Pro Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Phe Ser Ser Thr Pro Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser

965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile

1250 1255

<210> 53
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H1 Cal 血球凝集素 CT AA

<400> 53

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly

100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val

405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser

705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg

1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Ser Phe Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 54
<211> 1258
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H3 Minn 血球凝集素 CT AA

<400> 54

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser

145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu

450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe

755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly

1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Met Trp Ala Cys Gln
1235 1240 1245

Lys Gly Asn Ile Arg Cys Asn Ile Cys Ile
1250 1255

<210> 55
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H6 HK 血球凝集素 CT AA

<400> 55

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly

195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val

500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

805 810 815

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val

1100 1105 1110

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Gly Leu Trp Met Cys
1235 1240 1245

Ser Asn Gly Ser Met Gln Cys Arg Ile Cys Ile
1250 1255

<210> 56
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H7 Guangdong 血球凝集素 CT AA

<400> 56

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser

245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val

545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe

850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys

1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Val Phe Ile Cys Val
1235 1240 1245

Lys Asn Gly Asn Met Arg Cys Thr Ile Cys Ile
1250 1255

<210> 57
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H9 HK 血球凝集素 CT AA

<400> 57

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro

290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr

595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala

900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

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

1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Leu Phe Trp Ala Met
1235 1240 1245

Ser Asn Gly Ser Cys Arg Cys Asn Ile Cys Ile
1250 1255

<210> 58
<211> 1259
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 B/Wash 血球凝集素 CT AA

<400> 58

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

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

35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn

340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala

645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val

945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Val Val Tyr Met Val

1235 1240 1245

Ser Arg Asp Asn Val Ser Cys Ser Ile Cys Leu
1250 1255

<210> 59
<211> 1262
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的SARS-CoV-2 S蛋白GSAS+PP，具有H5i 血球凝集素 CT (選擇性 1) AA

<400> 59

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn

85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

Thr Phe Lys Cys Tyr Gly Val Ser Pro Thr Lys Leu Asn Asp Leu Cys

385 390 395 400

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr

690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

995 1000 1005

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Met Ala Gly Leu Ser Leu
1235 1240 1245

Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255 1260

<210> 60
<211> 1261
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血球凝集素 CT (選擇性 2) AA

<400> 60

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe

130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn

435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys

740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly

1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Ala Gly Leu Ser Leu Trp
1235 1240 1245

Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255 1260

<210> 61
<211> 1258
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血球凝集素 CT (選擇性 3) AA

<400> 61

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln

180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile
225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn

485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys
530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr

785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp
835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe

1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn
1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys Met Cys Ser
1235 1240 1245

Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 62
<211> 1256
<212> PRT
<213> 人工序列

<220>
<223> (PDI) 經修飾的 SARS-CoV-2 S 蛋白 GSAS+PP，具有 H5i 血球凝集素 CT (選擇性 4) AA

<400> 62

Met Ala Lys Asn Val Ala Ile Phe Gly Leu Leu Phe Ser Leu Leu Val
1 5 10 15

Leu Val Pro Ser Gln Ile Phe Ala Val Asn Leu Thr Thr Arg Thr Gln
20 25 30

Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro
35 40 45

Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe
50 55 60

Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser
65 70 75 80

Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn
85 90 95

Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly
100 105 110

Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile
115 120 125

Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe
130 135 140

Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser
145 150 155 160

Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr
165 170 175

Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln
180 185 190

Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly
195 200 205

Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp
210 215 220

Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile

225 230 235 240

Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser
245 250 255

Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala
260 265 270

Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr
275 280 285

Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro
290 295 300

Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly
305 310 315 320

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

Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn
340 345 350

Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser
355 360 365

Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser
370 375 380

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

Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val
405 410 415

Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr
420 425 430

Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn
435 440 445

Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu
450 455 460

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

Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn
485 490 495

Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val
500 505 510

Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His
515 520 525

Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys

530 535 540

Asn Lys Cys Val Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val
545 550 555 560

Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg
565 570 575

Asp Ile Ala Asp Thr Thr Asp Ala Val Arg Asp Pro Gln Thr Leu Glu
580 585 590

Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr
595 600 605

Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val
610 615 620

Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro
625 630 635 640

Thr Trp Arg Val Tyr Ser Thr Gly Ser Asn Val Phe Gln Thr Arg Ala
645 650 655

Gly Cys Leu Ile Gly Ala Glu His Val Asn Asn Ser Tyr Glu Cys Asp
660 665 670

Ile Pro Ile Gly Ala Gly Ile Cys Ala Ser Tyr Gln Thr Gln Thr Asn
675 680 685

Ser Pro Gly Ser Ala Ser Ser Val Ala Ser Gln Ser Ile Ile Ala Tyr
690 695 700

Thr Met Ser Leu Gly Ala Glu Asn Ser Val Ala Tyr Ser Asn Asn Ser
705 710 715 720

Ile Ala Ile Pro Thr Asn Phe Thr Ile Ser Val Thr Thr Glu Ile Leu
725 730 735

Pro Val Ser Met Thr Lys Thr Ser Val Asp Cys Thr Met Tyr Ile Cys
740 745 750

Gly Asp Ser Thr Glu Cys Ser Asn Leu Leu Leu Gln Tyr Gly Ser Phe
755 760 765

Cys Thr Gln Leu Asn Arg Ala Leu Thr Gly Ile Ala Val Glu Gln Asp
770 775 780

Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr
785 790 795 800

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

Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
820 825 830

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp

835 840 845

Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
850 855 860

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala
865 870 875 880

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

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
900 905 910

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
915 920 925

Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln
930 935 940

Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val
945 950 955 960

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
965 970 975

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
980 985 990

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

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg
1010 1015 1020

Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met
1025 1030 1035

Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly
1040 1045 1050

Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly
1055 1060 1065

Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn
1070 1075 1080

Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe
1085 1090 1095

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

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn
1115 1120 1125

Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn

1130 1135 1140

Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys
1145 1150 1155

Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val
1160 1165 1170

Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
1175 1180 1185

Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn
1190 1195 1200

Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr
1205 1210 1215

Ile Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu
1220 1225 1230

Ile Ala Ile Val Met Val Thr Ile Met Leu Cys Cys Ser Asn Gly
1235 1240 1245

Ser Leu Gln Cys Arg Ile Cys Ile
1250 1255

<210> 63
<211> 31
<212> PRT

<213> SARS-CoV-2

<400> 63

Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val
1 5 10 15

Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser
20 25 30

<210> 64
<211> 33
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 TMCT，具有間插肽序列(X)n

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa 可以是 0 至 10 個胺基酸的任何組合

<220>
<221> misc_feature
<222> (27)..(28)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (30)..(30)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 64

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Xaa Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile Cys
20 25 30

Ile

<210> 65
<211> 3780
<212> DNA
<213> 人工序列

<220>
<223> PDI-S 蛋白 GSAS+4P-DNA

<400> 65
atggcgaaaa acgttgcgat tttcggctta ttgttttctc ttcttgtgtt ggttccttct 60

cagatcttcg cggtgaatct tacgacgcga acacagttac cacccgcata tacaaatagc 120

ttcactcggg gtgtttatta ccccgacaaa gtgttcaggt cctccgtgct ccactcaaca 180

caggacctct ttcttccttt cttttctaac gtgacatggt ttcatgccat tcatgtatcc 240

ggcactaacg gtactaagag gttcgataat cctgtgctcc ctttcaatga cggcgtttac 300

tttgcaagca cagagaagag taacatcatc cgaggttgga tctttggcac taccctcgat 360

tcaaagacgc agagcctcct cattgtgaac aatgccacta acgtggtgat caaagtttgc 420

gagtttcagt tctgcaatga ccctttcttg ggggtgtact atcataagaa caacaagtct 480

tggatggaat ctgaattccg cgtctatagc agcgccaaca actgcacctt tgaatacgtg 540

tcccagccct tccttatgga cctggaggga aagcagggaa actttaagaa tctgagagag 600

ttcgtgttta aaaatatcga cggctatttt aagatctatt ctaagcacac gcctattaat 660

ctcgtgcgcg atcttccaca aggcttcagc gccctggaac cactcgtgga cctcccaatt 720

ggtatcaaca tcactagatt tcagactctg cttgccctcc accgatccta tctgacaccc 780

ggagactcct ctagcggctg gactgccggc gctgccgctt attacgttgg ttatcttcag 840

ccacgcacgt tcctgctgaa gtataacgag aatggtacta ttaccgatgc cgtggattgt 900

gcccttgacc ccctgtccga aactaagtgc acactcaagt cattcactgt ggaaaaagga 960

atctaccaga caagcaattt tcgggtccag cctactgaga gcattgtgcg ctttcctaac 1020

atcacaaatc tttgcccctt cggagaggtt ttcaatgcta cacggtttgc ctccgtgtat 1080

gcctggaacc gcaagagaat ttccaattgc gtggccgatt actccgtgct ctacaatagt 1140

gcaagcttta gcacctttaa gtgctatggc gtatccccta ctaagcttaa cgacttgtgt 1200

ttcacaaacg tgtatgccga ctcctttgtg atacggggcg acgaagttag acagatagca 1260

ccaggacaga cgggaaagat agctgactac aactataagc ttcctgatga cttcactggc 1320

tgcgttatcg cgtggaattc taacaacctg gactcaaaag tcggcggcaa ctataactat 1380

ctctatcggc tgttccgcaa gagtaacctt aagccctttg agagagatat aagcactgaa 1440

atctaccagg ctggcagtac gccctgtaat ggcgtggaag gctttaattg ttattttcca 1500

ctgcaatcct atggttttca gccaaccaat ggcgtgggct accaaccata ccgcgtcgtg 1560

gtgctctcct ttgaactgct ccacgctccc gcgactgtct gcggccccaa gaagtccacg 1620

aaccttgtga agaataagtg cgttaatttt aatttcaacg gcctcactgg aacaggagtg 1680

ctcactgaga gtaacaagaa gttcctgcca tttcaacaat ttggcagaga catagccgat 1740

actactgacg ccgttaggga cccccagacc ctcgagattc tcgatataac gccctgctcc 1800

ttcggtggag tttccgtgat cacgccaggc accaatacca gtaaccaggt cgccgtgctg 1860

tatcaggatg tcaactgtac tgaggtgccc gtagccatcc atgcggatca gctcacacca 1920

acttggaggg tgtacagcac cggctccaat gtattccaga ctcgggccgg atgccttatt 1980

ggcgccgaac acgtgaacaa tagttacgaa tgcgatattc caattggcgc cggaatctgt 2040

gctagctacc agactcagac gaactcccca ggcagcgcca gcagcgttgc cagccagtca 2100

atcatcgctt atacaatgtc acttggagcc gaaaactccg tggcttactc aaacaacagc 2160

atcgccatcc ccacaaactt caccatatcc gtgacaactg agattctgcc agtgtccatg 2220

actaagacgt ccgtagattg cactatgtac atatgcggcg acagcacaga atgttctaat 2280

ctgctgctgc aatatggaag cttctgcact caactgaaca gagcgctcac aggcatcgcc 2340

gtggagcagg ataagaatac ccaggaggtg ttcgcccaag ttaagcagat ctacaagacc 2400

ccacccataa aggatttcgg tggattcaat tttagtcaga tactcccaga cccatctaag 2460

ccatccaaga ggagccccat cgaggatctt ttgtttaaca aagttactct ggccgacgcc 2520

ggtttcatca agcagtacgg agattgcctc ggcgacatcg ctgctcgtga cctcatctgt 2580

gcgcaaaagt ttaacggtct gacggtgctg cctcccctcc ttactgatga aatgatcgcc 2640

cagtatacca gcgcactcct cgctggcacc ataacatccg gttggacatt cggcgctggt 2700

gcagcactgc agataccatt cgccatgcaa atggcatatc gtttcaacgg tatcggtgtc 2760

acacagaatg tcctatatga gaaccagaag ctgatcgcaa atcagttcaa tagtgccatc 2820

ggaaaaatcc aggatagcct tagcagcaca ccctcagccc ttggcaaact ccaggatgtc 2880

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<210> 70
<211> 3789
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<210> 71
<211> 3786
<212> DNA
<213> 人工序列

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<223> PDI-經修飾的 S 蛋白，具有 H5i 血球凝集素 CT (V2) DNA

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Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg Ser Asp Thr Leu Tyr
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Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser Asn Val Thr Gly Phe
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His Thr Ile Asn His Thr Phe Gly Asn Pro Val Ile Pro Phe Lys Asp
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Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn Val Val Arg Gly Trp
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Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met Gly Thr Gln Thr His
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Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr Phe Glu Tyr Ile Ser
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Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile Thr Asp Ala Val Asp
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Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg
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Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr Ala Ile His Ala Asp
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Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu His Val Asp Thr Ser
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Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe
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His Thr Ile Asn His Thr Phe Gly Asn Pro Val Ile Pro Phe Lys Asp
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Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn Val Val Arg Gly Trp
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195 200 205

Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp Leu Pro Ser Gly Phe
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Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro Ala Gln Asp Ile Trp
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Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile Thr Asp Ala Val Asp
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Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val Val Pro
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Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg
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Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly Pro Lys Leu Ser Thr
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Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr Gly Asn Asn Val Phe
625 630 635 640

Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu His Val Asp Thr Ser
645 650 655

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

Thr Val Ser Leu Leu Ala Ser Thr Ser Gln Lys Ser Ile Val Ala Tyr
675 680 685

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

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

Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys Asn Met Tyr Ile Cys
725 730 735

Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu Gln Tyr Gly Ser Phe
740 745 750

Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp
755 760 765

Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr
770 775 780

Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro
785 790 795 800

Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
805 810 815

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu
820 825 830

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

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala
850 855 860

Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr
865 870 875 880

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
885 890 895

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
900 905 910

Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln
915 920 925

Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val
930 935 940

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
945 950 955 960

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
965 970 975

Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly
980 985 990

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala
995 1000 1005

Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser
1010 1015 1020

Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys
1025 1030 1035

Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala Pro His Gly Val
1040 1045 1050

Val Phe Leu His Val Thr Tyr Val Pro Ser Gln Glu Arg Asn Phe
1055 1060 1065

Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys Ala Tyr Phe Pro
1070 1075 1080

Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser Trp Phe Ile Thr
1085 1090 1095

Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr Thr Asp Asn Thr
1100 1105 1110

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

Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu
1130 1135 1140

Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp
1145 1150 1155

Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln
1160 1165 1170

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

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile
1190 1195 1200

Lys Trp Pro Trp Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala
1205 1210 1215

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

Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg Ser Asp Thr Leu Tyr
50 55 60

Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser Asn Val Thr Gly Phe
65 70 75 80

His Thr Ile Asn His Thr Phe Gly Asn Pro Val Ile Pro Phe Lys Asp
85 90 95

Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn Val Val Arg Gly Trp
100 105 110

Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln Ser Val Ile Ile Ile
115 120 125

Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys Asn Phe Glu Leu Cys
130 135 140

Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met Gly Thr Gln Thr His
145 150 155 160

Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr Phe Glu Tyr Ile Ser
165 170 175

Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser Gly Asn Phe Lys His
180 185 190

Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly Phe Leu Tyr Val Tyr
195 200 205

Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp Leu Pro Ser Gly Phe
210 215 220

Asn Thr Leu Lys Pro Ile Phe Lys Leu Pro Leu Gly Ile Asn Ile Thr
225 230 235 240

Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro Ala Gln Asp Ile Trp
245 250 255

Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr Leu Lys Pro Thr Thr
260 265 270

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

Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys Ser Val Lys Ser Phe
290 295 300

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

Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe
325 330 335

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

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

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

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

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

Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Met Gly Cys Val Leu
420 425 430

Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser Thr Gly Asn Tyr Asn
435 440 445

Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg
450 455 460

Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly Lys Pro Cys Thr Pro
465 470 475 480

Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp Tyr Gly Phe Tyr Thr
485 490 495

Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe
500 505 510

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

Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn Phe Asn Gly Leu Thr
530 535 540

Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg Phe Gln Pro Phe Gln
545 550 555 560

Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp Ser Val Arg Asp Pro
565 570 575

Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys Ser Phe Gly Gly Val
580 585 590

Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser Glu Val Ala Val Leu
595 600 605

Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr Ala Ile His Ala Asp
610 615 620

Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr Gly Asn Asn Val Phe
625 630 635 640

Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu His Val Asp Thr Ser
645 650 655

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

Thr Val Ser Leu Leu Ala Ser Thr Ser Gln Lys Ser Ile Val Ala Tyr
675 680 685

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

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

Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys Asn Met Tyr Ile Cys
725 730 735

Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu Gln Tyr Gly Ser Phe
740 745 750

Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp
755 760 765

Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr
770 775 780

Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro
785 790 795 800

Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
805 810 815

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu
820 825 830

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

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala
850 855 860

Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr
865 870 875 880

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
885 890 895

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
900 905 910

Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln
915 920 925

Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val
930 935 940

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
945 950 955 960

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
965 970 975

Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly
980 985 990

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala
995 1000 1005

Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser
1010 1015 1020

Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys
1025 1030 1035

Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala Pro His Gly Val
1040 1045 1050

Val Phe Leu His Val Thr Tyr Val Pro Ser Gln Glu Arg Asn Phe
1055 1060 1065

Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys Ala Tyr Phe Pro
1070 1075 1080

Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser Trp Phe Ile Thr
1085 1090 1095

Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr Thr Asp Asn Thr
1100 1105 1110

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

Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu
1130 1135 1140

Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp
1145 1150 1155

Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln
1160 1165 1170

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

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile
1190 1195 1200

Lys Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile
1205 1210 1215

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

Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg Ser Asp Thr Leu Tyr
50 55 60

Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser Asn Val Thr Gly Phe
65 70 75 80

His Thr Ile Asn His Thr Phe Gly Asn Pro Val Ile Pro Phe Lys Asp
85 90 95

Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn Val Val Arg Gly Trp
100 105 110

Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln Ser Val Ile Ile Ile
115 120 125

Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys Asn Phe Glu Leu Cys
130 135 140

Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met Gly Thr Gln Thr His
145 150 155 160

Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr Phe Glu Tyr Ile Ser
165 170 175

Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser Gly Asn Phe Lys His
180 185 190

Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly Phe Leu Tyr Val Tyr
195 200 205

Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp Leu Pro Ser Gly Phe
210 215 220

Asn Thr Leu Lys Pro Ile Phe Lys Leu Pro Leu Gly Ile Asn Ile Thr
225 230 235 240

Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro Ala Gln Asp Ile Trp
245 250 255

Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr Leu Lys Pro Thr Thr
260 265 270

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

Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys Ser Val Lys Ser Phe
290 295 300

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

Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe
325 330 335

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

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

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

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

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

Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Met Gly Cys Val Leu
420 425 430

Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser Thr Gly Asn Tyr Asn
435 440 445

Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg
450 455 460

Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly Lys Pro Cys Thr Pro
465 470 475 480

Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp Tyr Gly Phe Tyr Thr
485 490 495

Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe
500 505 510

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

Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn Phe Asn Gly Leu Thr
530 535 540

Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg Phe Gln Pro Phe Gln
545 550 555 560

Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp Ser Val Arg Asp Pro
565 570 575

Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys Ser Phe Gly Gly Val
580 585 590

Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser Glu Val Ala Val Leu
595 600 605

Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr Ala Ile His Ala Asp
610 615 620

Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr Gly Asn Asn Val Phe
625 630 635 640

Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu His Val Asp Thr Ser
645 650 655

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

Thr Val Ser Leu Leu Ala Ser Thr Ser Gln Lys Ser Ile Val Ala Tyr
675 680 685

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

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

Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys Asn Met Tyr Ile Cys
725 730 735

Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu Gln Tyr Gly Ser Phe
740 745 750

Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp
755 760 765

Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr
770 775 780

Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro
785 790 795 800

Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
805 810 815

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu
820 825 830

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

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala
850 855 860

Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr
865 870 875 880

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
885 890 895

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
900 905 910

Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln
915 920 925

Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val
930 935 940

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
945 950 955 960

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
965 970 975

Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly
980 985 990

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala
995 1000 1005

Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser
1010 1015 1020

Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys
1025 1030 1035

Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala Pro His Gly Val
1040 1045 1050

Val Phe Leu His Val Thr Tyr Val Pro Ser Gln Glu Arg Asn Phe
1055 1060 1065

Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys Ala Tyr Phe Pro
1070 1075 1080

Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser Trp Phe Ile Thr
1085 1090 1095

Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr Thr Asp Asn Thr
1100 1105 1110

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

Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu
1130 1135 1140

Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp
1145 1150 1155

Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln
1160 1165 1170

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

Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile
1190 1195 1200

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

Arg Gly Val Tyr Tyr Pro Asp Glu Ile Phe Arg Ser Asp Thr Leu Tyr
50 55 60

Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser Asn Val Thr Gly Phe
65 70 75 80

His Thr Ile Asn His Thr Phe Gly Asn Pro Val Ile Pro Phe Lys Asp
85 90 95

Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn Val Val Arg Gly Trp
100 105 110

Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln Ser Val Ile Ile Ile
115 120 125

Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys Asn Phe Glu Leu Cys
130 135 140

Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met Gly Thr Gln Thr His
145 150 155 160

Thr Met Ile Phe Asp Asn Ala Phe Asn Cys Thr Phe Glu Tyr Ile Ser
165 170 175

Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser Gly Asn Phe Lys His
180 185 190

Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly Phe Leu Tyr Val Tyr
195 200 205

Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp Leu Pro Ser Gly Phe
210 215 220

Asn Thr Leu Lys Pro Ile Phe Lys Leu Pro Leu Gly Ile Asn Ile Thr
225 230 235 240

Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro Ala Gln Asp Ile Trp
245 250 255

Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr Leu Lys Pro Thr Thr
260 265 270

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

Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys Ser Val Lys Ser Phe
290 295 300

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

Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe
325 330 335

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

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

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

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

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

Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Met Gly Cys Val Leu
420 425 430

Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser Thr Gly Asn Tyr Asn
435 440 445

Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg
450 455 460

Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly Lys Pro Cys Thr Pro
465 470 475 480

Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp Tyr Gly Phe Tyr Thr
485 490 495

Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe
500 505 510

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

Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn Phe Asn Gly Leu Thr
530 535 540

Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg Phe Gln Pro Phe Gln
545 550 555 560

Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp Ser Val Arg Asp Pro
565 570 575

Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys Ser Phe Gly Gly Val
580 585 590

Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser Glu Val Ala Val Leu
595 600 605

Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr Ala Ile His Ala Asp
610 615 620

Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr Gly Asn Asn Val Phe
625 630 635 640

Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu His Val Asp Thr Ser
645 650 655

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

Thr Val Ser Leu Leu Ala Ser Thr Ser Gln Lys Ser Ile Val Ala Tyr
675 680 685

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

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

Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys Asn Met Tyr Ile Cys
725 730 735

Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu Leu Gln Tyr Gly Ser Phe
740 745 750

Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp
755 760 765

Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr
770 775 780

Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro
785 790 795 800

Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe
805 810 815

Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu
820 825 830

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

Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala
850 855 860

Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr
865 870 875 880

Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala
885 890 895

Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn
900 905 910

Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln
915 920 925

Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val
930 935 940

Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser
945 950 955 960

Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg
965 970 975

Leu Asp Pro Pro Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly
980 985 990

Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala
995 1000 1005

Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser
1010 1015 1020

Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys
1025 1030 1035

Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala Pro His Gly Val
1040 1045 1050

Val Phe Leu His Val Thr Tyr Val Pro Ser Gln Glu Arg Asn Phe
1055 1060 1065

Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys Ala Tyr Phe Pro
1070 1075 1080

Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser Trp Phe Ile Thr
1085 1090 1095

Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr Thr Asp Asn Thr
1100 1105 1110

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

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Lys Thr Trp Pro Arg Pro Ile Asp Val Ser Lys Ala Asp Gly Ile Ile
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Tyr Pro Gln Gly Arg Thr Tyr Ser Asn Ile Thr Ile Thr Tyr Gln Gly
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Thr Ser Phe Ala Thr Tyr His Thr Pro Ala Thr Asp Cys Ser Asp Gly
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Asn Tyr Asn Arg Asn Ala Ser Leu Asn Ser Phe Lys Glu Tyr Phe Asn
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Ile Leu Glu Trp Phe Gly Ile Thr Gln Thr Ala Gln Gly Val His Leu
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Tyr Val Tyr Lys Leu Gln Pro Leu Thr Phe Leu Leu Asp Phe Ser Val
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Ala Glu Gly Val Glu Cys Asp Phe Ser Pro Leu Leu Ser Gly Thr Pro
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Asn Leu Thr Lys Leu Leu Ser Leu Phe Ser Val Asn Asp Phe Thr Cys
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Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg
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Ala Tyr Gln Asn Leu Val Gly Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr
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Cys Leu Arg Ala Cys Val Ser Val Pro Val Ser Val Ile Tyr Asp Lys
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Glu Thr Lys Thr His Ala Thr Leu Phe Gly Ser Val Ala Cys Glu His
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Ile Ser Ser Thr Met Ser Gln Tyr Ser Arg Ser Thr Arg Ser Met Leu
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Lys Arg Arg Asp Ser Thr Tyr Gly Pro Leu Gln Thr Pro Val Gly Cys
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Val Leu Gly Leu Val Asn Ser Ser Leu Phe Val Glu Asp Cys Lys Leu
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755 760 765

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

Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr
485 490 495

Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg
500 505 510

Phe Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn
515 520 525

Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp
530 535 540

Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp
545 550 555 560

Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr Glu Gln Leu Gln Met
565 570 575

Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys
580 585 590

Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly
595 600 605

Asn Cys Val Glu Tyr Ser Leu Tyr Gly Val Ser Gly Arg Gly Val Phe
610 615 620

Gln Asn Cys Thr Ala Val Gly Val Arg Gln Gln Arg Phe Val Tyr Asp
625 630 635 640

Ala Tyr Gln Asn Leu Val Gly Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr
645 650 655

Cys Leu Arg Ala Cys Val Ser Val Pro Val Ser Val Ile Tyr Asp Lys
660 665 670

Glu Thr Lys Thr His Ala Thr Leu Phe Gly Ser Val Ala Cys Glu His
675 680 685

Ile Ser Ser Thr Met Ser Gln Tyr Ser Arg Ser Thr Arg Ser Met Leu
690 695 700

Lys Arg Arg Asp Ser Thr Tyr Gly Pro Leu Gln Thr Pro Val Gly Cys
705 710 715 720

Val Leu Gly Leu Val Asn Ser Ser Leu Phe Val Glu Asp Cys Lys Leu
725 730 735

Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp Thr Pro Ser Thr Leu
740 745 750

Thr Pro Ala Ser Val Gly Ser Val Pro Gly Glu Met Arg Leu Ala Ser
755 760 765

Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln Leu Asn Ser Ser Tyr
770 775 780

Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe Gly Val Thr Gln Glu
785 790 795 800

Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val Asp Cys Lys Gln Tyr
805 810 815

Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu Leu Arg Glu Tyr Gly
820 825 830

Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His Gly Ala Asn Leu Arg
835 840 845

Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser Val Lys Ser Ser Gln
850 855 860

Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp Phe Asn Leu Thr Leu
865 870 875 880

Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg Ser Ala Arg Ser Ala
885 890 895

Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile Ala Asp Pro Gly Tyr
900 905 910

Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly Pro Ala Ser Ala Arg
915 920 925

Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr Lys Val Leu Pro Pro
930 935 940

Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr Ser Ser Leu Leu Gly
945 950 955 960

Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu Ser Ser Phe Ala Ala
965 970 975

Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu Asn Gly Val Gly Ile
980 985 990

Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu Ile Ala Asn Lys Phe
995 1000 1005

Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe Thr Thr Thr Asn
1010 1015 1020

Glu Ala Phe His Lys Val Gln Asp Ala Val Asn Asn Asn Ala Gln
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Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe Gly Ala
1040 1045 1050

Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Pro Pro
1055 1060 1065

Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
1070 1075 1080

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser
1085 1090 1095

Ala Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys
1100 1105 1110

Val Lys Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr
1115 1120 1125

His Ile Val Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe
1130 1135 1140

Met His Val Gly Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser
1145 1150 1155

Ala Tyr Gly Leu Cys Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala
1160 1165 1170

Pro Val Asn Gly Tyr Phe Ile Lys Thr Asn Asn Thr Arg Ile Val
1175 1180 1185

Asp Glu Trp Ser Tyr Thr Gly Ser Ser Phe Tyr Ala Pro Glu Pro
1190 1195 1200

Ile Thr Ser Leu Asn Thr Lys Tyr Val Ala Pro Gln Val Thr Tyr
1205 1210 1215

Gln Asn Ile Ser Thr Asn Leu Pro Pro Pro Leu Leu Gly Asn Ser
1220 1225 1230

Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp Glu Phe Phe Lys Asn
1235 1240 1245

Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu Thr Gln Ile Asn
1250 1255 1260

Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser Leu Gln Gln
1265 1270 1275

Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys Glu Leu
1280 1285 1290

Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro Trp Tyr Gln Ile Leu
1295 1300 1305

Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala Leu Ala Ile Met
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Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln
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Cys Arg Ile Cys Ile
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35 40 45

Lys Thr Trp Pro Arg Pro Ile Asp Val Ser Lys Ala Asp Gly Ile Ile
50 55 60

Tyr Pro Gln Gly Arg Thr Tyr Ser Asn Ile Thr Ile Thr Tyr Gln Gly
65 70 75 80

Leu Phe Pro Tyr Gln Gly Asp His Gly Asp Met Tyr Val Tyr Ser Ala
85 90 95

Gly His Ala Thr Gly Thr Thr Pro Gln Lys Leu Phe Val Ala Asn Tyr
100 105 110

Ser Gln Asp Val Lys Gln Phe Ala Asn Gly Phe Val Val Arg Ile Gly
115 120 125

Ala Ala Ala Asn Ser Thr Gly Thr Val Ile Ile Ser Pro Ser Thr Ser
130 135 140

Ala Thr Ile Arg Lys Ile Tyr Pro Ala Phe Met Leu Gly Ser Ser Val
145 150 155 160

Gly Asn Phe Ser Asp Gly Lys Met Gly Arg Phe Phe Asn His Thr Leu
165 170 175

Val Leu Leu Pro Asp Gly Cys Gly Thr Leu Leu Arg Ala Phe Tyr Cys
180 185 190

Ile Leu Glu Pro Arg Ser Gly Asn His Cys Pro Ala Gly Asn Ser Tyr
195 200 205

Thr Ser Phe Ala Thr Tyr His Thr Pro Ala Thr Asp Cys Ser Asp Gly
210 215 220

Asn Tyr Asn Arg Asn Ala Ser Leu Asn Ser Phe Lys Glu Tyr Phe Asn
225 230 235 240

Leu Arg Asn Cys Thr Phe Met Tyr Thr Tyr Asn Ile Thr Glu Asp Glu
245 250 255

Ile Leu Glu Trp Phe Gly Ile Thr Gln Thr Ala Gln Gly Val His Leu
260 265 270

Phe Ser Ser Arg Tyr Val Asp Leu Tyr Gly Gly Asn Met Phe Gln Phe
275 280 285

Ala Thr Leu Pro Val Tyr Asp Thr Ile Lys Tyr Tyr Ser Ile Ile Pro
290 295 300

His Ser Ile Arg Ser Ile Gln Ser Asp Arg Lys Ala Trp Ala Ala Phe
305 310 315 320

Tyr Val Tyr Lys Leu Gln Pro Leu Thr Phe Leu Leu Asp Phe Ser Val
325 330 335

Asp Gly Tyr Ile Arg Arg Ala Ile Asp Cys Gly Phe Asn Asp Leu Ser
340 345 350

Gln Leu His Cys Ser Tyr Glu Ser Phe Asp Val Glu Ser Gly Val Tyr
355 360 365

Ser Val Ser Ser Phe Glu Ala Lys Pro Ser Gly Ser Val Val Glu Gln
370 375 380

Ala Glu Gly Val Glu Cys Asp Phe Ser Pro Leu Leu Ser Gly Thr Pro
385 390 395 400

Pro Gln Val Tyr Asn Phe Lys Arg Leu Val Phe Thr Asn Cys Asn Tyr
405 410 415

Asn Leu Thr Lys Leu Leu Ser Leu Phe Ser Val Asn Asp Phe Thr Cys
420 425 430

Ser Gln Ile Ser Pro Ala Ala Ile Ala Ser Asn Cys Tyr Ser Ser Leu
435 440 445

Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser
450 455 460

Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe
465 470 475 480

Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr
485 490 495

Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg
500 505 510

Phe Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn
515 520 525

Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp
530 535 540

Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp
545 550 555 560

Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr Glu Gln Leu Gln Met
565 570 575

Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys
580 585 590

Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly
595 600 605

Asn Cys Val Glu Tyr Ser Leu Tyr Gly Val Ser Gly Arg Gly Val Phe
610 615 620

Gln Asn Cys Thr Ala Val Gly Val Arg Gln Gln Arg Phe Val Tyr Asp
625 630 635 640

Ala Tyr Gln Asn Leu Val Gly Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr
645 650 655

Cys Leu Arg Ala Cys Val Ser Val Pro Val Ser Val Ile Tyr Asp Lys
660 665 670

Glu Thr Lys Thr His Ala Thr Leu Phe Gly Ser Val Ala Cys Glu His
675 680 685

Ile Ser Ser Thr Met Ser Gln Tyr Ser Arg Ser Thr Arg Ser Met Leu
690 695 700

Lys Arg Arg Asp Ser Thr Tyr Gly Pro Leu Gln Thr Pro Val Gly Cys
705 710 715 720

Val Leu Gly Leu Val Asn Ser Ser Leu Phe Val Glu Asp Cys Lys Leu
725 730 735

Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp Thr Pro Ser Thr Leu
740 745 750

Thr Pro Ala Ser Val Gly Ser Val Pro Gly Glu Met Arg Leu Ala Ser
755 760 765

Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln Leu Asn Ser Ser Tyr
770 775 780

Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe Gly Val Thr Gln Glu
785 790 795 800

Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val Asp Cys Lys Gln Tyr
805 810 815

Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu Leu Arg Glu Tyr Gly
820 825 830

Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His Gly Ala Asn Leu Arg
835 840 845

Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser Val Lys Ser Ser Gln
850 855 860

Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp Phe Asn Leu Thr Leu
865 870 875 880

Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg Ser Ala Arg Ser Ala
885 890 895

Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile Ala Asp Pro Gly Tyr
900 905 910

Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly Pro Ala Ser Ala Arg
915 920 925

Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr Lys Val Leu Pro Pro
930 935 940

Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr Ser Ser Leu Leu Gly
945 950 955 960

Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu Ser Ser Phe Ala Ala
965 970 975

Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu Asn Gly Val Gly Ile
980 985 990

Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu Ile Ala Asn Lys Phe
995 1000 1005

Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe Thr Thr Thr Asn
1010 1015 1020

Glu Ala Phe His Lys Val Gln Asp Ala Val Asn Asn Asn Ala Gln
1025 1030 1035

Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe Gly Ala
1040 1045 1050

Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Pro Pro
1055 1060 1065

Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
1070 1075 1080

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser
1085 1090 1095

Ala Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys
1100 1105 1110

Val Lys Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr
1115 1120 1125

His Ile Val Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe
1130 1135 1140

Met His Val Gly Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser
1145 1150 1155

Ala Tyr Gly Leu Cys Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala
1160 1165 1170

Pro Val Asn Gly Tyr Phe Ile Lys Thr Asn Asn Thr Arg Ile Val
1175 1180 1185

Asp Glu Trp Ser Tyr Thr Gly Ser Ser Phe Tyr Ala Pro Glu Pro
1190 1195 1200

Ile Thr Ser Leu Asn Thr Lys Tyr Val Ala Pro Gln Val Thr Tyr
1205 1210 1215

Gln Asn Ile Ser Thr Asn Leu Pro Pro Pro Leu Leu Gly Asn Ser
1220 1225 1230

Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp Glu Phe Phe Lys Asn
1235 1240 1245

Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu Thr Gln Ile Asn
1250 1255 1260

Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser Leu Gln Gln
1265 1270 1275

Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys Glu Leu
1280 1285 1290

Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro Trp Tyr Ile Trp Leu
1295 1300 1305

Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu Cys Val Phe Phe
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Ile Cys Ile
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Val Lys Ser Ala Cys Ile Glu Val Asp Ile Gln Gln Thr Phe Phe Asp
        35                  40                  45

Lys Thr Trp Pro Arg Pro Ile Asp Val Ser Lys Ala Asp Gly Ile Ile
    50                  55                  60

Tyr Pro Gln Gly Arg Thr Tyr Ser Asn Ile Thr Ile Thr Tyr Gln Gly
65                  70                  75                  80

Leu Phe Pro Tyr Gln Gly Asp His Gly Asp Met Tyr Val Tyr Ser Ala
                85                  90                  95

Gly His Ala Thr Gly Thr Thr Pro Gln Lys Leu Phe Val Ala Asn Tyr
            100                 105                 110

Ser Gln Asp Val Lys Gln Phe Ala Asn Gly Phe Val Val Arg Ile Gly
        115                 120                 125
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Ala Ala Ala Asn Ser Thr Gly Thr Val Ile Ile Ser Pro Ser Thr Ser
130 135 140

Ala Thr Ile Arg Lys Ile Tyr Pro Ala Phe Met Leu Gly Ser Ser Val
145 150 155 160

Gly Asn Phe Ser Asp Gly Lys Met Gly Arg Phe Phe Asn His Thr Leu
165 170 175

Val Leu Leu Pro Asp Gly Cys Gly Thr Leu Leu Arg Ala Phe Tyr Cys
180 185 190

Ile Leu Glu Pro Arg Ser Gly Asn His Cys Pro Ala Gly Asn Ser Tyr
195 200 205

Thr Ser Phe Ala Thr Tyr His Thr Pro Ala Thr Asp Cys Ser Asp Gly
210 215 220

Asn Tyr Asn Arg Asn Ala Ser Leu Asn Ser Phe Lys Glu Tyr Phe Asn
225 230 235 240

Leu Arg Asn Cys Thr Phe Met Tyr Thr Tyr Asn Ile Thr Glu Asp Glu
245 250 255

Ile Leu Glu Trp Phe Gly Ile Thr Gln Thr Ala Gln Gly Val His Leu
260 265 270

Phe Ser Ser Arg Tyr Val Asp Leu Tyr Gly Gly Asn Met Phe Gln Phe
275 280 285

Ala Thr Leu Pro Val Tyr Asp Thr Ile Lys Tyr Tyr Ser Ile Ile Pro
290 295 300

His Ser Ile Arg Ser Ile Gln Ser Asp Arg Lys Ala Trp Ala Ala Phe
305 310 315 320

Tyr Val Tyr Lys Leu Gln Pro Leu Thr Phe Leu Leu Asp Phe Ser Val
325 330 335

Asp Gly Tyr Ile Arg Arg Ala Ile Asp Cys Gly Phe Asn Asp Leu Ser
340 345 350

Gln Leu His Cys Ser Tyr Glu Ser Phe Asp Val Glu Ser Gly Val Tyr
355 360 365

Ser Val Ser Ser Phe Glu Ala Lys Pro Ser Gly Ser Val Val Glu Gln
370 375 380

Ala Glu Gly Val Glu Cys Asp Phe Ser Pro Leu Leu Ser Gly Thr Pro
385 390 395 400

Pro Gln Val Tyr Asn Phe Lys Arg Leu Val Phe Thr Asn Cys Asn Tyr
405 410 415

Asn Leu Thr Lys Leu Leu Ser Leu Phe Ser Val Asn Asp Phe Thr Cys
420 425 430

Ser Gln Ile Ser Pro Ala Ala Ile Ala Ser Asn Cys Tyr Ser Ser Leu
435 440 445

Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser
450 455 460

Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe
465 470 475 480

Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr
485 490 495

Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg
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Phe Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn
515 520 525

Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp
530 535 540

Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp
545 550 555 560

Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr Glu Gln Leu Gln Met
565 570 575

Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys
580 585 590

Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly
595 600 605

Asn Cys Val Glu Tyr Ser Leu Tyr Gly Val Ser Gly Arg Gly Val Phe
610 615 620

Gln Asn Cys Thr Ala Val Gly Val Arg Gln Gln Arg Phe Val Tyr Asp
625 630 635 640

Ala Tyr Gln Asn Leu Val Gly Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr
645 650 655

Cys Leu Arg Ala Cys Val Ser Val Pro Val Ser Val Ile Tyr Asp Lys
660 665 670

Glu Thr Lys Thr His Ala Thr Leu Phe Gly Ser Val Ala Cys Glu His
675 680 685

Ile Ser Ser Thr Met Ser Gln Tyr Ser Arg Ser Thr Arg Ser Met Leu
690 695 700

Lys Arg Arg Asp Ser Thr Tyr Gly Pro Leu Gln Thr Pro Val Gly Cys
705 710 715 720

Val Leu Gly Leu Val Asn Ser Ser Leu Phe Val Glu Asp Cys Lys Leu
725 730 735

Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp Thr Pro Ser Thr Leu
740 745 750

Thr Pro Ala Ser Val Gly Ser Val Pro Gly Glu Met Arg Leu Ala Ser
755 760 765

Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln Leu Asn Ser Ser Tyr
770 775 780

Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe Gly Val Thr Gln Glu
785 790 795 800

Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val Asp Cys Lys Gln Tyr
805 810 815

Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu Leu Arg Glu Tyr Gly
820 825 830

Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His Gly Ala Asn Leu Arg
835 840 845

Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser Val Lys Ser Ser Gln
850 855 860

Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp Phe Asn Leu Thr Leu
865 870 875 880

Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg Ser Ala Arg Ser Ala
885 890 895

Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile Ala Asp Pro Gly Tyr
900 905 910

Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly Pro Ala Ser Ala Arg
915 920 925

Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr Lys Val Leu Pro Pro
930 935 940

Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr Ser Ser Leu Leu Gly
945 950 955 960

Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu Ser Ser Phe Ala Ala
965 970 975

Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu Asn Gly Val Gly Ile
980 985 990

Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu Ile Ala Asn Lys Phe
995 1000 1005

Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe Thr Thr Thr Asn
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Glu Ala Phe His Lys Val Gln Asp Ala Val Asn Asn Asn Ala Gln
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Ala Leu Ser Lys Leu Ala Ser Glu Leu Ser Asn Thr Phe Gly Ala
1040 1045 1050

Ile Ser Ala Ser Ile Gly Asp Ile Ile Gln Arg Leu Asp Pro Pro
1055 1060 1065

Glu Gln Asp Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr
1070 1075 1080

Thr Leu Asn Ala Phe Val Ala Gln Gln Leu Val Arg Ser Glu Ser
1085 1090 1095

Ala Ala Leu Ser Ala Gln Leu Ala Lys Asp Lys Val Asn Glu Cys
1100 1105 1110

Val Lys Ala Gln Ser Lys Arg Ser Gly Phe Cys Gly Gln Gly Thr
1115 1120 1125

His Ile Val Ser Phe Val Val Asn Ala Pro Asn Gly Leu Tyr Phe
1130 1135 1140

Met His Val Gly Tyr Tyr Pro Ser Asn His Ile Glu Val Val Ser
1145 1150 1155

Ala Tyr Gly Leu Cys Asp Ala Ala Asn Pro Thr Asn Cys Ile Ala
1160 1165 1170

Pro Val Asn Gly Tyr Phe Ile Lys Thr Asn Asn Thr Arg Ile Val
1175 1180 1185

Asp Glu Trp Ser Tyr Thr Gly Ser Ser Phe Tyr Ala Pro Glu Pro
1190 1195 1200

Ile Thr Ser Leu Asn Thr Lys Tyr Val Ala Pro Gln Val Thr Tyr
1205 1210 1215

Gln Asn Ile Ser Thr Asn Leu Pro Pro Pro Leu Leu Gly Asn Ser
1220 1225 1230

Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp Glu Phe Phe Lys Asn
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Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu Thr Gln Ile Asn
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Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser Leu Gln Gln
1265 1270 1275

Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys Glu Leu
1280 1285 1290

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

Lys Thr Trp Pro Arg Pro Ile Asp Val Ser Lys Ala Asp Gly Ile Ile
50 55 60

Tyr Pro Gln Gly Arg Thr Tyr Ser Asn Ile Thr Ile Thr Tyr Gln Gly
65 70 75 80

Leu Phe Pro Tyr Gln Gly Asp His Gly Asp Met Tyr Val Tyr Ser Ala
85 90 95

Gly His Ala Thr Gly Thr Thr Pro Gln Lys Leu Phe Val Ala Asn Tyr
100 105 110

Ser Gln Asp Val Lys Gln Phe Ala Asn Gly Phe Val Val Arg Ile Gly
115 120 125

Ala Ala Ala Asn Ser Thr Gly Thr Val Ile Ile Ser Pro Ser Thr Ser
130 135 140

Ala Thr Ile Arg Lys Ile Tyr Pro Ala Phe Met Leu Gly Ser Ser Val
145 150 155 160

Gly Asn Phe Ser Asp Gly Lys Met Gly Arg Phe Phe Asn His Thr Leu
165 170 175

Val Leu Leu Pro Asp Gly Cys Gly Thr Leu Leu Arg Ala Phe Tyr Cys
180 185 190

Ile Leu Glu Pro Arg Ser Gly Asn His Cys Pro Ala Gly Asn Ser Tyr
195 200 205

Thr Ser Phe Ala Thr Tyr His Thr Pro Ala Thr Asp Cys Ser Asp Gly
210 215 220

Asn Tyr Asn Arg Asn Ala Ser Leu Asn Ser Phe Lys Glu Tyr Phe Asn
225 230 235 240

Leu Arg Asn Cys Thr Phe Met Tyr Thr Tyr Asn Ile Thr Glu Asp Glu
245 250 255

Ile Leu Glu Trp Phe Gly Ile Thr Gln Thr Ala Gln Gly Val His Leu
260 265 270

Phe Ser Ser Arg Tyr Val Asp Leu Tyr Gly Gly Asn Met Phe Gln Phe
275 280 285

Ala Thr Leu Pro Val Tyr Asp Thr Ile Lys Tyr Tyr Ser Ile Ile Pro
290 295 300

His Ser Ile Arg Ser Ile Gln Ser Asp Arg Lys Ala Trp Ala Ala Phe
305 310 315 320

Tyr Val Tyr Lys Leu Gln Pro Leu Thr Phe Leu Leu Asp Phe Ser Val
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Asp Gly Tyr Ile Arg Arg Ala Ile Asp Cys Gly Phe Asn Asp Leu Ser
340 345 350

