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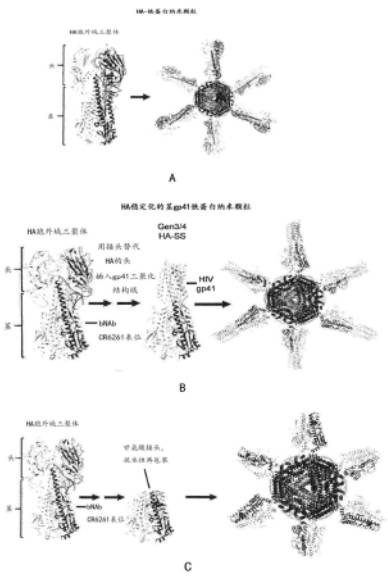
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(54)发明名称

稳定化的第2组流感血凝素茎区三聚体及其用途

(57)摘要

提供了引发广泛保护性抗体的疫苗。所述疫苗包含在其表面上展示来自第2组流感病毒的HA三聚体的纳米颗粒。所述纳米颗粒是融合蛋白，所述融合蛋白包含与第2组流感病毒HA蛋白稳定化的茎区连接的单体亚基(例如,铁蛋白)。所述融合蛋白自组装以形成展示HA的纳米颗粒。还提供了融合蛋白,编码此类蛋白的核酸分子,以及使用本发明的纳米颗粒检测抗流感抗体的测定法。



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1.一种纳米颗粒,其包含融合蛋白,所述融合蛋白包含与第2组流感病毒血凝素(HA)蛋白连接的单体亚基蛋白,所述第2组流感病毒血凝素(HA)蛋白中头部区域被长度少于10个氨基酸的接头序列替代;

其中通过向螺旋A添加ALMAQ(SEQ ID NO:36)或ELMEQ(SEQ ID NO:37)氨基酸残基将所述HA蛋白茎区中螺旋A的长度延长;并且其中HA蛋白的螺旋A和螺旋C之间的螺旋间环(inter-helix loop)已被包含GGPD(SEQ ID NO:39)的接头替代,从而提高所述融合蛋白的稳定性。

2.根据权利要求1所述的纳米颗粒,其中所述HA蛋白的茎区包含一个或多个突变,所述突变i)在所述HA蛋白内形成新的离子相互作用或盐桥;2)增强所述HA蛋白内的现有离子相互作用或盐桥;或增加所述HA蛋白内的疏水性包装,和

其中所述一个或多个突变位于所述HA蛋白中对应于由以下组成的组的氨基酸位置处:根据SEQ ID NO:4所示的参考HA蛋白序列的K396、L397、L400、S438、N440、E448、T452和N461。

3.根据权利要求2所述的纳米颗粒,其中所述一个或多个突变选自由以下组成的组:根据SEQ ID NO:4所示的参考HA蛋白序列的K396M、K396L、L397V、L400V、S438C、N440L、E448L、T452V和N461R。

4.根据权利要求3所述的纳米颗粒,其中所述HA蛋白包含在重组蛋白中对应于SEQ ID NO:4中N440的氨基酸位置的亮氨酸取代。

5.根据权利要求3所述的纳米颗粒,其中所述HA蛋白包含在重组蛋白中对应于SEQ ID NO:4中S438的氨基酸位置的半胱氨酸取代。

6.根据权利要求1所述的纳米颗粒,其中所述单体亚基蛋白是铁蛋白单体亚基蛋白或2,4,-二氧四氢蝶啶合酶单体亚基蛋白。

7.根据权利要求1所述的纳米颗粒,其中所述融合蛋白包含选自下组的氨基酸序列:SEQ ID NO:47-52、54-58、60-63、71-83、87-88、90-96、98-125、127-142和145-159。

8.根据权利要求7所述的纳米颗粒,其中所述融合蛋白包含SEQ ID NO:49或SEQ ID NO:106所示的氨基酸序列。

9.编码权利要求1-8中任意一项中所述的融合蛋白的核酸分子。

10.一种试剂盒,所述试剂盒包含权利要求9所述的核酸分子或权利要求1-8中任一项所述的纳米颗粒。

11.权利要求1-8中任一项所述的纳米颗粒用于制备针对流感病毒对个体接种疫苗的药物中的用途。

稳定化的第2组流感血凝素茎区三聚体及其用途

背景技术

[0001] 通过针对流感病毒的疫苗接种诱导的保护性免疫应答主要针对病毒HA蛋白,这是一种在病毒表面上负责病毒与宿主细胞受体相互作用的糖蛋白。病毒表面上的HA蛋白是HA蛋白单体的三聚体,其被酶促裂解后产生氨基末端HA1和羧基末端HA2多肽。球状头部仅由HA1多肽的主要部分组成,而将HA蛋白锚定入病毒脂质包膜的茎部由HA2和部分HA1组成。HA蛋白的球状头部包含两个结构域:受体结合结构域(RBD),包含唾液酸结合位点的~148个氨基酸残基的结构域,以及残留的酯酶结构域,其是正好位于RBD下方的较小的~75个氨基酸残基的区域。球状头部包含含有免疫显性表位的若干抗原位点。例如,包括Sa、Sb、Ca_1、Ca_2和Cb抗原位点(参见例如,Caton等,1982,Cell 31,417-427)。RBD-A区域包含Sa抗原位点和部分Sb抗原位点。

[0002] 针对流感的抗体通常靶向HA球状头部中的可变抗原位点,其围绕着保守的唾液酸结合位点,因此仅中和抗原性密切相关的病毒。HA头部的可变性是由流感病毒持续的抗原漂移造成的,并且使得流感是季节性流行病。而相反的是,HA茎是高度保守的并且几乎不会出现抗原漂移。不幸的是,与免疫显性的头部不同,保守的HA茎不具有较强的免疫原性。此外,病毒基因组的基因区段能够在宿主物种中经历重配(抗原漂移),产生能够导致大流行的具有改变的抗原性的新病毒[Salomon,R.等,Cell 136,402-410(2009)]。到目前为止,每年都会更新流感疫苗,以反映即将出现的流行病毒的预测HA和神经氨酸酶(NA)。

[0003] 最近,分离出一类全新的针对流感病毒的广泛中和抗体,其识别高度保守的HA茎[Corti,D.等,JClin Invest 120,1663-1673(2010);Ekiert,D.C.等,Science 324,246-251(2009);Kashyap,A.K.等,Proc Natl Acad Sci USA 105,5986-5991(2008);Okuno,Y.等,J Virol 67,2552-2558(1993);Sui,J.等,Nat Struct Mol Biol 16,265-273(2009);Ekiert,D.C.等,Science 333,843-850(2011);Corti,D.等,Science 333,850-856(2011)]。与毒株特异性抗体不同的是,这些抗体能够中和多种抗原性不同的病毒,因此诱导此类抗体已成为新一代通用疫苗开发的重点[Nabel,G.J.等,Nat Med 16,1389-1391(2010)]。然而,通过疫苗接种稳健地引发这些具有此类异质的中和性质的抗体是困难的[Steel,J.等,MBio 1,e0018(2010);Wang,T.T.等,PLoS Pathog 6,e1000796(2010);Wei,C.J.等,Science 329,1060-1064(2010)]。除去HA免疫显性的头部区域(其含有竞争性表位)并通过基因操纵将所得到的茎结构域稳定化是改善这些广泛中和茎抗体激发的一种可能方式。

[0004] 目前用于流感的疫苗策略使用化学灭活的或减毒的活流感病毒。这两种疫苗通常都在含胚卵中生产,其主要存在由于耗费时间的工艺和有限的生产能力导致的生产局限性。目前疫苗的另一个更关键的局限性是其功效是高度毒株特异性的。在2009年H1N1流感大流行期间,这些挑战变得更加明显,从而证实了开发能够克服这些局限性的新疫苗平台的必要性。病毒样颗粒代表了这种替代方法之一,并且目前正在临床试验中进行评价[Roldao,A.等,Expert Rev Vaccines 9,1149-1176(2010);Sheridan,C.Nat Biotechnol 27,489-491(2009)]。作为含胚卵的替代,通常含有HA、NA和基质蛋白1(M1)的VLP能够在哺

乳动物或昆虫细胞表达系统中大量生产[Haynes,J.R.Expert Rev Vaccines 8,435-445(2009)]。这种方法的优点是其是颗粒状、多价性的并且是正确折叠的三聚体HA刺突的真实展示,其忠实地模拟了感染性病毒粒子。而相反的是,由于其组装的性质,包膜VLP含有小而有限的宿主细胞成分,在重复使用该平台后可能会带来潜在的安全性、免疫原性挑战[Wu,C.Y.等,PLoS One 5,e9784(2010)]。而且,VLP诱导的免疫力与现有疫苗相同,并且因此不太可能显著改善疫苗诱导的保护性免疫的效力和广度。除了VLP以外,还在人体内对重组HA蛋白进行了评价[Treanor,J.J.等,Vaccine 19,1732-1737(2001);Treanor,J.J.JAMA 297,1577-1582(2007)],但是其诱导保护性中和抗体效价的能力是有限的。在这些试验中使用的重组HA蛋白是在昆虫细胞中生产的,并且可能未优先形成天然的三聚体[Stevens,J.Science 303,1866-1870(2004)]。

[0005] 尽管有了几种常规流感疫苗的替代品,但是过去几十年中生物技术的进步使得能够对生物材料进行工程化改造以使其可用于产生新型疫苗平台。铁蛋白是一种几乎存在于所有生物体中的铁储存蛋白,铁蛋白是已被广泛研究和工程化改造以用于多种潜在生物化学/生物医学目的的实例[Iwahori,K.美国专利2009/0233377(2009);Meldrum,F.C.等,Science 257,522-523(1992);Naitou,M.等,美国专利2011/0038025(2011);Yamashita,I.Biochim Biophys Acta 1800,846-857(2010)],包括用于展示外源性表位肽的潜在疫苗平台[Carter,D.C.等,美国专利2006/0251679(2006);Li,C.Q.等,Industrial Biotechnol 2,143-147(2006)]。将其作为疫苗平台的用途是特别引人注目的,因为其自组装和多价抗原提呈诱导比单价形式更强的B细胞应答以及诱导不依赖于T细胞的抗体应答[Bachmann,M.F.等,Annu Rev Immunol 15,235-270(1997);Dintzis,H.M.等,Proc NatlAcad Sci USA 73,3671-3675(1976)]。此外,铁蛋白由24个亚基构成组装成具有432对称性八面体笼的分子结构,使得具有在其表面上展示多聚抗原的潜能。

[0006] 此前的工作表明,能够对第1组血凝素蛋白的茎区进行修饰以形成稳定化的HA茎蛋白,其构象非常类似于全长、野生型(wt)流感血凝素蛋白的融合前构象。此外,当将此类经修饰的稳定化的茎(SS)HA蛋白与单体亚基蛋白(如铁蛋白)连接在一起时,使所得到的融合蛋白形成纳米颗粒,其表面展示SS-HA蛋白的三聚体。而且,此类纳米颗粒能够激发针对第1组流感病毒的免疫应答,表明由纳米颗粒展示的SS-HA蛋白三聚体具有与wt流感HA蛋白类似的构象。在国际专利申请号PCT/US2015/032695中公开了此类构建体,其全部内容通过引用并入本申请。然而,由上述纳米颗粒激发的抗体针对第1组流感病毒比其针对第2组流感病毒具有更高的保护性。

[0007] 因而,仍需要一种有效的流感疫苗,其对第2组流感病毒提供强有力的保护作用。而且,还需要一种流感疫苗,其保护个体免受流感病毒异质性毒株的侵害,包括未来进化的季节性和大流行的流感病毒毒株。本发明通过提供一种新型的基于纳米颗粒的疫苗满足了这一需求,所述疫苗由与纳米颗粒表面融合的缺乏可变的免疫显性头部区域的新型第2组HA稳定化的茎(SS)构成,这使得所述流感疫苗易于生产、高效并且能够激发对广泛的异质亚型具有保护作用的抗体。

[0008] 发明概述

[0009] 因此,本公开内容提供了包含第2组流感血凝素(HA)蛋白的重组蛋白,其中头部区域的氨基酸序列被接头替代,所述接头含有来自流感HA蛋白头部区域的少于5个连续的氨

基酸。在向哺乳动物施用这些重组蛋白后,这些重组蛋白在哺乳动物中激发针对第2组流感HA蛋白的免疫应答。

[0010] 重组蛋白可以包含来自第2组流感病毒血凝素(HA)蛋白茎区的第一氨基酸序列和来自第2组流感病毒血凝素(HA)蛋白茎区的第二氨基酸序列,其中第一和第二氨基酸序列通过接头序列共价连接在一起,以及其中第一氨基酸序列包含来自头部区域序列氨基末端上游的氨基酸序列的至少20个连续的氨基酸残基,和其中第二氨基酸序列包含来自头部区域序列羧基末端下游的氨基酸序列的至少20个连续的氨基酸残基。在该重组蛋白构建体中,第一氨基酸序列可以包含来自与头部区域的氨基末端紧邻的上游多肽序列的至少20个连续的氨基酸。或者或另外地,第一氨基酸序列可以包含来自SEQ ID NO:27、SEQ ID NO:28或SEQ ID NO:29的至少20个连续的氨基酸。或者或另外地,第二氨基酸序列可以包含来自与头部区域的羧基末端紧邻的下游多肽序列的至少20个连续的氨基酸。或者或另外地,第一氨基酸序列可以包含来自SEQ ID NO:31、SEQ ID NO:32或SEQ ID NO:33的至少20个连续的氨基酸。

[0011] 重组多肽可以包含C螺旋的氨基末端(即,C螺旋的膜远端),其与经修饰以含有第一半胱氨酸氨基酸的头部区域序列连接,以及含有第二半胱氨酸氨基酸的接头序列,以使得第一和第二半胱氨酸形成二硫键。

[0012] 重组蛋白可以含有螺旋间区域(即,将C螺旋的N-末端与A螺旋的羧基末端(即,A螺旋的膜远端)连接在一起的氨基酸序列),对该区域进行修饰以使得重组HA茎蛋白的三维结构近似于天然第2组HA蛋白中HA茎区的三维结构。重组蛋白可以含有长度小于8个氨基酸并且替代螺旋间区域的氨基酸接头序列。

[0013] 重组蛋白可以含有通过添加氨基酸延伸的A螺旋的膜远端。

[0014] 重组蛋白可以含有第三氨基酸接头,其与形成A螺旋的氨基酸序列的羧基末端连接在一起并且形成延长A螺旋长度的螺旋。可以通过接头肽将C螺旋的远端与第三接头的羧基末端连接在一起。接头肽的长度优选小于8个氨基酸。

[0015] 这些重组蛋白可以含有增加蛋白稳定性的一个或多个突变。这些稳定突变优选位于形成A螺旋和C螺旋的至少一个的氨基酸序列中。

[0016] 这些重组蛋白可以与来自铁蛋白或二氧四氢蝶啶合酶的单体亚基连接在一起。

[0017] 本公开内容的示例性重组蛋白可以包含与选自下组的氨基酸序列具有至少80%同一性、或至少85%同一性、或至少90%同一性、或至少95%同一性、或至少97%同一性或至少99%同一性的氨基酸序列:SEQ ID NO:47-159。

[0018] 本公开内容的示例性重组蛋白可以包含选自下组的氨基酸序列:SEQ ID NO:47-159。

[0019] 本公开内容还提供了一种纳米颗粒,所述纳米颗粒包含至少一种本公开内容的重组蛋白。

[0020] 本公开内容还提供了免疫原性组合物,所述免疫原性组合物包含至少一种蛋白,所述蛋白包含与这些重组蛋白具有至少95%同一性的氨基酸序列。这些免疫原性组合物可以包含蛋白,所述蛋白含有选自下组的氨基酸序列:SEQ ID NO:47-1598。这些免疫原性组合物可以包含由选自下组的氨基酸序列组成的蛋白:SEQ ID NO:47-159。因此,本公开内容还提供了疫苗组合物,所述疫苗组合物包含这些免疫原性组合物和佐剂。

[0021] 本公开内容还提供了一种在人体内预防或减轻流感病毒感染的病理学效应的方法,所述方法包括向需要其的人体施用免疫学有效量的本公开内容的的疫苗组合物。

[0022] 还提供了编码本公开内容的重组蛋白的核酸。优选地,核酸是DNA。还提供了载体,所述载体包含这些核酸。还提供了宿主细胞,所述宿主细胞包含这些载体。这些宿主细胞可以是细菌细胞、酵母细胞或哺乳动物细胞。这些宿主细胞可以是灭活的。

[0023] 本公开内容还提供了药物组合物,所述药物组合物包含本公开内容的重组蛋白。类似地,这些组合物可以是疫苗,所述疫苗包含本公开内容的重组蛋白,以及联合生理学上可接受的运载体。

[0024] 本公开内容还提供了接种疫苗的方法,所述方法包括向对象施用预防或治疗有效量的本公开内容的重组蛋白。

[0025] 本公开内容还提供了一种治疗流感相关疾病的方法,所述方法包括向需要其的对象施用预防或治疗有效量的本公开内容的重组蛋白。优选地,对象是人。

附图说明

[0026] 图1A-1C提供了对现有技术的总结。图1A是描述全长HA--铁蛋白纳米颗粒设计的带状图。图1B是描述通过HIV gp41三聚化结构域稳定化的HA茎-铁蛋白纳米颗粒设计的带状图。在专利申请PCT/US12/56822中对这两个设计进行了描述,其通过引用并入本申请。图1C是描述在PCT专利申请号PCT/US15/32695中公开的第1组HA稳定化的茎纳米颗粒设计的带状图,其通过引用并入本申请。

[0027] 图2描述了第2组HA茎纳米颗粒的自组装形成。带状图(从左到右)描述了第2组HA稳定化的茎纳米颗粒的设计。一个HA单体的头部区域用深灰色表示。同一单体的茎区用中灰色表示。另外两个单体用浅灰色表示。

[0028] 图3A和3B显示了在H3N2设计231中的突变,其能够形成第2组HA稳定化的茎纳米颗粒。图3A是描述基于PDB ID 2YP2的第2组H3N2稳定化的HA茎三聚体模型的带状图。在螺旋中的突变区域用深灰色表示。图3B显示了H3设计#231的序列(基于A/丹麦35/2005H3N2的HA茎,GenBank ABU92694)。序列中的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0029] 图4A-4D显示了H3N2设计231在替代HA1头的环中的突变。图4A显示了描述基于PDB ID 2YP2的第2组H3N2稳定化的HA茎三聚体模型的带状图。显示了在环中替代HA1头部区域的7个突变,以及在C螺旋中加入的与上述环形成二硫键的半胱氨酸。在螺旋区域中的所有其他突变用深灰色表示。图4B描述了具有由棍模型表示的侧链的突变环(表示为替代图4A中的头部区域)。图4C显示了环序列的变体。图4D显示了H3设计#231的序列。图4A-4C中所示的头部和螺旋区域中的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0030] 图5A-5C显示了H3N2设计231中在连接HA2 A螺旋和C螺旋的环中的突变。图5A是描述基于PDB ID 2YP2的第2组H3N2稳定化的HA茎三聚体模型的带状图。显示了连接HA2 A螺旋和C螺旋的四个残基。在螺旋中的突变用深灰色表示。图5B显示了具有由棍模型表示的侧链的环的特写(图5A中所示的区域)。图5C显示了H3设计#231的序列。图5A和5B中所示的螺旋中的突变和组成短接头的氨基酸如框中所示。作为参考,C-末端SGG接头用粗体表示,C-

末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0031] 图6A-6C显示了H3N2设计231中在A螺旋C-末端延伸中的突变。图6A显示了描述基于PDB ID 2YP2的第2组H3N2稳定化的HA茎三聚体模型的带状图。显示了A螺旋的5个残基延伸。在螺旋中的突变用深灰色表示。图6B显示了具有由棍模型表示的侧链的螺旋延伸的特写(亦如图6A中所示)。图6C显示了H3设计#231的序列。在螺旋中的突变以及组成5个残基延伸的氨基酸如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0032] 图7A和7B显示了在H3N2设计231中填充孔穴(cavity)的突变。图7A显示了描述基于PDB ID 2YP2的第2组H3N2稳定化HA茎三聚体模型的条带图。具有由棍模型表示的侧链的7个填充孔穴的突变用深灰色表示。图7B显示了H3设计#231的序列。螺旋和头部区域的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0033] 图8A和8B显示了H3稳定化铁蛋白纳米颗粒231(H3-SS-np_231)的表达和表征。图8A显示了H3-SS-np_231的凝胶过滤洗脱曲线,其在预期洗脱体积具有单峰。凝胶过滤后Expi293细胞中H3-SS-np_231的表达收率为7.7mg/L。图8B显示了H3-SS-np_231的负染电子显微镜2D类平均值,其揭示了具有从中空球体中突出的HA茎可见排布的颗粒的形成。

[0034] 图9A和9B显示了H3-SS-np_231的HA茎抗体识别。图9A列出了三种HA茎抗体动力学ELISA H3-SS-np_231识别测定的EC_{50}值。将H1-SS-np识别的值也显示为对照。在这两种情况下,将纳米颗粒固定在板上。图9B和图9C显示了CT149识别H3-SS-np_231的生物层干涉测量法(BLI,来自Octet)结合曲线

[0035] (图9B)以及HA茎抗体CT149和CR9114的BL1动力学常数(图9C)。

[0036] 图10A-10E显示了H3-SS-np_231的5种变体的凝胶过滤曲线。H3-SS-np_231变体249(图1 0A)、256(图10B)、258(图1 0C)、262(图10D)和264(图10E)的凝胶过滤Superose 6 10/30曲线。在每种情况下,在约14.5ml的体积下洗脱出单峰。凝胶过滤后从Expi293细胞的最终收率为6-8mg/L培养物。

[0037] 图11A-11F显示了H3-SS-np纳米颗粒变体的电子显微镜图。H3-SS-np变体的负染电子显微镜2D类平均值揭示了具有从中空球体中突出的HA茎可见排布的颗粒的形成。将H3-SS-np 231颗粒的图像(左上图)作为阳性对照。

[0038] 图12A-12D显示了H3-SS-np_231的5种变体的动力学ELISA结果。图12A-12C显示了FI6(图12A)、CT149(图12B)和CR8020(图12C)识别H3-SS-np_231变体249、256、258、262和264的动力学ELISA曲线。图12D列出了图12A-12C中所示曲线的EC_{50}值。

[0039] 图13A和13B显示了H3-SS-np变体235-295的动力学ELISA结果。图13A列出了显示广泛中和HA茎抗体FI6、CT149和D25(阴性对照)识别设计235-265的ELISA效价。图13B列出了显示D25和CT149识别设计266-296的ELISA效价。将来自表达设计免疫原的HEK293T细胞的上清液置于板中并使用上述抗体进行检测。

[0040] 图14显示了H3-SS-np(#231)和5种变体的动态扫描量热法(DSC)曲线。热容(Cp)对温度曲线描述了每种蛋白的熔融转变。记录每种设计的最早熔点(TM)。在每个括号中显示了设计编号。在该图中,Y轴上的Cp值以任意比例显示。

[0041] 图15A&15B显示了H3-SS-np免疫小鼠对第2组HA的免疫应答。向含A/中国香港/1/

1968(H3N2)HA(图15A)和A/中国安徽/1/2013(H7N9)(图15B)的板中加入来自使用6种不同形式的SAS-佐剂化H3-SS-np免疫3x的BALB/c小鼠(n＝10)的血清的ELISA抗体终点效价。将仅使用空铁蛋白纳米颗粒免疫小鼠的血清作为阴性对照。用水平线表示几何平均效价。深灰色阴影表示阴性对照的平均效价,浅灰色阴影表示达到阴性对照平均滴度4倍的区域。使用双侧Student t-检验进行统计学分析;*P＜0.05,**P＜0.01,****P＜0.0001。

[0042] 图16A-16D显示了H3-SS-np-免疫小鼠对第1组HA的免疫应答。向含A/新喀里多尼亚/20/1999(H1N1)HA(图16A)、A/加拿大/720/2005(H2N2)(图16B)、A/中国香港/1074/1999(H9N2)(图16C)和A/越南/1203/2004(H5N1)(图16D)的板中加入来自使用6种不同形式的SAS-佐剂化H3-SS-np 3x免疫的BALB/c小鼠(n＝10)的血清的ELISA抗体终点效价。将仅使用空铁蛋白纳米颗粒免疫小鼠的血清作为阴性对照。用水平线表示几何平均效价。深灰色阴影表示阴性对照的平均效价,浅灰色阴影表示达到阴性对照平均滴度4倍的区域。

[0043] 图17显示了与超嗜热菌二氧四氢蝶啶合酶(LS)60-mer十二面体纳米颗粒的N-末端融合的H3-SS#231的序列。H3-SS-np_231的突变如框中所示。将H3-SS#231与LS连接在一起的6个残基接头和在LS中缺失N-连接聚糖的单一LS突变(N1 02D)用粗体表示。C-末端LS用下划线表示。

[0044] 图18A-18F是H3-LS-np的6种变体的凝胶过滤曲线。A-F凝胶过滤Superose 6 10/30曲线针对H3-SS-LS-np变体01(图18A)、02(图18B)、03(图18C)、04(图18D)、06(图18E)和07(图18F)。除了H3-SS-LS-04以外,在每种情况下均洗脱出了单峰。在凝胶过滤后,从Expi293细胞的最终收率为1-2mg/L培养物。

[0045] 图19A-19B显示了H3-LS-np的4种变体的ELISA结果。图19A和19B显示了HA茎抗体CT149(图19A)和CR8020(图19B)识别H3-SS-LS-np变体01、02、03和04的ELISA曲线。在每幅图的下方显示了曲线的EC_{50}值。

[0046] 图20是3种H3-SS-LS变体的动态扫描量热法(DSC)曲线。热容(Cp)对温度曲线描述了每种蛋白的熔融转变。记录每种设计的最早熔点(TM)并进行颜色编码以匹配相关曲线。在每个括号中显示了设计编号。在该图中,Y轴上的Cp值以任意比例显示。

[0047] 图21A-21D显示了H3-SS-LS-np-免疫小鼠对多种HA的免疫应答。向含A/新喀里多尼亚/20/1999(H1N1)HA(图21A)、A/越南/1203/2004(H5N1)(图21B)、A/中国香港/1/1968(H3N2)(图21C)和A/中国安徽/1/201 3(H7N9)20(图21D)的板中加入来自使用4种不同形式的SAS-佐剂化H3-SS-LS-np免疫3x的BALB/c小鼠(n＝5)的血清的ELISA抗体终点效价。将仅使用空铁蛋白纳米颗粒和H3-SS-np(#231)免疫小鼠的血清作为对照。用水平线表示几何平均效价。

[0048] 图22A和22B显示了H3-SS-LS-np-免疫小鼠对H3N2和H7N9的中和血清应答。来自使用4种不同形式的SAS-佐剂化H3-SS-LS-np免疫3x的BALB/c小鼠(n＝5)的血清的假病毒中和效价。图22A显示了A/中国安徽/1/2013(H7N9)的中和。图21B显示了A/威斯康星/67/2005(H3N2)的中和。将使用空铁蛋白纳米颗粒、H1-SS-np和H3-SS-np(#231)免疫小鼠的血清作为对照。用水平线表示几何平均效价。水平虚线表示基线滴度为50。

[0049] 图23显示了能够形成第2组H7 HA稳定化的茎纳米颗粒的25个突变的序列位置。具有H3#231突变的H7-SS-np_16序列(基于A/中国安徽/1/2013(H7N9)HA,GenBank登录号YP_009118475.1)入框中所示。新的H7突变用星号表示(两个残基突变以匹配H3N2 HA)。作为参

考,C-末端SGG接头用粗体表示,C-末端铁蛋白用下划线表示,以及Asn至Gln的铁蛋白突变以除去N-连接聚糖用粗体表示。

[0050] 图24A-24F显示了H7-SS-np变体的纯化。经GNA凝集素亲和层析后针对H7-SS-np变体16(图24A)、1 8(图24B)、20(图24C)、21(图24D)、23(图24E)和26(图24F)的凝胶过滤Superose 6 10/30曲线。在凝胶过滤后,从Expi293细胞的最终收率为5-10 mg/L培养物。

[0051] 图25显示了H7-SS-np的电子显微镜图。H7-SS-np变体的负染电子显微镜2D类平均值揭示了具有从中空球体中突出的HA茎可见排布的颗粒的形成。将H1-SS-np颗粒的图像(左上图)作为阳性对照。

[0052] 图26A-26D显示了H7-SS-np变体的动力学ELISA结果。图26A-26C显示了FI6(图26A)、CT149(图26B)和CR8020(图26C)识别H7-SS-np变体16、18、20、21、23、25、26和H1-SS-np阳性对照的动力学ELISA曲线。图26D列出了在图26A-26C中所示曲线的EC_{50}值。ND,未确定。

[0053] 图27显示了H7-SS-np的HA茎抗体识别。显示了CT149识别6种H7-SS-np变体的生物层干涉测量法结合曲线(图27A:H7-SS-16;图27B:H7-SS-18;图27C:H7-SS-21;图27D:H7-SS-23;图27E:H7-SS-25;图27F:H7-SS-26),每组曲线的右侧列出了结合常数。通过胺偶联将纳米颗粒固化在传感器尖端并且在各种浓度的抗体Fab中孵育。

[0054] 图28显示了7种H7-SS-np变体的动态扫描量热法(DSC)曲线。热容(Cp)对温度曲线描述了每种蛋白的熔融转变。记录每种蛋白的最早熔点(TM)并进行颜色编码以匹配相关曲线。在每个括号中显示了H7-SS-np设计编号。在该图中,Y轴上的Cp值以任意比例显示。

[0055] 图29A-29D显示了H7-SS-np-免疫小鼠对多种HA的免疫应答。向含A/新喀里多尼亚/20/1999(H1N1)HA(图29A)、A/越南/1203/2004(H5N1)(图29B)、A/中国香港/1/1968(H3N2)(图29C)和A/中国安徽/1/2013(H7N9)(图29D)的板中加入来自使用6种不同形式的SAS-佐剂化H7-SS-np免疫3x的BALB/c小鼠(n=5)的血清的ELISA抗体终点效价。将仅使用空铁蛋白纳米颗粒H1-SS-np和H3-SS-np(#231)免疫小鼠的血清作为对照。用水平线表示几何平均效价。水平虚线表示基线滴度为50。

[0056] 图30A和30B显示了H7-SS-np-免疫小鼠对H3N2和H7N9的中和血清应答。来自使用6种不同形式的SAS-佐剂化H7-SS-np免疫3x的BALB/c小鼠(n=5)的血清的假病毒中和效价。图30A显示了A/中国安徽/1/2013(H7N9)的中和。图30B显示了A/威斯康星/67/2005(H3N2)的中和。将使用空铁蛋白纳米颗粒、H1-SS-np和H3-SS-np(#231)免疫小鼠的血清作为对照。用水平线表示几何平均效价。水平虚线表示基线滴度为50。

[0057] 图31显示了基于流感亚型10 HA(H10)蛋白序列的本发明蛋白构建体的4个不同实例的序列。流感HA序列的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白序列用下划线表示。

[0058] 图32A-32E显示了H10ssF变体1(图32A)、2(图32B)、3(图32C)、4(图32D)和5(图32E)的凝胶过滤Superdex 20010/30曲线。在每种情况下,在约12.5ml的体积下洗脱出单峰。凝胶过滤后从Expi293细胞的最终收率为6-8mg/L培养物。

[0059] 图33显示了H10ssF纳米颗粒变体的电子显微镜图。H10ssF变体的负染电子显微镜2D类平均值揭示了具有从中空球体中突出的HA茎可见排布的颗粒的形成。

[0060] 图34A-34D显示了H10ssF变体2-5的动力学ELISA结果。图A-C显示了ELISA曲线。图

D显示了从曲线计算得到的IC50值。将来自表达设计免疫原的HEK293T细胞的上清液加入板中并用上述抗体进行检测。

[0061] 图35A&35B显示了H10ssF免疫小鼠对第2组HA的免疫应答。来自使用5种不同形式的S5AS-佐剂化H10ssF(2μg/小鼠)免疫3x的BALB/c小鼠(n＝10)的血清对固化的A/中国香港/1/1968(H3N2)HA(图35A)和A/中国安徽/1/2013(H7N9)(图35B)的ELISA抗体终点效价。将仅使用空铁蛋白纳米颗粒、H7N9 AH13单价灭活疫苗(MIV)或H7ssF26免疫小鼠血清的应答作为对照。

[0062] 用水平线表示几何平均效价。下面的虚线表示基线滴度为50,上面的虚线表示记录到的最高值。

[0063] 图36A-36D显示了H10ssF免疫小鼠对致死性H3H2攻击的应答。图36A-C显示了使用空纳米颗粒(图36A)、H10ssF_4(图36B)或H10ssF_5(图36C)免疫,然后使用致死剂量A/菲律宾/1982(H3N2)流感攻击的BALB/c小鼠(n＝10)的体重减轻曲线。图36D显示了与A中相同的小鼠的生存曲线。将仅使用铁蛋白纳米颗粒(空np)免疫的小鼠作为阴性对照。

[0064] 图37A-37G显示了H10ssF免疫小鼠对致死性H7N9攻击的应答。图37A显示了使用致死剂量的A/中国上海/2/2013-样(H7N9)流感对H10ssF免疫BALB/c小鼠(n＝10)攻击的生存曲线。将仅使用铁蛋白纳米颗粒(空np)免疫的小鼠作为阴性对照。图37B显示了与图37A中相同的小鼠在攻击后6天的体重减轻情况。图37C-G显示了与图37A&37B中相同的小鼠在攻击后12天内的体重减轻情况。

[0065] 图38显示了基于流感亚型3HA(H3)蛋白序列的本发明蛋白构建体4个不同实例的序列。流感HA序列的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白序列用下划线表示。而且,Asn至Gln的铁蛋白突变以除去N-连接聚糖用加粗的框表示。

[0066] 图39显示了基于流感亚型7HA(H7)蛋白序列的本发明蛋白构建体4个不同实例的序列。流感HA序列的突变如框中所示。作为参考,C-末端SGG接头用粗体表示,C-末端铁蛋白序列用下划线表示。而且,Asn至Gln的铁蛋白突变以除去N-连接聚糖用加粗的框表示。

[0067] 图40A-40C显示了本发明的多种蛋白构建体活化表达种系回复16.a.26B细胞受体(BCR)的B细胞的能力。图中显示了B细胞与抗-IgM阳性对照(以及使用H1阴性对照无激活)(图40A)、H3-ss-np蛋白构建体(图40B)、H7-ss-np蛋白构建体(图40C)和H10ssF蛋白构建体(图40D)接触导致的钙通量(提示B细胞激活)。

[0068] 图41显示了在图40A-C中所示的B细胞激活测定中显示出活性的蛋白构建体HA部分的序列。流感HA序列的突变如框中所示。

具体实施方式

[0069] 本发明涉及一种针对流感病毒的新型疫苗。更具体地,本发明涉及新型的、基于第2组流感HA蛋白的疫苗,其激发针对广泛流感病毒HA蛋白茎区的免疫应答。还涉及自组装纳米颗粒,所述纳米颗粒在其表面上展示出第2组流感HA蛋白茎区融合前构象的免疫原性部分。可以将此类纳米颗粒用于针对流感病毒的个体疫苗接种。因此,本发明还涉及用于生产此类纳米颗粒和编码此类蛋白的核酸分子的蛋白构建体。另外,本发明涉及生产本发明的纳米颗粒的方法,以及使用此类纳米颗粒对个体接种疫苗的方法。

[0070] 在进一步描述本发明前,应当理解本发明不限于描述的具体实施方式,因此当然

可以有所变化。还应当理解,本申请中使用的术语仅为了描述具体的实施方式,而并不意图为限制性的,因为本发明的范围仅会以权利要求书为限。

[0071] 应当注意到,如本申请中及所附权利要求书中使用的,单数形式“一个”、“一种”和“该/所述”包括复数提及物,除非上下文另有明确规定。例如,核酸分子指一种或多种核酸分子。因此,术语“一个”、“一种”、“一个/种或多个/种”和“至少一个/种”可以互换使用。类似地,术语“包含”、“包括”和“具有”可以互换使用。进一步注意到,权利要求书可以撰写为排除任何任选要素。因此,此陈述意图充当与权利要求要素的叙述结合使用排除术语,如“单独”、“仅”等,或者使用“负”限定的前置基础。

[0072] 为方便起见,可以将某些缩写用于指本发明的蛋白构建体及其部分。例如,HA可以指流感血凝素蛋白或其部分。HA-SS指来自流感HA蛋白的稳定化的茎区或茎区的一部分。通常,这种名称的HA部分将指血凝素蛋白的亚型。例如,可以将来自亚型3血凝素的稳定化茎区称为H3-SS。可以将包含与流感HA蛋白跨膜结构域结合的HA-SS(例如,H3-SS)的蛋白构建体称为HA-SS-TM(例如,H3-SS-TM)。可以将包含与铁蛋白单体亚基结合的HA-SS的蛋白构建体称为HA-SS-np。还可以在这种名称后面加上表示含有特定改变的特定构建体的数字(例如,H3-SS-np_231(SEQ ID NO:47))。应当指出的是,还可以将这种构建体称为HAssF(例如,H3ssF_231)。在本发明的某些方面中,HA-SS与其他单体亚基(如二氧四氢蝶啶合酶)连接在一起。可以将这种构建体用名称HA-SS-LS(例如,H3-SS_LS-01(SEQ ID NO:83))或HAssL(例如,H3ssLS-01(SEQ ID NO:83))表示。

[0073] 除了上述以外,除非另有明确定义,否则本申请所公开的各种实施方式共有的下述术语和短语的定义如下文所述。

[0074] 如本申请中所使用的,蛋白构建体是由人工制备的蛋白,其中对蛋白的氨基酸序列进行修饰以使得所得到的经修饰的蛋白含有自然界中不存在的序列。蛋白构建体包含其中两条或多条氨基酸序列以自然界中不存在的方式共价连接的蛋白。连接在一起的氨基酸序列可以是相关的或不相关的。如本申请中所使用的,如果通常发现其氨基酸序列在其天然环境中(例如,细胞内)不是通过共价键连接在一起的,则多肽序列是不相关的。例如,通常发现铁蛋白单体亚基的氨基酸序列和第2组流感HA蛋白的氨基酸序列不是通过共价键连接在一起的。因此,认为此类序列是不相关的。

[0075] 蛋白构建体还可以包含相关的氨基酸序列。例如,流感HA蛋白的结构使得头部区域氨基酸序列的翼侧两端为茎区氨基酸序列。通过遗传手段,可以从头部区域中间除去氨基酸残基,同时保持头部区域的一部分翼侧的茎区序列,以形成HA蛋白经修饰的形式。尽管在最终分子中序列的顺序是相同的,但是氨基酸之间的空间关系与天然蛋白是不同的。因此,将此类分子认为是蛋白构建体。根据本发明,还可以将蛋白构建体称为融合蛋白。

[0076] 在蛋白构建体中的氨基酸序列可以彼此之间直接连接在一起或者可以使用接头将其连接在一起。接头、接头序列、接头肽等是用于将具有所需特征(例如,结构、表位、免疫原性、活性等)的两个蛋白连接在一起的短(例如,2-20个)氨基酸序列。接头序列其自身通常不具有活性并且通常用于将蛋白构建体的其他部分连接在一起,从而使其具有所需的构象。接头序列通常由小氨基酸残基和/或其批量(run)组成,如丝氨酸、丙氨酸和甘氨酸,但不排除使用其他氨基酸残基。例如,在接头序列中包含能够形成共价键的氨基酸(如半胱氨酸残基)可能是所需要的。

[0077] 如本申请中所使用的,术语免疫原性指特定蛋白或其特定区域激发对特定蛋白质,或包含与特定蛋白质具有高度同一性的氨基酸序列的蛋白的免疫应答的能力。根据本发明,两种具有高度同一性的蛋白具有至少80%相同、至少85%相同、至少87%相同、至少90%相同、至少92%相同、至少93%相同、至少94%相同、至少95%相同、至少96%相同、至少97%相同、至少98%相同或至少99%相同的氨基酸序列。确定两条氨基酸或核酸序列之间同一性百分率的方法是本领域公知道的。

[0078] 如本申请中所使用的,对本发明的疫苗或纳米颗粒的免疫应答是在对象中形成的对疫苗中存在的第2组HA蛋白的体液和/或细胞免疫应答。出于本发明的目的,“体液免疫应答”指由抗体分子(包括分泌性(IgA)或IgG分子)介导的免疫应答,而“细胞免疫应答”是由T淋巴细胞和/或其他白细胞介导的免疫应答。细胞免疫的一个重要方面牵涉细胞裂解T细胞(“CTL”)的抗原特异性应答。CTL对与由主要组织相容性复合物(MHC)编码的蛋白结合呈递,并且在细胞表面上表达的肽抗原具有特异性。CTL帮助诱导并促进对胞内微生物的破坏,或者此类微生物感染的细胞的裂解。细胞免疫的另一个方面牵涉辅助T细胞的抗原特异性应答。辅助T细胞作用为帮助刺激功能,并且聚焦非特异性效应细胞针对在其表面上展示与MHC分子结合的肽抗原的细胞的活性。细胞免疫应答还涉及生成由活化的T细胞和/或其他白细胞,包括那些自CD4+和CD8+T细胞衍生的细胞生成的细胞因子、趋化因子和其他此类分子。

[0079] 因此,免疫学应答可以是刺激CTL,和/或辅助T细胞生成或活化的应答。也可以刺激趋化因子和/或细胞因子的生成。疫苗也可以引发抗体介导的免疫应答。因此,免疫学应答可以包括下列一种或多种效应:B细胞的抗体(例如IgA或IgG)生成;和/或特异性针对疫苗中存在的第2组HA蛋白的抑制、细胞毒性、或辅助T细胞和/或T细胞的活化。这些应答可以用来中和感染性(例如,抗体依赖性保护),和/或介导抗体-补体,或抗体依赖性细胞细胞毒性(ADCC)以对经免疫个体提供保护。可以使用本领域中熟知的标准免疫测定法和中和测定法测定此类应答。

[0080] 如本申请中所使用的,术语抗原的、抗原性等指被抗体或一组抗体结合的蛋白。类似地,蛋白的抗原部分是被抗体或一组抗体识别的任何部分。根据本发明,由抗体识别蛋白指抗体选择性地与蛋白结合。如本申请中所使用的,短语选择性结合(selectively bind)、选择性结合(selective binding)等指相对于结合与HA无关的蛋白或者样品或测定中的非蛋白组分而言抗体优选地结合HA蛋白的能力。优选地结合HA的抗体是结合HA但是不与可能存在于样品或测定中的其他分子或组分显著结合的抗体。将例如抗-HA抗体与非-HA分子以足够大以干扰测定检测和/或确定样品中的抗流感抗体或HA蛋白水平的亲和性或亲合力结合认为是显著结合。可以存在于样品或测定中的其他分子和化合物的实例包括但不限于非-HA蛋白,如白蛋白、脂质和碳水化合物。根据本发明,非-HA蛋白是具有与本申请公开的流感HA蛋白的序列具有少于60%同一性的氨基酸序列的蛋白。在一些实施方式中,一种或多种抗体提供了广泛的异源亚基保护。在一些实施方式中,一种或多种抗体是中和性的。

[0081] 如本申请中所使用的,中和抗体是阻止流感病毒完成一轮复制的抗体。如本申请所定义的,一轮复制指病毒的生命周期,其以病毒附着宿主细胞开始并且以新形成的病毒从宿主细胞中出芽结束。此生命周期包括但不限于附着细胞,进入细胞,HA蛋白的切割和重排,病毒膜与内体膜的融合,病毒核糖核蛋白释放入胞质中,新病毒颗粒的形成和病毒颗粒

从宿主细胞膜中出芽的步骤。根据本发明,中和抗体是抑制一个或多个此类步骤的抗体。

[0082] 如本申请中所使用的,广泛中和抗体指中和超过一种流感病毒类型、亚型和/或毒株的抗体。例如,针对来自甲型流感病毒的HA蛋白引发的广泛中和抗体可以中和乙型或丙型病毒。作为进一步的实例,针对第2组流感病毒HA蛋白激发的广泛中和抗体可以中和第1组病毒。作为一个附加的实例,针对来自一种病毒亚型或毒株的HA蛋白激发的广泛中和抗体可以中和另一种病毒亚型或毒株。例如,针对来自H3流感病毒的HA蛋白激发的广泛中和抗体可以中和来自一种或多种选自下组的亚型的病毒:H1、H2、H4、H5、H6、H7、H8、H8、H10、H11、H12、H13、H14、H15、H16、H17或H18。

[0083] 根据本发明,用于分类流感病毒的所有命名是本领域技术人员通常使用的。因此,流感病毒的类型或组指甲型流感、乙型流感或丙型流感。本领域技术人员应当理解,病毒称为特定类型指相应M1(基质)蛋白或NP(核蛋白)的序列差异。甲型流感病毒进一步分成第1组和第2组。这些组进一步分成亚型,其涉及基于其HA蛋白序列的病毒分类。目前公认的亚型的实例是H1、H2、H3、H4、H5、H6、H7、H8、H8、H10、H11、H12、H13、H14、H15、H16、H17和H18。第1组流感亚型是H1、H2、H5、H6、H8、H9、H11、H12、H13、H16、H17和H18。第2组流感亚型是H3、H4、H7、H10、H14和H15。最后,术语毒株指亚型内彼此的差异在于在其基因组中具有小的遗传变异的病毒。

[0084] 如本申请中所使用的,流感血凝素蛋白或HA蛋白指全长流感血凝素蛋白或其任何部分,其能够用于生产本发明的蛋白构建体和纳米颗粒或能够激发免疫应答。优选的HA蛋白是那些能够形成三聚体的。全长流感HA蛋白的表位指此类蛋白中能引发针对同源流感毒株,即衍生HA的毒株的抗体应答的部分。在一些实施方式中,此类表位也能激发针对异源流感毒株,即与免疫原的HA的毒株具有不同HA的毒株的抗体应答。在一些实施方式中,表位激发广泛的异源亚基保护性应答。在一些实施方式中,表位激发中和抗体。

