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(54)发明名称

用于COVID-19疫苗的新型蛋白质和核酸序列

(57)摘要

本发明涉及突变的SARS-CoV-2刺突蛋白、其变体或片段、或编码其的mRNA或DNA用于预防COVID-19。

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1.一种突变的SARS-CoV-2刺突蛋白,其中对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

2.根据权利要求1所述的突变的SARS-CoV-2刺突蛋白,其具有SEQ ID NO:2、28、29、30或31的氨基酸序列。

3.权利要求1或2所述的突变的SARS-CoV-2刺突蛋白的变体,其中对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

4.根据权利要求3所述的突变的SARS-CoV-2刺突蛋白的变体,其中所述变体在以下位置具有与对应的突变的SARS-CoV-2刺突蛋白相同的氨基酸序列:

-从对应于SEQ ID NO:1的氨基酸818的位置处至对应于SEQ ID NO:1的氨基酸822的位置处的氨基酸序列,

-从对应于SEQ ID NO:1的氨基酸841的位置处至对应于SEQ ID NO:1的氨基酸844的位置处的氨基酸序列,和

-从对应于SEQ ID NO:1的氨基酸861的位置处至SEQ ID NO:1的位置865的氨基酸序列。

5.根据权利要求3或4所述的变体,其中所述突变的SARS-CoV-2刺突蛋白的以下氨基酸中的至少两个被脯氨酸替换:

-在对应于SEQ ID NO:1的氨基酸892、899和942的位置处的丙氨酸,

-在对应于SEQ ID NO:1的氨基酸817的位置处的苯丙氨酸,

-在对应于SEQ ID NO:1的氨基酸986的位置处的赖氨酸,和

-在对应于SEQ ID NO:1的氨基酸987的位置处的缬氨酸。

6.根据权利要求3至5所述的变体,其具有SEQ ID NO:3、SEQ ID NO:4、SEQ ID NO:5、SEQ ID NO:6、SEQ ID NO:7、SEQ ID NO:8、SEQ ID NO:32、SEQ ID NO:33、SEQ ID NO:34、SEQ ID NO:35、SEQ ID NO:36、SEQ ID NO:37、SEQ ID NO:38、SEQ ID NO:39、SEQ ID NO:40、SEQ ID NO:41、SEQ ID NO:42、SEQ ID NO:43、SEQ ID NO:44、SEQ ID NO:45、SEQ ID NO:46、SEQ ID NO:47、SEQ ID NO:48、SEQ ID NO:49、SEQ ID NO:50、SEQ ID NO:51、SEQ ID NO:52、SEQ ID NO:53、SEQ ID NO:54或SEQ ID NO:55的序列。

7.根据权利要求3至6所述的变体,其中对应于SEQ ID NO:1的氨基酸682、683和685的位置处的氨基酸精氨酸被谷氨酰胺替换。

8.根据权利要求3至6所述的变体,其中对应于SEQ ID NO:1的氨基酸685位置处的氨基酸精氨酸被丙氨酸替换。

9.根据权利要求3至8所述的变体,其进一步包含在对应于SEQ ID NO:1的以下列出的氨基酸的位置处的氨基酸修饰:

T19R、EF156/157del、R158G、L452R、T478K、D614G、P681R和D950N,或

A67V、H69del、V70del、T95I、G142D、V143del、Y144del、Y145del、N211del、L212I、ins214EPE、G339D、S371L、S373P、S375F、K417N、N440K、G446S、S477N、T478K、E484A、Q493R、G496S、Q498R、N501Y、Y505H、T547K、D614G、H655Y、N679K、P681H、N764K、D796Y、N856K、Q954H、N969K、L981F。

10.权利要求1或2所述的突变的SARS-CoV-2刺突蛋白的免疫原性片段或权利要求3至9所述的变体的免疫原性片段,其包含所述突变的SARS-CoV-2刺突蛋白或变体的至少一个序列,所述序列选自:

-从对应于SEQ ID NO:1的氨基酸818的位置处至对应于SEQ ID NO:1的氨基酸822的位置处的氨基酸序列,

-从对应于SEQ ID NO:1的氨基酸841的位置处至对应于SEQ ID NO:1的氨基酸844的位置处的氨基酸序列,和

-从对应于SEQ ID NO:1的氨基酸861的位置处至SEQ ID NO:1的位置865的氨基酸序列。

11.根据权利要求10所述的免疫原性片段,其含有所述突变的SARS-CoV-2刺突蛋白或变体的至少一个序列,所述序列选自:

-SEQ ID NO:2或SEQ ID NO:31的第818位至第822位的氨基酸序列,

-SEQ ID NO:2、SEQ ID NO:28、SEQ ID NO:30或SEQ ID NO:31的第841位至第844位的氨基酸序列,和

-SEQ ID NO:2、SEQ ID NO:29、SEQ ID NO:30或SEQ ID NO:31的第861位至第865位的氨基酸序列。

12.根据权利要求10或11所述的免疫原性片段,其进一步含有选自以下氨基酸序列的至少两个非重叠序列:

-SEQ ID NO:1的第232位至第246位的氨基酸序列,

-SEQ ID NO:1的第233位至第247位的氨基酸序列,

-SEQ ID NO:1的第471位至第503位的氨基酸序列,

-SEQ ID NO:1的第604位至第625位的氨基酸序列,

-SEQ ID NO:2或SEQ ID NO:31的第817位至第833位的氨基酸序列,

-SEQ ID NO:1的第891位至第907位的氨基酸序列

-SEQ ID NO:1的第897位至第913位的氨基酸序列,

-SEQ ID NO:1的第1164位至第1191位的氨基酸序列,和

-SEQ ID NO:1的第1182位至第1209位的氨基酸序列。

13.一种蛋白质,其包含权利要求1或2所述的突变的SARS-CoV-2刺突蛋白的序列、权利要求3至9所述的变体或权利要求10至12所述的免疫原性片段以及一个或多个其他序列。

14.一种mRNA,其编码权利要求1或2所述的突变的SARS-CoV-2刺突蛋白、权利要求3至9所述的变体、权利要求10至12所述的免疫原性片段或权利要求13所述的蛋白质。

15.根据权利要求14所述的mRNA,其具有序列,其中尿苷残基被选自以下的修饰核苷替换:吡啶-4-酮核糖核苷、5-氮杂-尿苷、2-硫代-5-氮杂尿苷、2-硫代尿苷、4-硫代-假尿苷、2-硫代-假尿苷、5-羟基尿苷、3-甲基尿苷、5-羧甲基-尿苷、1-羧甲基-假尿苷、5-丙炔基-尿苷、1-丙炔基-假尿苷、5-牛磺酸甲基尿苷、1-牛磺酸甲基-假尿苷、5-牛磺酸甲基-2-硫代-尿苷、1-牛磺酸甲基-4-硫代尿苷、5-甲基-尿苷、1-甲基-假尿苷、4-硫代-1-甲基-假尿苷、2-硫代-1-甲基假尿苷、1-甲基-1-脱氮-假尿苷、2-硫代-1-甲基-1-脱氮-假尿苷、二氢尿苷、二氢假尿苷、2-硫代-二氢尿苷、2-硫代-二氢假尿苷、2-甲氧基尿苷、2-甲氧基-4-硫代-尿苷、4-甲氧基-假尿苷、4-甲氧基-2-硫代-假尿苷,优选被1-甲基-假尿苷替换。

16.一种DNA,其编码权利要求1或2所述的突变的SARS-CoV-2刺突蛋白、权利要求3至9所述的变体、权利要求10至12所述的免疫原性片段或权利要求13所述的蛋白质。

17.一种质粒,其含有权利要求16所述的DNA。

18.一种病毒载体,优选选自腺病毒或痘病毒,其含有权利要求16所述的DNA。

19.权利要求1或2所述的突变的SARS-CoV-2刺突蛋白、权利要求3至9所述的变体、权利要求10至12所述的免疫原性片段或权利要求13所述的蛋白质、权利要求14或15所述的mRNA、权利要求16所述的DNA、权利要求17所述的质粒或权利要求18所述的病毒载体,用于在受试者中预防COVID-19。

20.一种疫苗组合物,其包含权利要求1或2所述的突变的SARS-CoV-2刺突蛋白、权利要求3至9所述的变体、权利要求10至12所述的免疫原性片段或权利要求13所述的蛋白质、权利要求14或15所述的mRNA、权利要求16所述的DNA、权利要求17所述的质粒或权利要求18所述的病毒载体。

用于COVID-19疫苗的新型蛋白质和核酸序列

技术领域

[0001] 本发明涉及适用于COVID-19疫苗的蛋白质和核酸序列。

背景技术

[0002] 冠状病毒(Cov)是一大类属于冠状病毒科(Coronaviridae)的单链包膜RNA病毒。已知能够感染人的有限数量的冠状病毒在过去被认为是相对无害的人呼吸道病原体,导致轻度感染。然而,两种冠状病毒亚型已经出现,严重急性呼吸系统综合征冠状病毒(SARS-CoV)和中东呼吸系统综合征冠状病毒(MERS-CoV),其导致人类严重的甚至有时是致命的呼吸道感染(Pereira,H等人,1989年,Coronaviridae.Andrewes'Viruses of Vertebrates,第5版,第42-57页;Holmes,K.V.等人,Virology 1996,1:1075-1093)。世界卫生组织(WHO)将该病毒命名为SARS-CoV-2,并将相关疾病命名为COVID-19。

[0003] 该病毒在全球快速传播,2020年3月11日,WHO宣布SARS-CoV-2感染为大流行。大多数感染COVID-19的人都会经历轻度至中度的呼吸道疾病(发烧、疲劳、干咳和呼吸困难),无需特殊治疗即可康复。老年人和那些有基础医疗问题(如心血管疾病、糖尿病、慢性呼吸道疾病和癌症)的人更容易患上严重疾病。

[0004] 对SARS-CoV-2感染患者的流行病学以及临床特征和结局的分析表明,有症状的COVID-19患者中有15%患有严重疾病(包括严重肺炎),5%的患者患有危重疾病并伴有危及生命的并发症。危重疾病包括急性呼吸窘迫综合征(ARDS)、败血症、败血性休克、心脏病、血栓栓塞事件(如肺栓塞)和多器官衰竭。

[0005] 还有越来越多的证据表明,对于那些患有危重的COVID-19疾病的人来说,长期后果(如罕见的神经和精神并发症)是可以合理预期的。这些可以包括中风、谵妄、焦虑、抑郁、大脑损伤或炎症以及睡眠障碍。

[0006] 由于全球病例和死亡人数急剧上升及其造成的社会和经济后果,努力开发安全有效的疫苗,以帮助控制和结束COVID-19大流行。

[0007] 正在开发不同的疫苗,其中一些已被批准用于预防COVID-19。

[0008] 所有COVID-19疫苗和候选疫苗均通过利用不同的策略和技术来诱导针对病毒蛋白抗原的免疫反应来发挥作用,所述策略和技术是:传统的灭活或减毒病毒疫苗(基于在宿主中引入多种不同的SARS-CoV-2抗原)、基于重组生产的SARS-CoV-2蛋白与佐剂组合的疫苗、以及基于基因的疫苗(如mRNA、DNA或载体疫苗),其递送编码病毒蛋白抗原的基因,以便在宿主的细胞中体内产生所述病毒蛋白抗原。

[0009] SARS-COV-2特征在于四种结构蛋白,即刺突(S)蛋白、包膜(E)蛋白、膜(M)蛋白和核衣壳(N)蛋白(Chen Y等人,J Med Virol 2020,92:418-423)。

[0010] 目前,大多数已批准或正在开发的COVID-19疫苗都使用刺突蛋白作为目标抗原。事实上,这种蛋白质被认为是一种能够诱导保护性免疫反应的重要抗原决定簇(Ou等人,Nat Commun 2020;11:1620)。此外,它也是病毒通过细胞进入受体血管紧张素转换酶II(ACE2)进入细胞的重要分子。因此,靶向S蛋白的抗体防止病毒进入宿主细胞并在宿主细胞

内复制。

[0011] SARS-CoV-2S蛋白具有SEQ.ID.No:1的1273个氨基酸序列,由位于N末端的信号肽(氨基酸1-13)、S1亚基(残基14-685)和S2亚基(残基686-1273)组成。S1亚基通过受体结合结构域(RBD)介导受体与ACE2的结合,S2亚基负责病毒和宿主细胞膜融合(Letko等人,Nat Microbiol 2020,5:562-569,Huang等人,Acta Pharmacologica Sinica 2020,41:1141-1149)。在融合过程中,S2亚基从融合前构象变为融合后(发夹)构象。随后,表面蛋白酶裂解S2亚基(Silverira等人,Life Sci 2021,267:1128919)。