Gln Leu His Cys Ser Tyr Glu Ser Phe Asp Val Glu Ser Gly Val Tyr
355 360 365

Ser Val Ser Ser Phe Glu Ala Lys Pro Ser Gly Ser Val Val Glu Gln
370 375 380

Ala Glu Gly Val Glu Cys Asp Phe Ser Pro Leu Leu Ser Gly Thr Pro
385 390 395 400

Pro Gln Val Tyr Asn Phe Lys Arg Leu Val Phe Thr Asn Cys Asn Tyr
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Asn Leu Thr Lys Leu Leu Ser Leu Phe Ser Val Asn Asp Phe Thr Cys
420 425 430

Ser Gln Ile Ser Pro Ala Ala Ile Ala Ser Asn Cys Tyr Ser Ser Leu
435 440 445

Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser
450 455 460

Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe
465 470 475 480

Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr
485 490 495

Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg
500 505 510

Phe Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn
515 520 525

Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp
530 535 540

Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp
545 550 555 560

Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr Glu Gln Leu Gln Met
565 570 575

Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys
580 585 590

Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly
595 600 605

Asn Cys Val Glu Tyr Ser Leu Tyr Gly Val Ser Gly Arg Gly Val Phe
610 615 620

Gln Asn Cys Thr Ala Val Gly Val Arg Gln Gln Arg Phe Val Tyr Asp
625 630 635 640

Ala Tyr Gln Asn Leu Val Gly Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr
645 650 655

Cys Leu Arg Ala Cys Val Ser Val Pro Val Ser Val Ile Tyr Asp Lys
660 665 670

Glu Thr Lys Thr His Ala Thr Leu Phe Gly Ser Val Ala Cys Glu His
675 680 685

Ile Ser Ser Thr Met Ser Gln Tyr Ser Arg Ser Thr Arg Ser Met Leu
690 695 700

Lys Arg Arg Asp Ser Thr Tyr Gly Pro Leu Gln Thr Pro Val Gly Cys
705 710 715 720

Val Leu Gly Leu Val Asn Ser Ser Leu Phe Val Glu Asp Cys Lys Leu
725 730 735

Pro Leu Gly Gln Ser Leu Cys Ala Leu Pro Asp Thr Pro Ser Thr Leu
740 745 750

Thr Pro Ala Ser Val Gly Ser Val Pro Gly Glu Met Arg Leu Ala Ser
755 760 765

Ile Ala Phe Asn His Pro Ile Gln Val Asp Gln Leu Asn Ser Ser Tyr
770 775 780

Phe Lys Leu Ser Ile Pro Thr Asn Phe Ser Phe Gly Val Thr Gln Glu
785 790 795 800

Tyr Ile Gln Thr Thr Ile Gln Lys Val Thr Val Asp Cys Lys Gln Tyr
805 810 815

Val Cys Asn Gly Phe Gln Lys Cys Glu Gln Leu Leu Arg Glu Tyr Gly
820 825 830

Gln Phe Cys Ser Lys Ile Asn Gln Ala Leu His Gly Ala Asn Leu Arg
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Gln Asp Asp Ser Val Arg Asn Leu Phe Ala Ser Val Lys Ser Ser Gln
850 855 860

Ser Ser Pro Ile Ile Pro Gly Phe Gly Gly Asp Phe Asn Leu Thr Leu
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Leu Glu Pro Val Ser Ile Ser Thr Gly Ser Arg Ser Ala Arg Ser Ala
885 890 895

Ile Glu Asp Leu Leu Phe Asp Lys Val Thr Ile Ala Asp Pro Gly Tyr
900 905 910

Met Gln Gly Tyr Asp Asp Cys Met Gln Gln Gly Pro Ala Ser Ala Arg
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Asp Leu Ile Cys Ala Gln Tyr Val Ala Gly Tyr Lys Val Leu Pro Pro
930 935 940

Leu Met Asp Val Asn Met Glu Ala Ala Tyr Thr Ser Ser Leu Leu Gly
945 950 955 960

Ser Ile Ala Gly Val Gly Trp Thr Ala Gly Leu Ser Ser Phe Ala Ala
965 970 975

Ile Pro Phe Ala Gln Ser Ile Phe Tyr Arg Leu Asn Gly Val Gly Ile
980 985 990

Thr Gln Gln Val Leu Ser Glu Asn Gln Lys Leu Ile Ala Asn Lys Phe
995 1000 1005

Asn Gln Ala Leu Gly Ala Met Gln Thr Gly Phe Thr Thr Thr Asn
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Glu Ala Phe His Lys Val Gln Asp Ala Val Asn Asn Asn Ala Gln
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Pro Val Asn Gly Tyr Phe Ile Lys Thr Asn Asn Thr Arg Ile Val
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Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp Glu Phe Phe Lys Asn
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Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys Glu Leu
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Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro Trp Tyr Ile Trp Leu
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Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu Cys Val Phe Phe
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Ser Asp Thr Leu Tyr Leu Thr Gln Asp Leu Phe Leu Pro Phe Tyr Ser
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Asn Val Thr Gly Phe His Thr Ile Asn His Thr Phe Gly Asn Pro Val
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Ile Pro Phe Lys Asp Gly Ile Tyr Phe Ala Ala Thr Glu Lys Ser Asn
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Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn Lys Ser Gln
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Ser Val Ile Ile Ile Asn Asn Ser Thr Asn Val Val Ile Arg Ala Cys
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Asn Phe Glu Leu Cys Asp Asn Pro Phe Phe Ala Val Ser Lys Pro Met
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Phe Glu Tyr Ile Ser Asp Ala Phe Ser Leu Asp Val Ser Glu Lys Ser
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Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn Lys Asp Gly
180 185 190

Phe Leu Tyr Val Tyr Lys Gly Tyr Gln Pro Ile Asp Val Val Arg Asp

195 200 205

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Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro
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Ala Gln Asp Ile Trp Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr
245 250 255

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

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

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

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Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn
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Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg
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Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys
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Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr
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Ala Ile His Ala Asp Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr
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Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu
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His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile
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Cys Ala Ser Tyr His Thr Val Ser Leu Leu Arg Ser Thr Ser Gln Lys
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Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser Ser Ile Ala
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Tyr Ser Asn Asn Thr Ile Ala Ile Pro Thr Asn Phe Ser Ile Ser Ile
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Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile
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Ala Ala Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys
755 760 765

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

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Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala
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Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly
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Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu
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Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn
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Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser
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Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys
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Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile
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Asp Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr
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Ser Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp
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His Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr
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Pro Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe
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Ala Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly
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Thr Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr
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Pro Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys
145 150 155 160

Met Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys
165 170 175

Gly Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly
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Asn His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His
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Thr Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser
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Tyr Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile
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Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile
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Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile
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Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys
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Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Phe Leu Ser Asp Asp Arg Thr
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Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser
515 520 525

Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln
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Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr
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565 570 575

Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn
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Tyr Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly
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Tyr Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser
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675 680 685

Tyr Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr
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Val Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile
755 760 765

Gln Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr
770 775 780

Asn Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln
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Leu Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly
850 855 860

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945 950 955 960

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995 1000 1005

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Ile Ile Gln Arg Leu Asp Val Leu Glu Gln Asp Ala Gln Ile Asp
1055 1060 1065

Arg Leu Ile Asn Gly Arg Leu Thr Thr Leu Asn Ala Phe Val Ala
1070 1075 1080

Gln Gln Leu Val Arg Ser Glu Ser Ala Ala Leu Ser Ala Gln Leu
1085 1090 1095

Ala Lys Asp Lys Val Asn Glu Cys Val Lys Ala Gln Ser Lys Arg
1100 1105 1110

Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val Ser Phe Val Val
1115 1120 1125

Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly Tyr Tyr Pro
1130 1135 1140

Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys Asp Ala
1145 1150 1155

Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe Ile
1160 1165 1170

Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly
1175 1180 1185

Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys
1190 1195 1200

Tyr Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu
1205 1210 1215

Pro Pro Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp
1220 1225 1230

Glu Leu Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn
1235 1240 1245

Phe Gly Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr
1250 1255 1260

Tyr Glu Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu
1265 1270 1275

Ser Tyr Ile Asp Leu Lys Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn
1280 1285 1290

Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val
1295 1300 1305

Ala Leu Ala Leu Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys
1310 1315 1320

Gly Thr Asn Cys Met Gly Lys Leu Lys Cys Asn Arg Cys Cys Asp
1325 1330 1335

Arg Tyr Glu Glu Tyr Asp Leu Glu Pro His Lys Val His Val His
1340 1345 1350

<210> 114
<211> 1242
<212> PRT
<213> SARS-CoV-1

<400> 114

Ser Asp Leu Asp Arg Cys Thr Thr Phe Asp Asp Val Gln Ala Pro Asn
1 5 10 15

Tyr Thr Gln His Thr Ser Ser Met Arg Gly Val Tyr Tyr Pro Asp Glu
20 25 30

Ile Phe Arg Ser Asp Thr Leu Tyr Leu Thr Gln Asp Leu Phe Leu Pro
35 40 45

Phe Tyr Ser Asn Val Thr Gly Phe His Thr Ile Asn His Thr Phe Gly
50 55 60

Asn Pro Val Ile Pro Phe Lys Asp Gly Ile Tyr Phe Ala Ala Thr Glu

65 70 75 80

Lys Ser Asn Val Val Arg Gly Trp Val Phe Gly Ser Thr Met Asn Asn
85 90 95

Lys Ser Gln Ser Val Ile Ile Ile Asn Asn Ser Thr Asn Val Val Ile
100 105 110

Arg Ala Cys Asn Phe Glu Leu Cys Asp Asn Pro Phe Phe Ala Val Ser
115 120 125

Lys Pro Met Gly Thr Gln Thr His Thr Met Ile Phe Asp Asn Ala Phe
130 135 140

Asn Cys Thr Phe Glu Tyr Ile Ser Asp Ala Phe Ser Leu Asp Val Ser
145 150 155 160

Glu Lys Ser Gly Asn Phe Lys His Leu Arg Glu Phe Val Phe Lys Asn
165 170 175

Lys Asp Gly Phe Leu Tyr Val Tyr Lys Gly Tyr Gln Pro Ile Asp Val
180 185 190

Val Arg Asp Leu Pro Ser Gly Phe Asn Thr Leu Lys Pro Ile Phe Lys
195 200 205

Leu Pro Leu Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala
210 215 220

Phe Ser Pro Ala Gln Asp Ile Trp Gly Thr Ser Ala Ala Ala Tyr Phe
225 230 235 240

Val Gly Tyr Leu Lys Pro Thr Thr Phe Met Leu Lys Tyr Asp Glu Asn
245 250 255

Gly Thr Ile Thr Asp Ala Val Asp Cys Ser Gln Asn Pro Leu Ala Glu
260 265 270

Leu Lys Cys Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln
275 280 285

Thr Ser Asn Phe Arg Val Val Pro Ser Gly Asp Val Val Arg Phe Pro
290 295 300

Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys
305 310 315 320

Phe Pro Ser Val Tyr Ala Trp Glu Arg Lys Lys Ile Ser Asn Cys Val
325 330 335

Ala Asp Tyr Ser Val Leu Tyr Asn Ser Thr Phe Phe Ser Thr Phe Lys
340 345 350

Cys Tyr Gly Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn
355 360 365

Val Tyr Ala Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile

370 375 380

Ala Pro Gly Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro
385 390 395 400

Asp Asp Phe Met Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp
405 410 415

Ala Thr Ser Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Tyr Leu Arg His
420 425 430

Gly Lys Leu Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser
435 440 445

Pro Asp Gly Lys Pro Cys Thr Pro Pro Ala Leu Asn Cys Tyr Trp Pro
450 455 460

Leu Asn Asp Tyr Gly Phe Tyr Thr Thr Thr Gly Ile Gly Tyr Gln Pro
465 470 475 480

Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr
485 490 495

Val Cys Gly Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val
500 505 510

Asn Phe Asn Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser
515 520 525

Ser Lys Arg Phe Gln Pro Phe Gln Gln Phe Gly Arg Asp Val Ser Asp
530 535 540

Phe Thr Asp Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile
545 550 555 560

Ser Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn
565 570 575

Ala Ser Ser Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp
580 585 590

Val Ser Thr Ala Ile His Ala Asp Gln Leu Thr Pro Ala Trp Arg Ile
595 600 605

Tyr Ser Thr Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile
610 615 620

Gly Ala Glu His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly
625 630 635 640

Ala Gly Ile Cys Ala Ser Tyr His Thr Val Ser Leu Leu Arg Ser Thr
645 650 655

Ser Gln Lys Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser
660 665 670

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

675 680 685

Ile Ser Ile Thr Thr Glu Val Met Pro Val Ser Met Ala Lys Thr Ser
690 695 700

Val Asp Cys Asn Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ala Asn
705 710 715 720

Leu Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu
725 730 735

Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala
740 745 750

Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys Tyr Phe Gly Gly
755 760 765

Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg
770 775 780

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

Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg
805 810 815

Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro
820 825 830

Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser
835 840 845

Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln
850 855 860

Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val
865 870 875 880

Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe
885 890 895

Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr
900 905 910

Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu
915 920 925

Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser
930 935 940

Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val
945 950 955 960

Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr
965 970 975

Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn

980 985 990

Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg
995 1000 1005

Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln
1010 1015 1020

Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro
1025 1030 1035

Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His Glu
1040 1045 1050

Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly
1055 1060 1065

Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile
1070 1075 1080

Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val
1085 1090 1095

Ile Gly Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu
1100 1105 1110

Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His
1115 1120 1125

Thr Ser Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala
1130 1135 1140

Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val
1145 1150 1155

Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly
1160 1165 1170

Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Val Trp Leu Gly
1175 1180 1185

Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Leu Leu
1190 1195 1200

Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Ala Cys Ser
1205 1210 1215

Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser Glu Pro Val
1220 1225 1230

Leu Lys Gly Val Lys Leu His Tyr Thr
1235 1240

<210> 115
<211> 1336
<212> PRT
<213> MERS

<400> 115

Tyr Val Asp Val Gly Pro Asp Ser Val Lys Ser Ala Cys Ile Glu Val
1 5 10 15

Asp Ile Gln Gln Thr Phe Phe Asp Lys Thr Trp Pro Arg Pro Ile Asp
20 25 30

Val Ser Lys Ala Asp Gly Ile Ile Tyr Pro Gln Gly Arg Thr Tyr Ser
35 40 45

Asn Ile Thr Ile Thr Tyr Gln Gly Leu Phe Pro Tyr Gln Gly Asp His
50 55 60

Gly Asp Met Tyr Val Tyr Ser Ala Gly His Ala Thr Gly Thr Thr Pro
65 70 75 80

Gln Lys Leu Phe Val Ala Asn Tyr Ser Gln Asp Val Lys Gln Phe Ala
85 90 95

Asn Gly Phe Val Val Arg Ile Gly Ala Ala Ala Asn Ser Thr Gly Thr
100 105 110

Val Ile Ile Ser Pro Ser Thr Ser Ala Thr Ile Arg Lys Ile Tyr Pro
115 120 125

Ala Phe Met Leu Gly Ser Ser Val Gly Asn Phe Ser Asp Gly Lys Met
130 135 140

Gly Arg Phe Phe Asn His Thr Leu Val Leu Leu Pro Asp Gly Cys Gly
145 150 155 160

Thr Leu Leu Arg Ala Phe Tyr Cys Ile Leu Glu Pro Arg Ser Gly Asn
165 170 175

His Cys Pro Ala Gly Asn Ser Tyr Thr Ser Phe Ala Thr Tyr His Thr
180 185 190

Pro Ala Thr Asp Cys Ser Asp Gly Asn Tyr Asn Arg Asn Ala Ser Leu
195 200 205

Asn Ser Phe Lys Glu Tyr Phe Asn Leu Arg Asn Cys Thr Phe Met Tyr
210 215 220

Thr Tyr Asn Ile Thr Glu Asp Glu Ile Leu Glu Trp Phe Gly Ile Thr
225 230 235 240

Gln Thr Ala Gln Gly Val His Leu Phe Ser Ser Arg Tyr Val Asp Leu
245 250 255

Tyr Gly Gly Asn Met Phe Gln Phe Ala Thr Leu Pro Val Tyr Asp Thr
260 265 270

Ile Lys Tyr Tyr Ser Ile Ile Pro His Ser Ile Arg Ser Ile Gln Ser
275 280 285

Asp Arg Lys Ala Trp Ala Ala Phe Tyr Val Tyr Lys Leu Gln Pro Leu
290 295 300

Thr Phe Leu Leu Asp Phe Ser Val Asp Gly Tyr Ile Arg Arg Ala Ile
305 310 315 320

Asp Cys Gly Phe Asn Asp Leu Ser Gln Leu His Cys Ser Tyr Glu Ser
325 330 335

Phe Asp Val Glu Ser Gly Val Tyr Ser Val Ser Ser Phe Glu Ala Lys
340 345 350

Pro Ser Gly Ser Val Val Glu Gln Ala Glu Gly Val Glu Cys Asp Phe
355 360 365

Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys Arg
370 375 380

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

Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala Ile
405 410 415

Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr Pro
420 425 430

Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile Ser
435 440 445

Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile Leu
450 455 460

Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys Tyr
465 470 475 480

Ser Tyr Ile Asn Lys Cys Ser Arg Phe Leu Ser Asp Asp Arg Thr Glu
485 490 495

Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser Ile
500 505 510

Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln Leu
515 520 525

Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr Val
530 535 540

Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln Tyr
545 550 555 560

Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn Asp
565 570 575

Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Leu Tyr
580 585 590

Gly Val Ser Gly Arg Gly Val Phe Gln Asn Cys Thr Ala Val Gly Val
595 600 605

Arg Gln Gln Arg Phe Val Tyr Asp Ala Tyr Gln Asn Leu Val Gly Tyr
610 615 620

Tyr Ser Asp Asp Gly Asn Tyr Tyr Cys Leu Arg Ala Cys Val Ser Val
625 630 635 640

Pro Val Ser Val Ile Tyr Asp Lys Glu Thr Lys Thr His Ala Thr Leu
645 650 655

Phe Gly Ser Val Ala Cys Glu His Ile Ser Ser Thr Met Ser Gln Tyr
660 665 670

Ser Arg Ser Thr Arg Ser Met Leu Lys Arg Arg Asp Ser Thr Tyr Gly
675 680 685

Pro Leu Gln Thr Pro Val Gly Cys Val Leu Gly Leu Val Asn Ser Ser
690 695 700

Leu Phe Val Glu Asp Cys Lys Leu Pro Leu Gly Gln Ser Leu Cys Ala
705 710 715 720

Leu Pro Asp Thr Pro Ser Thr Leu Thr Pro Arg Ser Val Arg Ser Val
725 730 735

Pro Gly Glu Met Arg Leu Ala Ser Ile Ala Phe Asn His Pro Ile Gln
740 745 750

Val Asp Gln Leu Asn Ser Ser Tyr Phe Lys Leu Ser Ile Pro Thr Asn
755 760 765

Phe Ser Phe Gly Val Thr Gln Glu Tyr Ile Gln Thr Thr Ile Gln Lys
770 775 780

Val Thr Val Asp Cys Lys Gln Tyr Val Cys Asn Gly Phe Gln Lys Cys
785 790 795 800

Glu Gln Leu Leu Arg Glu Tyr Gly Gln Phe Cys Ser Lys Ile Asn Gln
805 810 815

Ala Leu His Gly Ala Asn Leu Arg Gln Asp Asp Ser Val Arg Asn Leu
820 825 830

Phe Ala Ser Val Lys Ser Ser Gln Ser Ser Pro Ile Ile Pro Gly Phe
835 840 845

Gly Gly Asp Phe Asn Leu Thr Leu Leu Glu Pro Val Ser Ile Ser Thr
850 855 860

Gly Ser Arg Ser Ala Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys
865 870 875 880

Val Thr Ile Ala Asp Pro Gly Tyr Met Gln Gly Tyr Asp Asp Cys Met
885 890 895

Gln Gln Gly Pro Ala Ser Ala Arg Asp Leu Ile Cys Ala Gln Tyr Val
900 905 910

Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu Ala
915 920 925

Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp Thr
930 935 940

Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile Phe
945 950 955 960

Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu Asn
965 970 975

Gln Lys Leu Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met Gln
980 985 990

Thr Gly Phe Thr Thr Thr Asn Glu Ala Phe His Lys Val Gln Asp Ala
995 1000 1005

Val Asn Asn Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser Glu Leu
1010 1015 1020

Ser Asn Thr Phe Gly Ala Ile Ser Ala Ser Ile Gly Asp Ile Ile
1025 1030 1035

Gln Arg Leu Asp Val Leu Glu Gln Asp Ala Gln Ile Asp Arg Leu
1040 1045 1050

Ile Asn Gly Arg Leu Thr Thr Leu Asn Ala Phe Val Ala Gln Gln
1055 1060 1065

Leu Val Arg Ser Glu Ser Ala Ala Leu Ser Ala Gln Leu Ala Lys
1070 1075 1080

Asp Lys Val Asn Glu Cys Val Lys Ala Gln Ser Lys Arg Ser Gly
1085 1090 1095

Phe Cys Gly Gln Gly Thr His Ile Val Ser Phe Val Val Asn Ala
1100 1105 1110

Pro Asn Gly Leu Tyr Phe Met His Val Gly Tyr Tyr Pro Ser Asn
1115 1120 1125

His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys Asp Ala Ala Asn
1130 1135 1140

Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe Ile Lys Thr
1145 1150 1155

Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly Ser Ser
1160 1165 1170

Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys Tyr Val
1175 1180 1185

Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu Pro Pro
1190 1195 1200

Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu
1205 1210 1215

Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly
1220 1225 1230

Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu
1235 1240 1245

Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr
1250 1255 1260

Ile Asp Leu Lys Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp
1265 1270 1275

Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val Ala Leu
1280 1285 1290

Ala Leu Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys Gly Thr
1295 1300 1305

Asn Cys Met Gly Lys Leu Lys Cys Asn Arg Cys Cys Asp Arg Tyr
1310 1315 1320

Glu Glu Tyr Asp Leu Glu Pro His Lys Val His Val His
1325 1330 1335

<210> 116
<211> 60
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-SARS-COV-1 wtTMCT-AA 的 TMCT 區

<400> 116

Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys
20 25 30

Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp Asp Ser
35 40 45

Glu Pro Val Leu Lys Gly Val Lys Leu His Tyr Thr
50 55 60

<210> 117
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> YQILSIYSTVASSLALAIMMAGLSLWMCSNGSLQCRICI

<400> 117

Trp Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
1 5 10 15

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
20 25 30

Ser Leu Gln Cys Arg Ile Cys Ile
35 40

<210> 118
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-SARS-COV-1 H5iCT-AA 的 TMCT 區

<400> 118

Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Leu Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 119
<211> 34
<212> PRT
<213> 人工序列

<220>

<223> 經修飾的 PDI-SARS-COV-1 H5iCT(V4)-AA 的 TMCT 區

<400> 119

Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Leu Leu Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
20 25 30

Cys Ile

<210> 120
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-SARS-COV-1 H1cCT-AA 的 TMCT 區

<400> 120

Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Leu Leu Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 121
<211> 57
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-MERS-wtTMCT-AA 的 TMCT 區

<400> 121

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu
1 5 10 15

Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys Gly Thr Asn Cys Met
20 25 30

Gly Lys Leu Lys Cys Asn Arg Cys Cys Asp Arg Tyr Glu Glu Tyr Asp
35 40 45

Leu Glu Pro His Lys Val His Val His
50 55

<210> 122
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-MERS-H5iTMCT-AA 的 TMCT 區

<400> 122

Trp Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
1 5 10 15

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
20 25 30

Ser Leu Gln Cys Arg Ile Cys Ile
35 40

<210> 123
<211> 38
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-MERS-H5iCT-AA 的 TMCT 區

<400> 123

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu
1 5 10 15

Cys Val Phe Phe Ile Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu
20 25 30

Gln Cys Arg Ile Cys Ile
35

<210> 124
<211> 35
<212> PRT
<213> 人工序列

<220>

<223> 經修飾的 PDI-MERS-H5iCT(V4)-AA 的 TMCT 區

<400> 124

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu
1 5 10 15

Cys Val Phe Phe Ile Leu Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg
20 25 30

Ile Cys Ile
35

<210> 125
<211> 38
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-MERS-H1cCT-AA 的 TMCT 區

<400> 125

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val Ala Leu Ala Leu
1 5 10 15

Cys Val Phe Phe Ile Leu Ser Phe Trp Met Cys Ser Asn Gly Ser Leu
20 25 30

Gln Cys Arg Ile Cys Ile
35

<210> 126
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+H1 Cal 的 TMCT 區

<400> 126

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 127
<211> 36
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+H3 Minn 的 TMCT 區

<400> 127

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Met Trp Ala Cys Gln Lys Gly Asn Ile Arg Cys
20 25 30

Asn Ile Cys Ile
35

<210> 128
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+H6 HK 的 TMCT 區

<400> 128

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Gly Leu Trp Met Cys Ser Asn Gly Ser Met Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 129
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+H7 Guangdong 的 TMCT 區

<400> 129

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Val Phe Ile Cys Val Lys Asn Gly Asn Met Arg
20 25 30

Cys Thr Ile Cys Ile
35

<210> 130
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+H9 HK 的 TMCT 區

<400> 130

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Leu Phe Trp Ala Met Ser Asn Gly Ser Cys Arg
20 25 30

Cys Asn Ile Cys Ile
35

<210> 131
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-S-蛋白+ B/ Wash 的 TMCT 區

<400> 131

Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met
1 5 10 15

Val Thr Ile Met Leu Val Val Tyr Met Val Ser Arg Asp Asn Val Ser
20 25 30

Cys Ser Ile Cys Leu
35

<210> 132
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 冠狀病毒 S-蛋白的 TM 結構域的共通序列

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (12)..(12)
<223> Xaa 可以是任何天然存在的胺基酸

<220>

<221> misc_feature
<222> (14)..(16)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa 可能存在或不存在

<220>
<221> misc_feature
<222> (19)..(21)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 132

Trp Tyr Xaa Trp Leu Gly Phe Ile Ala Gly Leu Xaa Ala Xaa Xaa Xaa
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Xaa Val Xaa Xaa Xaa Leu
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<210> 133
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 冠狀病毒 S-蛋白的 TM 結構域的共通序列

<220>
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<222> (3)..(3)
<223> Xaa 可為 Ile 或 Val

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa 可為 Val 或 Ile

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa 可為 Leu 或 Ile

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa 可為 Ala 或 Val

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa 可為 Leu 或 Met

<220>
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<222> (17)..(17)
<223> Xaa 可為 Cys 或不存在

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> Xaa 可為 Phe 或 Thr

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> Xaa 可為 Phe 或 Ile

<220>
<221> misc_feature
<222> (21)..(21)

<223> Xaa 可以是任何天然存在的胺基酸

<400> 133

Trp Tyr Xaa Trp Leu Gly Phe Ile Ala Gly Leu Xaa Ala Xaa Xaa Xaa
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Xaa Val Xaa Xaa Xaa Leu
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<210> 134
<211> 33
<212> PRT
<213> 人工序列

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<223> 具有間插肽序列之經修飾的 SARS-CoV-1 S 蛋白的 TM/CT 區

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<223> X 可以是 0 至 10 個胺基酸的任何組合

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<222> (27)..(28)
<223> Xaa 可以是任何天然存在的胺基酸

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<221> misc_feature
<222> (30)..(30)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 134

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Val Thr Ile Leu Xaa Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile Cys
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Ile

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<223> 具有間插肽序列之經修飾的 MERS S 蛋白的 TM/CT 區

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<400> 135

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Ile Cys Ile
35

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Leu Asp Pro Arg Leu Lys Gly Ser Phe Asn Asn Arg Asp Thr Gly Pro
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Pro Ser Ile Ser Ile Asp Thr Val Asp Val Thr Asn Gly Leu Gly Thr
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Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Leu Asn
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Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu Lys
85 90 95

Gly Thr Asp Leu Leu Ser Thr Leu Trp Phe Lys Pro Pro Phe Leu Ser
100 105 110

Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val Phe
115 120 125

Lys Asp Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly Ser
130 135 140

Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Thr Ile
145 150 155 160

Asn Ser Thr Gln Asp Gly Val Asn Lys Leu Gln Gly Leu Leu Glu Val
165 170 175

Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr Pro His Thr Ile Cys His
180 185 190

Pro Asn Leu Gly Asn His Phe Lys Glu Leu Trp His Tyr Asp Thr Gly
195 200 205

Val Val Ser Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn Ala
210 215 220

Thr Tyr Leu Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr Ala
225 230 235 240

Tyr Phe Thr Asp Thr Gly Phe Val Thr Lys Phe Leu Phe Asn Val Tyr
245 250 255

Leu Gly Met Ala Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys Ile
260 265 270

Arg Arg Pro Lys Asp Gly Phe Ser Leu Glu Tyr Trp Val Thr Pro Leu
275 280 285

Thr Pro Arg Gln Tyr Leu Leu Ala Phe Asn Gln Asp Gly Ile Ile Phe
290 295 300

Asn Ala Val Asp Cys Met Ser Asp Phe Met Ser Glu Ile Lys Cys Lys
305 310 315 320

Thr Gln Ser Ile Ala Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr
325 330 335

Thr Val Gln Pro Val Ala Asp Val Tyr Arg Arg Lys Pro Asp Leu Pro
340 345 350

Asn Cys Asn Ile Glu Ala Trp Leu Asn Asp Lys Ser Val Pro Ser Pro
355 360 365

Leu Asn Trp Glu Arg Lys Thr Phe Ser Asn Cys Asn Phe Asn Met Ser
370 375 380

Ser Leu Met Ser Phe Ile Gln Ala Asp Ser Phe Thr Cys Asn Asn Ile
385 390 395 400

Asp Ala Ala Lys Ile Tyr Gly Met Cys Phe Ser Ser Ile Thr Ile Asp
405 410 415

Lys Phe Ala Ile Pro Asn Arg Arg Lys Val Asp Leu Gln Leu Gly Asn
420 425 430

Leu Gly Tyr Leu Gln Ser Ser Asn Tyr Arg Ile Asp Thr Thr Ala Thr
435 440 445

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

Ser Val Phe Val Pro Gln Pro Thr Gly Val Phe Thr Asn His Ser Val
485 490 495

Val Tyr Ala Gln His Cys Phe Lys Ala Pro Lys Asn Phe Cys Pro Cys
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Ser Ser Cys Ser Cys Pro Gly Lys Asn Asn Gly Ile Gly Thr Cys Pro
515 520 525

Ala Gly Thr Asn Ser Leu Thr Cys Asp Asn Leu Cys Thr Leu Asp Pro
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Ile Thr Leu Lys Ala Pro Asp Thr Tyr Lys Cys Pro Gln Ser Lys Ser
545 550 555 560

Leu Val Gly Ile Gly Glu His Cys Ser Gly Leu Ala Val Lys Ser Asp
565 570 575

Tyr Cys Gly Asn Asn Ser Cys Thr Cys Gln Pro Gln Ala Phe Leu Gly
580 585 590

Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp Lys Cys Asn Ile Phe Ala
595 600 605

Asn Phe Ile Leu His Asp Val Asn Asn Gly Leu Thr Cys Ser Thr Asp
610 615 620

Leu Gln Lys Ala Asn Thr Glu Ile Glu Leu Gly Val Cys Val Asn Tyr
625 630 635 640

Asp Leu Tyr Gly Ile Ser Gly Gln Gly Ile Phe Val Glu Val Asn Ala
645 650 655

Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn
660 665 670

Leu Tyr Gly Phe Arg Asp Tyr Ile Thr Asn Arg Thr Phe Met Ile His
675 680 685

Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala Tyr His Ala Asn Ser Ser
690 695 700

Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn
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Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile Asn Tyr Ser Phe Asp Ser
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Tyr Leu Gly Cys Val Val Asn Ala Tyr Asn Ser Thr Ala Ile Ser Val
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Gln Thr Cys Asp Leu Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Ser
755 760 765

Lys Asn Gly Gly Ser Gly Ser Ala Ile Thr Thr Gly Tyr Arg Phe Thr
770 775 780

Asn Phe Glu Pro Phe Thr Val Asn Ser Val Asn Asp Ser Leu Glu Pro
785 790 795 800

Val Gly Gly Leu Tyr Glu Ile Gln Ile Pro Ser Glu Phe Thr Ile Gly
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Asn Met Glu Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp
820 825 830

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

Val Glu Tyr Gly Ser Phe Cys Asp Asn Ile Asn Ala Ile Leu Thr Glu
850 855 860

Val Asn Glu Leu Leu Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu
865 870 875 880

Met Asn Gly Val Thr Leu Ser Thr Lys Leu Lys Asp Gly Val Asn Phe
885 890 895

Asn Val Asp Asp Ile Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser
900 905 910

Glu Cys Ser Lys Ala Ser Ser Arg Ser Ala Ile Glu Asp Leu Leu Phe
915 920 925

Asp Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn
930 935 940

Cys Thr Gly Gly Ala Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr
945 950 955 960

Lys Gly Ile Lys Val Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser
965 970 975

Gly Tyr Thr Leu Ala Ala Thr Ser Ala Ser Leu Phe Pro Pro Trp Thr
980 985 990

Ala Ala Ala Gly Val Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn
995 1000 1005

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

Lys Val Asn Glu Cys Val Lys Ser Gln Ser Ser Arg Ile Asn Phe
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Cys Gly Asn Gly Asn His Ile Ile Ser Leu Val Gln Asn Ala Pro
1145 1150 1155

Tyr Gly Leu Tyr Phe Ile His Phe Asn Tyr Val Pro Thr Lys Tyr
1160 1165 1170

Val Thr Ala Lys Val Ser Pro Gly Leu Cys Ile Ala Gly Asn Arg
1175 1180 1185

Gly Ile Ala Pro Lys Ser Gly Tyr Phe Val Asn Val Asn Asn Thr
1190 1195 1200

Trp Met Tyr Thr Gly Ser Gly Tyr Tyr Tyr Pro Glu Pro Ile Thr
1205 1210 1215

Glu Asn Asn Val Val Val Met Ser Thr Cys Ala Val Asn Tyr Thr
1220 1225 1230

Lys Ala Pro Tyr Val Met Leu Asn Thr Ser Ile Pro Asn Leu Pro
1235 1240 1245

Asp Phe Lys Glu Glu Leu Asp Gln Trp Phe Lys Asn Gln Thr Ser
1250 1255 1260

Val Ala Pro Asp Leu Ser Leu Asp Tyr Ile Asn Val Thr Phe Leu
1265 1270 1275

Asp Leu Gln Val Glu Met Asn Arg Leu Gln Glu Ala Ile Lys Val
1280 1285 1290

Leu Asn His Ser Tyr Ile Asn Leu Lys Asp Ile Gly Thr Tyr Glu
1295 1300 1305

Tyr Tyr Val Lys Trp Pro Trp Tyr Gln Ile Leu Ser Ile Tyr Ser
1310 1315 1320

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

Pro Ser Ile Ser Ile Asp Thr Val Asp Val Thr Asn Gly Leu Gly Thr
    50                  55                  60

Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Leu Asn
65                  70                  75                  80

Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu Lys
                85                  90                  95

Gly Thr Asp Leu Leu Ser Thr Leu Trp Phe Lys Pro Pro Phe Leu Ser
            100                 105                 110

Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val Phe
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Lys Asp Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly Ser
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Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Thr Ile
145 150 155 160

Asn Ser Thr Gln Asp Gly Val Asn Lys Leu Gln Gly Leu Leu Glu Val
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Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr Pro His Thr Ile Cys His
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Pro Asn Leu Gly Asn His Phe Lys Glu Leu Trp His Tyr Asp Thr Gly
195 200 205

Val Val Ser Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn Ala
210 215 220

Thr Tyr Leu Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr Ala
225 230 235 240

Tyr Phe Thr Asp Thr Gly Phe Val Thr Lys Phe Leu Phe Asn Val Tyr
245 250 255

Leu Gly Met Ala Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys Ile
260 265 270

Arg Arg Pro Lys Asp Gly Phe Ser Leu Glu Tyr Trp Val Thr Pro Leu
275 280 285

Thr Pro Arg Gln Tyr Leu Leu Ala Phe Asn Gln Asp Gly Ile Ile Phe
290 295 300

Asn Ala Val Asp Cys Met Ser Asp Phe Met Ser Glu Ile Lys Cys Lys
305 310 315 320

Thr Gln Ser Ile Ala Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr
325 330 335

Thr Val Gln Pro Val Ala Asp Val Tyr Arg Arg Lys Pro Asp Leu Pro
340 345 350

Asn Cys Asn Ile Glu Ala Trp Leu Asn Asp Lys Ser Val Pro Ser Pro
355 360 365

Leu Asn Trp Glu Arg Lys Thr Phe Ser Asn Cys Asn Phe Asn Met Ser
370 375 380

Ser Leu Met Ser Phe Ile Gln Ala Asp Ser Phe Thr Cys Asn Asn Ile
385 390 395 400

Asp Ala Ala Lys Ile Tyr Gly Met Cys Phe Ser Ser Ile Thr Ile Asp
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Lys Phe Ala Ile Pro Asn Arg Arg Lys Val Asp Leu Gln Leu Gly Asn
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Leu Gly Tyr Leu Gln Ser Ser Asn Tyr Arg Ile Asp Thr Thr Ala Thr
435 440 445

Ser Cys Gln Leu Tyr Tyr Asn Leu Pro Ala Ala Asn Val Ser Val Ser
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Arg Phe Asn Pro Ser Thr Trp Asn Lys Arg Phe Gly Phe Ile Glu Asp
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Ser Val Phe Val Pro Gln Pro Thr Gly Val Phe Thr Asn His Ser Val
485 490 495

Val Tyr Ala Gln His Cys Phe Lys Ala Pro Lys Asn Phe Cys Pro Cys
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Ser Ser Cys Ser Cys Pro Gly Lys Asn Asn Gly Ile Gly Thr Cys Pro
515 520 525

Ala Gly Thr Asn Ser Leu Thr Cys Asp Asn Leu Cys Thr Leu Asp Pro
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Ile Thr Leu Lys Ala Pro Asp Thr Tyr Lys Cys Pro Gln Ser Lys Ser
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Leu Val Gly Ile Gly Glu His Cys Ser Gly Leu Ala Val Lys Ser Asp
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Tyr Cys Gly Asn Asn Ser Cys Thr Cys Gln Pro Gln Ala Phe Leu Gly
580 585 590

Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp Lys Cys Asn Ile Phe Ala
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Asn Phe Ile Leu His Asp Val Asn Asn Gly Leu Thr Cys Ser Thr Asp
610 615 620

Leu Gln Lys Ala Asn Thr Glu Ile Glu Leu Gly Val Cys Val Asn Tyr
625 630 635 640

Asp Leu Tyr Gly Ile Ser Gly Gln Gly Ile Phe Val Glu Val Asn Ala
645 650 655

Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn
660 665 670

Leu Tyr Gly Phe Arg Asp Tyr Ile Thr Asn Arg Thr Phe Met Ile His
675 680 685

Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala Tyr His Ala Asn Ser Ser
690 695 700

Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn
705 710 715 720

Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile Asn Tyr Ser Phe Asp Ser
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Tyr Leu Gly Cys Val Val Asn Ala Tyr Asn Ser Thr Ala Ile Ser Val
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Gln Thr Cys Asp Leu Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Ser
755 760 765

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

Val Asn Glu Leu Leu Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu
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Met Asn Gly Val Thr Leu Ser Thr Lys Leu Lys Asp Gly Val Asn Phe
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Asn Val Asp Asp Ile Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser
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Glu Cys Ser Lys Ala Ser Ser Arg Ser Ala Ile Glu Asp Leu Leu Phe
915 920 925

Asp Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn
930 935 940

Cys Thr Gly Gly Ala Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr
945 950 955 960

Lys Gly Ile Lys Val Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser
965 970 975

Gly Tyr Thr Leu Ala Ala Thr Ser Ala Ser Leu Phe Pro Pro Trp Thr
980 985 990

Ala Ala Ala Gly Val Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn
995 1000 1005

Gly Leu Gly Val Thr Met Asp Val Leu Ser Gln Asn Gln Lys Leu
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Ile Ala Asn Ala Phe Asn Asn Ala Leu His Ala Ile Gln Gln Gly
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Phe Asp Ala Thr Asn Ser Ala Leu Val Lys Ile Gln Ala Val Val
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Asn Ala Asn Ala Glu Ala Leu Asn Asn Leu Leu Gln Gln Leu Ser
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Asn Arg Phe Gly Ala Ile Ser Ala Ser Leu Gln Glu Ile Leu Ser
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Arg Leu Asp Pro Pro Glu Ala Glu Ala Gln Ile Asp Arg Leu Ile
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Asn Gly Arg Leu Thr Ala Leu Asn Ala Tyr Val Ser Gln Gln Leu
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Ser Asp Ser Thr Leu Val Lys Phe Ser Ala Ala Gln Ala Met Glu
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Lys Val Asn Glu Cys Val Lys Ser Gln Ser Ser Arg Ile Asn Phe
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Tyr Gly Leu Tyr Phe Ile His Phe Asn Tyr Val Pro Thr Lys Tyr
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Val Thr Ala Lys Val Ser Pro Gly Leu Cys Ile Ala Gly Asn Arg
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Gly Ile Ala Pro Lys Ser Gly Tyr Phe Val Asn Val Asn Asn Thr
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Trp Met Tyr Thr Gly Ser Gly Tyr Tyr Tyr Pro Glu Pro Ile Thr
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Glu Asn Asn Val Val Val Met Ser Thr Cys Ala Val Asn Tyr Thr
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Lys Ala Pro Tyr Val Met Leu Asn Thr Ser Ile Pro Asn Leu Pro
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Asp Phe Lys Glu Glu Leu Asp Gln Trp Phe Lys Asn Gln Thr Ser
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Val Ala Pro Asp Leu Ser Leu Asp Tyr Ile Asn Val Thr Phe Leu
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Asp Leu Gln Val Glu Met Asn Arg Leu Gln Glu Ala Ile Lys Val
1280 1285 1290

Leu Asn His Ser Tyr Ile Asn Leu Lys Asp Ile Gly Thr Tyr Glu
1295 1300 1305

Tyr Tyr Val Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile Cys Leu
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Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu Lys
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Gly Thr Asp Leu Leu Ser Thr Leu Trp Phe Lys Pro Pro Phe Leu Ser
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Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val Phe
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Lys Asp Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly Ser
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Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Thr Ile
145 150 155 160

Asn Ser Thr Gln Asp Gly Val Asn Lys Leu Gln Gly Leu Leu Glu Val
165 170 175

Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr Pro His Thr Ile Cys His
180 185 190

Pro Asn Leu Gly Asn His Phe Lys Glu Leu Trp His Tyr Asp Thr Gly
195 200 205

Val Val Ser Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn Ala
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Thr Tyr Leu Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr Ala
225 230 235 240

Tyr Phe Thr Asp Thr Gly Phe Val Thr Lys Phe Leu Phe Asn Val Tyr
245 250 255

Leu Gly Met Ala Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys Ile
260 265 270

Arg Arg Pro Lys Asp Gly Phe Ser Leu Glu Tyr Trp Val Thr Pro Leu
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Thr Pro Arg Gln Tyr Leu Leu Ala Phe Asn Gln Asp Gly Ile Ile Phe
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Asn Ala Val Asp Cys Met Ser Asp Phe Met Ser Glu Ile Lys Cys Lys
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Thr Gln Ser Ile Ala Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr
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Thr Val Gln Pro Val Ala Asp Val Tyr Arg Arg Lys Pro Asp Leu Pro
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Asn Cys Asn Ile Glu Ala Trp Leu Asn Asp Lys Ser Val Pro Ser Pro
355 360 365

Leu Asn Trp Glu Arg Lys Thr Phe Ser Asn Cys Asn Phe Asn Met Ser
370 375 380

Ser Leu Met Ser Phe Ile Gln Ala Asp Ser Phe Thr Cys Asn Asn Ile
385 390 395 400

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

Ser Val Phe Val Pro Gln Pro Thr Gly Val Phe Thr Asn His Ser Val
485 490 495

Val Tyr Ala Gln His Cys Phe Lys Ala Pro Lys Asn Phe Cys Pro Cys
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Ser Ser Cys Ser Cys Pro Gly Lys Asn Asn Gly Ile Gly Thr Cys Pro
515 520 525

Ala Gly Thr Asn Ser Leu Thr Cys Asp Asn Leu Cys Thr Leu Asp Pro
530 535 540

Ile Thr Leu Lys Ala Pro Asp Thr Tyr Lys Cys Pro Gln Ser Lys Ser
545 550 555 560

Leu Val Gly Ile Gly Glu His Cys Ser Gly Leu Ala Val Lys Ser Asp
565 570 575

Tyr Cys Gly Asn Asn Ser Cys Thr Cys Gln Pro Gln Ala Phe Leu Gly
580 585 590

Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp Lys Cys Asn Ile Phe Ala
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625 630 635 640

Asp Leu Tyr Gly Ile Ser Gly Gln Gly Ile Phe Val Glu Val Asn Ala
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Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn
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Leu Tyr Gly Phe Arg Asp Tyr Ile Thr Asn Arg Thr Phe Met Ile His
675 680 685

Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala Tyr His Ala Asn Ser Ser
690 695 700

Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn
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Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile Asn Tyr Ser Phe Asp Ser
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Tyr Leu Gly Cys Val Val Asn Ala Tyr Asn Ser Thr Ala Ile Ser Val
740 745 750

Gln Thr Cys Asp Leu Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Ser
755 760 765

Lys Asn Gly Gly Ser Gly Ser Ala Ile Thr Thr Gly Tyr Arg Phe Thr
770 775 780

Asn Phe Glu Pro Phe Thr Val Asn Ser Val Asn Asp Ser Leu Glu Pro
785 790 795 800

Val Gly Gly Leu Tyr Glu Ile Gln Ile Pro Ser Glu Phe Thr Ile Gly
805 810 815

Asn Met Glu Glu Phe Ile Gln Thr Ser Ser Pro Lys Val Thr Ile Asp
820 825 830

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

Val Glu Tyr Gly Ser Phe Cys Asp Asn Ile Asn Ala Ile Leu Thr Glu
850 855 860

Val Asn Glu Leu Leu Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu
865 870 875 880

Met Asn Gly Val Thr Leu Ser Thr Lys Leu Lys Asp Gly Val Asn Phe
885 890 895

Asn Val Asp Asp Ile Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser
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Glu Cys Ser Lys Ala Ser Ser Arg Ser Ala Ile Glu Asp Leu Leu Phe
915 920 925

Asp Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu Ala Tyr Asn Asn
930 935 940