[0085] 如本申请中所使用的,变体指在序列上与参照序列相似但不相同的蛋白或核酸分子,其中变体蛋白(或由变体核酸分子编码的蛋白)的活性没有显著改变。这些序列变异可以是天然存在的变异或者其可以经由使用本领域技术人员已知的遗传工程化技术来工程化改造。此类技术的实例参见Sambr$_{oo}$kJ,Fritsch E F,Maniatis T等的Molecular Cloning--A Laboratory Manual,2nd Edition,Cold Spring Harbor Laboratory Press,1989,pp.9.31-9.57中,或在Current Protocols in Molecular Biology,John Wiley& Sons,N.Y.(1989),6.3.1-6.3.6中,这两篇的全部内容均通过引用并入本申请。

[0086] 就变体而言,氨基酸或核酸序列的任何类型变化是可允许的,只要所得的变体蛋白保留激发针对流感病毒的中和或非中和抗体的能力。此类变异的实例包括但不限于缺失、插入、取代及其组合。例如,就蛋白而言,本领域技术人员公知的是,一个或多个(例如,2、3、4、5、6、7、8、9或10)氨基酸经常可以从蛋白的氨基和/或羧基端末端除去,而不显著影响所述蛋白的活性。类似地,一个或多个(例如,2、3、4、5、6、7、8、9或10)氨基酸经常可以插入蛋白中,而不显著影响蛋白的活性。在已经进行插入的变体中,插入的氨基酸可以通过参考在其后插入的氨基酸残基来指代。例如,可以将在氨基酸残基402之后插入4个氨基酸残基称为402a-402d。而且,如果这些插入的氨基酸之一随后被另一氨基酸取代,可以通过参考字母位置指代此类变化。例如,可以将所插入的甘氨酸(在插入物中进一步的位置)被苏氨酸的取代称为S402dT。

[0087] 如记录的,相对于本申请公开的流感HA蛋白,本发明的变体蛋白可以含有氨基酸取代。任何氨基酸取代是可允许的,只要蛋白的活性不受显著影响即可。在这点上,本领域中应当理解,氨基酸可以基于其物理特性而分成组。此类组的实例包括但不限于带电荷的氨基酸、不带电荷的氨基酸、极性不带电荷的氨基酸和疏水性氨基酸。含有取代的优选变体是那些其中的氨基酸用来自相同组的氨基酸取代的变体。此类取代称为保守取代。

[0088] 天然存在的残基可以基于共同的侧链性质而分成下述类别:

[0089] 1)疏水性:Met、Ala、Val、Leu、Ile;

[0090] 2)中性亲水性:Cys、Ser、Thr;

[0091] 3)酸性:Asp、Glu;

[0092] 4)碱性:Asn、Gln、His、Lys、Arg;

[0093] 5)影响链取向的残基:Gly、Pro;和

[0094] 6)芳香性:Trp、Tyr、Phe。

[0095] 例如,非保守取代可以牵涉用这些类别之一的成员替换来自另一类别的成员。

[0096] 在进行氨基酸变化中,可以考虑氨基酸的亲水指数。基于每种氨基酸的疏水性和电荷性质,已给每种氨基酸的亲水指数赋值。亲水指数是:异亮氨酸(+4.5);缬氨酸(+4.2);亮氨酸(+3.8);苯丙氨酸(+2.8);半胱氨酸/胱氨酸(+2.5);甲硫氨酸(+1.9);丙氨酸(+1.8);甘氨酸(-0.4);苏氨酸(-0.7);丝氨酸(-0.8);色氨酸(-0.9);酪氨酸(-1.3);脯氨酸(-1.6);组氨酸(-3.2);谷氨酸(-3.5);谷氨酰胺(-3.5);天冬氨酸(-3.5);天冬酰胺(-3.5);赖氨酸(-3.9);和精氨酸(-4.5)。本领域一般了解亲水氨基酸指数在赋予蛋白相互作用性生物学功能中的重要性(Kyte等,1982,J.Mol.Biol.157:105-31)。已知可以用某些氨基酸替代其他具有相似亲水指数或分值的氨基酸,而仍然保留相似的生物学活性。在进行基于亲水指数的变化中,亲水指数在±2之内的氨基酸取代是优选的,在±1之内的那些氨基酸取代是特别优选的,且在±10.5之内的那些氨基酸取代是甚至更特别优选的。

[0097] 本领域还了解可以基于疏水性有效地进行类似氨基酸的取代,特别是在意图将由此产生的生物功能等同性蛋白或肽用于结合免疫学发明(本案就是如此)的情况中。蛋白的最大局部平均亲水性(如由其相邻氨基酸的亲水性所决定的)与其免疫原性和抗原性,即与蛋白质的生物学特性相关联。已将下列亲水性数值赋予这些氨基酸残基:精氨酸(+3.0);赖氨酸(+3.0);天冬氨酸(+3.0±1);谷氨酸(+3.0±1);丝氨酸(+0.3);天冬酰胺(+0.2);谷氨酰胺(+0.2);甘氨酸(0);苏氨酸(-0.4);脯氨酸(-0.5±1);丙氨酸(-0.5);组氨酸(-0.5);半胱氨酸(-1.0);甲硫氨酸(-1.3);缬氨酸(-1.5);亮氨酸(-1.8);异亮氨酸(-1.8);酪氨酸(-2.3);苯丙氨酸(-2.5);和色氨酸(-3.4)。在进行基于相似亲水性数值的变化时,亲水性数值在±2之内的氨基酸取代是优选的,在±1之内的那些氨基酸取代是特别优选的,且在±0.5之内的那些氨基酸取代是甚至更特别优选的。还可以基于亲水性鉴定来自一级氨基酸序列的表位。

[0098] 在期望此类取代时,本领域技术人员可以确定期望的氨基酸取代(无论是保守的还是非保守的)。例如,可以使用氨基酸取代来鉴定HA蛋白的重要残基,或者提高或降低本申请中描述的HA蛋白的免疫原性、溶解度或稳定性。下文在表1中显示了例示性的氨基酸取代。

[0099] 表1

[0100]

氨基酸取代	
初始氨基酸	示例性取代
Ala	Val, Leu, Ile
Arg	Lys, Gln, Asn
Asn	Gln
Asp	Glu
Cys	Ser, Ala
Gln	Asn
Glu	Asp
Gly	Pro, Ala
His	Asn, Gln, Lys, Arg
Ile	Leu, Val, Met, Ala
Leu	Ile, Val, Met, Ala
Lys	Arg, Gln, Asn
Met	Leu, Phe, Ile
Phe	Leu, Val, Ile, Ala, Tyr
Pro	Ala
Ser	Thr, Ala, Cys
Thr	Ser
Trp	Tyr, Phe
Tyr	Trp, Phe, Thr, Ser
Val	Ile, Met, Leu, Phe, Ala

[0101]

[0102] 如本申请中所使用的,短语“显著影响蛋白活性”指将蛋白活性降低至少10%、至少20%、至少30%、至少40%或至少50%。就本发明而言,此类活性可以例如以蛋白激发针对流感病毒的保护性抗体的能力测量。此类活性可以通过测量针对流感病毒的此类抗体的效价或者通过测量由激发的抗体中和的类型、亚型或毒株的数目测量。测定抗体效价的方法和实施病毒中和测定法的方法是本领域技术人员公知的。除了上文描述的活性外,可以测量的其他活性包括凝集红细胞的能力和蛋白对细胞的结合亲和性。测量此类活性的方法是本领域技术人员公知的。

[0103] 术语个体、对象和患者是本领域中公知的,并且在本申请中可互换使用,指对流感感染易感的任何人或其他动物。实例包括但不限于人和其他灵长类,包括非人灵长类,诸如

黑猩猩及其他猿和猴物种;家畜,诸如牛、绵羊、猪、海豹、山羊和马;驯养哺乳动物,诸如犬和猫;实验室动物,包括啮齿类,诸如小鼠、大鼠和豚鼠;禽类,包括驯养禽类、野生禽类和猎禽,诸如鸡、火鸡和其他鸡形目(gallinaceous)禽类、鸭、鹅等等。术语个体、对象和患者单独不表示特定年龄、性别、人种等等。因此,任何年龄的个体(无论雄性或雌性)意图为本公开内容覆盖,并且包括但不限于老年人、成人、儿童、婴孩(baby)、婴儿(infant)和幼童(toddler)。同样地,本发明的方法可以适用于任何人种,包括例如高加索人、非洲裔美国人、西班牙裔、拉美裔、亚裔和欧洲裔。感染的对象是已知在其体内具有流感病毒的对象。

[0104] 如本申请中所使用的,接种疫苗的对象是已经施用意图提供针对流感病毒的保护性效果的疫苗的对象。

[0105] 如本申请中所使用的,术语暴露的(exposed)、暴露(exposure)等指对象已经与已知感染流感病毒的动物个体接触。

[0106] 本申请中讨论的出版物仅提供其在本申请的提交日前的公开内容。本申请中的任何内容不应解释为承认凭借在先发明,本发明没有资格早于此类出版物。此外,提供的出版日期可以与实际出版日期不同,这可能需要独立确认。

[0107] 除非另有定义,本申请中使用的所有技术和科学术语与本发明所属领域的普通技术人员的通常理解具有相同的意义。虽然与本申请中描述的方法和材料类似或等同的任何方法和材料也可以用于实施或测试本发明,现在描述优选的方法和材料。本申请中提及的所有出版物通过提及收入本申请以公开并描述与结合出版物引用的方法和/或材料。

[0108] 应当领会,本发明的某些特征(为了清楚,其在不同实施方式的背景中描述)也可以在单一实施方式中组合提供。相反,本发明的各个特征(为了简洁,其在单一实施方式的背景中描述)也可以分开或在任何合适的亚组合中提供。实施方式的所有组合是本发明明确涵盖的,并且在本申请中公开,就像每种组合单独且明确公开一样。另外,所有亚组合也是本发明明确涵盖的,并且在本申请中公开,就像每种此类亚组合在本申请中单独且明确公开一样。

[0109] 本发明的一个实施方式是一种包含第2组流感HA蛋白的蛋白构建体,其中第2组流感HA蛋白的头部区域已被包含来自流感HA蛋白头部区域的少于5个连续的氨基酸残基的氨基酸序列替代。如本申请中所使用的,第2组HA蛋白指来自第2组流感病毒的全长流感HA蛋白或者其任何部分和/或变体,其可用于生产本发明的蛋白构建体和纳米颗粒。因此,本发明涉及能够激发对第2组流感HA蛋白茎区的免疫应答的分子。在一些实施方式中,已进一步改变(即,突变)HA蛋白构建体的序列,以便在能够向免疫系统提呈的形式中稳定蛋白的茎区。可用于实施本发明的第2组流感HA蛋白,以及由其制备的蛋白构建体的实例如下表2中所示。

[0110] 表2:

[0111]

PCT SEQ ID NO	注释
	单体亚基蛋白
1	来自幽门螺杆菌（*H. pylori*）的铁蛋白单体亚基蛋白的氨基酸序列， MLSDIIKLLNEQVNKEMQSSNLYMSMSSWCYTHSLDGAGLFLFDHAA EEYEHAKKLIIFLNENNVPVQLTSISAPEHKFEGLTQIFQKAYEHEQHIS ESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFKDILDKIELIGNE NHGLYLADQYVKGIAKSRKSGS
2	SEQ ID NO:2 的氨基酸 4-168；Asn19 被 Gln 替代， DIIKLLNEQVNKEMQSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEY EHAKKLIIFLNENNVPVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESIN NIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFKDILDKIELIGNENHG LYLADQYVKGIAKSRKSGS
3	来自超嗜热菌（*aquifex aeolicus*）的二氧四氢蝶啶合酶的氨基酸序列， MQIYEGKLTAEGLRFGIVASRFNHALVDRLVEGAIDCIVRHGGREEDIT LVRVPGSWEIPVAAGELARKEDIDAVIAIGVLIRGATPHFDYIASEVSK GLADLSLELRKPITFGVITADTLEQAIERAGTKHGNKGWEAALSAIEM ANLFKSLR
	全长 HA
4	来自甲型流感病毒（A/丹麦/35/2005（H3N2））的血凝素蛋白的氨基酸序列；GenBank：ABU92694.1
5	来自甲型流感病毒（A/孟加拉/558/2012（H3N2））的血凝素蛋白的氨基酸序列；登录号：AJB43527.1
6	来自甲型流感病毒（A/圣保罗/89403/2010（H3N2））的血凝素蛋白的氨基酸序列；登录号：AET10116.1
7	来自甲型流感病毒（A/孟加拉/541/2012（H3N2））的血凝素蛋白的氨基酸序列；登录号：AJB43525.1
8	来自甲型流感病毒（A/孟加拉/542/2012（H3N2））的血凝素蛋白的氨基酸序列；登录号：AJB43524.1
9	来自甲型流感病毒（A/托坎廷斯/979/2010（H3N2））的血凝素蛋白的氨基酸序列；登录号：AET10115.1
10	来自甲型流感病毒（A/突尼斯/17332/2011（H3N2））的血凝素蛋白的氨基酸序列；登录号：AFV68725.1

[0112]

PCT SEQ ID NO	注释
11	来自甲型流感病毒（A/挪威/88/2003（H3N2））的血凝素蛋白的氨基酸序列；登录号：ABR14669.1
12	来自甲型流感病毒（A/日本/AF2844/2012（H3N2））的血凝素蛋白的氨基酸序列；登录号：AFH57071.1
13	来自甲型流感病毒（A/德克萨斯/2977/2012（H3N2））的血凝素蛋白的氨基酸序列；登录号：AFM45466.1
14	来自甲型流感病毒（A/北卡来罗那/AF2716/2011（H3N2））的血凝素蛋白的氨基酸序列；登录号：ADY05375.1
15	来自甲型流感病毒（A/挪威/70/2005（H3N2））的血凝素蛋白的氨基酸序列；登录号：ABI22080.1
16	来自甲型流感病毒（A/鸭/千叶/24-203-44/2012（H7N1））的血凝素蛋白的氨基酸序列；登录号：BAN16716.1
17	来自甲型流感病毒（A/鸡/德国/2003（H7N7））的血凝素蛋白的氨基酸序列；登录号：CAG28959.1
18	来自甲型流感病毒（A/鸡/意大利/444/1999（H7N1））的血凝素蛋白的氨基酸序列；登录号：CAG28956.1
19	来自甲型流感病毒（A/野鸭/意大利/4810-7/2004（H7N7））的血凝素蛋白的氨基酸序列；登录号：ABG57092.1
20	来自甲型流感病毒（A/中国安徽/DEWH72-03/2013（H7N9））的血凝素蛋白的氨基酸序列；登录号：AHZ39710.1
21	来自甲型流感病毒（A/中国上海/JS01/2013（H7N9））的血凝素蛋白的氨基酸序列；登录号：AGW82612.1
22	来自甲型流感病毒（A/中国广东/02/2013（H791））的血凝素蛋白的氨基酸序列；登录号：AHD25003.1
23	来自甲型流感病毒（A/中国深圳/SP44/2014（H7N9））的血凝素蛋白的氨基酸序列；登录号：AJJ1957.1 AJJ91957.1
24	来自甲型流感病毒（A/中国北京/3/2013（H7N9））的血凝素蛋白的氨基酸序列；登录号：AHM24224.1
25	来自甲型流感病毒（A/中国香港/470129/2013（H7N9））的血凝素蛋白的氨基酸序列；登录号：AHF20528.1
26	来自甲型流感病毒（A/中国江西/IPB13/2013）的血凝素蛋白的氨基酸序列（H10N8；登录号：AHK10761.1）
	翼侧序列
27	甲型流感病毒（丹麦/35/2005（H3N2））头部区域氨基末端翼侧的氨基酸序列-全长（aa1-59） MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELV
28	甲型流感病毒（丹麦/35/2005（H3N2））头部区域氨基末端翼侧的氨基酸序列-部分（40个aa） PGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATELV
29	甲型流感病毒（丹麦/35/2005（H3N2））头部区域氨基末端翼侧的氨基酸序列-部分（25个aa） AVPNGTIVKTITNDQIEVTNATELV

[0113]

PCT SEQ ID NO	注释
30	甲型流感病毒（丹麦/35/2005（H3N2））头部区域羧基末端翼侧茎区的氨基酸序列 LKLATGMRNVPEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRLIGKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKVDLWSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIK
31	甲型流感病毒（丹麦/35/2005（H3N2））头部区域羧基末端翼侧茎区的氨基酸序列-部分-66 个 aa LKLATGMRNVPEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQING
32	甲型流感病毒（丹麦/35/2005（H3N2））头部区域羧基末端翼侧茎区的氨基酸序列-部分-50 个 aa LKLATGMRNVPEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGIGQ
33	甲型流感病毒（丹麦/35/2005（H3N2））头部区域羧基末端翼侧茎区的氨基酸序列-部分-25 个 aa LKLATGMRNVPEKQTRGIFGAIAGF
	接头序列
34	VFPGCGV –头部接头
35	CFNGIC -头部接头
36	A 螺旋延伸序列- ALMAQ
37	A 螺旋延伸序列- ELMEQ
38	螺旋间区域- GKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKVDLW
39	螺旋间接头- GGPD
	头部区域羧基翼侧（使用接头替代螺旋间区域）
40	DLKSTQAAINQINGKLNRLIALMAQGGPDSYNAELLVALENQHTIDLTD
41	NSEGIGQAADLKSTQAAINQINGKLNRLIALMAQGGPDSYNAELLVALENQHTIDLTDSEMNKLFERT
42	NSEGIGQAADLKSTQAAINQINGKLNRLIALMAQGGPDSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYH
43	LKLATGMRNVPEKQTRGIFGAIAGFIENGWEGMVDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRLIALMAQGGPDSYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIK
	螺旋间羧基翼侧-一直到茎的末端；不包含 TM 结构域
44	SYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMG
45	SYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRN
46	SYNAELLVALENQHTIDLTDSEMNKLFERTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRDEALNNRFQIK
	具有与单体亚基连接的 HA 的蛋白构建体
47	H3-SS-np_231 的氨基酸序列；（H3ssF_231）
48	H3-SS-np_249 的氨基酸序列；（H3ssF_249）
49	H3-SS-np_256 的氨基酸序列；（H3ssF_256）

[0114]

PCT SEQ ID NO	注释
50	H3-SS-np_258 的氨基酸序列; （H3ssF_258）
51	H3-SS-np_262 的氨基酸序列; （H3ssF_262）
52	H3-SS-np_264 的氨基酸序列; （H3ssF_264）
53	H3-SS-np_265 的氨基酸序列; （H3ssF_265）
54	H3-SS-np_266 的氨基酸序列; （H3ssF_266）
55	H3-SS-np_267 的氨基酸序列; （H3ssF_267）
56	H3-SS-np_268 的氨基酸序列; （H3ssF_268）
57	H3-SS-np_269 的氨基酸序列; （H3ssF_269）
58	H3-SS-np_270 的氨基酸序列; （H3ssF_270）
59	H3-SS-np_271 的氨基酸序列; （H3ssF_271）
60	H3-SS-np_272 的氨基酸序列; （H3ssF_272）
61	H3-SS-np_279 的氨基酸序列; （H3ssF_279）
62	H3-SS-np_281 的氨基酸序列; （H3ssF_281）
63	H3-SS-np_287 的氨基酸序列; （H3ssF_287）
64	H3-SS-np_288 的氨基酸序列; （H3ssF_288）
65	H3-SS-np_289 的氨基酸序列; （H3ssF_289）
66	H3-SS-np_291 的氨基酸序列; （H3ssF_291）
67	H3-SS-np_292 的氨基酸序列; （H3ssF_292）
68	H3-SS-np_293 的氨基酸序列; （H3ssF_293）
69	H3-SS-np_294 的氨基酸序列; （H3ssF_294）
70	H3-SS-np_295 的氨基酸序列; （H3ssF_295）
71	H3-SS-np_296（基于 H7 #21）的氨基酸序列; （H3ssF_296）
72	H3-SS-np_297（基于 H7 #23）的氨基酸序列; （H3ssF_297）
73	H3-SS-np_298（基于#249 和 H7 #23）的氨基酸序列; （H3ssF_298）
74	H3-SS-np_299（基于#249 和#258）的氨基酸序列; （H3ssF_299）
75	H3-SS-np_231_HK68 的氨基酸序列; （H3ssF_231_HK68）
76	H3-SS-np_231_BK79 的氨基酸序列; （H3ssF_231_BK79）
77	H3-SS-np_231 Wyo03 的氨基酸序列; （H3ssF_231_Wyo03）
78	H3-SS-np_231_Switz13 的氨基酸序列; （H3ssF_231_Switz13）
79	H3-SS-np_262_HK68 的氨基酸序列; （H3ssF_262_HK68）
80	H3-SS-np_262_BK79 的氨基酸序列; （H3ssF_262_BK79）
81	H3-SS-np_262_Wyo03 的氨基酸序列; （H3ssF_262_Wyo03）
82	H3-SS-np_262_Switz13 的氨基酸序列; （H3ssF_262Switz13）
83	H3-SS_LS-01（基于#231, N298D，接头延伸）; （H3ssLS-01）
84	H3-SS_LS-02(基于#231, M197C, I244C, N298D,接头延伸，添加谷氨酸); （H3ssLS-02）
85	H3-SS_LS-03(基于#231, N298D，接头延伸，添加谷氨酸); (H3ssLS-03)
86	H3-SS_LS-04(基于#231, M197, I244C, N298D，接头延伸，添加谷氨酸); （H3ssLS-04）
87	H3-SS_LS-05（基于#266, S300A，接头延伸）; （H3ssLS-05）
88	H3-SS_LS-06（基于#266, N298D，接头延伸）; （H3ssLS-06）
89	H3-SS_LS-07（基于#274, N298D，接头延伸）; （H3ssLS-07）
90	H3-SS-SA_01

[0115]

PCT SEQ ID NO	注释
91	H3-SS_SA_02
92	H7-SS-np_016（基于 H3 #231）的氨基酸序列；（H7ssF_016）
93	H7-SS-np_018（基于 H3 #262）的氨基酸序列；（H7ssF_018）
94	H7-SS-np_020（基于 H3 #264）的氨基酸序列；（H7ss_F020）
95	H7-SS-np_021（基于 H3 #231 的变体）的氨基酸序列；（H7ssF_021）
96	H7-SS-np_023（基于 H3 #231 的变体）的氨基酸序列；（H7ssF_023）
97	H7-SS-np_025（基于 H3 #265）的氨基酸序列；（H7ssF_025）
98	H7-SS-np_026（基于 H3 #256）的氨基酸序列；（H7ssF_026）
99	H7-SS-np_027（基于 H3 #249）的氨基酸序列；（H7ssF_027）
100	H7-SS-np_028（H7 #20 和#23 的组合）的氨基酸序列；（H7ssF_028）
101	H7-SS-SA_01（来自 H7-SS-np #16）的氨基酸序列；（H7ssSA_01）
102	H7-SS-SA_02（来自 H3-ss np #18）的氨基酸序列；（H7ssSA_02）
103	H10N8-SS-NP_01（类似于 H3 231，H7 16）的氨基酸序列；（H10ssF_01）
104	H10N8-SS-np_02（类似于 H3 262，H7 18）的氨基酸序列；（H10ssF_02）
105	H10N8-SS-np_03（类似于 H3 264，H7 20）的氨基酸序列；（H10ssF_03）
106	H10N8-SS-np_04（类似于 H3 256，H7 26）的氨基酸序列；（H10ssF_04）
107	H10N8-SS-np_05（类似于 H7 23）的氨基酸序列；（H10ssF_05）
108	H10N8-SS-np_06（类似于 H3 249，H7 27）的氨基酸序列；（H10ssF_06）
	具有与跨膜结构域连接的 HA 的蛋白构建体
109	H3-SS-TM_231_HK68
110	H3-SS-TM_231_BK79
111	H3-SS_TM_231_Wyo03
112	H3-SS-TM_231_Switz13
113	H3-SS-TM_256_Den05
114	H3-SS-TM_262_Den05
115	H3-SS-TM_264_Den05
116	H3-SS-TM_262_HK68
117	H3-SS-TM_262_BK79
118	H3-SS-TM_262_Wyo03
119	H3-SS-TM_262_Switz13
120	H7-SS-TM_016
121	H7-SS-TM_018
122	H7-SS-TM_020
123	H7-SS-TM_021
124	H7-SS-TM_023
125	H7-SS-TM_024
126	H7-SS-TM_025
127	H7-SS-TM_026
128	H7-SS_TM_027（具有 H7N7 A/英国/268/1996 的#16）
129	H7-SS_TM_028（具有 H7N7 A/荷兰/219/2003 的#16）
130	H3-SS-TM_256_HK68
131	H3-SS-TM_258_HK68
	具有与单体亚基连接的 HA 的蛋白构建体
132	H3-SS-np_300（基于在 N38 除去聚糖的 231）；（H3ssF_300）

[0116]

PCT SEQ ID NO	注释
133	H3-SS-np_301（Δ裂解环；基于 231）；（H3ssF_301）
134	H3-SS-np_302（Δ裂解环；基于 258）；（H3ssF_302）
135	H3-SS-np_303（Δ裂解环；基于 231）；（H3ssF_303）
136	H3-SS-np_304（Δ裂解环；基于 231）；（H3ssF_304）
137	H3-SS-np_305（Δ裂解环；基于 231）；（H3ssF_305）
138	H3-SS-np_306（添加聚糖；基于 231）；（H3ssF_306）
139	H3-SS-np_307（添加聚糖；基于 231）；（H3ssF_307）
140	H3-SS-np_308（添加聚糖；基于 231）；（H3ssF_308）
141	H3-SS-np_309（添加聚糖；基于 231）；（H3ssF_309）
142	H3-SS-np_310（添加聚糖；基于 231）；（H3ssF_310）
143	H3-SS-np_311（添加聚糖；基于 231）；（H3ssF_311）
144	H3-SS-np_312（添加聚糖；基于 231）；（H3ssF_312）
145	H3-SS-np_313（添加聚糖；基于 231）；（H3ssF_313）
146	H3-SS-np_314（添加聚糖；基于 231）；（H3ssF_314）
147	H3-SS-LS_08（基于 249）；（H3ssL_08）
148	H3-SS-LS_09（基于 249+256）；（H3ssL_09）
149	H3-SS-LS_10（基于 249+258）；（H3ssL_10）
150	H3-SS-LS_11（基于 256）；（H3ssL_11）
151	H3-SS-LS_12（基于 258）；（H3ssL_12）
152	H7-SS-LS_01（基于 H3 258）；（H7ssL_01）
153	H7-SS-LS_02（基于 H3 249）；（H7ssL_02）
154	H7-SS-LS_03（基于 H3 249 & 258）；（H7ssL_03）
155	H7-SS-LS_04（H7 20+26）；（H7ssL_04）
156	H7-SS-LS_05（H7 23+26）；（H7ssL05）
157	H7-SS-LS_06（H7 20+23+26）；（H7ssL06）
158	H3-SS-np_256_HK68；（H3ssF_256）
159	H3-SS-np_258_HK68；（H3ssF_258）

[0117] 上述列出的流感病毒以及来自其的序列是示例性的,可以使用任何其他第2组流感病毒,以及来自其的序列和蛋白实施本发明。

[0118] 病毒表面上的三聚体HA蛋白包含球状头部区域和茎(stem)或茎(stalk)区,所述茎区将HA蛋白锚定在病毒脂质包膜上。流感HA的头部区域仅由HA1多肽的大部分形成,而茎区由HA1和HA2区段构成。根据本发明,头部区域由第2组流感HA蛋白的氨基酸构成,其大致对应于甲型流感病毒(A/丹麦/35/2005(H3N2))全长HA蛋白(SEQ ID NO:4)的氨基酸60-329。类似地,如本申请中所使用的,茎区由第2组流感HA蛋白的氨基酸形成,其对应于甲型流感病毒(A/丹麦/35/2005(H3N2))全长HA蛋白(SEQ ID NO:4)的氨基酸1-59和330-519。如本申请中所使用的,对于头部区域和茎区,术语“大致”指在不影响本发明性质的前提下上述序列的长度可以改变几个(例如,1、2、3、4、5、6、7、8、9或10个)氨基酸。因此,例如,头部区域可以由氨基酸64-329、氨基酸60-326或氨基酸62-327构成。在通常情况下,头部区域和茎区与上述位置相差将不超过10个氨基酸。在本发明的某些方面中,头部区域由对应于甲型流感病毒(A/丹麦/35/2005(H3N2))Cys68至Cys321的氨基酸残基(SEQ ID NO:4)之间并包含其的氨基酸序列构成。对于HA蛋白而言,本领域技术人员应当理解的是,来自不同流感病毒的HA蛋白可能具有不同长度,因为其在蛋白中的序列不同(插入、缺失)。因此,对于对应

区域指与比较的区域在序列、结构和/或功能上等同或接近(例如,至少90%相同、至少95%相同、至少98%相同或至少99%相同)的另一蛋白的区域。例如,对于HA蛋白的茎区而言,在另一HA蛋白中的对应区域可能不具有相同残基数,但具有几乎等同的序列以及将执行相同的功能。作为一个实例,在上述实施方式中,甲型流感病毒(A/丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的头部区域从氨基酸60开始。在A/新喀里多尼亚/20/1999(H1)中头部区域起始的对应氨基酸是氨基酸C60。为了更好地阐明病毒之间的序列比较,本领域的人员使用编号系统,其将氨基酸位置与参照序列相关联。因此,来自不同流感病毒株HA蛋白中的相应氨基酸残基相对于其与蛋白的n-末端氨基酸的距离可能不具有相同的残基数。例如,使用H3编号系统,对于A/新喀里多尼亚/20/1999(1999NC,H1)的残基100不是指其是从N-末端氨基酸开始的第100个残基。而相反的是,A/新喀里多尼亚/20/1999(1999 NC,H1)的残基100与流感H3N2毒株的残基100对齐。本领域技术人员理解对这种编号系统的使用。尽管可以使用H3编号系统鉴定氨基酸的位置,但是除非另有说明,否则HA蛋白中氨基酸残基的位置将通过一般性参考来自本申请公开序列的相应氨基酸的位置来鉴定。

[0119] 发明人还发现了通过将流感病毒HA蛋白的特定序列与无关蛋白组合,并由此制备能够向免疫系统提呈HA蛋白的纳米颗粒,能够激发对HA蛋白靶区域的免疫应答。因此,本发明的一个实施方式是一种蛋白构建体,所述蛋白构建体包含与单体亚基蛋白的至少一部分连接的第2组流感病毒HA蛋白,其中第2组流感病毒HA蛋白的头部区域已被包含来自流感HA蛋白头部区域少于5个连续的氨基酸残基的氨基酸序列替代,并且其中蛋白构建体能够形成纳米颗粒。

[0120] 通过将第2组流感HA蛋白的至少一部分与单体构建体连接,本发明的蛋白构建体能够组装成在其表面上表达第2组流感HA蛋白三聚体的纳米颗粒。此类三聚体是预融合形式,并且与单体亚基连接,以及在纳米颗粒上表达以其三聚体形式稳定化的预融合蛋白。因此,HA蛋白以更加天然的形式存在,这意味着茎多肽的某些表面未暴露,从而降低了茎多肽可能诱导不利的抗体应答的风险。

[0121] 在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自第2组流感病毒HA蛋白茎区的至少一个免疫原性部分,其中蛋白构建体激发针对流感病毒的保护性抗体。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自选自下组的HA蛋白茎区的至少一个免疫原性部分:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。

[0122] 在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部分包含与选自下组SEQ ID NO:4-SEQ ID NO:26的序列具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部分包含选自下组SEQ ID NO:4-SEQ ID NO:26的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部分包含与选自下组SEQ ID NO:47-SEQ ID NO:159的序列具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部

分包含与选自下组SEQ ID NO:47-SEQ ID NO:159的序列具有至少80％同一性、至少85％同一性、至少90％同一性、至少95％同一性、至少97％同一性或至少99％同一性的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部分包含选自下组SEQ ID NO:47-SEQ ID NO:159的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少一个免疫原性部分,所述蛋白HA部分包含选自下组SEQ ID NO:47-SEQ ID NO:159的氨基酸序列。在一个实施方式中,包含第2组流感HA蛋白免疫原性部分的蛋白构建体激发产生针对流感病毒的广泛的保护性抗体。

[0123] 蛋白的免疫原性部分可以包含表位,所述表位是被免疫系统识别从而激发免疫应答的氨基酸残基的簇。此类表位可以由连续氨基酸残基(即在蛋白中彼此相邻的氨基酸残基)组成,或者其可以由非连续氨基酸残基(即在蛋白中彼此不相邻的氨基酸残基)组成,但是其在最终折叠的蛋白中在空间上紧密接近。本领域技术人员熟知的是,表位最少需要6个氨基酸残基以被免疫系统识别。因此,在某些方面中,来自第2组流感HA蛋白的免疫原性部分包含至少一个表位。在一个实施方式中,第2组流感病毒HA蛋白的至少一部分包含来自第2组流感HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自选自下组的第2流感HA蛋白的茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自第2组流感HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸,所述第2流感HA蛋白茎区具有与选自表2中列出的那些流感病毒的HA蛋白具有至少80％同一性、至少85％同一性、至少90％同一性、至少95％同一性、至少97％同一性或至少99％同一性的氨基酸序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自选自表2中列出的那些流感病毒及其变体的第2组流感HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自第2组流感HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75氨基酸或至少100个氨基酸,所述第2组流感HA蛋白茎区包含与选自下组SEQ ID NO:4-SEQ ID NO:26的序列具有至少80％同一性、至少85％同一性、至少90％同一性、至少95％同一性、至少97％同一性或至少99％同一性的序列。在某些方面中,第2组流感病毒HA蛋白的至少一部分包含来自第2组流感HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸,所述第2组流感HA蛋白茎区包含选自下组SEQ ID NO:4-SEQ ID NO:26的序列。在某些方面中第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸,所述蛋白HA部分包含与选自下组SEQ ID NO:47-SEQ ID NO:159的序列具有至少80％同一性、至少85％同一性、至少90％同一性、至少95％同一性、至少97％同一性或至少99％同一性的序列。在某些方面中第2组流感病毒HA蛋白的至少一部分包含来自某蛋白HA部分的至少6个氨基酸、至少10个氨基酸、至少25个氨基

酸、至少50个氨基酸、至少75氨基酸或至少100个氨基酸,所述蛋白HA部分包含选自下组SEQ ID NO:47-SEQ ID NO:159的序列。

[0124] 在本发明的某些方面中,氨基酸是来自第2组流感病毒HA蛋白茎区的连续的氨基酸。在某些方面中,包含来自第2组流感病毒HA蛋白茎区至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸的本发明的蛋白构建体激发产生针对流感病毒的广泛保护性抗体。在本发明的某些方面中,蛋白构建体包含来自第2组流感病毒HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸,所述第2组流感病毒HA蛋白茎区包含与选自下组SEQ ID NO:4-SEQ ID NO:26的序列具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列。在本发明的某些方面中,蛋白构建体包含来自第2组流感病毒HA蛋白茎区的至少6个氨基酸、至少10个氨基酸、至少25个氨基酸、至少50个氨基酸、至少75个氨基酸或至少100个氨基酸,所述第2组流感病毒HA蛋白茎区包含选自下组SEQ ID NO:4-SEQ ID NO:26的氨基酸序列。在某些方面中,氨基酸是不连续的,但是在最终蛋白中具有紧密的空间接近性。

[0125] 尽管本申请示例了来自几种例示性第2组流感HA蛋白的茎区序列的用途,本发明也可以使用来自包含公开的第2组流感HA序列变异的蛋白的茎区实施。因此,在本发明的某些方面中,第2组流感HA蛋白来自选自表2中列出的第2组病毒及其变体的病毒。在某些方面中,第2组流感病毒HA蛋白包含与第2组流感病毒HA蛋白茎区具有至少80%、至少85%、至少90%、至少92%、至少94%、至少96%、至少98%或至少99%同一性的氨基酸序列,所述第2组流感病毒HA蛋白茎区包含选自下组SEQ ID NO:4-SEQ ID NO:26的氨基酸序列。在某些方面中,第2组流感HA蛋白包含选自下组SEQ ID NO:4-SEQ ID NO:26的氨基酸序列。

[0126] 在本发明的某些方面中,在蛋白构建体中的HA蛋白的头部区域被接头序列替代。可以使用任何接头,只要茎区序列能够采用所需的构象即可。尽管可以将任何氨基酸用于制备接头序列,但是在本发明的某些方面中氨基酸是较小的或具有不带电荷的侧链的。优选使用的氨基酸包括但不限于半胱氨酸、丝氨酸、甘氨酸、丙氨酸、缬氨酸和脯氨酸。在一个实施方式中,接头由选自下组的一个或多个氨基酸构成:丝氨酸、甘氨酸、半胱氨酸、缬氨酸、脯氨酸和/或苯丙氨酸残基。在某些实施方式中,可能需要包含某种氨基酸残基,其侧链能够与另一氨基酸形成共价键(如二硫键)。此类氨基酸的一个实例是半胱氨酸。可以改变接头序列的长度,但优选的实施方式使用使得茎序列形成所需结构的最短可能序列。在某些方面中,接头序列的长度小于12个氨基酸。在一个实施方式中,接头序列的长度小于10个氨基酸。在一个实施方式中,接头序列的长度小于5个氨基酸。在优选的实施方式中,接头序列缺少来自HA蛋白头部区域的连续的氨基酸序列。在某些方面中,接头序列包含来自HA蛋白头部区域的小于5个连续的氨基酸。在某些方面中,头部区域序列被包含SEQ ID NO:34、SEQ ID NO:35或其变体的氨基酸序列替代。

[0127] 本发明人还发现通过进一步改变所公开的蛋白构建体的第2组流感病毒HA蛋白能够改善本发明的蛋白构建体和纳米颗粒的稳定性。例如,发明人发现了延长A螺旋的长度改善本发明蛋白构建体的性能。因此,一个实施方式是本发明的蛋白构建体其中已通过添加氨基酸将A螺旋延长。一个实施方式是本发明的蛋白构建体,其中所述蛋白构建体包含与单体亚基的至少一部分连接的第2组流感病毒HA蛋白,其中第2组流感病毒HA蛋白的头部区域

被包含来自流感HA蛋白头部区域的少于5个连续氨基酸残基的氨基酸序列替代,以及其中通过添加氨基酸残基将A螺旋的羧基末端(即,与C螺旋的氨基末端连接的部分)延伸。应当意识到的是,由于其目标是延伸螺旋,因而添加至A螺旋羧基末端的氨基酸序列优选地应形成螺旋。在本发明的某些方面中,通过向A螺旋的羧基末端添加包含SEQ ID NO:36或37的氨基酸序列或其形成螺旋的变体将A螺旋的长度延伸。在本发明的某些方面中,通过向A螺旋的羧基末端添加包含或由X_1LMX_2Q构成的序列或其形成螺旋的变体将A螺旋的长度延伸,其中在位置X_1和X_2的氨基酸是酸性氨基酸。应当注意的是,X_1和X_2可以但不必是相同的氨基酸残基。在某些方面中,此类接头第1位和第4位的残基选自下组:谷氨酰胺、谷氨酸、天冬酰胺、天冬氨酸、甘氨酸和脯氨酸。在一个实施方式中,通过向A螺旋的羧基末端添加由SEQ ID NO:36或37构成的氨基酸序列或其形成螺旋的变体将A螺旋延伸。在本发明的某些方面中,通过向A螺旋的羧基末端添加包含ALMAQ或ELMEQ的序列或其形成螺旋的变体将A螺旋的长度延伸。在本发明的某些方面中,通过向A螺旋的羧基末端添加由ALMAQ或ELMEQ构成的序列或其形成螺旋的变体将A螺旋的长度延伸。

[0128] 除了延伸A螺旋之外,发明人发现对将A螺旋的羧基末端与C螺旋的氨基末端连接的氨基酸序列进行修饰(在本申请中称为螺旋间区域或螺旋间环,其一个实例如SEQ ID NO:38所示),改善本发明蛋白构建体和纳米颗粒的稳定性和性能。更具体地,发明人发现缩短螺旋间区域的长度改善本发明蛋白构建体和纳米颗粒的稳定性和性能。因此,在本发明的某些方面中,对将本发明蛋白构建体中的A螺旋的羧基末端与C螺旋的氨基末端连接的氨基酸序列进行修饰以改善本发明蛋白构建体的稳定性。应当意识到的是,改善本发明蛋白构建体的稳定性指稳定本发明蛋白构建体的三维结构,特别是本发明蛋白构建体的茎区,以使得其近似于天然第2组流感HA蛋白茎区的三维结果,并能够激发针对第2组流感病毒的免疫应答。因此,在本发明的某些方面中,本发明蛋白构建体的螺旋间区域是缩短的。通过从现有螺旋间区域中除去氨基酸,或通过使用接头序列替代螺旋间区域的氨基酸能够实现这种缩短。在某些方面中,将本发明蛋白构建体的螺旋间区域缩短为小于6个氨基酸。在某些方面中,使用接头序列替代螺旋间区域的氨基酸。在本发明的某些方面中,对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的螺旋间区域的螺旋间区域氨基酸被接头序列替代。在本发明的某些方面中,对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)氨基酸402-437的螺旋间区域氨基酸被接头序列替代。在本发明的某些方面中,包含SEQ ID NO:4的氨基酸402-437的螺旋间区域被接头序列替代。在本发明的某些方面中,对应于如SEQ ID NO:38所示的甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的区域的螺旋间区域被接头序列替代。在本发明的某些方面中,包含与SEQ ID NO:38具有至少90%、至少97%、至少99%同一性的氨基酸序列的第2组流感病毒HA蛋白的螺旋间区域被接头序列替代。在一个实施方式中,包含SEQ ID NO:38的第2组流感病毒HA蛋白的区域被接头序列替代。在本发明的某些方面中,由SEQ ID NO:38构成的第2组流感病毒HA蛋白的区域被接头序列替代。在本发明的某些方面中,螺旋间区域被包含GGPD的接头序列(SEQ ID NO:39)替代。在本发明的某些方面中,对应于SEQ ID NO:4的氨基酸402-437的螺旋间区域被具有由GGPD构成的肽的物理空间和/或化学性质的接头序列替代。在本发明的某些方面中,对应于SEQ ID NO:4的氨基酸402-437的螺旋间区域被具有形成螺旋倾向的接头序列替代。在本发明的某些方面中,对应于SEQ ID NO:4的氨基酸402-437的螺旋间区

域被包含GGPD的接头序列(SEQ ID NO:39)或其保守性变体替代。在本发明的某些方面中,螺旋间区域被由GGPD构成的接头序列替代。

[0129] 如前所述,本发明的蛋白构建体可以含有本申请所述的一个、几个或所有突变和序列改变。因此,例如,其中A螺旋已被延伸的(如上所述)蛋白构建体,也可以具有缩短的或被接头序列替代的(如上所述)螺旋间区域。因此,本发明的一个方面是一种蛋白构建体,所述蛋白构建体包含与单体亚基蛋白的至少一部分连接的第2组流感病毒HA蛋白,其中第2组流感病毒HA蛋白的头部区域被包含来自流感HA蛋白头部区域的少于5个连续氨基酸残基的氨基酸序列替代,其中螺旋间区域缩短或被接头序列替代,以及蛋白构建体能够形成纳米颗粒。本申请公开了替代HA蛋白头部区域的方法,以及缩短或替代螺旋间区域的方法。应当理解的是,在其中通过添加氨基酸延伸A螺旋羧基末端的实施方式中,螺旋间区域将被将C螺旋的氨基末端与A螺旋延伸序列的羧基末端连接在一起的接头替代。

[0130] 发明人进一步发现能够通过在第2组流感病毒茎区的序列中进行位点特异性突变改善本发明蛋白构建体的稳定性。特别地,形成离子键、盐桥、增加疏水性包装等的突变能够增强本发明蛋白构建体和纳米颗粒的稳定性。因此,在本发明的某些方面中,本发明的蛋白构建体包含形成或增强离子相互作用或盐桥或者增加疏水性包装的一个或多个突变。尽管取代突变是优选的,但是可以进行对增强本发明蛋白构建体的稳定性具有所需作用的任何类型的突变。在本发明的某些方面中,在第2组流感病毒HA蛋白对应于SEQ ID NO:4选自下组K396、L397、L400、S438、N440、E448、T452和N461位置的氨基酸位置进行突变。在一个实施方式中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)K396的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)K396的氨基酸变为甲硫氨酸或亮氨酸。在一个实施方式中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L397的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L397的氨基酸变为缬氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L400的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L400的氨基酸变为缬氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)S438的氨基酸变为选自下组天冬酰胺、谷氨酰胺、丝氨酸、苏氨酸和半胱氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)S438的氨基酸变为半胱氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N440的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N440的氨基酸变为亮氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)E448的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)E448的氨基酸变为亮氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/

35/2005(H3N2))HA蛋白(SEQ ID NO:4)T452的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T452的氨基酸变为缬氨酸。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N461的氨基酸变为选自下组组氨酸、赖氨酸、谷氨酸、天冬氨酸和精氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N461的氨基酸变为选自下组组氨酸、赖氨酸和精氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N461的氨基酸变为精氨酸。

[0131] 可以稳定本发明蛋白构建体的其他突变包括在对应于SEQ ID NO:4选自下组G39、T46、N54、T58、L331、N338和Q392的位置的氨基酸位置的突变。应当理解的是,在这些位置的突变可以包括其中插入的氨基酸在性质上与本申请提出的那些相似的突变。

[0132] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)G39的氨基酸变为选自下组半胱氨酸、丝氨酸、苏氨酸、脯氨酸、天冬酰胺和谷氨酸胺的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)G39的氨基酸变为半胱氨酸。