[0012] 迄今为止EMA批准的疫苗都是基于核酸的,所述核酸诱导在宿主中产生刺突蛋白作为蛋白抗原:Pfizer和BioNTech开发的基于mRNA的Comirnaty疫苗,Moderna开发的基于mRNA的Moderna COVID-19疫苗,由牛津大学和AstraZeneca开发的DNA、病毒载体递送疫苗Vaxzevria,以及由Janssen-Cilag International开发的COVID-19Vaccine Janssen。

[0013] 正在开发其他基于这些方法的疫苗以及使用重组生产的SARS-CoV-2刺突蛋白作为活性成分的疫苗,例如Novavax的疫苗NVX-CoV2373以及Medicago和GSK的Co-VLP(Forni等人,Cell Death&Differentiation 2021,28:626-639)。

[0014] 最近的证据表明,SARS-CoV-2刺突蛋白对与促进病毒感染无关的细胞信号传导具有潜在活性。

[0015] 特别是,已经证明刺突蛋白可以在体外诱导鼠和人巨噬细胞的促炎反应(Shirato等人,Heliyon 2021,7(2)e06187),以及可以激活在培养的人血管细胞中的细胞信号传导事件(Suzuki等人,Vascular Pharmacology 2021,137:106823)。

[0016] 这方面非常相关的,因为大多数COVID-19疫苗都会在生物体中引入刺突蛋白。

[0017] 据报道,迄今为止批准的mRNA和DNA疫苗通过肌肉内注射施用后,刺突蛋白主要在肌细胞、成纤维细胞、树突状细胞和淋巴细胞中表达,但使用某些疫苗在其他器官中也检测到了表达水平(信息可参见https://www.ema.europa.eu/)。

[0018] 鉴于上述情况,因此需要研究由疫苗接种产生的刺突蛋白在体内的存在是否会干扰生物过程,从而引起短期和长期的副作用。

[0019] 核激素受体是一种配体调节的转录因子家族,由甲状腺激素和类固醇激素以及各种其他脂溶性信号(包括视黄酸和维生素D)激活。

[0020] 类固醇激素,特别是雄激素和雌激素,已被证明可以调节广泛的生理功能,如第二性征的发育和维持、新陈代谢、血盐平衡、免疫和炎症反应、对压力的反应和/或神经元功能。

[0021] 此外,这些激素水平或活性的不平衡与许多病理过程有关。

[0022] 特别是,雌激素与乳腺癌、子宫内膜癌、肾癌和子宫癌的病因有关(Okamoto等人,Toxicology Letters 2020,318:99-103),而雄激素在前列腺癌的发病机制中发挥着关键作用(Cold Spring Harb Perspect Med 2017;7:a030452)。

[0023] 此外,施用外源性雄激素和雌激素与止血和纤溶途径的许多方面的调节紊乱有关,从而导致促血栓环境的产生,增加血栓事件的风险(Rosca等人,J.Clin.Med.2021,10:147;Abou-Ismail等人,Thrombosis Research 2020,192:40-51;Walker等人,JAMA Intern Med.2020,180(2):190-197)。

[0024] 这些分子的活性由核受体雌激素和雄激素受体介导,这些受体作为激素激活的转

录因子发挥作用。这些受体涉及不同的活性,但共有显著的结构和功能相似性。在没有配体的情况下,它们以转录失活的形式存在于靶细胞内。在经配体激活后,它们与靶基因的启动子结合,与许多相互作用的蛋白质形成转录复合物,统称为共调节因子,可以激活(共激活因子(CoA))或失活(共阻遏因子(CoR))转录活性,从而触发激活或抑制靶基因表达(Patel等人,Pharm Ther 2018,186:1-24;Zella等人,Arch Biochem Biophys 2007,460(2):206-212)。在核受体和共激活因子之间的相互作用是由不同核激素受体的共激活因子蛋白中存在和共有的LxxLL基序(其中L是亮氨酸,x是任何氨基酸)介导的。这些基序对于这些蛋白质与受体的结合以及增强其转录活性是必要且充分的(Patel等人,Pharm Ther2018,186:1-24;Zella等人,Arch Biochem Biophys 2007,460(2):206-212;Chang等人,Trends Pharm Sci2005,26(5):225-228)。

发明内容

[0025] 本发明人现在令人惊讶地发现,SARS-CoV-2刺突蛋白含有许多与核共激活因子1(NCOA1)的基序同源的LxxLL样基序,其能够结合NCOA1结合结构域并激活雌激素和雄激素受体的转录活性。此外,NCOA1结合结构域在不同核受体中的序列同源性支持刺突蛋白还具有激活其他核受体(如维生素D和甲状腺激素受体)诱导的转录的潜在能力。

[0026] 由此发现推导出疫苗中产生或含有的刺突蛋白可以干扰核受体,特别是雌激素和雄激素受体的活性,在这些受体介导的生理和病理活性之间造成不平衡,从而产生不需要的、严重的副作用。

[0027] 本发明人已经鉴定了SARS-CoV-2刺突蛋白的LxxLL基序中的突变,这些突变消除了蛋白与雌激素和雄激素受体的NCOA1结合结构域的结合活性。

[0028] 因此,这些序列用于开发更安全的针对COVID-19的疫苗。

[0029] 因此,本发明的一个目的是突变的SARS-CoV-2刺突蛋白或其变体,其中在对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

[0030] 本发明的另一个目的是根据本发明的突变的SARS-CoV-2刺突蛋白,其具有氨基酸序列SEQ ID NO:2、SEQ ID NO:28、SEQ ID NO:29、SEQ ID NO:30或SEQ ID NO:31的氨基酸序列。

[0031] 本发明的另一个目的是根据本发明的突变的SARS-CoV-2刺突蛋白或变体的免疫原性片段。

[0032] 本发明的另一个目的是编码根据本发明的突变的SARS-CoV-2刺突蛋白、变体或免疫原性片段的mRNA。

[0033] 本发明的另一个目的是所述突变的SARS-CoV-2刺突蛋白、变体、片段、mRNA或DNA用于在受试者中预防COVID-19。

[0034] 本发明的另一个目的是包含所述突变的SARS-CoV-2刺突蛋白、变体或片段、mRNA或DNA的疫苗。

[0035] 本发明的另一个目的是所述疫苗用于在受试者中预防COVID-19。

附图说明

[0036] 图1显示了与核受体共激活因子复合的雌激素受体(ER)。整个复合物以卡通表示;ER单体以灰色表面显示,而NCOA区段以黑色卡通和线条表示。

[0037] 图2显示了ER1和ER2最显著的相互作用的网络。在最可靠的相互作用蛋白中,核受体共激活因子(Nuclear receptor COActivator,NCOA)直接结合核受体并刺激转录活性。

[0038] 图3显示了刺突蛋白中LDX区和其他LDX辅因子-受体结构域之间的序列比对。

[0039] 图4显示了刺突蛋白-ER盲对接的3D最佳对接假设。这些蛋白质以卡通形式表示。ER二聚体为白色卡通,而刺突蛋白以黑色表面表示。

[0040] 图5显示了刺突蛋白-ER基序定向对接的3D最佳对接假设。这些蛋白质以卡通形式表示。ER二聚体为白色卡通,而刺突蛋白以黑色表面表示。

[0041] 图6显示了单独或在雷洛昔芬的存在下,用载剂(CTR)、雌二醇(ESTR)、野生型刺突蛋白(SPIKE)或两者的组合处理MCF-7乳腺癌细胞诱导的细胞增殖(以对照的百分比表示),如实施例2中所述进行测量。

[0042] 图7显示了通过用载剂(CTRL),肽2、5或7,野生型刺突蛋白、野生型刺突蛋白加雷洛昔芬或单独的雷洛昔芬处理MCF-7乳腺癌细胞诱导的细胞增殖(以对照的百分比表示),如实施例2所述进行测量。

[0043] 图8显示了通过用肽2、5或7或野生型刺突蛋白处理LNCap前列腺癌细胞诱导的细胞增殖(以对照的百分比表示),如实施例2中所述。

[0044] 图9显示了用对照(CTR)、雌激素(ESTR)、野生型刺突蛋白(SPIKE)或雷洛昔芬和野生型刺突蛋白(RAL+SPIKE)处理后,用蛋白质组分析人XL细胞因子阵列试剂盒(Proteome Profiler Human XL Cytokine Array Kit)(THP1细胞系经TPA/LPS分化并处理24小时的)进行的蛋白质组分析的结果,如实施例3中所述。

[0045] 图10显示了从RAW264.7巨噬细胞分化的破骨细胞,用1nM雌二醇和10ng/mL刺突蛋白wt或突变体SP5、SP7或SP5+SP7处理,通过酶联免疫吸附测定确定的耐酒石酸酸性磷酸酶(TRAP)的活性(U/L),如实施例4b所述。

具体实施方式

[0046] 如将在实验部分中详细描述的,本发明基于令人惊讶的发现:SARS-CoV-2刺突蛋白暴露了三个LxxLL样基序,其能够介导核受体,特别是雌激素和雄激素受体的结合和激活。如实施例中将显示的,这些基序中的每一个都能够激活由雌激素或雄激素受体诱导的癌细胞的增殖。

[0047] 这一发现引起了人们对COVID-19疫苗的潜在副作用的担忧,所述COVID-19疫苗基于在宿主中施用或生产包含一个或多个上述基序的SARS-CoV-2刺突蛋白或其变体或片段。

[0048] 发明人发现,对应于鉴定的三个基序中的一个或多个基序引入特定的氨基酸突变,消除了刺突蛋白与这些受体之间相互作用的能力,同时不改变针对SARS-CoV-2的抗原特异性免疫反应的效率。

[0049] 因此,相较于使用野生型SARS-CoV-2刺突蛋白,在新的或市售的基于刺突蛋白的COVID-19疫苗中使用具有携带这些突变的序列的SARS-CoV-2刺突蛋白或编码其的mRNA或DNA序列,允许维持同样有效的免疫反应,并具有更高的安全性。

[0050] 本发明涉及突变的SARS-CoV-2刺突蛋白、其变体和片段以及编码其的mRNA和DNA，适合用作预防COVID-19的疫苗中的活性成分。

[0051] 因此，本发明的第一个目的是突变的SARS-CoV-2刺突蛋白或其变体，其中在对应于野生型SARS-Cov-2蛋白序列(UniProtKB-PODTC2,SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

[0052] 优选地，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

[0053] 优选地，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，至少SEQ ID NO:1的氨基酸818、821和822，或氨基酸841或氨基酸861、864和865被丙氨酸替换。

[0054] 优选地，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，至少SEQ ID NO:1的氨基酸818、821和822或氨基酸841和844或氨基酸861、864和865被丙氨酸替换。

[0055] 根据一个实施方案，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、861、864和865的位置处的异亮氨酸或亮氨酸被丙氨酸替换。

[0056] 根据该实施方案，突变的SARS-CoV-2刺突蛋白具有SEQ ID NO:2的氨基酸序列。

[0057] 根据另一个优选的实施方案，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-CoV-2蛋白序列(SEQ ID NO:1)的氨基酸841和844的位置处的氨基酸异亮氨酸或亮氨酸被丙氨酸替换。根据该实施方案，突变的SARS-CoV-2刺突蛋白具有SEQ ID NO:28的氨基酸序列。

[0058] 根据另一个优选的实施方案，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-CoV-2蛋白序列(SEQ ID NO:1)的氨基酸861、864和865的位置处的氨基酸异亮氨酸或亮氨酸被丙氨酸替换。根据该实施方案，突变的SARS-CoV-2刺突蛋白具有SEQ ID NO:29的氨基酸序列。

[0059] 根据另一个优选的实施方案，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-CoV-2蛋白序列(SEQ ID NO:1)的氨基酸841、844、861、864和865位置处的氨基酸异亮氨酸或亮氨酸被丙氨酸替换。根据该实施方案，突变的SARS-CoV-2刺突蛋白具有SEQ ID NO:30的氨基酸序列。

[0060] 根据另一个优选的实施方案，在根据本发明的所述突变的SARS-CoV-2刺突蛋白或其变体中，对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸被丙氨酸替换。根据该实施方案，突变的SARS-CoV-2刺突蛋白具有SEQ ID NO:31的氨基酸序列。