Cys Thr Gly Gly Ala Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr
945 950 955 960

Lys Gly Ile Lys Val Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser
965 970 975

Gly Tyr Thr Leu Ala Ala Thr Ser Ala Ser Leu Phe Pro Pro Trp Thr
980 985 990

Ala Ala Ala Gly Val Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn
995 1000 1005

Gly Leu Gly Val Thr Met Asp Val Leu Ser Gln Asn Gln Lys Leu
1010 1015 1020

Ile Ala Asn Ala Phe Asn Asn Ala Leu His Ala Ile Gln Gln Gly
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Phe Asp Ala Thr Asn Ser Ala Leu Val Lys Ile Gln Ala Val Val
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Asn Ala Asn Ala Glu Ala Leu Asn Asn Leu Leu Gln Gln Leu Ser
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Asn Arg Phe Gly Ala Ile Ser Ala Ser Leu Gln Glu Ile Leu Ser
1070 1075 1080

Arg Leu Asp Pro Pro Glu Ala Glu Ala Gln Ile Asp Arg Leu Ile
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Asn Gly Arg Leu Thr Ala Leu Asn Ala Tyr Val Ser Gln Gln Leu
1100 1105 1110

Ser Asp Ser Thr Leu Val Lys Phe Ser Ala Ala Gln Ala Met Glu
1115 1120 1125

Lys Val Asn Glu Cys Val Lys Ser Gln Ser Ser Arg Ile Asn Phe
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Cys Gly Asn Gly Asn His Ile Ile Ser Leu Val Gln Asn Ala Pro
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Tyr Gly Leu Tyr Phe Ile His Phe Asn Tyr Val Pro Thr Lys Tyr
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Val Thr Ala Lys Val Ser Pro Gly Leu Cys Ile Ala Gly Asn Arg
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Gly Ile Ala Pro Lys Ser Gly Tyr Phe Val Asn Val Asn Asn Thr
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Trp Met Tyr Thr Gly Ser Gly Tyr Tyr Tyr Pro Glu Pro Ile Thr
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Glu Asn Asn Val Val Val Met Ser Thr Cys Ala Val Asn Tyr Thr
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Lys Ala Pro Tyr Val Met Leu Asn Thr Ser Ile Pro Asn Leu Pro
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Asp Phe Lys Glu Glu Leu Asp Gln Trp Phe Lys Asn Gln Thr Ser
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Val Ala Pro Asp Leu Ser Leu Asp Tyr Ile Asn Val Thr Phe Leu
1265 1270 1275

Asp Leu Gln Val Glu Met Asn Arg Leu Gln Glu Ala Ile Lys Val
1280 1285 1290

Leu Asn His Ser Tyr Ile Asn Leu Lys Asp Ile Gly Thr Tyr Glu
1295 1300 1305

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

Pro Ser Ile Ser Ile Asp Thr Val Asp Val Thr Asn Gly Leu Gly Thr
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Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Leu Asn
65 70 75 80

Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu Lys
85 90 95

Gly Thr Asp Leu Leu Ser Thr Leu Trp Phe Lys Pro Pro Phe Leu Ser
100 105 110

Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val Phe
115 120 125

Lys Asp Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly Ser
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Cys Lys Gly Phe Ser Ser Asp Val Leu Ser Asp Val Ile Arg Tyr Asn
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Phe Tyr Ile Asn Gly Tyr Arg Tyr Phe Thr Leu Gly Asn Val Glu Ala
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Val Thr Leu Asp Lys Cys Thr Lys Tyr Asn Ile Tyr Asp Val Ser Gly
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Tyr Thr Ser Thr Ser Gly Asn Leu Leu Gly Phe Lys Asp Val Thr Lys
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Gly Thr Ile Tyr Ser Ile Thr Pro Cys Asn Pro Pro Asp Gln Leu Val
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Val Ser Tyr Asp Ser Val Ser Ala Ile Val Thr Ala Asn Leu Ser Ile
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Thr Val Ala Thr Ala Leu Asn Lys Ile Gln Asp Val Val Asn Gln Gln
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Gly Asn Ser Leu Asn His Leu Thr Ser Gln Leu Arg Gln Asn Phe Gln
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Gln Ser Lys Arg Tyr Gly Phe Cys Gly Asn Gly Thr His Ile Phe Ser
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Ile Thr Gly Val Pro Gln Pro Val Glu Gly Val Ser Ser Phe Met Asn
435 440 445

Val Thr Leu Asp Lys Cys Thr Lys Tyr Asn Ile Tyr Asp Val Ser Gly
450 455 460

Val Gly Val Ile Arg Val Ser Asn Asp Thr Phe Leu Asn Gly Ile Thr
465 470 475 480

Tyr Thr Ser Thr Ser Gly Asn Leu Leu Gly Phe Lys Asp Val Thr Lys
485 490 495

Gly Thr Ile Tyr Ser Ile Thr Pro Cys Asn Pro Pro Asp Gln Leu Val
500 505 510

Val Tyr Gln Gln Ala Val Val Gly Ala Met Leu Ser Glu Asn Phe Thr
515 520 525

Ser Tyr Gly Phe Ser Asn Val Val Glu Leu Pro Lys Phe Phe Tyr Ala
530 535 540

Ser Asn Gly Thr Tyr Asn Cys Thr Asp Ala Val Leu Thr Tyr Ser Ser
545 550 555 560

Phe Gly Val Cys Ala Asp Gly Ser Ile Ile Ala Val Gln Pro Ala Asn
565 570 575

Val Ser Tyr Asp Ser Val Ser Ala Ile Val Thr Ala Asn Leu Ser Ile
580 585 590

Pro Ser Asn Trp Thr Thr Ser Val Gln Val Glu Tyr Leu Gln Ile Thr
595 600 605

Ser Thr Pro Ile Val Val Asp Cys Ser Thr Tyr Val Cys Asn Gly Asn
610 615 620

Val Arg Cys Val Glu Leu Leu Lys Gln Tyr Thr Ser Ala Cys Lys Thr
625 630 635 640

Ile Glu Asp Ala Leu Arg Asn Ser Ala Arg Leu Glu Ser Ala Asp Val
645 650 655

Ser Glu Met Leu Thr Phe Asp Lys Lys Ala Phe Thr Leu Ala Asn Val
660 665 670

Ser Ser Phe Gly Asp Tyr Asn Leu Ser Ser Val Ile Pro Ser Leu Pro
675 680 685

Thr Ser Gly Ser Arg Val Ala Gly Arg Ser Ala Ile Glu Asp Ile Leu
690 695 700

Phe Ser Lys Leu Val Thr Ser Gly Leu Gly Thr Val Asp Ala Asp Tyr
705 710 715 720

Lys Lys Cys Thr Lys Gly Leu Ser Ile Ala Asp Leu Ala Cys Ala Gln
725 730 735

Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val Ala Asp Ala Glu Arg
740 745 750

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

Leu Thr Ser Ala Val Ser Ile Pro Phe Ser Leu Ala Ile Gln Ala Arg
770 775 780

Leu Asn Tyr Val Ala Leu Gln Thr Asp Val Leu Gln Glu Asn Gln Lys
785 790 795 800

Ile Leu Ala Ala Ser Phe Asn Lys Ala Met Thr Asn Ile Val Asp Ala
805 810 815

Phe Thr Gly Val Asn Asp Ala Ile Thr Gln Thr Ser Gln Ala Leu Gln
820 825 830

Thr Val Ala Thr Ala Leu Asn Lys Ile Gln Asp Val Val Asn Gln Gln
835 840 845

Gly Asn Ser Leu Asn His Leu Thr Ser Gln Leu Arg Gln Asn Phe Gln
850 855 860

Ala Ile Ser Ser Ser Ile Gln Ala Ile Tyr Asp Arg Leu Asp Pro Pro
865 870 875 880

Gln Ala Asp Gln Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Ala Ala
885 890 895

Leu Asn Val Phe Val Ser His Thr Leu Thr Lys Tyr Thr Glu Val Arg
900 905 910

Ala Ser Arg Gln Leu Ala Gln Gln Lys Val Asn Glu Cys Val Lys Ser
915 920 925

Gln Ser Lys Arg Tyr Gly Phe Cys Gly Asn Gly Thr His Ile Phe Ser
930 935 940

Ile Val Asn Ala Ala Pro Glu Gly Leu Val Phe Leu His Thr Val Leu
945 950 955 960

Leu Pro Thr Gln Tyr Lys Asp Val Glu Ala Trp Ser Gly Leu Cys Val
965 970 975

Asp Gly Thr Asn Gly Tyr Val Leu Arg Gln Pro Asn Leu Ala Leu Tyr
980 985 990

Lys Glu Gly Asn Tyr Tyr Arg Ile Thr Ser Arg Ile Met Phe Glu Pro
995 1000 1005

Arg Ile Pro Thr Met Ala Asp Phe Val Gln Ile Glu Asn Cys Asn
1010 1015 1020

Val Thr Phe Val Asn Ile Ser Arg Ser Glu Leu Gln Thr Ile Val
1025 1030 1035

Pro Glu Tyr Ile Asp Val Asn Lys Thr Leu Gln Glu Leu Ser Tyr
1040 1045 1050

Lys Leu Pro Asn Tyr Thr Val Pro Asp Leu Val Val Glu Gln Tyr
1055 1060 1065

Asn Gln Thr Ile Leu Asn Leu Thr Ser Glu Ile Ser Thr Leu Glu
1070 1075 1080

Asn Lys Ser Ala Glu Leu Asn Tyr Thr Val Gln Lys Leu Gln Thr
1085 1090 1095

Leu Ile Asp Asn Ile Asn Ser Thr Leu Val Asp Leu Lys Trp Leu
1100 1105 1110

Asn Arg Val Glu Thr Tyr Ile Lys Trp Pro Trp Trp Gln Ile Leu
1115 1120 1125

Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala Leu Ala Ile Met
1130 1135 1140

Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln
1145 1150 1155

Cys Arg Ile Cys Ile
1160

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Leu Val Pro Ser Gln Ile Phe Ala Gln Thr Thr Asn Gly Leu Asn Thr
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Ser Tyr Ser Val Cys Asn Gly Cys Val Gly Tyr Ser Glu Asn Val Phe
35 40 45

Ala Val Glu Ser Gly Gly Tyr Ile Pro Ser Asp Phe Ala Phe Asn Asn
50 55 60

Trp Phe Leu Leu Thr Asn Thr Ser Ser Val Val Asp Gly Val Val Arg
65 70 75 80

Ser Phe Gln Pro Leu Leu Leu Asn Cys Leu Trp Ser Val Ser Gly Leu
85 90 95

Arg Phe Thr Thr Gly Phe Val Tyr Phe Asn Gly Thr Gly Arg Gly Asp
100 105 110

Cys Lys Gly Phe Ser Ser Asp Val Leu Ser Asp Val Ile Arg Tyr Asn
115 120 125

Leu Asn Phe Glu Glu Asn Leu Arg Arg Gly Thr Ile Leu Phe Lys Thr
130 135 140

Ser Tyr Gly Val Val Val Phe Tyr Cys Thr Asn Asn Thr Leu Val Ser
145 150 155 160

Gly Asp Ala His Ile Pro Phe Gly Thr Val Leu Gly Asn Phe Tyr Cys
165 170 175

Phe Val Asn Thr Thr Ile Gly Asn Glu Thr Thr Ser Ala Phe Val Gly
180 185 190

Ala Leu Pro Lys Thr Val Arg Glu Phe Val Ile Ser Arg Thr Gly His
195 200 205

Phe Tyr Ile Asn Gly Tyr Arg Tyr Phe Thr Leu Gly Asn Val Glu Ala
210 215 220

Val Asn Phe Asn Val Thr Thr Ala Glu Thr Thr Asp Phe Cys Thr Val
225 230 235 240

Ala Leu Ala Ser Tyr Ala Asp Val Leu Val Asn Val Ser Gln Thr Ser
245 250 255

Ile Ala Asn Ile Ile Tyr Cys Asn Ser Val Ile Asn Arg Leu Arg Cys
260 265 270

Asp Gln Leu Ser Phe Asp Val Pro Asp Gly Phe Tyr Ser Thr Ser Pro
275 280 285

Ile Gln Ser Val Glu Leu Pro Val Ser Ile Val Ser Leu Pro Val Tyr
290 295 300

His Lys His Thr Phe Ile Val Leu Tyr Val Asp Phe Lys Pro Gln Ser
305 310 315 320

Gly Gly Gly Lys Cys Phe Asn Cys Tyr Pro Ala Gly Val Asn Ile Thr
325 330 335

Leu Ala Asn Phe Asn Glu Thr Lys Gly Pro Leu Cys Val Asp Thr Ser
340 345 350

His Phe Thr Thr Lys Tyr Val Ala Val Tyr Ala Asn Val Gly Arg Trp
355 360 365

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

Asn Asn Phe Val Lys Phe Gly Ser Val Cys Phe Ser Leu Lys Asp Ile
385 390 395 400

Pro Gly Gly Cys Ala Met Pro Ile Val Ala Asn Trp Ala Tyr Ser Lys
405 410 415

Tyr Tyr Thr Ile Gly Ser Leu Tyr Val Ser Trp Ser Asp Gly Asp Gly
420 425 430

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

Val Thr Leu Asp Lys Cys Thr Lys Tyr Asn Ile Tyr Asp Val Ser Gly
450 455 460

Val Gly Val Ile Arg Val Ser Asn Asp Thr Phe Leu Asn Gly Ile Thr
465 470 475 480

Tyr Thr Ser Thr Ser Gly Asn Leu Leu Gly Phe Lys Asp Val Thr Lys
485 490 495

Gly Thr Ile Tyr Ser Ile Thr Pro Cys Asn Pro Pro Asp Gln Leu Val
500 505 510

Val Tyr Gln Gln Ala Val Val Gly Ala Met Leu Ser Glu Asn Phe Thr
515 520 525

Ser Tyr Gly Phe Ser Asn Val Val Glu Leu Pro Lys Phe Phe Tyr Ala
530 535 540

Ser Asn Gly Thr Tyr Asn Cys Thr Asp Ala Val Leu Thr Tyr Ser Ser
545 550 555 560

Phe Gly Val Cys Ala Asp Gly Ser Ile Ile Ala Val Gln Pro Ala Asn
565 570 575

Val Ser Tyr Asp Ser Val Ser Ala Ile Val Thr Ala Asn Leu Ser Ile
580 585 590

Pro Ser Asn Trp Thr Thr Ser Val Gln Val Glu Tyr Leu Gln Ile Thr
595 600 605

Ser Thr Pro Ile Val Val Asp Cys Ser Thr Tyr Val Cys Asn Gly Asn
610 615 620

Val Arg Cys Val Glu Leu Leu Lys Gln Tyr Thr Ser Ala Cys Lys Thr
625 630 635 640

Ile Glu Asp Ala Leu Arg Asn Ser Ala Arg Leu Glu Ser Ala Asp Val
645 650 655

Ser Glu Met Leu Thr Phe Asp Lys Lys Ala Phe Thr Leu Ala Asn Val
660 665 670

Ser Ser Phe Gly Asp Tyr Asn Leu Ser Ser Val Ile Pro Ser Leu Pro
675 680 685

Thr Ser Gly Ser Arg Val Ala Gly Arg Ser Ala Ile Glu Asp Ile Leu
690 695 700

Phe Ser Lys Leu Val Thr Ser Gly Leu Gly Thr Val Asp Ala Asp Tyr
705 710 715 720

Lys Lys Cys Thr Lys Gly Leu Ser Ile Ala Asp Leu Ala Cys Ala Gln
725 730 735

Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val Ala Asp Ala Glu Arg
740 745 750

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

Leu Thr Ser Ala Val Ser Ile Pro Phe Ser Leu Ala Ile Gln Ala Arg
770 775 780

Leu Asn Tyr Val Ala Leu Gln Thr Asp Val Leu Gln Glu Asn Gln Lys
785 790 795 800

Ile Leu Ala Ala Ser Phe Asn Lys Ala Met Thr Asn Ile Val Asp Ala
805 810 815

Phe Thr Gly Val Asn Asp Ala Ile Thr Gln Thr Ser Gln Ala Leu Gln
820 825 830

Thr Val Ala Thr Ala Leu Asn Lys Ile Gln Asp Val Val Asn Gln Gln
835 840 845

Gly Asn Ser Leu Asn His Leu Thr Ser Gln Leu Arg Gln Asn Phe Gln
850 855 860

Ala Ile Ser Ser Ser Ile Gln Ala Ile Tyr Asp Arg Leu Asp Pro Pro
865 870 875 880

Gln Ala Asp Gln Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Ala Ala
885 890 895

Leu Asn Val Phe Val Ser His Thr Leu Thr Lys Tyr Thr Glu Val Arg
900 905 910

Ala Ser Arg Gln Leu Ala Gln Gln Lys Val Asn Glu Cys Val Lys Ser
915 920 925

Gln Ser Lys Arg Tyr Gly Phe Cys Gly Asn Gly Thr His Ile Phe Ser
930 935 940

Ile Val Asn Ala Ala Pro Glu Gly Leu Val Phe Leu His Thr Val Leu
945 950 955 960

Leu Pro Thr Gln Tyr Lys Asp Val Glu Ala Trp Ser Gly Leu Cys Val
965 970 975

Asp Gly Thr Asn Gly Tyr Val Leu Arg Gln Pro Asn Leu Ala Leu Tyr
980 985 990

Lys Glu Gly Asn Tyr Tyr Arg Ile Thr Ser Arg Ile Met Phe Glu Pro
995 1000 1005

Arg Ile Pro Thr Met Ala Asp Phe Val Gln Ile Glu Asn Cys Asn
1010 1015 1020

Val Thr Phe Val Asn Ile Ser Arg Ser Glu Leu Gln Thr Ile Val
1025 1030 1035

Pro Glu Tyr Ile Asp Val Asn Lys Thr Leu Gln Glu Leu Ser Tyr
1040 1045 1050

Lys Leu Pro Asn Tyr Thr Val Pro Asp Leu Val Val Glu Gln Tyr
1055 1060 1065

Asn Gln Thr Ile Leu Asn Leu Thr Ser Glu Ile Ser Thr Leu Glu
1070 1075 1080

Asn Lys Ser Ala Glu Leu Asn Tyr Thr Val Gln Lys Leu Gln Thr
1085 1090 1095

Leu Ile Asp Asn Ile Asn Ser Thr Leu Val Asp Leu Lys Trp Leu
1100 1105 1110

Asn Arg Val Glu Thr Tyr Ile Lys Trp Pro Trp Trp Val Trp Leu
1115 1120 1125

Cys Ile Ser Val Val Leu Ile Phe Val Val Ser Met Leu Leu Leu
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Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys
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Ile

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Leu Val Pro Ser Gln Ile Phe Ala Gln Thr Thr Asn Gly Leu Asn Thr
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Ser Tyr Ser Val Cys Asn Gly Cys Val Gly Tyr Ser Glu Asn Val Phe
35 40 45

Ala Val Glu Ser Gly Gly Tyr Ile Pro Ser Asp Phe Ala Phe Asn Asn
50 55 60

Trp Phe Leu Leu Thr Asn Thr Ser Ser Val Val Asp Gly Val Val Arg
65 70 75 80

Ser Phe Gln Pro Leu Leu Leu Asn Cys Leu Trp Ser Val Ser Gly Leu
85 90 95

Arg Phe Thr Thr Gly Phe Val Tyr Phe Asn Gly Thr Gly Arg Gly Asp
100 105 110

Cys Lys Gly Phe Ser Ser Asp Val Leu Ser Asp Val Ile Arg Tyr Asn
115 120 125

Leu Asn Phe Glu Glu Asn Leu Arg Arg Gly Thr Ile Leu Phe Lys Thr
130 135 140

Ser Tyr Gly Val Val Val Phe Tyr Cys Thr Asn Asn Thr Leu Val Ser
145 150 155 160

Gly Asp Ala His Ile Pro Phe Gly Thr Val Leu Gly Asn Phe Tyr Cys
165 170 175

Phe Val Asn Thr Thr Ile Gly Asn Glu Thr Thr Ser Ala Phe Val Gly
180 185 190

Ala Leu Pro Lys Thr Val Arg Glu Phe Val Ile Ser Arg Thr Gly His
195 200 205

Phe Tyr Ile Asn Gly Tyr Arg Tyr Phe Thr Leu Gly Asn Val Glu Ala
210 215 220

Val Asn Phe Asn Val Thr Thr Ala Glu Thr Thr Asp Phe Cys Thr Val
225 230 235 240

Ala Leu Ala Ser Tyr Ala Asp Val Leu Val Asn Val Ser Gln Thr Ser
245 250 255

Ile Ala Asn Ile Ile Tyr Cys Asn Ser Val Ile Asn Arg Leu Arg Cys
260 265 270

Asp Gln Leu Ser Phe Asp Val Pro Asp Gly Phe Tyr Ser Thr Ser Pro
275 280 285

Ile Gln Ser Val Glu Leu Pro Val Ser Ile Val Ser Leu Pro Val Tyr
290 295 300

His Lys His Thr Phe Ile Val Leu Tyr Val Asp Phe Lys Pro Gln Ser
305 310 315 320

Gly Gly Gly Lys Cys Phe Asn Cys Tyr Pro Ala Gly Val Asn Ile Thr
325 330 335

Leu Ala Asn Phe Asn Glu Thr Lys Gly Pro Leu Cys Val Asp Thr Ser
340 345 350

His Phe Thr Thr Lys Tyr Val Ala Val Tyr Ala Asn Val Gly Arg Trp
355 360 365

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

Asn Asn Phe Val Lys Phe Gly Ser Val Cys Phe Ser Leu Lys Asp Ile
385 390 395 400

Pro Gly Gly Cys Ala Met Pro Ile Val Ala Asn Trp Ala Tyr Ser Lys
405 410 415

Tyr Tyr Thr Ile Gly Ser Leu Tyr Val Ser Trp Ser Asp Gly Asp Gly
420 425 430

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

Val Thr Leu Asp Lys Cys Thr Lys Tyr Asn Ile Tyr Asp Val Ser Gly
450 455 460

Val Gly Val Ile Arg Val Ser Asn Asp Thr Phe Leu Asn Gly Ile Thr
465 470 475 480

Tyr Thr Ser Thr Ser Gly Asn Leu Leu Gly Phe Lys Asp Val Thr Lys
485 490 495

Gly Thr Ile Tyr Ser Ile Thr Pro Cys Asn Pro Pro Asp Gln Leu Val
500 505 510

Val Tyr Gln Gln Ala Val Val Gly Ala Met Leu Ser Glu Asn Phe Thr
515 520 525

Ser Tyr Gly Phe Ser Asn Val Val Glu Leu Pro Lys Phe Phe Tyr Ala
530 535 540

Ser Asn Gly Thr Tyr Asn Cys Thr Asp Ala Val Leu Thr Tyr Ser Ser
545 550 555 560

Phe Gly Val Cys Ala Asp Gly Ser Ile Ile Ala Val Gln Pro Ala Asn
565 570 575

Val Ser Tyr Asp Ser Val Ser Ala Ile Val Thr Ala Asn Leu Ser Ile
580 585 590

Pro Ser Asn Trp Thr Thr Ser Val Gln Val Glu Tyr Leu Gln Ile Thr
595 600 605

Ser Thr Pro Ile Val Val Asp Cys Ser Thr Tyr Val Cys Asn Gly Asn
610 615 620

Val Arg Cys Val Glu Leu Leu Lys Gln Tyr Thr Ser Ala Cys Lys Thr
625 630 635 640

Ile Glu Asp Ala Leu Arg Asn Ser Ala Arg Leu Glu Ser Ala Asp Val
645 650 655

Ser Glu Met Leu Thr Phe Asp Lys Lys Ala Phe Thr Leu Ala Asn Val
660 665 670

Ser Ser Phe Gly Asp Tyr Asn Leu Ser Ser Val Ile Pro Ser Leu Pro
675 680 685

Thr Ser Gly Ser Arg Val Ala Gly Arg Ser Ala Ile Glu Asp Ile Leu
690 695 700

Phe Ser Lys Leu Val Thr Ser Gly Leu Gly Thr Val Asp Ala Asp Tyr
705 710 715 720

Lys Lys Cys Thr Lys Gly Leu Ser Ile Ala Asp Leu Ala Cys Ala Gln
725 730 735

Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val Ala Asp Ala Glu Arg
740 745 750

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

Leu Thr Ser Ala Val Ser Ile Pro Phe Ser Leu Ala Ile Gln Ala Arg
770 775 780

Leu Asn Tyr Val Ala Leu Gln Thr Asp Val Leu Gln Glu Asn Gln Lys
785 790 795 800

Ile Leu Ala Ala Ser Phe Asn Lys Ala Met Thr Asn Ile Val Asp Ala
805 810 815

Phe Thr Gly Val Asn Asp Ala Ile Thr Gln Thr Ser Gln Ala Leu Gln
820 825 830

Thr Val Ala Thr Ala Leu Asn Lys Ile Gln Asp Val Val Asn Gln Gln
835 840 845

Gly Asn Ser Leu Asn His Leu Thr Ser Gln Leu Arg Gln Asn Phe Gln
850 855 860

Ala Ile Ser Ser Ser Ile Gln Ala Ile Tyr Asp Arg Leu Asp Pro Pro
865 870 875 880

Gln Ala Asp Gln Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Ala Ala
885 890 895

Leu Asn Val Phe Val Ser His Thr Leu Thr Lys Tyr Thr Glu Val Arg
900 905 910

Ala Ser Arg Gln Leu Ala Gln Gln Lys Val Asn Glu Cys Val Lys Ser
915 920 925

Gln Ser Lys Arg Tyr Gly Phe Cys Gly Asn Gly Thr His Ile Phe Ser
930 935 940

Ile Val Asn Ala Ala Pro Glu Gly Leu Val Phe Leu His Thr Val Leu
945 950 955 960

Leu Pro Thr Gln Tyr Lys Asp Val Glu Ala Trp Ser Gly Leu Cys Val
965 970 975

Asp Gly Thr Asn Gly Tyr Val Leu Arg Gln Pro Asn Leu Ala Leu Tyr
980 985 990

Lys Glu Gly Asn Tyr Tyr Arg Ile Thr Ser Arg Ile Met Phe Glu Pro
995 1000 1005

Arg Ile Pro Thr Met Ala Asp Phe Val Gln Ile Glu Asn Cys Asn
1010 1015 1020

Val Thr Phe Val Asn Ile Ser Arg Ser Glu Leu Gln Thr Ile Val
1025 1030 1035

Pro Glu Tyr Ile Asp Val Asn Lys Thr Leu Gln Glu Leu Ser Tyr
1040 1045 1050

Lys Leu Pro Asn Tyr Thr Val Pro Asp Leu Val Val Glu Gln Tyr
1055 1060 1065

Asn Gln Thr Ile Leu Asn Leu Thr Ser Glu Ile Ser Thr Leu Glu
1070 1075 1080

Asn Lys Ser Ala Glu Leu Asn Tyr Thr Val Gln Lys Leu Gln Thr
1085 1090 1095

Leu Ile Asp Asn Ile Asn Ser Thr Leu Val Asp Leu Lys Trp Leu
1100 1105 1110

Asn Arg Val Glu Thr Tyr Ile Lys Trp Pro Trp Trp Val Trp Leu
1115 1120 1125

Cys Ile Ser Val Val Leu Ile Phe Val Val Ser Met Leu Leu Leu
1130 1135 1140

Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys Ile
1145 1150 1155

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Leu Val Pro Ser Gln Ile Phe Ala Gln Thr Thr Asn Gly Leu Asn Thr
20 25 30

Ser Tyr Ser Val Cys Asn Gly Cys Val Gly Tyr Ser Glu Asn Val Phe
35 40 45

Ala Val Glu Ser Gly Gly Tyr Ile Pro Ser Asp Phe Ala Phe Asn Asn
50 55 60

Trp Phe Leu Leu Thr Asn Thr Ser Ser Val Val Asp Gly Val Val Arg
65 70 75 80

Ser Phe Gln Pro Leu Leu Leu Asn Cys Leu Trp Ser Val Ser Gly Leu
85 90 95

Arg Phe Thr Thr Gly Phe Val Tyr Phe Asn Gly Thr Gly Arg Gly Asp
100 105 110

Cys Lys Gly Phe Ser Ser Asp Val Leu Ser Asp Val Ile Arg Tyr Asn
115 120 125

Leu Asn Phe Glu Glu Asn Leu Arg Arg Gly Thr Ile Leu Phe Lys Thr
130 135 140

Ser Tyr Gly Val Val Val Phe Tyr Cys Thr Asn Asn Thr Leu Val Ser
145 150 155 160

Gly Asp Ala His Ile Pro Phe Gly Thr Val Leu Gly Asn Phe Tyr Cys
165 170 175

Phe Val Asn Thr Thr Ile Gly Asn Glu Thr Thr Ser Ala Phe Val Gly
180 185 190

Ala Leu Pro Lys Thr Val Arg Glu Phe Val Ile Ser Arg Thr Gly His
195 200 205

Phe Tyr Ile Asn Gly Tyr Arg Tyr Phe Thr Leu Gly Asn Val Glu Ala
210 215 220

Val Asn Phe Asn Val Thr Thr Ala Glu Thr Thr Asp Phe Cys Thr Val
225 230 235 240

Ala Leu Ala Ser Tyr Ala Asp Val Leu Val Asn Val Ser Gln Thr Ser
245 250 255

Ile Ala Asn Ile Ile Tyr Cys Asn Ser Val Ile Asn Arg Leu Arg Cys
260 265 270

Asp Gln Leu Ser Phe Asp Val Pro Asp Gly Phe Tyr Ser Thr Ser Pro
275 280 285

Ile Gln Ser Val Glu Leu Pro Val Ser Ile Val Ser Leu Pro Val Tyr
290 295 300

His Lys His Thr Phe Ile Val Leu Tyr Val Asp Phe Lys Pro Gln Ser
305 310 315 320

Gly Gly Gly Lys Cys Phe Asn Cys Tyr Pro Ala Gly Val Asn Ile Thr
325 330 335

Leu Ala Asn Phe Asn Glu Thr Lys Gly Pro Leu Cys Val Asp Thr Ser
340 345 350

His Phe Thr Thr Lys Tyr Val Ala Val Tyr Ala Asn Val Gly Arg Trp
355 360 365

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

Asn Asn Phe Val Lys Phe Gly Ser Val Cys Phe Ser Leu Lys Asp Ile
385 390 395 400

Pro Gly Gly Cys Ala Met Pro Ile Val Ala Asn Trp Ala Tyr Ser Lys
405 410 415

Tyr Tyr Thr Ile Gly Ser Leu Tyr Val Ser Trp Ser Asp Gly Asp Gly
420 425 430

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

Val Thr Leu Asp Lys Cys Thr Lys Tyr Asn Ile Tyr Asp Val Ser Gly
450 455 460

Val Gly Val Ile Arg Val Ser Asn Asp Thr Phe Leu Asn Gly Ile Thr
465 470 475 480

Tyr Thr Ser Thr Ser Gly Asn Leu Leu Gly Phe Lys Asp Val Thr Lys
485 490 495

Gly Thr Ile Tyr Ser Ile Thr Pro Cys Asn Pro Pro Asp Gln Leu Val
500 505 510

Val Tyr Gln Gln Ala Val Val Gly Ala Met Leu Ser Glu Asn Phe Thr
515 520 525

Ser Tyr Gly Phe Ser Asn Val Val Glu Leu Pro Lys Phe Phe Tyr Ala
530 535 540

Ser Asn Gly Thr Tyr Asn Cys Thr Asp Ala Val Leu Thr Tyr Ser Ser
545 550 555 560

Phe Gly Val Cys Ala Asp Gly Ser Ile Ile Ala Val Gln Pro Ala Asn
565 570 575

Val Ser Tyr Asp Ser Val Ser Ala Ile Val Thr Ala Asn Leu Ser Ile
580 585 590

Pro Ser Asn Trp Thr Thr Ser Val Gln Val Glu Tyr Leu Gln Ile Thr
595 600 605

Ser Thr Pro Ile Val Val Asp Cys Ser Thr Tyr Val Cys Asn Gly Asn
610 615 620

Val Arg Cys Val Glu Leu Leu Lys Gln Tyr Thr Ser Ala Cys Lys Thr
625 630 635 640

Ile Glu Asp Ala Leu Arg Asn Ser Ala Arg Leu Glu Ser Ala Asp Val
645 650 655

Ser Glu Met Leu Thr Phe Asp Lys Lys Ala Phe Thr Leu Ala Asn Val
660 665 670

Ser Ser Phe Gly Asp Tyr Asn Leu Ser Ser Val Ile Pro Ser Leu Pro
675 680 685

Thr Ser Gly Ser Arg Val Ala Gly Arg Ser Ala Ile Glu Asp Ile Leu
690 695 700

Phe Ser Lys Leu Val Thr Ser Gly Leu Gly Thr Val Asp Ala Asp Tyr
705 710 715 720

Lys Lys Cys Thr Lys Gly Leu Ser Ile Ala Asp Leu Ala Cys Ala Gln
725 730 735

Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val Ala Asp Ala Glu Arg
740 745 750

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

Leu Thr Ser Ala Val Ser Ile Pro Phe Ser Leu Ala Ile Gln Ala Arg
770 775 780

Leu Asn Tyr Val Ala Leu Gln Thr Asp Val Leu Gln Glu Asn Gln Lys
785 790 795 800

Ile Leu Ala Ala Ser Phe Asn Lys Ala Met Thr Asn Ile Val Asp Ala
805 810 815

Phe Thr Gly Val Asn Asp Ala Ile Thr Gln Thr Ser Gln Ala Leu Gln
820 825 830

Thr Val Ala Thr Ala Leu Asn Lys Ile Gln Asp Val Val Asn Gln Gln
835 840 845

Gly Asn Ser Leu Asn His Leu Thr Ser Gln Leu Arg Gln Asn Phe Gln
850 855 860

Ala Ile Ser Ser Ser Ile Gln Ala Ile Tyr Asp Arg Leu Asp Pro Pro
865 870 875 880

Gln Ala Asp Gln Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Ala Ala
885 890 895

Leu Asn Val Phe Val Ser His Thr Leu Thr Lys Tyr Thr Glu Val Arg
900 905 910

Ala Ser Arg Gln Leu Ala Gln Gln Lys Val Asn Glu Cys Val Lys Ser
915 920 925

Gln Ser Lys Arg Tyr Gly Phe Cys Gly Asn Gly Thr His Ile Phe Ser
930 935 940

Ile Val Asn Ala Ala Pro Glu Gly Leu Val Phe Leu His Thr Val Leu
945 950 955 960

Leu Pro Thr Gln Tyr Lys Asp Val Glu Ala Trp Ser Gly Leu Cys Val
965 970 975

Asp Gly Thr Asn Gly Tyr Val Leu Arg Gln Pro Asn Leu Ala Leu Tyr
980 985 990

Lys Glu Gly Asn Tyr Tyr Arg Ile Thr Ser Arg Ile Met Phe Glu Pro
995 1000 1005

Arg Ile Pro Thr Met Ala Asp Phe Val Gln Ile Glu Asn Cys Asn
1010 1015 1020

Val Thr Phe Val Asn Ile Ser Arg Ser Glu Leu Gln Thr Ile Val
1025 1030 1035

Pro Glu Tyr Ile Asp Val Asn Lys Thr Leu Gln Glu Leu Ser Tyr
1040 1045 1050

Lys Leu Pro Asn Tyr Thr Val Pro Asp Leu Val Val Glu Gln Tyr
1055 1060 1065

Asn Gln Thr Ile Leu Asn Leu Thr Ser Glu Ile Ser Thr Leu Glu
1070 1075 1080

Asn Lys Ser Ala Glu Leu Asn Tyr Thr Val Gln Lys Leu Gln Thr
1085 1090 1095

Leu Ile Asp Asn Ile Asn Ser Thr Leu Val Asp Leu Lys Trp Leu
1100 1105 1110

Asn Arg Val Glu Thr Tyr Ile Lys Trp Pro Trp Trp Val Trp Leu
1115 1120 1125

Cys Ile Ser Val Val Leu Ile Phe Val Val Ser Met Leu Leu Leu
1130 1135 1140

Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys
1145 1150 1155

Ile

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Gly Asp Leu Asn Cys Thr Leu Asp Pro Arg Leu Lys Gly Ser Phe Asn
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Asn Arg Asp Thr Gly Pro Pro Ser Ile Ser Ile Asp Thr Val Asp Val
35 40 45

Thr Asn Gly Leu Gly Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn
50 55 60

Thr Thr Leu Phe Leu Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr
65 70 75 80

Arg Asn Met Ala Leu Lys Gly Thr Asp Leu Leu Ser Thr Leu Trp Phe
85 90 95

Lys Pro Pro Phe Leu Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val
100 105 110

Lys Asn Thr Lys Val Phe Lys Asp Gly Val Met Tyr Ser Glu Phe Pro
115 120 125

Ala Ile Thr Ile Gly Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val
130 135 140

Val Gln Pro Arg Thr Ile Asn Ser Thr Gln Asp Gly Val Asn Lys Leu
145 150 155 160

Gln Gly Leu Leu Glu Val Ser Val Cys Gln Tyr Asn Met Cys Glu Tyr
165 170 175

Pro His Thr Ile Cys His Pro Asn Leu Gly Asn His Phe Lys Glu Leu
180 185 190

Trp His Tyr Asp Thr Gly Val Val Ser Cys Leu Tyr Lys Arg Asn Phe
195 200 205

Thr Tyr Asp Val Asn Ala Thr Tyr Leu Tyr Phe His Phe Tyr Gln Glu
210 215 220

Gly Gly Thr Phe Tyr Ala Tyr Phe Thr Asp Thr Gly Phe Val Thr Lys
225 230 235 240

Phe Leu Phe Asn Val Tyr Leu Gly Met Ala Leu Ser His Tyr Tyr Val
245 250 255

Met Pro Leu Thr Cys Ile Arg Arg Pro Lys Asp Gly Phe Ser Leu Glu

260 265 270

Tyr Trp Val Thr Pro Leu Thr Pro Arg Gln Tyr Leu Leu Ala Phe Asn
275 280 285

Gln Asp Gly Ile Ile Phe Asn Ala Val Asp Cys Met Ser Asp Phe Met
290 295 300

Ser Glu Ile Lys Cys Lys Thr Gln Ser Ile Ala Pro Pro Thr Gly Val
305 310 315 320

Tyr Glu Leu Asn Gly Tyr Thr Val Gln Pro Val Ala Asp Val Tyr Arg
325 330 335

Arg Lys Pro Asp Leu Pro Asn Cys Asn Ile Glu Ala Trp Leu Asn Asp
340 345 350

Lys Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Lys Thr Phe Ser Asn
355 360 365

Cys Asn Phe Asn Met Ser Ser Leu Met Ser Phe Ile Gln Ala Asp Ser
370 375 380

Phe Thr Cys Asn Asn Ile Asp Ala Ala Lys Ile Tyr Gly Met Cys Phe
385 390 395 400

Ser Ser Ile Thr Ile Asp Lys Phe Ala Ile Pro Asn Arg Arg Lys Val
405 410 415

Asp Leu Gln Leu Gly Asn Leu Gly Tyr Leu Gln Ser Ser Asn Tyr Arg
420 425 430

Ile Asp Thr Thr Ala Thr Ser Cys Gln Leu Tyr Tyr Asn Leu Pro Ala
435 440 445

Ala Asn Val Ser Val Ser Arg Phe Asn Pro Ser Thr Trp Asn Lys Arg
450 455 460

Phe Gly Phe Ile Glu Asp Ser Val Phe Val Pro Gln Pro Thr Gly Val
465 470 475 480

Phe Thr Asn His Ser Val Val Tyr Ala Gln His Cys Phe Lys Ala Pro
485 490 495

Lys Asn Phe Cys Pro Cys Ser Ser Cys Ser Cys Pro Gly Lys Asn Asn
500 505 510

Gly Ile Gly Thr Cys Pro Ala Gly Thr Asn Ser Leu Thr Cys Asp Asn
515 520 525

Leu Cys Thr Leu Asp Pro Ile Thr Leu Lys Ala Pro Asp Thr Tyr Lys
530 535 540

Cys Pro Gln Ser Lys Ser Leu Val Gly Ile Gly Glu His Cys Ser Gly
545 550 555 560

Leu Ala Val Lys Ser Asp Tyr Cys Gly Asn Asn Ser Cys Thr Cys Gln

565 570 575

Pro Gln Ala Phe Leu Gly Trp Ser Ala Asp Ser Cys Leu Gln Gly Asp
580 585 590

Lys Cys Asn Ile Phe Ala Asn Phe Ile Leu His Asp Val Asn Asn Gly
595 600 605

Leu Thr Cys Ser Thr Asp Leu Gln Lys Ala Asn Thr Glu Ile Glu Leu
610 615 620

Gly Val Cys Val Asn Tyr Asp Leu Tyr Gly Ile Ser Gly Gln Gly Ile
625 630 635 640

Phe Val Glu Val Asn Ala Thr Tyr Tyr Asn Ser Trp Gln Asn Leu Leu
645 650 655

Tyr Asp Ser Asn Gly Asn Leu Tyr Gly Phe Arg Asp Tyr Ile Thr Asn
660 665 670

Arg Thr Phe Met Ile His Ser Cys Tyr Ser Gly Arg Val Ser Ala Ala
675 680 685

Tyr His Ala Asn Ser Ser Glu Pro Ala Leu Leu Phe Arg Asn Ile Lys
690 695 700

Cys Asn Tyr Val Phe Asn Asn Ser Leu Thr Arg Gln Leu Gln Pro Ile
705 710 715 720

Asn Tyr Ser Phe Asp Ser Tyr Leu Gly Cys Val Val Asn Ala Tyr Asn
725 730 735

Ser Thr Ala Ile Ser Val Gln Thr Cys Asp Leu Thr Val Gly Ser Gly
740 745 750

Tyr Cys Val Asp Tyr Ser Lys Asn Arg Arg Ser Arg Arg Ala Ile Thr
755 760 765

Thr Gly Tyr Arg Phe Thr Asn Phe Glu Pro Phe Thr Val Asn Ser Val
770 775 780

Asn Asp Ser Leu Glu Pro Val Gly Gly Leu Tyr Glu Ile Gln Ile Pro
785 790 795 800

Ser Glu Phe Thr Ile Gly Asn Met Glu Glu Phe Ile Gln Thr Ser Ser
805 810 815

Pro Lys Val Thr Ile Asp Cys Ala Ala Phe Val Cys Gly Asp Tyr Ala
820 825 830

Ala Cys Lys Leu Gln Leu Val Glu Tyr Gly Ser Phe Cys Asp Asn Ile
835 840 845

Asn Ala Ile Leu Thr Glu Val Asn Glu Leu Leu Asp Thr Thr Gln Leu
850 855 860

Gln Val Ala Asn Ser Leu Met Asn Gly Val Thr Leu Ser Thr Lys Leu

865 870 875 880

Lys Asp Gly Val Asn Phe Asn Val Asp Asp Ile Asn Phe Ser Pro Val
885 890 895

Leu Gly Cys Leu Gly Ser Glu Cys Ser Lys Ala Ser Ser Arg Ser Ala
900 905 910

Ile Glu Asp Leu Leu Phe Asp Lys Val Lys Leu Ser Asp Val Gly Phe
915 920 925

Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly Ala Glu Ile Arg Asp Leu
930 935 940

Ile Cys Val Gln Ser Tyr Lys Gly Ile Lys Val Leu Pro Pro Leu Leu
945 950 955 960

Ser Glu Asn Gln Ile Ser Gly Tyr Thr Leu Ala Ala Thr Ser Ala Ser
965 970 975

Leu Phe Pro Pro Trp Thr Ala Ala Ala Gly Val Pro Phe Tyr Leu Asn
980 985 990

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

Gln Asn Gln Lys Leu Ile Ala Asn Ala Phe Asn Asn Ala Leu His
1010 1015 1020

Ala Ile Gln Gln Gly Phe Asp Ala Thr Asn Ser Ala Leu Val Lys
1025 1030 1035

Ile Gln Ala Val Val Asn Ala Asn Ala Glu Ala Leu Asn Asn Leu
1040 1045 1050

Leu Gln Gln Leu Ser Asn Arg Phe Gly Ala Ile Ser Ala Ser Leu
1055 1060 1065

Gln Glu Ile Leu Ser Arg Leu Asp Ala Leu Glu Ala Glu Ala Gln
1070 1075 1080

Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr Ala Leu Asn Ala Tyr
1085 1090 1095

Val Ser Gln Gln Leu Ser Asp Ser Thr Leu Val Lys Phe Ser Ala
1100 1105 1110

Ala Gln Ala Met Glu Lys Val Asn Glu Cys Val Lys Ser Gln Ser
1115 1120 1125

Ser Arg Ile Asn Phe Cys Gly Asn Gly Asn His Ile Ile Ser Leu
1130 1135 1140

Val Gln Asn Ala Pro Tyr Gly Leu Tyr Phe Ile His Phe Asn Tyr
1145 1150 1155

Val Pro Thr Lys Tyr Val Thr Ala Lys Val Ser Pro Gly Leu Cys

1160 1165 1170

Ile Ala Gly Asn Arg Gly Ile Ala Pro Lys Ser Gly Tyr Phe Val
1175 1180 1185

Asn Val Asn Asn Thr Trp Met Tyr Thr Gly Ser Gly Tyr Tyr Tyr
1190 1195 1200

Pro Glu Pro Ile Thr Glu Asn Asn Val Val Val Met Ser Thr Cys
1205 1210 1215

Ala Val Asn Tyr Thr Lys Ala Pro Tyr Val Met Leu Asn Thr Ser
1220 1225 1230

Ile Pro Asn Leu Pro Asp Phe Lys Glu Glu Leu Asp Gln Trp Phe
1235 1240 1245

Lys Asn Gln Thr Ser Val Ala Pro Asp Leu Ser Leu Asp Tyr Ile
1250 1255 1260

Asn Val Thr Phe Leu Asp Leu Gln Val Glu Met Asn Arg Leu Gln
1265 1270 1275

Glu Ala Ile Lys Val Leu Asn His Ser Tyr Ile Asn Leu Lys Asp
1280 1285 1290

Ile Gly Thr Tyr Glu Tyr Tyr Val Lys Trp Pro Trp Tyr Val Trp
1295 1300 1305

Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val Leu Leu Phe
1310 1315 1320