[0133] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T46的氨基酸变为选自下组半胱氨酸、丝氨酸、苏氨酸、脯氨酸、天冬酰胺和谷氨酸胺的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T46的氨基酸变为半胱氨酸。

[0134] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N54的氨基酸变为选自下组组氨酸、精氨酸和赖氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N54的氨基酸变为组氨酸。

[0135] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T58的氨基酸变为选自下组甲硫氨酸、亮氨酸、异亮氨酸、丙氨酸和缬氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T58的氨基酸变为亮氨酸。

[0136] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L331的氨基酸变为选自下组组氨酸、精氨酸和赖氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)L331的氨基酸变为赖氨酸。

[0137] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N338的氨基酸变为选自下组半胱氨酸、丝氨酸、脯氨酸、天冬酰胺、谷氨酰胺和苏氨酸的氨基酸残基。在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)N338的氨基酸变为半胱氨酸。

[0138] 在本发明的某些方面中,将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)Q392的氨基酸变为选自下组半胱氨酸、丝氨酸、脯氨酸、天冬酰胺、谷氨酰胺和苏氨酸的氨基酸残基。将对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)Q392的氨基酸变为半胱氨酸。

[0139] 除了上述以外,发明人发现了将突变加入聚糖连接位点可能是有益的。因此,在本发明的某些方面中,蛋白构建体包含一个或多个突变,或者一个或多个突变对,其选自下组:Q49N/E51T(加入第1组聚糖的突变)、E56N/V59T(在头部接头和临近残基中的突变)、V59N/P61T(在头部接头中的突变)、G62N/G64T(在头部接头中的突变)、V329N/L331T(在头部接头和临近残基的突变)、L331N/L333T、D437N/Y439T(在螺旋间接头和临近残基中的突变)、Q432N/G434T(插入G)(在螺旋间接头和临近残基中的突变)、Q372N/S374T和A492N/I494T。

[0140] 此外,在本发明的某些方面中,可以使用甘氨酸接头替代对应于甲型流感病毒(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)中氨基酸339-357的环。

[0141] 如前所述,本发明的蛋白构建体可以含有本申请所述的一个、几个或所有突变和序列改变。因此,例如,其中A螺旋已被延伸的(如本申请所述的)蛋白构建体,也可以具有缩短的或被接头序列替代的(如本申请所述的)螺旋间区域,以及也可以含有一个或多个本申请所述的位点特异性突变。因此,本发明的一个方面是一种蛋白构建体,所述蛋白构建体包含与单体亚基蛋白的至少一部分连接的第2组流感病毒HA蛋白,其中第2组流感病毒HA蛋白的头部区域被包含来自流感HA蛋白头部区域的少于5个连续氨基酸残基的氨基酸序列替代,其中螺旋间区域缩短或被接头序列替代,其中蛋白构建体的HA部分包含一个或多个位点特异性突变,其位于对应于SEQ ID NO:4中选自下组K396、L397、L400、S438、N440、E448、T452、N461、G39、T46、N54、T58、L331、N338和D437位置的位置,以及其中蛋白构建体能够形成纳米颗粒。此类构建体还可以含有一个或多个突变,或者一个或多个突变对,其选自下组:Q49N/E5 1T、E56N/V59T(在头部接头和临近残基中的突变)、V59N/P61T(在头部接头中的突变)、G62N/G64T(在头部接头中的突变)、V329N/L33 1T(在头部接头和临近残基中的突变)、L33 1N/L333T、D437N/Y439T(在螺旋间接头和临近残基中的突变)、Q432N/G434T(插入G)(在螺旋间接头和临近残基中的突变)、Q372N/S374T和A492N/I494T。本申请公开了替代HA蛋白的头部区域、延伸A螺旋、缩短或替代螺旋间区域和适宜的位点特异性突变的方法。应当理解的是,在其中通过添加氨基酸延伸A螺旋羧基末端的实施方式中,螺旋间区域将被将C螺旋的氨基末端与A螺旋延伸序列的羧基末端连接在一起的接头替代。

[0142] 到目前为止已经描述了用于生产纳米颗粒疫苗的本发明蛋白构建体的具体方面。为了有助于澄清本发明,现在发明人将以替代地和更加详细的方式描述各个方面。应当理解的是,下文描述的本发明的各个方面也适用于本申请已经描述的蛋白构建体的实施方式和方面。

[0143] 可以使用将第3组流感HA蛋白各部分连接在一起的重组技术制备本发明的蛋白构建体,以及对其序列进行改变。重组技术也可以用于加入适宜接头和单体亚基。以这种方式,可以生产本发明的蛋白构建体以及随后的纳米颗粒疫苗,所述蛋白构建体包含生产蛋白构建体所必需的特定序列。因此,本发明的一个实施方式是一种蛋白构建体(在本申请中也称为融合蛋白),所述蛋白构建体包含来自第2流感病毒HA蛋白茎区的第一氨基酸序列和来自第2流感病毒HA蛋白茎区的第二氨基酸序列,第一和第二氨基酸序列通过接头序列共价连接在一起,其中第一氨基酸序列包含来自头部区域序列氨基末端上游氨基酸序列的至少20个连续的氨基酸残基;其中第二氨基酸序列包含来自头部区域序列羧基末端下游氨基酸序列的至少20个连续的氨基酸残基;以及其中第一或第二氨基酸序列与单体亚基结构域

的至少一部分连接在一起,以使得蛋白结构域能够形成纳米颗粒。

[0144] 在本发明的某些方面中,第一氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白的茎区:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在本发明的某些方面中,第一氨基酸序列来自表2中列出的第2组病毒HA蛋白的茎区。在本发明的某些方面中,第一氨基酸序列来自第2组流感HA蛋白的茎区,其中HA蛋白包含与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第一氨基酸序列来自第2组流感HA蛋白的茎区,其中HA蛋白包含选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列。

[0145] 在本发明的某些方面中,第二氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白的茎区:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在本发明的某些方面中,第二氨基酸序列来自表2中列出的第2组病毒HA蛋白的茎区。在本发明的某些方面中,第二氨基酸序列来自第2组流感HA蛋白的茎区,其中HA蛋白包含与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第二氨基酸序列来自第2组流感HA蛋白的茎区,其中HA蛋白包含选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列。

[0146] 如上所述,第一氨基酸序列包含来自头部区域序列氨基末端上游的氨基酸序列的至少20个连续的氨基酸残基。根据本发明,术语上游指与头部区域的第一氨基酸残基的氨基末端连接的氨基酸序列实体。优选的上游序列是与头部区域序列紧邻的那些。在本发明的某些方面中,头部区域的氨基末端位于对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)Q60的氨基酸残基。在本发明的某些方面中,第一氨基酸序列包含来自第2流感病毒HA蛋白区域的至少20个连续的氨基酸残基,所述区域对应于如SEQ ID NO:4所示的甲型流感(丹麦/35/2005(H3N2))HA蛋白的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29的序列具有至少85%、至少90%、至少95%或至少97%的同一性。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29。

[0147] 在本发明的某些方面中,第一氨基酸序列包含来自HA蛋白的氨基酸区域的至少40个连续的氨基酸残基,所述HA蛋白的氨基酸区域对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与SEQ ID NO:27或SEQ ID NO:28具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第一氨基酸序列包含来自SEQ ID NO:27或SEQ ID NO:28的至少40个连续的氨基酸残基。

[0148] 在本发明的某些方面中,第一氨基酸序列包含与SEQ ID NO:27具有至少85%、至少90%、至少95%或至少97%同一性的序列。在一个实施方式中,第一氨基酸序列包含SEQ ID NO:27。

[0149] 如上所述,第二氨基酸序列包含来自头部区域序列羧基末端下游的氨基酸序列的至少20个连续的氨基酸残基。根据本发明,术语下游指与头部区域的羧基末端氨基酸残基

连接的氨基酸序列实体。优选的上游序列是与头部区域序列紧邻的那些。在本发明的某些方面中,头部区域的羧基末端位于对应于如SEQ ID NO:4所示的甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T329的氨基酸位置。因此,在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少20个连续的氨基酸,所述区域对应于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少20个连续的氨基酸,所述区域包含甲型流感(丹麦/35/2005(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在一个实施方式中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33的序列具有至少85%、至少90%、至少95%或至少97%同一性。在一个实施方式中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33。

[0150] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少40个连续的氨基酸,所述区域对应于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少40个连续的氨基酸,所述区域包含甲型流感((丹麦/35/2005)(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32。

[0151] 在本发明的某些方面中,第二氨基酸序列包含与SEQ ID NO:36具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在一个实施方式中,第二氨基酸序列包含SEQ ID NO:36。

[0152] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸,所述区域对应于甲型流感病毒(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸,所述区域包含甲型流感病毒((丹麦/35/2005)(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个、至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸残基,所述序列与SEQ ID NO:30具有至少85%、至少90%、至少95%或至少97%同一性。在一个实施方式中,第二氨基酸序列包含来自SEQ ID NO:30的至少40个、至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸残基。

[0153] 如上所述,蛋白构建体的第一和第二氨基酸序列可以通过接头序列连接在一起。可以使用任何接头序列只要接头序列具有来自HA蛋白头部区域的小于5个连续的氨基酸残基,以及只要第一和第二氨基酸能够形成所需构象即可。在一个实施方式中,接头序列的长度小于10个氨基酸、小于7个氨基酸或小于5个氨基酸。在一个实施方式中,接头序列包含甘

氨酸和丝氨酸。在一个实施方式中,接头序列将第一氨基酸序列的羧基末端与第二氨基酸序列的氨基末端连接在一起。在本发明的某些方面中,接头序列将第二氨基酸序列的羧基末端与第一氨基酸序列的氨基末端连接在一起。本发明的某些方面中,接头序列在化学和特殊性质上类似于由SEQ ID NO:34或SEQ ID NO:35构成的肽。在本发明的某些方面中,接头序列包含SEQ ID NO:34或SEQ ID NO:35,或者其保守性变体。在一个实施方式中,接头包含SEQ ID NO:34或SEQ ID NO:35。在本发明的某些方面中,接头由SEQ ID NO:34或SEQ ID NO:35构成。

[0154] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感病毒HA蛋白的氨基酸序列,其对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸330-519,其中对应于HA蛋白(SEQ ID NO:4)螺旋间区域的区域被接头肽替代。在本发明的某些方面中,甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的螺旋间区域基本上由SEQ ID NO:4的氨基酸402-437构成。因此,在本发明的某些方面中,第二氨基酸序列包含来自第2组流感病毒HA蛋白的氨基酸序列,其对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸330-519,其中对应于SEQ ID NO:4的氨基酸402-437的区域被接头肽替代。在本发明的某些方面中,第二氨基酸序列包含与SEQ ID NO:30具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列,其中对应于螺旋间区域的区域(即,SEQ ID NO:4的氨基酸402-437)被接头肽替代。在本发明的某些方面中,第二氨基酸序列包含SEQ ID NO:30,其中对应于螺旋间区域的区域(即,SEQ ID NO:4的氨基酸402-437)被接头肽替代。在本发明的某些方面中,第二氨基酸序列包含SEQ ID NO:30,其中SEQ ID NO:30的氨基酸73-108被接头肽替代。可以将任何接头序列作为第二氨基酸序列中的接头肽,只要蛋白构建体能够形成所需构象即可。在本发明的某些方面中,接头肽的长度小于10个氨基酸、小于7个氨基酸或小于5个氨基酸。在一个实施方式中,接头肽的长度是4个氨基酸。在本发明的某些方面中,接头序列包含选自下组甘氨酸、丝氨酸、脯氨酸和天冬氨酸的一个或多个氨基酸。在本发明的某些方面中,接头肽包含与由SEQ ID NO:39构成的肽具有类似的化学和空间性质的氨基酸序列。在本发明的某些方面中,接头肽包含SEQ ID NO:39,或其保守性变体。在本发明的某些方面中,接头肽包含SEQ ID NO:38.。在本发明的某些方面中,接头肽由SEQ ID NO:39构成。

[0155] 在本发明的某些方面中,第二氨基酸序列包含与选自下组SEQ ID NO:40、SEQ ID NO:41、SEQ ID NO:42和SEQ ID NO:43的序列具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的序列。在本发明的某些方面中,第二氨基酸序列包含选自下组SEQ ID NO:40、SEQ ID NO:41、SEQ ID NO:42和SEQ ID NO:43的序列。

[0156] 本发明的一个实施方式是一种蛋白构建体(也称为融合蛋白),所述蛋白构建体包含来自第2组流感病毒HA蛋白茎区的第一氨基酸序列,来自第2组流感病毒HA蛋白茎区的第二氨基酸序列,以及来自第2组流感病毒HA蛋白茎区的第三氨基酸序列;

[0157] 其中第一氨基酸序列包含来自甲型流感病毒HA蛋白头部区域序列氨基末端上游氨基酸序列的至少20个连续的氨基酸残基,或者与甲型流感病毒HA蛋白头部区域序列氨基末端上游氨基酸序列的至少40个连续的氨基酸具有至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列;

[0158] 其中第二氨基酸序列包含将头部区域序列的羧基末端与甲型流感病毒HA蛋白的螺旋间区域连接在一起的氨基酸序列的至少20个连续的氨基酸残基,或者与来自将头部区域序列的羧基末端与甲型流感病毒HA蛋白的螺旋间区域连接在一起的氨基酸序列的至少40个连续的氨基酸残基具有至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列;

[0159] 其中第三氨基酸序列包含将螺旋间区域的羧基末端与钾型流感病毒HA蛋白跨膜结构域(TM)连接在一起的氨基酸序列的至少20个连续的氨基酸残基,或者与来自将螺旋间区域的羧基末端与甲型流感病毒HA蛋白的跨膜结构域连接在一起的氨基酸序列的至少40个连续的氨基酸残基具有至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的氨基酸序列;

[0160] 其中第一和第二氨基酸序列通过接头序列连接在一起;其中第二和第三氨基酸序列通过接头肽连接在一起;以及

[0161] 其中将第一和第三氨基酸序列与单体亚基结构域的至少一部分连接在一起,以使得蛋白构建体能够形成纳米颗粒。

[0162] 在本发明的某些方面中,第一氨基酸序列来自第2组流感HA蛋白。在一个实施方式中,第一氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在本发明的某些方面中,第一氨基酸序列是来自表2中列出的第2组病毒的第2组流感HA蛋白。在本发明的某些方面中,第一氨基酸序列来自第2流感HA蛋白的茎区,其具有与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第一氨基酸序列来自第2组流感HA蛋白的茎区,其包含选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列。

[0163] 在本发明的某些方面中,第一氨基酸序列包含来自第2组流感病毒HA蛋白某一区域的至少20个连续的氨基酸残基,所述区域对应于甲型流感丹麦/35/2005(H3N2)的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29。

[0164] 在本发明的某些方面中,第一氨基酸序列包含来自HA蛋白氨基酸区域的至少40个连续的氨基酸残基,所述区域对应于甲型流感丹麦/35/2005(H3N2)的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与SEQ ID NO:27和SEQ ID NO:28具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第一氨基酸序列包含来自SEQ ID NO:27和SEQ ID NO:28的至少40个连续的氨基酸残基。

[0165] 在本发明的某些方面中,第一氨基酸序列包含对应于甲型流感病毒丹麦/35/2005(H3N2)HA蛋白(SEQ ID NO:4)的氨基酸残基1-59的序列。在本发明的某些方面中,第一氨基酸序列包含与SEQ ID NO:27具有至少85%、至少90%、至少95%或至少97%同一性的序列。

在本发明的某些方面中,第一氨基酸序列包含SEQ ID NO:27。在本发明的某些方面中,第一氨基酸序列由SEQ ID NO:27构成。

[0166] 在本发明的某些方面中,第二氨基酸序列来自第2组流感HA蛋白。在本发明的某些方面中,第二氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在本发明的某些方面中,第二氨基酸序列来自表2中列出的第2组病毒的第2组流感HA蛋白。在本发明的某些方面中,第二氨基酸序列来自第2流感HA蛋白的茎区,其具有与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第二氨基酸序列来自第2组流感HA蛋白的茎区,其包含选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列。

[0167] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感病毒HA蛋白某一区域的至少20个连续的氨基酸残基,所述区域对应于甲型流感(丹麦/35/2005(H3N2))(SEQ ID NO:4)的氨基酸残基330-401。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32。

[0168] 在本发明的某些方面中,第二氨基酸序列包含与SEQ ID NO:31具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第二氨基酸序列包含SEQ ID NO:31。

[0169] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白的至少60个或至少72个连续的氨基酸,所述第2组流感HA蛋白紧邻HA蛋白头部区域序列羧基末端的下游。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白氨基酸区域的至少60个或至少72个连续的氨基酸,所述第2组流感HA蛋白氨基酸区域对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸残基330-401。

[0170] 第一和第二氨基酸序列通过接头序列连接在一起。在本发明的某些方面中,接头序列的长度小于10个氨基酸、小于7个氨基酸或小于5个氨基酸。在本发明的某些方面中,接头序列包含甘氨酸和丝氨酸。在本发明的某些方面中,接头序列将第一氨基酸序列的羧基末端与第二氨基酸序列的氨基末端连接在一起。在本发明的某些方面中,接头序列将第二氨基酸序列的羧基末端与第一氨基酸序列的氨基末端连接在一起。在本发明的某些方面中,接头序列在化学和特殊性质上类似于由SEQ ID NO:34或SEQ ID NO:35构成的肽。在本发明的某些方面中,接头包含SEQ ID NO:34或SEQ ID NO:35,或者其保守性变体。在一个实施方式中,接头包含SEQ ID NO:34或SEQ ID NO:35。在本发明的某些方面中,接头由SEQ ID

NO:34或SEQ ID NO:35构成。

[0171] 在本发明的某些方面中,第三氨基酸序列来自第2组流感HA蛋白。在本发明的某些方面中,第三氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H15流感病毒HA蛋白。在本发明的某些方面中,第三氨基酸序列来自表2中列出的第2组病毒的第2组流感HA蛋白。在本发明的某些方面中,第三氨基酸序列来自第2流感HA蛋白的茎区,其具有与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第三氨基酸序列来自第2组流感HA蛋白的茎区,其包含选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-159的序列。

[0172] 在本发明的某些方面中,第三氨基酸序列包含来自第2组流感病毒HA蛋白某一区域的至少20个连续的氨基酸残基,所述区域对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸残基438-519。在本发明的某些方面中,第三氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第三氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46。在本发明的某些方面中,第三氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第三氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46。

[0173] 在本发明的某些方面中,第三氨基酸序列包含与选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第三氨基酸序列包含选自下组SEQ ID NO:44、SEQ ID NO:45和SEQ ID NO:46的氨基酸序列。

[0174] 在本发明的某些方面中,第三氨基酸序列包含来自第2组流感HA蛋白的至少60个或至少75个连续的氨基酸,所述第2组流感HA蛋白紧邻第2组甲型流感(丹麦/35/2005(H3N2))HA蛋白螺旋间区域序列羧基末端的下游。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感病毒HA蛋白氨基酸区域的至少60个或至少75个连续的氨基酸,所述第2组流感病毒HA蛋白氨基酸区域对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸残基438-519。

[0175] 接头肽可以包含任何氨基酸序列,只要蛋白构建体能够形成所需构象即可。在本发明的某些方面中,接头肽的长度小于10个氨基酸、小于7个氨基酸或小于5个氨基酸。在本发明的某些方面中,接头肽的长度是4个氨基酸。在本发明的某些方面中,接头序列包含选自下组甘氨酸、丝氨酸、脯氨酸和天冬氨酸的氨基酸。在本发明的某些方面中,接头肽包含SEQ ID NO:39。在本发明的某些方面中,接头肽由SEQ ID NO:39构成。

[0176] 如已经讨论的,本发明蛋白构建体中各种位置的突变均能够稳定蛋白构建体和/或包含所述构建体的纳米颗粒的三维结构。因此,在本发明的某些方面中,第一氨基酸序列在对应于SEQ ID NO:4中选自下组G39、T46和T58位置的氨基酸位置包含至少一个突变。在

本发明的某些方面中,第一氨基酸序列包含至少一个选自下组G39C、T46C、N54H和T58L(基于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的序列编号)的突变。

[0177] 在本发明的某些方面中,第二氨基酸序列在对应于SEQ ID NO:4中选自下组L331、N338、Q392、K396、L397和L400位置的氨基酸位置包含至少一个突变。在本发明的某些方面中,第一氨基酸序列包含至少一个选自下组L331K、N338C、Q392C和L400V(基于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的序列编号)的突变。

[0178] 在本发明的某些方面中,第三氨基酸序列在对应于SEQ ID NO:4中选自下组S438、N440、E448、T452和N461位置的氨基酸位置包含至少一个突变。在本发明的某些方面中,第一氨基酸序列包含至少一个选自下组S438C、N440L、E448L、T452V和N461R(基于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的序列编号)的突变。

[0179] 如上所述,本发明的蛋白构建体能够与单体亚基蛋白的至少一部分连接在一起,以使得蛋白构建体能够形成纳米颗粒。在本发明的某些方面中,单体亚基蛋白的至少一部分与第三氨基酸序列连接在一起。在一个优选的实施方式中,单体亚基蛋白的至少一部分与第三氨基酸序列的羧基末端连接在一起。在本发明的某些方面中,该部分包含来自单体亚基的至少50个、至少100个或至少150个氨基酸。在本发明的某些方面中,单体亚基是铁蛋白。在本发明的某些方面中,单体亚基是二氧四氢蝶啶合酶。在本发明的某些方面中,该部分包含来自SEQ ID NO:1、SEQ ID NO:2或SEQ ID NO:3的至少50个、至少100个或至少150个氨基酸。在本发明的某些方面中,单体亚基包含与SEQ ID NO:1、SEQ ID NO:2或SEQ ID NO:3具有至少85%同一性、至少90%同一性或至少95%同一性的序列。在本发明的某些方面中,单体亚基包含选自下组SEQ ID NO:1、SEQ ID NO:2和SEQ ID NO:3的序列。

[0180] 尽管已作为单独的实施方式对针对本申请公开的第2组流感病毒HA蛋白的修饰进行了描述,但是应当意识到的是可以在一个蛋白构建体中包含所有此类修饰。例如,可以制备一种蛋白构建体,其中通过接头将第一氨基酸序列与第二氨基酸序列连接在一起,其中第二氨基酸序列包含来自第2组流感HA蛋白头部区域羧基末端下游区域的氨基酸序列,但是其中对应于第2组甲型流感(丹麦/35/2005(H3N2))HA蛋白氨基酸402-437的螺旋间区域已被接头肽替代,以及其中已将一个或多个突变在对应于第2组甲型流感(丹麦/35/2005)(H3N2)HA蛋白选自下组L33 1、N338、K396、L397、L400、S438、N440、E448、T452和N461位置的位置引入第二氨基酸序列,以增加在折叠的蛋白中这些氨基酸残基之间相互作用的强度。

[0181] 尽管可以将到目前为止所述的蛋白构建体用于生产能够针对一种或多种流感病毒产生免疫应答的纳米颗粒,但是在一些实施方式中,通过工程化改造将进一步的突变引入本发明蛋白的氨基酸序列可能是有用的。例如,改变单体亚基蛋白、三聚化结构域或接头序列中的位点(如酶识别位点或糖基化位点)以给予蛋白有益的性质(例如,溶解度、半衰期、免于免疫监视的蛋白掩饰部分)可能是有用的。在这点上,已知铁蛋白的单体亚基不是天然糖基化的。然而,若其在哺乳动物或酵母细胞中以分泌性蛋白质表达,则其可以是糖基化的。因此,在本发明的某些方面中,来自单体铁蛋白亚基的氨基酸序列中的潜在N连接糖基化位点突变为使得突变的铁蛋白亚基序列在突变位点处不再是糖基化的。突变单体铁蛋白亚基的一种此类序列以SEQ ID NO:2表示。在国际申请号PCT/US201 5/032695中公开了对有用的突变更加详细的描述。

[0182] 在一些情况下,阻断针对蛋白构建体中的某些氨基酸序列产生免疫应答可能是所

需要的。这可以通过在待阻断位点附近添加糖基化位点来完成,使得聚糖在空间上阻断免疫系统到达被阻断位点的能力。因此,在本发明的某些方面中,改变蛋白构建体的序列以引入一个或多个糖基化位点。此类位点的实例包括但不限于Asn-X-Ser、Asn-X-Thr和Asn-X-Cys。在一些情况下,可以将糖基化位点引入接头序列。在其中引入糖基化位点的有用位点的进一步实例包括但不限于在第2组流感HA蛋白中对应于甲型流感新喀里多尼亚/20/1999(H1)HA蛋白的氨基酸45-47或氨基酸370-372的位置。引入糖基化位点的方法是本领域技术人员公知的。

[0183] 本发明的蛋白和蛋白构建体由本发明的核酸分子编码。此外,其由本发明的核酸构建体表达。如在本申请中所使用的,核酸构建体是重组表达载体,即如下的载体,该载体与编码蛋白的核酸分子连接,使得核酸分子在对例如对象或器官、组织或细胞施用核酸构建体时可以实现蛋白表达。载体还使核酸分子能够转运到环境(诸如但不限于生物体、组织或细胞培养物)内的细胞。本公开内容的核酸构建体通过人工干预生成。核酸构建体可以是DNA、RNA或其变体。载体可以是DNA质粒、病毒载体、或其他载体。在本发明的某些方面中,载体可以是巨细胞病毒(CMV)、逆转录病毒、腺病毒、腺相关病毒、疱疹病毒、痘病毒、脊髓灰质炎病毒、辛德比斯病毒(sindbis virus)、或任何其他DNA或RNA病毒载体。在本发明的某些方面中,载体可以是假型慢病毒或逆转录病毒载体。在本发明的某些方面中,载体可以是DNA质粒。在本发明的某些方面中,载体可以是DNA质粒,其包含病毒构件和质粒构件以实现核酸分子的递送和表达。用于构建本公开的核酸构建体的方法是公知的。参见例如,Molecular Cloning:A Laboratory Manual,第3版,Sambrook等,2001 Cold Spring Harbor Laboratory Press和Current Protocols in Molecular Biology,Ausubel等编著,John Wiley&Sons,1994。在本发明的某些方面中,载体是DNA质粒,诸如CMV/R质粒,诸如CMV/R或CMV/R 8KB(在本申请中称为CMV/R 8kb)。本申请中提供了CMV/R和CMV/R 8kb的实例。CMV/R也记载于2006年8月22日公告的US 7,094,598B2中。

[0184] 如本申请中所使用的,核酸分子包含编码本发明的蛋白构建体的核酸序列。核酸分子能以重组方式、合成方式或者通过重组和合成程序的组合生成。本公开内容的核酸分子可以具有野生型核酸序列或经密码子修饰的核酸序列,例如以掺入被人翻译系统更好识别的密码子。在本发明的某些方面中,核酸分子可以基因工程化改造为引入或消除编码不同氨基酸的密码子,诸如以引入编码N连接的糖基化位点的密码子。生产本公开内容的核酸分子的方法是本领域中公知的,特别是在知晓核酸序列后。应意识到的是,核酸构建体可以包含一种核酸分子或一种以上核酸分子。还应当意识到的是,核酸分子可以编码一种蛋白或一种以上蛋白。

[0185] 在本发明的某些方面中,本发明的核酸分子编码本发明的蛋白构建体。在本发明的某些方面中,核酸分子编码与表2中列出的蛋白构建体具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性、至少99%同一性的蛋白。在本发明的某些方面中,核酸分子编码某一蛋白,所述蛋白包含于选自下组SEQ ID NO:47-159的序列具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性、至少99%同一性的氨基酸序列。

[0186] 本发明还包含用于生产本发明的蛋白构建体的表达系统。在本发明的某些方面中,本发明的核酸分子与启动子可操作地连接。如本申请中所使用的,可操作地连接意味着

当活化连接的启动子时,可以表达由连接的核酸分子编码的蛋白。可用于实施本发明的启动子是本领域技术人员公知的。本发明的一个实施方式是包含本发明的核酸分子的重组细胞。本发明的一个实施方式是包含本发明的核酸分子的重组病毒。

[0187] 如上文所述,可以使用本领域中目前公知的任何合适的常规重组技术完成本发明的蛋白构建体的重组生产。例如,可以在大肠杆菌中使用编码适宜单体亚基蛋白(如幽门螺杆菌铁蛋白单体亚基)的核酸分子实施编码融合蛋白的核酸分子的生产,并将其融合至编码本申请公开的适宜流感蛋白的核酸分子。然后可以将所述构建体转化至蛋白表达细胞中,培养至适宜规模并诱导以生产融合蛋白。

[0188] 如已经描述的,由于本发明的蛋白构建体包含单体亚基蛋白,因而其能够自组装。根据本发明,将源自此类自组装的超分子称为表达HA的基于单体亚基的纳米颗粒。为了容易讨论,表达HA的基于单体亚基的纳米颗粒将简称为一种或所述纳米颗粒(np)。本发明的纳米颗粒与制备其的单体蛋白纳米颗粒具有相似的结构特征。例如,对于铁蛋白而言,基于铁蛋白的纳米颗粒含有24个亚基且具有432对称。在本发明的纳米颗粒的情况下,亚基是包含与第2组流感病毒HA蛋白连接在一起的单体亚基(例如,铁蛋白、二氧四氢蝶啶合酶等)的蛋白构建体。此类纳米颗粒在其表面上展示出作为HA三聚体的第2流感病毒HA蛋白的至少一部分。在此类构造中,HA三聚体易接近免疫系统,因此可以激发免疫应答。因此,本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒包含本申请所公开的或所述的任何蛋白构建体。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒包含本发明的蛋白构建体,其中所述蛋白构建体包含来自与单体亚基蛋白连接在一起的第2组流感病毒HA蛋白茎区的氨基酸。在本发明的某些方面中,纳米颗粒在其表面上展示出作为HA三聚体的第2组流感病毒HA蛋白。在本发明的某些方面中,第2组流感病毒HA蛋白能够激发针对流感病毒的保护性抗体。

[0189] 本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒包含本发明的蛋白构建体。在本发明的某些方面中,蛋白构建体包含第2组流感HA蛋白,其中第2组流感HA蛋白的头部区域已被包含来自流感HA蛋白头部区域的少于5个连续氨基酸的氨基酸序列替代。在本发明的某些方面中,通过延长A螺旋的长度已将蛋白构建体的HA蛋白改变。在本发明的某些方面中,通过缩短螺旋间区域或使用接头序列替代螺旋间区域已将蛋白构建体的HA蛋白改变。在本发明的某些方面中,还通过突变特异性位点以稳定化三聚体结构已将蛋白构建体的HA蛋白改变。适宜位置的实例包括但不限于对应于SEQ ID NO:4中选自下组L331、N338、K396、L397、L400、S438、N440、E448、T452、N461、G39、T46、N54和T58位置的位置,并且其中蛋白构建体能够形成纳米颗粒。本申请公开了替代HA蛋白头部区域、延伸A螺旋、缩短或替代螺旋间区域和适宜位点特异性突变的方法。在本发明的某些方面中,纳米颗粒包含蛋白构建体,所述蛋白构建体包含来自第2组流感病毒HA蛋白茎区的第一氨基酸序列和来自第2组流感HA蛋白茎区的第二氨基酸序列,第一和第二氨基酸序列通过接头序列共价连接在一起,

[0190] 其中第一氨基酸序列包含来自头部区域序列氨基末端上游氨基酸序列的至少20个连续的氨基酸残基;

[0191] 其中第二氨基酸序列包含来自头部区域序列羧基末端下游氨基酸序列的至少20个连续的氨基酸残基;以及

[0192] 其中第一或第二氨基酸序列与单体亚基结构域的至少一部分连接在一起以使得蛋白构建体能够形成纳米颗粒。

[0193] 在本发明的某些方面中,第一氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白的茎区:流感H3病毒HA蛋白、流感H4病毒HA蛋白、H7流感病毒HA蛋白、H10流感病毒HA蛋白、H14流感病毒HA蛋白和H1 5流感病毒HA蛋白。在本发明的某些方面中,第一氨基酸序列来自表2中列出的第2组病毒的HA蛋白的茎区。在本发明的某些方面中,第一氨基酸序列来自第2组流感HA蛋白的茎区,其具有与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第一氨基酸序列来自包含某一序列的第2组流感HA蛋白的茎区,所述序列选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159。

[0194] 在本发明的某些方面中,第二氨基酸序列来自选自下组的病毒的第2组流感病毒HA蛋白的茎区:流感H3病毒、流感H4病毒、H7流感病毒、H10流感病毒、H14流感病毒和H15流感病毒。在本发明的某些方面中,第二氨基酸序列来自表2中列出的第2组病毒的HA蛋白的茎区。在本发明的某些方面中,第二氨基酸序列来自第2组流感HA蛋白的茎区,其具有与选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159的序列具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第二氨基酸序列来自包含某一序列的第2组流感HA蛋白的茎区,所述序列选自下组SEQ ID NO:4-SEQ ID NO:26和SEQ ID NO:47-SEQ ID NO:159。

[0195] 如上所述,第一氨基酸序列包含来自头部区域序列氨基末端上游的氨基酸序列的至少20个连续的氨基酸残基。根据本发明,术语上游指与头部区域的第一氨基酸残基的氨基末端连接的氨基酸序列实体。优选的上游序列是与头部区域序列紧邻的那些。在本发明的某些方面中,头部区域的氨基末端位于对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)Q60的氨基酸残基。在本发明的某些方面中,第一氨基酸序列包含来自第2流感病毒HA蛋白区域的至少20个连续的氨基酸残基,所述区域对应于如SEQ ID NO:4所示的甲型流感(丹麦/35/2005(H3N2))HA蛋白的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29的序列具有至少85%、至少90%、至少95%或至少97%的同一性。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:27、SEQ ID NO:28和SEQ ID NO:29。

[0196] 在本发明的某些方面中,第一氨基酸序列包含来自HA蛋白的氨基酸区域的至少40个连续的氨基酸残基,所述HA蛋白的氨基酸区域对应于甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)的氨基酸残基1-59。在本发明的某些方面中,第一氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与SEQ ID NO:27或SEQ ID NO:28具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第一氨基酸序列包含来自SEQ ID NO:27或SEQ ID NO:28的至少40个连续的氨基酸残基。

[0197] 在本发明的某些方面中,第一氨基酸序列包含与SEQ ID NO:27具有至少85%、至少90%、至少95%或至少97%同一性的序列。在一个实施方式中,第一氨基酸序列包含SEQ ID NO:27。

[0198] 如上所述,第二氨基酸序列包含来自头部区域序列羧基末端下游的氨基酸序列的

至少20个连续的氨基酸残基。根据本发明,术语下游指与头部区域的羧基末端氨基酸残基连接的氨基酸序列实体。优选的上游序列是与头部区域序列紧邻的那些。在本发明的某些方面中,头部区域的羧基末端位于对应于如SEQ ID NO:4所示的甲型流感(丹麦/35/2005(H3N2))HA蛋白(SEQ ID NO:4)T329的氨基酸位置。因此,在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少20个连续的氨基酸,所述区域对应于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少20个连续的氨基酸,所述区域包含甲型流感(丹麦/35/2005(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在一个实施方式中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33的序列具有至少85%、至少90%、至少95%或至少97%同一性。在一个实施方式中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32和SEQ ID NO:33。

[0199] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少40个连续的氨基酸,所述区域对应于甲型流感(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少40个连续的氨基酸,所述区域包含甲型流感((丹麦/35/2005)(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个连续的氨基酸残基,所述序列与选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32的序列具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少20个连续的氨基酸残基,所述序列选自下组SEQ ID NO:30、SEQ ID NO:31和SEQ ID NO:32。

[0200] 在本发明的某些方面中,第二氨基酸序列包含与SEQ ID NO:37具有至少85%、至少90%、至少95%或至少97%同一性的氨基酸序列。在本发明的某些方面中,第二氨基酸序列包含SEQ ID NO:37。

[0201] 在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸,所述区域对应于甲型流感病毒(丹麦/35/2005)(H3N2)HA蛋白的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自第2组流感HA蛋白某一区域的至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸,所述区域包含甲型流感病毒((丹麦/35/2005)(H3N2))(SEQ ID NO:4)的氨基酸残基330-519。在本发明的某些方面中,第二氨基酸序列包含来自某一序列的至少40个、至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸残基,所述序列与SEQ ID NO:30具有至少85%、至少90%、至少95%或至少97%同一性。在本发明的某些方面中,第二氨基酸序列包含来自SEQ ID NO:30的至少40个、至少60个、至少72个、至少75个、至少100个、至少150个、至少175个或至少190个连续的氨基酸残基。

[0202] 在本发明的某些方面中,纳米颗粒包含蛋白构建体,所述蛋白构建体包含与表2中所示的蛋白构建体具有至少80%、至少约85%、至少约90%、至少约95%、至少约97%或至少约99%同一性的氨基酸序列,其中所述纳米颗粒能够选择性地结合抗流感抗体。在本发

明的某些方面中,纳米颗粒包含蛋白构建体,所述蛋白构建体包含与选自下组SEQ ID NO:47-159的序列具有至少80%、至少约85%、至少约90%、至少约95%、至少约97%或至少约99%同一性的氨基酸序列,其中所述纳米颗粒能够选择性地结合抗流感抗体。在本发明的某些方面中,纳米颗粒包含蛋白构建体,所述蛋白构建体包含选自SEQ ID NO:47-159的氨基酸序列。

[0203] 可以将本发明的纳米颗粒用于激发针对流感病毒的免疫应答。一种类型的免疫应答是B细胞应答,其导致针对激发免疫应答的抗原的抗体的生成。因此,在本发明的某些方面中,纳米颗粒激发与选自下组的病毒甲型流感病毒、乙型流感病毒和丙型流感病毒中的甲型流感HA蛋白茎区结合的抗体。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与选自下组的流感HA蛋白茎区结合的抗体:H1流感病毒HA蛋白、H2流感病毒HA蛋白、流感H3病毒HA蛋白、流感H4病毒HA蛋白、流感H5病毒HA蛋白、流感H6病毒HA蛋白、H7流感病毒HA蛋白、H8流感病毒HA蛋白、H9流感病毒HA蛋白、H10流感病毒HA蛋白、H11流感病毒HA蛋白、H12流感病毒HA蛋白、H13流感病毒HA蛋白、H14流感病毒HA蛋白、H15流感病毒HA蛋白、H16流感病毒HA蛋白、H17流感病毒HA蛋白和H18流感病毒HA蛋白。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒能够激发与表2中列出病毒的流感HA蛋白的茎区结合的抗体。

[0204] 虽然所有抗体能够结合激发导致抗体生成的免疫应答的抗原,但是优选的抗体是那些提供针对流感病毒的广泛异源亚型保护的抗体。因此,本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与来自选自下组的病毒甲型流感病毒、乙型流感病毒和丙型流感病毒的流感HA蛋白茎区结合的保护性抗体。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与选自下组的流感HA蛋白茎区结合的保护性抗体:H1流感病毒HA蛋白、H2流感病毒HA蛋白、流感H3病毒HA蛋白、流感H4病毒HA蛋白、流感H5病毒HA蛋白、流感H6病毒HA蛋白、H7流感病毒HA蛋白、H8流感病毒HA蛋白、H9流感病毒HA蛋白、H10流感病毒HA蛋白、H11流感病毒HA蛋白、H12流感病毒HA蛋白、H13流感病毒HA蛋白、H14流感病毒HA蛋白、H15流感病毒HA蛋白、H16流感病毒HA蛋白、H17流感病毒HA蛋白和H18流感病毒HA蛋白。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与表2中列出病毒的流感HA蛋白茎区结合的抗体。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与某种蛋白结合的抗体,所述蛋白包含与选自下组SEQ ID NO:4-26的序列具有至少80%同一性的氨基酸序列。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与某种蛋白结合的抗体,所述蛋白包含选自下组SEQ ID NO:4-26的氨基酸序列。

[0205] 由本发明的蛋白激发的保护性抗体可以通过影响病毒生命周期中的任何步骤针对病毒感染提供保护作用。例如,保护性抗体可以阻止流感病毒附着细胞、进入细胞、病毒核糖核蛋白释放到胞质中、在感染细胞中形成新病毒颗粒及新病毒颗粒从感染的宿主细胞膜出芽。在本发明的某些方面中,由本发明的蛋白激发的保护性抗体阻止流感病毒进入宿主细胞。在本发明的某些方面中,由本发明的蛋白激发的保护性抗体阻止病毒膜与内体膜的融合。在本发明的某些方面中,由本发明的蛋白激发的保护性抗体阻止核糖核蛋白释放到宿主细胞的胞质中。在本发明的某些方面中,由本发明的蛋白激发的保护性抗体阻止新病毒在受感染宿主细胞中的组装。在本发明的某些方面中,由本发明的蛋白激发的保护性抗体阻止新形成的病毒从受感染的宿主细胞中释放。

[0206] 由于流感病毒茎区是高度保守的,由本发明的纳米颗粒激发的保护性抗体可以具

有广泛的保护作用。也就是说,由本发明的纳米颗粒激发的保护性抗体可以针对超过一种类型、亚型和/或毒株的流感病毒提供保护作用。因此,本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与流感HA蛋白茎区结合的广泛的保护性抗体。一个实施方式是一种纳米颗粒,所述纳米颗粒激发与来自选自下组甲型流感病毒、乙型流感病毒和丙型流感病毒的一种以上类型流感病毒的HA蛋白茎区结合的抗体。一个实施方式是一种纳米颗粒,所述纳米颗粒激发与选自下组的一种以上亚型流感病毒的HA蛋白茎区结合的抗体:H1流感病毒、H2流感病毒、流感H3病毒、流感H4病毒、流感H5病毒、流感H6病毒、H7流感病毒、H8流感病毒、H9流感病毒、H10流感病毒、H11流感病毒、H12流感病毒、H13流感病毒、H14流感病毒、H15流感病毒、H16流感病毒、H17流感病毒和H18流感病毒。一个实施方式是一种纳米颗粒,所述纳米颗粒激发与来自一种以上的流感病毒毒株HA蛋白的茎区结合的抗体。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与一种以上蛋白结合的抗体,所述蛋白包含与选自下组SEQ ID NO:4-SEQ ID NO:26的序列具有至少80%同一性的氨基酸序列。本发明的一个实施方式是一种纳米颗粒,所述纳米颗粒激发与一种以上蛋白结合的抗体,所述蛋白包含选自下组SEQ ID NO:4-26的氨基酸序列。

[0207] 如上所述,HA序列与单体亚基蛋白的一部分连接在一起。如本申请中所使用的,单体亚基蛋白指能够与其他单体亚基蛋白结合以使得单体亚基蛋白自组装成纳米颗粒的蛋白单体。可以将任何单体亚基蛋白用于生产本发明的蛋白构建体,只要蛋白构建体能够形成在其表面上展示HA蛋白的多聚体结构即可。在本发明的某些方面中,单体亚基是铁蛋白。

[0208] 铁蛋白是一种存在于所有动物、细菌和植物中的球状蛋白质,其主要作用为控制经由对矿化核心及从矿化核心中转运水合铁离子和质子形成多核$Fe(III)_2O_3$的速率和位置。铁蛋白的球状形式由单体亚基蛋白(又称为单体铁蛋白亚基)构成,所述单体亚基蛋白是具有约17-20kDa的分子量的多肽。一个此类单体铁蛋白亚基序列的实例以SEQ ID NO:1表示。每个单体铁蛋白亚基具有螺旋束的拓扑学,所述螺旋束包含4个反平行螺旋基序,第5个较短螺旋(c端螺旋)大致处于与4螺旋束的长轴垂直。依照约定,螺旋从N端起分别标记为A、B、C、及D和E。N端序列位于衣壳三次轴相邻,并且延伸至表面,而E螺旋以四次轴包装在一起,C端延伸到颗粒核心中。此包装的结果为在衣壳表面上产生两个孔。预期到这一个或两个孔代表水合铁扩散到衣壳中及扩散出衣壳的点。在生成后,这些单体铁蛋白亚基蛋白自身装配成球状铁蛋白蛋白。因此,铁蛋白的球状形式包含24个单体铁蛋白亚基蛋白,并且具有的衣壳样结构具有432对称。

[0209] 根据本发明,本发明的单体铁蛋白亚基是铁蛋白蛋白的全长、单一多肽,或者能够指导单体铁蛋白亚基自身装配成蛋白的球状形式的其任何部分此。此类蛋白的实例包括但不限于SEQ ID NO:1和SEQ ID NO:2。来自任何已知铁蛋白蛋白的单体铁蛋白亚基的氨基酸序列可以用于生产本发明的蛋白构建体,只要单体铁蛋白亚基能够自身装配成在其表面上展示HA的纳米颗粒。在本发明的某些方面中,单体亚基来自选自下组的铁蛋白蛋白:细菌铁蛋白蛋白、植物铁蛋白蛋白、藻铁蛋白蛋白、昆虫铁蛋白蛋白、真菌铁蛋白蛋白和哺乳动物铁蛋白蛋白。在本发明的某些方面中,铁蛋白蛋白来自幽门螺杆菌。

[0210] 本发明的蛋白构建体不需要包含铁蛋白蛋白单体亚基多肽的全长序列。可以利用单体铁蛋白亚基蛋白的部分或区域,只要该部分包含指导单体铁蛋白亚基自身装配成蛋白球状形式的氨基酸序列。此类区域的一个实例位于幽门螺杆菌铁蛋白蛋白的氨基酸5至167

之间。更特定的区域记载于Zhang,Y.Self-Assembly in the Ferritin Nano-Cage Protein Super Family.2011,Int.J.Mol.Sci.,12,5406-5421中,其全部内容通过引用并入本申请。