[0061] 正如上面所讨论的和实验部分所证明的，在上述突变的SARS-CoV-2刺突蛋白中引入的氨基酸替换能够抑制刺突蛋白对核激素受体的活性，同时不改变SARS-CoV-2刺突蛋白的构象和抗原特性。

[0062] 根据本发明的突变的SARS-CoV-2刺突蛋白可以通过引入进一步的取代、或缺失或插入来修饰，这些取代、或缺失或插入提高突变蛋白的稳定性或提高针对SARS-CoV-2病毒相关变体的免疫原性活性，其特征在于为刺突蛋白氨基酸序列内的修饰。

[0063] 因此，本发明的另一个目的是如上所述的任何突变的SARS-CoV-2刺突蛋白的变

体。

[0064] 在根据本发明的变体中,对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处的氨基酸异亮氨酸或亮氨酸中的至少一个被丙氨酸替换。

[0065] 优选地,所述变体在对应于野生型SARS-Cov-2蛋白序列(SEQ ID NO:1)的氨基酸818、821、822、841、844、861、864和865的位置处具有与相应突变的SARS-COV-2蛋白相同的氨基酸。

[0066] 更优选地,所述变体在以下位置具有与相应突变的SARS-CoV-2刺突蛋白或变体相同的氨基酸序列:

[0067] -从对应于SEQ ID NO:1的氨基酸818的位置处至对应于SEQ ID NO:1的氨基酸822的位置处的氨基酸序列,

[0068] -从对应于SEQ ID NO:1的氨基酸841的位置处至对应于SEQ ID NO:1的氨基酸844的位置处的氨基酸序列,和

[0069] -从对应于SEQ ID NO:1的氨基酸861的位置处至SEQ ID NO:1的位置865的氨基酸序列。

[0070] 优选地,变体在对应于上述SEQ ID NO:1的氨基酸818、821、822、841、844、861、864和865的位置处存在氨基酸替换。

[0071] 根据本发明,突变的SARS-CoV-2刺突蛋白的“变体”是指具有与如上所述的突变的SARS-CoV-2刺突蛋白的序列不同的氨基酸序列的蛋白质,其中含有一个或多个氨基酸取代、缺失或插入。所述氨基酸取代、缺失或插入可以在除对应于SEQ ID NO:1的氨基酸818、821、822、841、844、861、864和865的位置之外的任何位置处。优选地,所述取代、缺失或插入不干扰根据本发明的突变的SARS-CoV-2刺突蛋白的构象和抗原特性。更优选地,所述取代、缺失或插入改善突变的SARS-CoV-2刺突蛋白的抗原特性和/或稳定性。优选地,变体具有与如上所述的相应突变的SARS-CoV-2刺突蛋白具有至少80%、85%、90%、95%、98%、99%的氨基酸同一性的序列。

[0072] 在一个优选的实施方案中,所述变体具有序列,所述序列带有使蛋白质稳定在融合前构象中的氨基酸替换。使用这种构象的刺突蛋白作为抗原会诱导产生抗体,这些抗体能够在感染的早期阶段和病毒进入细胞之前对病毒做出反应,使病毒失活,从而显著提高疫苗的疗效。

[0073] 已经鉴定出许多刺突蛋白变体,其具有将刺突蛋白稳定在融合前状态的氨基酸替换。例如,其中,突变体SARS-2-S刺突蛋白(S-2P)具有氨基酸替换K986P和V987P,由Pfizer/BioNTech(BNT162b)和Moderna(mRNA-1273)的mRNA疫苗编码。此外,文献中还描述了SARS-CoV-2刺突蛋白的替换变体,其具有稳定的融合前构象,且与S-2P相比具有更高的表达产量。这些突变体的特征在于替换A892P和A942P或F817P和A899P。最后,文献中描述的就稳定性和表达而言最有前途的变体是HexaPro变体,其包含上述所有6个氨基酸替换。

[0074] 根据一个优选的实施方案,在根据本发明的变体中,所述突变的SARS-CoV-2刺突蛋白的以下氨基酸中的至少两个被脯氨酸替换:

[0075] -在对应于SEQ ID NO:1的氨基酸892、899和942的位置处的丙氨酸,

[0076] -在对应于SEQ ID NO:1的氨基酸817的位置处的苯丙氨酸,

[0077] -在对应于SEQ ID NO:1的氨基酸986的位置处的赖氨酸,和

[0078] -在对应于SEQ ID NO:1的氨基酸987的位置处的缬氨酸。

[0079] 下文提供了根据本发明的该实施方案的突变的SARS-CoV-2刺突蛋白的特别优选的变体,其稳定了突变的SARS-CoV-2刺突蛋白的融合前构象。

[0080] 第一个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第986位的氨基酸赖氨酸和SEQ ID NO:2的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:3)。

[0081] 第二个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:4)。

[0082] 第三个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第817位的氨基酸苯丙氨酸和SEQ ID NO:2的第899位的丙氨酸被脯氨酸替换(SEQ ID NO:5)。

[0083] 第四个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第986位的氨基酸赖氨酸、SEQ ID NO:2的第987位的缬氨酸以及SEQ ID NO:2的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:6)。

[0084] 第五个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第817位的氨基酸苯丙氨酸,SEQ ID NO:2的第892位、第899位和第942位的丙氨酸,SEQ ID NO:2的第986位的赖氨酸以及SEQ ID NO:2的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:7)。

[0085] 第六个变体是SEQ ID NO:2的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:2的第817位的氨基酸苯丙氨酸,SEQ ID NO:2的第892位、第899位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:8)。

[0086] 第七个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第986位的氨基酸赖氨酸和SEQ ID NO:28的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:32)。

[0087] 第八个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:33)。

[0088] 第九个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第817位的氨基酸苯丙氨酸和SEQ ID NO:28的第899位的丙氨酸被脯氨酸替换(SEQ ID NO:34)。

[0089] 第十个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第986位的氨基酸赖氨酸、SEQ ID NO:28的第987位的缬氨酸以及SEQ ID NO:28的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:35)。

[0090] 第十一个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第817位的氨基酸苯丙氨酸,SEQ ID NO:28的第892位、第899位和第942位的丙氨酸,SEQ ID NO:28的第986位的赖氨酸以及SEQ ID NO:28的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:36)。

[0091] 第十二个变体是SEQ ID NO:28的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:28的第817位的氨基酸苯丙氨酸,SEQ ID NO:28的第892位、第899位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:37)。

[0092] 第十三个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第986位的氨基酸赖氨酸和SEQ ID NO:29的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:38)。

[0093] 第十四个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:39)。

[0094] 第十五个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第817位的氨基酸苯丙氨酸和SEQ ID NO:29的第899位的丙氨酸被脯氨酸替换(SEQ ID NO:40)。

[0095] 第十六个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第986位的氨基酸赖氨酸、SEQ ID NO:29的第987位的缬氨酸以及SEQ ID NO:29的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:41)。

[0096] 第十七个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第817位的氨基酸苯丙氨酸,SEQ ID NO:29的第892位、第899位和第942位的丙氨酸,SEQ ID NO:29的第986位的赖氨酸以及SEQ ID NO:29的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:42)。

[0097] 第十八个变体是SEQ ID NO:29的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:29的第817位的氨基酸苯丙氨酸,SEQ ID NO:29的第892位、第899位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:43)。

[0098] 第十九个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第986位的氨基酸赖氨酸和SEQ ID NO:30的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:44)。

[0099] 第二十个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:45)。

[0100] 第二十一个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第817位的氨基酸苯丙氨酸和SEQ ID NO:30的第899位的丙氨酸被脯氨酸替换(SEQ ID NO:46)。

[0101] 第二十二个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第986位的氨基酸赖氨酸、SEQ ID NO:30的第987位的缬氨酸以及SEQ ID NO:30的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:47)。

[0102] 第二十三个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第817位的氨基酸苯丙氨酸,SEQ ID NO:30的第892位、第899位和第942位的丙氨酸,SEQ ID NO:30的第986位的赖氨酸以及SEQ ID NO:30的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:48)。

[0103] 第二十四个变体是SEQ ID NO:30的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:30的第817位的氨基酸苯丙氨酸,SEQ ID NO:30的第892位、第899位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:49)。

[0104] 第二十五个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第986位的氨基酸赖氨酸和SEQ ID NO:31的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:50)。

[0105] 第二十六个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:51)。

[0106] 第二十七个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第817位的氨基酸苯丙氨酸和SEQ ID NO:31的第899位的丙氨酸被脯氨酸替换(SEQ ID NO:52)。

[0107] 第二十八个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第986位的氨基酸赖氨酸、SEQ ID NO:31的第987位的缬氨酸以及SEQ ID NO:31的第892位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:53)。

[0108] 第二十九个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第817位的氨基酸苯丙氨酸,SEQ ID NO:31的第892位、第899位和第942位的丙氨酸,SEQ ID NO:31的第986位的赖氨酸以及SEQ ID NO:31的第987位的缬氨酸被脯氨酸替换(SEQ ID NO:54)。

[0109] 第三十个变体是SEQ ID NO:31的突变的SARS-CoV-2蛋白的变体,其中SEQ ID NO:31的第817位的氨基酸苯丙氨酸,SEQ ID NO:31的第892位、第899位和第942位的丙氨酸被脯氨酸替换(SEQ ID NO:55)。

[0110] 为了使得用作COVID-19疫苗中的活性成分的SARS-CoV-2刺突蛋白稳定,使用使该蛋白具有蛋白酶抗性的蛋白变体也被认为是有利的。例如,候选疫苗NVX-CoV2373含有具有氨基酸替换R682Q、R683Q、R685Q的SARS-CoV-2刺突蛋白的变体作为活性成分,所述替换不会干扰蛋白质的抗原特性,并赋予显著增加的对蛋白酶的抗性。另一种防止蛋白质被蛋白酶弗林切割的氨基酸替换是氨基酸替换R685A。

[0111] 根据进一步优选的实施方案,还与任何上述优选实施方案组合,在根据本发明的突变的SARS-CoV-2刺突蛋白的变体中,对应于SEQ ID NO:1的氨基酸682、683和685的位置处的氨基酸精氨酸被谷氨酰胺替换。

[0112] 根据该实施方案的特别优选的变体是如上所述的任何变体,进一步包含对应于SEQ ID NO:1的氨基酸682、683和685的位置处的氨基酸精氨酸被谷氨酰胺替换。

[0113] 根据该实施方案的突变的SARS-CoV-2蛋白的特别优选的变体是具有SEQ ID NO:9至SEQ ID NO:15的氨基酸序列的变体(变体31至37)。

[0114] 根据进一步优选的实施方案,还与任何上述优选的实施方案组合,在根据本发明的突变的SARS-CoV-2刺突蛋白的变体中,对应于SEQ ID NO:1的氨基酸685的位置处的氨基酸精氨酸被丙氨酸替换。

[0115] 根据该实施方案的特别优选的变体是如上所述的任何变体,进一步包含对应于SEQ ID NO:1的氨基酸685的位置处的氨基酸精氨酸被丙氨酸替换。

[0116] 为了增加针对在刺突蛋白氨基酸序列中带有修饰的SARS-COV-2病毒变体的免疫反应,正在开发基于插入此类修饰的SARS-COV-2刺突蛋白序列的疫苗。

[0117] 因此,根据进一步优选的实施方案,还与任何上述优选的实施方案组合,根据本发明的突变的SARS-CoV-2刺突蛋白的变体包含在德尔塔(B.1.617.2):和奥密克戎(BA.1)病毒变体的刺突蛋白中发现的氨基酸修饰。

[0118] 根据该实施方案,突变的SARS-CoV-2刺突蛋白的变体在以下列出的SEQ ID NO:1的氨基酸对应位置处含有以下氨基酸修饰:

[0119] -T19R、EF156/157del、R158G、L452R、T478K、D614G、P681R和D950N,或

[0120] -A67V、H69del、V70del、T95I、G142D、V143del、Y144del、Y145del、N211del、L212I、ins214EPE、G339D、S371L、S373P、S375F、K417N、N440K、G446S、S477N、T478K、E484A、Q493R、G496S、Q498R、N501Y、Y505H、T547K、D614G、H655Y、N679K、P681H、N764K、D796Y、N856K、Q954H、N969K、L981F。