Phe Ile Cys Cys Cys Thr Gly Cys Gly Thr Ser Cys Phe Lys Lys
1325 1330 1335

Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly Tyr Gln Glu Leu Val
1340 1345 1350

Ile Lys Thr Ser His Asp Asp
1355 1360

<210> 159
<211> 1173
<212> PRT
<213> 229E 冠狀病毒

<400> 159

Met Phe Val Leu Leu Val Ala Tyr Ala Leu Leu His Ile Ala Gly Cys
1 5 10 15

Gln Thr Thr Asn Gly Leu Asn Thr Ser Tyr Ser Val Cys Asn Gly Cys
20 25 30

Val Gly Tyr Ser Glu Asn Val Phe Ala Val Glu Ser Gly Gly Tyr Ile
35 40 45

Pro Ser Asp Phe Ala Phe Asn Asn Trp Phe Leu Leu Thr Asn Thr Ser
50 55 60

Ser Val Val Asp Gly Val Val Arg Ser Phe Gln Pro Leu Leu Leu Asn
65 70 75 80

Cys Leu Trp Ser Val Ser Gly Leu Arg Phe Thr Thr Gly Phe Val Tyr
85 90 95

Phe Asn Gly Thr Gly Arg Gly Asp Cys Lys Gly Phe Ser Ser Asp Val
100 105 110

Leu Ser Asp Val Ile Arg Tyr Asn Leu Asn Phe Glu Glu Asn Leu Arg
115 120 125

Arg Gly Thr Ile Leu Phe Lys Thr Ser Tyr Gly Val Val Val Phe Tyr
130 135 140

Cys Thr Asn Asn Thr Leu Val Ser Gly Asp Ala His Ile Pro Phe Gly
145 150 155 160

Thr Val Leu Gly Asn Phe Tyr Cys Phe Val Asn Thr Thr Ile Gly Asn
165 170 175

Glu Thr Thr Ser Ala Phe Val Gly Ala Leu Pro Lys Thr Val Arg Glu
180 185 190

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

Phe Thr Leu Gly Asn Val Glu Ala Val Asn Phe Asn Val Thr Thr Ala
210 215 220

Glu Thr Thr Asp Phe Cys Thr Val Ala Leu Ala Ser Tyr Ala Asp Val
225 230 235 240

Leu Val Asn Val Ser Gln Thr Ser Ile Ala Asn Ile Ile Tyr Cys Asn
245 250 255

Ser Val Ile Asn Arg Leu Arg Cys Asp Gln Leu Ser Phe Asp Val Pro
260 265 270

Asp Gly Phe Tyr Ser Thr Ser Pro Ile Gln Ser Val Glu Leu Pro Val
275 280 285

Ser Ile Val Ser Leu Pro Val Tyr His Lys His Thr Phe Ile Val Leu
290 295 300

Tyr Val Asp Phe Lys Pro Gln Ser Gly Gly Gly Lys Cys Phe Asn Cys
305 310 315 320

Tyr Pro Ala Gly Val Asn Ile Thr Leu Ala Asn Phe Asn Glu Thr Lys
325 330 335

Gly Pro Leu Cys Val Asp Thr Ser His Phe Thr Thr Lys Tyr Val Ala
340 345 350

Val Tyr Ala Asn Val Gly Arg Trp Ser Ala Ser Ile Asn Thr Gly Asn
355 360 365

Cys Pro Phe Ser Phe Gly Lys Val Asn Asn Phe Val Lys Phe Gly Ser
370 375 380

Val Cys Phe Ser Leu Lys Asp Ile Pro Gly Gly Cys Ala Met Pro Ile
385 390 395 400

Val Ala Asn Trp Ala Tyr Ser Lys Tyr Tyr Thr Ile Gly Ser Leu Tyr
405 410 415

Val Ser Trp Ser Asp Gly Asp Gly Ile Thr Gly Val Pro Gln Pro Val
420 425 430

Glu Gly Val Ser Ser Phe Met Asn Val Thr Leu Asp Lys Cys Thr Lys
435 440 445

Tyr Asn Ile Tyr Asp Val Ser Gly Val Gly Val Ile Arg Val Ser Asn
450 455 460

Asp Thr Phe Leu Asn Gly Ile Thr Tyr Thr Ser Thr Ser Gly Asn Leu
465 470 475 480

Leu Gly Phe Lys Asp Val Thr Lys Gly Thr Ile Tyr Ser Ile Thr Pro
485 490 495

Cys Asn Pro Pro Asp Gln Leu Val Val Tyr Gln Gln Ala Val Val Gly
500 505 510

Ala Met Leu Ser Glu Asn Phe Thr Ser Tyr Gly Phe Ser Asn Val Val
515 520 525

Glu Leu Pro Lys Phe Phe Tyr Ala Ser Asn Gly Thr Tyr Asn Cys Thr
530 535 540

Asp Ala Val Leu Thr Tyr Ser Ser Phe Gly Val Cys Ala Asp Gly Ser
545 550 555 560

Ile Ile Ala Val Gln Pro Arg Asn Val Ser Tyr Asp Ser Val Ser Ala
565 570 575

Ile Val Thr Ala Asn Leu Ser Ile Pro Ser Asn Trp Thr Thr Ser Val
580 585 590

Gln Val Glu Tyr Leu Gln Ile Thr Ser Thr Pro Ile Val Val Asp Cys
595 600 605

Ser Thr Tyr Val Cys Asn Gly Asn Val Arg Cys Val Glu Leu Leu Lys
610 615 620

Gln Tyr Thr Ser Ala Cys Lys Thr Ile Glu Asp Ala Leu Arg Asn Ser
625 630 635 640

Ala Arg Leu Glu Ser Ala Asp Val Ser Glu Met Leu Thr Phe Asp Lys
645 650 655

Lys Ala Phe Thr Leu Ala Asn Val Ser Ser Phe Gly Asp Tyr Asn Leu
660 665 670

Ser Ser Val Ile Pro Ser Leu Pro Thr Ser Gly Ser Arg Val Ala Gly
675 680 685

Arg Ser Ala Ile Glu Asp Ile Leu Phe Ser Lys Leu Val Thr Ser Gly
690 695 700

Leu Gly Thr Val Asp Ala Asp Tyr Lys Lys Cys Thr Lys Gly Leu Ser
705 710 715 720

Ile Ala Asp Leu Ala Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu
725 730 735

Pro Gly Val Ala Asp Ala Glu Arg Met Ala Met Tyr Thr Gly Ser Leu
740 745 750

Ile Gly Gly Ile Ala Leu Gly Gly Leu Thr Ser Ala Val Ser Ile Pro
755 760 765

Phe Ser Leu Ala Ile Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln Thr
770 775 780

Asp Val Leu Gln Glu Asn Gln Lys Ile Leu Ala Ala Ser Phe Asn Lys
785 790 795 800

Ala Met Thr Asn Ile Val Asp Ala Phe Thr Gly Val Asn Asp Ala Ile
805 810 815

Thr Gln Thr Ser Gln Ala Leu Gln Thr Val Ala Thr Ala Leu Asn Lys
820 825 830

Ile Gln Asp Val Val Asn Gln Gln Gly Asn Ser Leu Asn His Leu Thr
835 840 845

Ser Gln Leu Arg Gln Asn Phe Gln Ala Ile Ser Ser Ser Ile Gln Ala
850 855 860

Ile Tyr Asp Arg Leu Asp Thr Ile Gln Ala Asp Gln Gln Val Asp Arg
865 870 875 880

Leu Ile Thr Gly Arg Leu Ala Ala Leu Asn Val Phe Val Ser His Thr
885 890 895

Leu Thr Lys Tyr Thr Glu Val Arg Ala Ser Arg Gln Leu Ala Gln Gln
900 905 910

Lys Val Asn Glu Cys Val Lys Ser Gln Ser Lys Arg Tyr Gly Phe Cys
915 920 925

Gly Asn Gly Thr His Ile Phe Ser Ile Val Asn Ala Ala Pro Glu Gly
930 935 940

Leu Val Phe Leu His Thr Val Leu Leu Pro Thr Gln Tyr Lys Asp Val
945 950 955 960

Glu Ala Trp Ser Gly Leu Cys Val Asp Gly Thr Asn Gly Tyr Val Leu
965 970 975

Arg Gln Pro Asn Leu Ala Leu Tyr Lys Glu Gly Asn Tyr Tyr Arg Ile
980 985 990

Thr Ser Arg Ile Met Phe Glu Pro Arg Ile Pro Thr Met Ala Asp Phe
995 1000 1005

Val Gln Ile Glu Asn Cys Asn Val Thr Phe Val Asn Ile Ser Arg
1010 1015 1020

Ser Glu Leu Gln Thr Ile Val Pro Glu Tyr Ile Asp Val Asn Lys
1025 1030 1035

Thr Leu Gln Glu Leu Ser Tyr Lys Leu Pro Asn Tyr Thr Val Pro
1040 1045 1050

Asp Leu Val Val Glu Gln Tyr Asn Gln Thr Ile Leu Asn Leu Thr
1055 1060 1065

Ser Glu Ile Ser Thr Leu Glu Asn Lys Ser Ala Glu Leu Asn Tyr
1070 1075 1080

Thr Val Gln Lys Leu Gln Thr Leu Ile Asp Asn Ile Asn Ser Thr
1085 1090 1095

Leu Val Asp Leu Lys Trp Leu Asn Arg Val Glu Thr Tyr Ile Lys
1100 1105 1110

Trp Pro Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe
1115 1120 1125

Val Val Ser Met Leu Leu Leu Cys Cys Cys Ser Thr Gly Cys Cys
1130 1135 1140

Gly Phe Phe Ser Cys Phe Ala Ser Ser Ile Arg Gly Cys Cys Glu
1145 1150 1155

Ser Thr Lys Leu Pro Tyr Tyr Asp Val Glu Lys Ile His Ile Gln
1160 1165 1170

<210> 160
<211> 1346
<212> PRT
<213> OC43 冠狀病毒

<400> 160

Val Ile Gly Asp Leu Asn Cys Thr Leu Asp Pro Arg Leu Lys Gly Ser
1 5 10 15

Phe Asn Asn Arg Asp Thr Gly Pro Pro Ser Ile Ser Ile Asp Thr Val
20 25 30

Asp Val Thr Asn Gly Leu Gly Thr Tyr Tyr Val Leu Asp Arg Val Tyr
35 40 45

Leu Asn Thr Thr Leu Phe Leu Asn Gly Tyr Tyr Pro Thr Ser Gly Ser
50 55 60

Thr Tyr Arg Asn Met Ala Leu Lys Gly Thr Asp Leu Leu Ser Thr Leu
65 70 75 80

Trp Phe Lys Pro Pro Phe Leu Ser Asp Phe Ile Asn Gly Ile Phe Ala
85 90 95

Lys Val Lys Asn Thr Lys Val Phe Lys Asp Gly Val Met Tyr Ser Glu
100 105 110

Phe Pro Ala Ile Thr Ile Gly Ser Thr Phe Val Asn Thr Ser Tyr Ser
115 120 125

Val Val Val Gln Pro Arg Thr Ile Asn Ser Thr Gln Asp Gly Val Asn
130 135 140

Lys Leu Gln Gly Leu Leu Glu Val Ser Val Cys Gln Tyr Asn Met Cys
145 150 155 160

Glu Tyr Pro His Thr Ile Cys His Pro Asn Leu Gly Asn His Phe Lys
165 170 175

Glu Leu Trp His Tyr Asp Thr Gly Val Val Ser Cys Leu Tyr Lys Arg
180 185 190

Asn Phe Thr Tyr Asp Val Asn Ala Thr Tyr Leu Tyr Phe His Phe Tyr
195 200 205

Gln Glu Gly Gly Thr Phe Tyr Ala Tyr Phe Thr Asp Thr Gly Phe Val

210 215 220

Thr Lys Phe Leu Phe Asn Val Tyr Leu Gly Met Ala Leu Ser His Tyr
225 230 235 240

Tyr Val Met Pro Leu Thr Cys Ile Arg Arg Pro Lys Asp Gly Phe Ser
245 250 255

Leu Glu Tyr Trp Val Thr Pro Leu Thr Pro Arg Gln Tyr Leu Leu Ala
260 265 270

Phe Asn Gln Asp Gly Ile Ile Phe Asn Ala Val Asp Cys Met Ser Asp
275 280 285

Phe Met Ser Glu Ile Lys Cys Lys Thr Gln Ser Ile Ala Pro Pro Thr
290 295 300

Gly Val Tyr Glu Leu Asn Gly Tyr Thr Val Gln Pro Val Ala Asp Val
305 310 315 320

Tyr Arg Arg Lys Pro Asp Leu Pro Asn Cys Asn Ile Glu Ala Trp Leu
325 330 335

Asn Asp Lys Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Lys Thr Phe
340 345 350

Ser Asn Cys Asn Phe Asn Met Ser Ser Leu Met Ser Phe Ile Gln Ala
355 360 365

Asp Ser Phe Thr Cys Asn Asn Ile Asp Ala Ala Lys Ile Tyr Gly Met
370 375 380

Cys Phe Ser Ser Ile Thr Ile Asp Lys Phe Ala Ile Pro Asn Arg Arg
385 390 395 400

Lys Val Asp Leu Gln Leu Gly Asn Leu Gly Tyr Leu Gln Ser Ser Asn
405 410 415

Tyr Arg Ile Asp Thr Thr Ala Thr Ser Cys Gln Leu Tyr Tyr Asn Leu
420 425 430

Pro Ala Ala Asn Val Ser Val Ser Arg Phe Asn Pro Ser Thr Trp Asn
435 440 445

Lys Arg Phe Gly Phe Ile Glu Asp Ser Val Phe Val Pro Gln Pro Thr
450 455 460

Gly Val Phe Thr Asn His Ser Val Val Tyr Ala Gln His Cys Phe Lys
465 470 475 480

Ala Pro Lys Asn Phe Cys Pro Cys Ser Ser Cys Ser Cys Pro Gly Lys
485 490 495

Asn Asn Gly Ile Gly Thr Cys Pro Ala Gly Thr Asn Ser Leu Thr Cys
500 505 510

Asp Asn Leu Cys Thr Leu Asp Pro Ile Thr Leu Lys Ala Pro Asp Thr

515 520 525

Tyr Lys Cys Pro Gln Ser Lys Ser Leu Val Gly Ile Gly Glu His Cys
530 535 540

Ser Gly Leu Ala Val Lys Ser Asp Tyr Cys Gly Asn Asn Ser Cys Thr
545 550 555 560

Cys Gln Pro Gln Ala Phe Leu Gly Trp Ser Ala Asp Ser Cys Leu Gln
565 570 575

Gly Asp Lys Cys Asn Ile Phe Ala Asn Phe Ile Leu His Asp Val Asn
580 585 590

Asn Gly Leu Thr Cys Ser Thr Asp Leu Gln Lys Ala Asn Thr Glu Ile
595 600 605

Glu Leu Gly Val Cys Val Asn Tyr Asp Leu Tyr Gly Ile Ser Gly Gln
610 615 620

Gly Ile Phe Val Glu Val Asn Ala Thr Tyr Tyr Asn Ser Trp Gln Asn
625 630 635 640

Leu Leu Tyr Asp Ser Asn Gly Asn Leu Tyr Gly Phe Arg Asp Tyr Ile
645 650 655

Thr Asn Arg Thr Phe Met Ile His Ser Cys Tyr Ser Gly Arg Val Ser
660 665 670

Ala Ala Tyr His Ala Asn Ser Ser Glu Pro Ala Leu Leu Phe Arg Asn
675 680 685

Ile Lys Cys Asn Tyr Val Phe Asn Asn Ser Leu Thr Arg Gln Leu Gln
690 695 700

Pro Ile Asn Tyr Ser Phe Asp Ser Tyr Leu Gly Cys Val Val Asn Ala
705 710 715 720

Tyr Asn Ser Thr Ala Ile Ser Val Gln Thr Cys Asp Leu Thr Val Gly
725 730 735

Ser Gly Tyr Cys Val Asp Tyr Ser Lys Asn Arg Arg Ser Arg Arg Ala
740 745 750

Ile Thr Thr Gly Tyr Arg Phe Thr Asn Phe Glu Pro Phe Thr Val Asn
755 760 765

Ser Val Asn Asp Ser Leu Glu Pro Val Gly Gly Leu Tyr Glu Ile Gln
770 775 780

Ile Pro Ser Glu Phe Thr Ile Gly Asn Met Glu Glu Phe Ile Gln Thr
785 790 795 800

Ser Ser Pro Lys Val Thr Ile Asp Cys Ala Ala Phe Val Cys Gly Asp
805 810 815

Tyr Ala Ala Cys Lys Leu Gln Leu Val Glu Tyr Gly Ser Phe Cys Asp

820 825 830

Asn Ile Asn Ala Ile Leu Thr Glu Val Asn Glu Leu Leu Asp Thr Thr
835 840 845

Gln Leu Gln Val Ala Asn Ser Leu Met Asn Gly Val Thr Leu Ser Thr
850 855 860

Lys Leu Lys Asp Gly Val Asn Phe Asn Val Asp Asp Ile Asn Phe Ser
865 870 875 880

Pro Val Leu Gly Cys Leu Gly Ser Glu Cys Ser Lys Ala Ser Ser Arg
885 890 895

Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Lys Leu Ser Asp Val
900 905 910

Gly Phe Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly Ala Glu Ile Arg
915 920 925

Asp Leu Ile Cys Val Gln Ser Tyr Lys Gly Ile Lys Val Leu Pro Pro
930 935 940

Leu Leu Ser Glu Asn Gln Ile Ser Gly Tyr Thr Leu Ala Ala Thr Ser
945 950 955 960

Ala Ser Leu Phe Pro Pro Trp Thr Ala Ala Ala Gly Val Pro Phe Tyr
965 970 975

Leu Asn Val Gln Tyr Arg Ile Asn Gly Leu Gly Val Thr Met Asp Val
980 985 990

Leu Ser Gln Asn Gln Lys Leu Ile Ala Asn Ala Phe Asn Asn Ala Leu
995 1000 1005

His Ala Ile Gln Gln Gly Phe Asp Ala Thr Asn Ser Ala Leu Val
1010 1015 1020

Lys Ile Gln Ala Val Val Asn Ala Asn Ala Glu Ala Leu Asn Asn
1025 1030 1035

Leu Leu Gln Gln Leu Ser Asn Arg Phe Gly Ala Ile Ser Ala Ser
1040 1045 1050

Leu Gln Glu Ile Leu Ser Arg Leu Asp Ala Leu Glu Ala Glu Ala
1055 1060 1065

Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr Ala Leu Asn Ala
1070 1075 1080

Tyr Val Ser Gln Gln Leu Ser Asp Ser Thr Leu Val Lys Phe Ser
1085 1090 1095

Ala Ala Gln Ala Met Glu Lys Val Asn Glu Cys Val Lys Ser Gln
1100 1105 1110

Ser Ser Arg Ile Asn Phe Cys Gly Asn Gly Asn His Ile Ile Ser

1115 1120 1125

Leu Val Gln Asn Ala Pro Tyr Gly Leu Tyr Phe Ile His Phe Asn
1130 1135 1140

Tyr Val Pro Thr Lys Tyr Val Thr Ala Lys Val Ser Pro Gly Leu
1145 1150 1155

Cys Ile Ala Gly Asn Arg Gly Ile Ala Pro Lys Ser Gly Tyr Phe
1160 1165 1170

Val Asn Val Asn Asn Thr Trp Met Tyr Thr Gly Ser Gly Tyr Tyr
1175 1180 1185

Tyr Pro Glu Pro Ile Thr Glu Asn Asn Val Val Val Met Ser Thr
1190 1195 1200

Cys Ala Val Asn Tyr Thr Lys Ala Pro Tyr Val Met Leu Asn Thr
1205 1210 1215

Ser Ile Pro Asn Leu Pro Asp Phe Lys Glu Glu Leu Asp Gln Trp
1220 1225 1230

Phe Lys Asn Gln Thr Ser Val Ala Pro Asp Leu Ser Leu Asp Tyr
1235 1240 1245

Ile Asn Val Thr Phe Leu Asp Leu Gln Val Glu Met Asn Arg Leu
1250 1255 1260

Gln Glu Ala Ile Lys Val Leu Asn His Ser Tyr Ile Asn Leu Lys
1265 1270 1275

Asp Ile Gly Thr Tyr Glu Tyr Tyr Val Lys Trp Pro Trp Tyr Val
1280 1285 1290

Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val Leu Leu
1295 1300 1305

Phe Phe Ile Cys Cys Cys Thr Gly Cys Gly Thr Ser Cys Phe Lys
1310 1315 1320

Lys Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly Tyr Gln Glu Leu
1325 1330 1335

Val Ile Lys Thr Ser His Asp Asp
1340 1345

<210> 161
<211> 1157
<212> PRT
<213> 229E 冠狀病毒

<400> 161

Gln Thr Thr Asn Gly Leu Asn Thr Ser Tyr Ser Val Cys Asn Gly Cys
1 5 10 15

Val Gly Tyr Ser Glu Asn Val Phe Ala Val Glu Ser Gly Gly Tyr Ile
20 25 30

Pro Ser Asp Phe Ala Phe Asn Asn Trp Phe Leu Leu Thr Asn Thr Ser
35 40 45

Ser Val Val Asp Gly Val Val Arg Ser Phe Gln Pro Leu Leu Leu Asn
50 55 60

Cys Leu Trp Ser Val Ser Gly Leu Arg Phe Thr Thr Gly Phe Val Tyr
65 70 75 80

Phe Asn Gly Thr Gly Arg Gly Asp Cys Lys Gly Phe Ser Ser Asp Val
85 90 95

Leu Ser Asp Val Ile Arg Tyr Asn Leu Asn Phe Glu Glu Asn Leu Arg
100 105 110

Arg Gly Thr Ile Leu Phe Lys Thr Ser Tyr Gly Val Val Val Phe Tyr
115 120 125

Cys Thr Asn Asn Thr Leu Val Ser Gly Asp Ala His Ile Pro Phe Gly
130 135 140

Thr Val Leu Gly Asn Phe Tyr Cys Phe Val Asn Thr Thr Ile Gly Asn
145 150 155 160

Glu Thr Thr Ser Ala Phe Val Gly Ala Leu Pro Lys Thr Val Arg Glu
165 170 175

Phe Val Ile Ser Arg Thr Gly His Phe Tyr Ile Asn Gly Tyr Arg Tyr
180 185 190

Phe Thr Leu Gly Asn Val Glu Ala Val Asn Phe Asn Val Thr Thr Ala
195 200 205

Glu Thr Thr Asp Phe Cys Thr Val Ala Leu Ala Ser Tyr Ala Asp Val
210 215 220

Leu Val Asn Val Ser Gln Thr Ser Ile Ala Asn Ile Ile Tyr Cys Asn
225 230 235 240

Ser Val Ile Asn Arg Leu Arg Cys Asp Gln Leu Ser Phe Asp Val Pro
245 250 255

Asp Gly Phe Tyr Ser Thr Ser Pro Ile Gln Ser Val Glu Leu Pro Val
260 265 270

Ser Ile Val Ser Leu Pro Val Tyr His Lys His Thr Phe Ile Val Leu
275 280 285

Tyr Val Asp Phe Lys Pro Gln Ser Gly Gly Gly Lys Cys Phe Asn Cys
290 295 300

Tyr Pro Ala Gly Val Asn Ile Thr Leu Ala Asn Phe Asn Glu Thr Lys
305 310 315 320

Gly Pro Leu Cys Val Asp Thr Ser His Phe Thr Thr Lys Tyr Val Ala
325 330 335

Val Tyr Ala Asn Val Gly Arg Trp Ser Ala Ser Ile Asn Thr Gly Asn
340 345 350

Cys Pro Phe Ser Phe Gly Lys Val Asn Asn Phe Val Lys Phe Gly Ser
355 360 365

Val Cys Phe Ser Leu Lys Asp Ile Pro Gly Gly Cys Ala Met Pro Ile
370 375 380

Val Ala Asn Trp Ala Tyr Ser Lys Tyr Tyr Thr Ile Gly Ser Leu Tyr
385 390 395 400

Val Ser Trp Ser Asp Gly Asp Gly Ile Thr Gly Val Pro Gln Pro Val
405 410 415

Glu Gly Val Ser Ser Phe Met Asn Val Thr Leu Asp Lys Cys Thr Lys
420 425 430

Tyr Asn Ile Tyr Asp Val Ser Gly Val Gly Val Ile Arg Val Ser Asn
435 440 445

Asp Thr Phe Leu Asn Gly Ile Thr Tyr Thr Ser Thr Ser Gly Asn Leu
450 455 460

Leu Gly Phe Lys Asp Val Thr Lys Gly Thr Ile Tyr Ser Ile Thr Pro
465 470 475 480

Cys Asn Pro Pro Asp Gln Leu Val Val Tyr Gln Gln Ala Val Val Gly
485 490 495

Ala Met Leu Ser Glu Asn Phe Thr Ser Tyr Gly Phe Ser Asn Val Val
500 505 510

Glu Leu Pro Lys Phe Phe Tyr Ala Ser Asn Gly Thr Tyr Asn Cys Thr
515 520 525

Asp Ala Val Leu Thr Tyr Ser Ser Phe Gly Val Cys Ala Asp Gly Ser
530 535 540

Ile Ile Ala Val Gln Pro Arg Asn Val Ser Tyr Asp Ser Val Ser Ala
545 550 555 560

Ile Val Thr Ala Asn Leu Ser Ile Pro Ser Asn Trp Thr Thr Ser Val
565 570 575

Gln Val Glu Tyr Leu Gln Ile Thr Ser Thr Pro Ile Val Val Asp Cys
580 585 590

Ser Thr Tyr Val Cys Asn Gly Asn Val Arg Cys Val Glu Leu Leu Lys
595 600 605

Gln Tyr Thr Ser Ala Cys Lys Thr Ile Glu Asp Ala Leu Arg Asn Ser
610 615 620

Ala Arg Leu Glu Ser Ala Asp Val Ser Glu Met Leu Thr Phe Asp Lys
625 630 635 640

Lys Ala Phe Thr Leu Ala Asn Val Ser Ser Phe Gly Asp Tyr Asn Leu
645 650 655

Ser Ser Val Ile Pro Ser Leu Pro Thr Ser Gly Ser Arg Val Ala Gly
660 665 670

Arg Ser Ala Ile Glu Asp Ile Leu Phe Ser Lys Leu Val Thr Ser Gly
675 680 685

Leu Gly Thr Val Asp Ala Asp Tyr Lys Lys Cys Thr Lys Gly Leu Ser
690 695 700

Ile Ala Asp Leu Ala Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu
705 710 715 720

Pro Gly Val Ala Asp Ala Glu Arg Met Ala Met Tyr Thr Gly Ser Leu
725 730 735

Ile Gly Gly Ile Ala Leu Gly Gly Leu Thr Ser Ala Val Ser Ile Pro
740 745 750

Phe Ser Leu Ala Ile Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln Thr
755 760 765

Asp Val Leu Gln Glu Asn Gln Lys Ile Leu Ala Ala Ser Phe Asn Lys
770 775 780

Ala Met Thr Asn Ile Val Asp Ala Phe Thr Gly Val Asn Asp Ala Ile
785 790 795 800

Thr Gln Thr Ser Gln Ala Leu Gln Thr Val Ala Thr Ala Leu Asn Lys
805 810 815

Ile Gln Asp Val Val Asn Gln Gln Gly Asn Ser Leu Asn His Leu Thr
820 825 830

Ser Gln Leu Arg Gln Asn Phe Gln Ala Ile Ser Ser Ser Ile Gln Ala
835 840 845

Ile Tyr Asp Arg Leu Asp Thr Ile Gln Ala Asp Gln Gln Val Asp Arg
850 855 860

Leu Ile Thr Gly Arg Leu Ala Ala Leu Asn Val Phe Val Ser His Thr
865 870 875 880

Leu Thr Lys Tyr Thr Glu Val Arg Ala Ser Arg Gln Leu Ala Gln Gln
885 890 895

Lys Val Asn Glu Cys Val Lys Ser Gln Ser Lys Arg Tyr Gly Phe Cys
900 905 910

Gly Asn Gly Thr His Ile Phe Ser Ile Val Asn Ala Ala Pro Glu Gly
915 920 925

Leu Val Phe Leu His Thr Val Leu Leu Pro Thr Gln Tyr Lys Asp Val
930 935 940

Glu Ala Trp Ser Gly Leu Cys Val Asp Gly Thr Asn Gly Tyr Val Leu
945 950 955 960

Arg Gln Pro Asn Leu Ala Leu Tyr Lys Glu Gly Asn Tyr Tyr Arg Ile
965 970 975

Thr Ser Arg Ile Met Phe Glu Pro Arg Ile Pro Thr Met Ala Asp Phe
980 985 990

Val Gln Ile Glu Asn Cys Asn Val Thr Phe Val Asn Ile Ser Arg Ser
995 1000 1005

Glu Leu Gln Thr Ile Val Pro Glu Tyr Ile Asp Val Asn Lys Thr
1010 1015 1020

Leu Gln Glu Leu Ser Tyr Lys Leu Pro Asn Tyr Thr Val Pro Asp
1025 1030 1035

Leu Val Val Glu Gln Tyr Asn Gln Thr Ile Leu Asn Leu Thr Ser
1040 1045 1050

Glu Ile Ser Thr Leu Glu Asn Lys Ser Ala Glu Leu Asn Tyr Thr
1055 1060 1065

Val Gln Lys Leu Gln Thr Leu Ile Asp Asn Ile Asn Ser Thr Leu
1070 1075 1080

Val Asp Leu Lys Trp Leu Asn Arg Val Glu Thr Tyr Ile Lys Trp
1085 1090 1095

Pro Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val
1100 1105 1110

Val Ser Met Leu Leu Leu Cys Cys Cys Ser Thr Gly Cys Cys Gly
1115 1120 1125

Phe Phe Ser Cys Phe Ala Ser Ser Ile Arg Gly Cys Cys Glu Ser
1130 1135 1140

Thr Lys Leu Pro Tyr Tyr Asp Val Glu Lys Ile His Ile Gln
1145 1150 1155

<210> 162
<211> 56
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-OC43-COV wtTMCT-AA 的 TMCT 區

<400> 162

Trp Tyr Val Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val
1 5 10 15

Leu Leu Phe Phe Ile Cys Cys Cys Thr Gly Cys Gly Thr Ser Cys Phe
20 25 30

Lys Lys Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly Tyr Gln Glu Leu
35 40 45

Val Ile Lys Thr Ser His Asp Asp
50 55

<210> 163
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-OC43-COV H5iTMCT-AA 的 TMCT 區

<400> 163

Trp Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
1 5 10 15

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
20 25 30

Ser Leu Gln Cys Arg Ile Cys Ile
35 40

<210> 164
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-OC43-COV H5iCT-AA 的 TMCT 區

<400> 164

Trp Tyr Val Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val
1 5 10 15

Leu Leu Phe Phe Ile Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 165
<211> 34
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-OC43-COV H5iCT(V4)-AA 的 TMCT 區

<400> 165

Trp Tyr Val Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val
1 5 10 15

Leu Leu Phe Phe Ile Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile
20 25 30

Cys Ile

<210> 166
<211> 37

<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-OC43-COV H1cCT-AA 的 TMCT 區

<400> 166

Trp Tyr Val Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val
1 5 10 15

Leu Leu Phe Phe Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln
20 25 30

Cys Arg Ile Cys Ile
35

<210> 167
<211> 58
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-229E-wtTMCT-AA 的 TMCT 區

<400> 167

Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val Val Ser
1 5 10 15

Met Leu Leu Leu Cys Cys Cys Ser Thr Gly Cys Cys Gly Phe Phe Ser
20 25 30

Cys Phe Ala Ser Ser Ile Arg Gly Cys Cys Glu Ser Thr Lys Leu Pro
35 40 45

Tyr Tyr Asp Val Glu Lys Ile His Ile Gln
50 55

<210> 168
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-229E-H5iTMCT-AA 的 TMCT 區

<400> 168

Trp Trp Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
1 5 10 15

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
20 25 30

Ser Leu Gln Cys Arg Ile Cys Ile
35 40

<210> 169
<211> 36
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-229E-H5iCT-AA 的 TMCT 區

<400> 169

Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val Val Ser
1 5 10 15

Met Leu Leu Leu Ser Leu Trp Met Cys Ser Asn Gly Ser Leu Gln Cys
20 25 30

Arg Ile Cys Ile
35

<210> 170
<211> 33
<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-229E-H5iCT(V4)-AA 的 TMCT 區

<400> 170

Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val Val Ser
1 5 10 15

Met Leu Leu Leu Cys Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile Cys
20 25 30

Ile

<210> 171
<211> 35

<212> PRT
<213> 人工序列

<220>
<223> 經修飾的 PDI-229E-H1cCT-AA 的 TMCT 區

<400> 171

Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val Val Ser Met
1 5 10 15

Leu Leu Leu Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg
20 25 30

Ile Cys Ile
35

<210> 172
<211> 34
<212> PRT
<213> 人工序列

<220>
<223> 具有間插肽序列 Xn 之經修飾的 OC43-CoV S 蛋白的 TM/CT 區

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> Xaa 可以是 0 至 10 個胺基酸的任何組合

<220>
<221> misc_feature
<222> (28)..(29)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (31)..(31)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 172

Trp Tyr Val Trp Leu Leu Ile Cys Leu Ala Gly Val Ala Met Leu Val
1 5 10 15

Leu Leu Phe Phe Ile Xaa Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile
20 25 30

Cys Ile

<210> 173
<211> 33
<212> PRT
<213> 人工序列

<220>
<223> 具有間插肽序列 Xn 之經修飾的 OC43-CoV S 蛋白的 TM/CT 區

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa 可以是 0 至 10 個胺基酸的任何組合

<220>
<221> misc_feature
<222> (27)..(28)
<223> Xaa 可以是任何天然存在的胺基酸

<220>
<221> misc_feature
<222> (30)..(30)
<223> Xaa 可以是任何天然存在的胺基酸

<400> 173

Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe Val Val Ser
1 5 10 15

Met Leu Leu Leu Xaa Cys Ser Asn Gly Ser Xaa Xaa Cys Xaa Ile Cys
20 25 30

Ile

【發明申請專利範圍】

【請求項1】　一種經修飾的冠狀病毒S-蛋白，依序地包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；以及

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白。

【請求項2】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述TM係直接融合至所述CT。

【請求項3】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述TM係包括嵌合TM，其源自所述冠狀病毒S-蛋白之TM的N-端序列和源自所述流感HA蛋白之TM的C-端序列。

【請求項4】　如請求項3所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TM包括源自所述冠狀病毒S-蛋白之TM的N-端序列，所述冠狀病毒S-蛋白之TM包括對應於SEQ ID NO： 18或SEQ ID NO： 169之胺基酸1-20的至少20個胺基酸；或對應於SEQ ID NO： 118或SEQ ID NO：164之胺基酸1-21的至少21個胺基酸；或對應於SEQ ID NO： 123之胺基酸1-22的至少22個胺基酸；及來自所述流感HA蛋白之TM的C-端的一個或多於一個的胺基酸。

【請求項5】　如請求項4所述之經修飾的冠狀病毒S-蛋白，其中，來自所述流感HA蛋白之TM的C-端的所述一個或多於一個的胺基酸係選自AGL或AGL的保留取代、MAGL或MAGL的保留取代。

【請求項6】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述CT係包括嵌合CT，其源自所述冠狀病毒S-蛋白之CT的N-端序列和源自所述流感

HA蛋白之CT的C-端序列。

【請求項7】　如請求項6所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合CT包括源自所述流感HA蛋白之CT的C-端序列，所述流感HA蛋白之CT包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸；及來自所述冠狀病毒S-蛋白之CT的N-端的一個或多於一個的胺基酸。

【請求項8】　如請求項7所述之經修飾的冠狀病毒S-蛋白，其中，來自所述冠狀病毒S-蛋白之CT的N-端的所述一個或多於一個的胺基酸係選自C或C的保留取代、CC或CC的保留取代、或CCM或CCM的保留取代。

【請求項9】　如請求項3所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TM包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的胺基酸；或對應於SEQ ID NO：118或SEQ ID NO：164之胺基酸1-21的胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的胺基酸。

【請求項10】　如請求項4所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合CT包括對應於SEQ ID NOs：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸。

【請求項11】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TMCT包括嵌合TM及嵌合CT，所述嵌合TM包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的胺基酸；或對應於SEQ ID NO：118或SEQ ID NO：164之胺基酸1-21的胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的胺基酸，所述嵌合CT包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸或其組合。

【請求項12】　如請求項1至11中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與野生型冠狀病毒S-蛋白胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白包括一個或多於一個的胺基酸取代。

【請求項13】 如請求項12所述之經修飾的冠狀病毒S-蛋白，其中，所述一個或多於一個的胺基酸取代包括：

i) 限制在 S1 次單位與 S2 次單位之間的切割位點處之加工的取代；

ii) 一個或多於一個的胺基酸取代為一個或多於一個的脯胺酸；或

iii) 限制在 S1 次單位與 S2 次單位之間的切割位點處之加工的取代以及一個或多於一個的胺基酸取代為一個或多於一個的脯胺酸。

【請求項14】 如請求項12或13所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置971和972處的胺基酸。

【請求項15】 如請求項12或13所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置802、927、971和972處的胺基酸。

【請求項16】 如請求項14或15所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白進一步包括對應於在位置667、668、670處，或其組合的胺基酸的一個或多於一個的胺基酸取代。

【請求項17】 如請求項16所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代。

【請求項18】 如請求項16所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺

酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802、927、971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代。

【請求項19】 如請求項14至18中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2之參考胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白進一步包括對應於在位置923處的胺基酸的胺基酸取代。

【請求項20】 如請求項19所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802、927、971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代，及對應於在SEQ ID NO：2之位置923處的胺基酸的所述胺基酸取代為苯丙胺酸或苯丙胺酸的保留取代。

【請求項21】 如請求項12至20中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與沒有在宿主或宿主細胞中表現的一個或多於一個的取代的對應S-蛋白的產量相比時，在所述宿主或宿主細胞中表現時，所述一個或多於一個的胺基酸取代使S-蛋白保持在融合前狀態或生產更高產量的經修飾的S-蛋白。

【請求項22】 如請求項1至21中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述S-蛋白包括S1次單位和S2次單位，其中所述S2次單位包括所述嵌合TMCT。

【請求項23】 如請求項1至22中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述流感HA蛋白係源自B型流感或H1、H2、H3、H4、H5、H6、H7、H8、H9、H10、H11、H12、H13、H14、H15或H16亞型流感。

【請求項24】 如請求項1至23中任一項所述之經修飾的冠狀病毒S-蛋白，

其中，所述冠狀病毒S-蛋白係源於SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV。

【請求項25】 如請求項1至23中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述胞外結構域係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，所述TM或所述TM的部分係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，或其中，所述胞外結構域和所述TM或所述TM的部分係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV。

【請求項26】 如請求項1至25中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述TMCT包括具有與SEQ ID NO：18、19、37、38、39、64、126、127、128、129、130、131、118、119、 120、123、124、125、134、135、164、165、166、169、170、171、172或173之序列約80%至約100%同一性的序列。

【請求項27】 如請求項1至26中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白係作為前驅蛋白產生，所述前驅蛋白包括所述經修飾的冠狀病毒S-蛋白和訊號肽。

【請求項28】 如請求項27所述之經修飾的冠狀病毒S-蛋白，其中，所述訊號肽對於所述經修飾的冠狀病毒S-蛋白係原生的或非原生的。

【請求項29】 如請求項27或28所述之經修飾的冠狀病毒S-蛋白，其中，所述訊號肽係源自蛋白質二硫鍵異構酶(PDI)的訊號肽。

【請求項30】 如請求項1至29中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白包括植物特異性N-聚醣。

【請求項31】 如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白的胺基酸序列包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、

155、156或157之胺基酸；或SEQ ID NO：47之胺基酸24-1259，SEQ ID NO：48之胺基酸25-1259；SEQ ID NO： 49之胺基酸25-1259；SEQ ID NO：50之胺基酸25-1259；SEQ ID NO：51之胺基酸25-1259；SEQ ID NO：52之胺基酸25-1259；SEQ ID NO：53之胺基酸25-1259；SEQ ID NO：54之胺基酸25-1259；SEQ ID NO：55之胺基酸25-1259；SEQ ID NO：56之胺基酸25-1259；SEQ ID NO：57之胺基酸25-1259；SEQ ID NO：58之胺基酸25-1259；SEQ ID NO： 59之胺基酸25-1262；SEQ ID NO：60之胺基酸25-1261；SEQ ID NO：61之胺基酸25-1258；或SEQ ID NO：62之胺基酸25-1256；SEQ ID NO：95之胺基酸25-1243；SEQ ID NO：96之胺基酸25-1240；SEQ ID NO：97之胺基酸25-1243；SEQ ID NO：108之胺基酸25-1341；SEQ ID NO：109之胺基酸25-1338；SEQ ID NO：110之胺基酸25-1341；或SEQ ID NO：144之胺基酸25-1351；SEQ ID NO：145之胺基酸25-1348；SEQ ID NO：146之胺基酸25-1351；SEQ ID NO：155之胺基酸25-1159；SEQ ID NO：156之胺基酸25-1156；或SEQ ID NO：157之胺基酸25-1159。

【請求項32】 如請求項1至30中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述CT或所述CT的部分包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：15；或SEQ ID NO：6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568；或SEQ ID NO：18之胺基酸22-37；或SEQ ID NO：19之胺基酸21-40；或SEQ ID NO：37之胺基酸21-39；或SEQ ID NO：38之胺胺基酸25-36；或SEQ ID NO：39之胺基酸24-34；或 SEQ ID NO：126、128、129、130或131之胺基酸22-37；或SEQ ID NO：127之胺基酸22-36。

【請求項33】 如請求項27所述之經修飾的冠狀病毒S-蛋白，其中，所述前驅蛋白包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：1之胺基酸1-1234；SEQ ID NO：5之胺基酸1-1234；或SEQ ID NO：30之胺基酸1-1243；SEQ ID NO：95之胺基酸1-1227；SEQ ID NO：108之胺基酸1-1325；SEQ ID NO：

112之胺基酸1-1216、SEQ ID NO：113之胺基酸1-1318；SEQ ID NO：144之胺基酸1-1335；SEQ ID NO：155之胺基酸1-1143；SEQ ID NO：158之胺基酸1-1325；SEQ ID NO：159之胺基酸1-1135，且其中，所述CT的胺基酸序列包括具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：15；或SEQ ID NO：6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568。

【請求項34】 一種核酸，包括編碼如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白的核苷酸序列。

【請求項35】 一種三聚體，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白。

【請求項36】 一種病毒樣顆粒(VLP)，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白或如請求項35所述之三聚體。

【請求項37】 如請求項36所述之病毒樣顆粒(VLP)，其中，所述VLP進一步包括植物脂質。

【請求項38】 一種組合物，包括有效劑量之如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；或如請求項36或37所述之病毒樣顆粒(VLP)；以及醫藥上可接受之載體、佐劑、媒介物或賦形劑。

【請求項39】 一種用於誘導免疫反應之疫苗，所述疫苗包括有效劑量之如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；如請求項36或37所述之病毒樣顆粒(VLP)；或如請求項38所述之組合物。

【請求項40】 如請求項39所述之疫苗，其中，所述疫苗係多價疫苗，包括病毒樣顆粒(VLP)的混合物。

【請求項41】 一種用於受試者中誘導對冠狀病毒感染的免疫力之方法，所述方法包括將如請求項38所述之組合物或如請求項39或40所述之疫苗投與至所述受試者。

【請求項42】 如請求項41所述之方法，其中，所述組合物或所述疫苗係一次投與至所述受試者。

【請求項43】 如請求項41所述之方法，其中，所述組合物或所述疫苗係多次投與至所述受試者。

【請求項44】 如請求項41所述之方法，其中，所述組合物或所述疫苗係作為初始劑量投與，且在從投與所述初始劑量1天至6個月之間係投與一劑或多於一劑的後續劑量。

【請求項45】 一種使用如請求項38所述之組合物或如請求項39或40所述之疫苗製備之抗體或抗體片段。

【請求項46】 一種非人宿主或宿主細胞，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；如請求項34所述之核酸；或如請求項36或37所述之病毒樣顆粒(VLP)。

【請求項47】 一種在非人宿主或宿主細胞中製造經修飾的冠狀病毒S-蛋白之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造所述經修飾的冠狀病毒 S-蛋白。

【請求項48】 一種在非人宿主或宿主細胞中製造病毒樣顆粒(VLP)之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造所述 VLP。

【請求項49】 如請求項48或49所述之方法，其中，所述方法進一步包括收

穫所述非人宿主或宿主細胞的步驟c)。

【請求項50】 一種在非人宿主或宿主細胞中增加經修飾的冠狀病毒S-蛋白之製造的產量之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許由所述核酸編碼的所述經修飾的冠狀病毒 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與表現未經修飾的冠狀病毒 S-蛋白的宿主或宿主細胞相比，以更高的產量製造所述經修飾的冠狀病毒 S-蛋白。

【請求項51】 一種在非人宿主或宿主細胞中增加病毒樣顆粒(VLP)之製造的產量之方法，包括以下步驟：

步驟 a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒S-蛋白依序地包括:源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；或

提供包括編碼經修飾的冠狀病毒 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白依序地包括：源自冠狀病毒 S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

步驟 b) 在允許由所述核酸編碼的所述經修飾冠狀病毒的 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與表現未經修飾的冠狀病毒 S-蛋白的宿主或宿主細胞相比，以更高的產量製造包括所述經修飾的冠狀病毒 S-蛋白的

VLP。

【請求項52】 一種在非人宿主或宿主細胞中製造病毒樣顆粒(VLP)之方法，包括以下步驟：

步驟 a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒S-蛋白依序地包括:源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；或

提供包括編碼經修飾的冠狀病毒 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白依序地包括：源自冠狀病毒 S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞。