[0211] 在本发明的某些方面中,第2组流感病毒HA蛋白与铁蛋白的至少50个、至少100个或至少150个氨基酸连接在一起,其中蛋白构建体能够形成纳米颗粒。在本发明的某些方面中,第2组流感病毒HA蛋白与SEQ ID NO:1或SEQ ID NO:2的至少50个、至少100个或至少150个氨基酸连接在一起,其中蛋白构建体能够形成纳米颗粒。在本发明的某些方面中,第2组流感病毒HA蛋白与某一蛋白连接在一起,所述蛋白包含与铁蛋白的序列具有至少85%、至少90%或至少95%同一性的氨基酸序列,其中蛋白构建体能够形成纳米颗粒。在本发明的某些方面中,第2组流感病毒HA蛋白与某一蛋白连接在一起,所述蛋白包含与SEQ ID NO:1或SEQ ID NO:2具有至少85%、至少90%、至少95%同一性的氨基酸序列,其中蛋白构建体能够形成纳米颗粒。

[0212] 在本发明的某些方面中,单体亚基是二氧四氢蝶啶合酶。在本发明的某些方面中,第2组流感病毒HA蛋白与二氧四氢蝶啶合酶的至少50个、至少100个或至少150个氨基酸连接在一起,其中蛋白构建体能够形成纳米颗粒。因此,在本发明的某些方面中,第2组流感病毒HA与同二氧四氢蝶啶合酶具有至少85%、至少90%、至少95%同一性的蛋白连接在一起,其中蛋白构建体能够形成纳米颗粒。

[0213] 如本申请中所使用的,本发明的纳米颗粒指由本发明的蛋白构建体(融合蛋白)自组装形成的三维颗粒。本发明的纳米颗粒通常为球状,但不排除其他形状,并且通常直径为约20nm至约100nm。本发明的纳米颗粒可以但不必包含其他分子,例如蛋白、脂质、碳水化合物等,而不是形成它们的蛋白质构建体。

[0214] 由于本发明的纳米颗粒能够激发针对流感病毒的免疫应答,因而其可以作为疫苗以保护个体免于流感病毒的感染。因此,本发明的一个实施方式是一种疫苗,所述疫苗包含本发明的纳米颗粒。本发明的疫苗还可以含有其他成分如佐剂、缓冲剂等。虽然可以使用任何佐剂,优选的实施方式可以含有:化学佐剂,诸如磷酸铝、苯扎氯铵、乌苯美司和QS21;遗传佐剂,诸如IL-2基因或其片段、粒细胞巨噬细胞集落刺激因子(GM-CSF)基因或其片段、IL-18基因或其片段、趋化因子(C-C基序)配体21(CCL21)基因或其片段、IL-6基因或其片段、CpG、LPS、TLR激动剂和其他免疫刺激基因;蛋白质佐剂,诸如IL-2或其片段、粒细胞巨噬细胞集落刺激因子(GM-CSF)或其片段、IL-18或其片段、趋化因子(C-C基序)配体21(CCL21)或其片段、IL-6或其片段、CpG、LPS、TLR激动剂和其他免疫刺激细胞因子或其片段;脂质佐剂,诸如阳离子脂质体、N3(阳离子脂质)、单磷酰脂质A(MPL1);其他佐剂,包括霍乱毒素、肠毒素、Fms样酪氨酸激酶-3配体(Flt-3L)、布比卡因、丁哌卡因和左旋咪唑。

[0215] 本发明的一个实施方式是一种纳米颗粒疫苗,所述纳米颗粒疫苗包含一种以上流感HA蛋白。此类疫苗可以包含在单一纳米颗粒上或者作为纳米颗粒的混合物(至少两种纳米颗粒具有独特的流感血凝素蛋白)的不同流感HA蛋白的组合。多价疫苗可以包含必要多的流感HA蛋白,以导致产生针对期望宽度的病毒株提供保护必需的免疫应答。在本发明的某些方面中,疫苗包含来自至少两种不同流感毒株的HA蛋白(二价)。在本发明的某些方面中,疫苗包含来自至少三种不同流感毒株的HA蛋白(三价)。在本发明的某些方面中,疫苗包含来自至少四种不同流感毒株的HA蛋白(四价)。在本发明的某些方面中,疫苗包含来自至

少五种不同流感毒株的HA蛋白(五价)。在本发明的某些方面中,疫苗包含来自至少六种不同流感毒株的HA蛋白(六价)。在不同实施方式中,疫苗包含来自7、8、9或10种不同流感病毒株的HA蛋白。此类组合的实例是纳米颗粒疫苗,所述纳米颗粒疫苗包含第1组甲型流感病毒HA蛋白、第2组甲型流感病毒HA蛋白和乙型流感HA蛋白。在本发明的某些方面中,流感HA蛋白是H1 HA、H3 HA和B HA。多价疫苗的另一个实例是纳米颗粒疫苗,所述纳米颗粒疫苗包含来自四种不同流感病毒的HA蛋白。在本发明的某些方面中,多价疫苗包含与表2中列出的一种或多种HA蛋白具有至少80%同一性、至少85%同一性、至少90%同一性、至少95%同一性、至少97%同一性或至少99%同一性的一种或多种HA蛋白。在本发明的某些方面中,多价疫苗包含表2中列出的一种或多种HA蛋白。

[0216] 本发明的一个实施方式是一种针对流感病毒对个体接种疫苗的方法,所述方法包括向个体施用纳米颗粒,以使得在个体中产生针对流感病毒的免疫应答,其中所述纳米颗粒包含与第2组流感病毒HA蛋白连接在一起的单体亚基蛋白,以及其中所述纳米颗粒在其表面上展示出流感HA。在本发明的某些方面中,纳米颗粒是单价纳米颗粒。在本发明的某些方面中,纳米颗粒是多价纳米颗粒。本发明的另一实施方式是一种针对流感病毒感染对个体接种疫苗的方法,所述方法包括:

[0217] a)获得包含单体亚基的纳米颗粒,其中所述单体亚基与流感血凝素蛋白连接在一起,以及其中所述纳米颗粒在其表面上展示第2组流感病毒HA蛋白;以及

[0218] b)向个体施用所述纳米颗粒,以使得产生针对流感病毒的免疫应答。

[0219] 本发明的一个实施方式是一种针对流感病毒对个体接种疫苗的方法,所述方法包括向个体施用实施方式的疫苗,以使得在个体中产生针对流感病毒的免疫应答,其中所述疫苗包含至少一种纳米颗粒,所述纳米颗粒包含与流感HA蛋白结合在一起的单体亚基,以及其中所述纳米颗粒在其表面上展示流感HA。在本发明的某些方面中,疫苗是单价疫苗。在本发明的某些方面中,疫苗是多价疫苗。本发明的一个实施方式是一种针对流感病毒感染对个体接种疫苗的方法,所述方法包括:

[0220] a)获得包含至少一种纳米颗粒的疫苗,所述纳米颗粒含有本发明的蛋白构建体,其中所述蛋白构建体包含与第2组流感病毒HA蛋白结合在一起的单体亚基蛋白,和其中所述纳米颗粒在其表面上展示流感HA;以及

[0221] b)向个体施用所述疫苗,以使得产生针对流感病毒的免疫应答。

[0222] 在本发明的某些方面中,纳米颗粒是单价纳米颗粒。在本发明的某些方面中,纳米颗粒是多价纳米颗粒。

[0223] 在本发明的某些方面中,纳米颗粒具有八面体对称性。在本发明的某些方面中,流感HA蛋白能够激发针对流感病毒的抗体。在本发明的某些方面中,流感HA蛋白能够激发针对流感病毒的广泛抗体。在优选的实施方式中,所激发的抗体是保护性抗体。在一个优选的实施方式中,所激发的抗体具有广泛的异源亚基保护作用。

[0224] 使用引发/加强方案,本发明的疫苗可以用于对个体接种疫苗。此类方案记载于美国专利公开号20110177122中,其全部内容通过引用并入本申请。在此类方案中,可以对个体施用第一疫苗组合物(引发),然后在一段时间后,可以对个体施用第二疫苗组合物(加强)。加强性组合物的施用一般是施用引发性组合物后几周或几个月,优选约2-3周或4周,或8周,或16周,或20周,或24周,或28周,或32周。在本发明的某些方面中,加强性组合物配

制为在施用引发性组合物后约1周,或2周,或3周,或4周,或5周,或6周,或7周,或8周,或9周,或16周,或20周,或24周,或28周,或32周施用。

[0225] 第一和第二疫苗组合物可以但不需要是相同组合物。因此,在本发明的某些方面中,施用疫苗的步骤包括施用第一疫苗组合物,然后在后来的时间时,施用第二疫苗组合物。在本发明的某些方面中,第一疫苗组合物包含本发明的纳米颗粒。在本发明的某些方面中,第一疫苗组合物包含本发明的纳米颗粒。

[0226] 在本发明的某些方面中,待接种疫苗的个体已暴露于流感病毒。如本申请中所使用的,术语暴露的(exposed)、暴露(exposure)等指对象已经与已知感染流感病毒的动物个体接触。可以使用本领域技术人员公知的技术施用本发明的疫苗。用于配制和施用的技术可以参见例如"Remington's Pharmaceutical Sciences",第18版,1990,Mack Publishing Co.,Easton,PA。可以通过多种手段施用疫苗,所述手段包括但不限于传统注射器、无针注射装置、或微粒轰击基因枪。合适的施用路径包括但不限于胃肠外投递,诸如肌肉内、皮内、皮下、髓内注射,及胸内、直接室内、静脉内、腹膜内、鼻内、或眼内注射等等。对于注射,本发明的一个实施方式的化合物可以配制为水溶液,优选生理学相容缓冲液,诸如汉克斯(Hanks)氏溶液、林格(Ringer)氏溶液、或生理盐水缓冲液。

[0227] 在本发明的某些方面中,本发明的疫苗或纳米颗粒可以用于保护个体免于异源流感病毒的感染。也就是说,使用来自一种流感病毒株的HA蛋白生成的疫苗能够保护个体免于不同流感株的感染。例如,使用来自甲型流感/丹麦/35/2005(H3N2)的HA蛋白制备的疫苗能够用于保护个体免于被表2中列出的流感病毒感染。

[0228] 在本发明的某些方面中,本发明的疫苗或纳米颗粒可以用于保护个体免于抗原趋异的流感病毒的感染。抗原趋异的指流感病毒株随时间突变,由此改变对免疫系统展示的氨基酸的趋势。随时间的所述突变又称为抗原性漂移。因此,例如,使用来自甲型流感/丹麦/35/2005(H3N2)流感病毒株的HA蛋白生成的疫苗能够保护个体免于较早的、抗原趋异的丹麦流感毒株,及进化的(或趋异的)未来流感株的感染。

[0229] 由于本发明的纳米颗粒展示与完整HA抗原性相似的第2组流感病毒HA蛋白,因而可以将其用于检测针对流感病毒的抗体(抗流感抗体)的测定中。

[0230] 因此,本发明的一个实施方式是一种使用本发明的纳米颗粒用于检测抗流感病毒抗体的方法。通常可以通过以下方式实现本发明的检测方法:

[0231] a.将待检测抗流感抗体存在情况的样品的至少一部分与本发明的纳米颗粒接触;以及

[0232] b.纳米颗粒/抗体复合物的存在情况;

[0233] 其中存在纳米颗粒/抗体复合物表明所述样品含有抗流感抗体。

[0234] 在本发明的某些方面中,从待检测抗流感病毒抗体存在情况的个体中获得或收集样品。个体可以或可以不疑似具有抗流感抗体或已暴露于流感病毒。样品是从个体中获得的任何标本,所述个体能够用于检测抗流感病毒抗体的存在情况。优选的样品是能够用于检测抗流感抗体存在情况的体液。可以用于实施本方法的体液的实例包括但不限于血液、血浆、血清、泪液和唾液。本领域技术人员能够容易地鉴定适于实施所公开方法的样品。

[0235] 血液或来源于血液的流体如血浆、血清等特别适合作为样品。可以使用本领域公知的方法从个体收集和制备此类样品。测定前可以将样品冷藏或冷冻。

[0236] 可以将任何本发明的纳米颗粒用于实施所公开的方法,只要纳米颗粒与抗流感病毒抗体结合即可。已在本申请中详细描述了有用的纳米颗粒及其制备方法。在一个优选的实施方式中,纳米颗粒包含蛋白构建体,所述蛋白构建体包含来自单体亚基蛋白的至少25个、至少50个、至少75个、至少100个或至少150个连续的氨基酸,所述单体亚基蛋白与来自第2组流感病毒HA蛋白的至少一个表位结合(或融合)在一起,以使得所述纳米颗粒在其表面上包含第2组流感病毒HA蛋白表位的三聚体,以及其中所述蛋白构建体能够自组装成纳米颗粒。

[0237] 如本申请中所使用的,术语接触指将待检测抗流感抗体存在情况的样品引入本发明的纳米颗粒,例如通过将样品与本发明的纳米颗粒组合或混合,以使得所述纳米颗粒能够与样品中的抗体(如果存在的话)物理接触。当在样品中存在抗流感病毒抗体时,然后形成抗体/纳米颗粒复合物。此类复合物形成指抗流感病毒抗体选择性地与纳米颗粒中蛋白构建体的HA部分结合以形成能够被检测的稳定复合物的能力。在适于形成复合物的条件下完成样品中的抗流感病毒抗体与纳米颗粒的结合。此类条件(例如,适宜浓度、缓冲液、温度、反应时间)以及优化此类条件的方法是本领域技术人员公知的。可以使用本领域公知的多种标准方法对结合进行测量,包括但不限于凝集测定、沉淀测定、酶免疫测定(例如,ELISA)、免疫沉淀测定、免疫印迹测定和其他免疫测定,例如在Sambrook等,Molecular Cloning:A Laboratory Manual(Cold Spring Harbor Labs Press,1989)和Harlow等,Antibodies,a Laboratory Manual(Cold Spring Harbor Labs Press,1988)中所描述的,其全部内容均通过引用并入本申请。这些参考文献还提供了复合物形成条件的实例。

[0238] 如本申请中所使用的,短语选择性结合HA、选择的结合至HA等指抗体优先结合HA蛋白,而不是与HA无关的蛋白或样品或测定中的非蛋白组分结合的能力。选择性结合HA的抗体是与HA结合但不显著地与可能存在于样品或测定中的其他分子或成分结合的抗体。将例如抗-HA抗体与非-HA分子以足够大以干扰测定检测和/或确定样品中的抗流感抗体或HA蛋白水平的亲和性或亲合力结合认为是显著结合。可以存在于样品或测定中的其他分子和化合物的实例包括但不限于非-HA蛋白,如白蛋白、脂质和碳水化合物。

[0239] 在本发明的某些方面中,可以在溶液中形成抗流感病毒抗体/纳米颗粒复合物(在本申请中也称为抗体/纳米颗粒复合物)。在本发明的某些方面中,可以形成其中纳米颗粒固化在(例如,包被于)基底上的抗体/纳米颗粒复合物。固化技术是本领域技术人员公知的。适宜的基底材料包括但不限于塑料、玻璃、凝胶、赛璐珞(celluloid)、织物、纸和颗粒材料。基底的实例包括但不限于乳胶、聚苯乙烯、尼龙、硝酸纤维素、琼脂糖、棉花、PVDF(聚偏二氟乙烯)和磁性树脂。基底材料适宜的形状包括但不限于孔(例如,微孔板)、酶标板、浸渍片(dipstick)、试纸、小珠、侧向流动装置、膜、滤器、试管、皿、赛璐珞型基质、磁性颗粒和其他颗粒。特别优选的基底包括例如ELISA板、浸渍条、放射性免疫测定板、琼脂糖小珠、塑料小珠、乳胶小珠、棉线、塑料片、免疫印迹膜、免疫印迹纸和流通膜。在本发明的某些方面中,基底(如颗粒)可以包含检测标记物。对于基底材料实例的描述,参见例如Kemeny,D.M.(1991)A Practical Guide to ELISA,Pergamon Press,Elmsford,NY pp 33-44和Price,C.and Newman,D.编著Principles and Practice of Immunoassay,第2版,(1997)Stockton Press,NY,NY,其全部内容均通过引用并入本申请。

[0240] 根据本发明,一旦形成,就能够检测抗流感病毒抗体/纳米颗粒复合物。检测可以

是定性的、定量的或半定量的。如本申请中所使用的,短语检测复合物形成、检测复合物等指鉴定与纳米颗粒复合的抗流感病毒抗体的存在情况。如果形成了复合物,则可以(但不是必需的)对复合物的量进行定量。可以使用本领域公知的多种标准方法(参见例如,Sambrook等,如上所述)对假定的抗流感病毒抗体与纳米颗粒之间的复合物形成或选择性结合情况进行测量(即,检测、确定),本申请公开了其实例。可以采用多种方法对复合物进行检测,包括但不限于使用下述测定中的一种或多种:血凝素抑制测定、径向扩散测定、酶联免疫测定、竞争性酶联免疫测定、放射性免疫测定、荧光免疫测定、化学发光测定、侧向流动测定、流通测定、基于颗粒的测定(例如,使用颗粒,例如但不限于磁性颗粒或塑料聚合物,如乳胶或聚苯乙烯小珠)、免疫沉淀测定、BioCoreJ测定(例如,使用胶体金)、免疫斑点测定(例如,CMG Immunodot System,Fribourg,Switzerland)、免疫印迹测定(例如,western印迹)、磷光测定、流通测定、色谱测定、基于PAGE的测定、表面等离子体共振测定、分光光度测定和电子传感测定。此类测定是本领域技术人员熟知的。

[0241] 可以根据其使用方法,将测定用于给出定性或定量结果。一些测定,如凝集、颗粒分离和沉淀测定,能够目测观察(例如,通过肉眼或机器,如光密度计或分光光度计),而不需要检测标记物。

[0242] 在其他测定中,将检测标记物与纳米颗粒或与选择性与纳米颗粒结合的试剂缀合(即,附着)有助于检测复合物形成情况。可以将检测标记物在不干扰纳米颗粒与抗流感病毒抗体结合能力的位点与纳米颗粒或纳米颗粒结合试剂缀合。缀合的方法是本领域技术人员公知的。检测标记物的实例包括但不限于放射性标记、荧光标记、化学发光标记、发色标记、酶标记、磷光标记、电子标记、金属溶胶标记、有色小珠、物理标签或配体。配体指与另一分子选择性结合的分子。优选的检测标记物包括但不限于荧光素、放射性同位素、磷酸酶(例如,碱性磷酸酶)、生物素、亲和素、过氧化物酶(例如,辣根过氧化物酶)、β-半乳糖苷酶以及生物素相关化合物或亲和素相关化合物(例如,抗生物素蛋白链菌素或ImmunoPure7 NeutrAvidin)。

[0243] 在本发明的某些方面中,可以通过将样品与同检测标记缀合的特异性化合物(如抗体)接触检测抗体/纳米颗粒复合物,所述特异性化合物与抗流感抗体、铁蛋白或抗体/纳米颗粒复合物结合。检测标记物可以以不阻断化合物结合被检测复合物的能力的方式与特定化合物缀合。优选的检测标记物包括但不限于荧光素、放射性同位素、磷酸酶(例如,碱性磷酸酶)、生物素、亲和素、过氧化物酶(例如,辣根过氧化物酶)、β-半乳糖苷酶以及生物素相关化合物或亲和素相关化合物(例如,抗生物素蛋白链菌素或ImmunoPure7NeutrAvidin)。

[0244] 在另一个实施方式中,通过使复合物与指示剂分子接触来检测复合物。此类指示分子包括能够与抗流感病毒抗体/纳米颗粒复合物、抗流感病毒抗体或纳米颗粒结合的分子。这样,指示分子可以包括例如与抗流感病毒抗体结合的试剂,如识别免疫球蛋白的抗体。作为抗体的优选指示分子包括例如与其中产生抗流感病毒抗体的个体物种的抗体具有反应性的抗体。指示分子本身能够附接至本发明的可检测标记物。例如,可以将抗体与生物素、辣根过氧化物酶、碱性磷酸酶或荧光素缀合。

[0245] 本发明还可以包括能够检测指示分子存在情况的二级分子或其他结合分子的一个或多个层和/或类型。例如,未标记的(即,未与可检测标记物缀合的)选择性结合指示分

子的第二抗体可以与选择性结合第二抗体标记物(即,与可检测标记物缀合的)的第三抗体结合。本领域技术人员能够容易地选择适宜的第二抗体、第三抗体和其他第二或第三分子。本领域技术人员还可以基于第二分子的特征选择优选的第三分子。可以将相同策略应用于随后的层。

[0246] 优选地,将指示分子与检测标记物缀合。如有需要,加入显色剂,并且将基底置于检测装置以进行分析。在一些方案中,在一个或全部两个复合物形成步骤之后加入洗涤步骤,以除去过量的试剂。如果使用此类步骤,其涉及本领域技术人员公知的条件,以除去过量试剂但保留复合物。

[0247] 由于本发明的测定能够检测样品(包括血液样品)中的抗流感病毒抗体,因而可以将此类测定用于鉴定具有抗流感抗体的个体。因此,本发明的一个实施方式是一种鉴定具有抗流感病毒抗体的个体的方法,所述方法包括:

[0248] a.将来自待检测抗流感抗体的个体的样品与本发明的纳米颗粒接触;以及

[0249] b.分析所接触的样品中纳米颗粒/抗体复合物的存在情况,

[0250] 其中存在纳米颗粒/抗体复合物表明个体具有抗流感抗体。

[0251] 可以使用任何所公开的测定形式进行所公开的方法。有用的测定形式的实例包括但不限于径向扩散测定、酶联免疫测定、竞争性酶联免疫测定、放射性免疫测定、荧光免疫测定、化学发光测定、侧向流动测定、流通测定、基于颗粒的测定(例如,使用颗粒,例如但不限于磁性颗粒或塑料聚合物,如乳胶或聚苯乙烯小珠)、免疫沉淀测定、BioCoreJ测定(例如,使用胶体金)、免疫斑点测定(例如,CMG Immunodot System,Fribourg,Switzerland)、免疫印迹测定(例如,western印迹)、磷光测定、流通测定、色谱测定、基于PAGE的测定、表面等离子体共振测定、分光光度测定和电子传感测定。

[0252] 如果在样品中未检测到抗流感抗体,则这样的结果表明个体不具有抗流感病毒抗体。待检测的个体可以或可以不是疑似具有流感病毒抗体。所公开的方法还可以用于检测是否个体已暴露于一种或多种特定类型、组、亚组或毒株的流感病毒。为了进行此类测定,从在过去某个时间(例如,约1年以上、约2年以上、约3年以上、约4年以上、约5年以上等)已检测针对一种或多种特定类型、组、亚组或毒株的流感病毒的抗体检测为阴性(即,缺乏抗体)的个体中获得样品。然后使用本发明基于纳米颗粒的测定检测针对一种或多种类型、组、亚组或毒株的流感病毒的抗流感病毒抗体的存在情况。如果测定表明存在此类抗体,则将个体鉴定为在检测鉴定其针对流感抗体为阴性之后的某个时间其已暴露于一种或多种类型、组、亚组或毒株的流感病毒。因此,本发明的一个实施方式是一种鉴定已暴露于流感病毒的个体的方法,所述方法包括:

[0253] a.将来自待检测抗流感抗体个体样品的至少一部分与本发明的纳米颗粒接触;以及

[0254] b.分析所接触样品中抗体/纳米颗粒复合物的存在情况或水平,其中抗体/纳米颗粒复合物的存在或水平表明最近抗流感抗体的存在或水平;

[0255] c.将最近抗流感抗体的水平与过去抗流感抗体的水平进行比较;

[0256] 其中与过去抗流感抗体水平相比最近抗流感抗体水平增加表明在确定过去抗流感抗体水平之后个体暴露于流感病毒。

[0257] 本发明的方法还用于确定个体对疫苗的应答。因此,一个实施方式是一种用于测

量个体对流感疫苗应答的方法,所述方法包括:

[0258] a.向个体施用流感病毒疫苗;

[0259] b.将来自个体的样品的至少一部分与本发明的纳米颗粒接触;

[0260] c.分析所接触样品中抗体/纳米颗粒复合物的存在情况或水平,其中抗体/纳米颗粒复合物的存在情况或水平表明最近抗流感抗体的存在情况或水平,

[0261] 其中与个体中免疫接种前抗体的水平相比样品中抗体水平的增加表明疫苗在个体中诱导了免疫应答。

[0262] 向个体施用的流感疫苗可以(但不是必需的)包含本发明的疫苗,只要包含HA蛋白的纳米颗粒能够与由所施用的疫苗诱导的抗流感抗体结合即可。施用流感疫苗的方法是本领域技术人员公知的。

[0263] 可以使用任何所公开的测定形式对从个体中获得的样品进行分析。在本发明的某些方面中,使用选择下组的测定形式对样品进行分析:径向扩散测定、酶联免疫测定、竞争性酶联免疫测定、放射性免疫测定、荧光免疫测定、化学发光测定、侧向流动测定、流通测定、基于颗粒的测定(例如,使用颗粒,例如但不限于磁性颗粒或塑料聚合物,如乳胶或聚苯乙烯小珠)、免疫沉淀测定、BioCoreJ测定(例如,使用胶体金)、免疫斑点测定(例如,CMG Immunodot System,Fribourg,Switzerland)、免疫印迹测定(例如,western印迹)、磷光测定、流通测定、色谱测定、基于PAGE的测定、表面等离子体共振测定、分光光度测定和电子传感测定。

[0264] 在本发明的某些方面中,所述方法包括在施用疫苗之前确定个体中存在的抗流感抗体水平的步骤。然而,如果可获得此类信息,还可以从先前的医疗记录中确定个体中存在的抗流感抗体的水平。

[0265] 尽管不是必需进行所公开的方法,但是在施用疫苗的步骤与确定个体中抗流感抗体水平的步骤之间等待一段时间可能是优选的。在本发明的某些方面中,在施用疫苗之后至少1天、至少2天、至少3天、至少4天、至少5天、至少6天、至少1周、至少2周、至少3周、至少4周、至少2个月、至少3个月或至少6个月确定个体中存在的抗流感抗体的水平。

[0266] 本发明还包括适于检测抗流感抗体的试剂盒。适宜的检测方法包括利用本发明的纳米颗粒的本申请公开的技术。试剂盒还可以包含检测标记物(如与纳米颗粒选择性结合的抗体)或其他指示分子。试剂盒还可以含有相关成分,例如但不限于缓冲液、标记、容器、插入物、小管、小瓶、注射器等。.

[0267] 实施例

[0268] 本实施例表征了使用本申请公开的参数和方法设计的5种第2组HA纳米颗粒H10变体的性质和活性。所有这些变体均基于人A/中国江西/IPB13/2013(H10N8)毒株。将编码H10变体的核酸分子引入Expi293细胞,并且在适于表达所编码的变体蛋白的条件下培养所述细胞。使用凝集素亲和层析后接体积排阻色谱(SEC)从细胞培养物上清中纯化表达的纳米颗粒。纯化纳米颗粒的色谱图如图32A-32E所示。

[0269] 使用负染电子显微镜分析纯化的纳米颗粒,其表明形成了单个纳米颗粒,其具有的HA茎以周期性排列向外突出。每个变体的代表性电镜图如图33所示。

[0270] 采用ELISA法通过测量与HA抗体FI6、CT149和CR8020的亲和性评价H10ssF变体的抗原性。该评价的结果如图34A-34D中所示。

[0271] 然后在小鼠中检测纳米颗粒针对各种流感毒株激发免疫应答的能力。使用2ug变体纳米颗粒中的一种和SAS佐剂免疫接种BALB/c小鼠(n＝10)。以定期间隔再重复免疫接种2次。最后一次免疫2周后,收集血清并(通过ELISA)检测其识别H3N2和H7N9的HA蛋白的能力。如图35A&35B中所示的结果表明血清与H3N2和H7N9蛋白具有交叉反应性。

[0272] 然后使用致死剂量的H3N2(A/菲律宾/1982)或H7N9(A/中国上海/2/2013-样)攻击免疫的小鼠,监测其体重减轻和存活情况。如图36A-36D和图37A-37G中所示的结果表明使用变体纳米颗粒的免疫接触针对这两次再攻击均产生了保护作用,未出现显著的体重减轻。这些结果表明H10ssF免疫原能够提供针对H3N2和H7N9毒株的异源亚基保护。

[0273] 已发现使用VH1-18v-基因的人广泛中和茎单克隆抗体(mAb)(16.a.26)能够有效地中和第1组和第2组流感病毒。因此,对包括H3N2、H7N9和H10N8亚型在内的几种HA-SS-np变体进行了评价,评价其激活表达种系回复形式mAb 16.a.26的B细胞的能力。在该测定中,B细胞的激活由Ca++通量显示。如图40所示,该评价的结果表明变体纳米颗粒H3ssF_256、H7ssF_26和H10ssF_04均导致高水平的激活,其与使用IgM阳性对照观察到的结果类似。如图41中所示,所有这三种设计均具有相同的A C螺旋-末端延伸(ELMEQ),表明这种特殊的基序对激发针对流感HA蛋白的16.a.26bNAb应答是有用的。

[0001] 序列表

[0002] <110> 美国卫生与公众服务部

[0003] Boyington, Jeffrey C.

[0004] Graham, Barney S.

[0005] Mascola, John R.

[0006] Yassine, Hadi M.

[0007] Corbett, Kizzmekia S.

[0008] Moin, Syed M.

[0009] Wang, Lingshu

[0010] Kanekiyo, Masaru

[0011] <120> 稳定化的第2组流感血凝素茎区三聚体及其用途

[0012] <130> 6137NIAID-64-PCT

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[1284] His Ser Val Ser Thr Ala Glu Gln Thr Lys Leu Tyr Gly Ser Gly Asn

[1285] 195 200 205

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[1316] Leu Ala Asp Ser Glu Met Asp Lys Leu Tyr Glu Arg Val Lys Arg Gln
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[1321] 485 490 495
[1322] Asp His Ser Lys Tyr Arg Glu Glu Ala Met Gln Asn Arg Ile Gln Ile
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[1415] Gln Lys Leu Pro Gly Asn Asp Asn Ser Thr Ala Thr Leu Cys Leu Gly

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[1420] 50 55

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[1425] <400> 28

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[1427] 1 5 10 15

[1428] Val Pro Asn Gly Thr Ile Val Lys Thr Ile Thr Asn Asp Gln Ile Glu

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[1430] Val Thr Asn Ala Thr Glu Leu Val

[1431] 35 40

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[1438] 1 5 10 15

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[1445] <400> 30

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[1447] 1 5 10 15

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[1450] Met Val Asp Gly Trp Tyr Gly Phe Arg His Gln Asn Ser Glu Gly Ile

[1451] 35 40 45

[1452] Gly Gln Ala Ala Asp Leu Lys Ser Thr Gln Ala Ala Ile Asn Gln Ile

[1453] 50 55 60

[1454] Asn Gly Lys Leu Asn Arg Leu Ile Gly Lys Thr Asn Glu Lys Phe His

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[1456] Gln Ile Glu Lys Glu Phe Ser Glu Val Glu Gly Arg Ile Gln Asp Leu

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[1458] Glu Lys Tyr Val Glu Asp Thr Lys Val Asp Leu Trp Ser Tyr Asn Ala

[1459] 100 105 110

[1460] Glu Leu Leu Val Ala Leu Glu Asn Gln His Thr Ile Asp Leu Thr Asp

[1461] 115 120 125

[1462] Ser Glu Met Asn Lys Leu Phe Glu Arg Thr Lys Lys Gln Leu Arg Glu

[1463] 130 135 140

[1464] Asn Ala Glu Asp Met Gly Asn Gly Cys Phe Lys Ile Tyr His Lys Cys

[1465] 145 150 155 160

[1466] Asp Asn Ala Cys Ile Gly Ser Ile Arg Asn Gly Thr Tyr Asp His Asp

[1467] 165 170 175

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[1469] 180 185 190

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[1474] <400> 31

[1475] Leu Lys Leu Ala Thr Gly Met Arg Asn Val Pro Glu Lys Gln Thr Arg

[1476] 1 5 10 15

[1477] Gly Ile Phe Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly

[1478] 20 25 30

[1479] Met Val Asp Gly Trp Tyr Gly Phe Arg His Gln Asn Ser Glu Gly Ile

[1480] 35 40 45

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[1483] Asn Gly

[1484] 65

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[1489] <400> 32

[1490] Leu Lys Leu Ala Thr Gly Met Arg Asn Val Pro Glu Lys Gln Thr Arg

[1491] 1 5 10 15

[1492] Gly Ile Phe Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly

[1493] 20 25 30

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[1495] 35 40 45

[1496] Gly Gln

[1497] 50

[1498] <210> 33

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[1500] <212> PRT

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[1504] 1 5 10 15

[1505] Gly Ile Phe Gly Ala Ile Ala Gly Phe

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[1515] 1 5

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[1542] 1 5
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[1551] 1 5 10 15
[1552] Val Glu Gly Arg Ile Gln Asp Leu Glu Lys Tyr Val Glu Asp Thr Lys
[1553] 20 25 30
[1554] Val Asp Leu Trp
[1555] 35
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[1570] <223> 合成的
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[1574] Asn Arg Leu Ile Ala Leu Met Ala Gln Gly Gly Pro Asp Ser Tyr Asn
[1575] 20 25 30
[1576] Ala Glu Leu Leu Val Ala Leu Glu Asn Gln His Thr Ile Asp Leu Thr
[1577] 35 40 45
[1578] Asp
[1579] <210> 41
[1580] <211> 68
[1581] <212> PRT
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[1584] <223> 合成的
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[1587] 1 5 10 15
[1588] Ala Ile Asn Gln Ile Asn Gly Lys Leu Asn Arg Leu Ile Ala Leu Met
[1589] 20 25 30
[1590] Ala Gln Gly Gly Pro Asp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu
[1591] 35 40 45
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[1593] 50 55 60
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[1595] 65
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[1606] 20 25 30

[1607] Ala Gln Gly Gly Pro Asp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu

[1608] 35 40 45

[1609] Glu Asn Gln His Thr Ile Asp Leu Thr Asp Ser Glu Met Asn Lys Leu

[1610] 50 55 60

[1611] Phe Glu Arg Thr Lys Lys Gln Leu Arg Glu Asn Ala Glu Asp Met Gly

[1612] 65 70 75 80

[1613] Asn Gly Cys Phe Lys Ile Tyr His

[1614] 85

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[1616] <211> 163

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[1626] Met Val Asp Gly Trp Tyr Gly Phe Arg His Gln Asn Ser Glu Gly Ile

[1627] 35 40 45

[1628] Gly Gln Ala Ala Asp Leu Lys Ser Thr Gln Ala Ala Ile Asn Gln Ile

[1629] 50 55 60

[1630] Asn Gly Lys Leu Asn Arg Leu Ile Ala Leu Met Ala Gln Gly Gly Pro

[1631] 65 70 75 80

[1632] Asp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu Glu Asn Gln His Thr

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[1634] Ile Asp Leu Thr Asp Ser Glu Met Asn Lys Leu Phe Glu Arg Thr Lys

[1635] 100 105 110

[1636] Lys Gln Leu Arg Glu Asn Ala Glu Asp Met Gly Asn Gly Cys Phe Lys

[1637] 115 120 125

[1638] Ile Tyr His Lys Cys Asp Asn Ala Cys Ile Gly Ser Ile Arg Asn Gly
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[1640] Thr Tyr Asp His Asp Val Tyr Arg Asp Glu Ala Leu Asn Asn Arg Phe
[1641] 145 150 155 160
[1642] Gln Ile Lys
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[1651] 1 5 10 15
[1652] Asp Leu Thr Asp Ser Glu Met Asn Lys Leu Phe Glu Arg Thr Lys Lys
[1653] 20 25 30
[1654] Gln Leu Arg Glu Asn Ala Glu Asp Met Gly
[1655] 35 40
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[1666] 20 25 30
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[1681] 20 25 30

[1682] Gln Leu Arg Glu Asn Ala Glu Asp Met Gly Asn Gly Cys Phe Lys Ile

[1683] 35 40 45

[1684] Tyr His Lys Cys Asp Asn Ala Cys Ile Gly Ser Ile Arg Asn Gly Thr

[1685] 50 55 60

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[1701] 35 40 45

[1702] Gln Ile Glu Val Thr Asn Ala Thr Glu Leu Val Phe Pro Gly Cys Gly

[1703] 50 55 60

[1704] Val Leu Lys Leu Ala Thr Gly Met Arg Asn Val Pro Glu Lys Gln Thr

[1705] 65 70 75 80

[1706] Arg Gly Ile Phe Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu

[1707] 85 90 95

[1708] Gly Met Val Asp Gly Trp Tyr Gly Phe Arg His Gln Asn Ser Glu Gly

[1709] 100 105 110

[1710] Ile Gly Gln Ala Ala Asp Leu Lys Ser Thr Gln Ala Ala Ile Asn Gln

[1711] 115 120 125

[1712] Ile Asn Gly Met Val Asn Arg Val Ile Ala Leu Met Ala Gln Gly Gly

[1713] 130 135 140

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[1715] 145 150 155 160

[1716] Val Ile Asp Leu Thr Asp Ser Glu Met Arg Lys Leu Phe Glu Arg Thr
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[1719] 180 185 190
[1720] Lys Ile Tyr His Lys Cys Asp Asn Ala Cys Ile Gly Ser Ile Arg Asn
[1721] 195 200 205
[1722] Gly Thr Tyr Asp His Asp Val Tyr Arg Asp Glu Ala Leu Asn Asn Arg
[1723] 210 215 220
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[1791] Lys Phe Glu Gly Leu Thr Gln Ile Phe Gln Lys Ala Tyr Glu His Glu
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[1793] Gln His Ile Ser Glu Ser Ile Asn Asn Ile Val Asp His Ala Ile Lys

[1794] 325 330 335
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[2996] Glu Leu Ile Gly Asn Glu Asn His Gly Leu Tyr Leu Ala Asp Gln Tyr
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[7517] Tyr Arg Glu Glu Ala Met Gln Asn Arg Ile Gln Ile Asp Ala Gly Pro

[7518] 210 215 220

[7519] Pro Pro Gly Gly Met Gln Ile Tyr Glu Gly Lys Leu Thr Ala Glu Gly

[7520] 225 230 235 240

[7521] Leu Arg Phe Gly Ile Val Ala Ser Arg Phe Asn His Ala Leu Val Asp

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[7523] Arg Leu Val Glu Gly Ala Ile Asp Cys Ile Val Arg His Gly Gly Arg

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[7685] 210 215 220

[7686] Phe Gln Ile Lys Ser Gly Gly Asp Ile Ile Lys Leu Leu Asn Glu Gln

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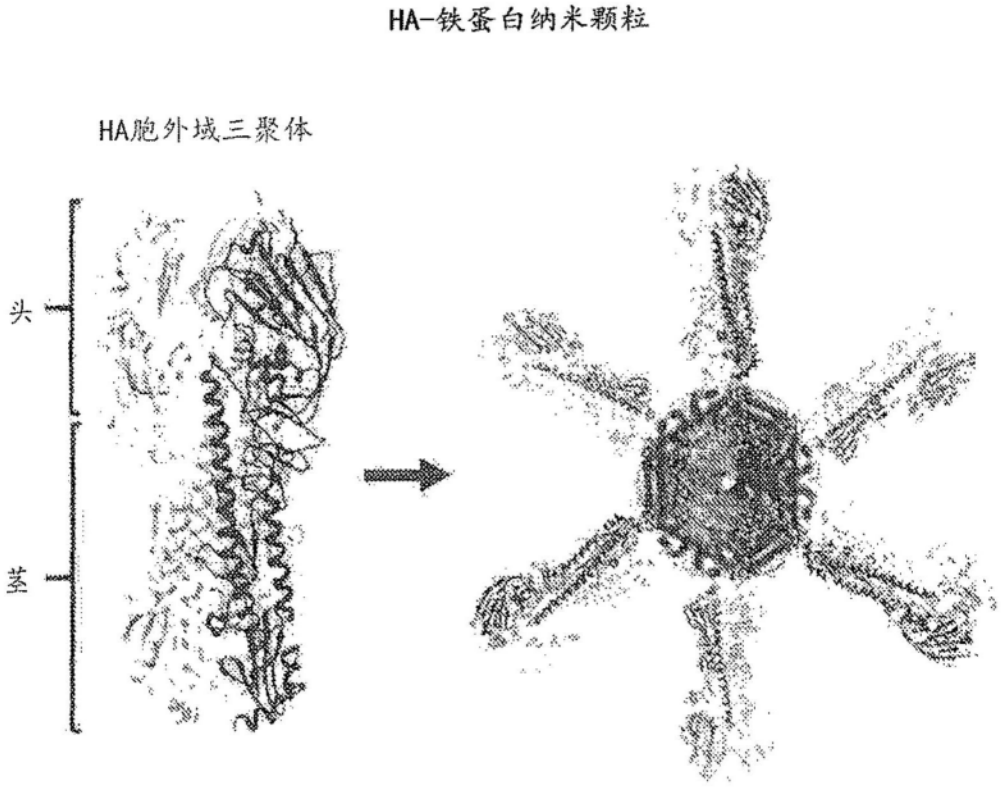


图1A

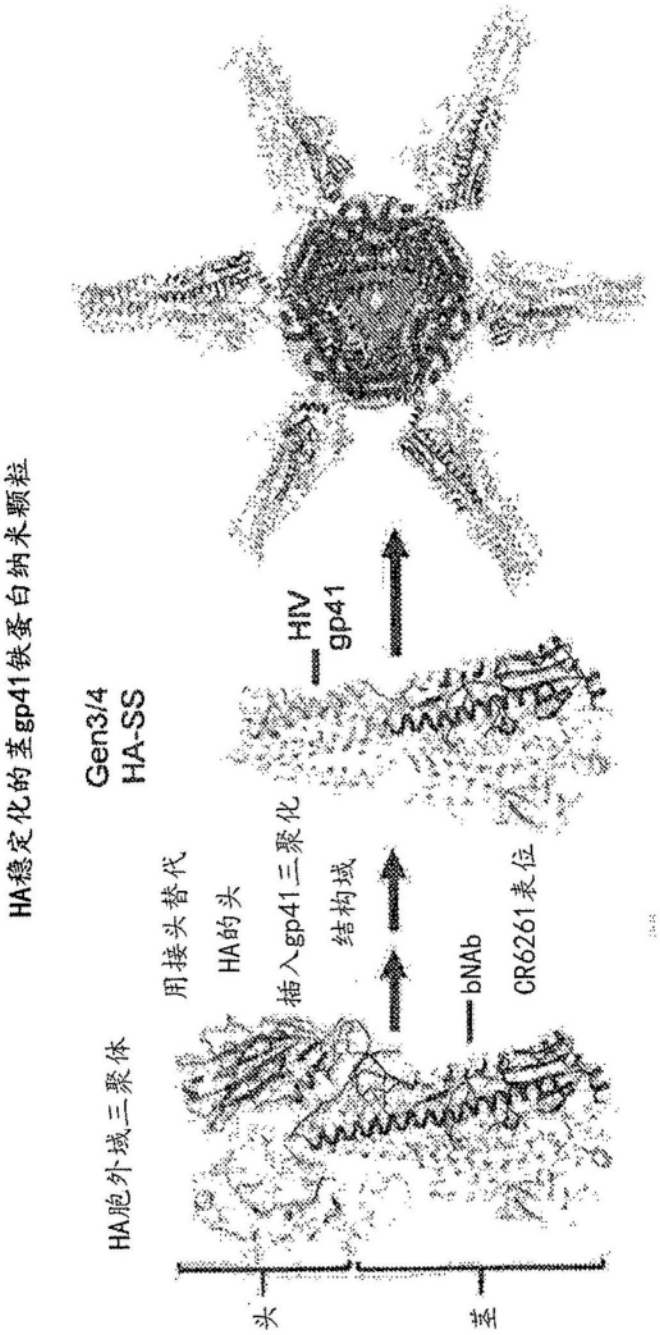

HA稳定化的茎gp41铁蛋白纳米颗粒
Gen3/4
HA-SS
HIV
gp41
用接头替代
HA的头
插入gp41三聚化
结构域
bNAb
CR6261表位
HA胞外域三聚体
头
茎