[0121] 根据该实施方案的特别优选的变体是如上所述的任何变体,在以下列出的SEQ ID NO:1的氨基酸对应位置处进一步包含以下氨基酸修饰:

[0122] T19R、EF156/157del、R158G、L452R、T478K、D614G、P681R和D950N,或

[0123] A67V、H69del、V70del、T95I、G142D、V143del、Y144del、Y145del、N211del、L212I、ins214EPE、G339D、S371L、S373P、S375F、K417N、N440K、G446S、S477N、T478K、E484A、Q493R、G496S、Q498R、N501Y、Y505H、T547K、D614G、H655Y、N679K、P681H、N764K、D796Y、N856K、Q954H、N969K、L981F。

[0124] 许多候选COVID-19疫苗基于SARS-CoV-2刺突蛋白的免疫原性片段或编码其的mRNA或DNA(Forni等人,Cell Death&Differentiation 2021,28:626-639)。

[0125] 如实验部分所证明的,发明人在野生型刺突蛋白中鉴定的LxxLL基序具有激活核受体的能力。

[0126] 因此,在这种类型的疫苗的背景下,由于上文已经讨论的原因,使用根据本发明的突变的SARS-CoV-2刺突蛋白或其变体的免疫原性片段是有利的。

[0127] 因此,本发明的另一个目的是如上所述的突变的SARS-CoV-2刺突蛋白的免疫原性片段或其变体的免疫原性片段,所述片段包含所述突变的SARS-CoV-2刺突蛋白或变体的至少一个序列,其选自:

[0128] -从对应于SEQ ID NO:1的氨基酸818的位置处至对应于SEQ ID NO:1的氨基酸822的位置处的氨基酸序列,

[0129] -从对应于SEQ ID NO:1的氨基酸841的位置处至对应于SEQ ID NO:1的氨基酸844的位置处的氨基酸序列,和

[0130] -从对应于SEQ ID NO:1的氨基酸861的位置处至SEQ ID NO:1的位置865的氨基酸序列。

[0131] 因此,本发明的另一个目的是如上所述的突变的SARS-CoV-2刺突蛋白的免疫原性片段或其变体的免疫原性片段,所述片段包含所述突变的SARS-CoV-2刺突蛋白或变体的至少一个序列,其选自:

[0132] -SEQ ID NO:2或SEQ ID NO:31的第818位至第822位的氨基酸序列,

[0133] -SEQ ID NO:2、SEQ ID NO:28、SEQ ID NO:30或SEQ ID NO:31的第841位至第844位的氨基酸序列,和

[0134] -SEQ ID NO:2、SEQ ID NO:29、SEQ ID NO:30或SEQ ID NO:31的第861位至第865位的氨基酸序列。

[0135] 因此,本发明的另一个目的是如上所述的突变的SARS-CoV-2刺突蛋白或其变体的免疫原性片段,所述片段包含SEQ ID NO:2、SEQ ID NO:28、SEQ ID NO:29、SEQ ID NO:30或SEQ ID NO:31的从氨基酸818至氨基酸865的氨基酸序列对应的序列。

[0136] 根据本发明的突变的SARS-CoV-2刺突蛋白或其变体的“片段”是指具有对应于根

据本发明的突变的SARS-CoV-2刺突蛋白或其变体的N末端和/或C末端截短序列的氨基酸序列的蛋白质。

[0137] 根据本发明的免疫原性片段含有能够在宿主中触发保护性免疫反应的表位。

[0138] 已鉴定出野生型SARS-CoV-2刺突蛋白的表位,其具有降低的触发自身免疫反应的风险并刺激保护性抗体的产生,所述表位对应于SEQ ID NO:1的序列232-246、233-247、471-503、604-625、817-833、891-907、897-913、1164-1191、1182-1209。相反,发现肽597-603诱导通过表位序列依赖性增强感染的抗体。

[0139] 因此,优选地,根据本发明的免疫原性片段还含有选自以下氨基酸序列的至少两个非重叠序列:

[0140] -SEQ ID NO:1的第232位至第246位的氨基酸序列,

[0141] -SEQ ID NO:1的第233位至第247位的氨基酸序列,

[0142] -SEQ ID NO:1的第471位至第503位的氨基酸序列,

[0143] -SEQ ID NO:1的第604位至第625位的氨基酸序列,

[0144] -SEQ ID NO:2或SEQ ID NO:31的第817位至第833位的氨基酸序列,

[0145] -SEQ ID NO:1的第891位至第907位的氨基酸序列

[0146] -SEQ ID NO:1的第897位至第913位的氨基酸序列,

[0147] -SEQ ID NO:1的第1164位至第1191位的氨基酸序列,和

[0148] -SEQ ID NO:1的第1182位至第1209位的氨基酸序列。

[0149] 优选地,根据本发明的免疫原性片段包含SEQ ID NO:2、SEQ ID NO:29、SEQ ID NO:30或SEQ ID NO:31的第865位至第1209位的氨基酸序列。

[0150] 优选地,根据本发明的免疫原性片段包含SEQ ID NO:1的第471位至第817位的氨基酸序列。

[0151] 优选地,根据本发明的免疫原性片段包含SEQ ID NO:1的第232位至第470位的氨基酸序列。

[0152] 优选地,本发明的变体或片段不包含SEQ ID NO:1的第597位至第603位的氨基酸序列。

[0153] 本发明的另一个目的是包含根据本发明的突变的SARS-CoV-2刺突蛋白、其变体或片段的氨基酸序列以及一个或多个附加序列的蛋白质。

[0154] 根据一个优选的实施方案,所述附加序列不具有免疫原性,用于赋予蛋白质或片段特定的功能特性,例如关于组织分布。

[0155] 根据另一个优选的实施方案,所述附加序列能够刺激针对突变的SARS-CoV-2刺突蛋白、其变体或片段的表位的免疫反应。

[0156] 本发明的另一个目的是编码上述突变的SARS-CoV-2刺突蛋白、变体、肽或蛋白的mRNA。

[0157] 根据一个优选的实施方案,为了增加稳定性并避免体内降解,所述mRNA是核苷修饰的mRNA序列。

[0158] 根据一个优选的实施方案,在所述核苷修饰的mRNA序列中,尿苷残基被选自以下的修饰的核苷替换:吡啶-4-酮核糖核苷、5-氮杂-尿苷、2-硫代-5-氮杂尿苷、2-硫代尿苷、4-硫代-假尿苷、2-硫代-假尿苷、5-羟基尿苷、3-甲基尿苷、5-羧甲基-尿苷、1-羧甲基-假尿

苷、5-丙炔基-尿苷、1-丙炔基-假尿苷、5-牛磺酸甲基尿苷、1-牛磺酸甲基-假尿苷、5-牛磺酸甲基-2-硫代-尿苷、1-牛磺酸甲基-4-硫代尿苷、5-甲基-尿苷、1-甲基-假尿苷、4-硫代-1-甲基-假尿苷、2-硫代-1-甲基假尿苷、1-甲基-1-脱氮-假尿苷、2-硫代-1-甲基-1-脱氮-假尿苷、二氢尿苷、二氢假尿苷、2-硫代-二氢尿苷、2-硫代-二氢假尿苷、2-甲氧基尿苷、2-甲氧基-4-硫代-尿苷、4-甲氧基-假尿苷、4-甲氧基-2-硫代-假尿苷,优选用1-甲基-假尿苷修饰。

[0159] 根据另一个实施方案,优选为了进一步稳定mRNA,与野生型SARS-CoV-2刺突蛋白的相应编码区中存在的G/C含量相比,根据本发明的mRNA的编码区含有增加的G/C含量。这是通过在序列中引入允许增加G/C比率的同义密码子取代来实现的。

[0160] 根据另一个实施方案,优选地,在根据本发明的mRNA中,密码子使用已经针对在人细胞中的表达进行了优化。

[0161] 本发明的进一步目的是编码如上所述的突变的SARS-CoV-2刺突蛋白、其变体或肽的DNA序列。

[0162] 根据一个优选的实施方案,所述DNA包含在质粒中。优选地,所述质粒至少含有启动子和终止密码子。

[0163] 根据可替选的优选实施方案,所述DNA包含在病毒载体中。所述病毒载体可以是非复制的或复制的。所述病毒载体优选选自腺病毒或痘病毒。更优选地,所述病毒载体选自5型腺病毒(Ad5)载体、26型腺病毒(Ad26)载体、复制缺陷型猿猴腺病毒ChAdOx1载体。

[0164] 根据本发明的蛋白质、mRNA或DNA可以通过本领域公知的方法来制备。

[0165] 本发明的另一个目的是如上所述的突变的SARS-CoV-2刺突蛋白、其变体或肽或编码其的mRNA或DNA用于在受试者中预防COVID-19。

[0166] 本发明的另一个目的是疫苗组合物,其包含如上定义的突变的SARS-CoV-2刺突蛋白、其变体或片段或编码其的mRNA或DNA。

[0167] 疫苗组合物优选用于预防COVID-19。

[0168] 疫苗可以根据用于制备基于蛋白质或核酸的疫苗的公知的技术来配制,例如描述在Batty等人,AdvDrug Delivery Rev 2021,169:168-189中。

[0169] 优选地,所述疫苗含有佐剂。

[0170] 根据本发明的“佐剂”是能够提高组合物的免疫刺激特性的组分。

[0171] 所述佐剂选自本领域技术人员公知的并且适合于所使用的特定抗原和制剂的佐剂。

[0172] 根据本发明的疫苗可以通过肠胃外施用,优选皮内、肌肉内或皮下施用、口服施用或经鼻施用进行施用。

[0173] 实验部分

[0174] 实施例1

[0175] 生物信息分析

[0176] 材料和方法

[0177] 1.相互作用组分析

[0178] STRING数据库[Szklarczyk D等人,Nucleic Acids Res.2021,49:D605-D612,doi:10.1093/nar/gkaa1074]整合了蛋白质之间所有已知和预测的关联(包括物理相互作

用和功能关联),用于分析生物分子之间的功能关联。每个蛋白质-蛋白质相互作用都用“分数”注释。该分数并不表示相互作用的强度或特异性,而仅表示置信度。所有分数从0到1排列,其中1表示最高可能的置信度。

[0179] 2.3D模型选择

[0180] 刺突蛋白3D模型是基于返回其野生型形式并完全糖基化的PDB 6VYB构建的。三个原聚体的不对称糖基化是通过已发表的N-聚糖和O-聚糖的糖分析数据得出的(Casalini L等人,ACS Cent.Sci.2020,6:1722-1734,https://doi.org/10.1021/acscentsci.0c01056)。使用Amber14SB力场对蛋白质进行建模(Maier J A等人,J.Chem.Theory Comput.2015,11:3696-3713,https://doi.org/10.1021/acs.jctc.5b00255)以及碳水化合物部分通过GLYCAM06力场的GLYCAM06j-1版本进行建模(Kirschner KN等人,J.Comput.Chem.2008,29:622-655,https://doi.org/10.1002/jcc.20820)。如此制备的结构用作分子对接模拟(Molecular Docking simulations)的起点。拓扑文件是使用pdb2gmx GROMACS工具利用amber99sb力场生成的(Lindorff-Larsen K等人,Proteins 2010,78:1950-1958,https://dx.doi.org/10.1002/prot.22711)。将蛋白质插入三斜晶盒中(triclinic box),从溶质延伸至15 Å,浸入TIP3P水分子中(Jorgensen WL等人,J Chem Phys 1983,79:926-935,https://dx.doi.org/10.1063/1.445869)。使用genion GROMACS工具添加平衡离子以中和总电荷。将能量最小化后,通过对蛋白质原子施加1000kJ mol-1nm-2的位置限制,使得系统松弛5ns。在此步骤之后,使用GROMACS2018.3模拟包(超级计算机Galileo和Marconi-100,CINECA,博洛尼亚,意大利)进行长度为1微秒、时间步长为2fs的无限制性MD模拟(Abraham MJ等人,SoftwareX 2015,1:19-25,https://dx.doi.org/10.1016/j.softx.2015.06.001)。采用V-rescale温度耦合将温度保持恒定在300K(Bussi G等人,J Chem Phys,2007126:014101.https://dx.doi.org/10.1063/1.2408420)。Particle-Mesh Ewald方法用于处理长程静电相互作用(Darden T等人,J.Chem.Phys 1993,98:10089,https://doi.org/10.1063/1.464397)。每个轨迹的前5ns被排除在分析之外。对1微秒MD模拟后获得的轨迹进行聚类以获得代表性结构。特别是,用于对接研究的结构是从MD实验中提取的第一个聚类的第一个形心。