【請求項53】 如請求項48、51或52所述之方法，其中，所述VLP係進一步從所述非人宿主或宿主細胞中提取和純化。

【請求項54】 一種藉由如請求項48、51或52所述之方法製造的病毒樣顆粒(VLP)。

【請求項55】 一種藉由如請求項47或50所述之方法製造的經修飾的冠狀病毒S-蛋白。

【請求項56】 如請求項47至55中任一項所述之方法，或如請求項46所述之非人宿主或宿主細胞，其中，所述非人宿主或宿主細胞包括植物、植物的部分、植物細胞、真菌、真菌細胞、昆蟲、昆蟲細胞、動物或動物細胞。

【請求項57】 一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流感血球凝集素(HA)蛋白，且其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述S-蛋白包括在位置667、668、670、971和972處的取代。

【請求項58】 一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流感血球凝集素(HA)蛋白，且其中，所述S-蛋白包括位置667處的甘胺酸取代、位置668處的絲胺酸取代、位置670處的絲胺酸取代、位置971處的脯胺酸取代、位置972處的脯胺酸取代，所述位置對應於SEQ ID NO：2的參考胺基酸序列。

【請求項59】 一種包括病毒樣顆粒(VLP)之組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白包括SEQ ID NO：21的序列或SEQ ID NO：51的胺基酸25-1259。

【請求項60】 一種包括病毒樣顆粒(VLP)之組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流感血球凝集素(HA)蛋白，且其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述S-蛋白包括在位置667、668、670、802、923、927、971和972處的取代。

【發明圖式】

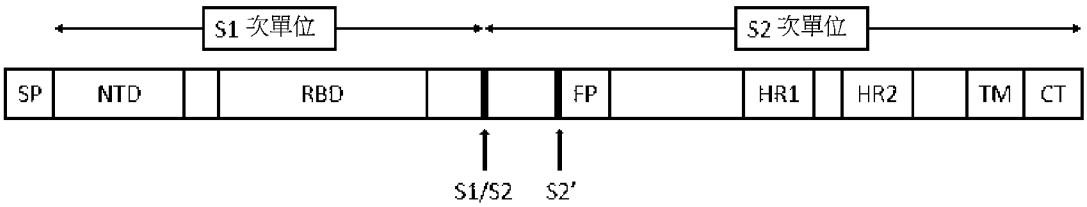


圖1

圖式

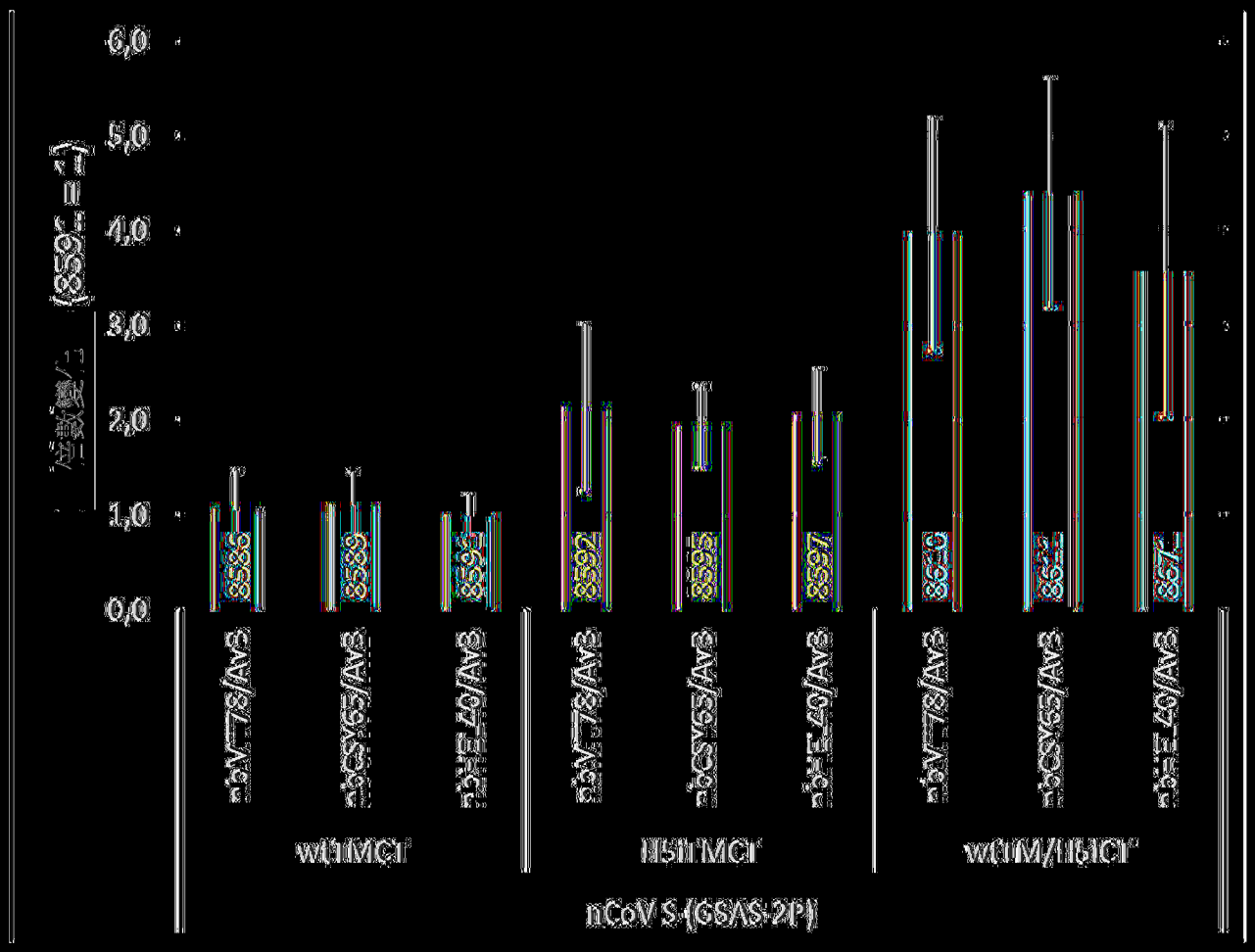


圖3A

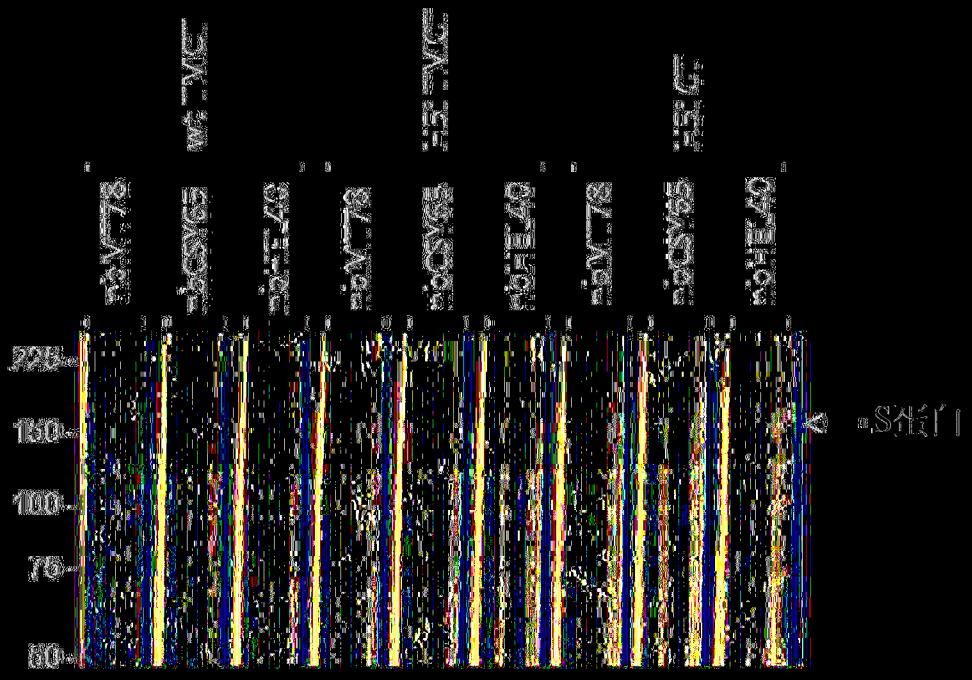
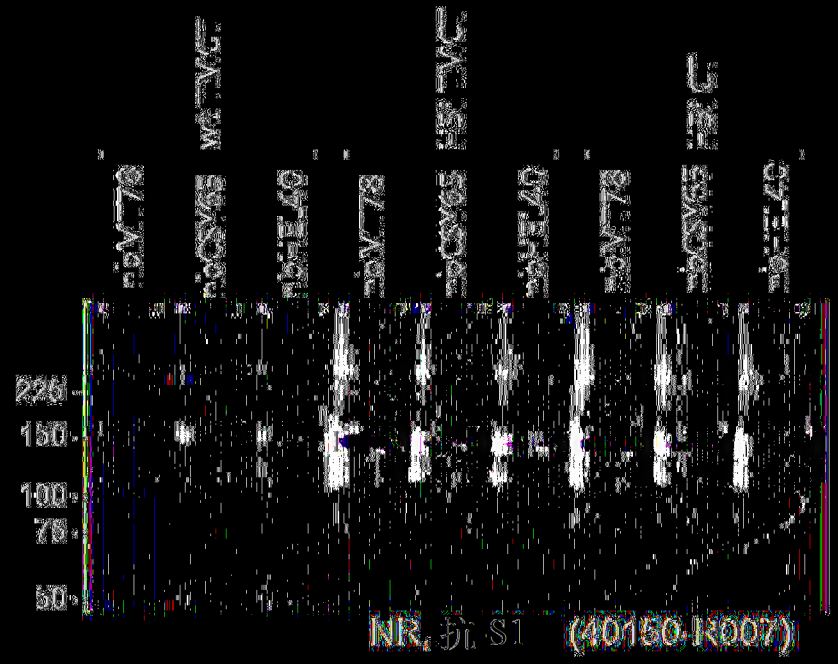
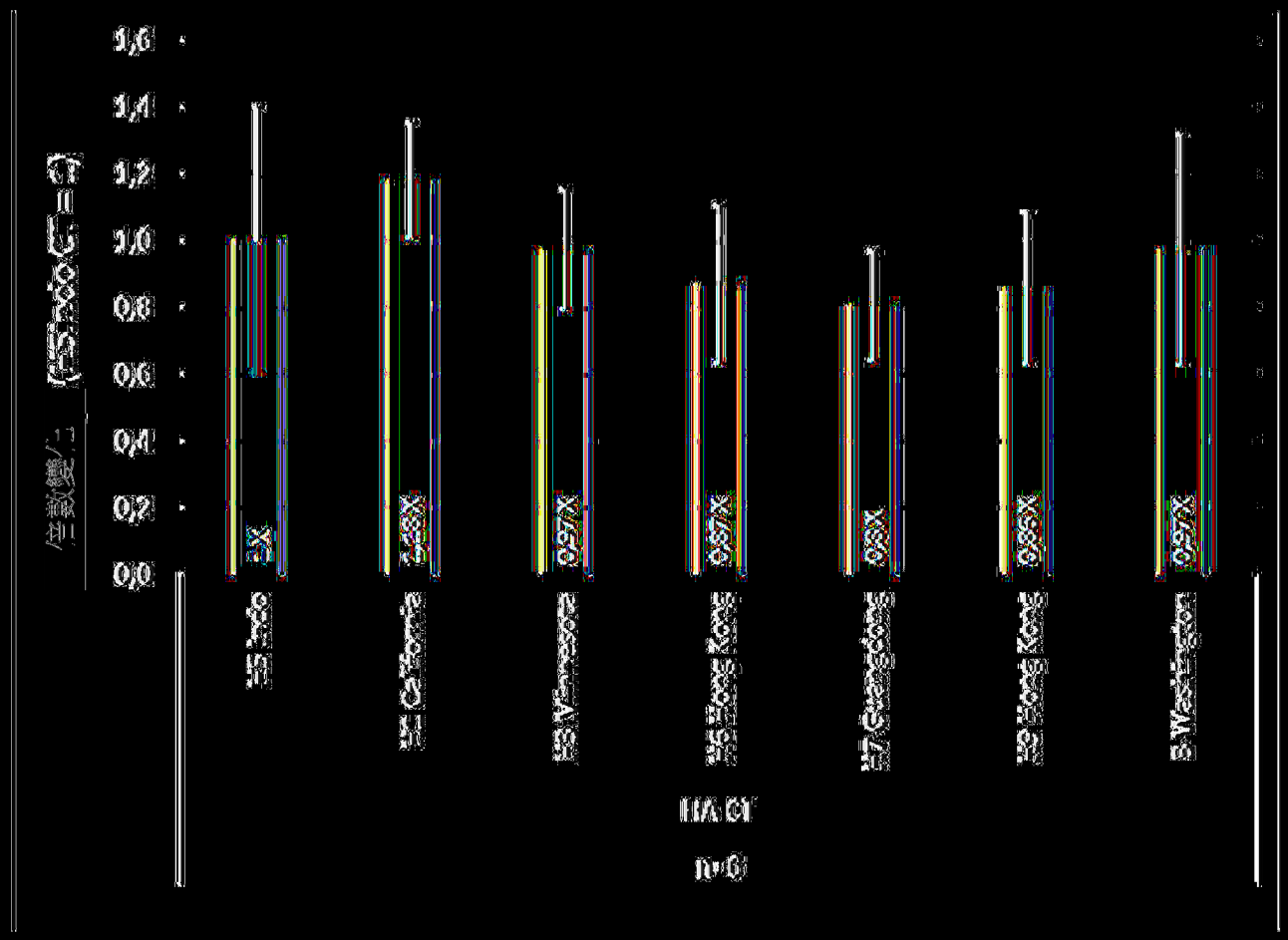


圖3B


225
150
100
75
50
NR, 方 S1
(40150-1R007)


225
150
100
75
50
非緊原方 S2
(NR3100-36578)

圖3C


1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Wash-off (%)
Wash-off (%)
Wash-off (%)

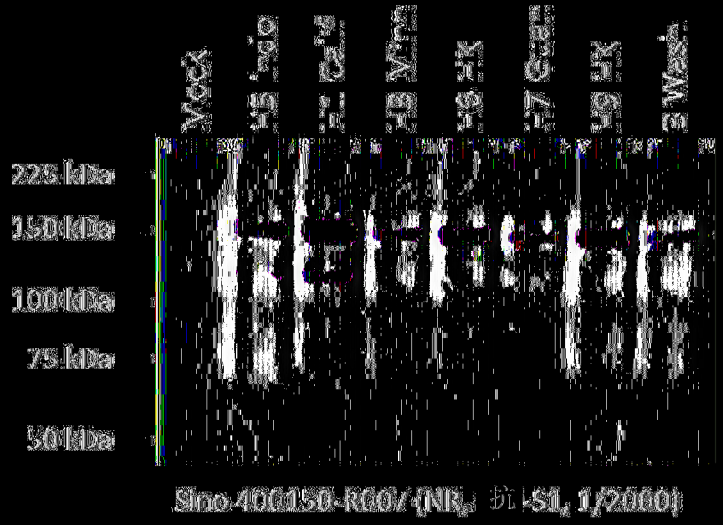

Mock
Sino-400150-R007-IN8
Sino-400150-R007-IN8
Sino-400150-R007-IN8
Sino-400150-R007-IN8
Sino-400150-R007-IN8
Sino-400150-R007-IN8
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa
Sino-400150-R007-IN8, 抗-S1, 1/2000

圖4B


Mock
ME100-565728-IN8
ME100-565728-IN8
ME100-565728-IN8
ME100-565728-IN8
ME100-565728-IN8
ME100-565728-IN8
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa
ME100-565728-IN8, 抗-S2, 1/5000

圖4C

SARS CoV-2 S protein with wtTM/wtCT

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

H5 A/Indonesia/5/05 Hemagglutinin with H5TM/H5CT

…KLSGVKLESIGTYQILSIYSTVASSLALAIMMAGLSFWMCSNGSLQCRICI

Modified SARS-CoV-2 S protein with wtTM/H5CT

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMLSFWMCSNGSLQCRICI

Modified SARS-CoV-2 S protein with wtTM/H5CT (V1)

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMMAGLSFWMCSNGSLQCRICI

Modified SARS-CoV-2 S protein with wtTM/H5CT (V2)

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMAGLSFWMCSNGSLQCRICI

Modified SARS-CoV-2 S protein with wtTM/H5CT (V3)

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMCSNGSLQCRICI

Modified SARS-CoV-2 S protein with wtTM/H5CT (V4)

…YEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCSNGSLQCRIC



圖5B

圖6A

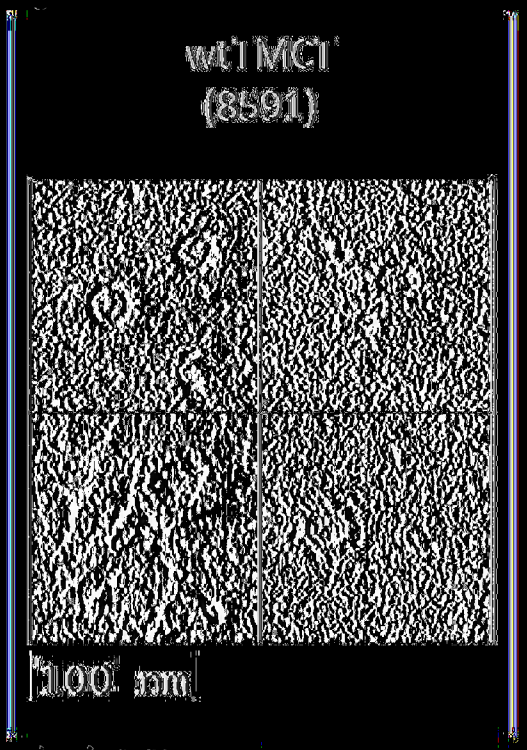


圖6B

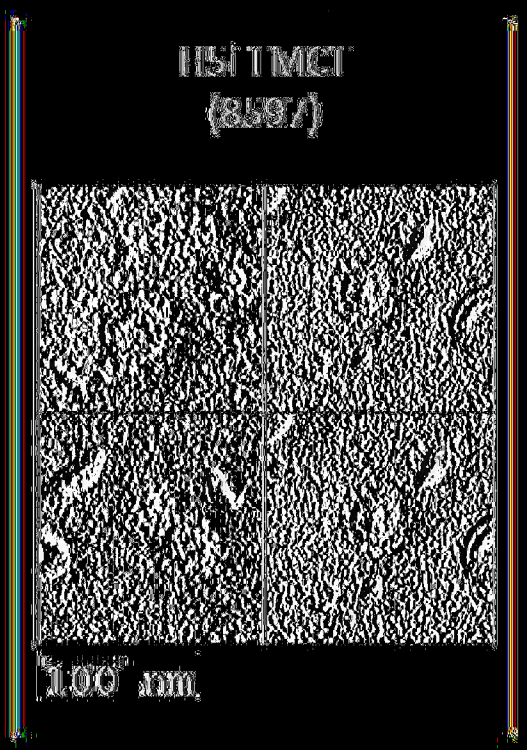


圖6C

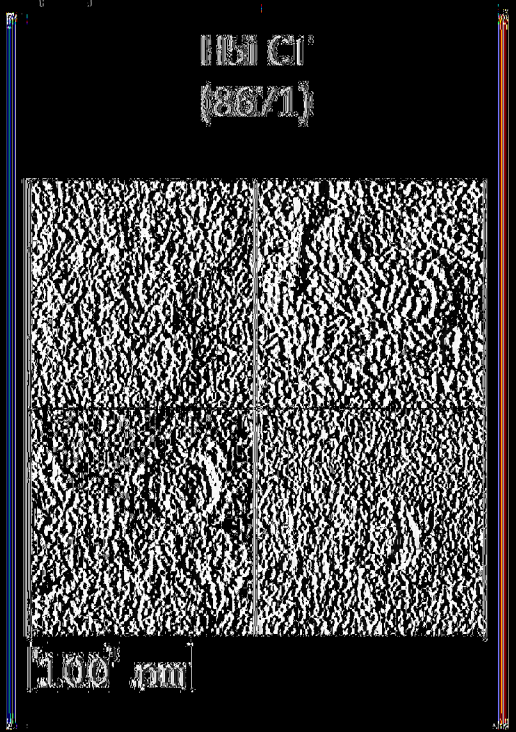


圖6D

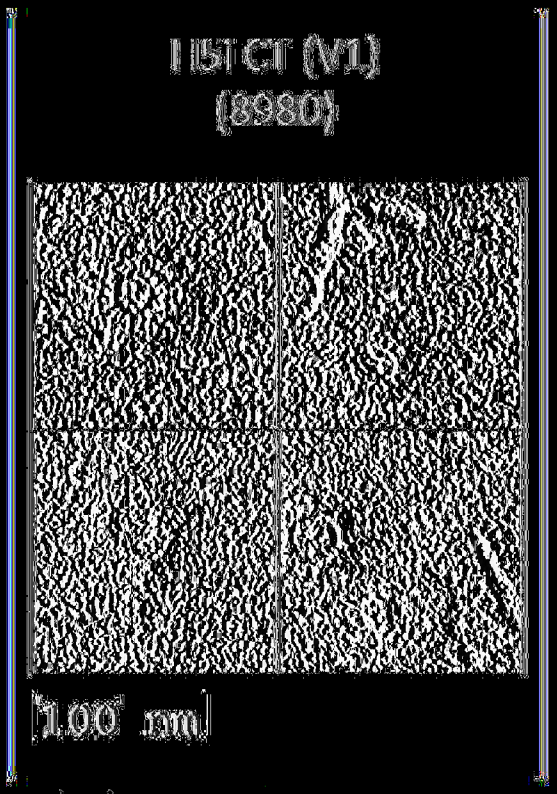


圖6E

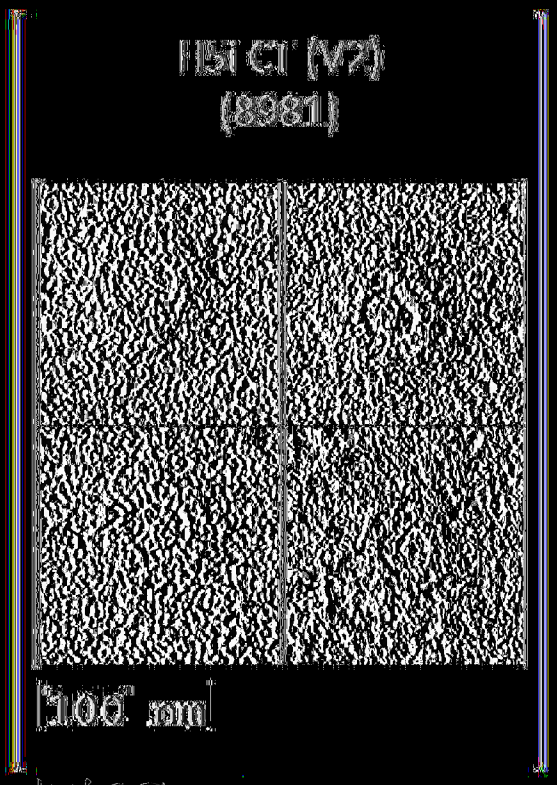


圖6F

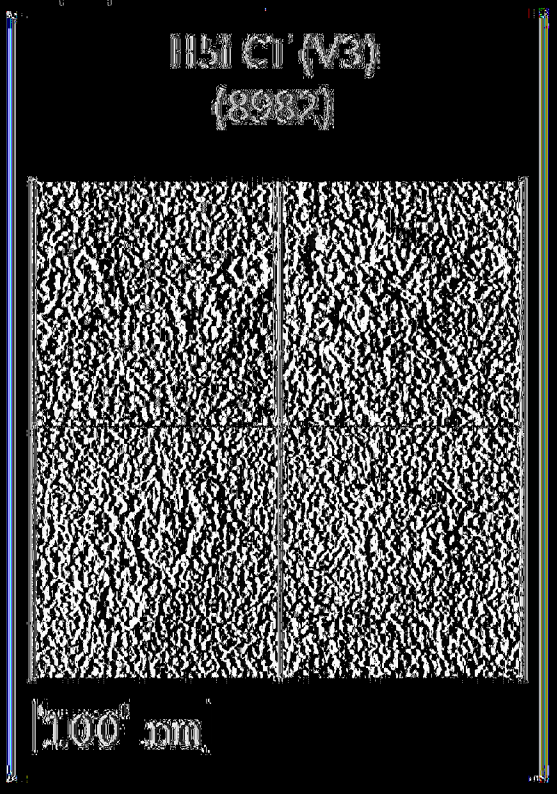


圖6G

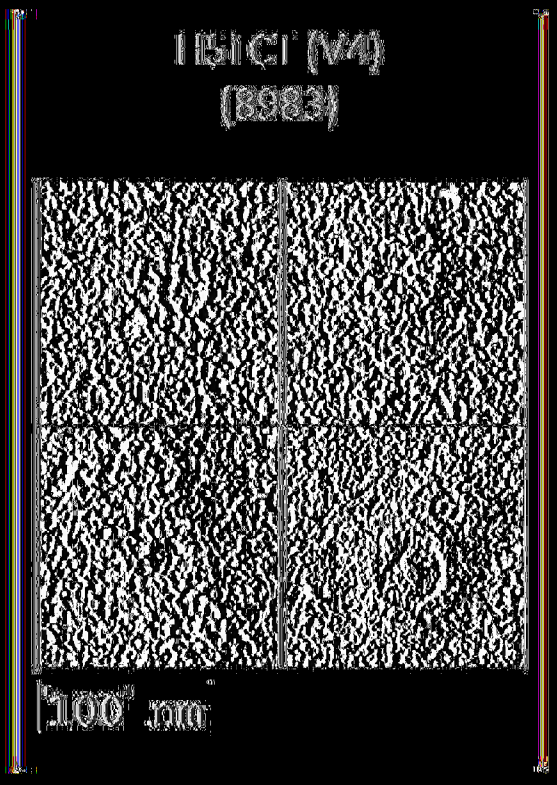


圖6H

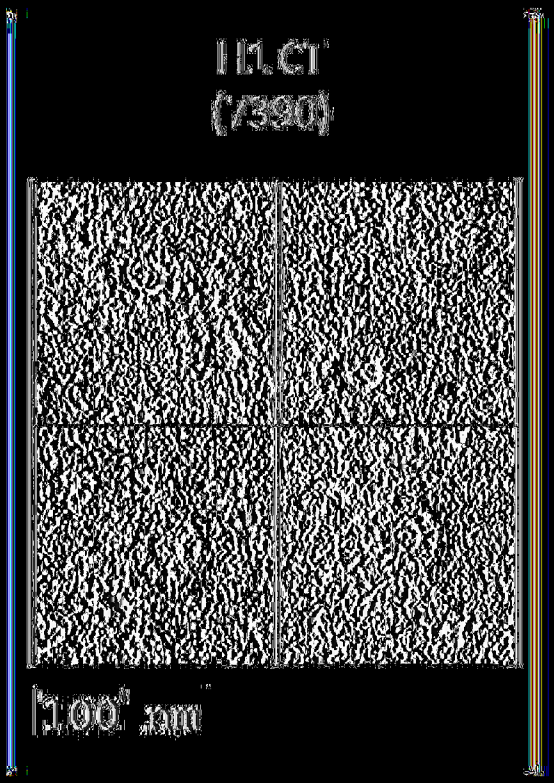


圖6I

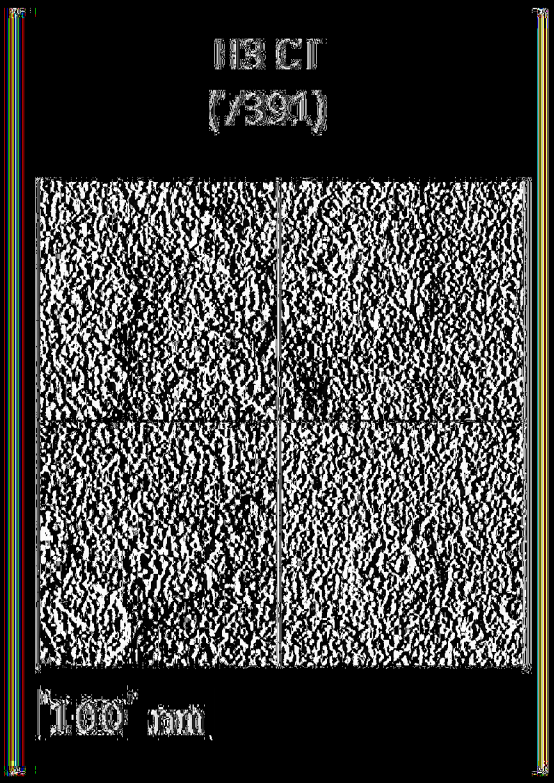


圖6J

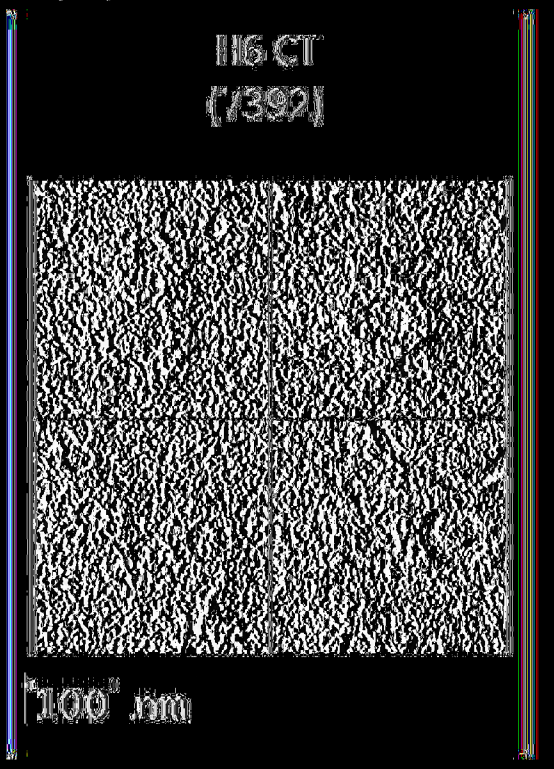


圖6K

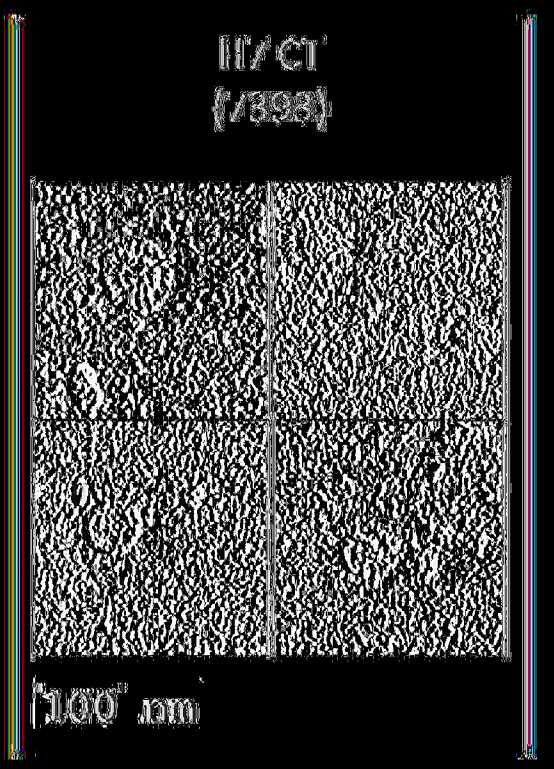


圖6L

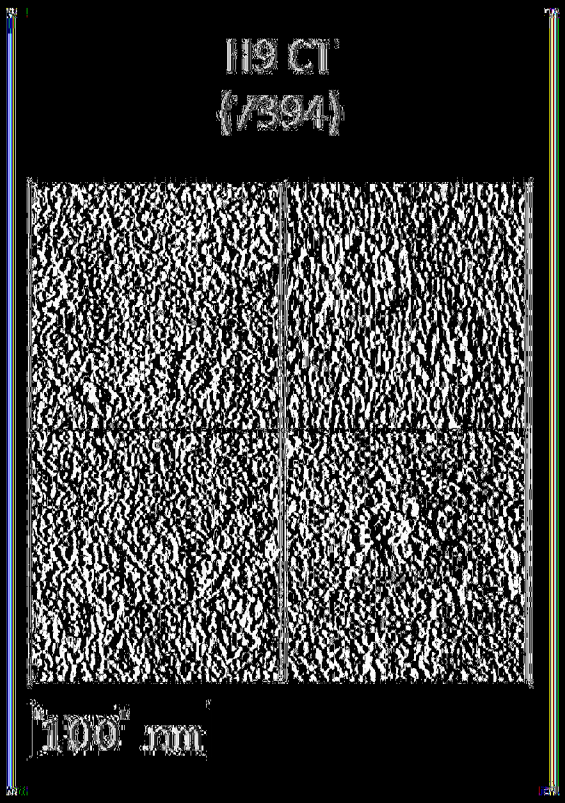
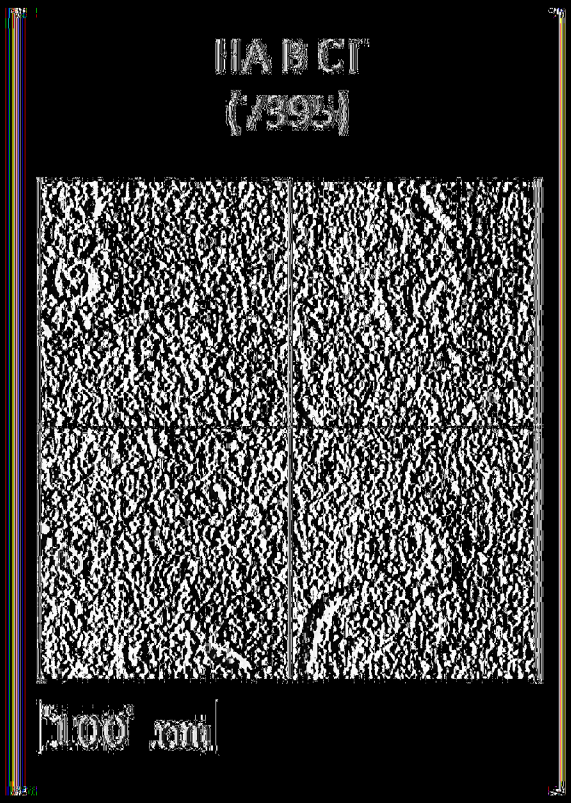


圖6M



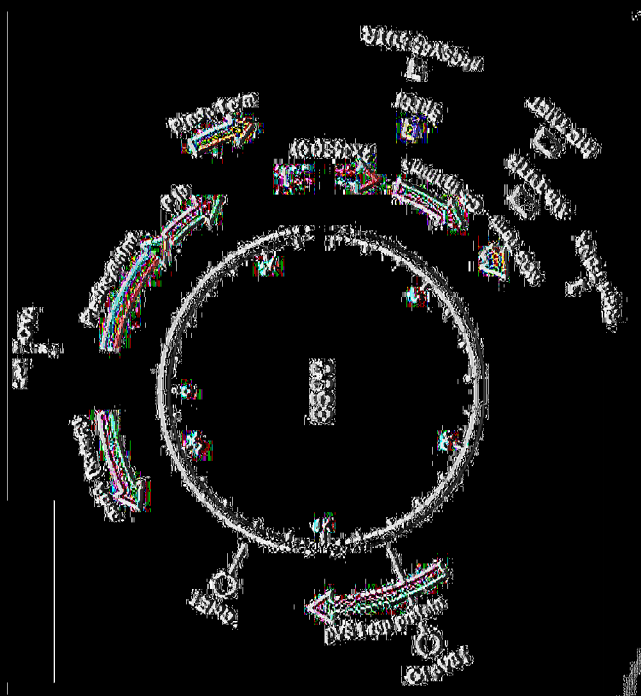


圖7B



圖7C

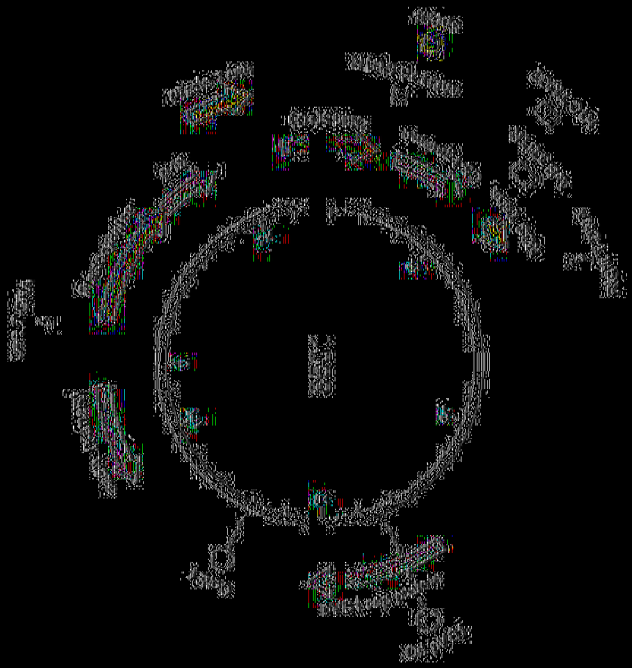


圖7A

HOT
63
HOT
96
HOT
96A

FIG. 3A
FIG. 3B
FIG. 3C

圖11A

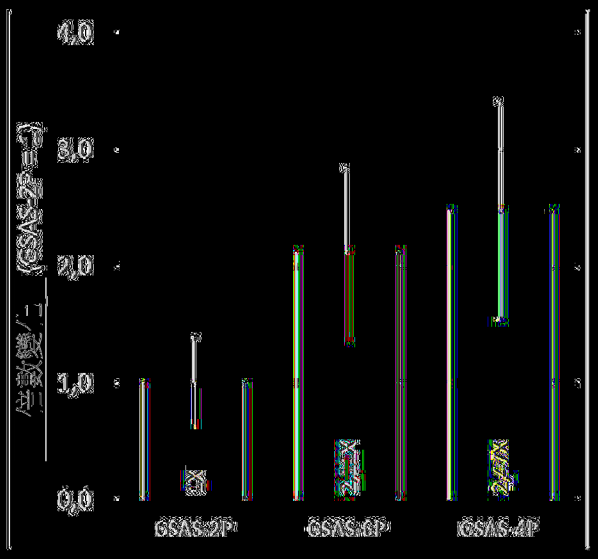
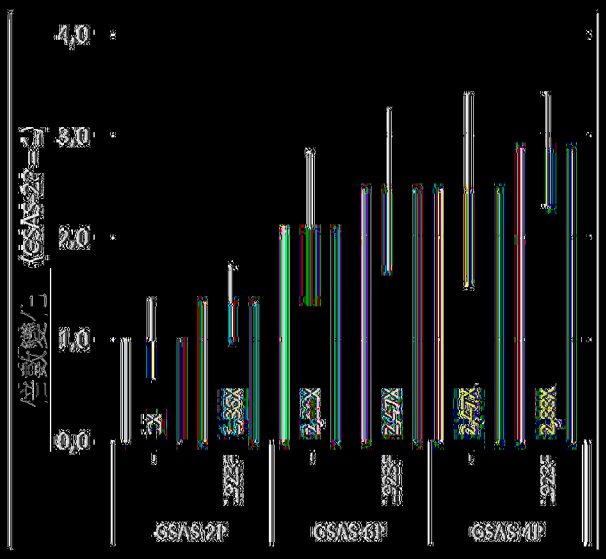