图1B

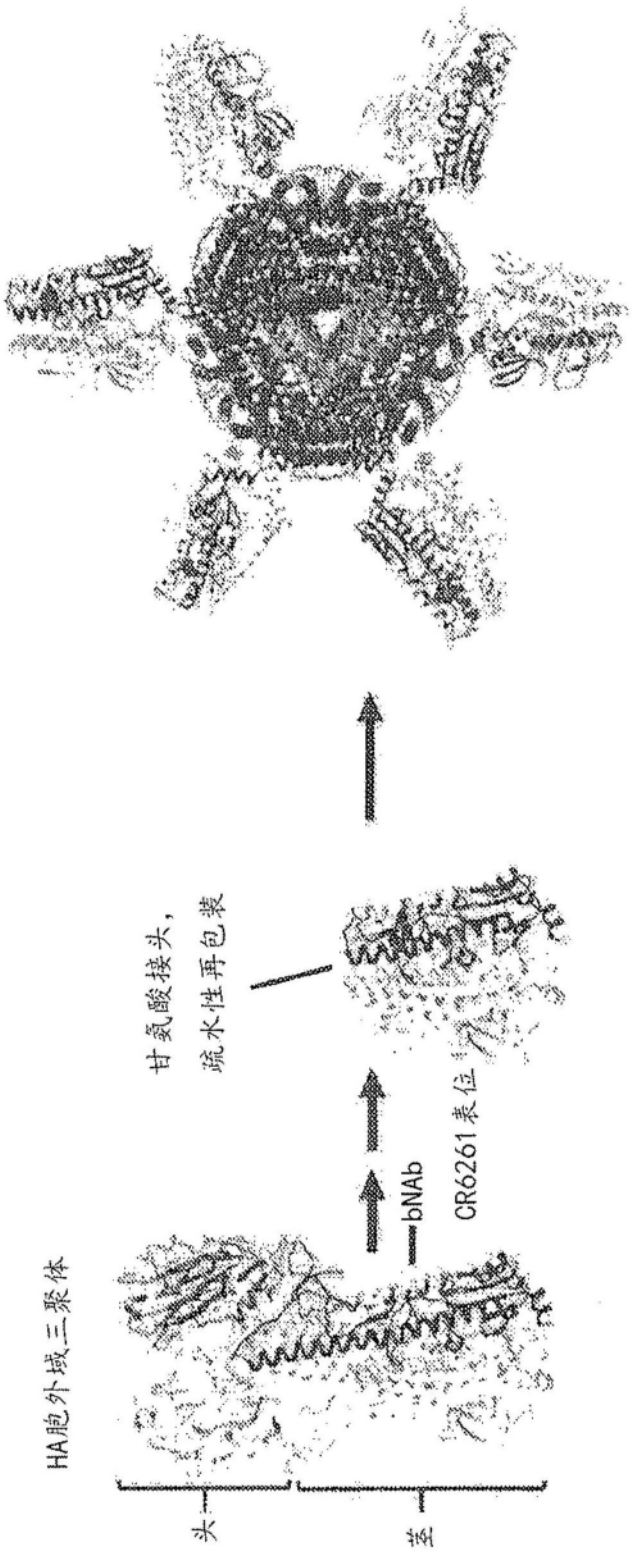


图1C

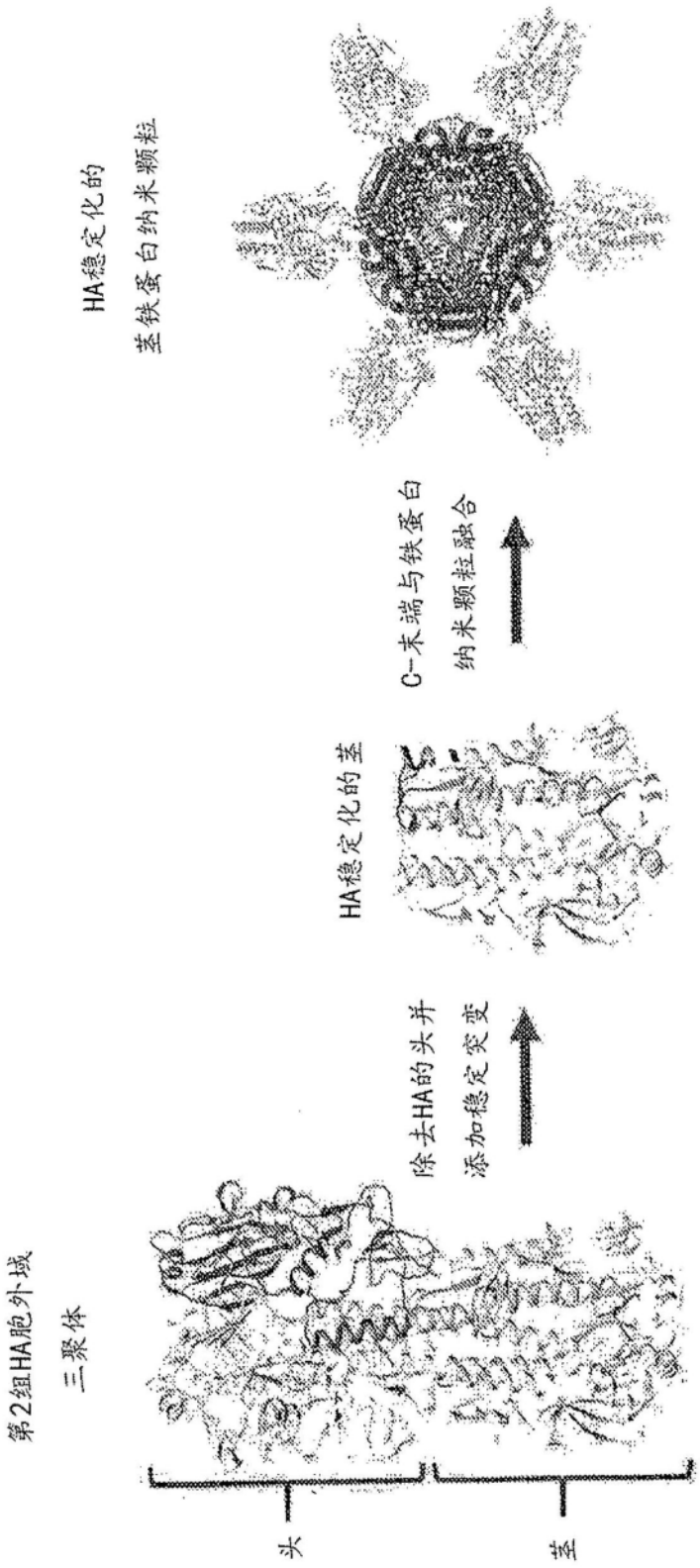

第2组HA胞外域
三聚体
头
茎
除去HA的头并
添加稳定突变
HA稳定化的茎
C-末端与铁蛋白
纳米颗粒融合
HA稳定化的
茎铁蛋白纳米颗粒

图2

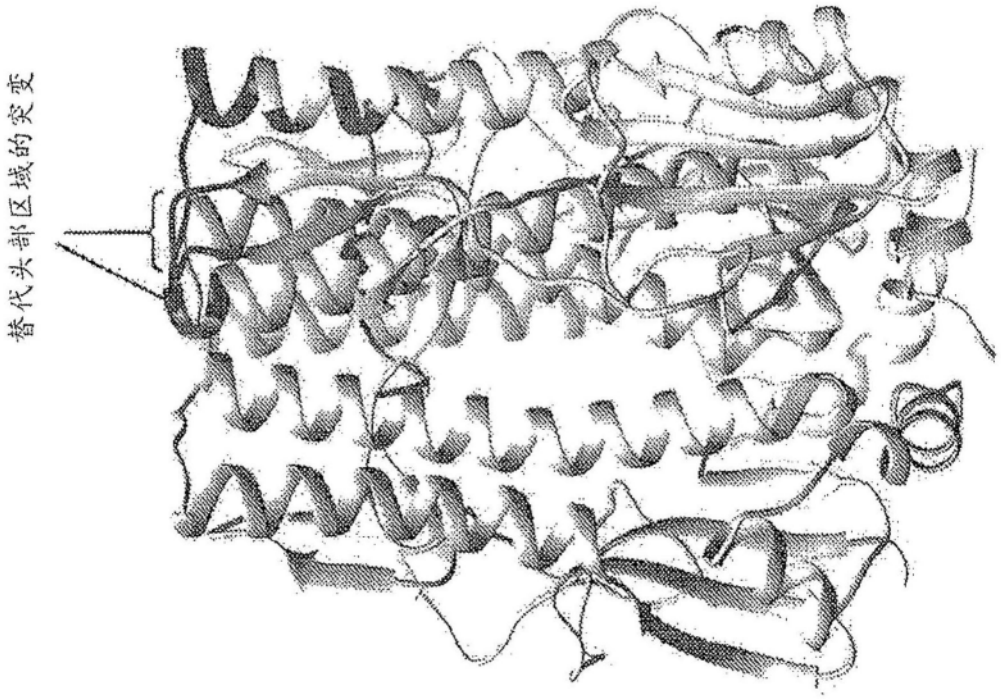


图3A

>H3-SS-np_231
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图3B

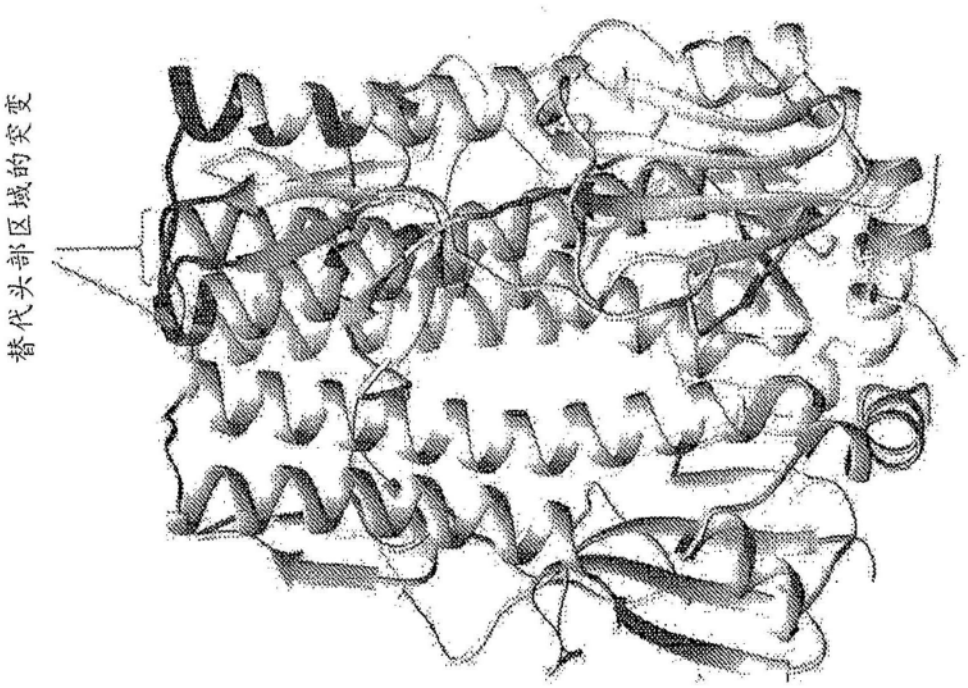


图4A



图4B

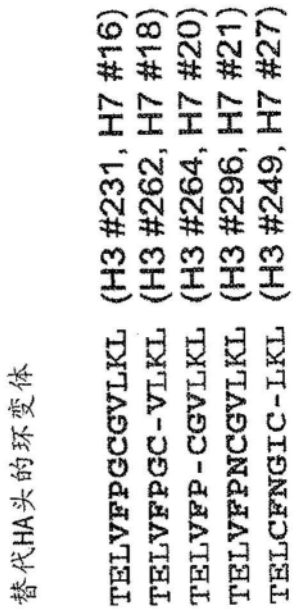

替代HA头的环变体
TELVFPGCGVLKL (H3 #231, H7 #16)
TELVFPGC-VLKL (H3 #262, H7 #18)
TELVFP-CGVLKL (H3 #264, H7 #20)
TELVFPNCGVLKL (H3 #296, H7 #21)
TELCFNGIC-LKL (H3 #249, H7 #27)

图4C

>H3-SS-np_231
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVK
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YRDEALNNRFQIKSVELKLGYKDWILWISFAISCFLLCVVLLG
YTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPVQLTSIS
APEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHATF
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IAKSRKSGS

图4D

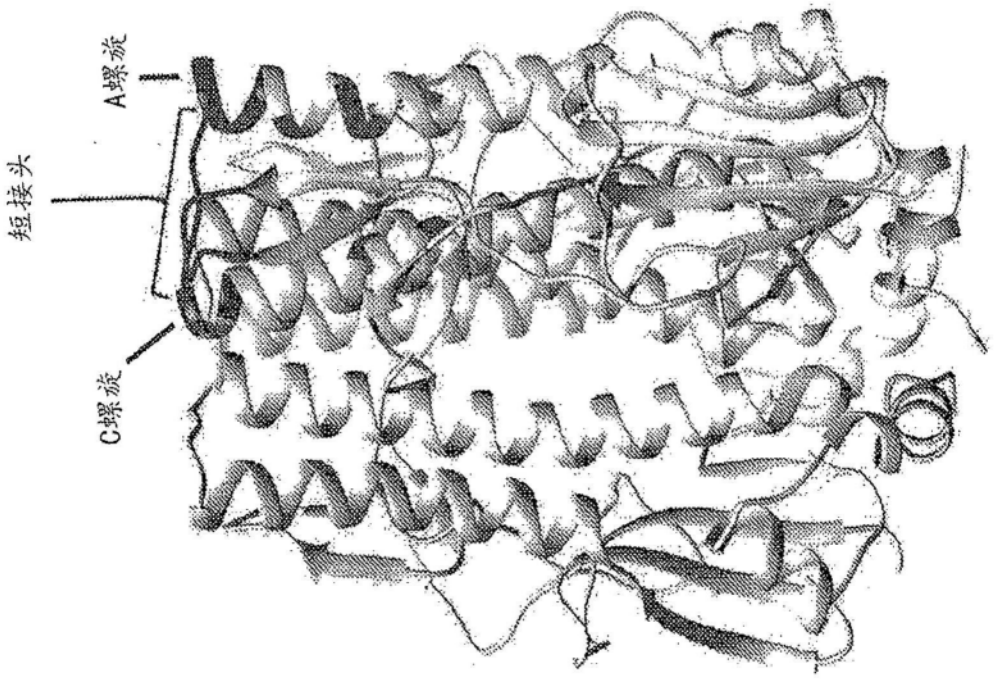


图5A

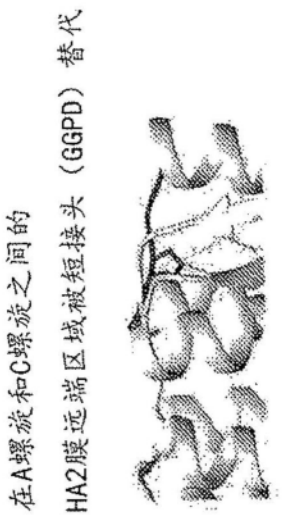


图5B

>H3-SS-np_231
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图5C

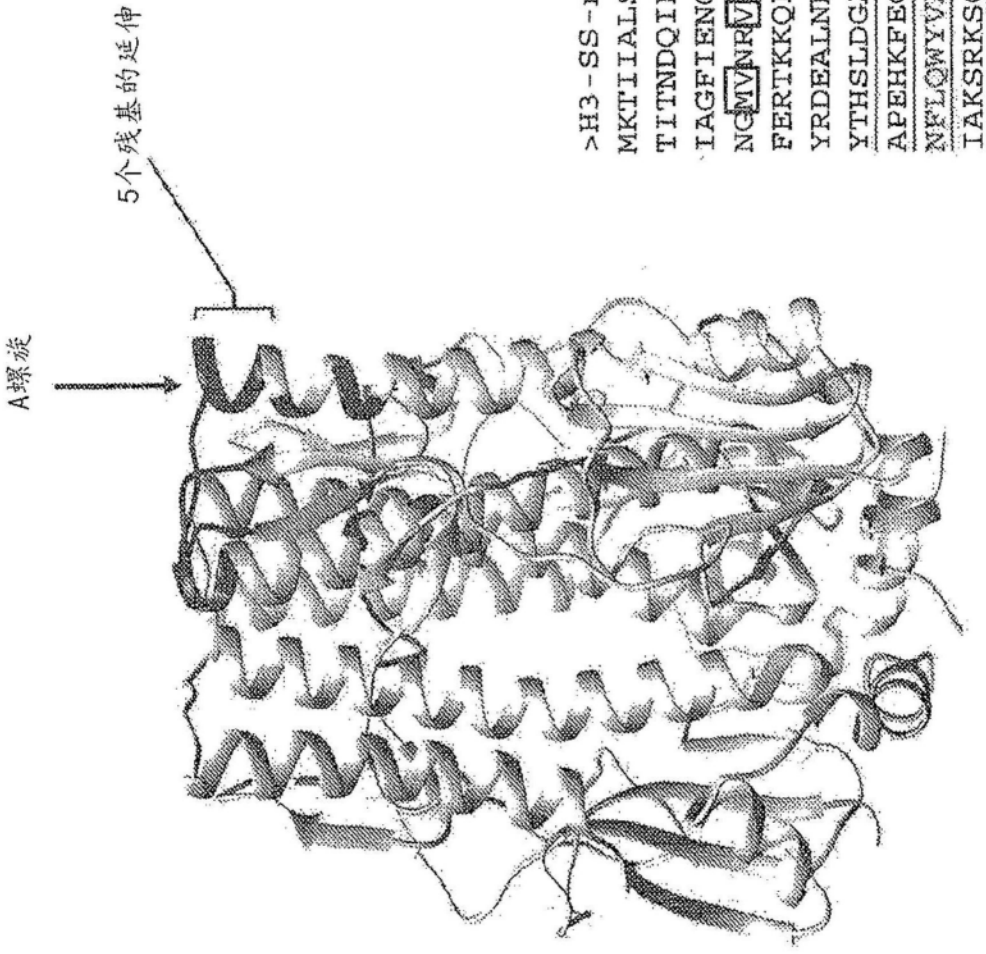


图 6A

3. HA2 A螺旋5个残基的延伸（ALMAQ）



图 6B

>H3-SS-np_231
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YTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPVQLTSIS
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IAKSRKSGS

图 6C

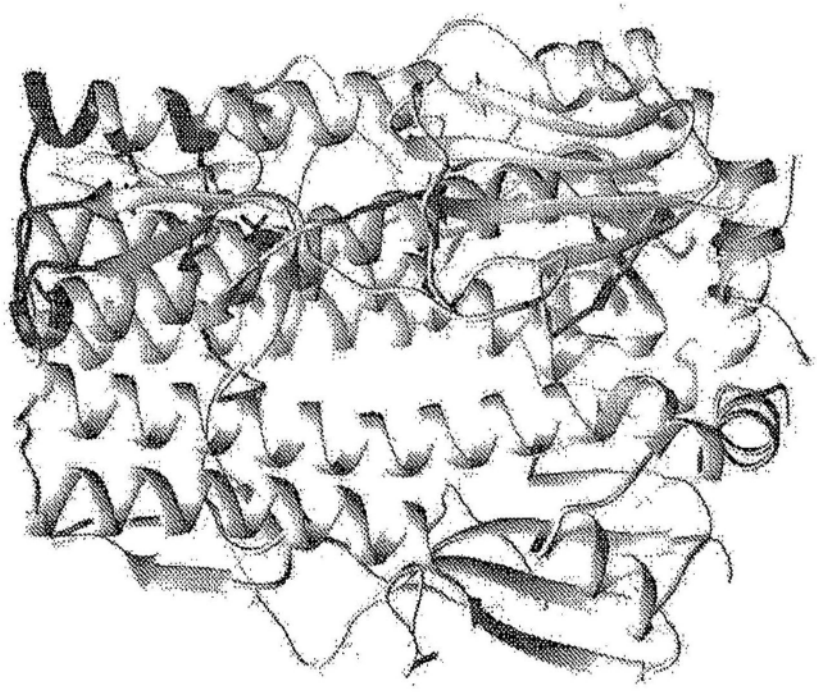


图7A

>H3-SS-np_231
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图7B

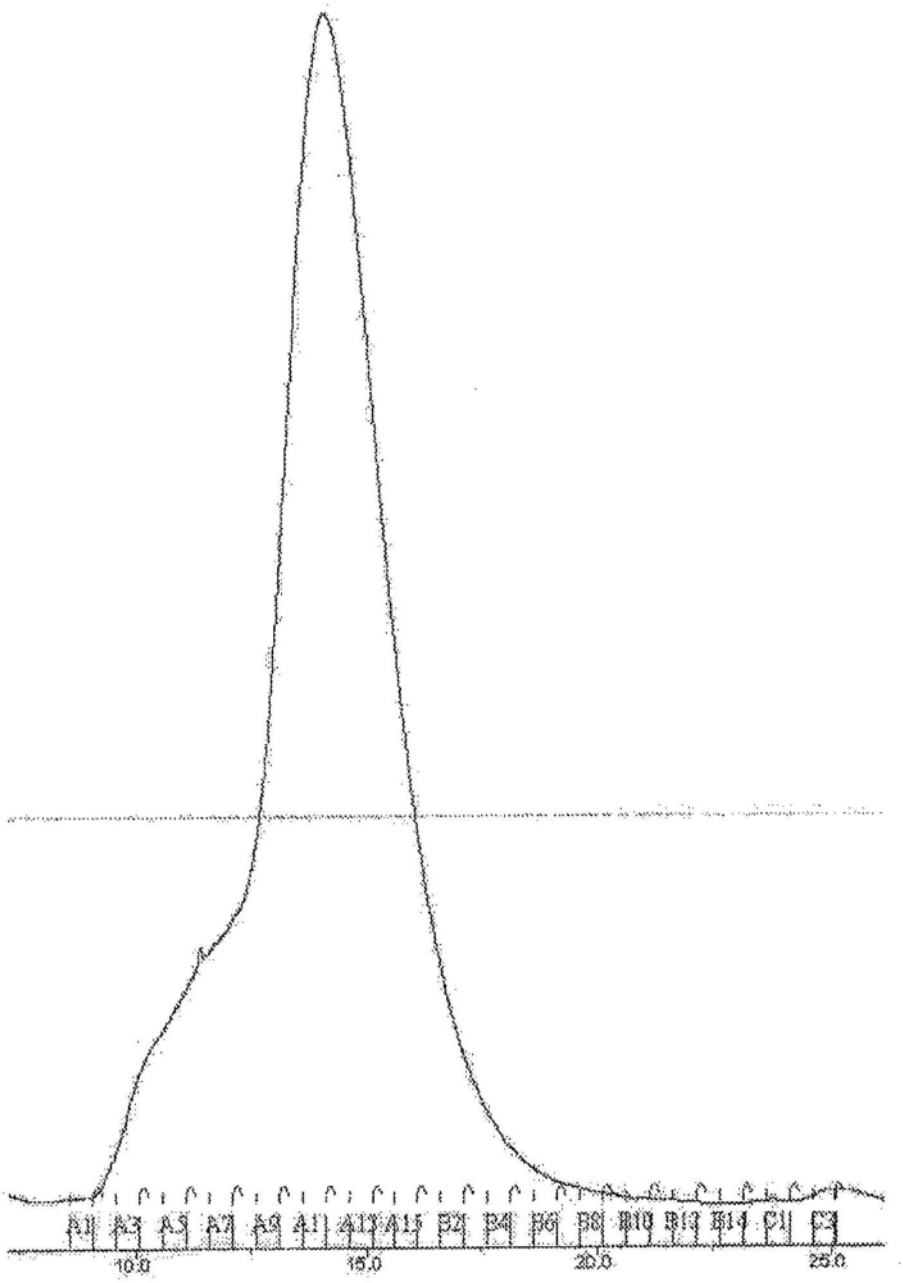


图8A

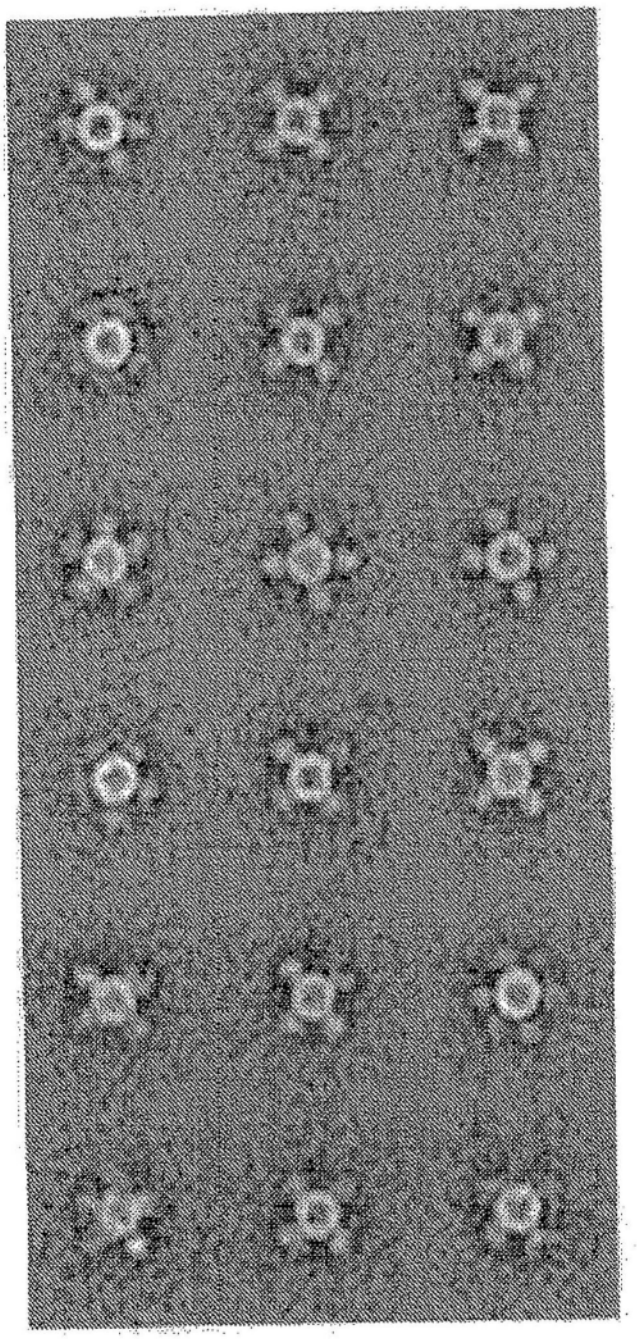


图8B

	EC50 (ug/ml)	
mAb	H1-SS-np	H3-SS-np_231
D25	---	---
CR8020	15.56	0.02
CT149	0.03	0.03
F16	0.14	0.08

图9A

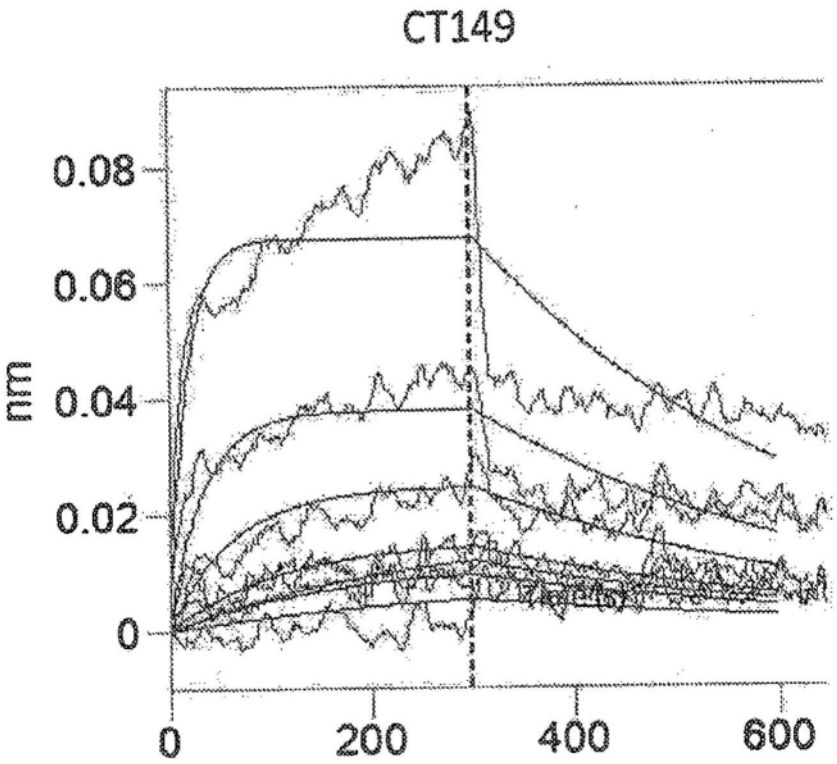


图9B

Fab	K_D (M)	K_D误差	k_{on}(1/Ms)
CT149	2.69E-09	2.66E-10	1.06E+06
CR9114	6.41E-11	1.29E-09	2.00E+05

图9C

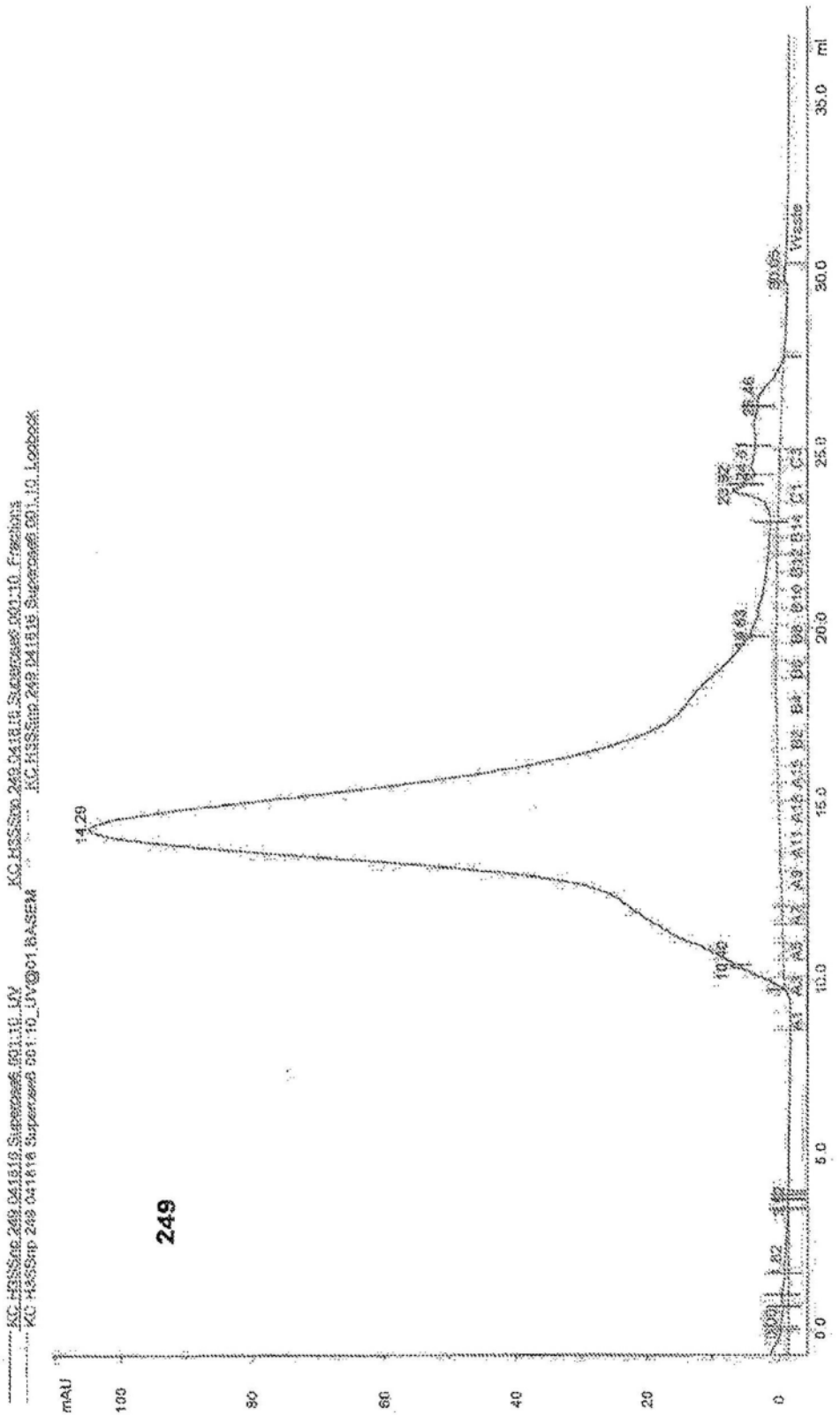


图10A

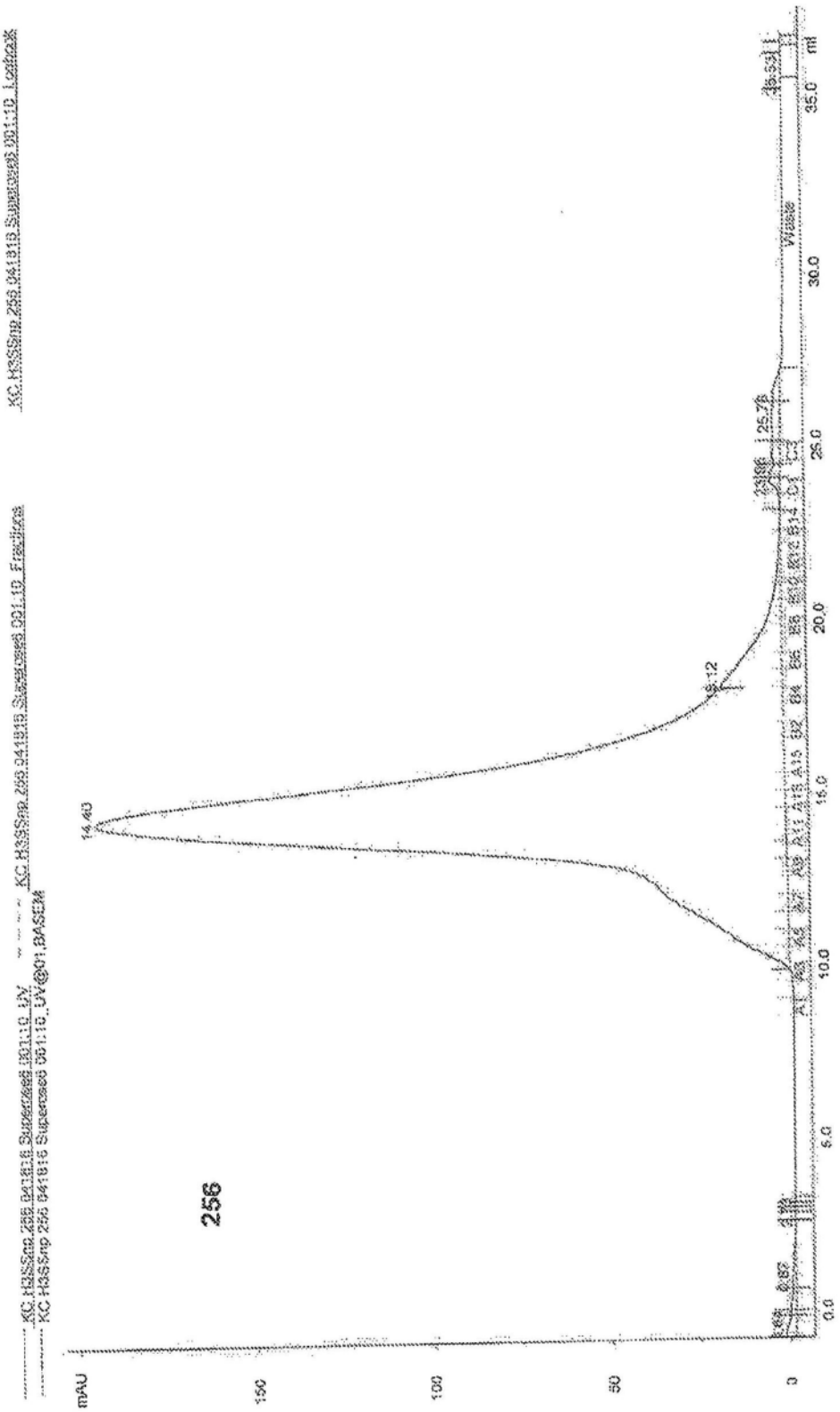

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14.40
15.12
mAU
150
100
50
0
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5.0
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15.0
20.0
25.0
30.0
35.0
min
Waste

图10B

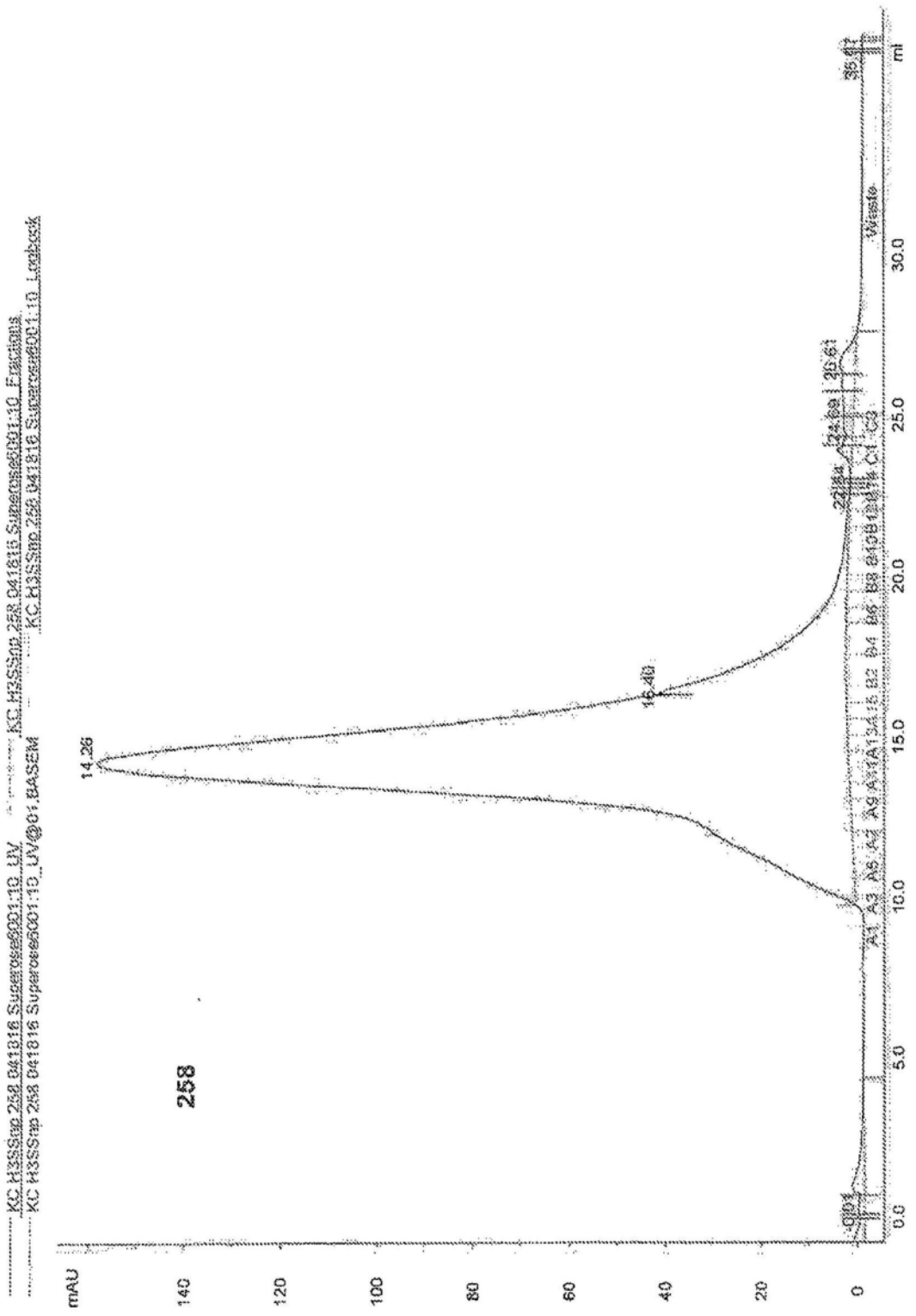

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KC H3SSnp 258 041816 Superose6001.10_UV@01.BASEM
KC H3SSnp 258 041816 Superose6001.10 Fractions
KC H3SSnp 258 041816 Superose6001.10 Logbook
258
14.26
16.40
mAU
ml
Waste

图10C

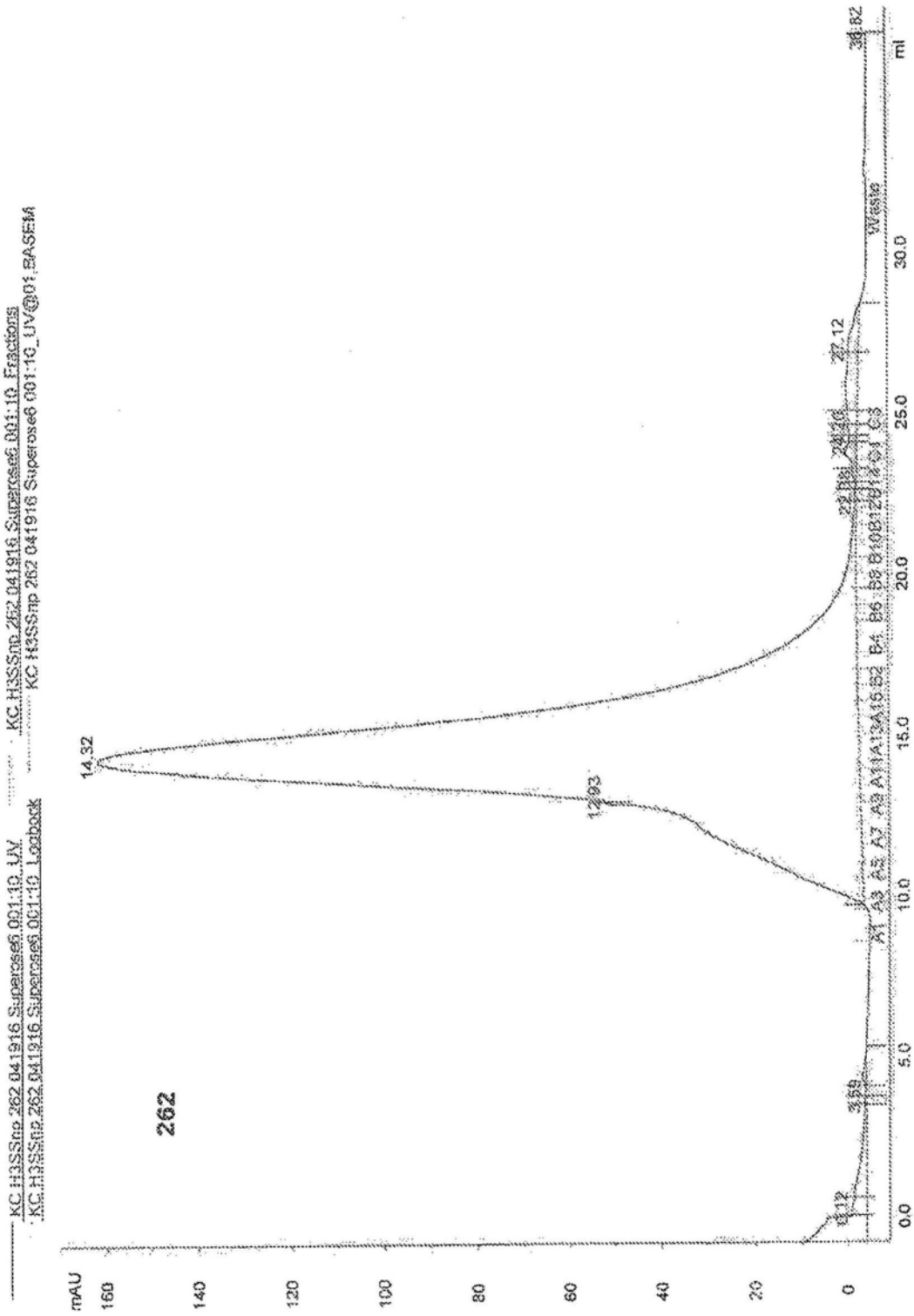

KC H3SSnp 262 041916 Superose6 001:1G_UV
KC H3SSnp 262 041916 Superose6 001:1G Loopback
KC H3SSnp 262 041916 Superose6 001:1G Fractions
KC H3SSnp 262 041916 Superose6 001:1G_UV@01.BASEM
262
14.32
12.93
mAU
160
140
120
100
80
60
40
20
0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
ml

图10D

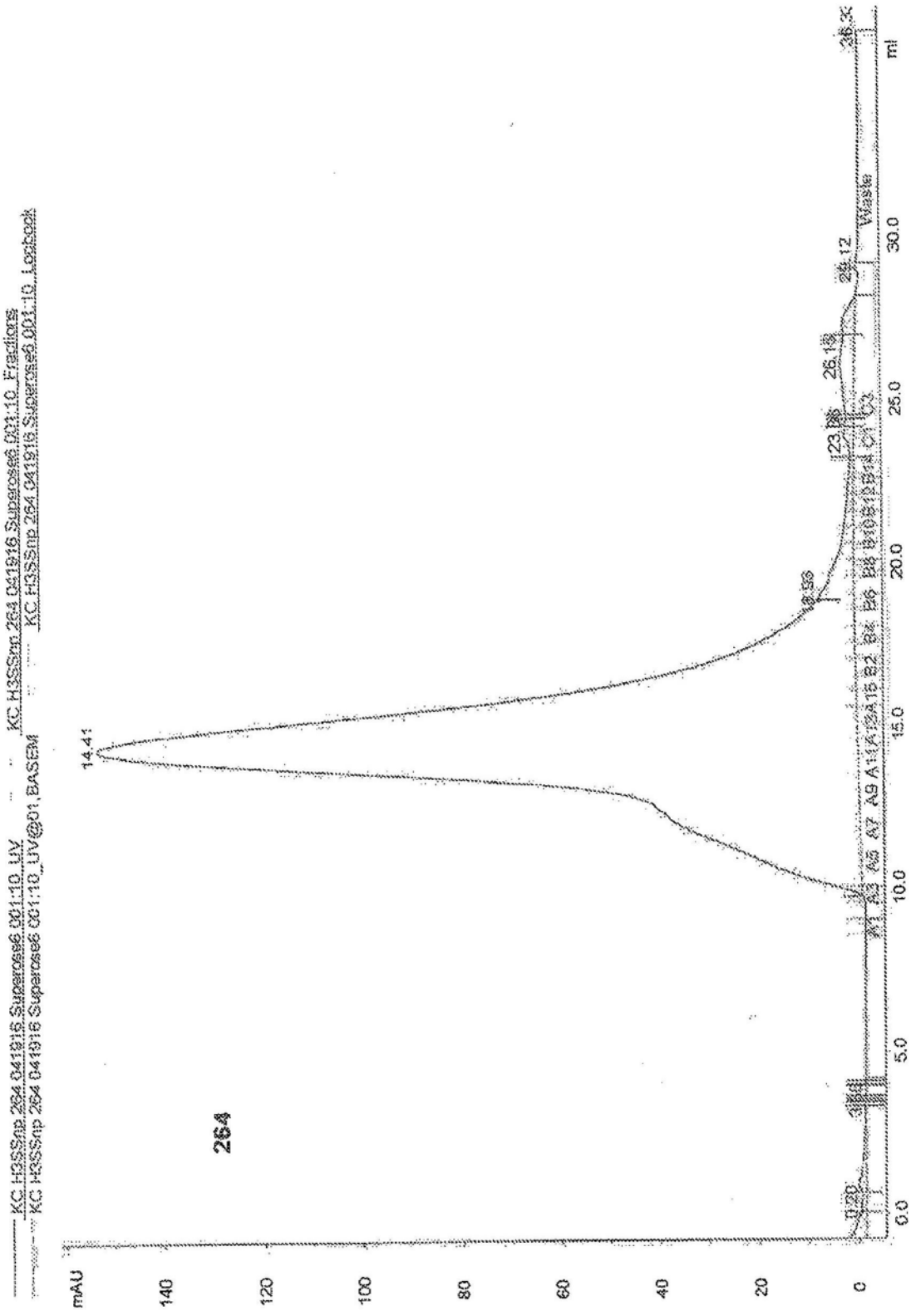

KC H3SSnp 264 041916 Superose6 001:10_UV
KC H3SSnp 264 041916 Superose6 001:10_Fractions
KC H3SSnp 264 041916 Superose6 001:10_UV@01_BASEM
KC H3SSnp 264 041916 Superose6 001:10_Logbook
264
mAU
ml
14.41
Waste