[0181] 对于雌激素受体,使用代码为3OLL的XRAY PDB模型,其包含雌二醇和核受体共激活因子1(Möcklinghoff S等人,ChemBioChem 2010,11:2251-2254,https://doi.org/10.1002/cbic.201000532)。

[0182] 3.蛋白质-蛋白质对接程序

[0183] 提供了两种单独蛋白质的输入,一种用于受体,另一种用于配体。特别地,刺突蛋白和ER分别用作受体和配体。然后,HDOCK工具对接至通过基于FFT的搜索方法假定的样品结合模式,然后对蛋白质-蛋白质相互作用进行评分。最后,提供了前100个预测的复合结构,并对最佳的10个假设进行了目视检查,以确认计算的可靠性。描述了整个工作流程(Yan Y等人,Nat Protoc 2020,15:1829-1852,https://doi.org/10.1038/s41596-020-0312-x)。

[0184] 鉴于缺乏刺突蛋白与核雌激素受体(ER)之间结合机制的结构信息,第一个检查涉及识别已知与雌激素受体相互作用的蛋白质。鉴定出这些与ER相互作用的蛋白后,第二步涉及研究刺突蛋白和ER效应蛋白之间的任何序列相似性。

[0185] 实施例1a

[0186] 核受体共激活因子和LxxLL基序

[0187] 许多转录因子和辅因子表现出共同的结构基序,其确保了与效应蛋白的相互作用。参与这些蛋白质-蛋白质相互作用的基序被称为LxxLL(LDX),其与转录调节的不同方面相关(Plevin MJ等人,Trends Biochem Sci 2005,30:66-69.https://dx.doi.org/10.1016/j.tibs.2004.12.001)。最初是在与核受体配体结合结构域(LBD)的激活功能2(AF-2)区域结合的蛋白质中鉴定出LxxLL序列。这些基序是使用许多核受体结合蛋白(包括共激活因子(NCOA-1、2和3))调节核受体的基础(Heery DM等人,Nature 1997,387:733-736,https://doi.org/10.1038/42750)。

[0188] 显示ER和NCOA之间相互作用的实验和结构确认,使得聚焦LxxLL基序成为可能,并以此为起点对刺突蛋白序列进行作图,寻找能够模拟ER与其核共激活因子之间的相互作用的刺突蛋白的结构基序和同源部分(图1)。

[0189] 实施例1b

[0190] 雌激素受体结合蛋白网络分析

[0191] ER1和ER2最重要的相互作用网络(图2)突出了,在最可靠的与ER1和ER2相互作用的蛋白中,核受体共激活因子(NCOA)直接结合核受体并刺激转录活性。将NACO和刺突蛋白之间的序列比对与病毒蛋白的三维分析相结合,发现刺突蛋白含有LDX基序(LPPLL,刺突蛋白野生型中的aa 861-865)和两个与LxxLL同源的基序(刺突蛋白野生型中的IEDLL,aa 818-822和LGDIA,aa 841-846),从结构角度来看也是有效的(事实上,这些区域呈现α-螺旋构象),位于外区(outer zone),原则上可能作为与ER的相互作用区的位点发挥作用。不同的LDX结构域与特定的辅因子-受体相互作用相关,刺突蛋白LDX1类似于NCOA1 LDX4,属于III类结构域(图3)(Savkur RS等人,J Pept Res 2004,63:207-212,https://dx.doi.org/10.1111/j.1399-3011.2004.00126.x)。

[0192] 实施例1c

[0193] 刺突蛋白-ER盲对接

[0194] 经实验验证,ER不结合病毒蛋白的受体结合结构域(RBD)(数据未显示)。为了确认和验证计算机预测,使用HDOCK服务器[http://hdock.phys.hust.edu.cn/]通过两种蛋白质之间的盲对接方式来评价ER与病毒RBD以外的区域相互作用的能力。盲对接方法不考虑任何结构性偏差,是完全不受指导的(unguided)。发现的最佳结合假设证明ER对刺突蛋白的侧向区域具有高亲和力,属于所谓的“融合肽部分”(图4)。

[0195] 实施例1d

[0196] 刺突蛋白-ER基序定向的对接

[0197] 通过优化蛋白质与蛋白质之间的相互作用,被NCOA识别的ER残基的结构信息被用来指导ER与刺突蛋白的对接研究。以蛋白质结构和残基限制作为输入,通过HDOCK服务器生成合适的模型。鉴于ER和NCOA之间相互作用的结构信息已知,进行了第二次对接研究,考虑了保证与NCOA相互作用的ER残基,从而指导分子对接过程。从指导的对接研究中获得的最佳结合假设如图5所示,其突出显示了ER与包含与LxxLL模式同源的基序的刺突蛋白区域的结合。

[0198] 实施例2

[0199] 癌细胞系增殖活性的体外评价

[0200] 材料和方法

[0201] 肽2、5和7

[0202] 从同源和LxxLL样核心开始合成了三种肽(命名为2、5和7),其具有以下氨基酸序列:

[0203] 肽2:SKRSFIEDLLFNKVTL(SEQ ID NO:16)

[0204] 肽5:IKQYGDCLGDIAARDLI(SEQ ID NO:17)

[0205] 肽7:NGLTVLPPLLTDEMI(SEQ ID NO:18)。

[0206] 每个肽都包含一个野生型刺突蛋白中发现的LxxLL基序。

[0207] 这些肽由CASLO ApS(Technical University of Denmark,DTU-Science Park Diplomvej 381,DK-2800Kongens Lyngby,Denmark)使用基于Fmoc的固相肽合成方案合成。每个肽在N末端被乙酰化,在C末端被酰胺化;它们以冻干盐酸盐保存。通过分析型RP-HPLC(C18-250 mm×4.6mm I.D.,流速1mL/min;在220nm处检测吸光度)评估肽的纯度,通过MALDI-TOF质谱法进行验证。

[0208] 测试浓度

[0209] 刺突蛋白在培养基中的终浓度为10ng/ml。雷洛昔芬在培养基中的终浓度为2μM。雌二醇储备溶液在乙醇中制备,在培养基中稀释至终浓度1nM使用。将肽在PBS中稀释至4mg/ml浓度,然后将10ug/ml用作测定的浓度(培养基中的终浓度)。

[0210] 增殖测定法

[0211] 为了评价细胞增殖,进行了BrdU测定法(Abcam,UK)。将BrdU掺入至新合成的活跃增殖细胞的DNA中。将20μL稀释的1×BrdU标记添加到合适的孔中,孵育24小时。将BrdU掺入至分裂细胞的DNA中。为了使抗体能够与掺入的BrdU细胞结合,必须对细胞进行固定、透化和DNA变性。这一切都是通过使用固定液一步处理完成的。将检测剂抗BrdU单克隆抗体移液至孔中,允许孵育一小时,在此期间它与任何掺入的BrdU结合。进行不同的洗涤以洗掉未结合的抗体,并添加辣根过氧化物酶缀合的山羊抗小鼠抗体,该抗体与检测剂抗体结合。然后,加入TMB过氧化物酶底物并在室温下避光孵育30分钟。最后,添加终止溶液以终止反应。使用设置为450nm的分光光度微量滴定酶标仪读取板。

[0212] 乳腺癌细胞系

[0213] MCF-7细胞系是一种激素依赖性侵袭性导管/乳腺癌细胞(雌激素和孕激素受体均为阳性)。

[0214] MCF-7获自ATCC,在补充有10%胎牛血清(FBS,Corning,USA)、青霉素/链霉素和谷氨酰胺(Sigma,USA)的DMEM(杜氏改良培养基)中、在37℃、5%CO2和95%湿度的培养箱中(Thermo,USA)中生长。处理前,为了降低FBS中的雌激素水平,将细胞在无酚红培养基(含有5%葡聚糖包被的活性炭处理的血清)中培养24小时,然后在补充有0.2% BSA的无酚红、无血清培养基中孵育至少24小时。

[0215] 在第一组实验中,用雌二醇,野生型刺突蛋白,雷洛昔芬,雌二醇和雷洛昔芬、野生型刺突蛋白和雷洛昔芬,雌二醇、刺突蛋白和雷洛昔芬处理细胞24小时,测量增殖。

[0216] 结果表示在图6中。可以看出,雌二醇和刺突蛋白均能够实质上增加细胞增殖,这种活性通过与雷洛昔芬共同处理而被抵消。这些数据表明野生型刺突蛋白能够通过ER介导

的机制诱导乳腺癌细胞的增殖。

[0217] 在第二组实验中,用肽2、5和7,野生型刺突蛋白,刺突蛋白加雷洛昔芬或单独雷洛昔芬处理细胞24小时,测量增殖。

[0218] 结果表示在图7中。平均值和SD如下表1所示:

[0219] 表1

[0220]

MCF-7							
	ctrl	2	5	7	刺突蛋白	刺突蛋白+ral	ral
平均值	100,0	155,7	170,6	205,5	179,9	165,3	109,5
SD	0,53	1,31	1,54	0,97	0,57	2,13	0,68

[0221] 可以看出,这些肽都能够诱导类似于刺突蛋白诱导的增殖。获得的数据证明野生型刺突蛋白中的每个LxxL基序都能够诱导雌激素受体的激活。

[0222] 前列腺癌细胞系

[0223] 已建立的雄激素依赖性细胞系LNCap被用作本研究的模型。细胞在补充有10%胎牛血清(FBS,Corning,USA)、青霉素/链霉素和谷氨酰胺(Sigma,USA)的DMEM中,在37℃、5% CO2和95%湿度的培养箱中(Thermo,USA)培养。处理前,为了降低FBS中的雌激素水平,将细胞在无酚红培养基(含有5%葡聚糖包被的活性炭处理的血清)中培养24小时,然后在补充有0.2% BSA的无酚红、无血清培养基中孵育至少24小时。然后用肽2、5和7或野生型刺突蛋白处理细胞24小时,测量增殖。

[0224] 结果表示在图8中。平均值和SD如下表2所示:

[0225] 表2

[0226]

LNCaP					
	ctrl	2	5	7	刺突蛋白
平均值	100,0	242,2	236,2	230,2	245,9
SD	0,21	0,72	0,24	0,7	0,29

[0227] 获得的结果证明肽和刺突蛋白都能够通过激活雄激素受体来诱导增殖。

[0228] 实施例3

[0229] 蛋白质组分析

[0230] 人单核细胞THP-1购自ATCC,按照制造商的说明进行培养。然后,使用20ng/ml佛波醇12-肉豆蔻酸酯13-乙酸酯(PMA)使THP-1进行分化72小时,随后通过LPS刺激(100ng/ml)24小时,用雌二醇、雷洛昔芬和野生型刺突蛋白、野生型刺突蛋白+雷洛昔芬、雌二醇+野生型刺突蛋白、雌二醇+雷洛昔芬+野生型刺突蛋白以实施例2中使用的浓度持续处理24小时。然后,收集培养基,进行蛋白质组图谱测定。

[0231] 具体而言,将来自THP-1处理的细胞的条件培养基离心以除去颗粒并立即进行测定。按照建议调节样品量(500μl)。试剂按照制造商的方案(R&D,USA)制备。简言之,将膜与阵列缓冲液(Array Buffer)6一起在摇台振动器上孵育1小时。样品制备方法如下:在两个独立的试管中添加1ml的阵列缓冲液4,然后向每个制备的样品中添加15μl重构的小鼠细胞因子检测抗体混合物(>40种小鼠细胞因子),孵育1小时。然后,吸出阵列缓冲液6,用样品/抗体混合物替换,在4℃下孵育过夜。次日洗涤膜3次,链霉亲和素-HRP(1:2000)在摇台振动器上室温孵育30分钟。再次洗涤膜,将1ml制备的化学试剂混合物置于每个膜上。使用

UVITEC数字分析仪(Alliance,Cambridge,UK)获得多个曝光时间。将透明叠加模板放在阵列图像上,将其与每个阵列的三个角上成对的参考点对齐,即可以识别出显影膜上的阳性信号。包含参考点以证明在测定过程中阵列已与链霉亲和素-HRP一起孵育。通过Fiji软件分析像素密度(代表每种细胞因子的重复点对的平均信号),从每个点中减去平均背景。