4.0
3.0
2.0
1.0
0.0
GSAS-2P
GSAS-6P
GSAS-4P

圖11B


4.0
3.0
2.0
1.0
0.0
GSAS-2P
GSAS-6P
GSAS-4P

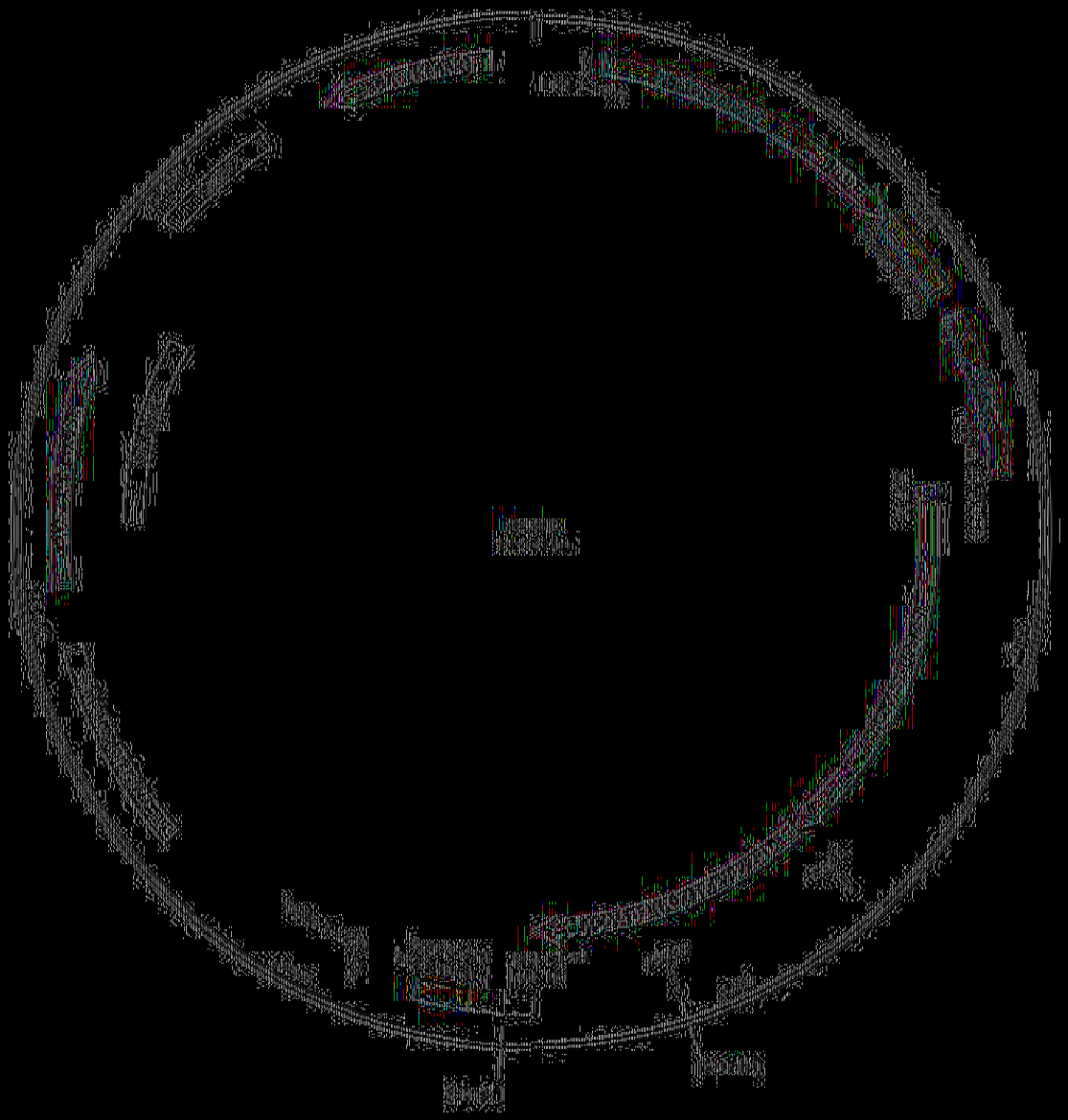


圖12A

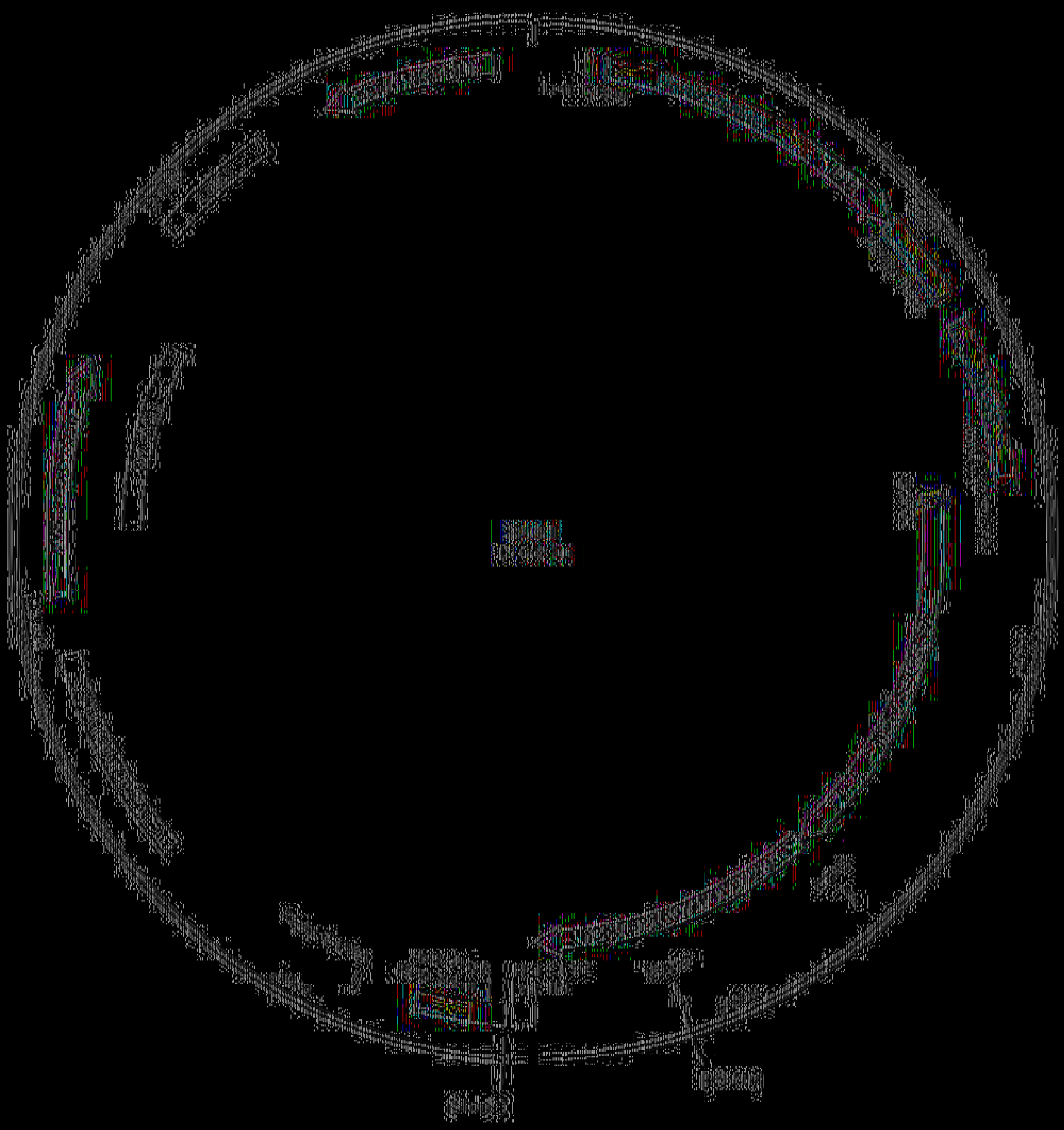


圖12B

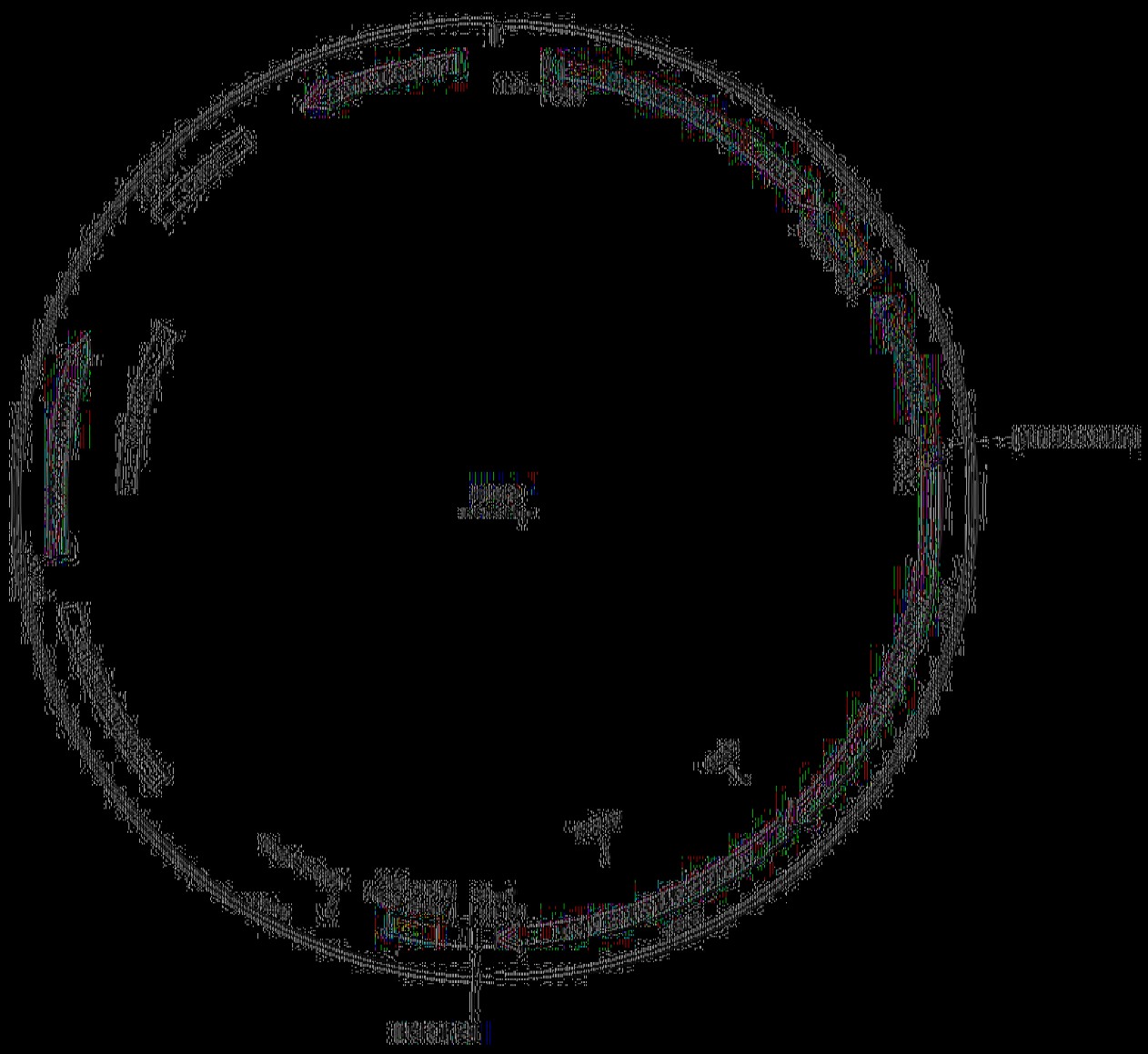


圖12C

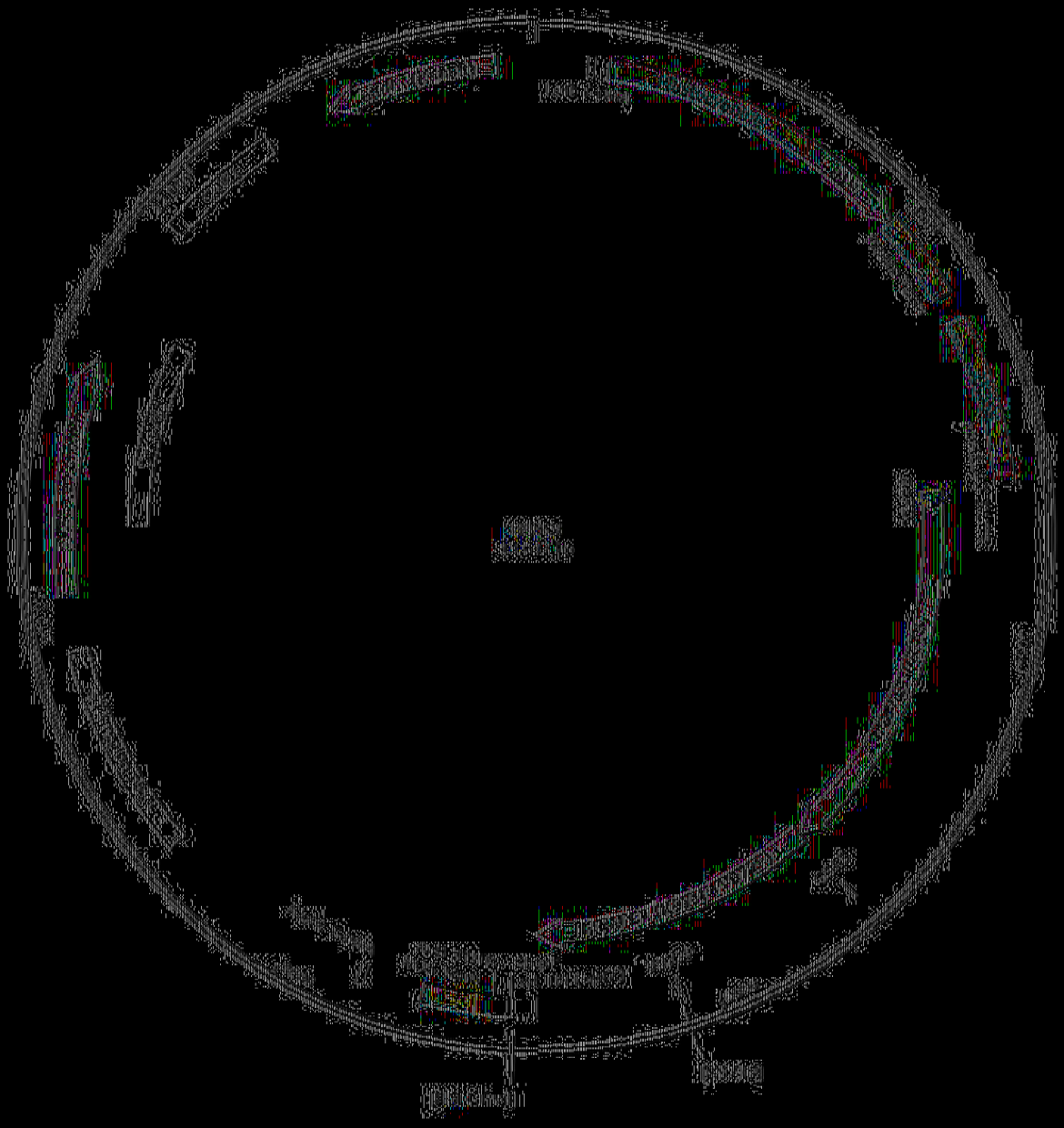


圖12D

圖13A

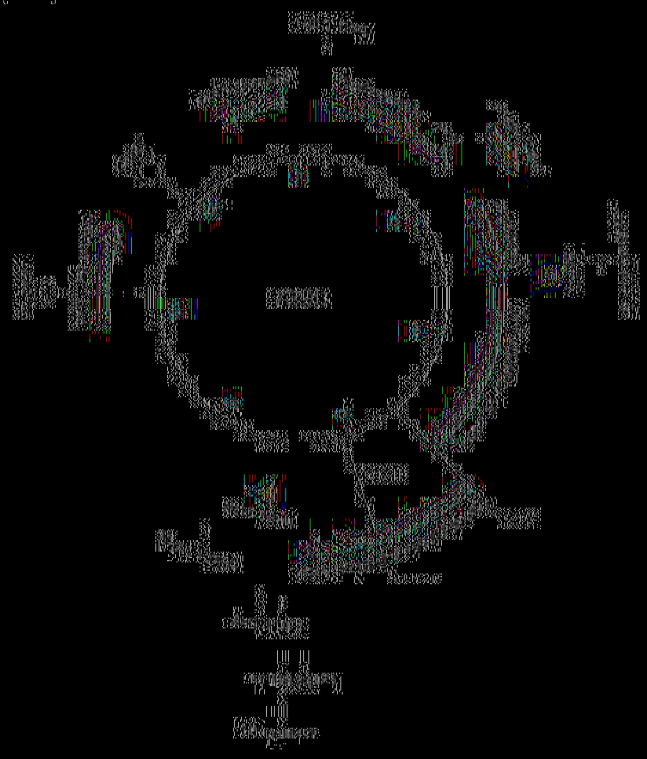


圖13B

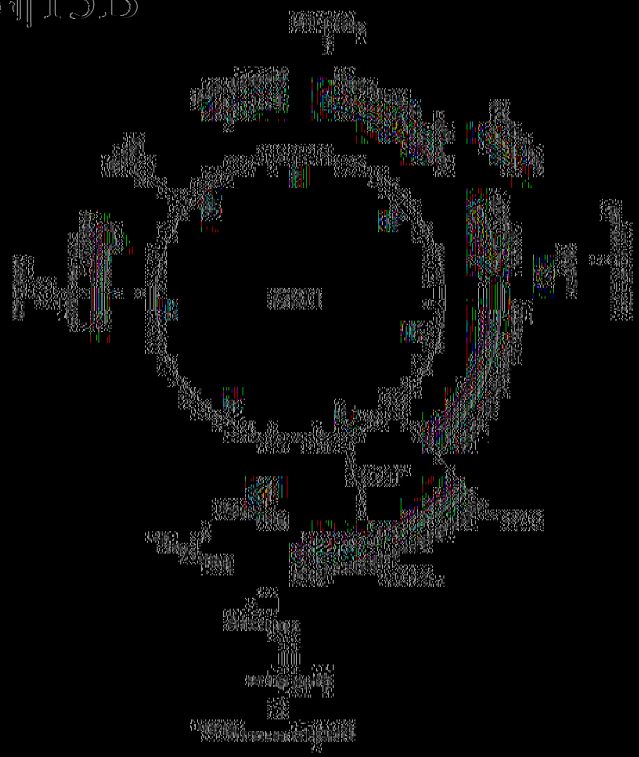


圖13C

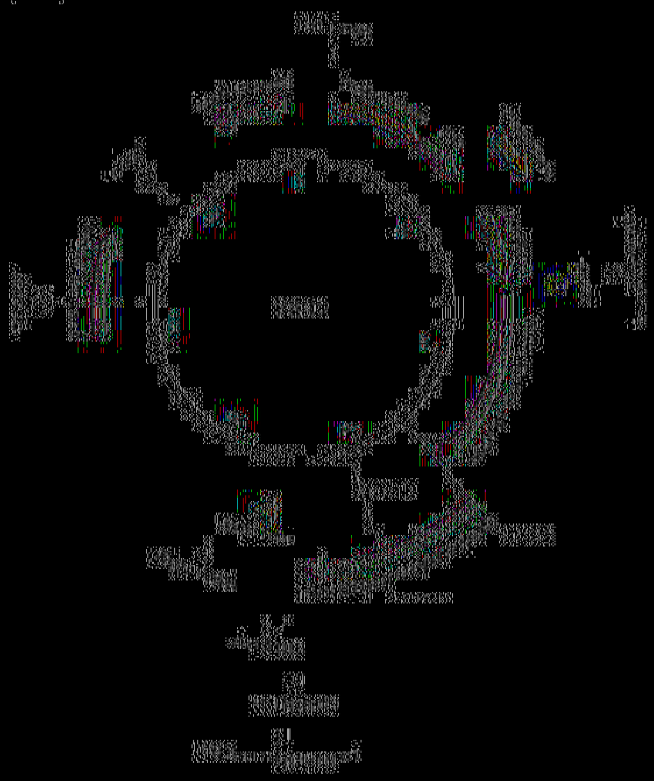


圖13D



圖13E

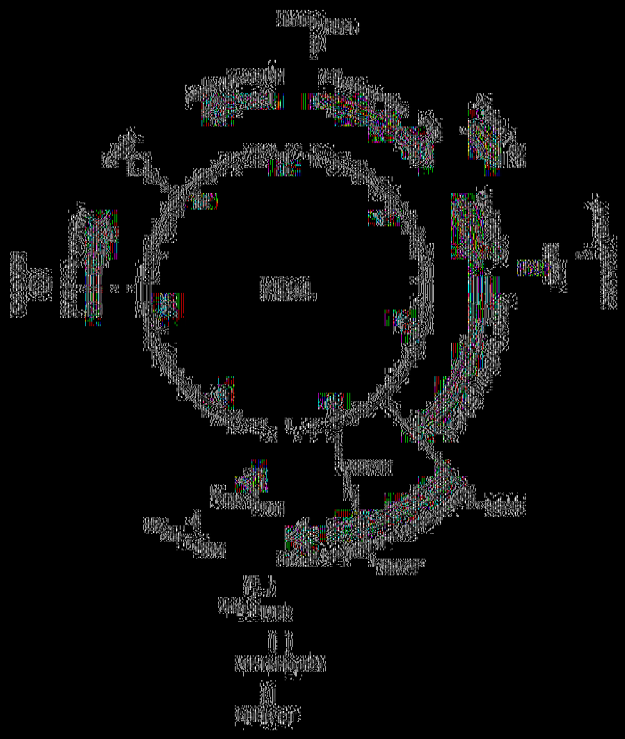
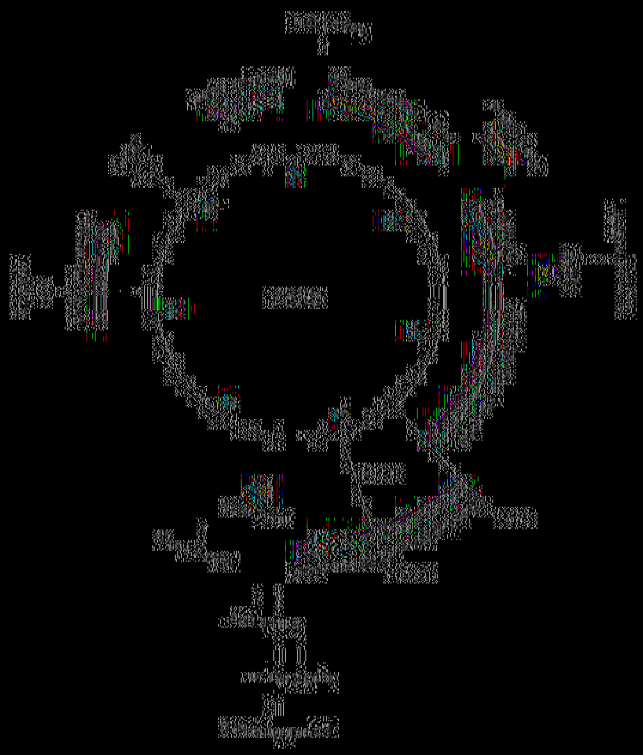


圖13F



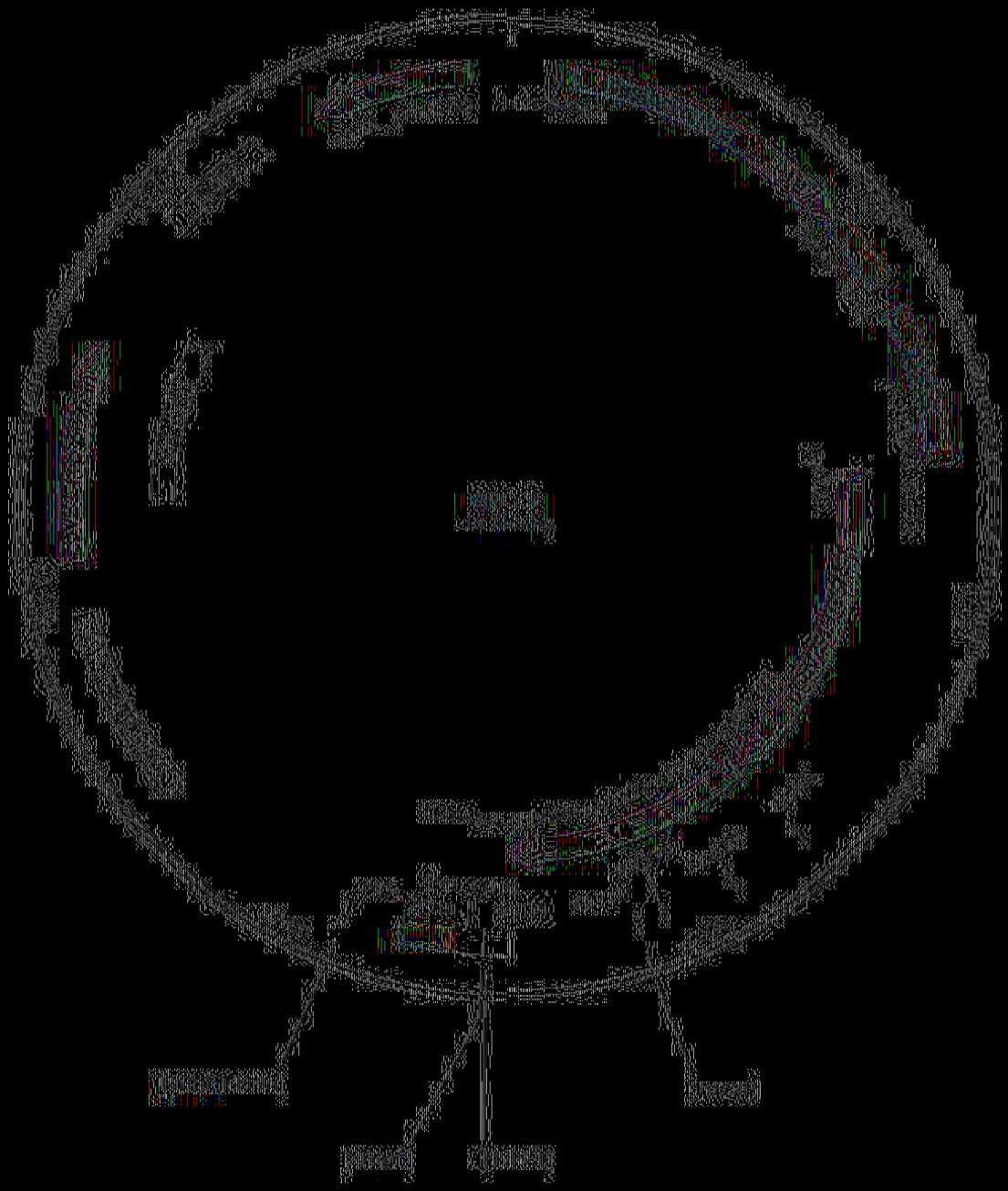
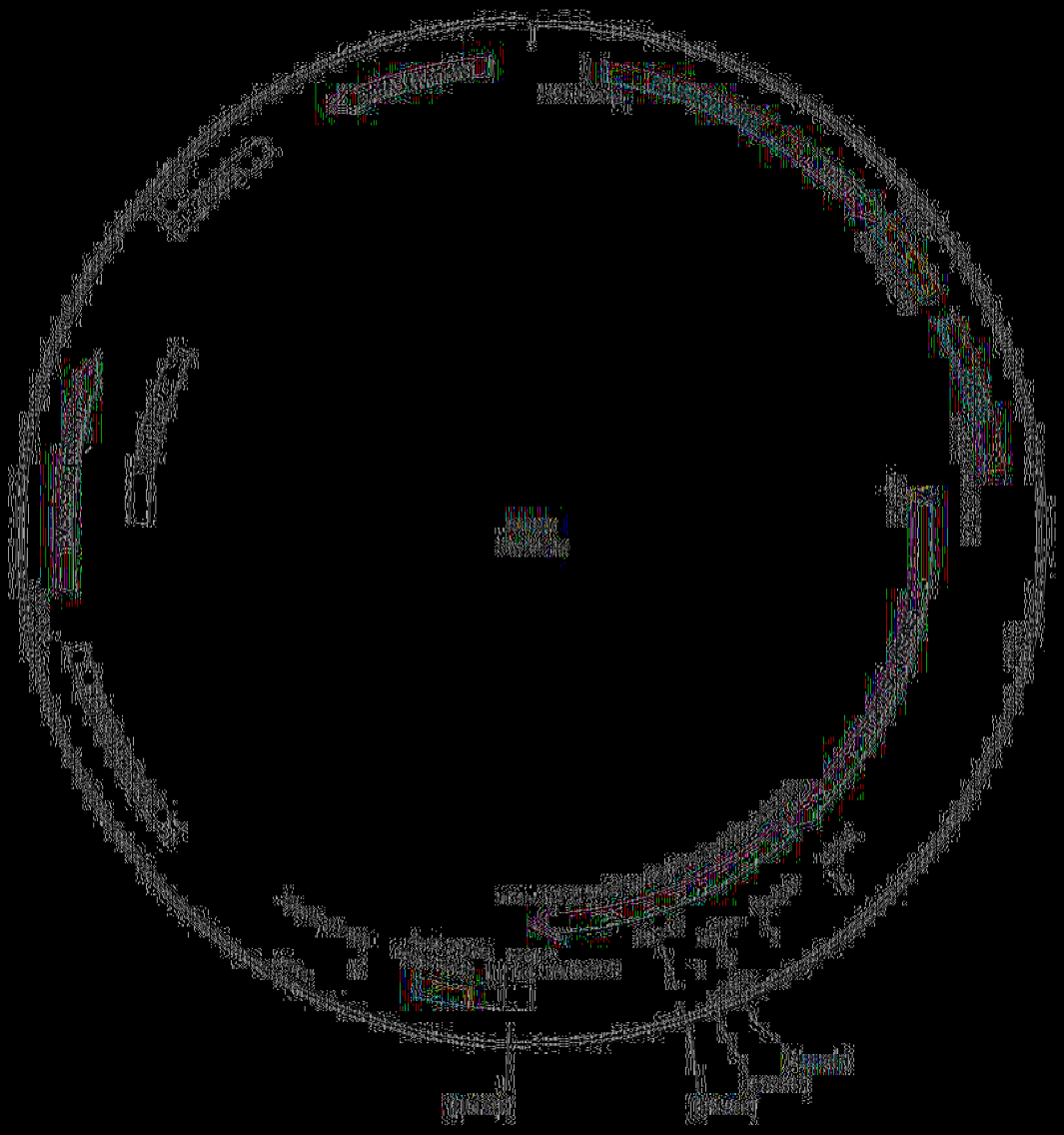


圖14A



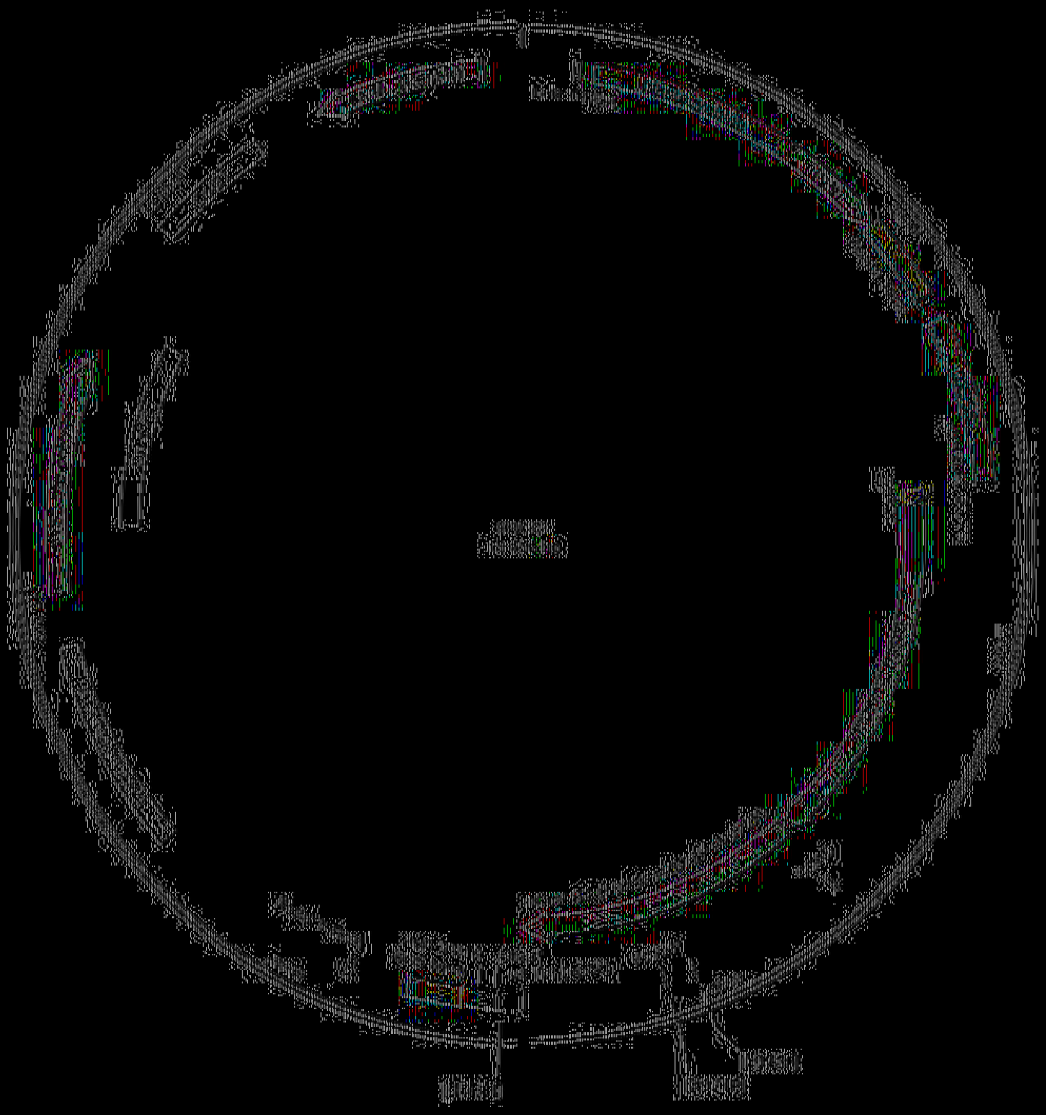


圖15A

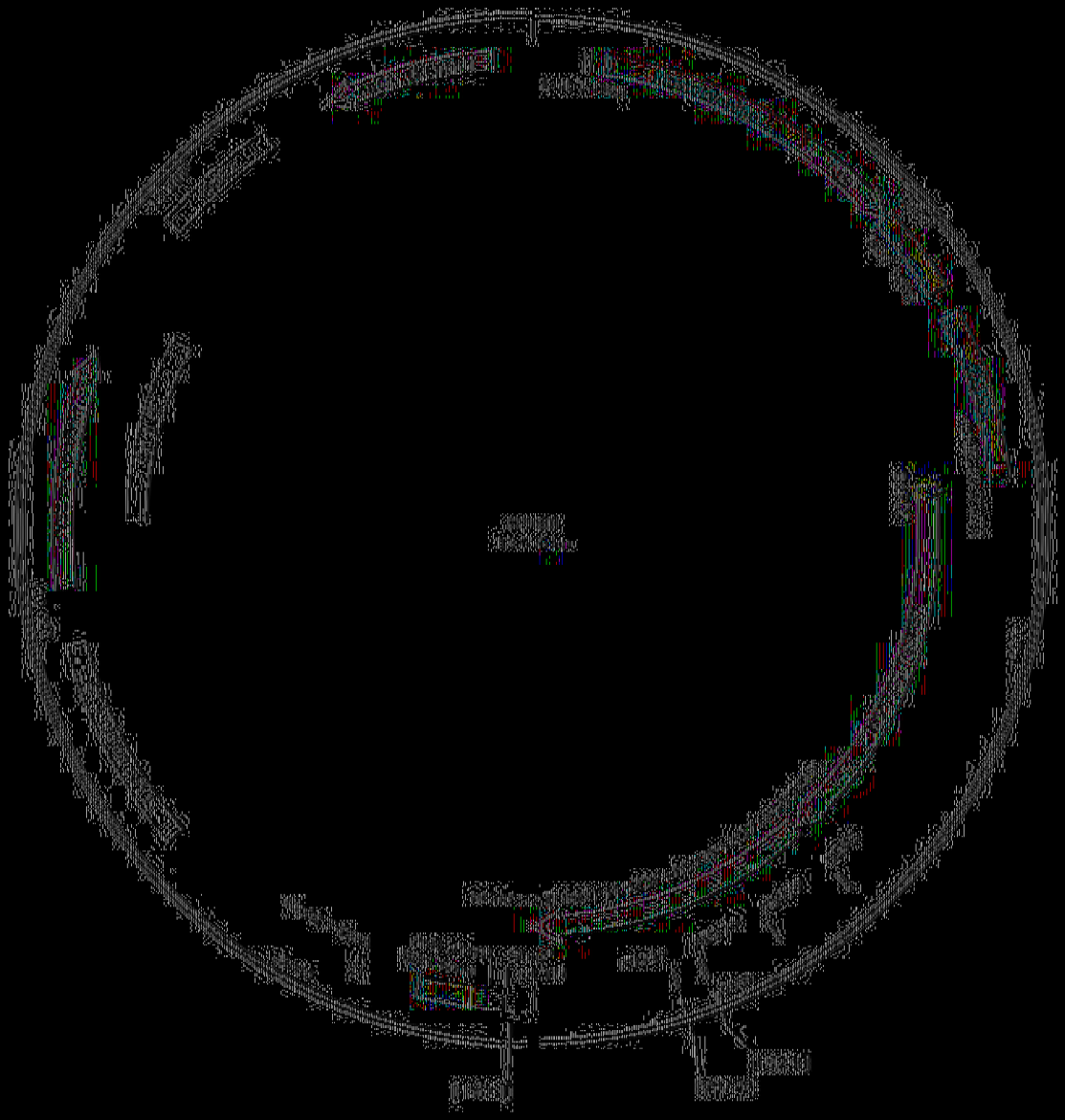


圖15B



15C

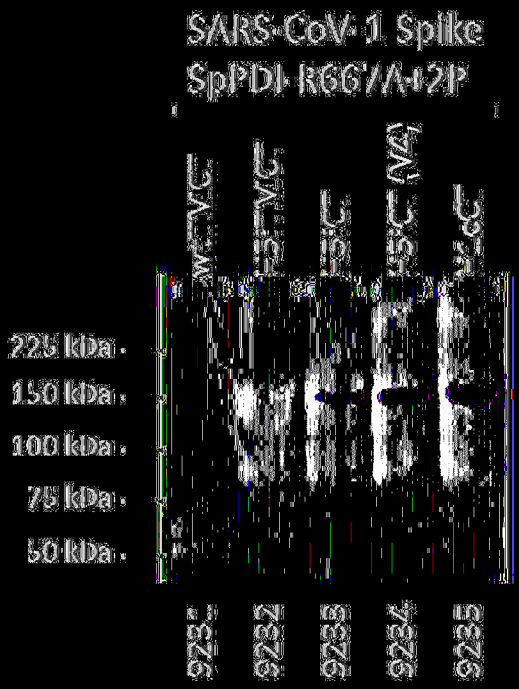

SARS-CoV-1 Spike
SpPDI-R667A-2P
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa
923-1
923-2
923-3
923-4
923-5

圖16A

圖16B

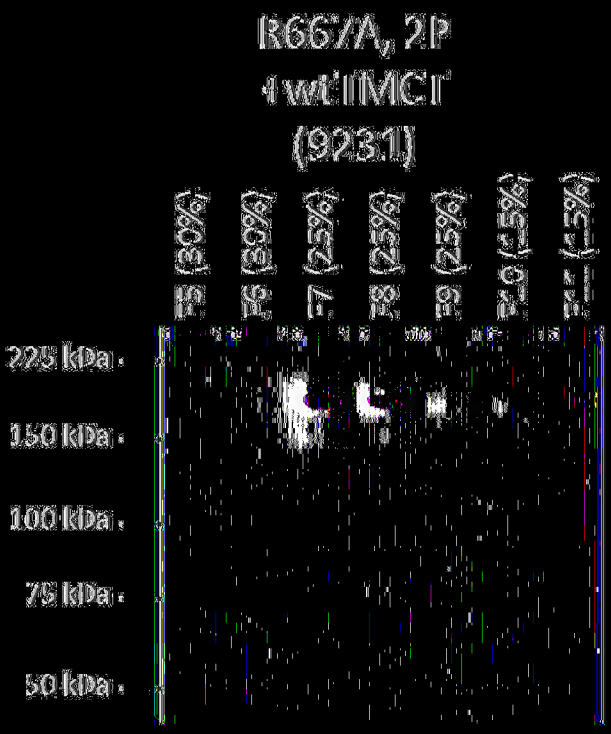
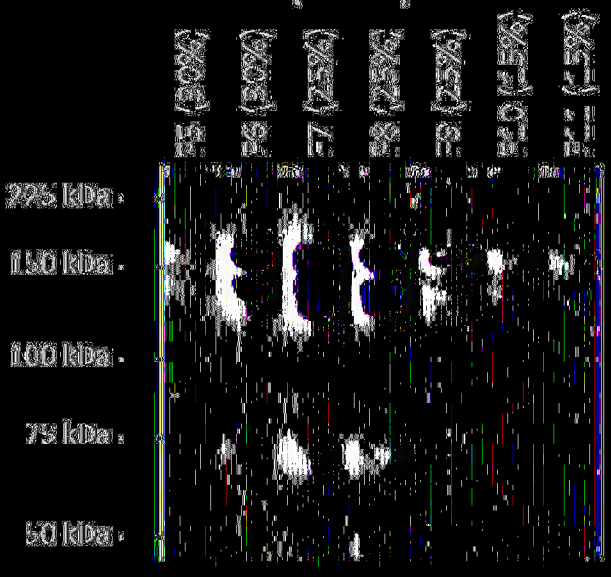

R66/A, 2P
+wtTMCT
(9231)
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa

圖16C


R66/A, 2P
+HBTTMCT
(9232)
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa

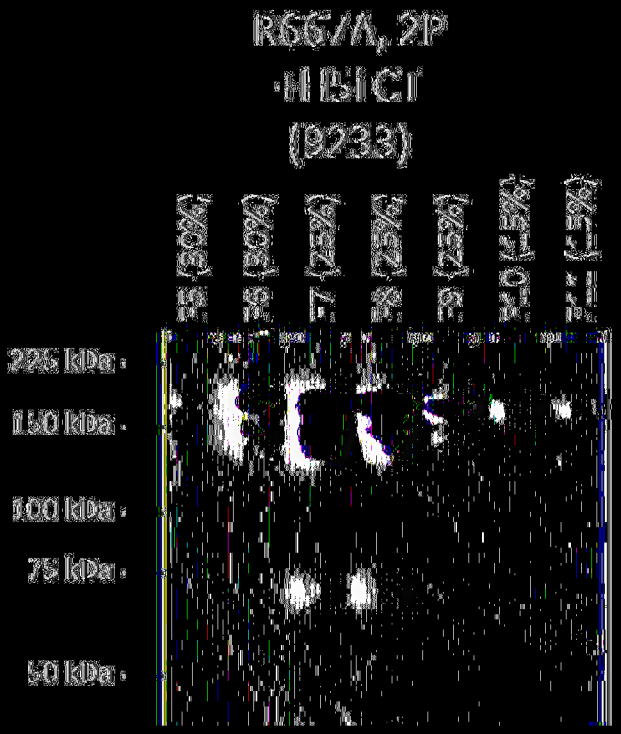


圖16D

圖17A

R66/A, 2P
-Awt1MCT
(9231)

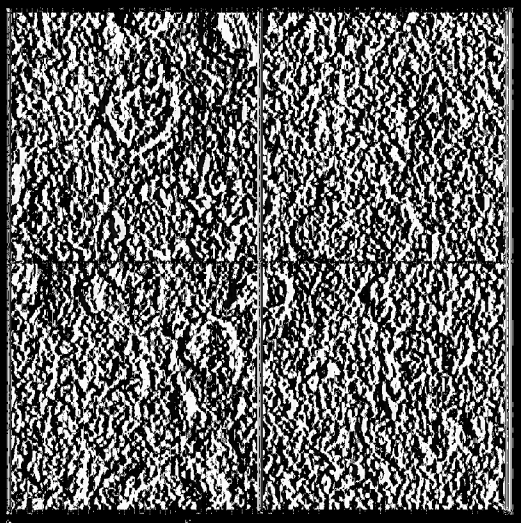


圖17B

R66/A, 2P
-H51T1MCT
(9232)

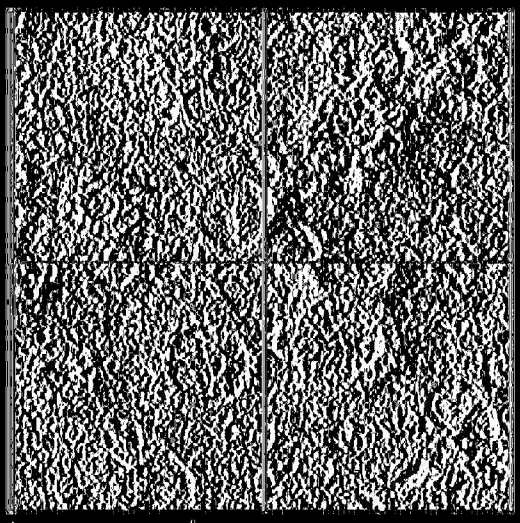
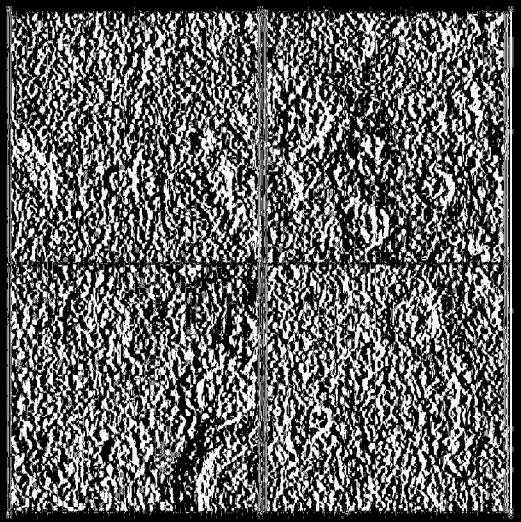


圖17C

R66/A, 2P
-H1961CT
(9233)