图10E

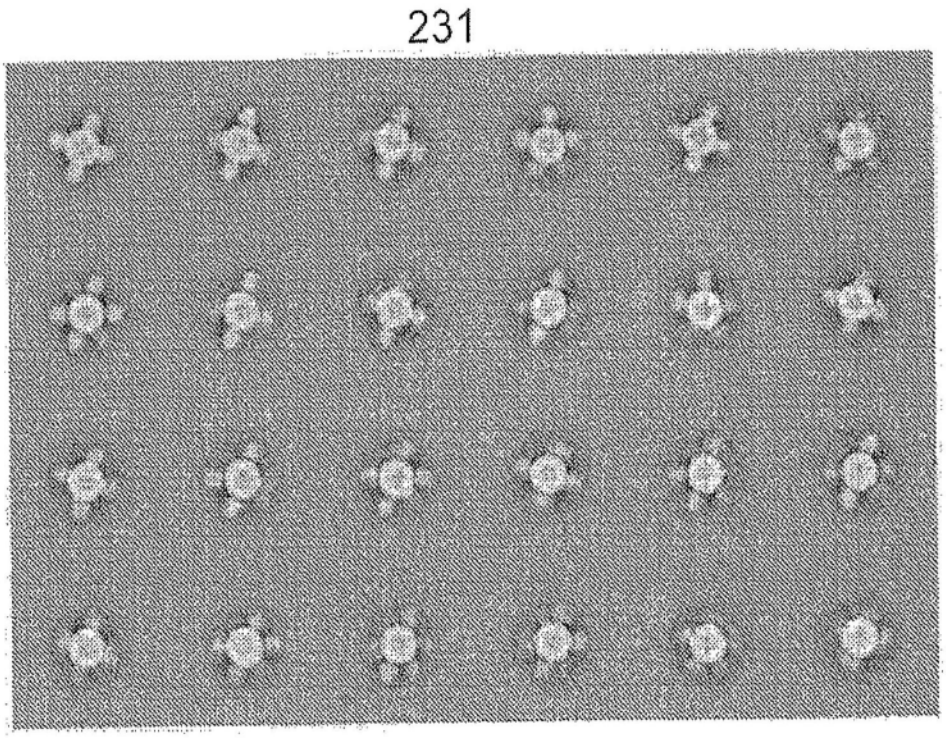


图11A

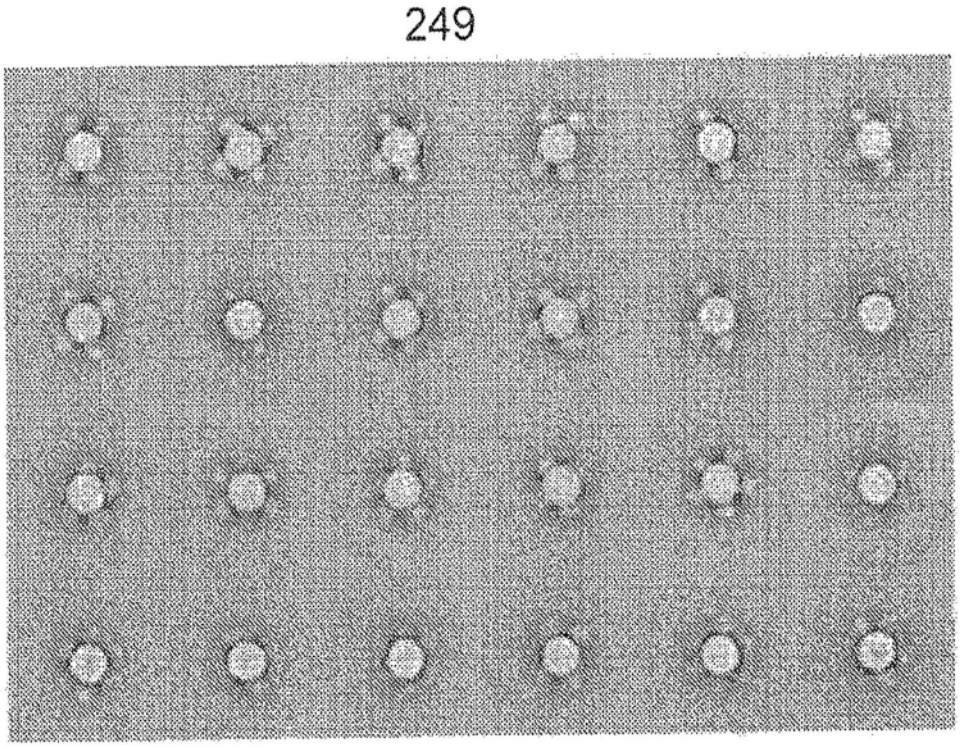


图11B

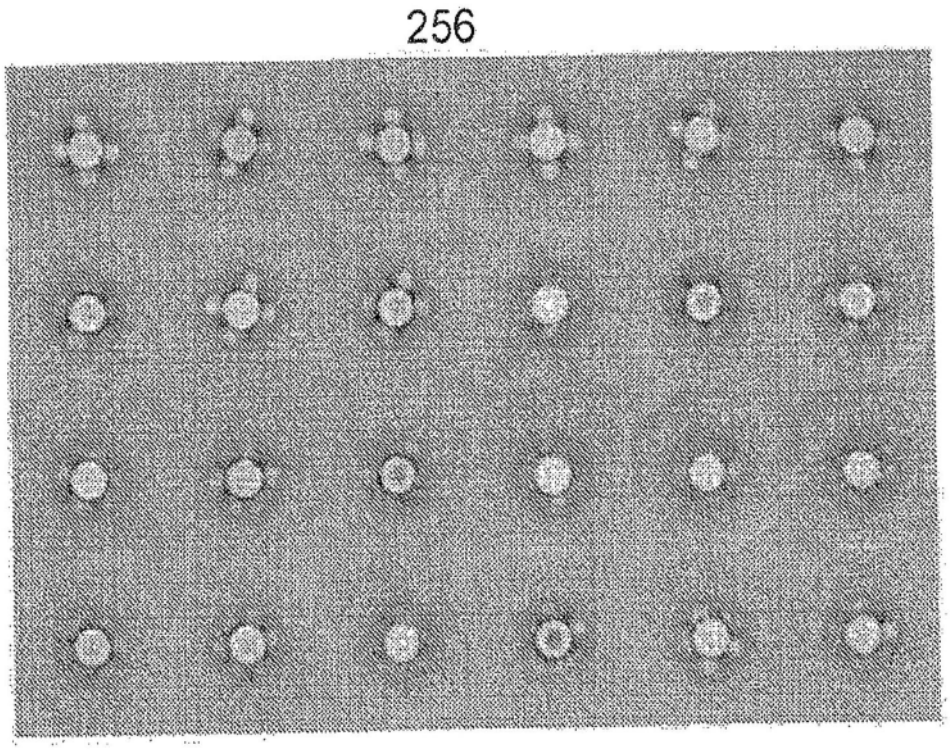


图11C

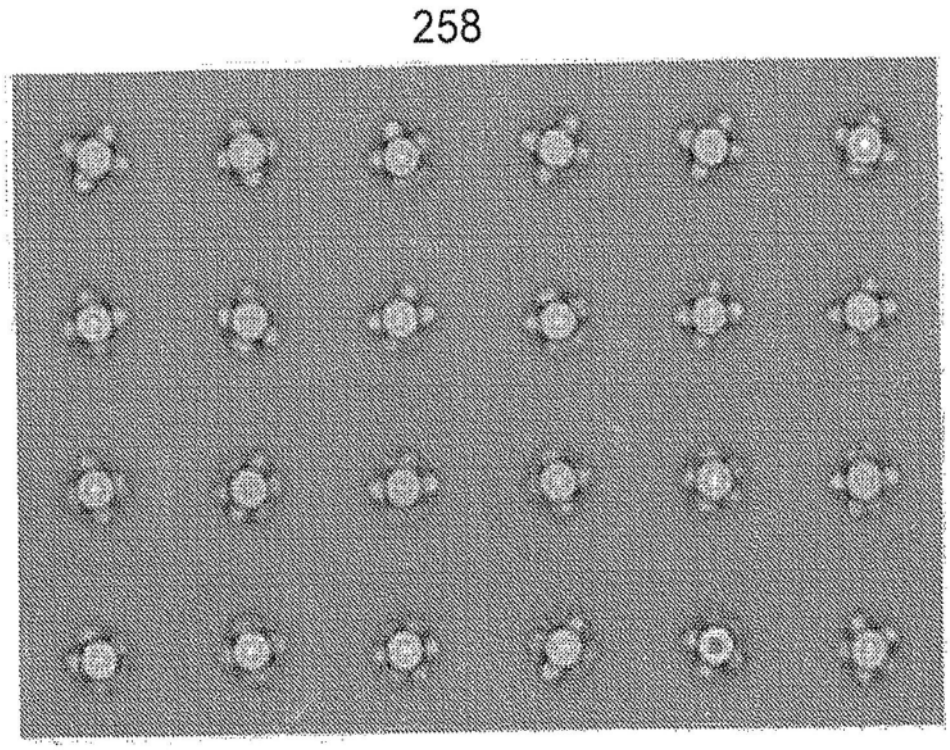


图11D

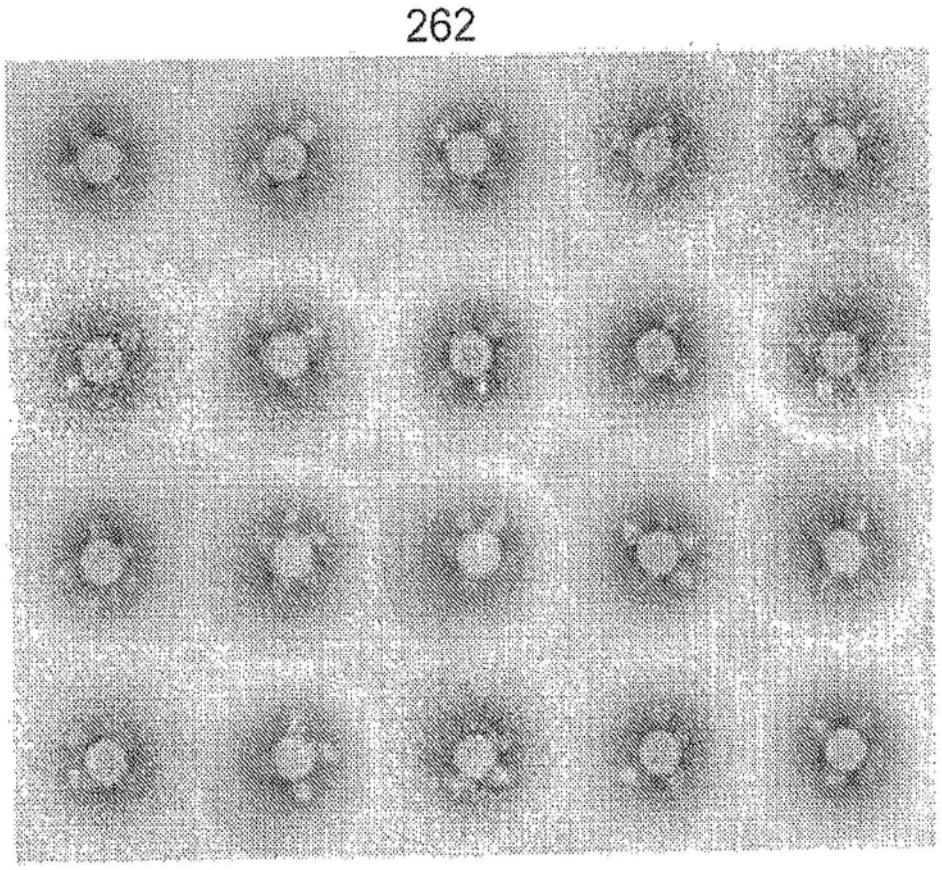


图11E

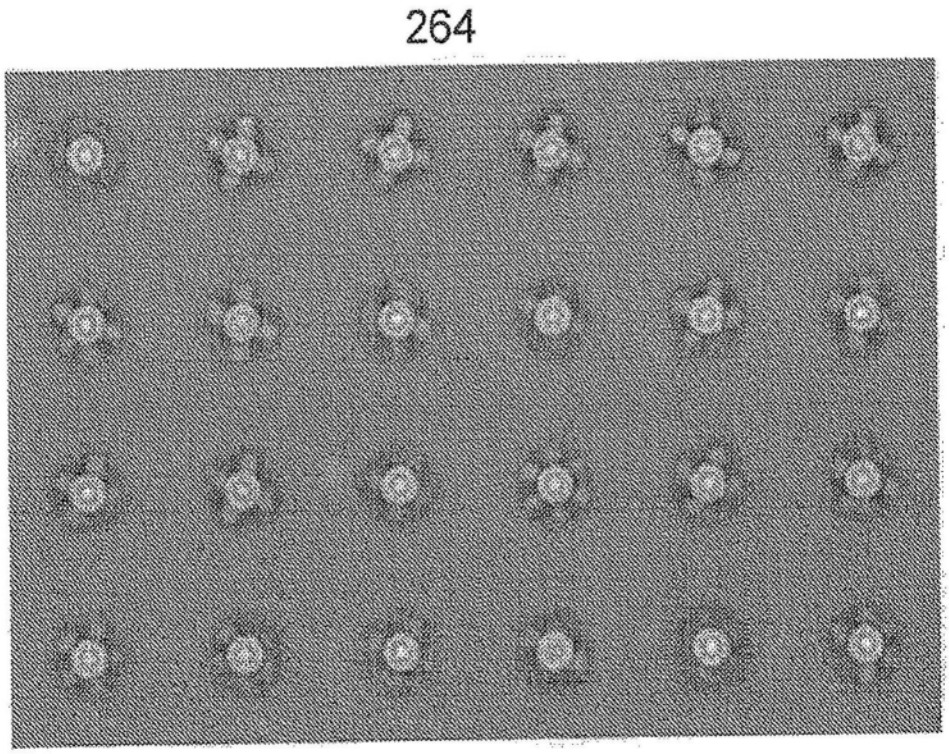

264

图11F

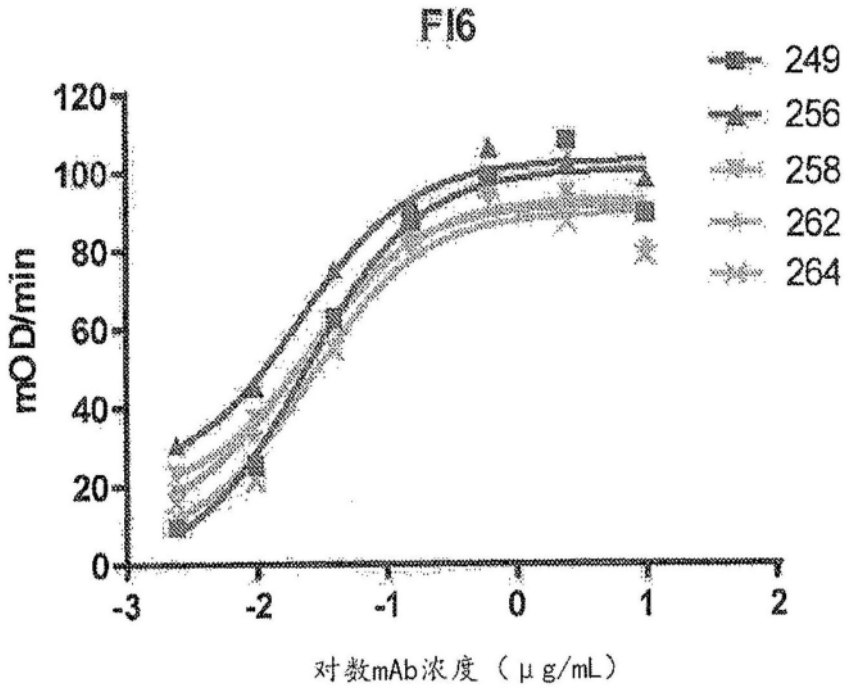

FI6
249
256
258
262
264
120
100
80
60
40
20
0
mOD/min
-3
-2
-1
0
1
2
对数mAb浓度（μg/mL）

图12A

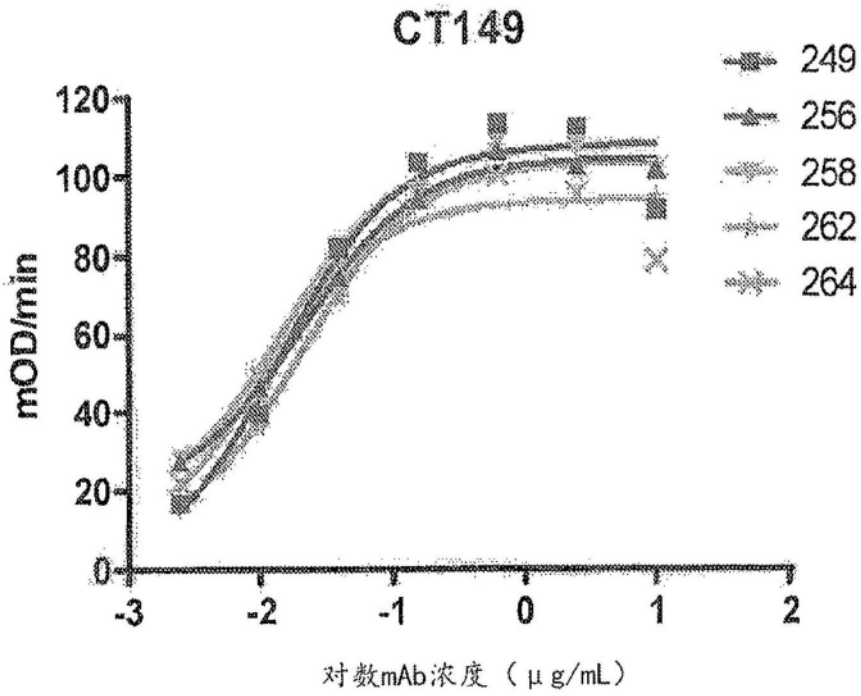

CT149
249
256
258
262
264
120
100
80
60
40
20
0
mOD/min
-3
-2
-1
0
1
2
对数mAb浓度（μg/mL）

图12B

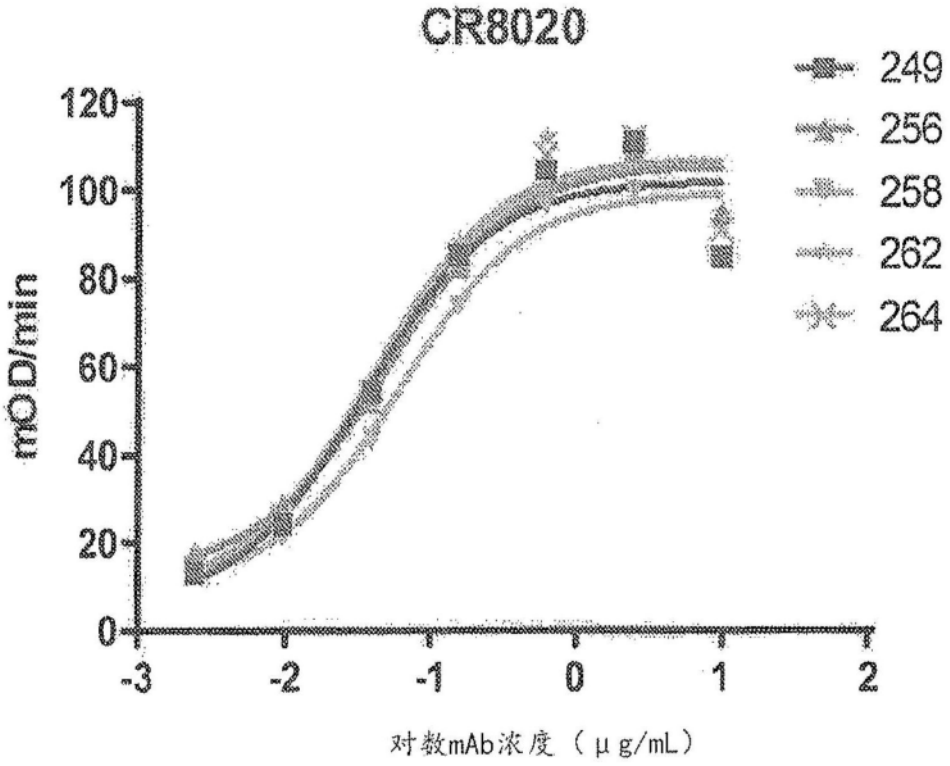

CR8020
249
256
258
262
264
120
100
80
60
40
20
0
mOD/min
-3
-2
-1
0
1
2
对数mAb浓度（μg/mL）

图12C

H3-SS-np#	抗体EC_{50}（μg/mL）		
	CR8020	CT149	FI6
249	0.036	0.013	0.024
256	0.050	0.020	0.022
258	0.060	0.140	0.028
262	0.039	0.019	0.022
264	0.041	0.010	0.026

图12D

H3-SS-np设计235-265的ELISA表征

96孔转染检测-H3SSnp构建体#235-#265-ELISA板关键

ELISA板关键		1	2	3	4	5	6	7	8	9	10	11	12
	A	阴性对照	FL H3 Np	H1-SS-np	190	231	235	236	237	238	239	240	241
	B	242	243	244	245	246	247	248	249	250	251	252	253
	C	254	255	256	257	258	259	260	261	262	263	264	265
	D	empty np	FL H3 Np	H1-SS-np	231								

96孔转染检测-H3SSnp构建体#235-#265-动力学ELISA（5分钟，8个读取）

		1	2	3	4	5	6	7	8	9	10	11	12
	A	0.28	-0.05	0.41	0.00	0.20	0.28	0.22	0.53	0.45	0.20	0.57	-0.29
	B	0.22	-0.12	0.30	0.29	0.08	0.40	0.41	1.53	0.19	-0.54	0.11	0.00
D25（阴性对照）	C	0.42	0.42	0.09	0.31	0.27	0.43	0.41	0.14	0.66	0.00	0.11	0.15
	D	0.21	0.49	0.37	0.28	0.64	0.56	0.59	-0.09	0.39	0.48	0.82	NoFit
	A	0.46	1.79	5.79	0.85	2.65	0.39	0.41	0.63	0.67	0.87	2.41	0.88
	B	0.52	0.51	0.40	0.15	0.45	0.58	-0.12	4.08	0.05	0.73	0.58	0.54
FI6	C	0.59	0.40	8.89	0.26	2.38	2.46	2.46	3.80	3.55	0.87	3.88	7.33
	D	0.45	23.62	69.48	29.20	0.59	0.67	NoFit	0.46	0.49	0.80	0.55	0.41

96孔转染检测-H3SSnp构建体#235-#265-动力学ELISA（5分钟，8个读取）

		1	2	3	4	5	6	7	8	9	10	11	12
	A	0.65	0.53	0.25	0.40	0.24	0.30	0.52	0.28	0.72	0.20	0.50	0.74
	B	0.49	0.42	0.38	0.43	0.33	0.34	0.27	0.42	5.34	0.60	0.81	0.68
D25（阴性对照）	C	0.31	0.54	-3.05	0.41	0.31	0.07	0.78	0.49	0.66	0.37	0.45	1.13
	D	1.42	1.05	1.21	1.36	0.39	0.33	0.43	0.77	1.13	-0.14	-2.21	2.33
	A	0.52	3.56	3.59	1.07	3.66	1.17	0.28	1.96	0.16	2.34	0.73	-1.76
	B	0.09	-0.33	0.31	0.29	0.34	0.43	0.07	12.43	0.33	0.66	0.29	1.48
CT149	C	0.08	-0.01	8.28	0.41	4.35	5.12	5.61	7.62	7.48	3.75	9.66	10.32
	D	0.39	11.20	115.53	75.59	0.25	0.08	0.36	0.18	0.12	0.67	0.57	0.25

D行中为纯化的蛋白对照：铁蛋白纳米颗粒（空np）、全长H3-np（FL H3 Np）、H1-SS-np和H3-SS-np 231阳性>2.35

图13A

H3-SS-np设计266-296的ELISA表征

		1	2	3	4	5	6	7	8	9	10	11	12
	A	阴性对照	H1-SS-np	231	266	267	268	269	270	271	272	273	274
关键	B	275	276	277	278	279	280	281	282	283	284	285	286
	C	287	288	289	290	291	292	293	294	295	231蛋白		
		1	2	3	4	5	6	7	8	9	10	11	12
	A	NoFit	-0.1	-0.3	NoFit	0.0	0.2	-0.2	0.1	0.7	-0.1	-0.2	1.2
D25	B	0.5	0.2	0.3	NoFit	0.3	NoFit	0.5	1.9	0.2	0.5	0.2	0.3
(阴性对照)	C	-1.2	0.5	NoFit	0.0	0.3	NoFit	-0.3	0.3	-3.1	03		
		1	2	3	4	5	6	7	8	9	10	11	12
	A	0.1	1.2	1.2	4.9	5.2	5.5	4.9	2.5	1.5	3.2	0.7	1.8
CT149	B	0.6	0.6	0.9	0.8	2.1	0.4	1.6	0.6	0.3	0.5	0.1	-3.9
	C	2.1	3.1	3.6	0.5	2.2	1.8	2.1	1.8	1.9	26.0		

阳性 ≥ 1.5

图13B

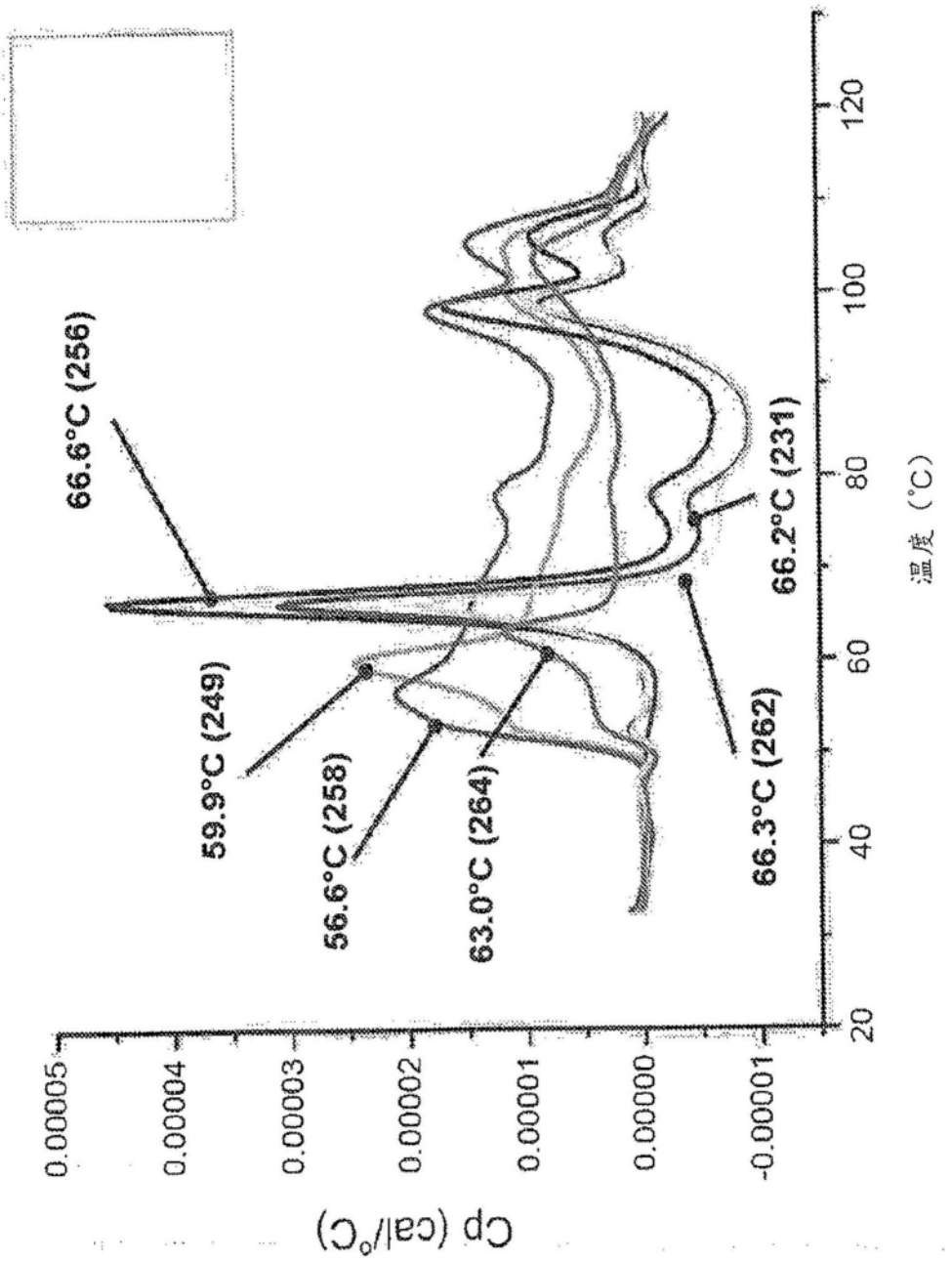

66.6°C (256)
59.9°C (249)
56.6°C (258)
63.0°C (264)
66.3°C (262)
66.2°C (231)
0.00005
0.00004
0.00003
0.00002
0.00001
0.00000
-0.00001
Cp (cal/°C)
20
40
60
80
100
120
温度（°C）

图14

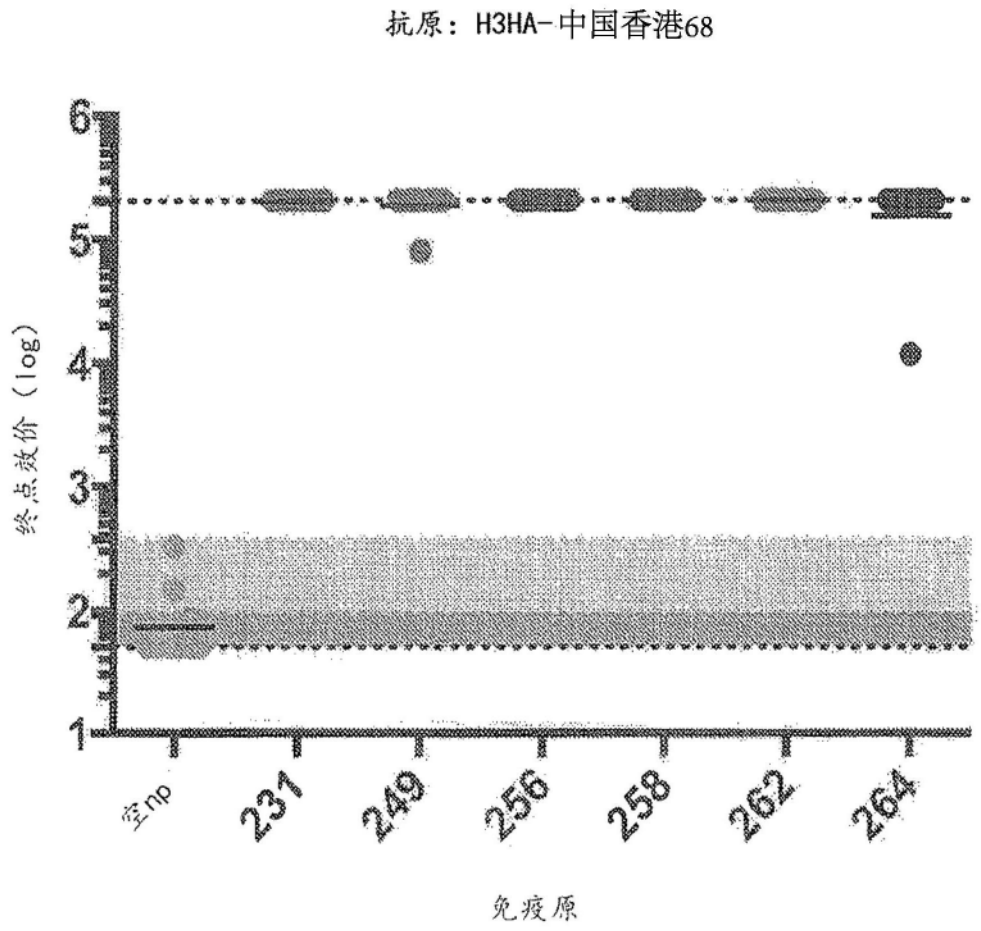


图15A

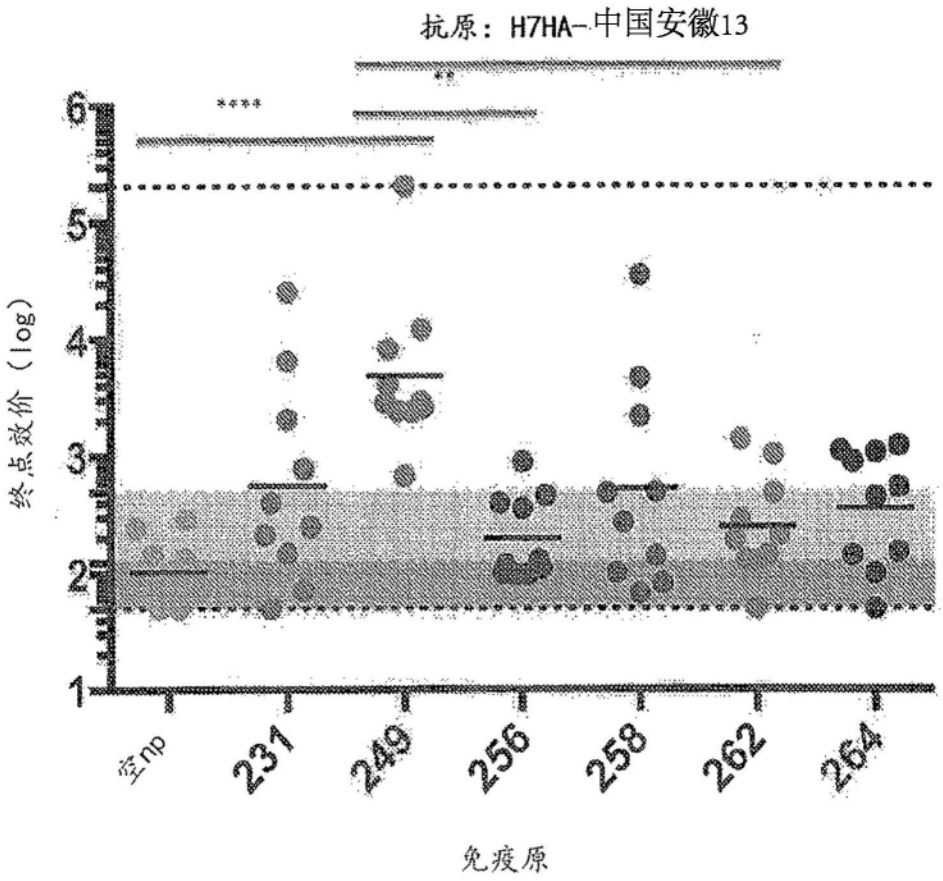


图15B

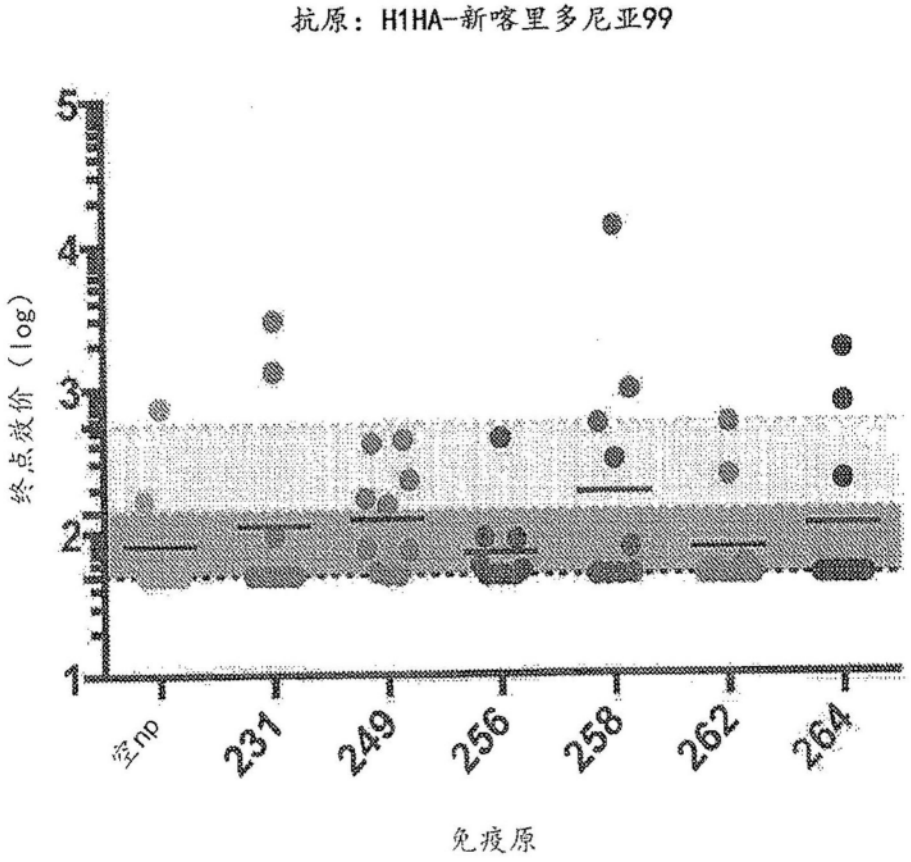

抗原：H1HA-新喀里多尼亚99
终点效价（log）
5
4
3
2
1
空np
231
249
256
258
262
264
免疫原

图16A

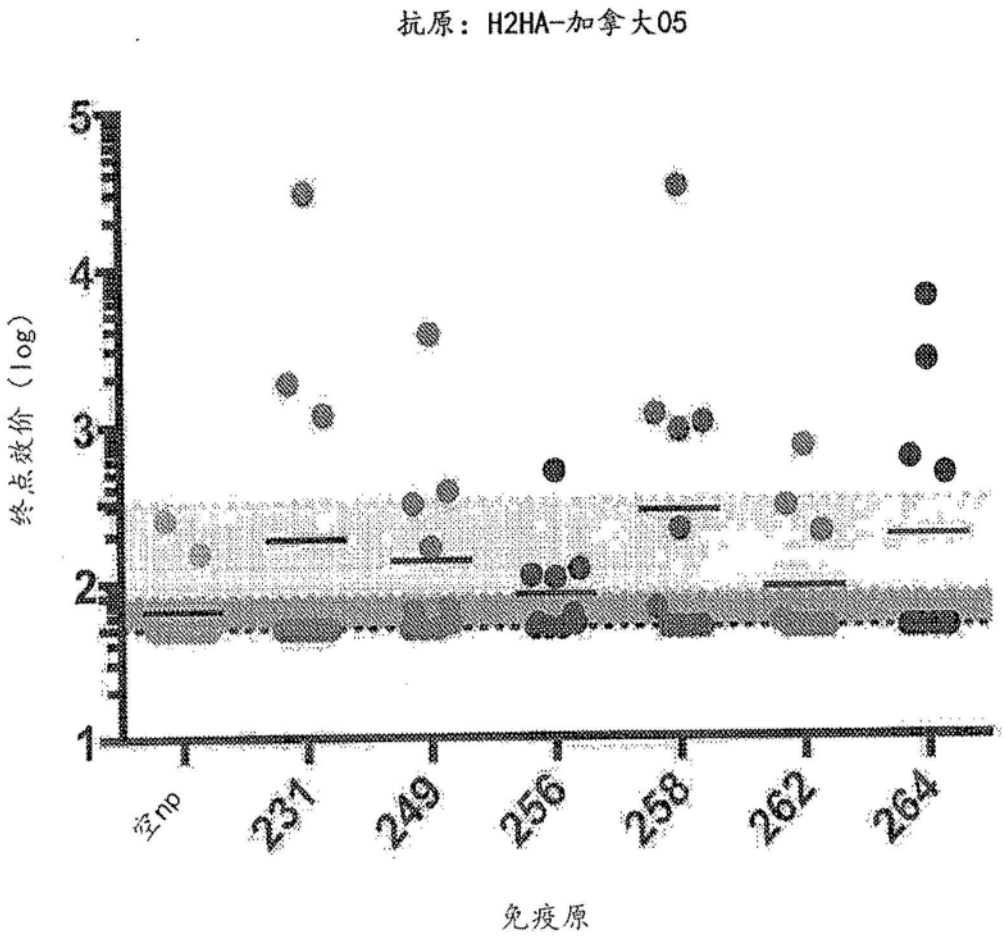


图16B

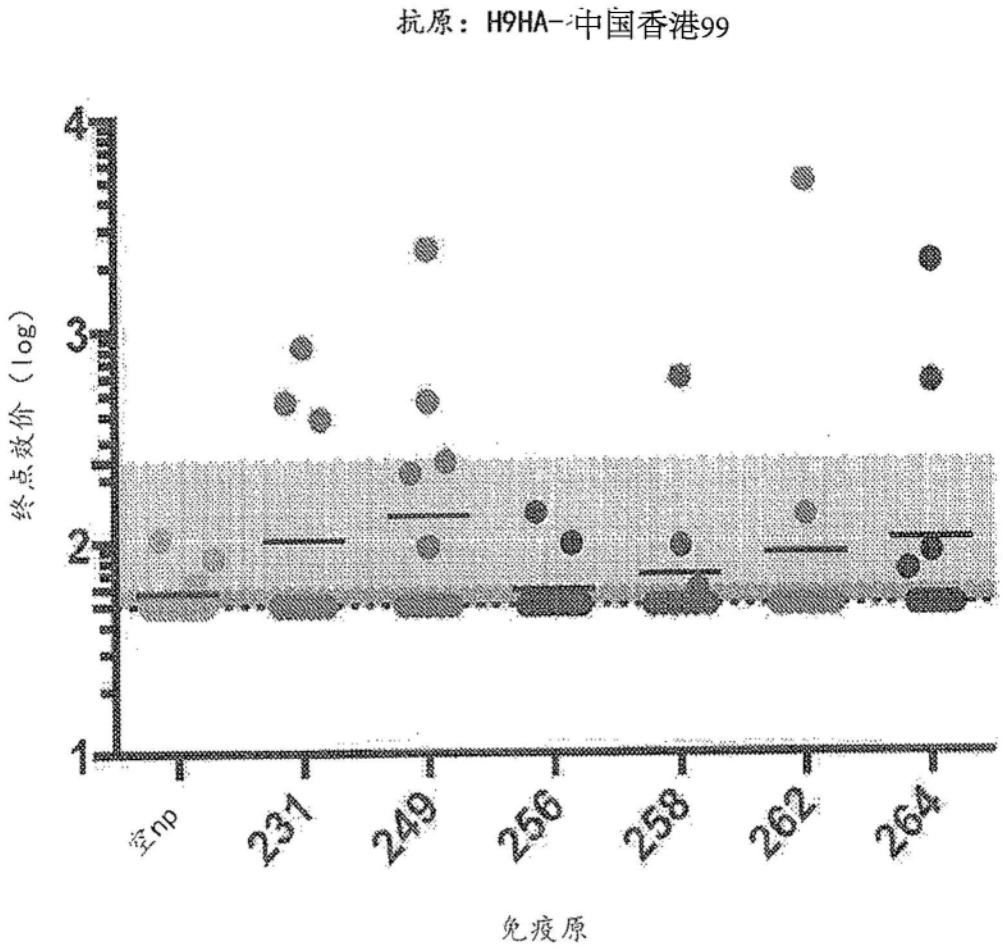


图16C

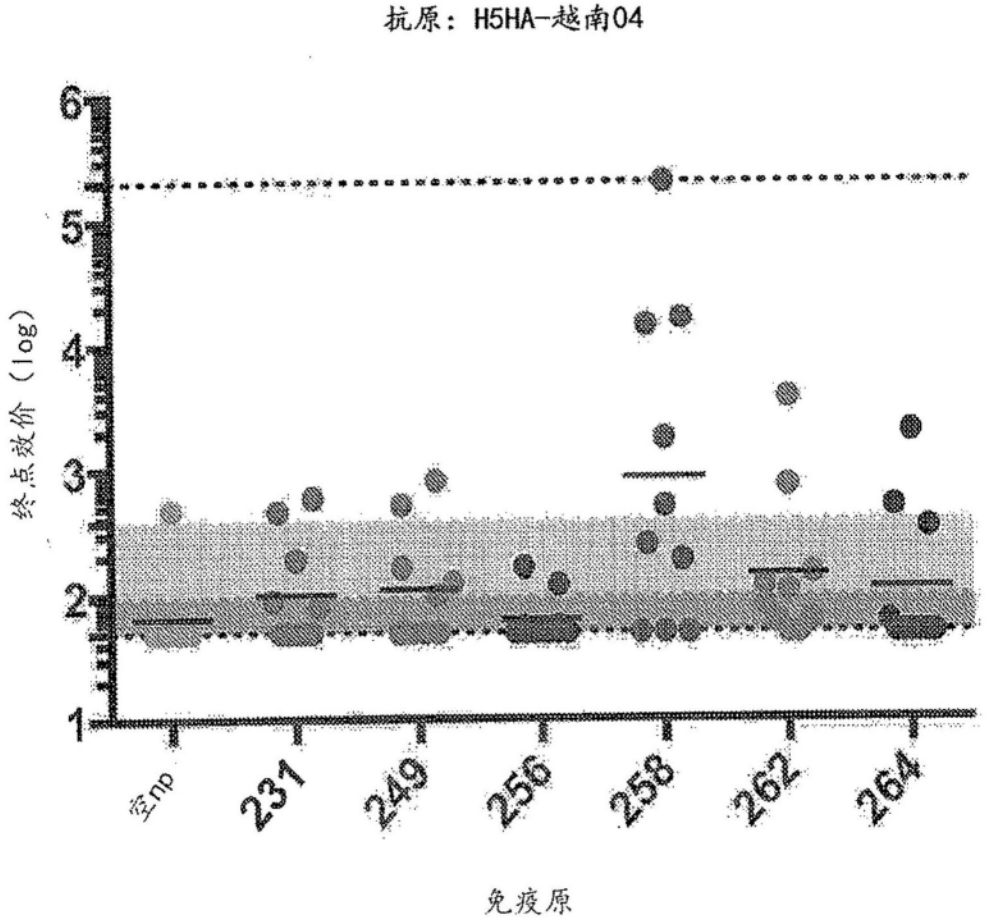


图16D

>H3-SS_LS-01 (#231, LS N102D除去聚糖)
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQ
IEVTNATELVETPGCGVLKLATGMRNVPEKQTRGIFGAIAGFIENGWEGM
VDGWYGFRHQNSEGIGQAADLKSTQAAINQINGKLNRVIEKTNEKFHQI
YLAELLVAIENQHTIDLTDSEMRKLFERTKKQLRENAEDMGNGCFKIYH
KCDNACIGSIRNGTYDHDVYRDEALNNRFQIKAGPPGGMQIYEGKLTAE
GLRFGIVASRFNHALVDRLVEGAIDCIVRHGGREEDITLVRVPGSWEIP
VAAGELARKEDIDAVIAIGVLIRGATPHFDYIASEVSKGLADLSLELRK
PITFGVITADTLEQAIERAGTKHGNKGWEAALSAIEMANLFKSLR