[0232] 结果报告在图9中。可以看出,IL-8的丰度似乎最强,其被雌二醇和野生型刺突蛋白上调。雷洛昔芬可有效抵消刺突蛋白的影响。雌二醇和野生型刺突蛋白都上调非酶促的类几丁质酶-3样蛋白-1(CHI3L1),但雷洛昔芬只能抵消刺突蛋白单独的影响。

[0233] 雌二醇和野生型刺突蛋白都上调骨调素(OPN),雷洛昔芬能够抵消刺突蛋白单独的影响。

[0234] 实施例4

[0235] 野生型刺突蛋白和突变体的生产和纯化

[0236] 生成编码野生型刺突蛋白的第16至1213位氨基酸(胞外结构域)和编码下文所述的相应SP5、SP7和SP5+SP7突变体的核苷酸序列,将其插入质粒DNA载体中,所述载体具有人巨细胞病毒(CMV)立即早期增强子和启动子、用于蛋白质分泌的鼠Ig kappa链前导序列、牛生长激素聚腺苷酸化(bGH-PolyA)信号、用于在真核细胞中蛋白质表达的特定终止序列以及在细菌中用于质粒扩增的来自金黄色葡萄球菌(Staphylococcus aureus)的卡那霉素抗性基因。

[0237] 具体突变的序列如下:

[0238] • SP5:参照SEQ ID NO:1的突变L841A、I844A,

[0239] • SP7:参照SEQ ID NO:1的突变L861A、L864A、L865A,

[0240] • SP5+SP7:参照SEQ ID NO:1的突变L841A、I844A、L861A、L864A、L865A,

[0241] 每个还含有参照SEQ ID NO:1的稳定化的氨基酸替换R685A、K986P和V987P。

[0242] 根据制造商的说明,用ExpiFectamine 293(Thermo Fisher)脂质阳离子转染试剂瞬时转染Expi293F高密度细胞,产生刺突蛋白和SP5、SP7和SP5+SP7。从转染开始孵育5天后收集含有蛋白质的上清液,通过离心和过滤使其澄清用于后续的纯化步骤。使用IMAC(固定金属螯合物亲和色谱法)使用PureCube Ni-NTA琼脂糖树脂浆料(Cube-Biotech)对蛋白质进行批量纯化。简而言之,将树脂浆料离心,与平衡缓冲液(50mM NaH2PO4、500mM NaCl、pH 7.4、10mM咪唑)一起孵育。将平衡后的树脂与含有重组蛋白的培养物的上清液合并,于4℃下在旋转平台上孵育o/n。随后通过离心收集树脂,洗涤,用含有300mM咪唑的洗脱缓冲液洗脱蛋白质,按照产品数据表中所示,使用Slide-A-lyzers(Thermo Fisher)在磷酸盐缓冲液(PBS)中进行透析。透析回收后,用分光光度计测量280nm处的吸光度,对蛋白质进行定量。通过在还原和非还原条件下进行SDS-PAGE和蛋白质印迹分析来评估蛋白质的纯度。如实施例4a中所述,通过BioLayer干涉仪BLI评价它们与hACE2受体的结合能力的进一步表征和相关亲和力。

[0243] 实施例4a

[0244] hACE-2受体结合测定法

[0245] 使用Octet Red(Forte Bio)系统进行结合研究以验证所产生的刺突蛋白(wt和SP5、SP7和SP5+SP7)结合hACE2受体的能力。所有步骤均在每孔含有200μl溶液的96孔板(96孔微孔板,底部F,黑色,655209,来自Greiner bio-one)中以600rpm搅拌在25℃下进行。在

该研究中使用动力学缓冲液1×(目录号18-1105,Forte Bio)稀释所有蛋白质和分析物,并用于洗涤传感器。通过首先使用抗人Fc Octet生物传感器(抗人IgG Fc Capture Biosensors,目录号18-5060,FORTEBIO)捕获hACE2-hFc蛋白来进行动力学测定。将生物传感器浸入1×缓冲液中10分钟,然后测量基础信号60秒,在此时加载hACE2-hFc 300秒(直到生物传感器完全饱和)。在1×动力学缓冲液中进行洗涤步骤120秒后,将与hACE2-hFc缀合的生物传感器尖端浸入含有不同浓度抗原(刺突蛋白wt蛋白及其突变体SP5、SP7和SP5+SP7)的孔中300秒,以评价结合曲线,然后在动力学缓冲液中进行900秒的解离时间。收集结合曲线数据,然后使用数据分析软件v11.1(FORTEBIO)进行分析。在抗原结合循环开始时和减去单个参照之后对齐结合传感图。Kd值使用1:1整体Langmuir结合模型计算。

[0246] 具有各种抗原的生物传感器尖端也浸入含有动力学缓冲液的孔中,以允许减去单个参照以补偿捕获抗原的自然解离。生物传感器的尖端无需再生即可使用。

[0247] 如下表3所示的结果证明wt刺突蛋白及其突变体以高亲和力结合hACE2受体。

[0248] 表3

[0249]

	刺突蛋白WT	刺突蛋白SP5	刺突蛋白SP7	刺突蛋白SP5+SP7
KD(M)	6.36×10^{-10}	2.55×10^{-10}	4.15×10^{-10}	2.38×10^{-8}
KD误差(M)	5.92×10^{-12}	4.73×10^{-12}	5.13×10^{-12}	5.00×10^{-9}

[0250] 实施例4b

[0251] 雌激素样活性

[0252] 为了评价刺突蛋白的雌激素样活性,通过酶联免疫吸附测定(Myobiosource,目录号MBS1601167)评价耐酒石酸酸性磷酸酶(TRAP)活性。

[0253] RAW264.7(鼠巨噬细胞ATCC,USA)按照制造商的方案进行培养。然后将1.5×10^{5}个细胞/cm^{2}接种于24孔培养皿中,以终浓度35ng/ml添加核因子kb配体的小鼠受体激活因子(RANKL,MiltenyiBiotec,德国)以启动破骨细胞(OC)发育(第0天),如前所述(Collin-Osdoby和Osdoby 2012,PMID:22130930)。第3天,在显微镜下检查细胞,并用含有RANKL的新鲜培养基重新饲育。第6天,RAW-OC群体普遍存在,准备进行处理,然后进行生化研究。用1nM雌二醇或10ng/ml刺突蛋白wt、SP5、SP7或SP5+SP7处理细胞24小时。处理24小时后,通过无菌管快速收集细胞,并使用PBS(pH 7.4)重悬,将细胞悬液稀释至约1百万/ml的浓度。然后,对细胞进行反复冻融循环,以释放内部成分。同时,将试剂盒的试剂恢复至室温。标准曲线、试剂和样品按照制造商的方案制备。简而言之,将50μl标准品添加到“标准孔”中,将40μl样品添加到“样品孔”中。然后,将10μl的抗TRAP抗体添加到样品孔中,将50μl链霉亲和素-HRP添加到样品孔和标准孔中。将板盖上密封剂,在摇台上充分混匀,在37℃下孵育1小时。用洗涤缓冲液洗涤板5次,每孔加入50μl底物溶液A,再加50μl底物溶液B,37℃避光孵育10分钟。最后,向每个孔中添加50μl终止溶液,立即使用设置为450nm的酶标仪测定光密度。结果显示在图10中。平均值和SD如下表4所示:

[0254] 表4

[0255]

来自RAW264.7巨噬细胞的破骨细胞（TRAP水平U/L）							
	CTR w/o RANKL	使用RANKL的CTR	雌二醇	刺突蛋白WT	刺突蛋白SP5	刺突蛋白SP7	刺突蛋白SP5+SP7
平均值	0.18	2.02	0.25	0.26	1.90	2.11	2.04
SD	0.05	0.71	0.05	0.05	0.24	0.14	0.24

[0256] 结果表明,刺突蛋白wt对细胞发挥与用雌二醇观察到的相同的作用。相反,所有突变体SP5、SP7和SP5+SP7表现出与用RANKL刺激的对照相同的TRAP水平,表明这些突变阻止了刺突蛋白激活雌激素受体的能力。

序列表

<110> 东佩制药股份公司

<120> 用于COVID-19疫苗的新型蛋白质和核酸序列

<130> 254-WO

<160> 55

<170> BiSSAP 1.3.6

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<211> 1273

<212> PRT

<213> SARS冠状病毒

<220>

<223> 野生型Sars CoV-2刺突蛋白

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His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
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Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
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Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
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Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr

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

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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr

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

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

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Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys

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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

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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro

370 375 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe

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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

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Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe

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Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys

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Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val

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

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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile

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

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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn

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Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala

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Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn

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

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His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu

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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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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

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Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala

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Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala

675 680 685

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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

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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

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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

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

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Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
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Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
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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 Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880
Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895
Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910
Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr

1265 1270

<210> 4

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars CoV-2刺突蛋白的变体2

<400> 4

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 Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro 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 Pro 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 5
<211> 1273
<212> PRT
<213> 人工序列
<220>
<223> 突变的Sars CoV-2刺突蛋白的变体3
<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
Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val

1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120

Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135

Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200

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

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

Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 6

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars CoV-2刺突蛋白的变体4

<400> 6

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

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

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

Ala 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 Pro 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 Pro Ser Ala
930 935 940

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

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

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

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

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<213> 人工序列
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<223> 突变的Sars CoV-2刺突蛋白的的变体5

<400> 7

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
Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro 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 Pro Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230

Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<223> 突变的Sars CoV-2刺突蛋白的变体6
<400> 8

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30
Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60
Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95
Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110
Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125
Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190
Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220
Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240
Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255
Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270
Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285
Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300
Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320
Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335
Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350
Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365
Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400
Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430
Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys

515 520 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn

530 535 540

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

545 550 555 560

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

565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe

580 585 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val

595 600 605

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

610 615 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser

625 630 635 640

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

645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala

660 665 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala

675 680 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser

690 695 700

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

705 710 715 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val

725 730 735

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

740 745 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr

755 760 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln

770 775 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe

785 790 795 800

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

805 810 815

Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly

820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro 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 Pro 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu

1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<220>
<223> 突变的Sars CoV-2刺突蛋白的变体31
<400> 9
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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60
Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95
Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110
Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile

115 120 125

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540
Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560
Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575
Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590
Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605
Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620
His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640
Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655
Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670
Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gln Gln Ala Gln 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 Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly

820 825 830

Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp

835 840 845

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

850 855 860

Ala 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 Leu

1010 1015 1020

Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val

1025 1030 1035 1040

Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala

1045 1050 1055

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 10
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<400> 10

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Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe
20 25 30

Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60
Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95
Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110
Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125
Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190
Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205
Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220
Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240
Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255
Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270
Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285
Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300
Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320
Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335
Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala

340 345 350
Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
355 360 365
Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400
Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430
Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540
Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560
Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575
Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590
Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605
Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620
His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640
Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
660 665 670
Ser Tyr Gln Thr Gln Thr Asn Ser Pro Gln Gln Ala Gln 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 Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880
Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895
Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910
Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val

965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<400> 11

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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
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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 Gln Gln Ala Gln 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
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Phe Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro Ala Leu Gln Ile
885 890 895
Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Pro 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 Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu

1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
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Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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<223> 突变的Sars CoV-2刺突蛋白的变体34
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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
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405 410 415
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430
Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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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 Gln Gln Ala Gln 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
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Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
725 730 735
Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
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
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Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp 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
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Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
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Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
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Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
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Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

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<223> 突变的Sars CoV-2刺突蛋白的变体35
<400> 13

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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
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405 410 415
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430
Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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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 Gln Gln Ala Gln 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 Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro 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 Pro Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu

1010 1015 1020

Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040

Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070

Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085

Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120

Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135

Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200

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

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

Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 14

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars CoV-2刺突蛋白的变体36

<400> 14

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 Gln Gln Ala Gln 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
Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro 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 Pro Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 15

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars CoV-2刺突蛋白的变体37

<400> 15

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 Gln Gln Ala Gln 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
Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ile Ala Ala Arg Asp

835 840 845

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

Ala 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 Pro Ala Leu Gln Ile
885 890 895

Pro Phe Pro 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 Pro 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 Leu
1010 1015 1020

Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040

Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070

Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085

Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120

Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135

Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 16
<211> 16
<212> PRT
<213> 人工序列
<220>
<223> 肽2
<400> 16
Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu
1 5 10 15

<210> 17
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> 肽5
<400> 17
Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu
1 5 10 15
Ile