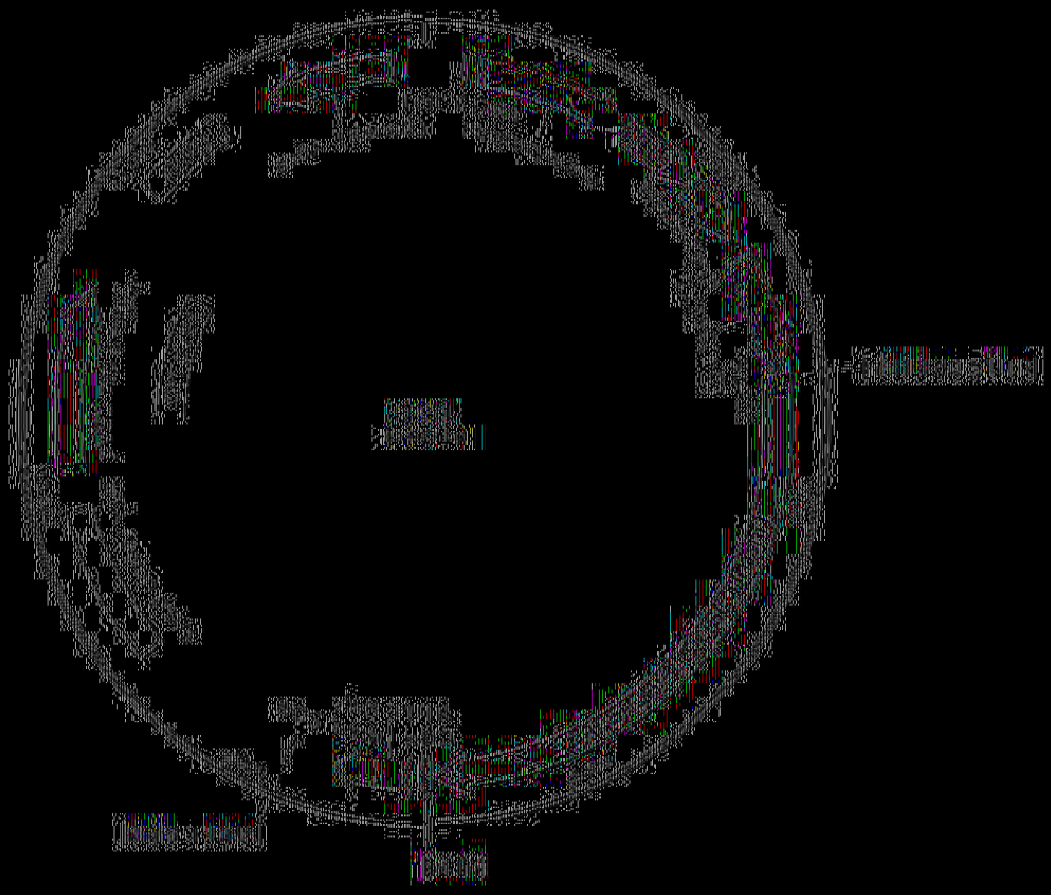


圖18A



圖18B

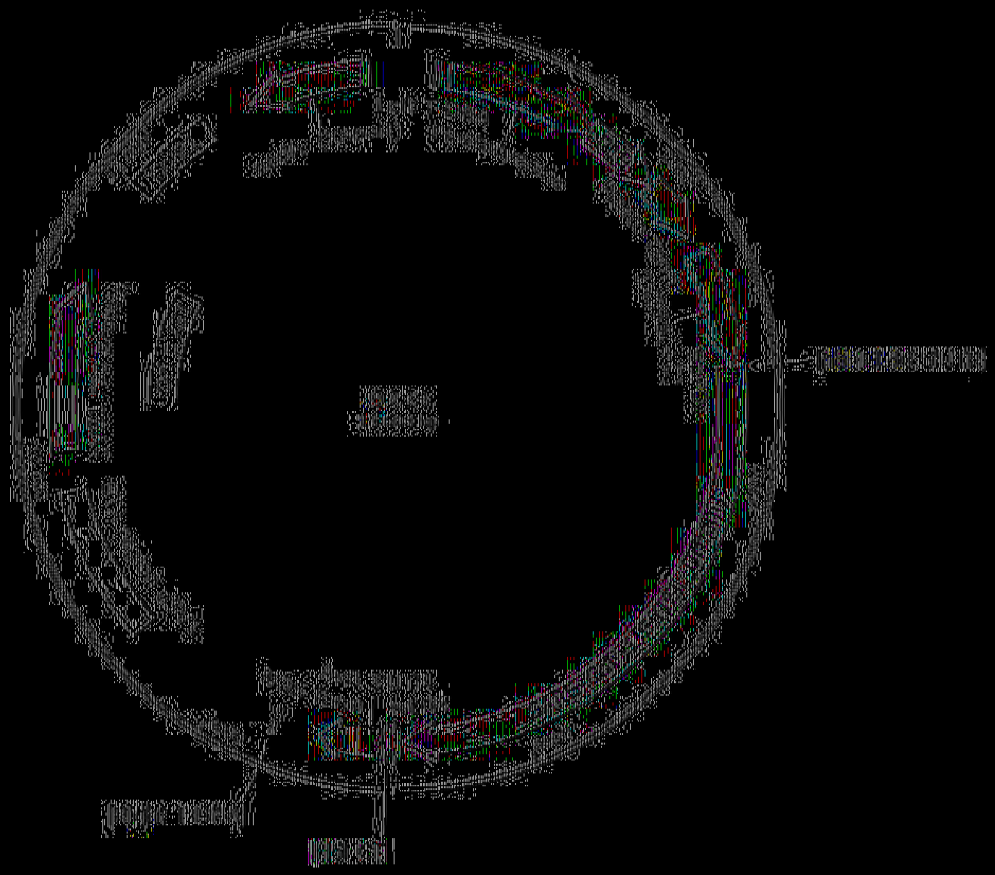


圖18C

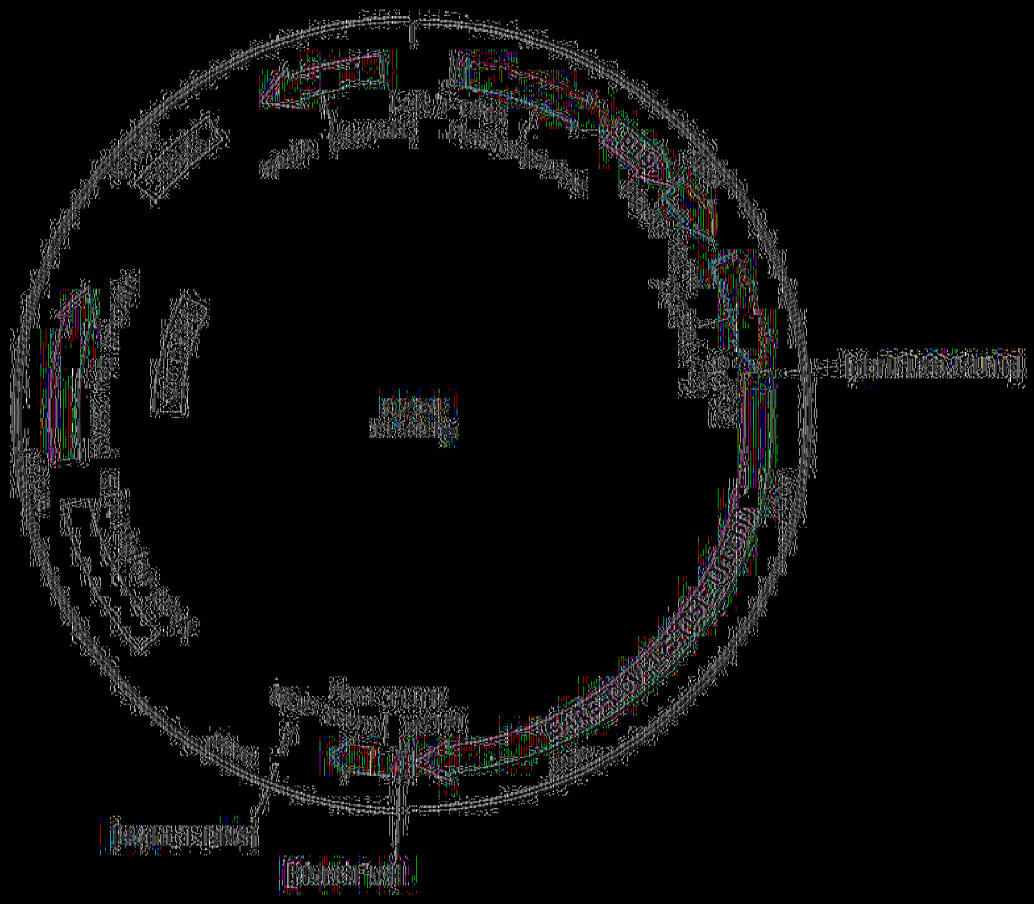


圖18D

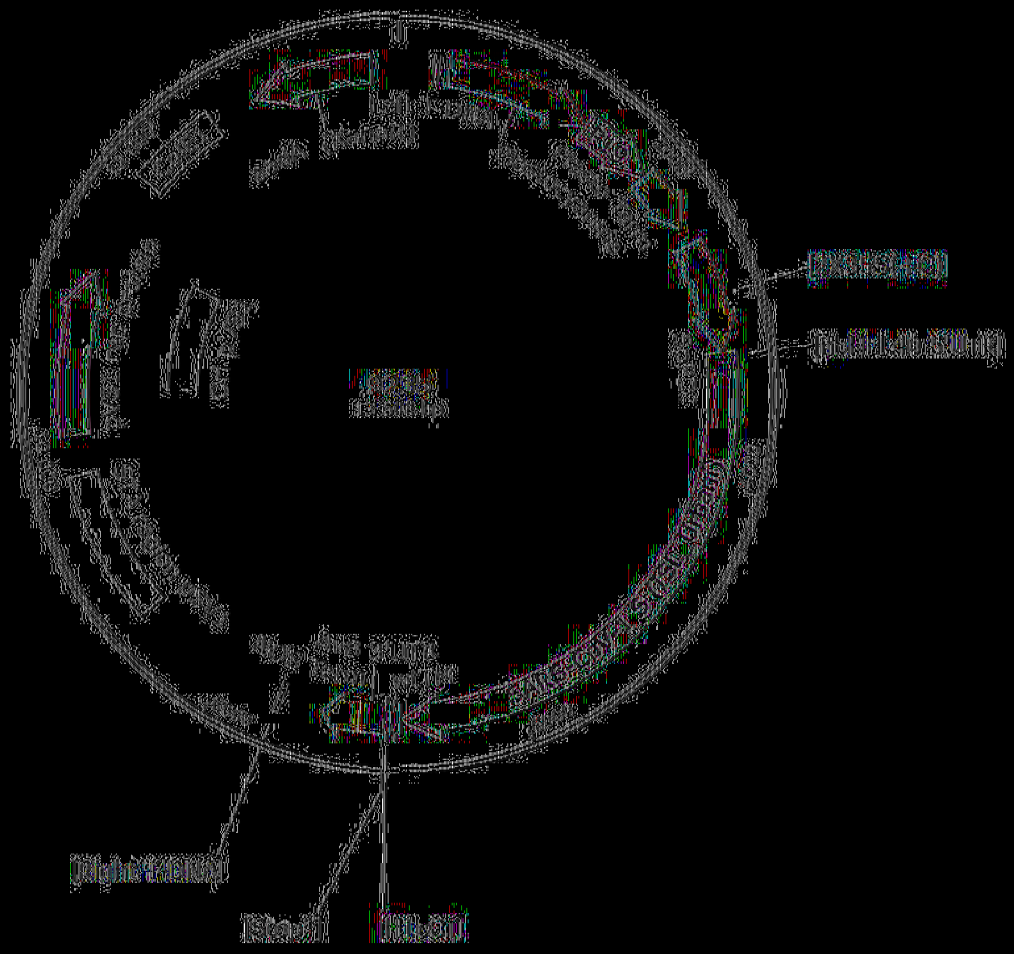


圖18E

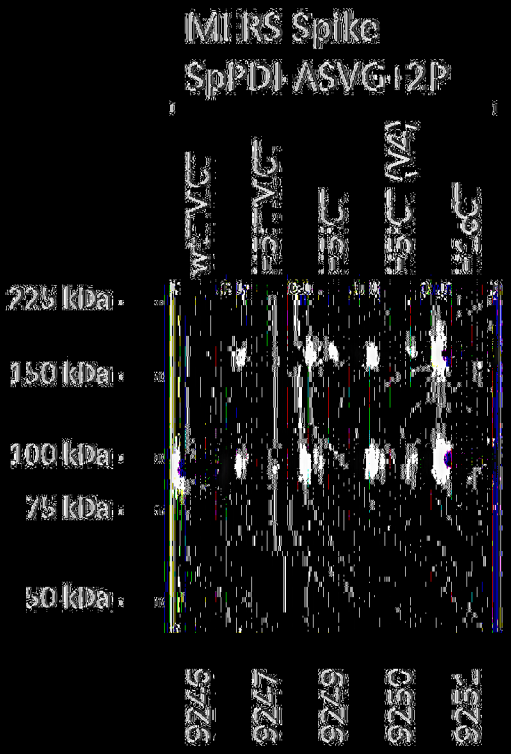

MERS Spike
SpPDI-ASVG-I2P
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa
9245
9247
9249
9250
9251