图17

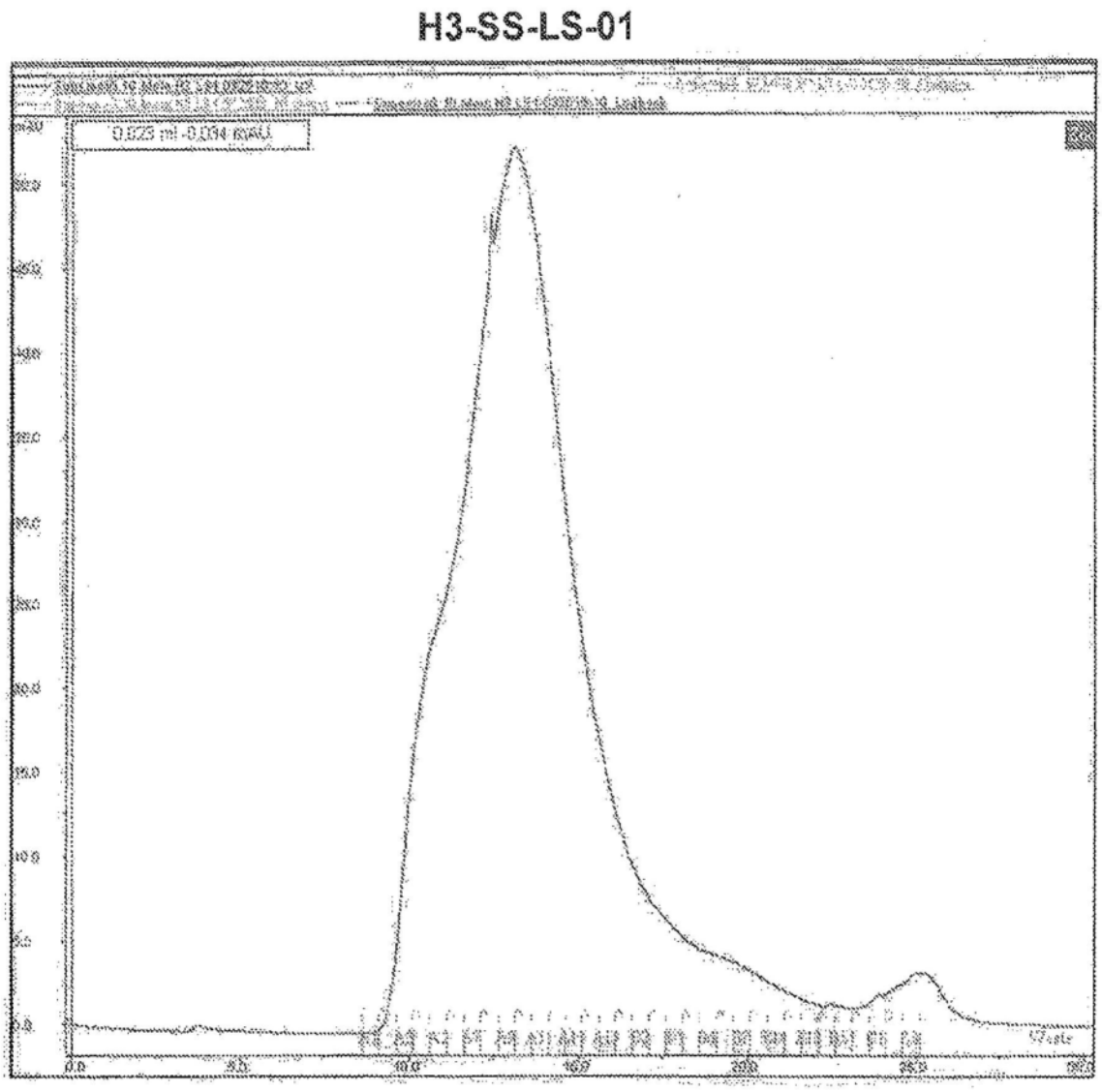


图18A

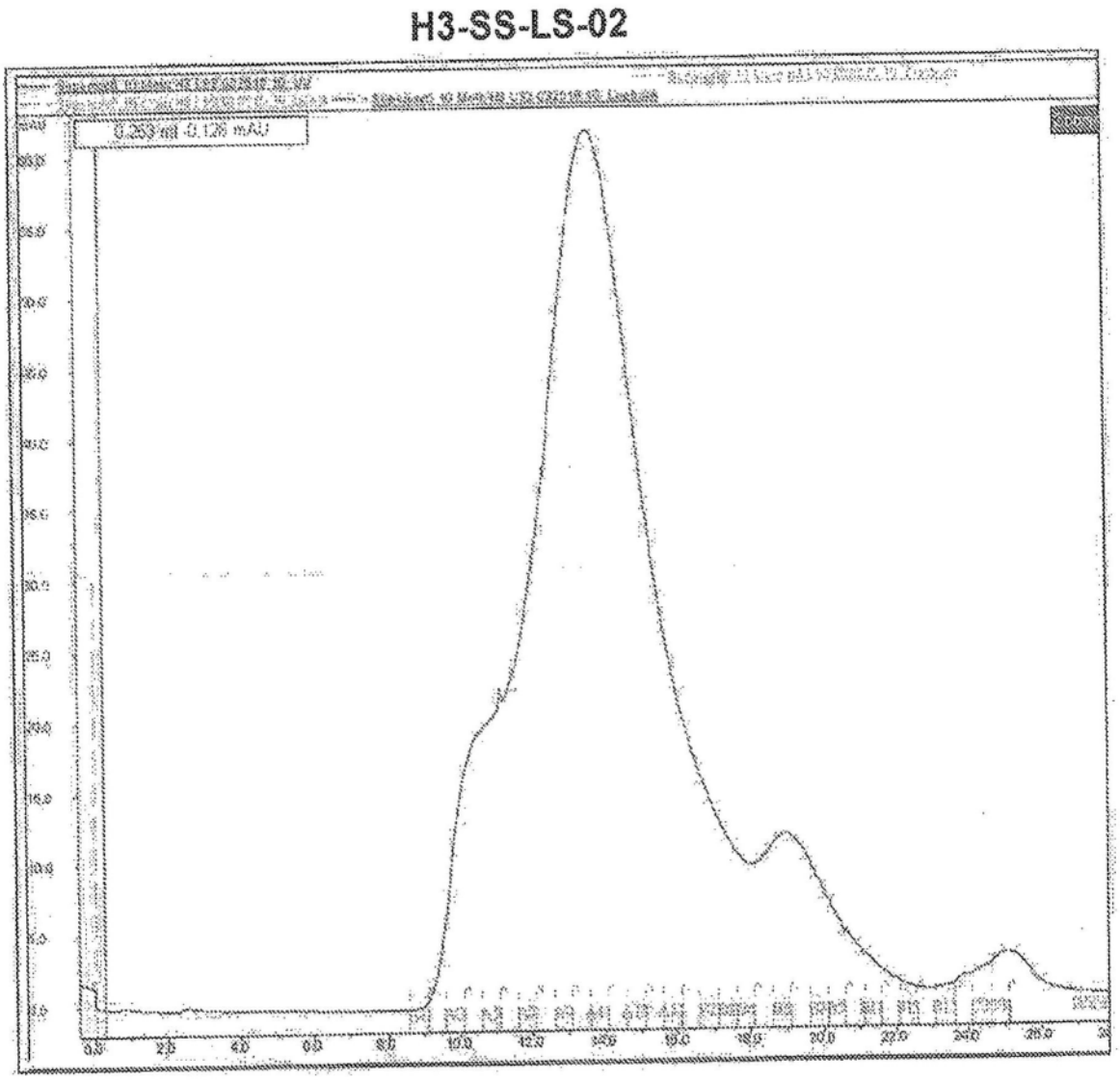


图18B

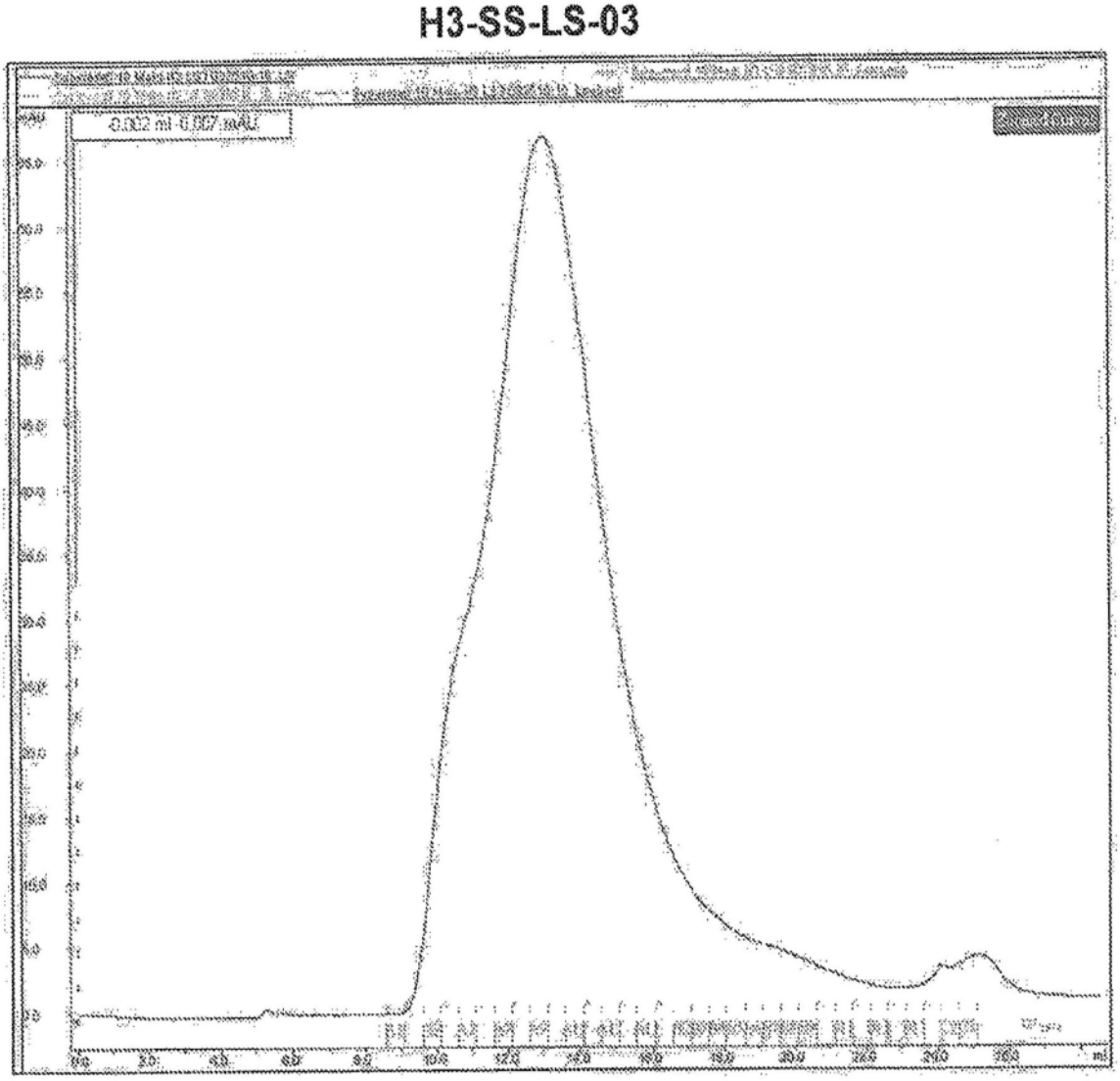


图18C

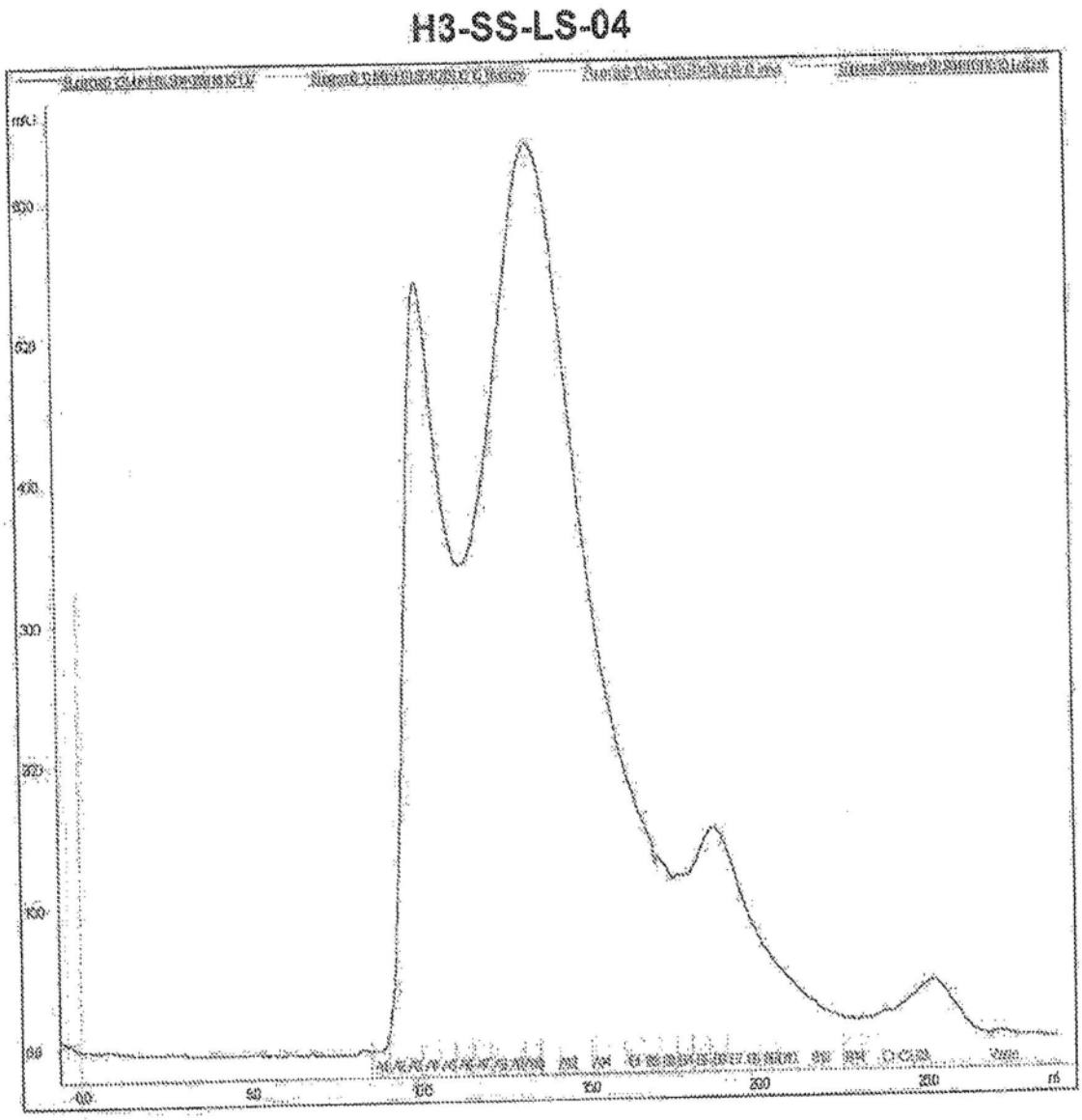


图18D

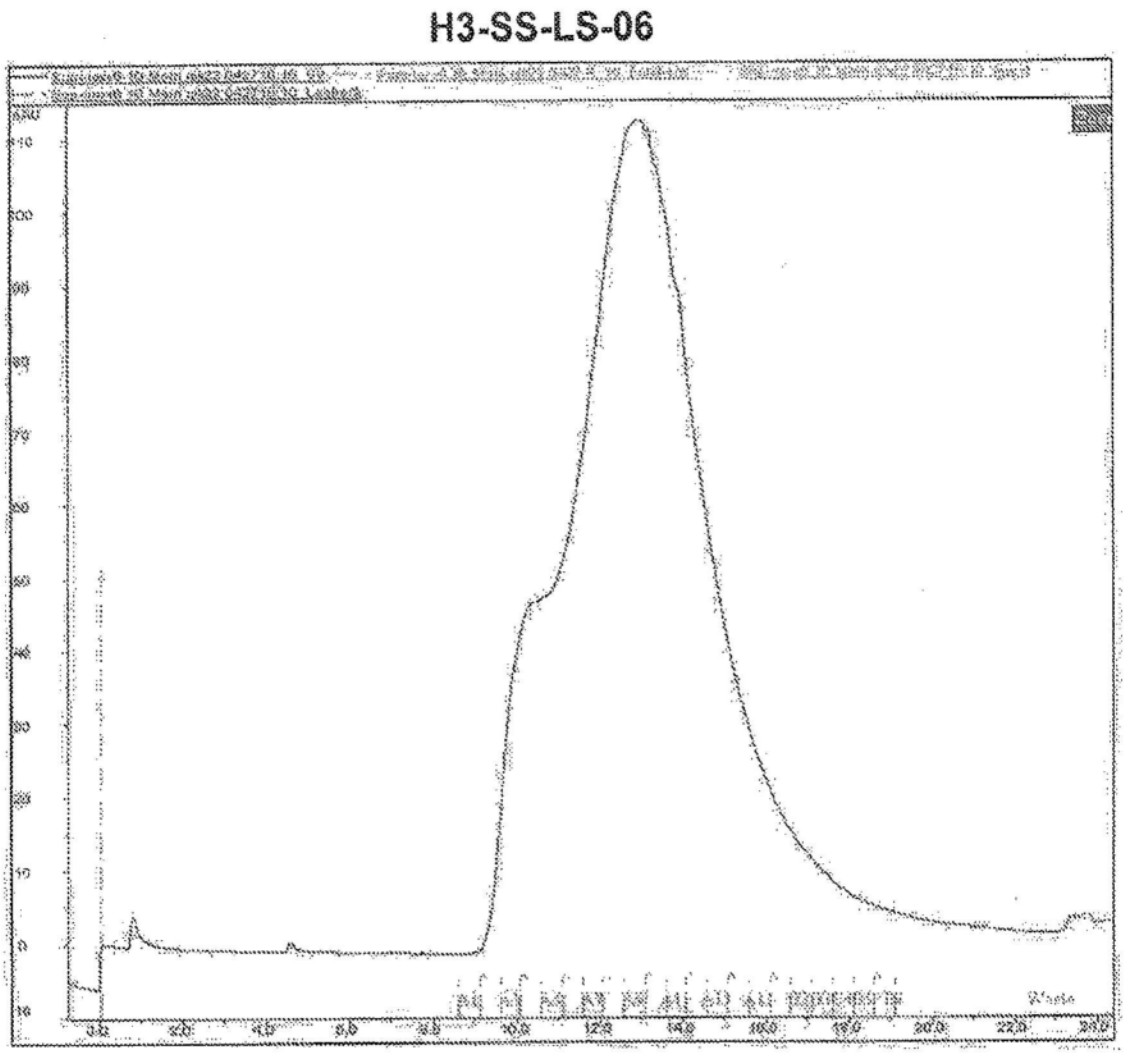


图18E

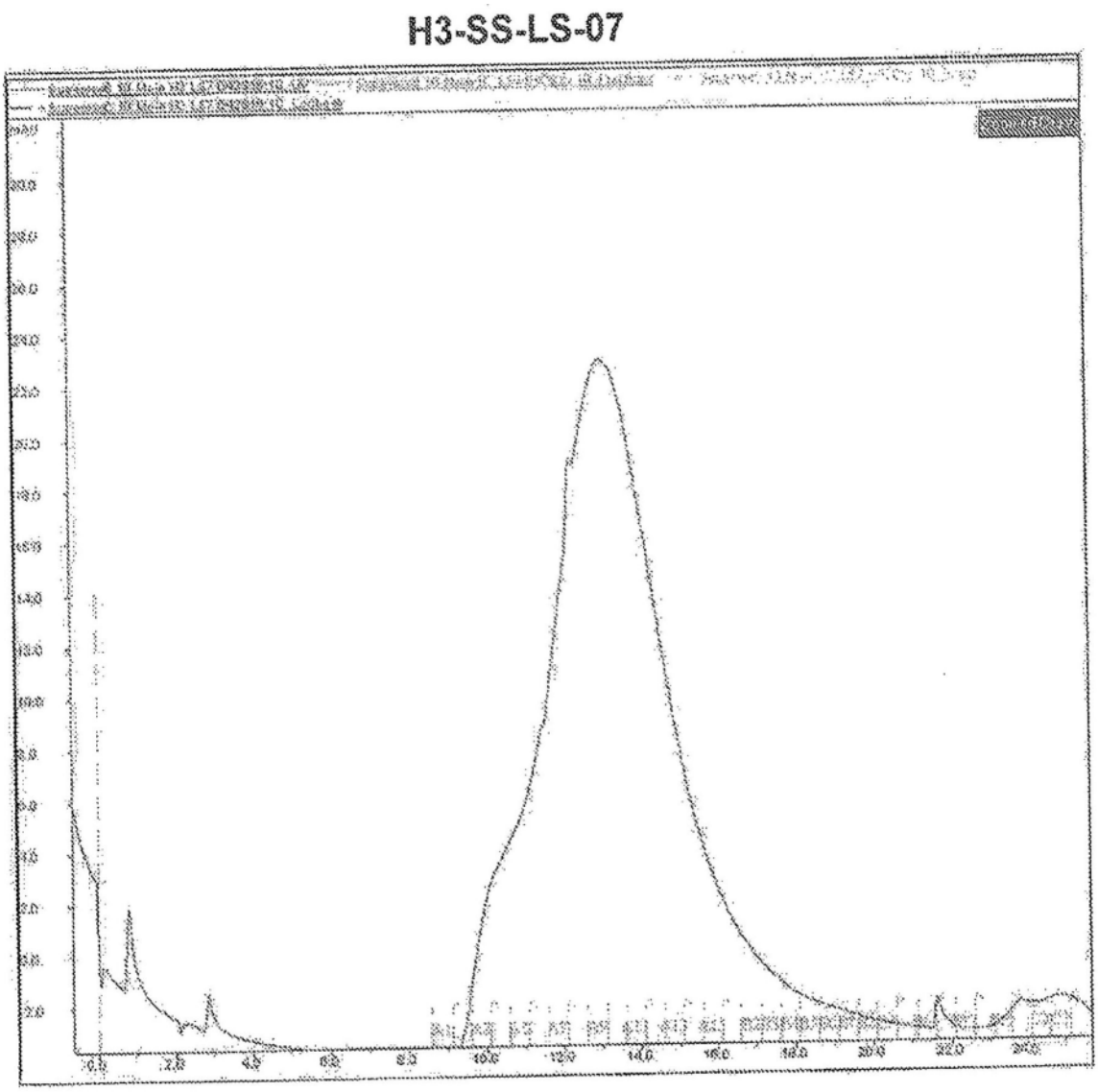
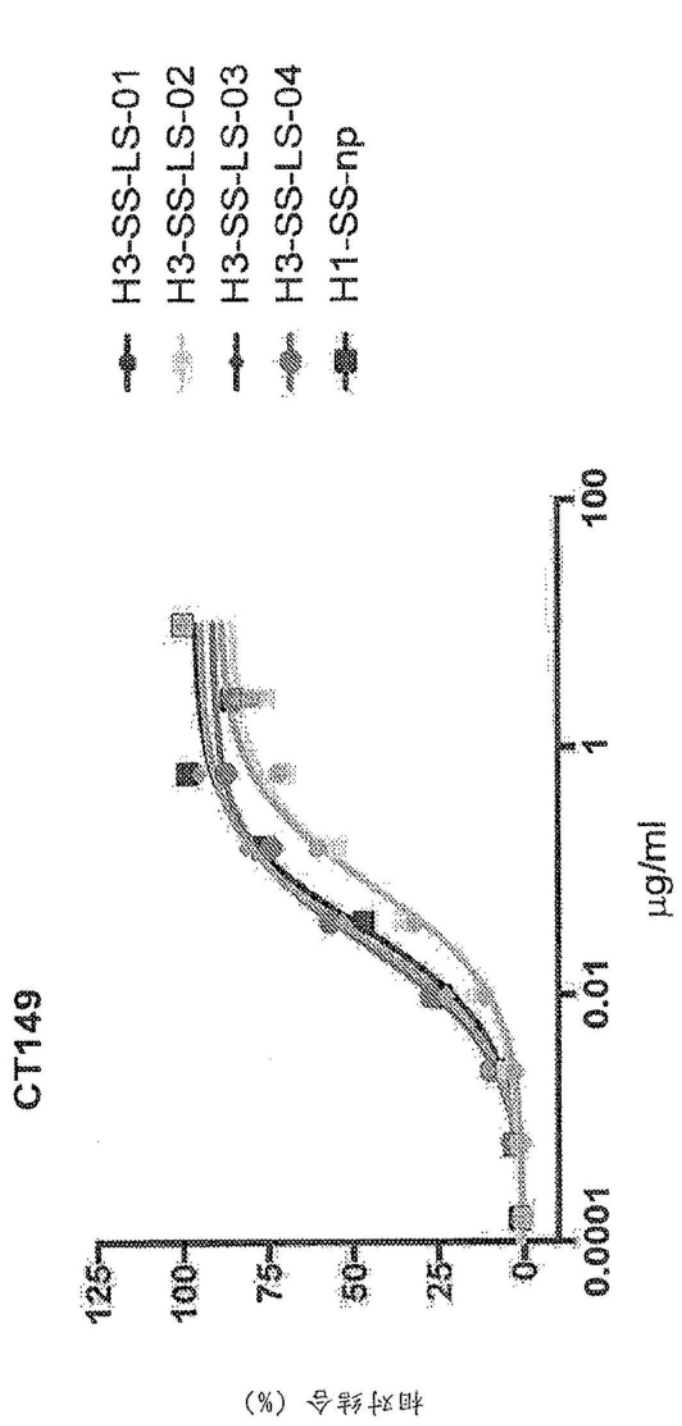
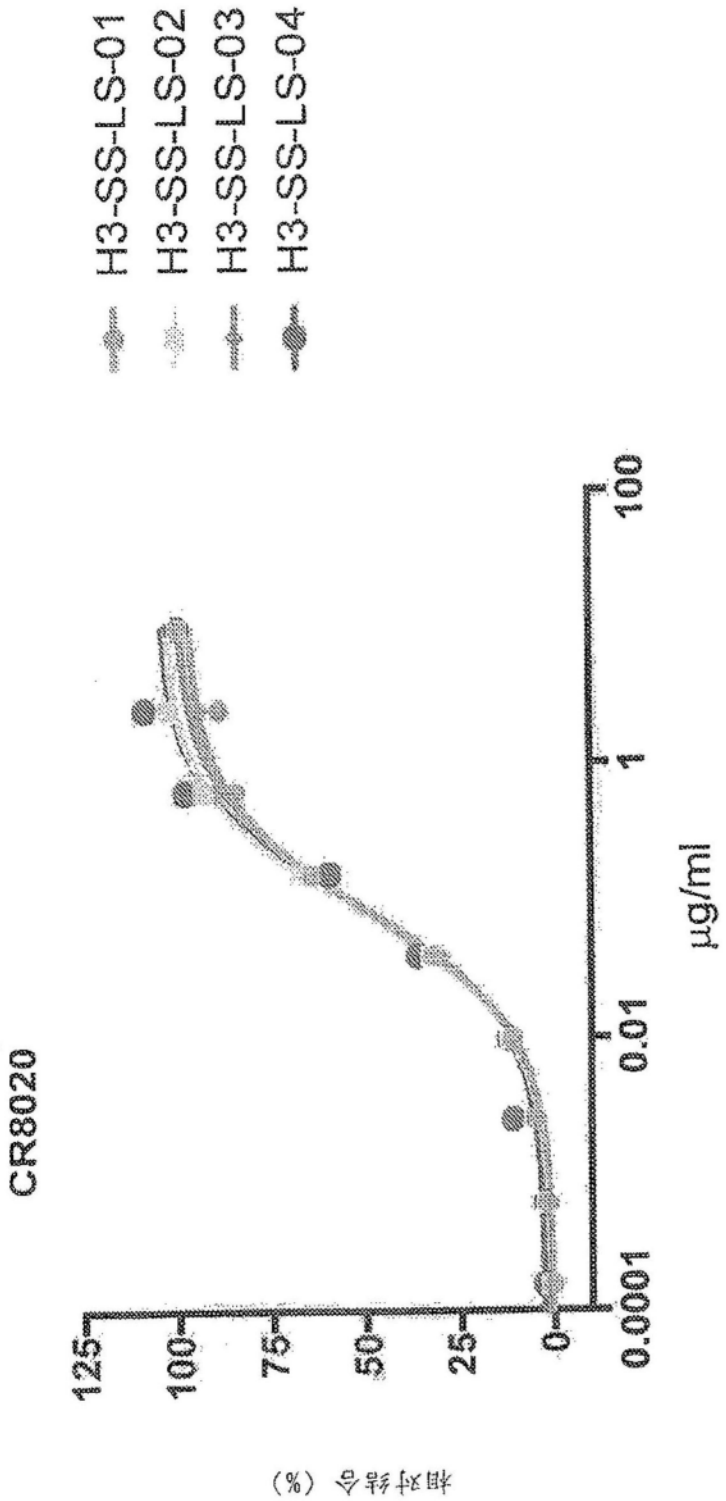


图18F



	H3-SS-LS-01	H3-SS-LS-02	H3-SS-LS-03	H3-SS-LS-04	H1-SS-np
IC50	0.07853	0.07698	0.02964	0.02494	0.03721

图19A



	H3-SS-LS-01	H3-SS-LS-02	H3-SS-LS-03	H3-SS-LS-04
IC50	0.08182	0.08213	0.08877	0.09565

图19B

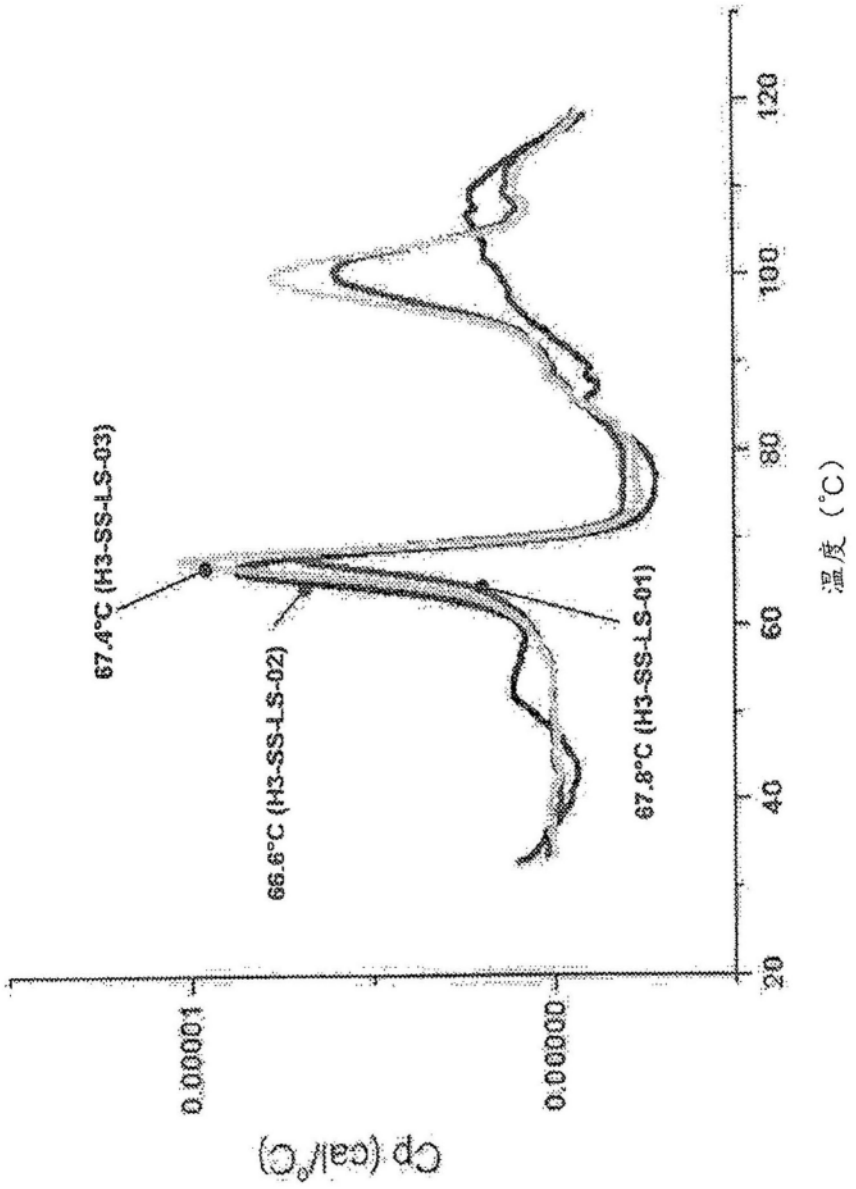

67.4°C (H3-SS-LS-03)
66.6°C (H3-SS-LS-02)
67.8°C (H3-SS-LS-01)
0.00001
0.00000
Cp (cal/°C)
20
40
60
80
100
120
温度（°C）

图20

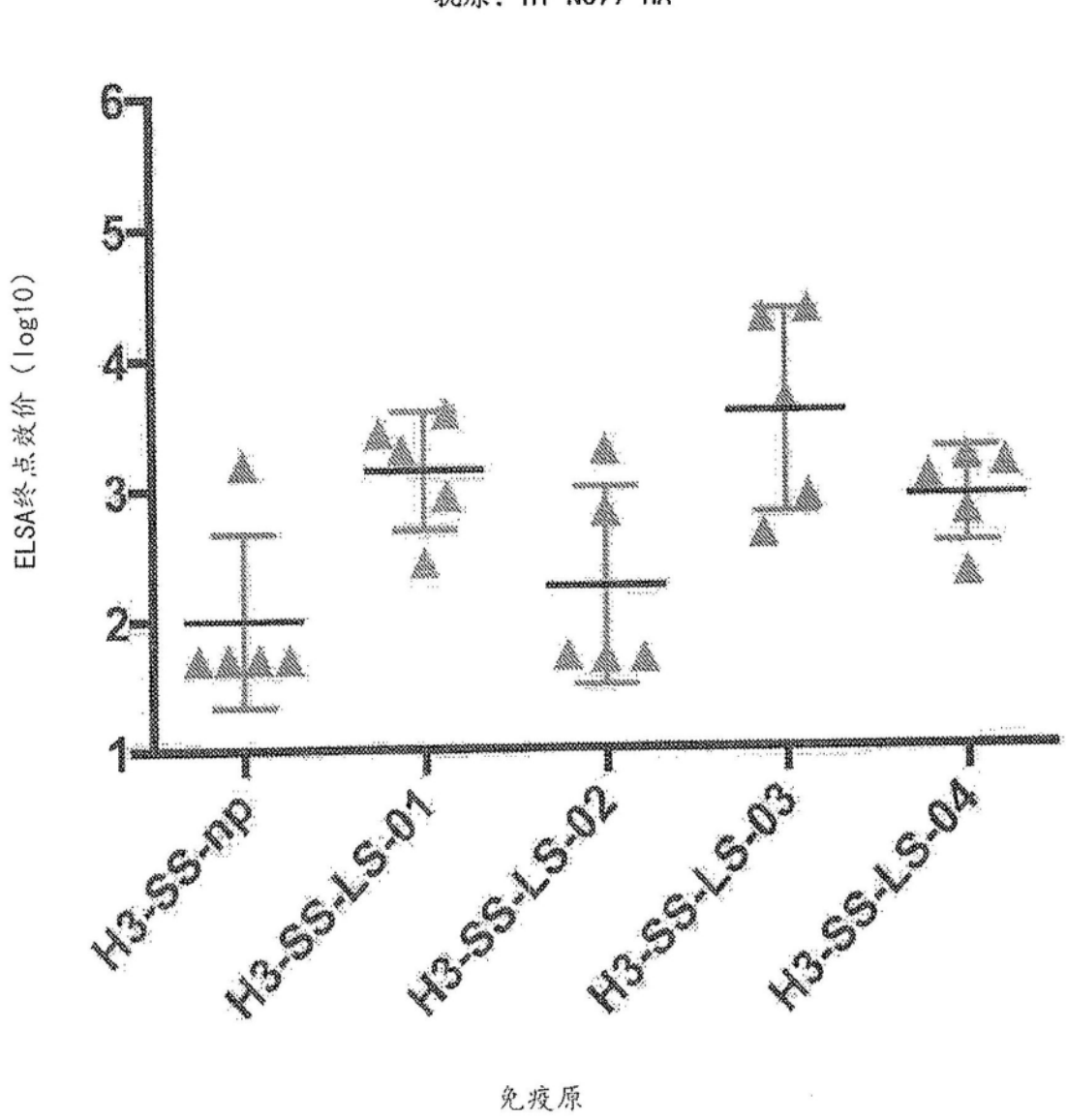

抗原：H1 NC99 HA
ELSA终点效价（log10）
6
5
4
3
2
1
H3-SS-nP
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图21A

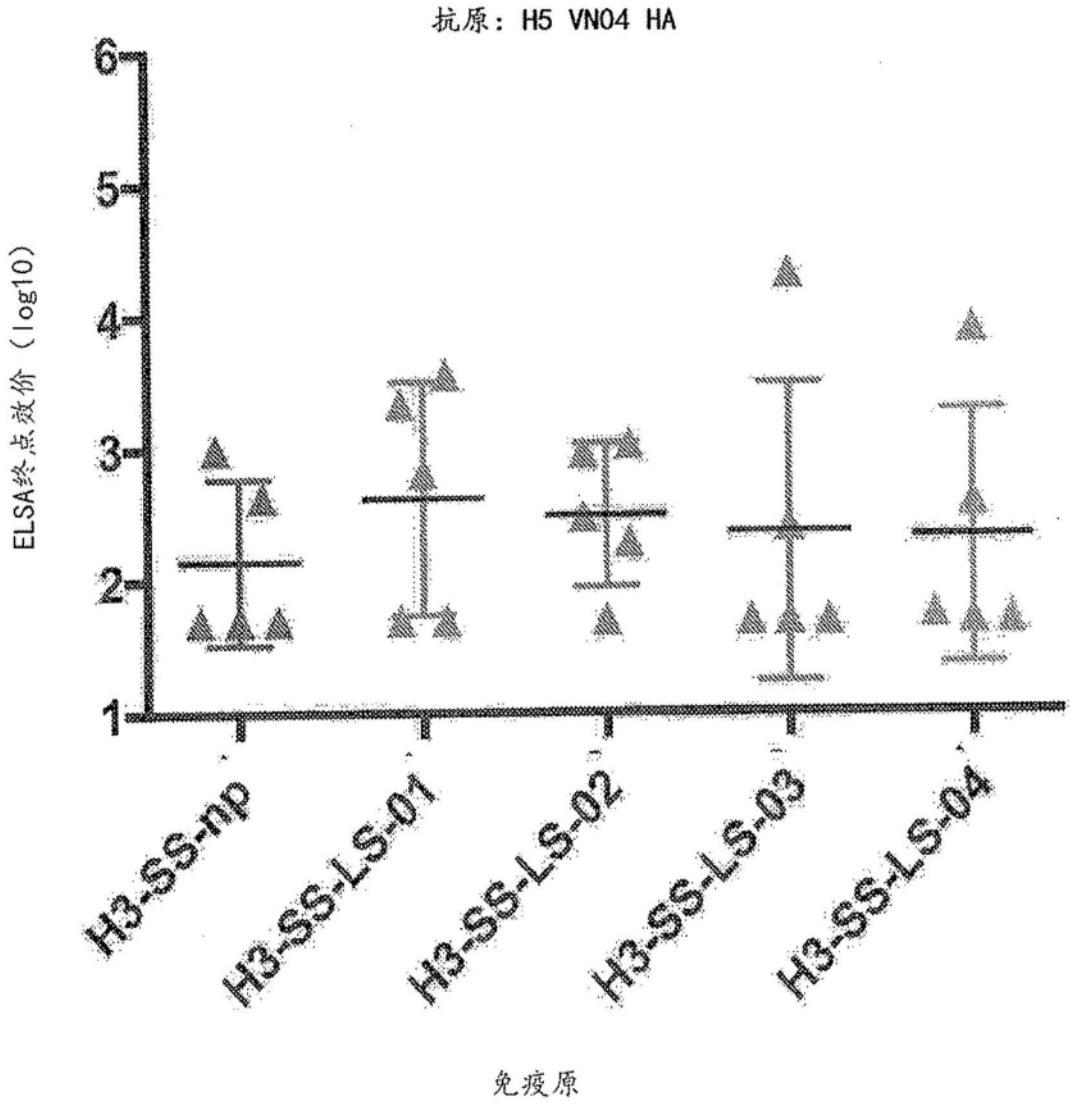

抗原：H5 VN04 HA
ELSA终点效价（log10）
6
5
4
3
2
1
H3-SS-np
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图21B

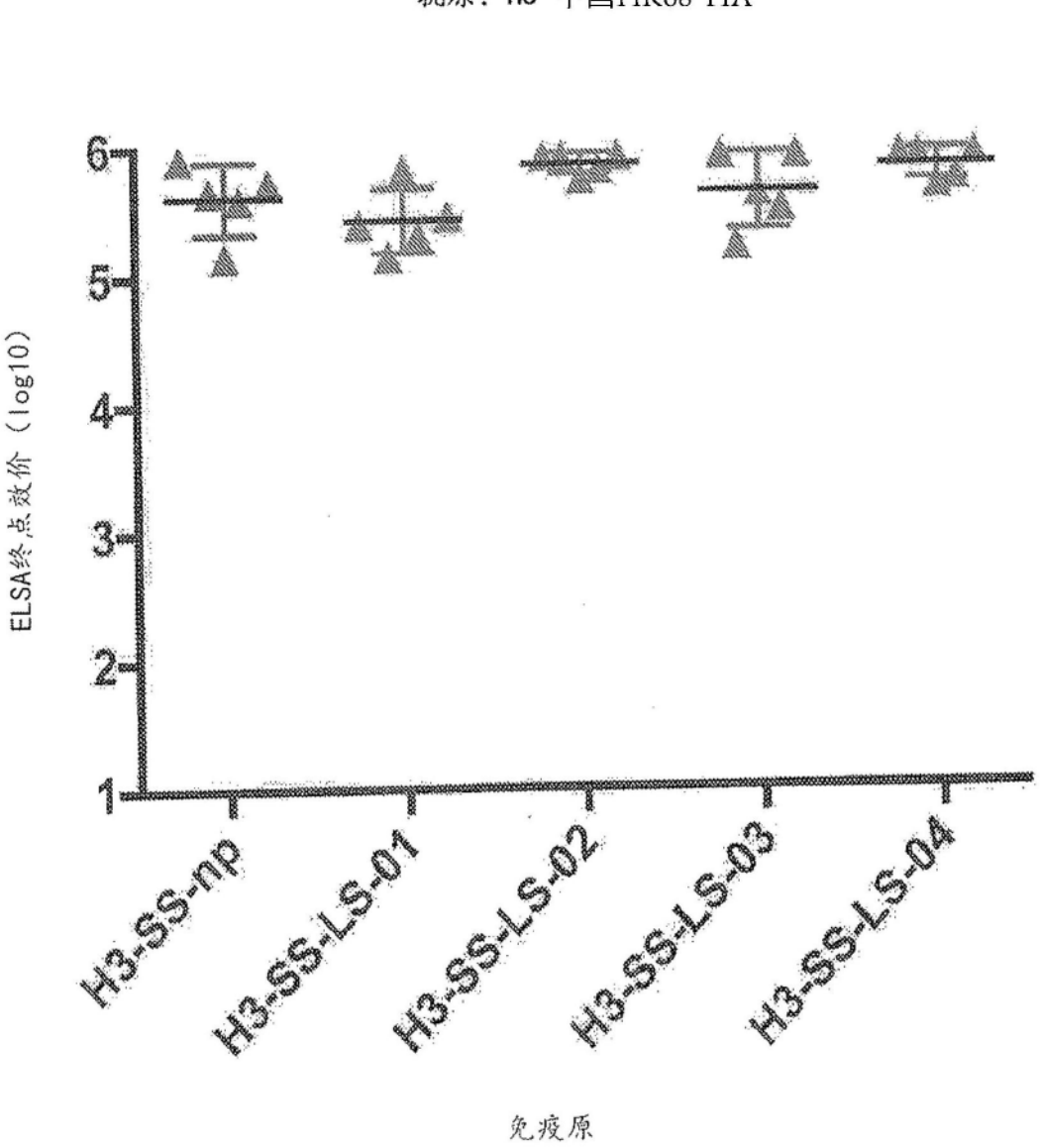

抗原：H3 中国HK68 HA
ELSA终点效价（log10）
6
5
4
3
2
1
H3-SS-np
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图21C