<210> 18
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 肽7
<400> 18
Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile
1 5 10 15
<210> 19
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> SPIKELMX1 aa第812位至第828位
<400> 19
Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr
1 5 10 15
Leu
<210> 20
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA1LXD1 aa第627位至第643位
<400> 20
Ser Gln Thr Ser His Lys Leu Val Gln Leu Leu Thr Thr Thr Ala Glu
1 5 10 15
Gln
<210> 21
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA2LDX1 aa第635位至第651位
<400> 21
Ser Lys Gly Gln Thr Lys Leu Leu Gln Leu Leu Thr Thr Lys Ser Asp
1 5 10 15
Gln
<210> 22
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> NCOA1LXD2 aa第684位至第700位
<400> 22
Thr Glu Arg His Lys Ile Leu His Arg Leu Leu Gln Glu Gly Ser Pro
1 5 10 15
Ser
<210> 23
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA2LDX2 aa第684位至第700位
<400> 23
Lys Glu Lys His Lys Ile Leu His Arg Leu Leu Gln Asp Ser Ser Ser
1 5 10 15
Pro
<210> 24
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA1LXD3 aa第743位至第759位
<400> 24
Ser Lys Asp His Gln Leu Leu Arg Tyr Leu Leu Asp Lys Asp Glu Lys
1 5 10 15
Asp
<210> 25
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA2LDX3 aa第739位至第755位
<400> 25
Lys Lys Glu Asn Ala Leu Leu Arg Tyr Leu Leu Asp Lys Asp Asp Thr
1 5 10 15
Lys
<210> 26
<211> 17
<212> PRT

<213> 人工序列
<220>
<223> NCOA1LXD4 aa第907位至第923位
<400> 26
Gln Cys Ile Ser Ser Gln Leu Asp Glu Leu Leu Cys Pro Pro Thr Thr
1 5 10 15
Val
<210> 27
<211> 17
<212> PRT
<213> 人工序列
<220>
<223> NCOA2LDX4 aa第1073位至第1089位
<400> 27
Pro Ser Asp Glu Gly Ala Leu Leu Asp Gln Leu Tyr Leu Ala Leu Arg
1 5 10 15
Asn
<210> 28
<211> 1273
<212> PRT
<213> 人工序列
<220>
<223> 突变的Sars-CoV-2刺突蛋白
<400> 28
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

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Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
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Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
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Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
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Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
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Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
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Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
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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
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770 775 780
Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
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Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255
Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270
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275 280 285
Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala

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675 680 685
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Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val

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

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Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ala Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260
Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 32
<211> 1273
<212> PRT
<213> 人工序列
<220>
<223> 突变的Sars-CoV-2刺突蛋白的变体7
<400> 32
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 Ala Gly Asp Ala Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
850 855 860
Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865 870 875 880
Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
885 890 895
Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
900 905 910
Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu

1010 1015 1020

Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040

Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070

Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085

Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120

Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135

Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200

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

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

Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 33

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars-CoV-2刺突蛋白的变体8

<400> 33

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 Ala Gly Asp Ala 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 Pro 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 Pro 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 34

<211> 1273

<212> PRT

<213> 人工序列

<220>

<223> 突变的Sars-CoV-2刺突蛋白的变体9

<400> 34

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
Pro 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 Ala Gly Asp Ala 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 Pro 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 Leu
1010 1015 1020

Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040

Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055

Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070

Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085

Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120

Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135

Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
1220 1225 1230
Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
1235 1240 1245
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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
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
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Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
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Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
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Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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
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Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
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Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
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Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
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Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400
Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
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Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
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Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn

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Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe

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Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys

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

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

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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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His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser

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Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala

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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

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

740 745 750

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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800
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1155 1160 1165
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp

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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser

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Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr

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

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Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe

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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr

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

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

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370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
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580 585 590
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His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
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645 650 655
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675 680 685
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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
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Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
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Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala

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Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys

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

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

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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro

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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe

385 390 395 400

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

405 410 415

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

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Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn

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Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn

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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
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Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
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Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
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
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785 790 795 800

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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 Ala Pro Pro Ala
850 855 860
Ala 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 Pro 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 Pro Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990
Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
995 1000 1005
Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp

1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200

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

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

Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
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<400> 42

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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
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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

Pro 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 Ala Pro Pro Ala
850 855 860

Ala 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 Pro Ala Leu Gln Ile
885 890 895

Pro Phe Pro 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 Pro Ser Ala
930 935 940

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

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

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

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

Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070

Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
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Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60
Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95
Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110
Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
115 120 125
Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190
Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205
Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
210 215 220
Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225 230 235 240
Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
245 250 255
Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
260 265 270
Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
275 280 285
Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
290 295 300
Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305 310 315 320
Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
325 330 335
Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
340 345 350
Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu

355 360 365
Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400
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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
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Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
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Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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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
Pro 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 Ala Pro Pro Ala
850 855 860
Ala Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
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945 950 955 960
Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
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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 Leu
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
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Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
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Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
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Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
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Leu Lys Gly Val Lys Leu His Tyr Thr
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<400> 44

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
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His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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
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Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
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Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
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515 520 525
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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

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Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ala Ala Ala Arg Asp

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

850 855 860

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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
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
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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
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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 Leu
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
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Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
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Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
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Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
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Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
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Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile

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<223> 突变的Sars-CoV-2刺突蛋白的变体20

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

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

Ala 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 Pro Ala Leu Gln Ile
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Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
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Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Pro Ser Ala
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
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Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
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Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
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Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
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Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
370 375 380
Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385 390 395 400
Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
405 410 415
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
420 425 430
Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
435 440 445
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
450 455 460
Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465 470 475 480
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
530 535 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545 550 555 560
Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
565 570 575
Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
580 585 590
Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
595 600 605
Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
610 615 620
His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625 630 635 640
Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
645 650 655
Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
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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
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Pro 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 Ala Gly Asp Ala Ala Ala Arg Asp
835 840 845
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850 855 860
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865 870 875 880
Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
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Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Pro Ser Ala
930 935 940
Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
965 970 975
Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
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 Leu
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Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180
Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200
Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
1205 1210 1215
Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
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Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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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
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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

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Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
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485 490 495
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
500 505 510
Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
515 520 525
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
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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
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
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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
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Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
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Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ala Ala Ala Arg Asp
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Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
915 920 925
Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Pro Ser Ala
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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
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
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1075 1080 1085

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1090 1095 1100

Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
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Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150

Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165

Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
1170 1175 1180

Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu
1185 1190 1195 1200

Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
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Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile
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Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys
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<210> 50
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<223> 突变的Sars-CoV-2刺突蛋白的变体25
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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
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Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
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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
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Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190
Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205
Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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
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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
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
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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
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Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
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His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
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675 680 685
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690 695 700
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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
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820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ala Ala Ala Arg Asp
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Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860
Ala Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
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Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
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Leu Asn Asp Ile Leu Ser Arg Leu Asp Pro Pro Glu Ala Glu Val Gln
980 985 990

Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val
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Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu
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Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
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Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
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Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
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Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
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Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
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1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp
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Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile
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<223> 突变的Sars-CoV-2刺突蛋白的变体26

<400> 51

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35 40 45
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80
Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
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Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
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Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
130 135 140
Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145 150 155 160
Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
165 170 175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
180 185 190
Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
195 200 205
Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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

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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

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

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Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn

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565 570 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe

580 585 590

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Met 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 Val
1250 1255 1260

Leu Lys Gly Val Lys Leu His Tyr Thr
1265 1270

<210> 55
<211> 1273
<212> PRT
<213> 人工序列
<220>
<223> 突变的Sars-CoV-2刺突蛋白的变体30
<400> 55

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
Pro Ala Glu Asp Ala Ala Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
820 825 830
Phe Ile Lys Gln Tyr Gly Asp Cys Ala Gly Asp Ala Ala Ala Arg Asp
835 840 845
Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Ala Pro Pro Ala
850 855 860

Ala 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 Pro Ala Leu Gln Ile
885 890 895
Pro Phe Pro 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 Pro 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 Leu
1010 1015 1020
Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val
1025 1030 1035 1040
Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ser Ala
1045 1050 1055
Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu
1060 1065 1070
Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His
1075 1080 1085
Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val
1090 1095 1100
Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr
1105 1110 1115 1120
Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr
1125 1130 1135
Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu
1140 1145 1150
Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu Gly Asp
1155 1160 1165
Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp

1170 1175 1180

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

1185 1190 1195 1200

Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Ile

1205 1210 1215

Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile

1220 1225 1230

Met Leu Cys Cys Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Cys Cys

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Leu Lys Gly Val Lys Leu His Tyr Thr

1265 1270

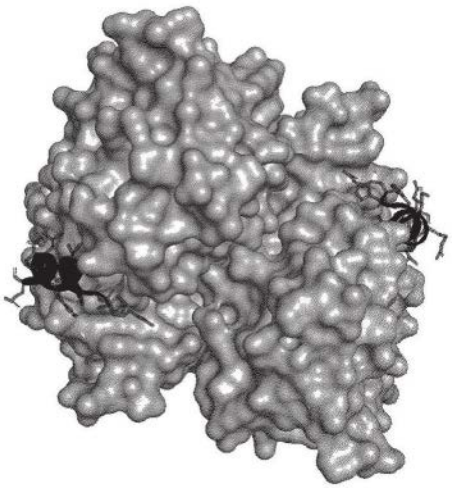


图1

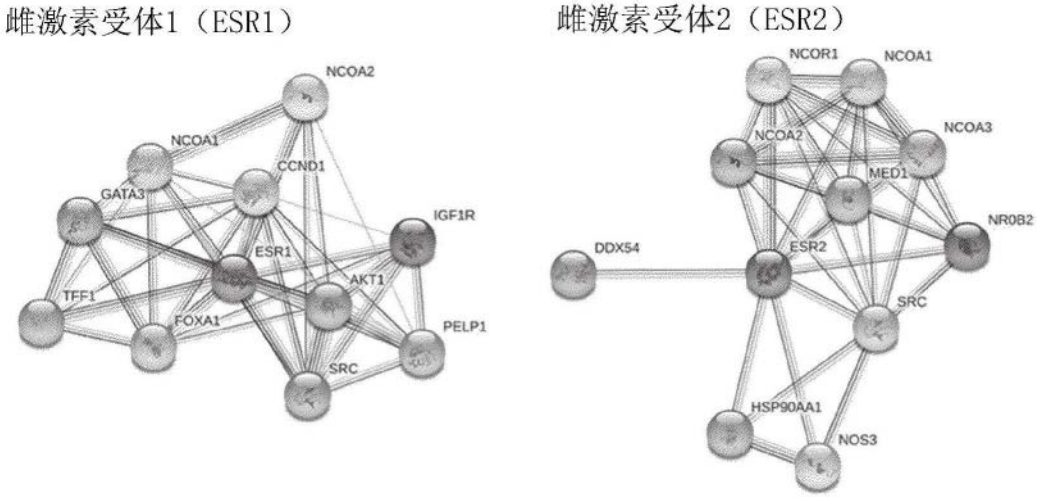


图2

SPIKELMX1	PSKRSFIEDLLFNKVTL	aa	位置	812-828
NCOA1LXD1	SQTSHKLVQLLTTTAEQ	aa	位置	627-643
NCOA2LDX1	SKGQTKLLQLLTTKSDQ	aa	位置	635-651
SPIKELMX1	PSKRSFIEDLLFNKVTL	aa	位置	812-828
NCOA1LXD2	TERHKILHRLLQEGSPS	aa	位置	684-700
NCOA2LDX2	KEKHKILHRLLQDSSSP	aa	位置	684-700
SPIKELMX1	PSKRSFIEDLLFNKVTL	aa	位置	812-828
NCOA1LXD3	SKDHQLLRYLLDKDEKD	aa	位置	743-759
NCOA2LDX3	KKENALLRYLLDKDDTK	aa	位置	739-755
SPIKELMX1	PSKRSFIEDLLFNKVTL	aa	位置	812-828
NCOA1LXD4	QCISSQLDELLCPPTTV	aa	位置	907-923
NCOA2LDX4	PSDEGALLDQLYLALRN	aa	位置	1073-1089