圖19A

圖19B

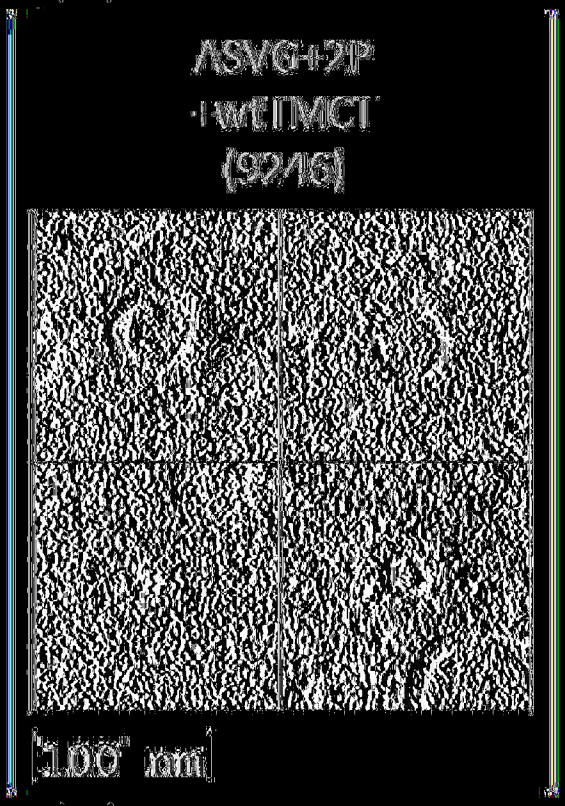


圖19C

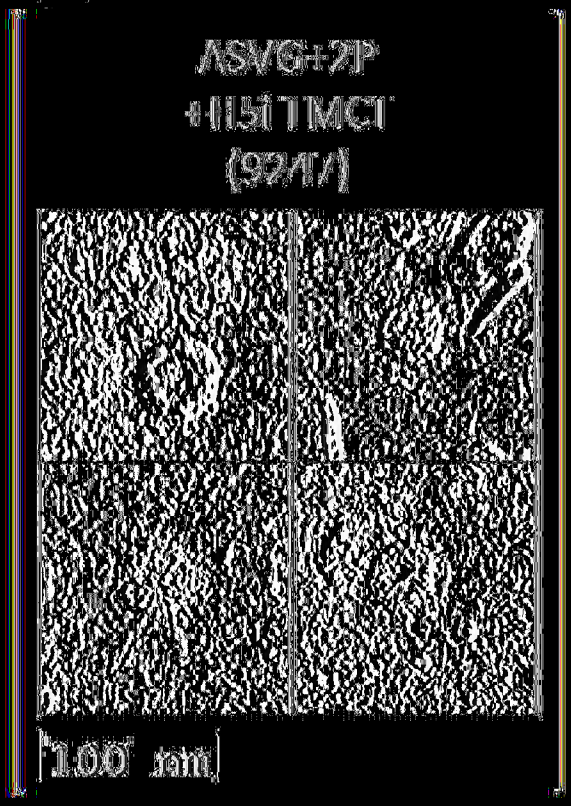


圖19D

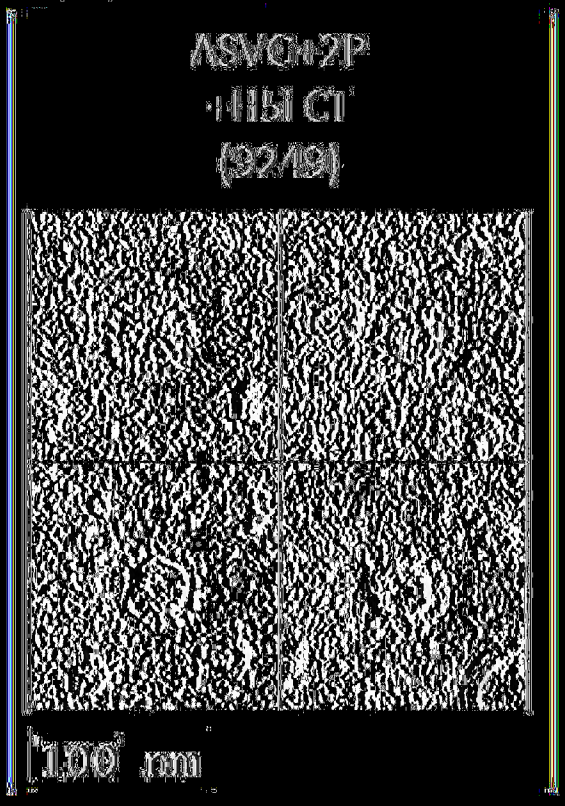


圖19E

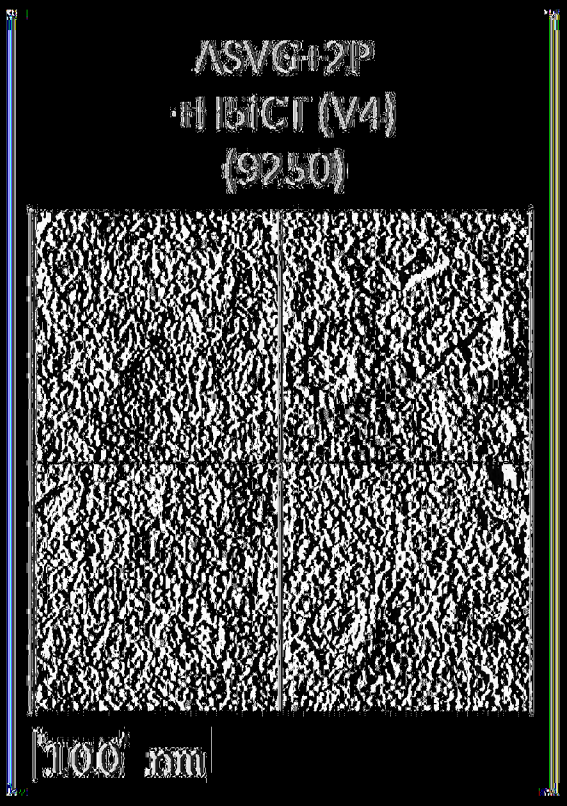


圖19F

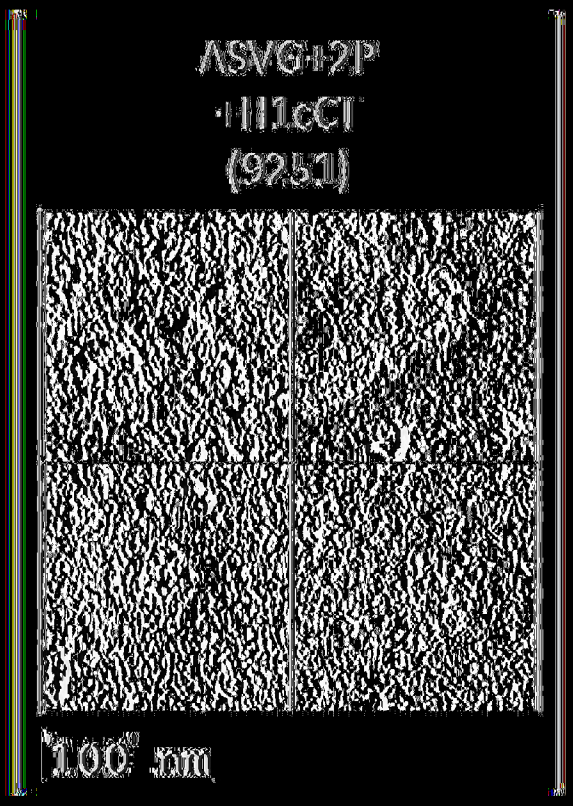




圖20A

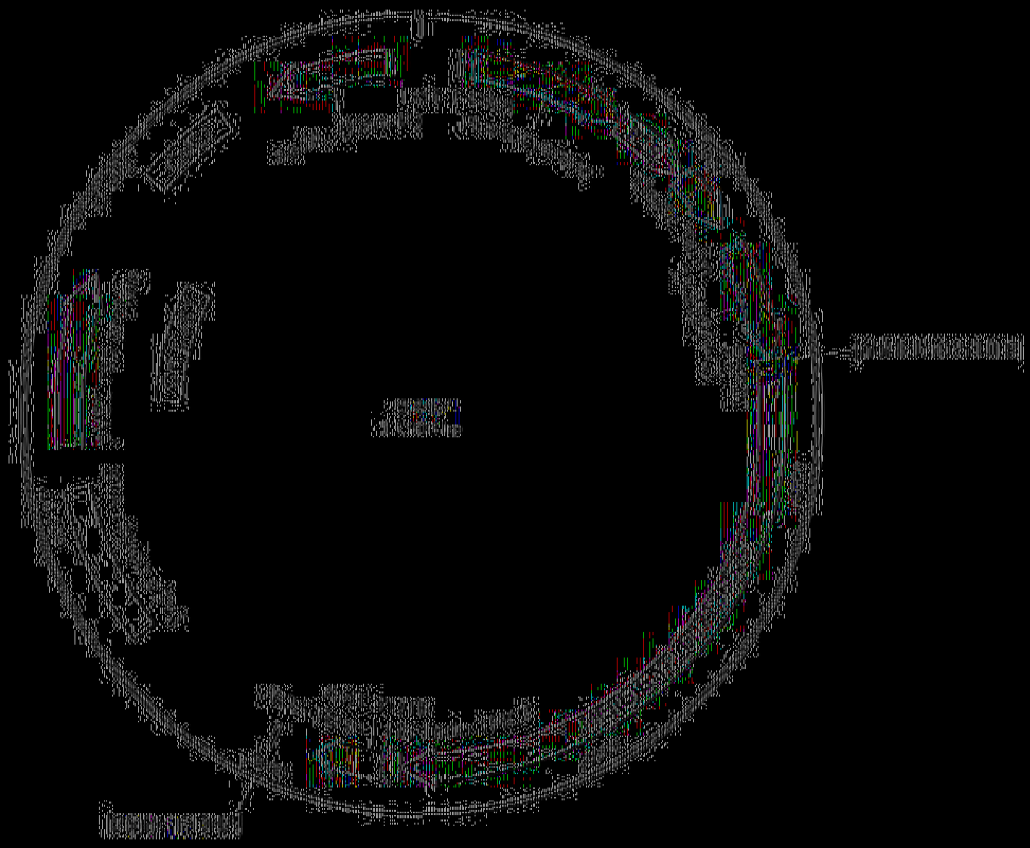


圖20B

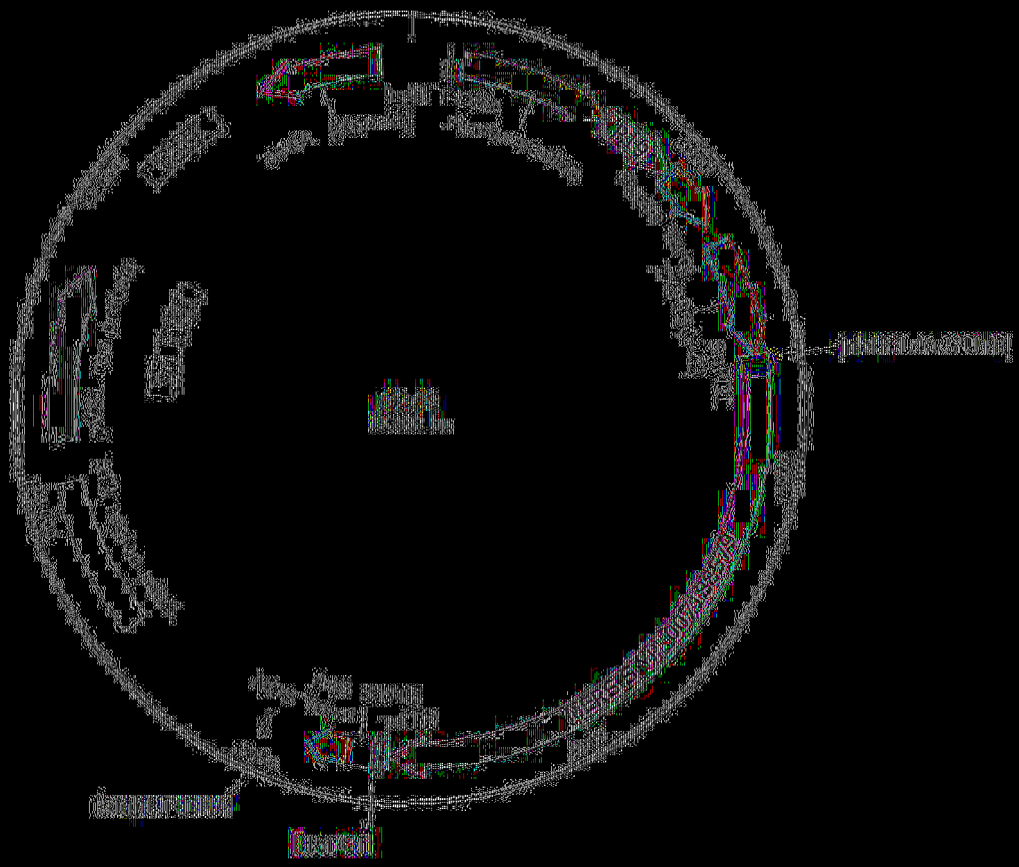


圖20C

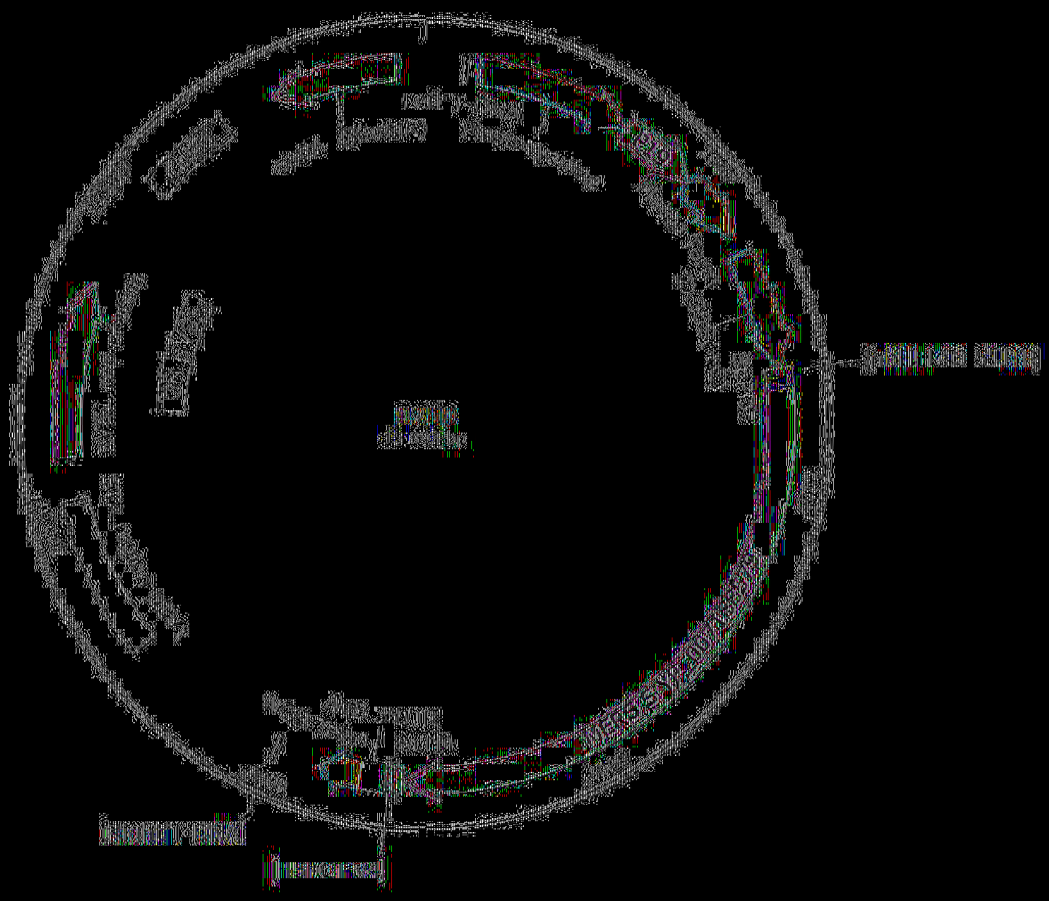


圖20D



圖20E

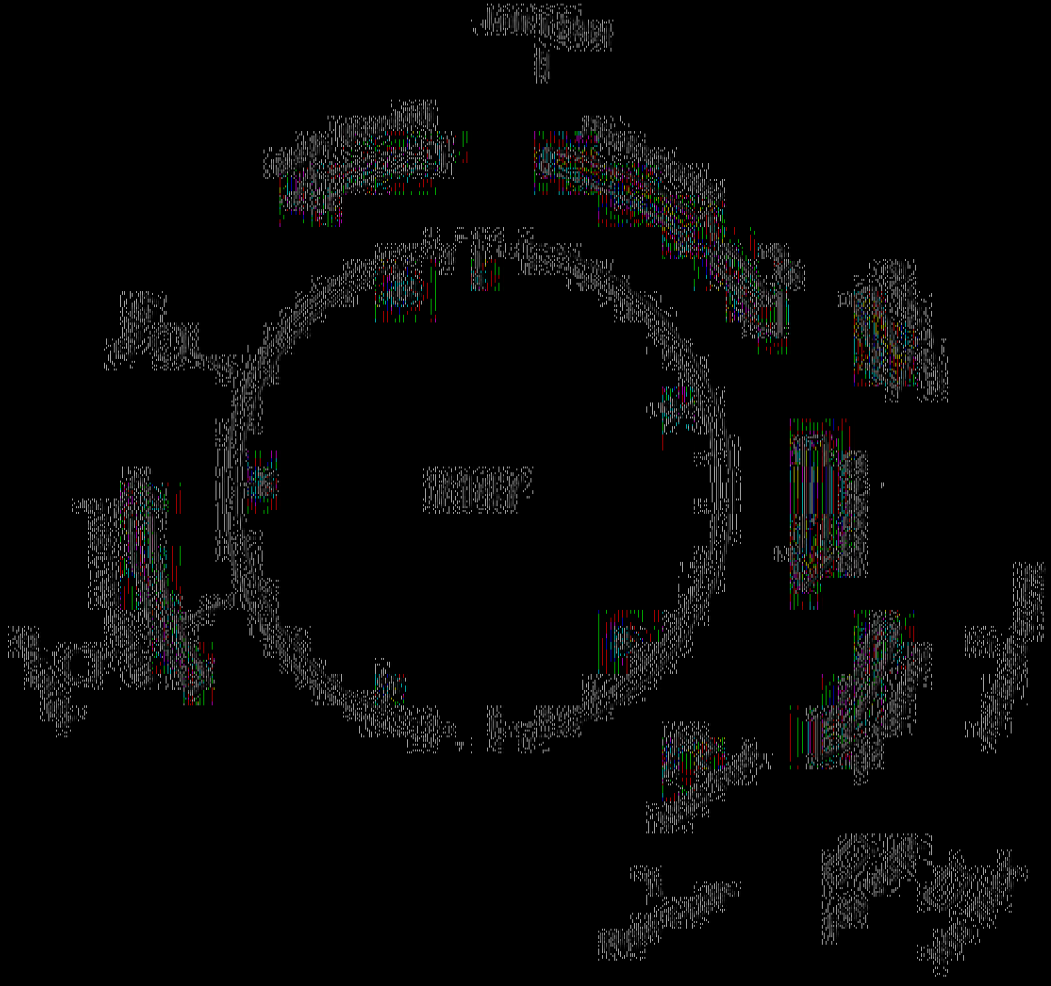


圖21

```
Native_YERS_S_no_signal_peptide_SEQ_ID_115     QDAQ□□RL□□VGRL□□□□NAEVAQQ□VRSESAA□SAQ□AKDKVNECVKAQSKRSGFCGQGTT  1105
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_114  AEVQ□□RL□□□GRL□QS□Q□VV□QQ□□RAAE□RASAV□AA□KVSECV□GQSKRVDFCGKGYH  1017
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_2    AEVQ□□RL□□□GRL□QS□Q□VV□QQ□□RAAE□RASAV□AA□KVSECV□GQSKRVDFCGKGYH  1033
                                                    ::.******.*** :*::::*******:: .    ***:**  *:.***  .*****  .****:* *

Native_YERS_S_no_signal_peptide_SEQ_ID_115     □VSEVVKAPKG□YEVV□VGYPSN□□EVVSAYG□CDAAVPI□NC□APVAGYF□KCNN□RVD  1165
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_114  □VSFPQAAPHGVVF□EVVYPSQERKF□□APAL□CEIGKA---YFPREGVFVFN------GT  1069
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_2    □VSFPQSAPHGVVF□EVVYPAQEKNF□□APAL□CEIGKA---HFPREGVFVSN------GT  1085
                                                    ::***   ****:.*:*** * *::: .:.:* .:*. ::  * ** *:. .

Native_YERS_S_no_signal_peptide_SEQ_ID_115     EMSVTGSSFYAPEPI□SA□KVVAPQVF□QK□□SFVI□PPPI□GVSIGCDVSFVSKV  1224
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_114  SMF□□QAVEESPQ□□□□□□CA□FVSGVCVF□G□□NVFVYSPFQ□--PFCSFEKPFSCSKV  1227
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_2    EMFVSQAVEYPQ□□□□□□CA□FVSGVCVF□G□VNVFVYSPFQ□--PFCSFEKPFSCSKV  1243
                                                    * *  .*: *: ***: **   .  .  . :.:.:  **          .*:*****:****

Native_YERS_S_no_signal_peptide_SEQ_ID_115     VSI□SIPNVGS□HQ□NV□□□□□□CI□YEVV□SF□QQVVKA□NESY□□CKFI□GVY□YVKWPWY□WF  1284
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_114  FESFCVI□GI□SG□NASWV□□QKF□□RNFVAKV□NESF□□□QFI□GKYEQY□KWPWYVWF  1187
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_2    FESFCVI□GI□SG□NASWV□□QKF□□RNFVAKV□NESF□□□QFI□GKYEQY□KWPWY□WF  1203
                                                    ::  :**:.*** **:::::::::  *:  *:***.* **** ****:****:*  * ******:**

Native_YERS_S_no_signal_peptide_SEQ_ID_115     GFI□AGLVAL□LCVFI□□CC□GCGCNVGKL□KCNIGCCNYEYVPHPFKVEVF----□336
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_114  GFI□AGI□A□VVVI□□□CCVI□SCCSCI□KCACSCGSCCKF-DEDDSEPVL□KGVKL□YYF--□242
Native_SARS-CoV-2_S_no_signal_peptide_SEQ_ID_2    GFI□AGI□A□VVVI□□□CCVI□SCCSCI□KGCCSCGSCCKF-DEDDSEPVL□KGVKL□YYF--□258
                                                    **********:::. .::: * *.*.: :  **  .*. ***.  :: * ** **:
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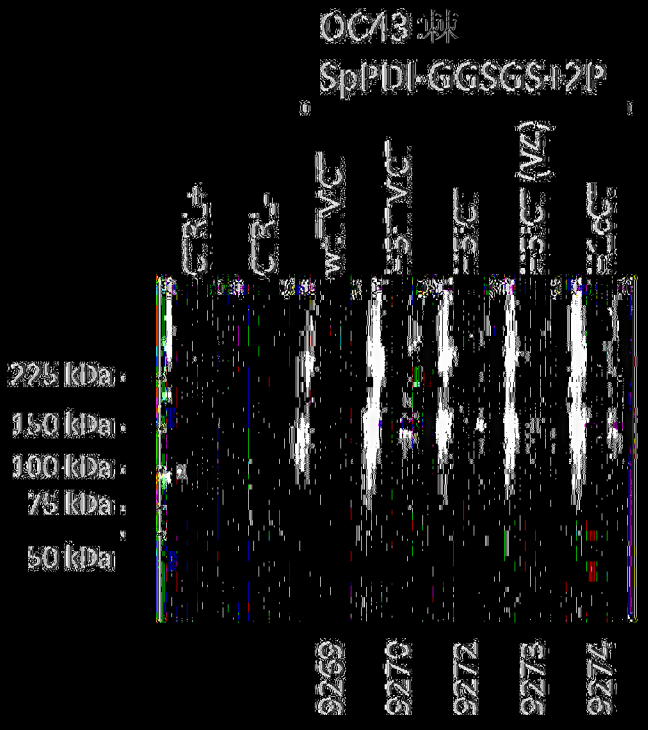

OC43 刺突
SpPDI-GGSGS-I2P
Beta
Delta
BA.1
BA.5
Eris
BA.2.86 (VA)
JN.1
225 kDa
150 kDa
100 kDa
75 kDa
50 kDa
2269
2270
2272
2273
2274
抗-刺突蛋白(S1)

圖23A

圖23B

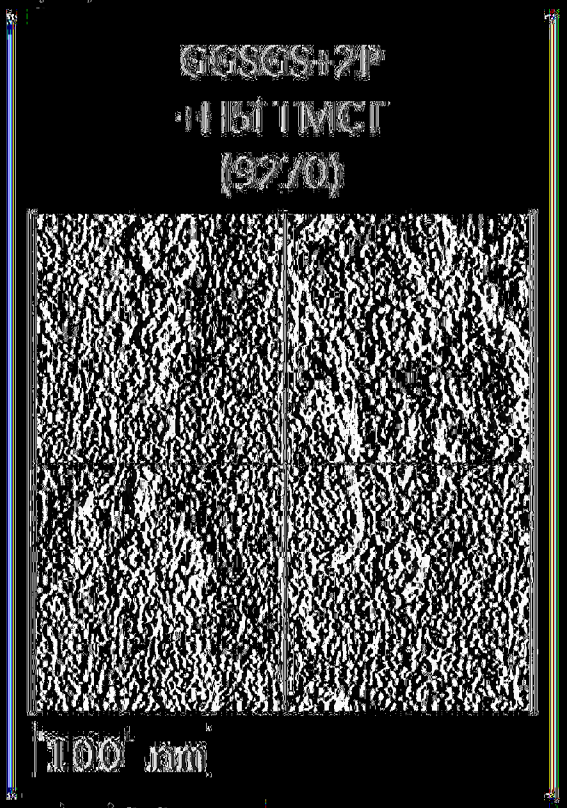


圖23C

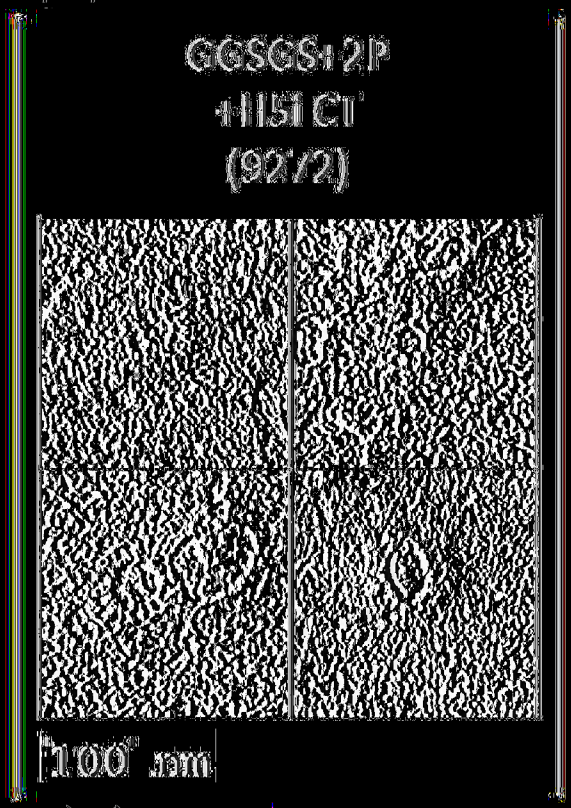


圖23D

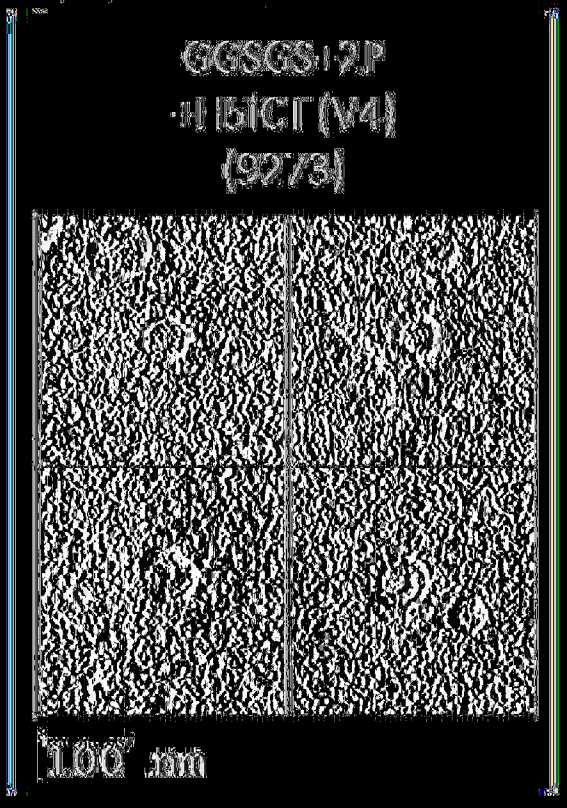
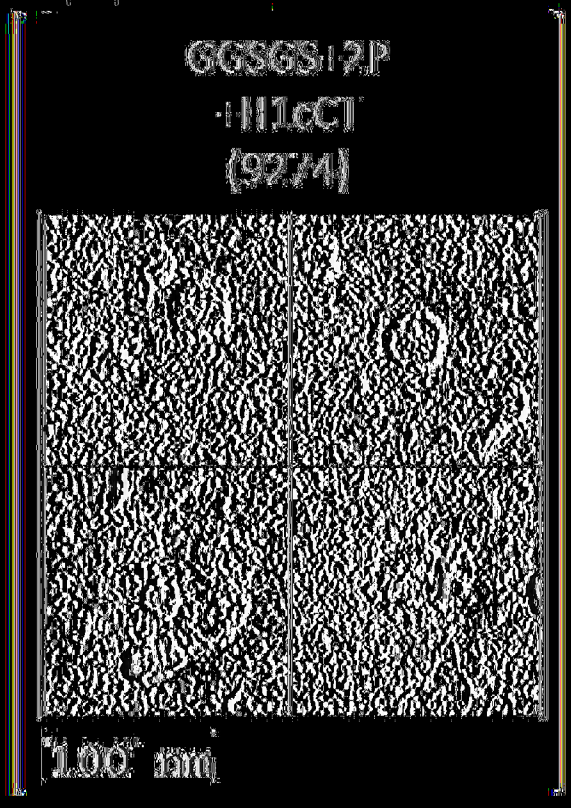


圖23E



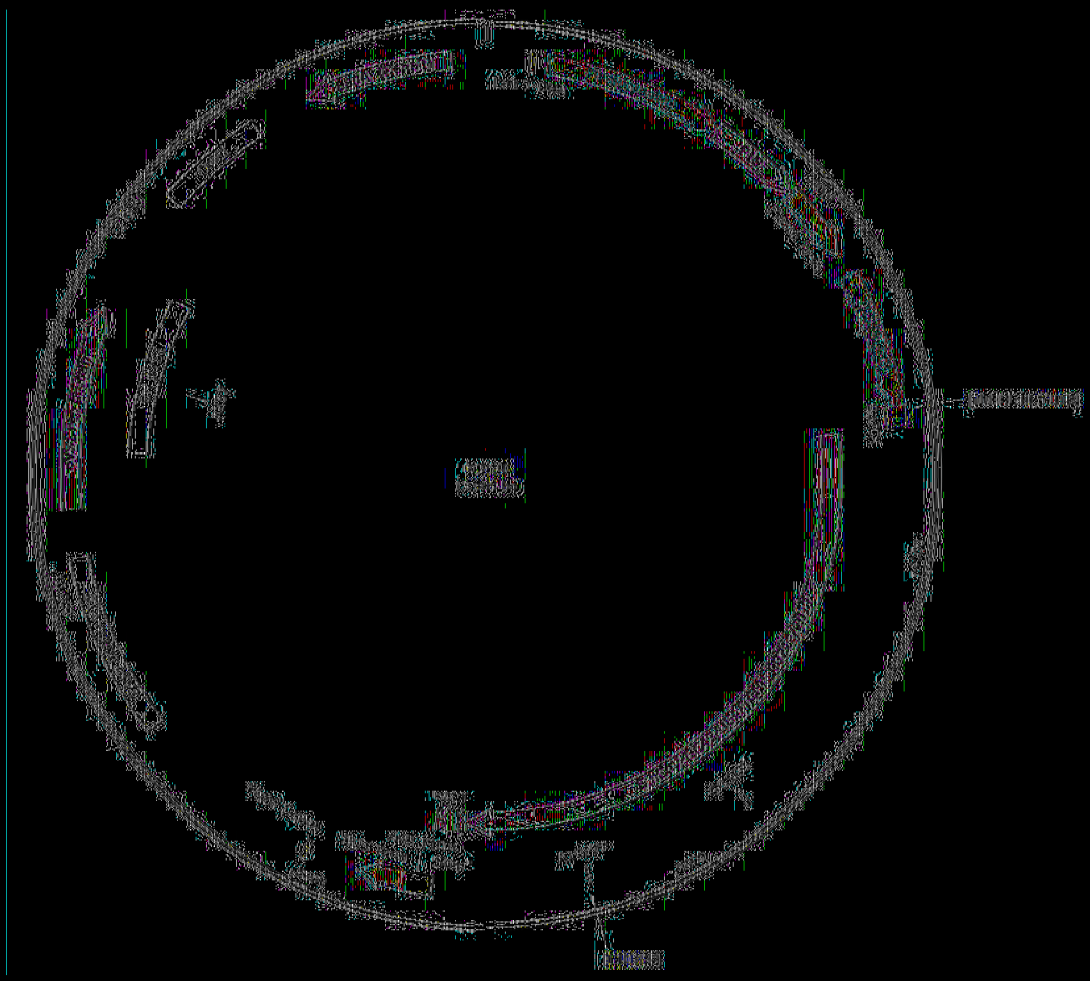
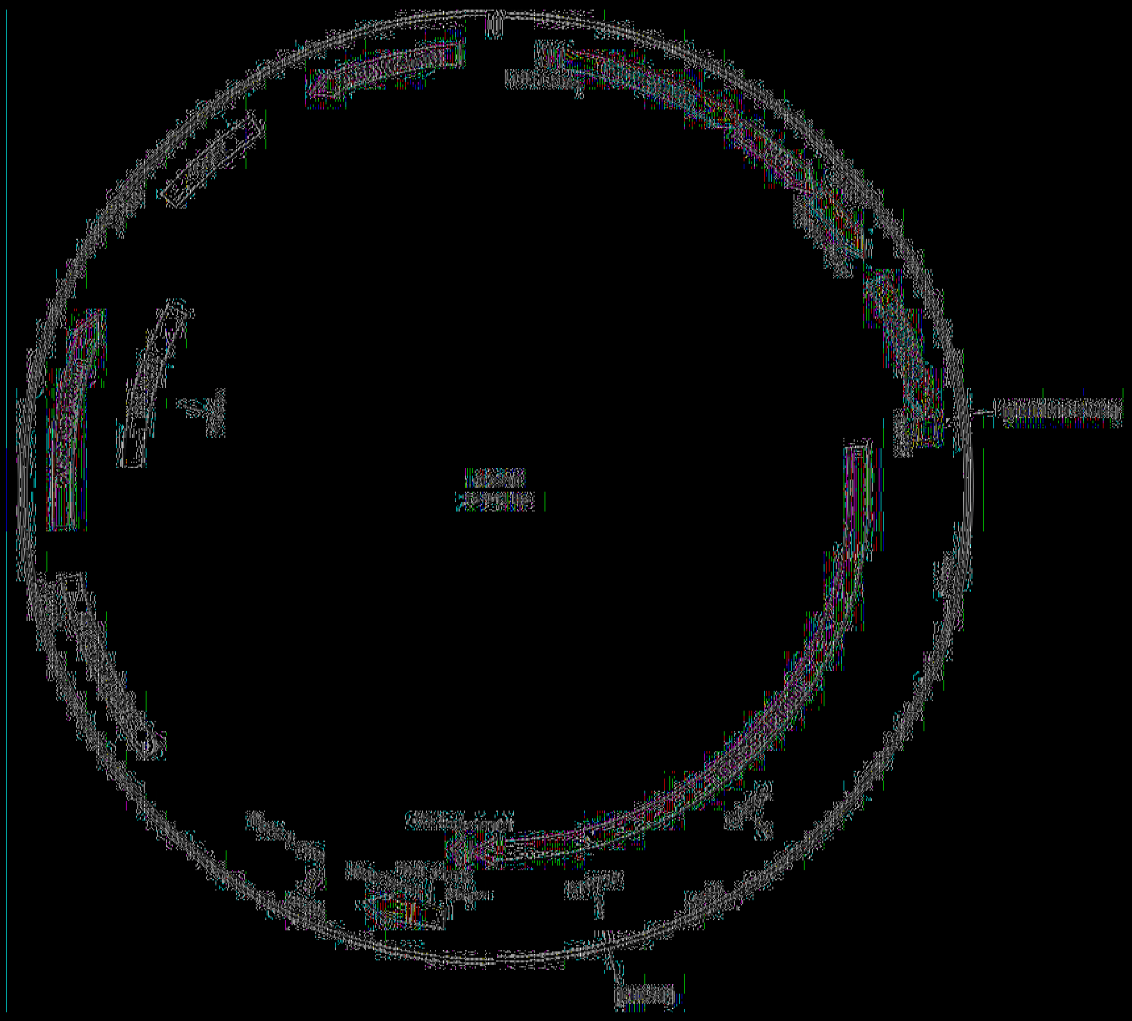


圖24A



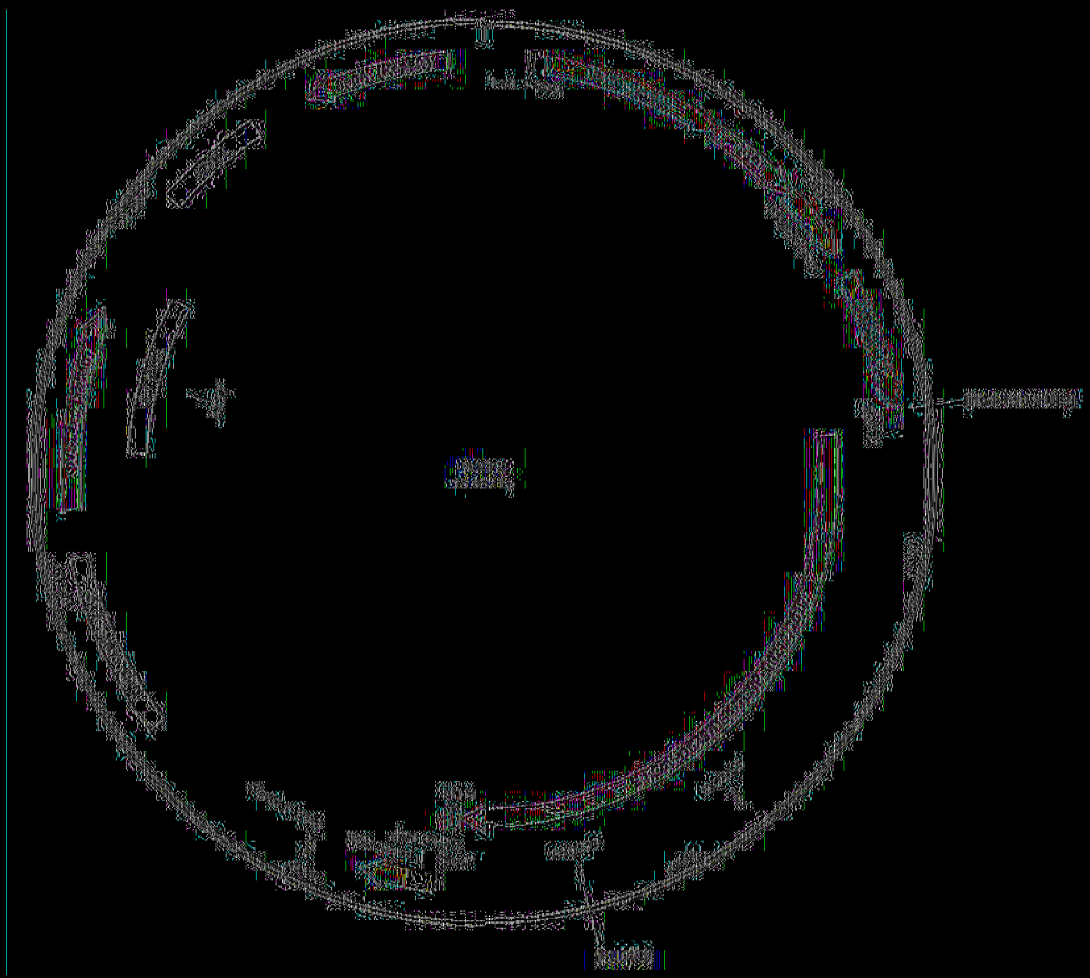


FIG. 24C

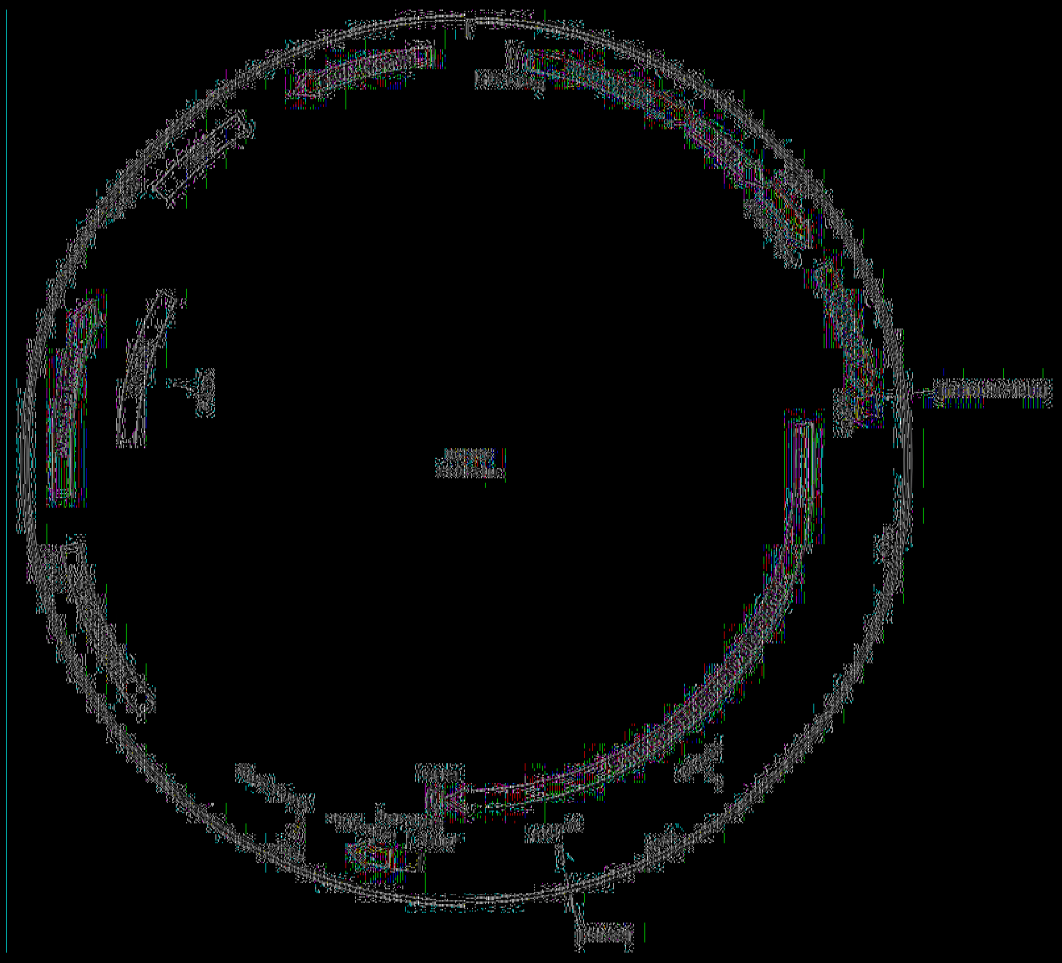


圖2A

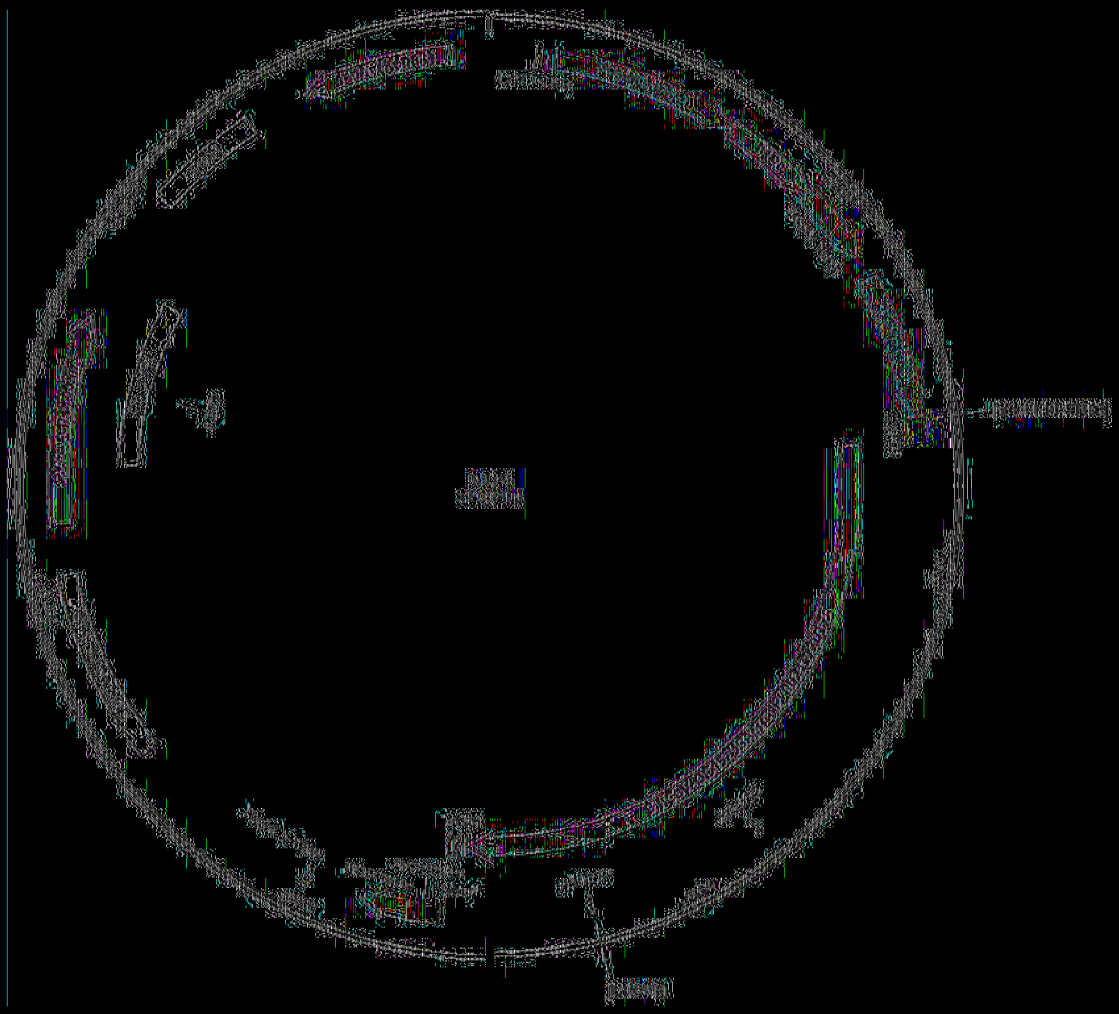


圖24E

圖25A

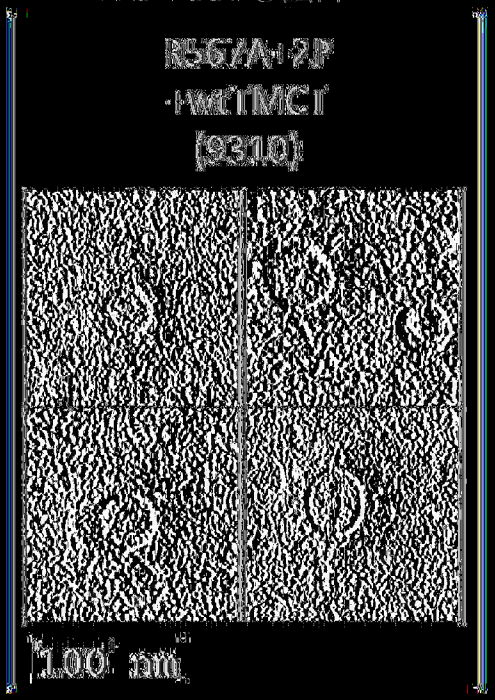


圖25B

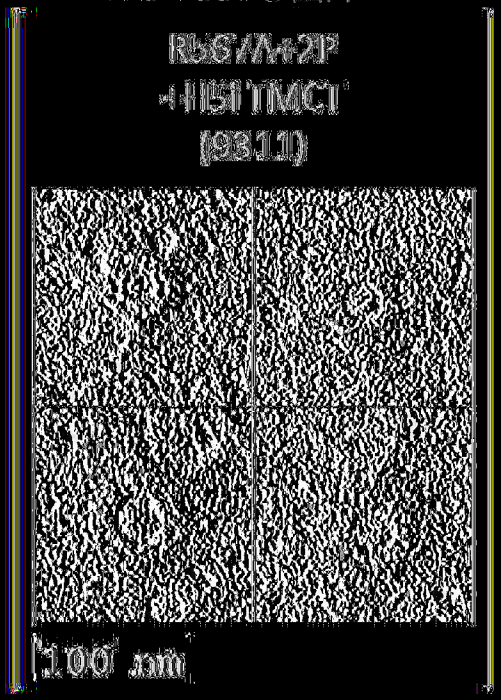


圖25C

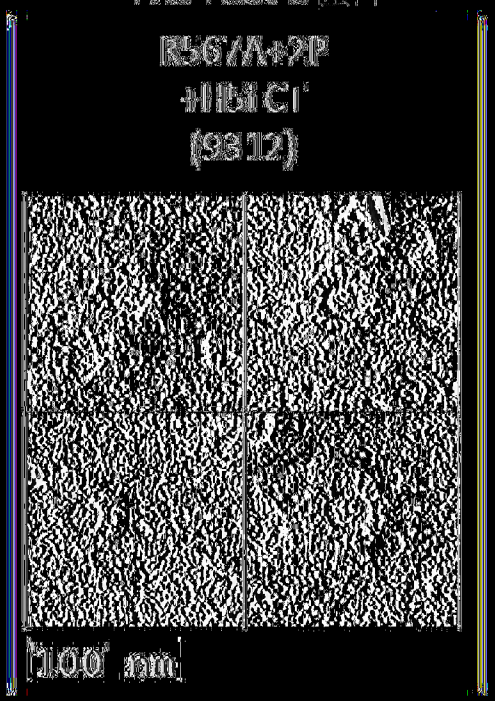


圖25D

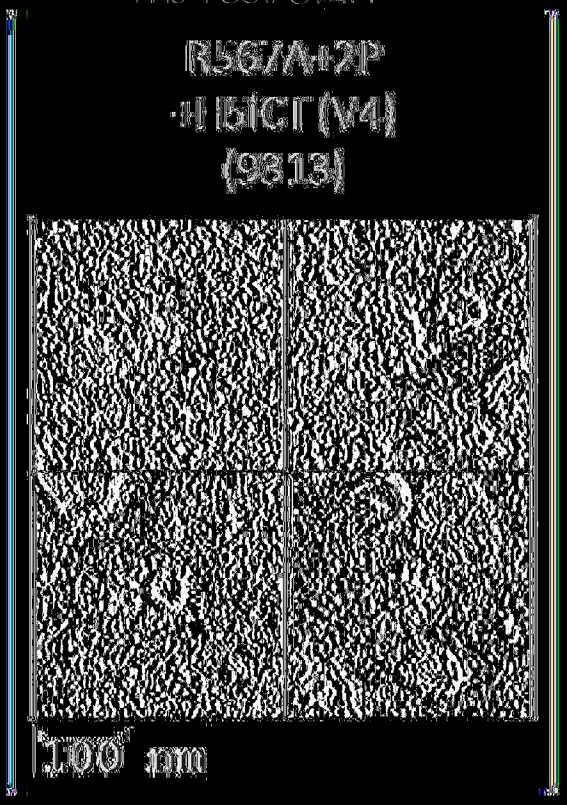
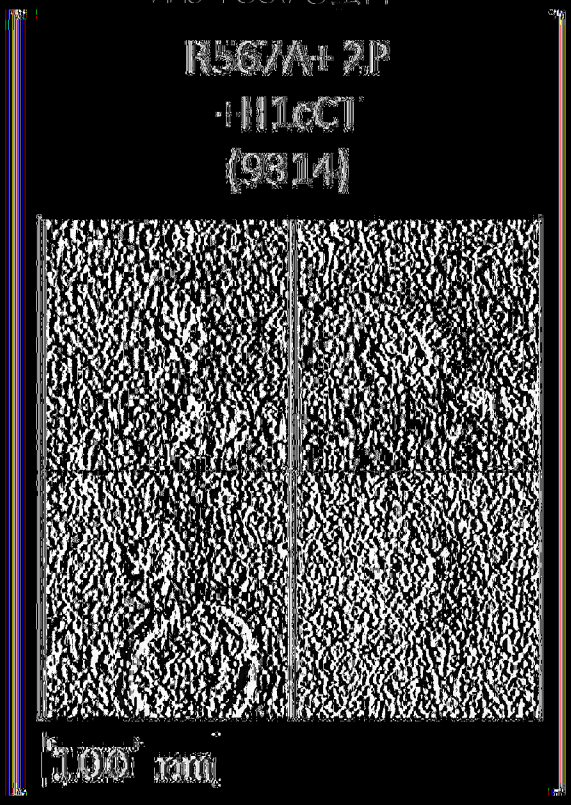

229E CoV S蛋白
R56/A+2P
+H5CT (V4)
(9313)
100 nm

圖25E


229E CoV S蛋白
R56/A+ 2P
+H1cCT
(9314)
100 nm

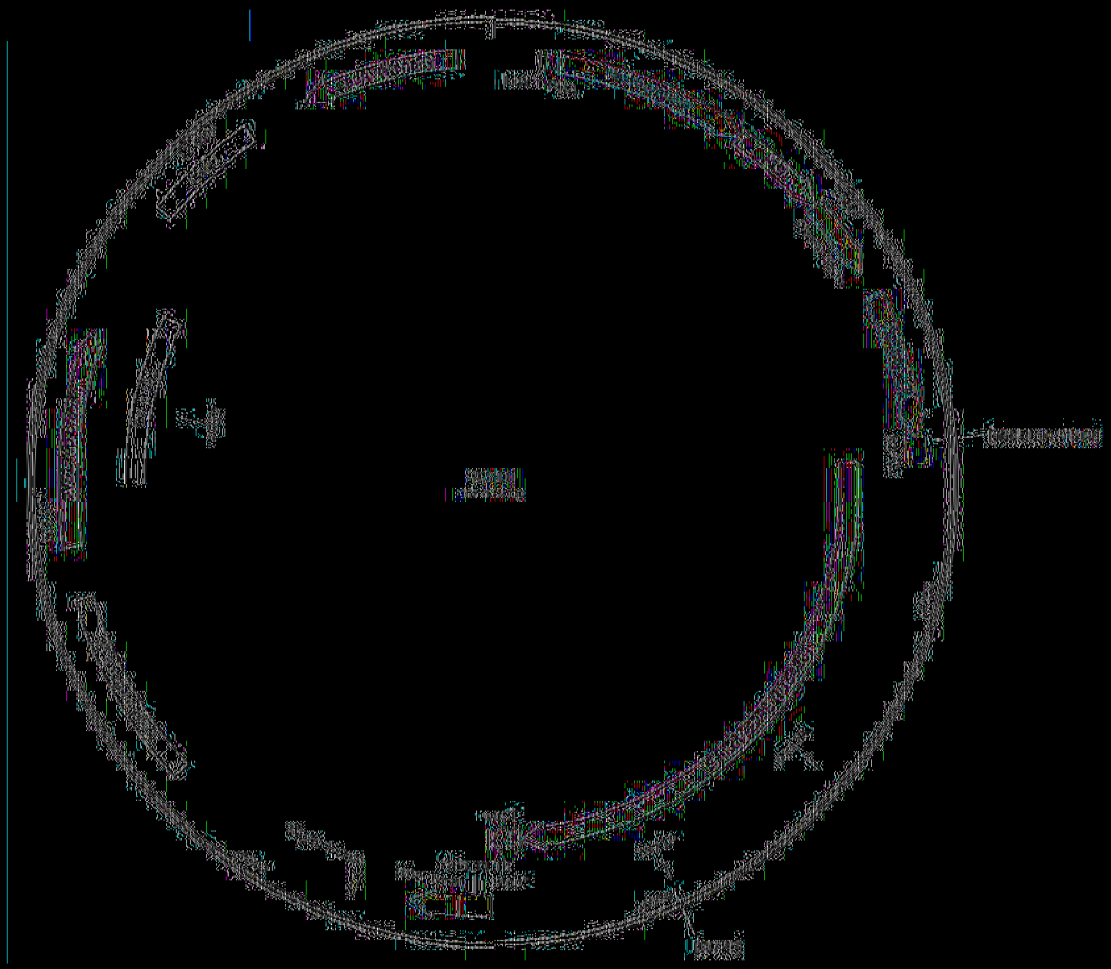
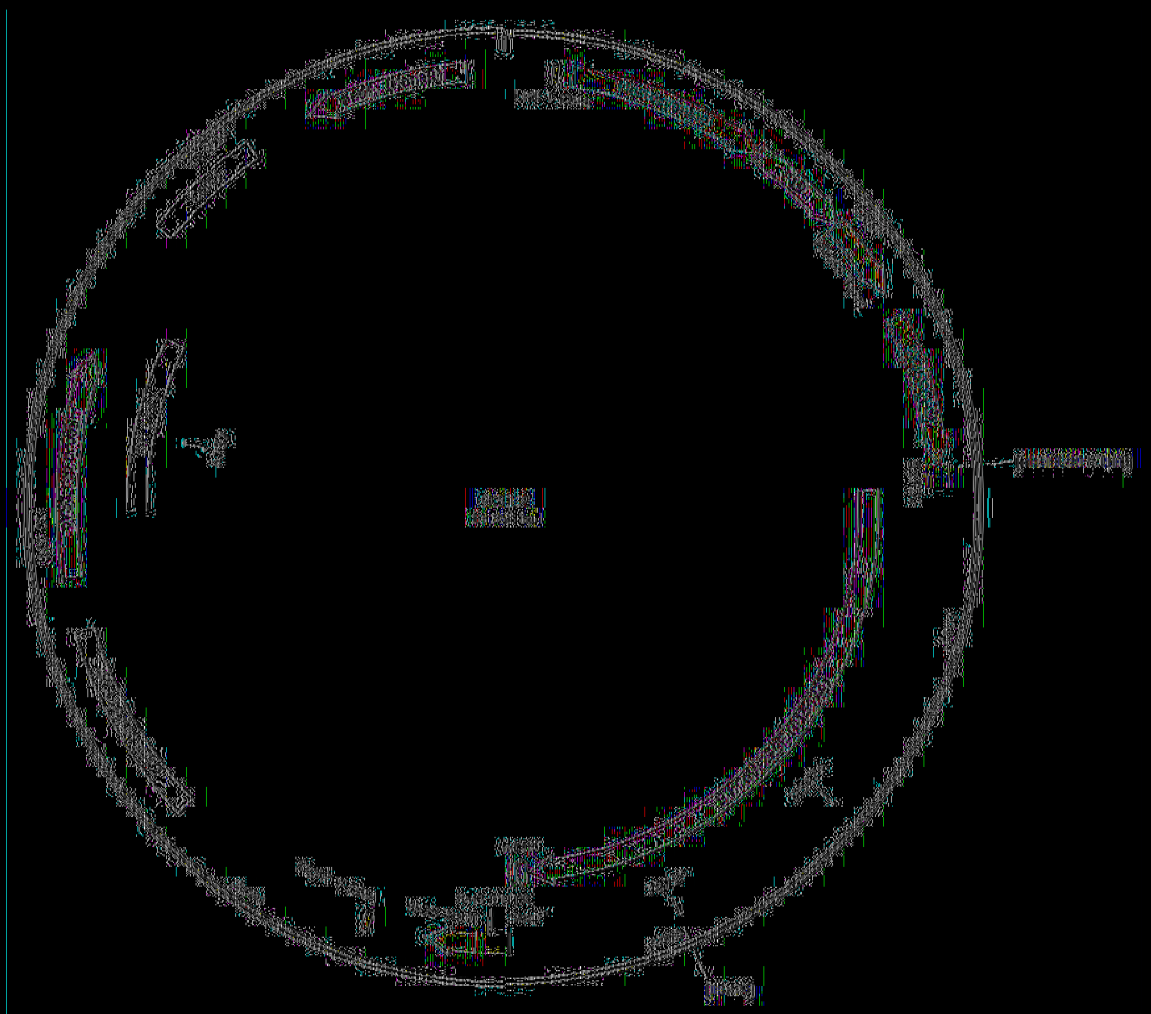


圖 26A



圖26B



26C

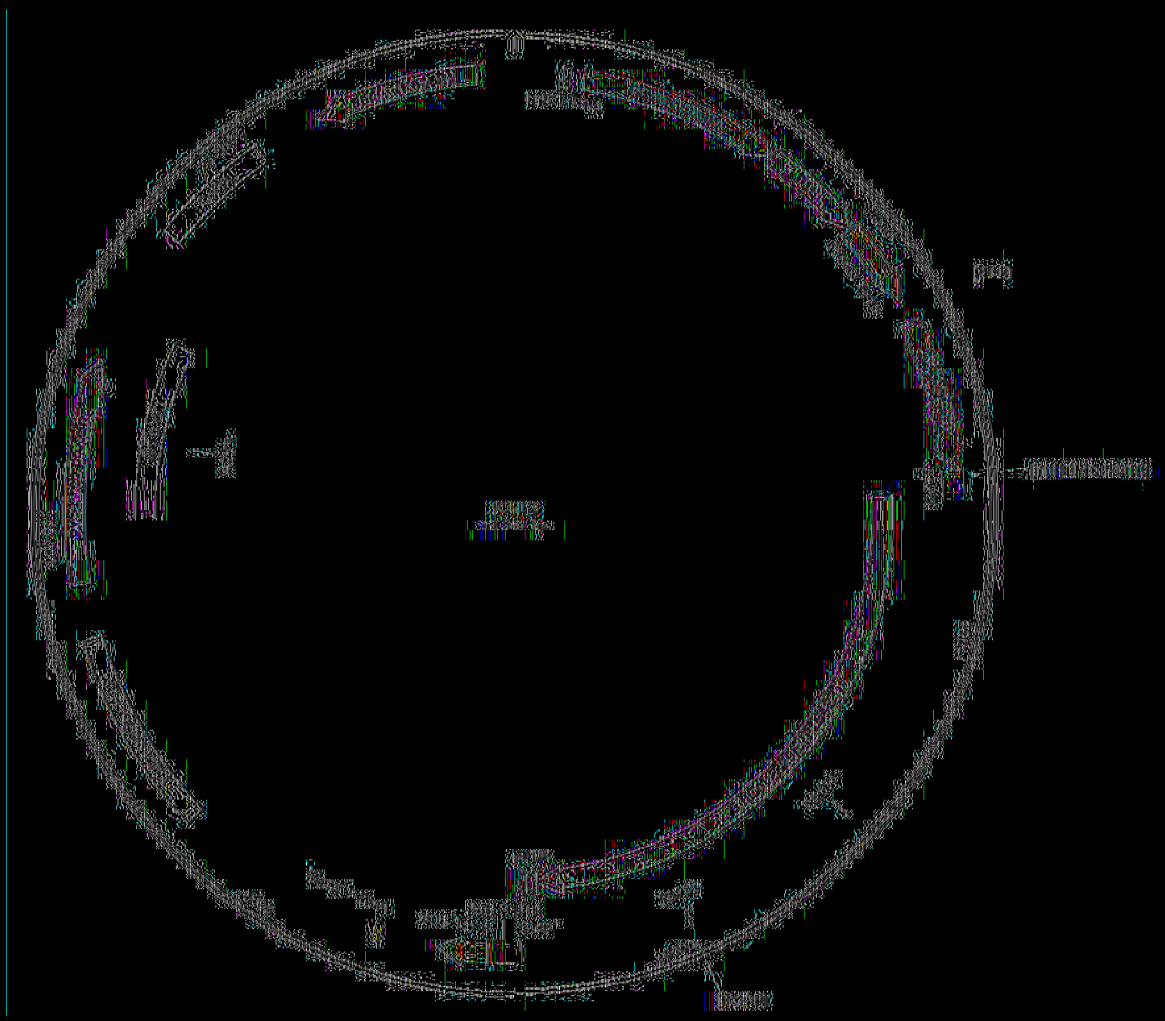


圖 2 6D

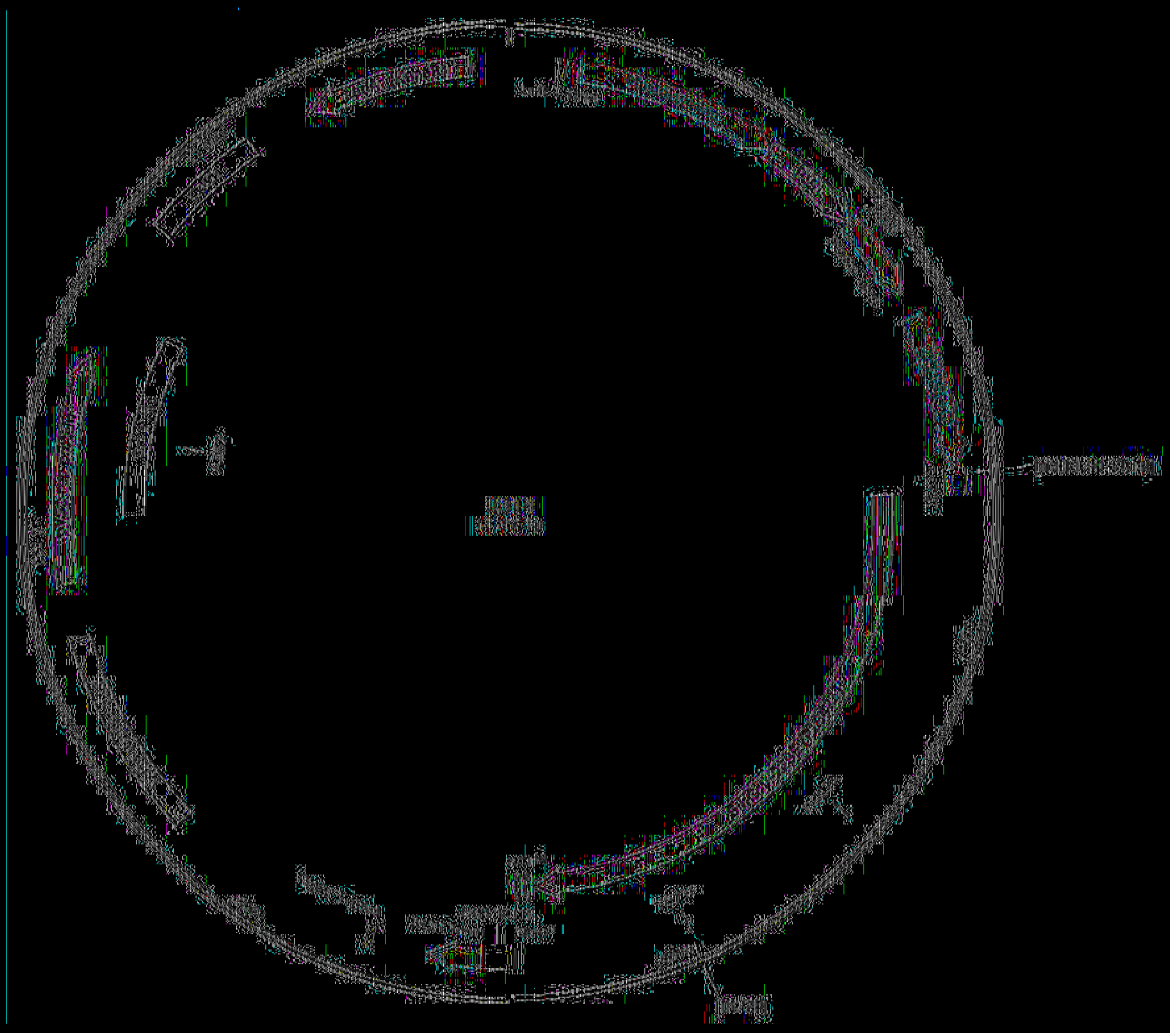


圖26E

110年12月30日修正替換頁

【發明申請專利範圍】

【請求項1】　一種經修飾的冠狀病毒S-蛋白，依序地包括：

- 源自冠狀病毒 S-蛋白的胞外結構域；以及

- 跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：

- 跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白；以及

- 胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白。

【請求項2】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述TM係直接融合至所述CT。

【請求項3】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述TM係包括嵌合TM，其源自所述冠狀病毒S-蛋白之TM的N-端序列和源自所述流感HA蛋白之TM的C-端序列。

【請求項4】　如請求項3所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TM包括源自所述冠狀病毒S-蛋白之TM的N-端序列，所述冠狀病毒S-蛋白之TM包括對應於SEQ ID NO： 18或SEQ ID NO： 169之胺基酸1-20的至少20個胺基酸；或對應於SEQ ID NO： 118或SEQ ID NO：164之胺基酸1-21的至少21個胺基酸；或對應於SEQ ID NO： 123之胺基酸1-22的至少22個胺基酸；及來自所述流感HA蛋白之TM的C-端的一個或多於一個的胺基酸。

【請求項5】　如請求項4所述之經修飾的冠狀病毒S-蛋白，其中，來自所述流感HA蛋白之TM的C-端的所述一個或多於一個的胺基酸係選自AGL或AGL的保留取代、MAGL或MAGL的保留取代。

【請求項6】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述CT係包括嵌合CT，其源自所述冠狀病毒S-蛋白之CT的N-端序列和源自所述流感

HA蛋白之CT的C-端序列。

【請求項7】　如請求項6所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合CT包括源自所述流感HA蛋白之CT的C-端序列，所述流感HA蛋白之CT包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸；及來自所述冠狀病毒S-蛋白之CT的N-端的一個或多於一個的胺基酸。

【請求項8】　如請求項7所述之經修飾的冠狀病毒S-蛋白，其中，來自所述冠狀病毒S-蛋白之CT的N-端的所述一個或多於一個的胺基酸係選自C或C的保留取代、CC或CC的保留取代、或CCM或CCM的保留取代。

【請求項9】　如請求項3所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TM包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的胺基酸；或對應於SEQ ID NO：118或SEQ ID NO：164之胺基酸1-21的胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的胺基酸。

【請求項10】　如請求項4所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合CT包括對應於SEQ ID NOs：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸。

【請求項11】　如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述嵌合TMCT包括嵌合TM及嵌合CT，所述嵌合TM包括對應於SEQ ID NO：18或SEQ ID NO：169之胺基酸1-20的胺基酸；或對應於SEQ ID NO：118或SEQ ID NO：164之胺基酸1-21的胺基酸；或對應於SEQ ID NO：123之胺基酸1-22的胺基酸，所述嵌合CT包括對應於SEQ ID NO：18、126、128、129、130或131之胺基酸27-37的胺基酸；或對應於SEQ ID NO：127之胺基酸27-36的胺基酸或其組合。

【請求項12】　如請求項1至11中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與野生型冠狀病毒S-蛋白胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白包括一個或多於一個的胺基酸取代。

【請求項13】 如請求項12所述之經修飾的冠狀病毒S-蛋白，其中，所述一個或多於一個的胺基酸取代包括：

i) 限制在 S1 次單位與 S2 次單位之間的切割位點處之加工的取代；

ii) 一個或多於一個的胺基酸取代為一個或多於一個的脯胺酸；或

iii) 限制在 S1 次單位與 S2 次單位之間的切割位點處之加工的取代以及一個或多於一個的胺基酸取代為一個或多於一個的脯胺酸。

【請求項14】 如請求項12或13所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置971和972處的胺基酸。

【請求項15】 如請求項12或13所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述一個或多於一個的胺基酸取代對應於在位置802、927、971和972處的胺基酸。

【請求項16】 如請求項14或15所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白進一步包括對應於在位置667、668、670處，或其組合的胺基酸的一個或多於一個的胺基酸取代。

【請求項17】 如請求項16所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代。

【請求項18】 如請求項16所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺

酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802、927、971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代。

【請求項19】 如請求項14至18中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與SEQ ID NO：2之參考胺基酸序列相比時，所述經修飾的冠狀病毒S-蛋白進一步包括對應於在位置923處的胺基酸的胺基酸取代。

【請求項20】 如請求項19所述之經修飾的冠狀病毒S-蛋白，其中，對應於在SEQ ID NO：2之位置667處的胺基酸的所述胺基酸取代為甘胺酸或甘胺酸的保留取代，對應於在SEQ ID NO：2之位置668處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置670處的胺基酸的所述胺基酸取代為絲胺酸或絲胺酸的保留取代，對應於在SEQ ID NO：2之位置802、927、971和972處的胺基酸的所述胺基酸取代為脯胺酸或脯胺酸的保留取代，及對應於在SEQ ID NO：2之位置923處的胺基酸的所述胺基酸取代為苯丙胺酸或苯丙胺酸的保留取代。

【請求項21】 如請求項12至20中任一項所述之經修飾的冠狀病毒S-蛋白，其中，與沒有在宿主或宿主細胞中表現的一個或多於一個的取代的對應S-蛋白的產量相比時，在所述宿主或宿主細胞中表現時，所述一個或多於一個的胺基酸取代使S-蛋白保持在融合前狀態或生產更高產量的經修飾的S-蛋白。

【請求項22】 如請求項1至21中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述S-蛋白包括S1次單位和S2次單位，其中所述S2次單位包括所述嵌合TMCT。

【請求項23】 如請求項1至22中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述流感HA蛋白係源自B型流感或H1、H2、H3、H4、H5、H6、H7、H8、H9、H10、H11、H12、H13、H14、H15或H16亞型流感。

【請求項24】 如請求項1至23中任一項所述之經修飾的冠狀病毒S-蛋白，

其中，所述冠狀病毒S-蛋白係源於SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV。

【請求項25】 如請求項1至23中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述胞外結構域係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，所述TM或所述TM的部分係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV，或其中，所述胞外結構域和所述TM或所述TM的部分係源自SARS-CoV-2、SARS-CoV-1、MERS-CoV、OC43-CoV或229E-CoV。

【請求項26】 如請求項1至25中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述TMCT包括具有與SEQ ID NO：18、19、37、38、39、64、126、127、128、129、130、131、118、119、120、123、124、125、134、135、164、165、166、169、170、171、172或173之序列約80%至約100%同一性的序列。

【請求項27】 如請求項1至26中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白係作為前驅蛋白產生，所述前驅蛋白包括所述經修飾的冠狀病毒S-蛋白和訊號肽。

【請求項28】 如請求項27所述之經修飾的冠狀病毒S-蛋白，其中，所述訊號肽對於所述經修飾的冠狀病毒S-蛋白係原生的或非原生的。

【請求項29】 如請求項27或28所述之經修飾的冠狀病毒S-蛋白，其中，所述訊號肽係源自蛋白質二硫鍵異構酶(PDI)的訊號肽。

【請求項30】 如請求項1至29中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白包括植物特異性N-聚醣。

【請求項31】 如請求項1所述之經修飾的冠狀病毒S-蛋白，其中，所述經修飾的冠狀病毒S-蛋白的胺基酸序列包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：5、21、30、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、95、96、97、108、109、110、144、145、146、

155、156或157之胺基酸；或SEQ ID NO：47之胺基酸24-1259，SEQ ID NO：48之胺基酸25-1259；SEQ ID NO： 49之胺基酸25-1259；SEQ ID NO：50之胺基酸25-1259；SEQ ID NO：51之胺基酸25-1259；SEQ ID NO：52之胺基酸25-1259；SEQ ID NO：53之胺基酸25-1259；SEQ ID NO：54之胺基酸25-1259；SEQ ID NO：55之胺基酸25-1259；SEQ ID NO：56之胺基酸25-1259；SEQ ID NO：57之胺基酸25-1259；SEQ ID NO：58之胺基酸25-1259；SEQ ID NO： 59之胺基酸25-1262；SEQ ID NO：60之胺基酸25-1261；SEQ ID NO：61之胺基酸25-1258；或SEQ ID NO：62之胺基酸25-1256；SEQ ID NO：95之胺基酸25-1243；SEQ ID NO：96之胺基酸25-1240；SEQ ID NO：97之胺基酸25-1243；SEQ ID NO：108之胺基酸25-1341；SEQ ID NO：109之胺基酸25-1338；SEQ ID NO：110之胺基酸25-1341；或SEQ ID NO：144之胺基酸25-1351；SEQ ID NO：145之胺基酸25-1348；SEQ ID NO：146之胺基酸25-1351；SEQ ID NO：155之胺基酸25-1159；SEQ ID NO：156之胺基酸25-1156；或SEQ ID NO：157之胺基酸25-1159。

【請求項32】 如請求項1至30中任一項所述之經修飾的冠狀病毒S-蛋白，其中，所述CT或所述CT的部分包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：15；或SEQ ID NO：6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568；或SEQ ID NO：18之胺基酸22-37；或SEQ ID NO：19之胺基酸21-40；或SEQ ID NO：37之胺基酸21-39；或SEQ ID NO：38之胺胺基酸25-36；或SEQ ID NO：39之胺基酸24-34；或 SEQ ID NO：126、128、129、130或131之胺基酸22-37；或SEQ ID NO：127之胺基酸22-36。

【請求項33】 如請求項27所述之經修飾的冠狀病毒S-蛋白，其中，所述前驅蛋白包括與具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：1之胺基酸1-1234；SEQ ID NO：5之胺基酸1-1234；或SEQ ID NO：30之胺基酸1-1243；SEQ ID NO：95之胺基酸1-1227；SEQ ID NO：108之胺基酸1-1325；SEQ ID NO：

112之胺基酸1-1216、SEQ ID NO：113之胺基酸1-1318；SEQ ID NO：144之胺基酸1-1335；SEQ ID NO：155之胺基酸1-1143；SEQ ID NO：158之胺基酸1-1325；SEQ ID NO：159之胺基酸1-1135，且其中，所述CT的胺基酸序列包括具有以下序列之胺基酸80%至100%的同一性：SEQ ID NO：15；或SEQ ID NO：6、8、7、9、10、12、13或14之胺基酸35-50；或SEQ ID NO：11之胺基酸34-49；或SEQ ID NO：3之胺基酸553-568。

【請求項34】 一種核酸，包括編碼如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白的核苷酸序列。

【請求項35】 一種三聚體，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白。

【請求項36】 一種病毒樣顆粒(VLP)，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白或如請求項35所述之三聚體。

【請求項37】 如請求項36所述之病毒樣顆粒(VLP)，其中，所述VLP進一步包括植物脂質。

【請求項38】 一種組合物，包括有效劑量之如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；或如請求項36或37所述之病毒樣顆粒(VLP)；以及醫藥上可接受之載體、佐劑、媒介物或賦形劑。

【請求項39】 一種用於誘導免疫反應之疫苗，所述疫苗包括有效劑量之如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；如請求項36或37所述之病毒樣顆粒(VLP)；或如請求項38所述之組合物。

【請求項40】 如請求項39所述之疫苗，其中，所述疫苗係多價疫苗，包括病毒樣顆粒(VLP)的混合物。

【請求項41】 一種如請求項38所述之組合物或如請求項39或40所述之疫苗在製備用於冠狀病毒感染之藥物之用途。

【請求項42】 如請求項41所述之用途，其中，所述組合物或所述疫苗係用

於誘導受試者對所述冠狀病毒感染的免疫力。

【請求項43】 如請求項41所述之用途，其中，所述組合物或所述疫苗係用於誘導由細胞介導的免疫反應。

【請求項44】 如請求項41所述之用途，其中，所述組合物或所述疫苗係作為初始劑量投與，且在從投與所述初始劑量1天至6個月之間係投與一劑或多於一劑的後續劑量。

【請求項45】 一種使用如請求項38所述之組合物或如請求項39或40所述之疫苗製備之抗體或抗體片段。

【請求項46】 一種非人宿主或宿主細胞，包括如請求項1至33中任一項所述之經修飾的冠狀病毒S-蛋白；如請求項35所述之三聚體；如請求項34所述之核酸；或如請求項36或37所述之病毒樣顆粒(VLP)。

【請求項47】 一種在非人宿主或宿主細胞中製造經修飾的冠狀病毒S-蛋白之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造所述經修飾的冠狀病毒 S-蛋白。

【請求項48】 一種在非人宿主或宿主細胞中製造病毒樣顆粒(VLP)之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞，從而製造所述 VLP。

【請求項49】 如請求項48或49所述之方法，其中，所述方法進一步包括收穫所述非人宿主或宿主細胞的步驟c)。

【請求項50】 一種在非人宿主或宿主細胞中增加經修飾的冠狀病毒S-蛋白之製造的產量之方法，包括以下步驟：

步驟 a) 將如請求項 34 所述之核酸導入至所述非人宿主或宿主細胞，或提供包括如請求項 34 所述之核酸的所述非人宿主或宿主細胞；及

步驟 b) 在允許由所述核酸編碼的所述經修飾的冠狀病毒 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與表現未經修飾的冠狀病毒 S-蛋白的宿主或宿主細胞相比，以更高的產量製造所述經修飾的冠狀病毒 S-蛋白。

【請求項51】 一種在非人宿主或宿主細胞中增加病毒樣顆粒(VLP)之製造的產量之方法，包括以下步驟：

步驟 a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白依序地包括：源自冠狀病毒 S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；或

提供包括編碼經修飾的冠狀病毒 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白依序地包括：源自冠狀病毒 S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

步驟 b) 在允許由所述核酸編碼的所述經修飾冠狀病毒的 S-蛋白表現的條件下培養所述非人宿主或宿主細胞，從而與表現未經修飾的冠狀病毒 S-蛋白的宿主或宿主細胞相比，以更高的產量製造包括所述經修飾的冠狀病毒 S-蛋白的 VLP。

【請求項52】 一種在非人宿主或宿主細胞中製造病毒樣顆粒(VLP)之方法，包括以下步驟：

步驟 a) 將編碼經修飾的冠狀病毒 S-蛋白的核酸導入至非人宿主或宿主細胞，所述經修飾的冠狀病毒S-蛋白依序地包括:源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；或

提供包括編碼經修飾的冠狀病毒 S-蛋白之核酸的非人宿主或宿主細胞，所述經修飾的冠狀病毒 S-蛋白依序地包括：源自冠狀病毒 S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述 TMCT 係嵌合 TMCT，所述嵌合 TMCT 包括：跨膜結構域(TM)，其中所述 TM 或所述 TM 的部分係源自冠狀病毒 S-蛋白以及胞質尾(CT)，其中所述 CT 或所述 CT 的部分係源自流感血球凝集素(HA)蛋白；以及

步驟 b) 在允許所述核酸表現的條件下培養所述非人宿主或宿主細胞。

【請求項53】 如請求項48、51或52所述之方法，其中，所述VLP係進一步從所述非人宿主或宿主細胞中提取和純化。

【請求項54】 一種藉由如請求項48、51或52所述之方法製造的病毒樣顆粒(VLP)。

【請求項55】 一種藉由如請求項47或50所述之方法製造的經修飾的冠狀病毒S-蛋白。

【請求項56】 如請求項47至53中任一項所述之方法，其中，所述非人宿主或宿主細胞包括植物、植物的部分、植物細胞、真菌、真菌細胞、昆蟲、昆蟲細胞、動物或動物細胞。

【請求項57】 如請求項46所述之非人宿主或宿主細胞，其中，所述非人宿

主或宿主細胞包括植物、植物的部分、植物細胞、真菌、真菌細胞、昆蟲、昆蟲細胞、動物或動物細胞

【請求項58】 一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流感血球凝集素(HA)蛋白，且其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述S-蛋白包括在位置667、668、670、971和972處的取代。

【請求項59】 一種包括病毒樣顆粒(VLP)的組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流感血球凝集素(HA)蛋白，且其中，所述S-蛋白包括位置667處的甘胺酸取代、位置668處的絲胺酸取代、位置670處的絲胺酸取代、位置971處的脯胺酸取代、位置972處的脯胺酸取代，所述位置對應於SEQ ID NO：2的參考胺基酸序列。

【請求項60】 一種包括病毒樣顆粒(VLP)之組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白包括SEQ ID NO：21的序列或SEQ ID NO：51的胺基酸25-1259。

【請求項61】 一種包括病毒樣顆粒(VLP)之組合物，所述VLP包括經修飾的冠狀病毒S-蛋白，所述經修飾的冠狀病毒S-蛋白依序地包括：源自冠狀病毒S-蛋白的胞外結構域；以及跨膜和胞質尾結構域(TMCT)，其中所述TMCT係嵌合TMCT，所述嵌合TMCT包括：跨膜結構域(TM)，其中所述TM或所述TM的部分係源自冠狀病毒S-蛋白以及胞質尾(CT)，其中所述CT或所述CT的部分係源自流

感血球凝集素(HA)蛋白，且其中，與SEQ ID NO：2的參考胺基酸序列相比時，所述S-蛋白包括在位置667、668、670、802、923、927、971和972處的取代。