图3

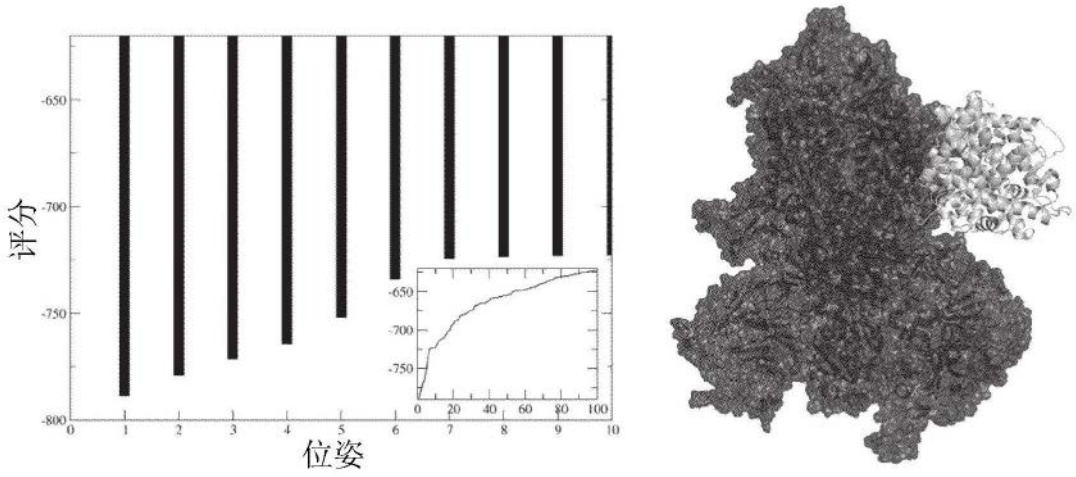

评分
位姿
-650
-700
-750
-800
0
1
2
3
4
5
6
7
8
9
10
0
20
40
60
80
100

图4

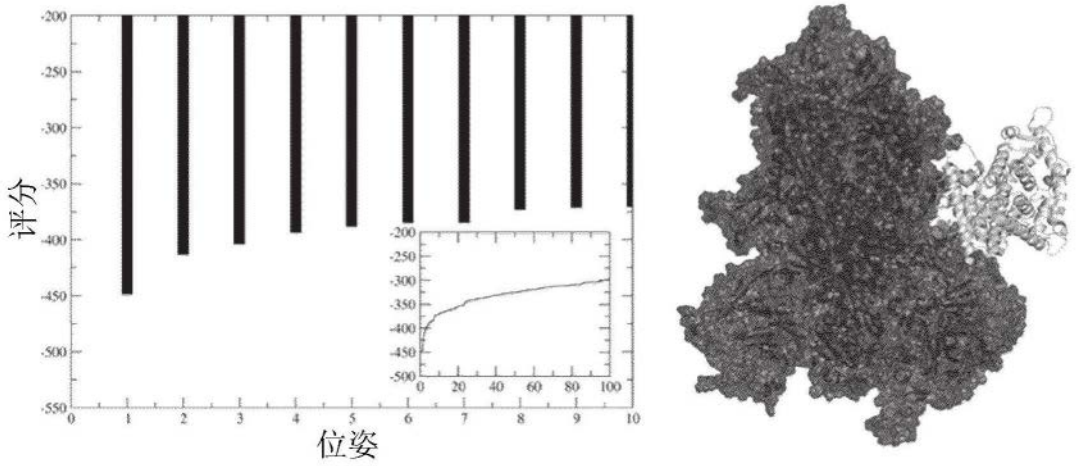

评分
位姿
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-250
-300
-350
-400
-450
-500
-550
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5
6
7
8
9
10
0
20
40
60
80
100

图5

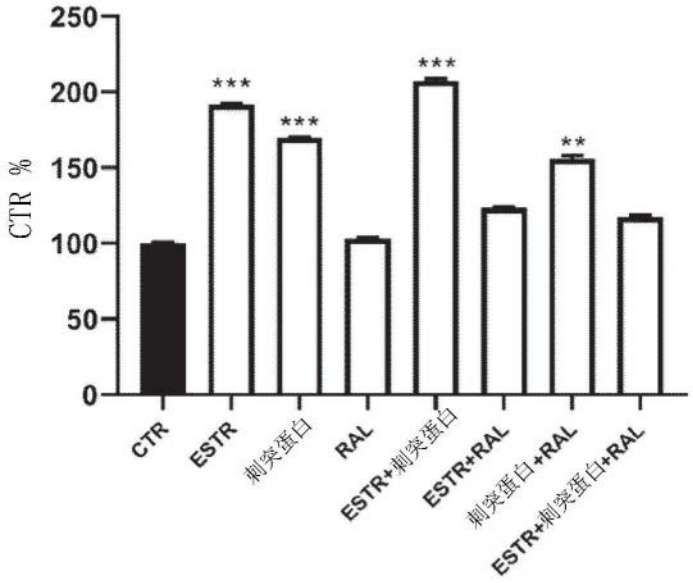

250
200
150
100
50
0
CTR %
***
***
***
**
CTR
ESTR
刺突蛋白
RAL
ESTR+刺突蛋白
ESTR+RAL
刺突蛋白+RAL
ESTR+刺突蛋白+RAL

图6

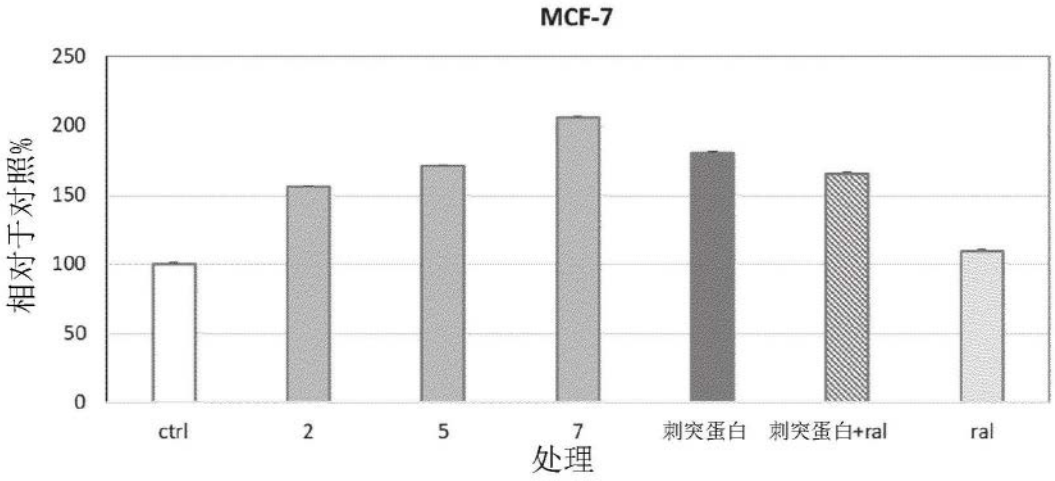

MCF-7
250
200
150
100
50
0
相对于对照%
ctrl
2
5
7
刺突蛋白
刺突蛋白+ral
ral
处理

图7

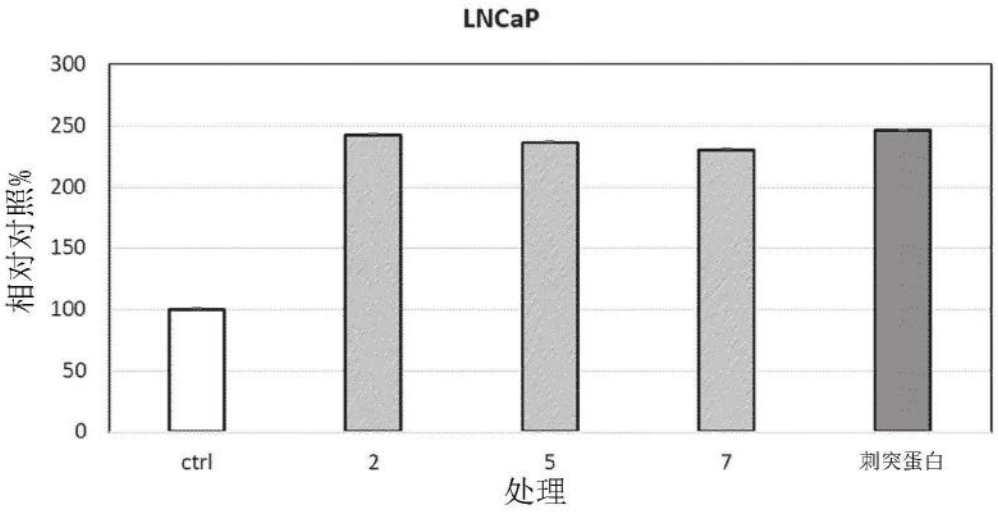

LNCaP
300
250
200
150
100
50
0
相对对照%
ctrl
2
5
7
刺突蛋白
处理

图8

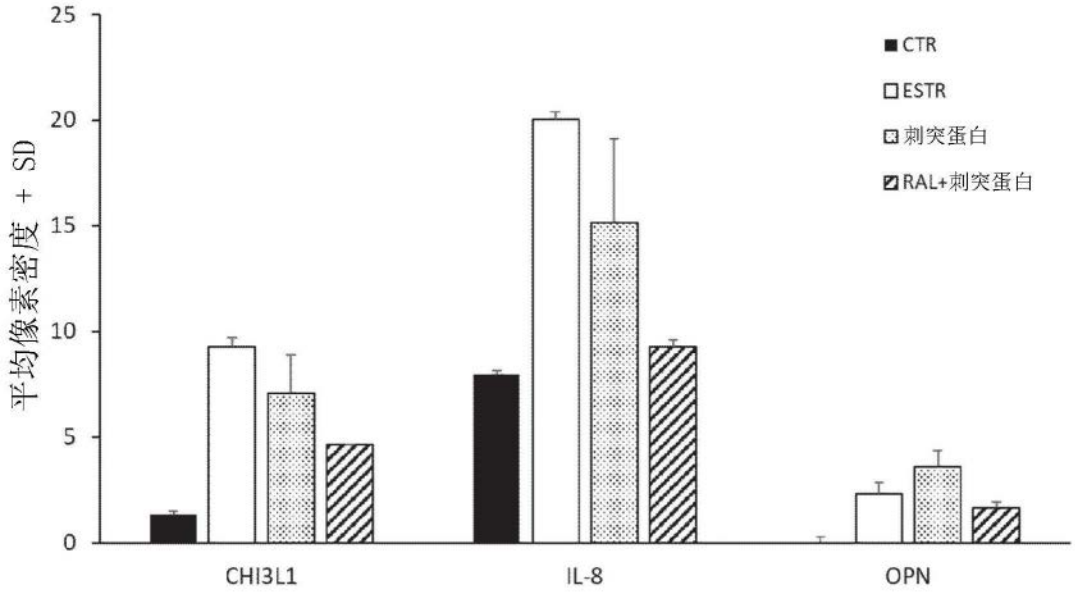

25
20
15
10
5
0
平均像素密度 + SD
CTR
ESTR
刺突蛋白
RAL+刺突蛋白
CHI3L1
IL-8
OPN

图9

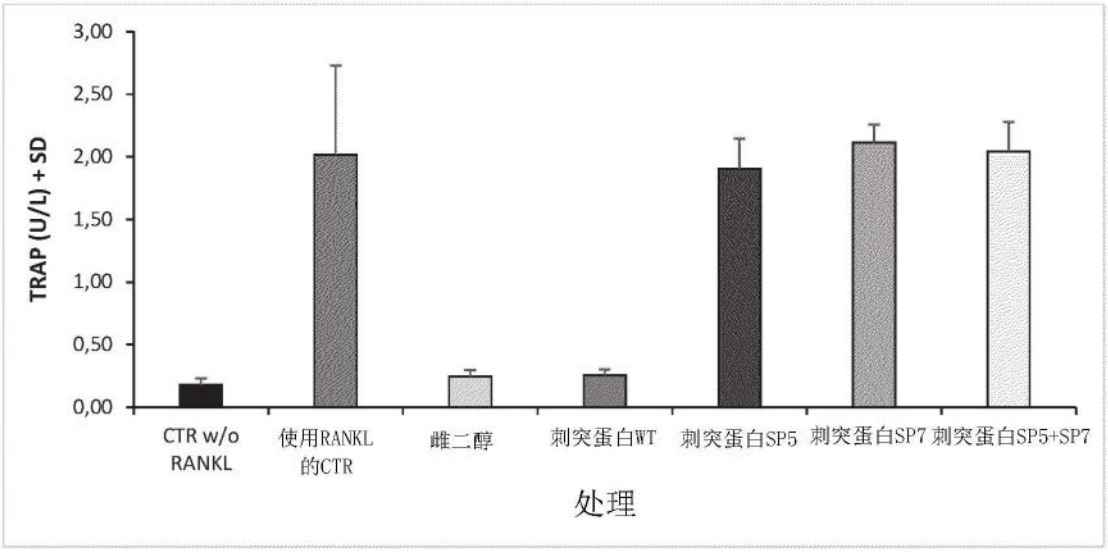

3,00
2,50
2,00
1,50
1,00
0,50
0,00
TRAP (U/L) + SD
CTR w/o RANKL
使用RANKL的CTR
雌二醇
刺突蛋白WT
刺突蛋白SP5
刺突蛋白SP7
刺突蛋白SP5+SP7
处理

图10