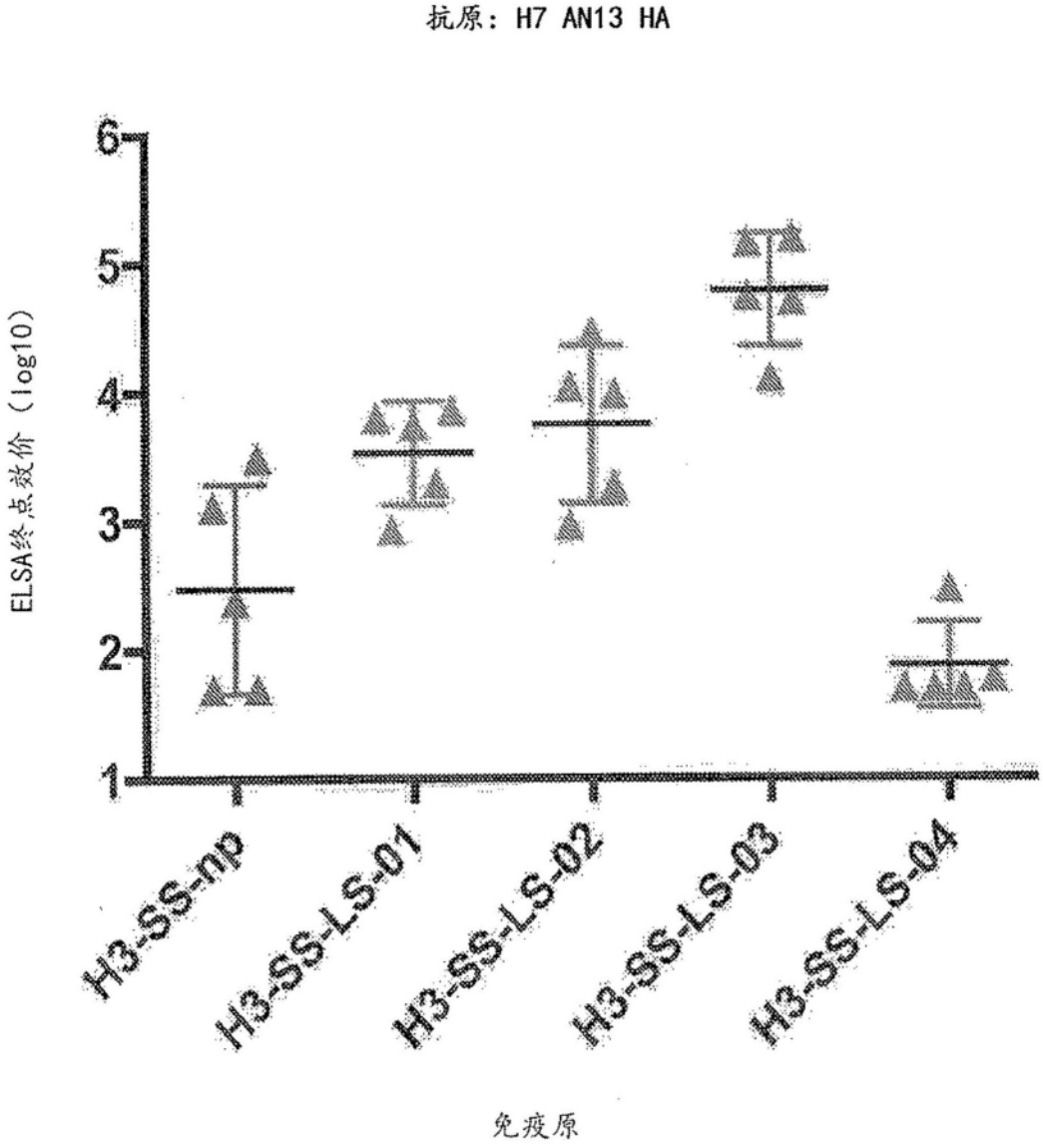

抗原：H7 AN13 HA
ELSA终点效价（log10）
6
5
4
3
2
1
H3-SS-np
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图21D

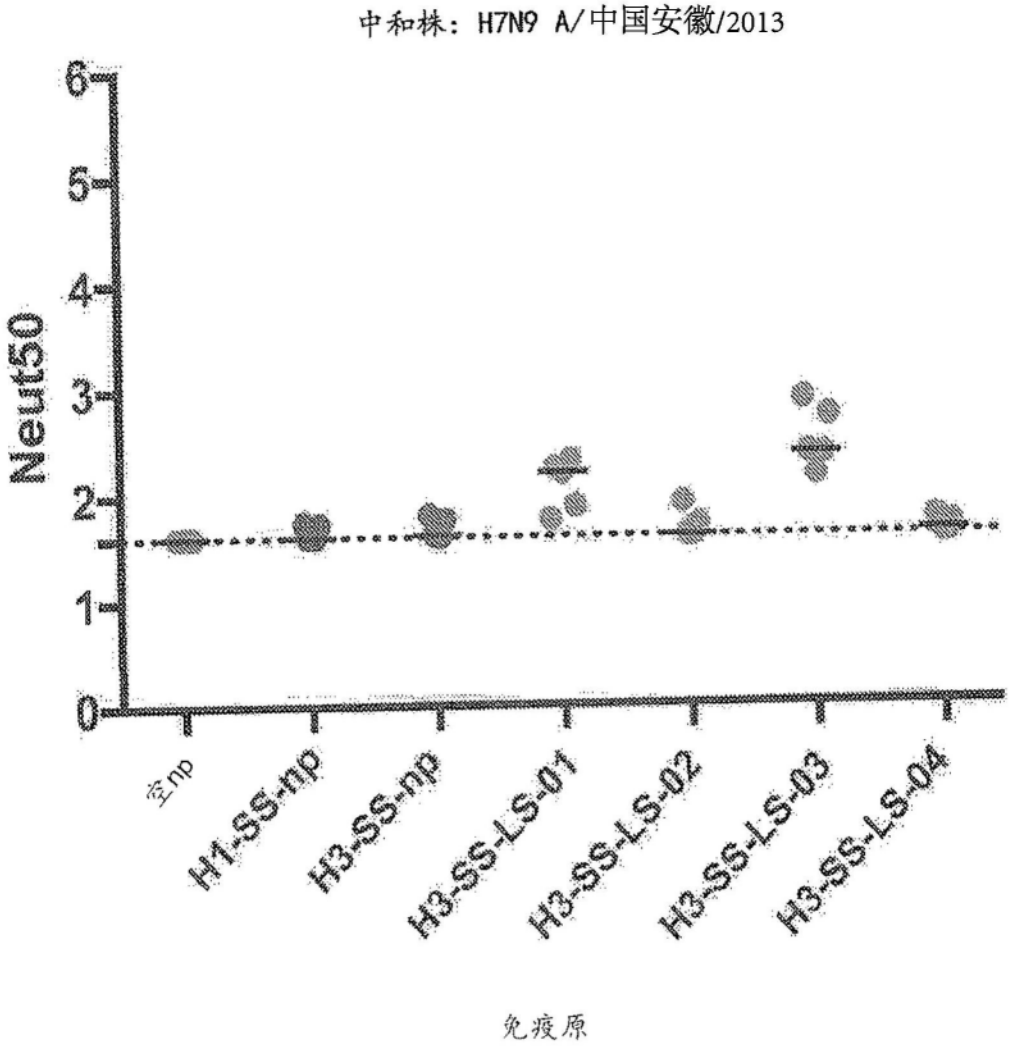

中和株：H7N9 A/中国安徽/2013
Neut50
0
1
2
3
4
5
6
空np
H1-SS-np
H3-SS-np
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图22A

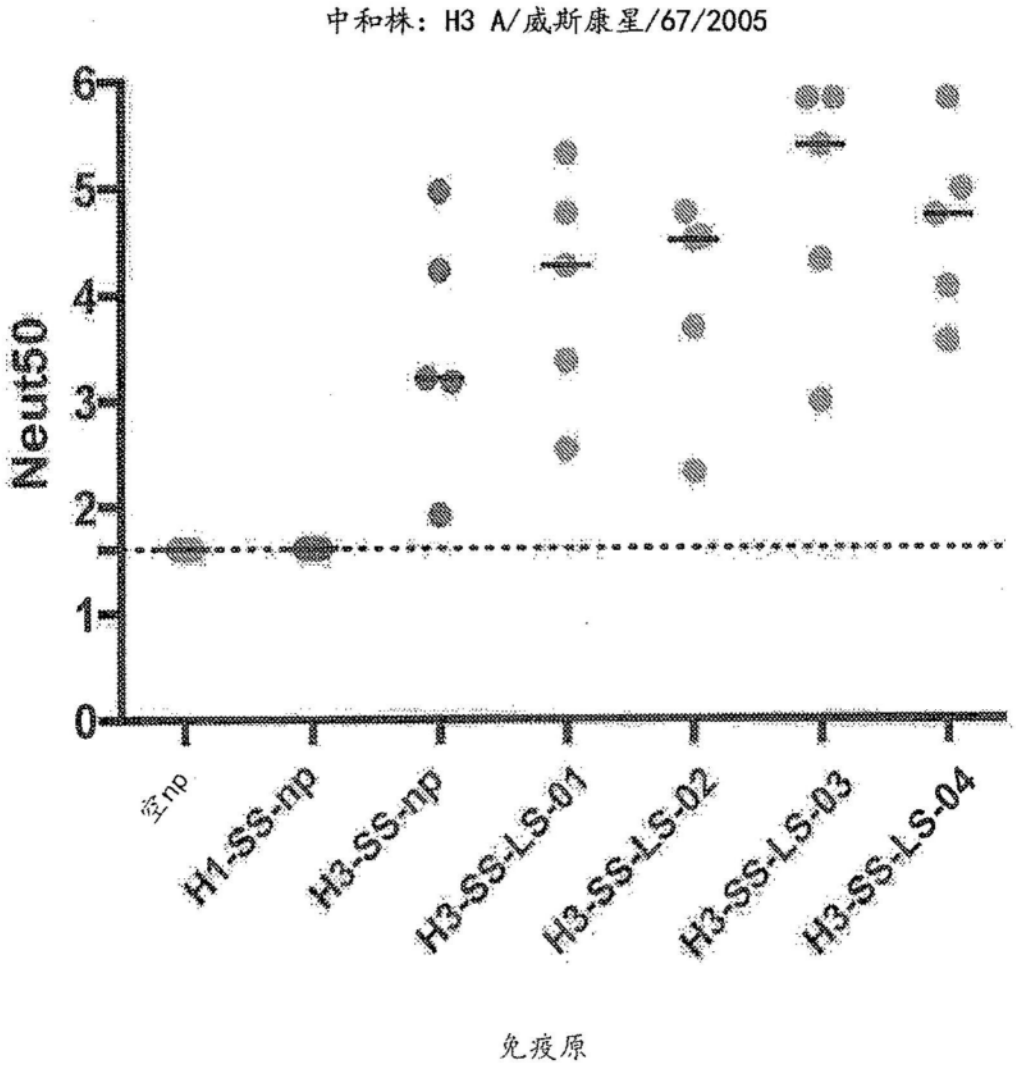

中和株：H3 A/威斯康星/67/2005
Neut50
0
1
2
3
4
5
6
空np
H1-SS-np
H3-SS-np
H3-SS-LS-01
H3-SS-LS-02
H3-SS-LS-03
H3-SS-LS-04
免疫原

图22B

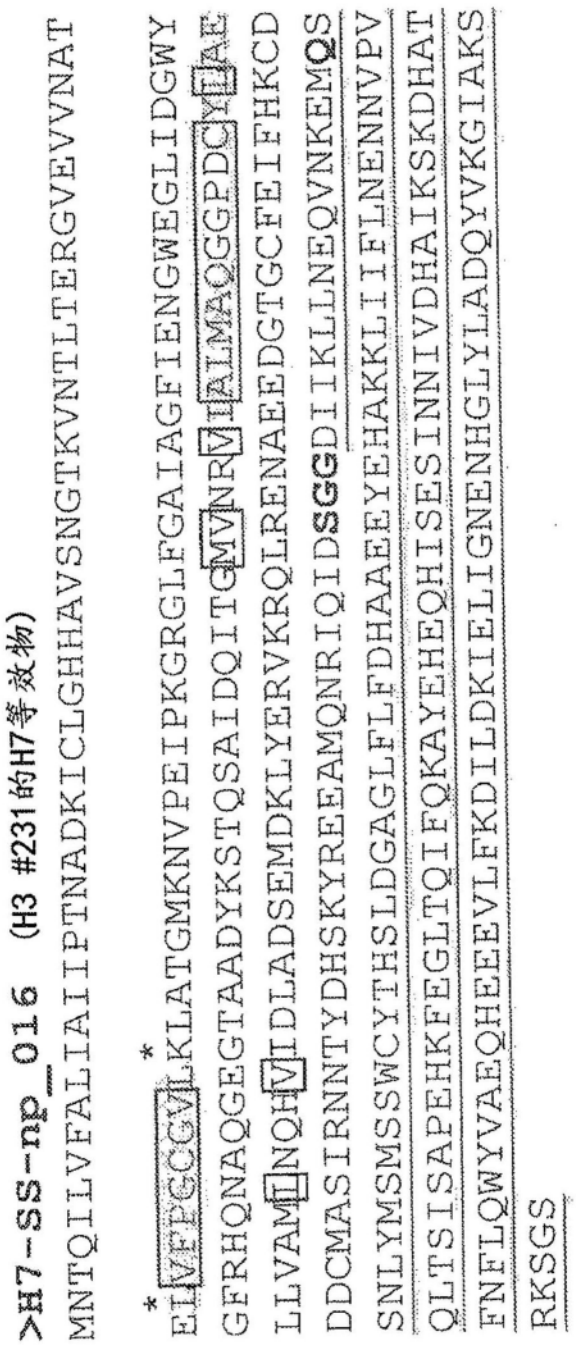

>H7-SS-np_016 (H3 #231的H7等效物)
MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNAT
ELVFPGCGVLKLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGWY
GFRHQNAQGEGTAADYKSTQSAIDQITGMVNRMIALMAQGGPDCYLAE
LLVAMLNQHVIDLADSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCD
DDCMASIRNNTYDHSKYREEAMQNRIQIDSGGDIIKLLNEQVNKEMQS
SNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNVPV
QLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHAT
FNFLQWYVAEQHEEEVLFKDILDKIELIGNENHGLYLADQYVKGIAKS
RKSGS

图23

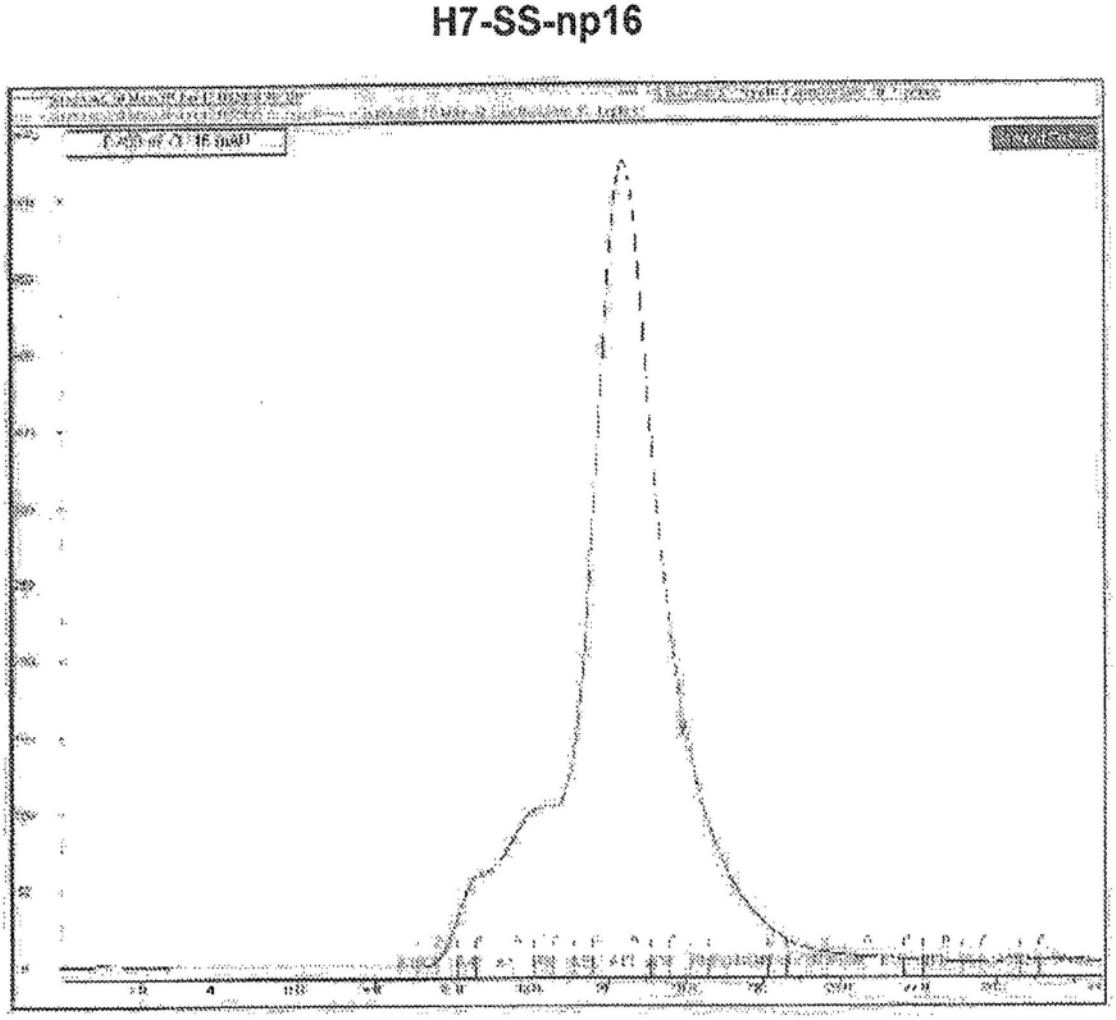


图24A

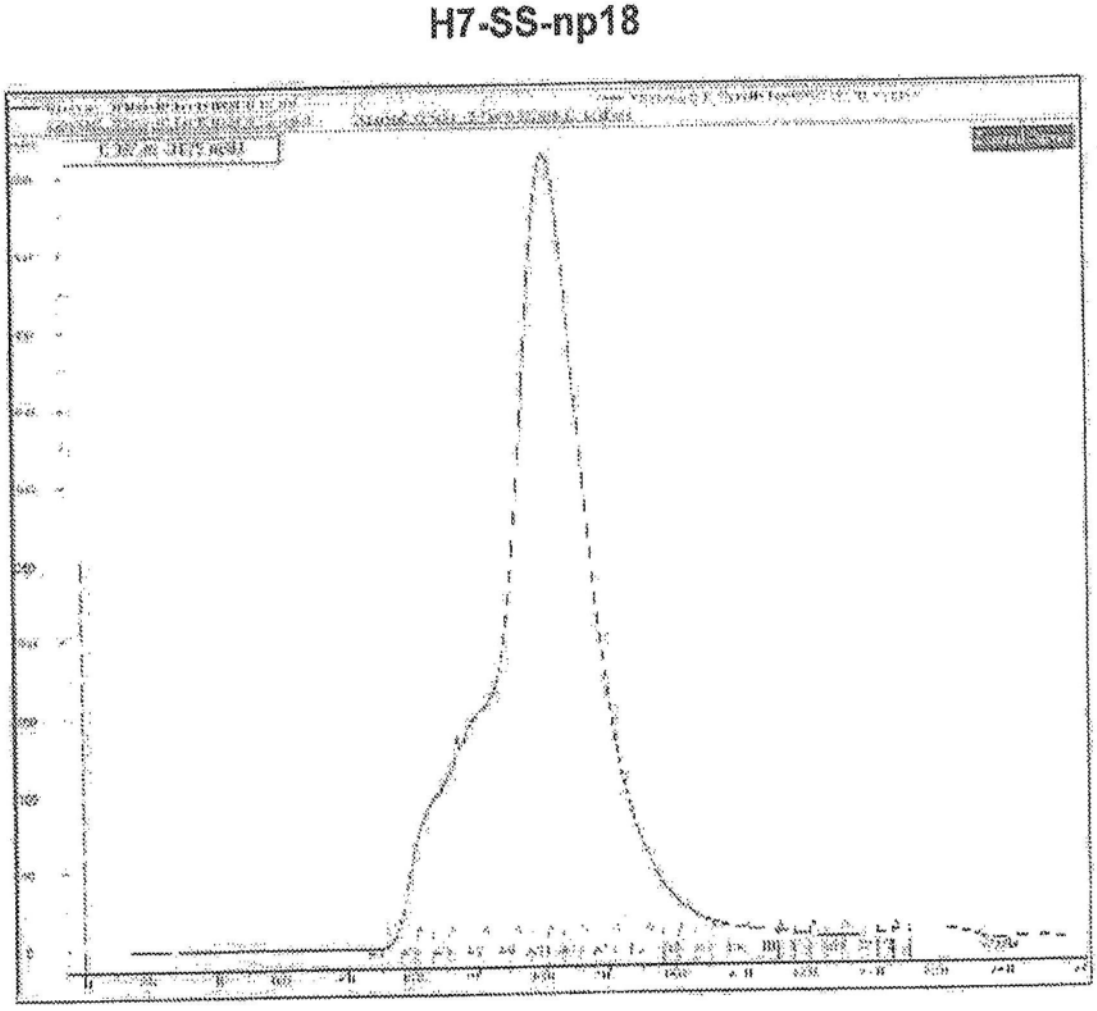


图24B

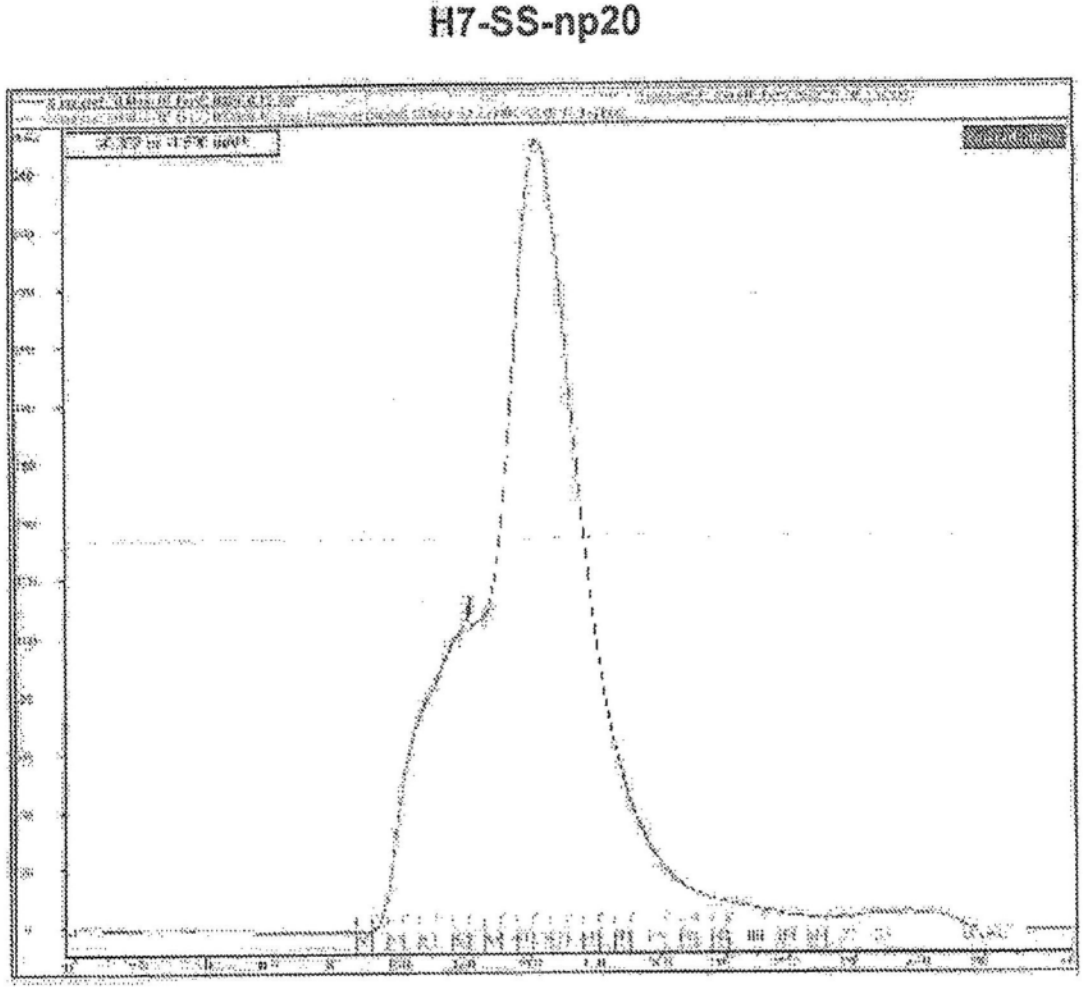


图24C

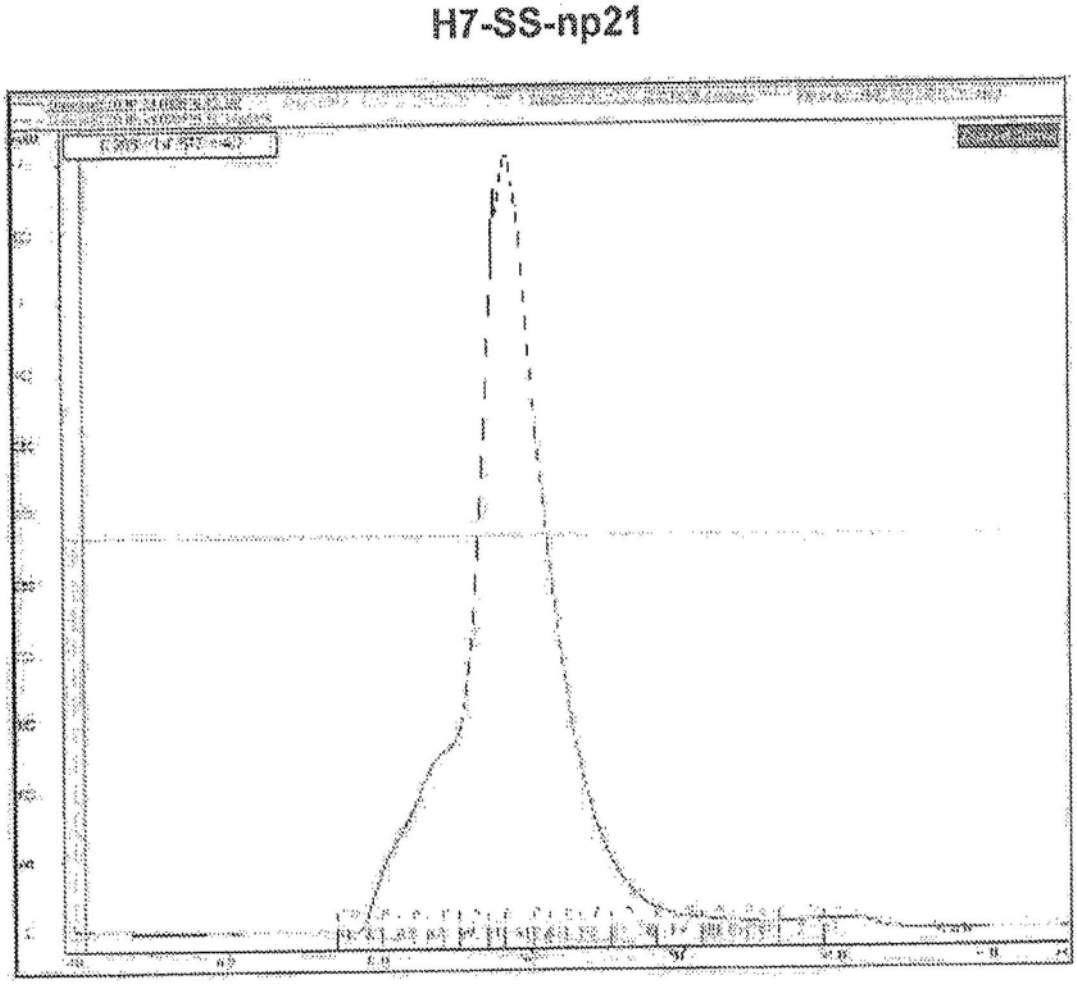


图24D

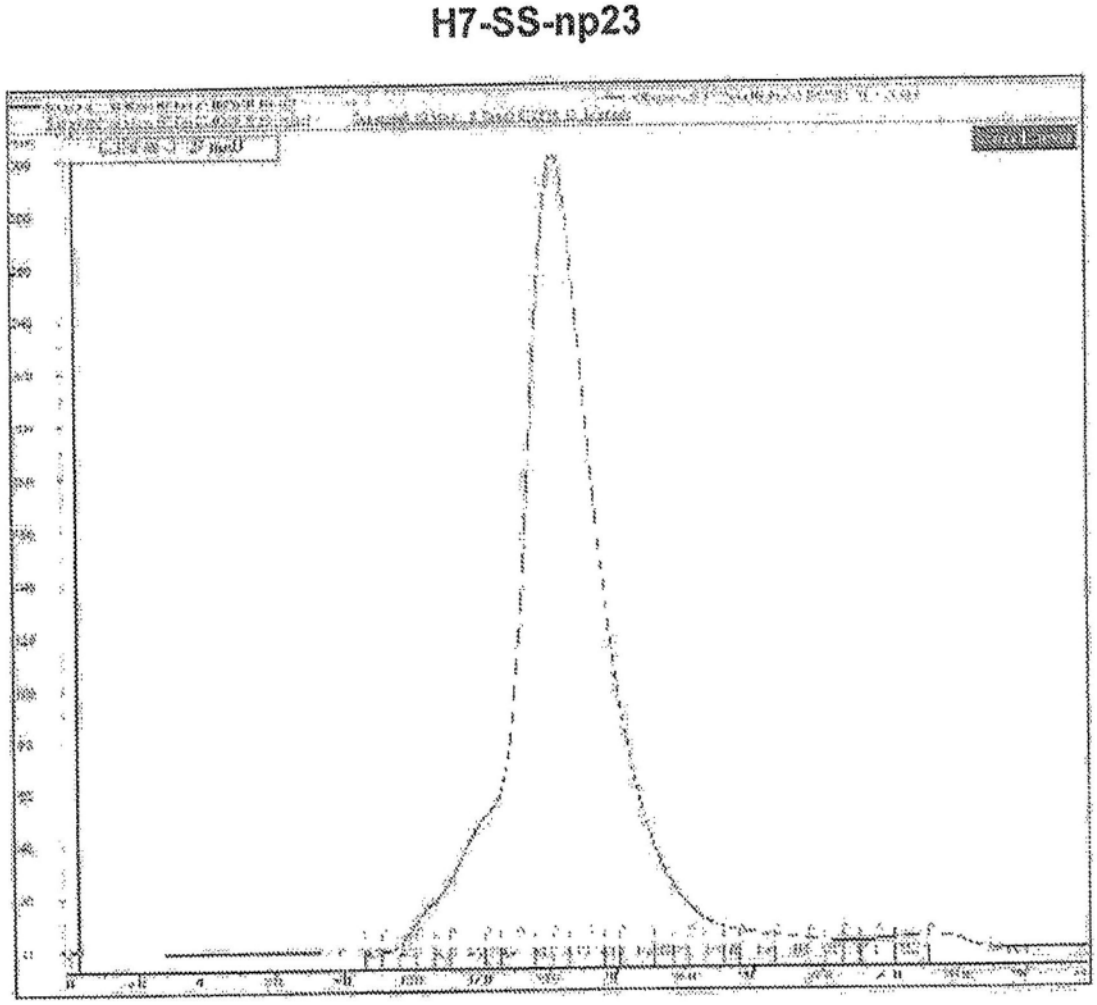


图24E

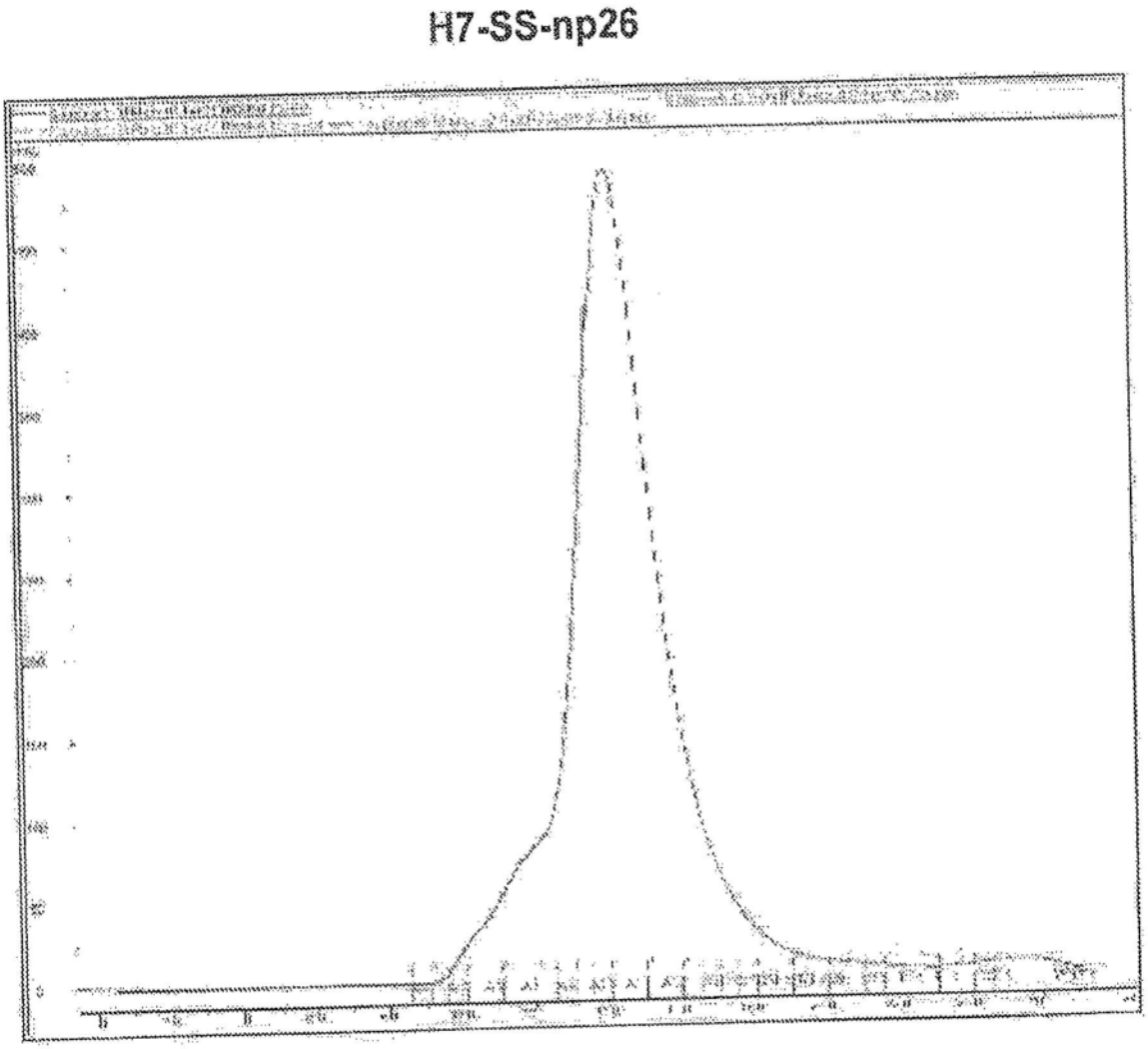


图24F

H1-SS-np（对照）

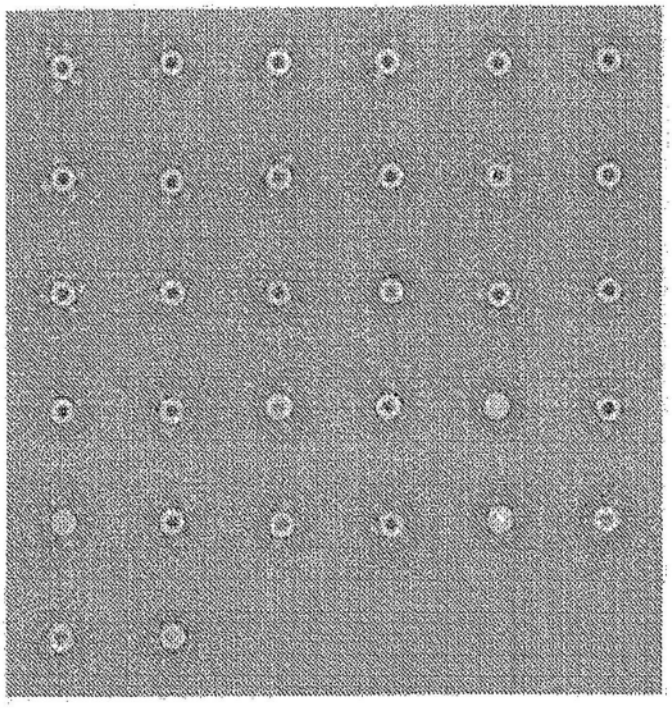


图25A

H7-SS-16

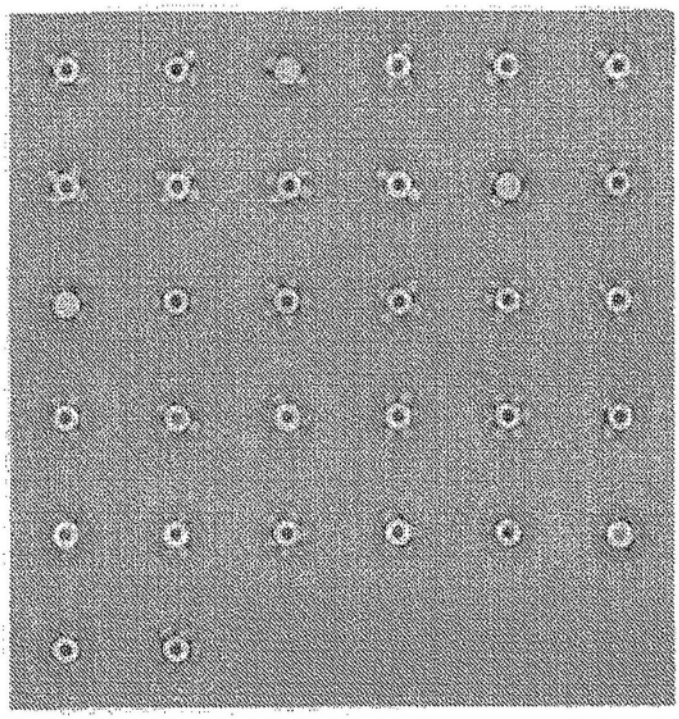


图25B

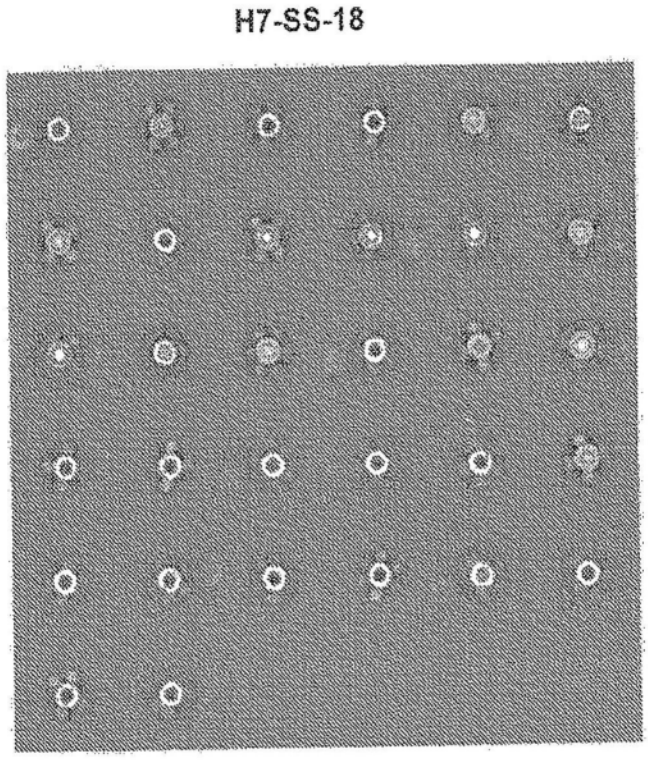


图25C

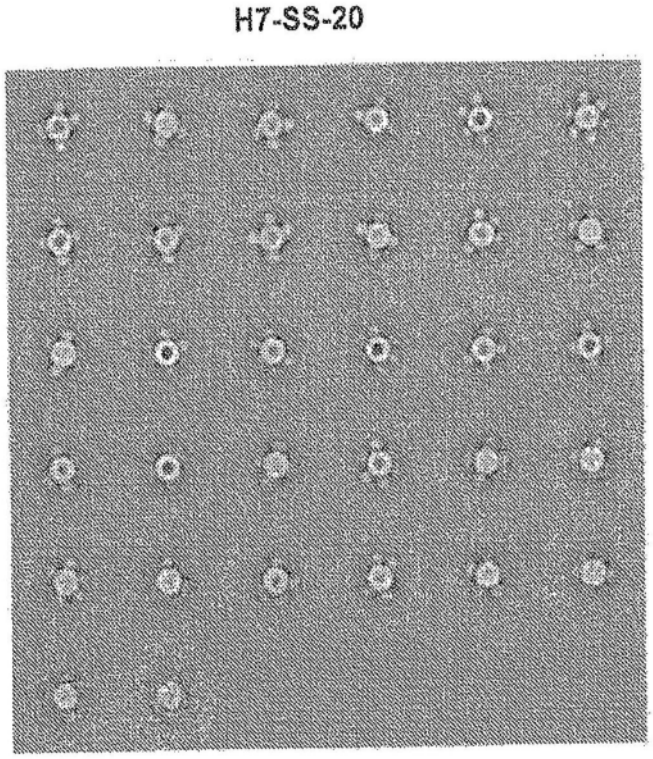


图25D

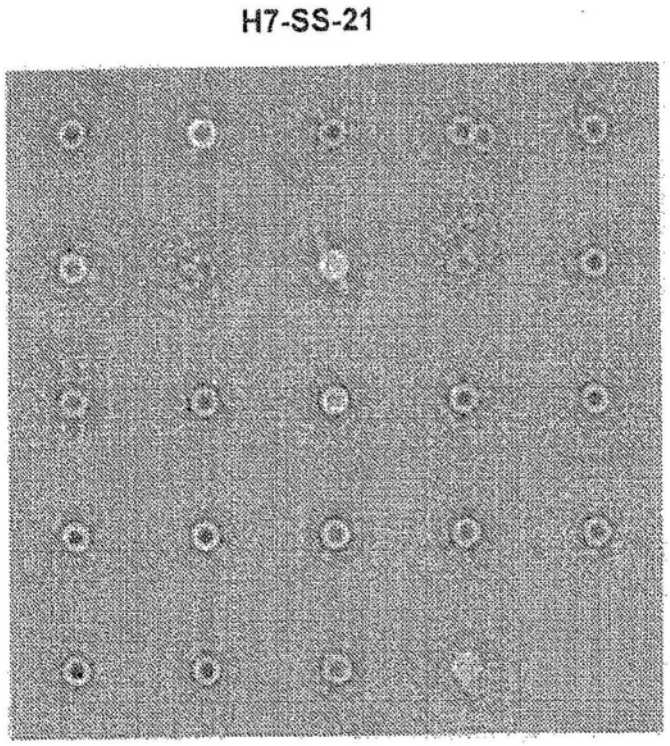


图25E

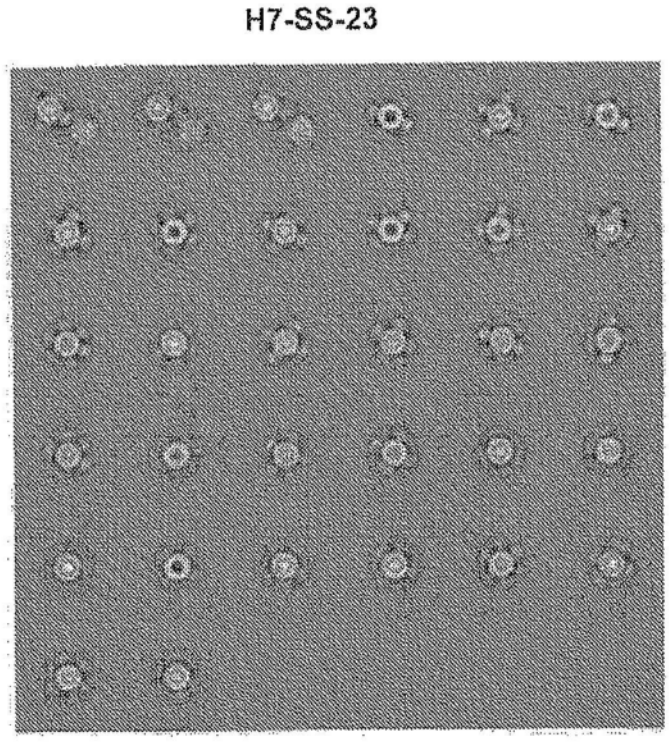


图25F

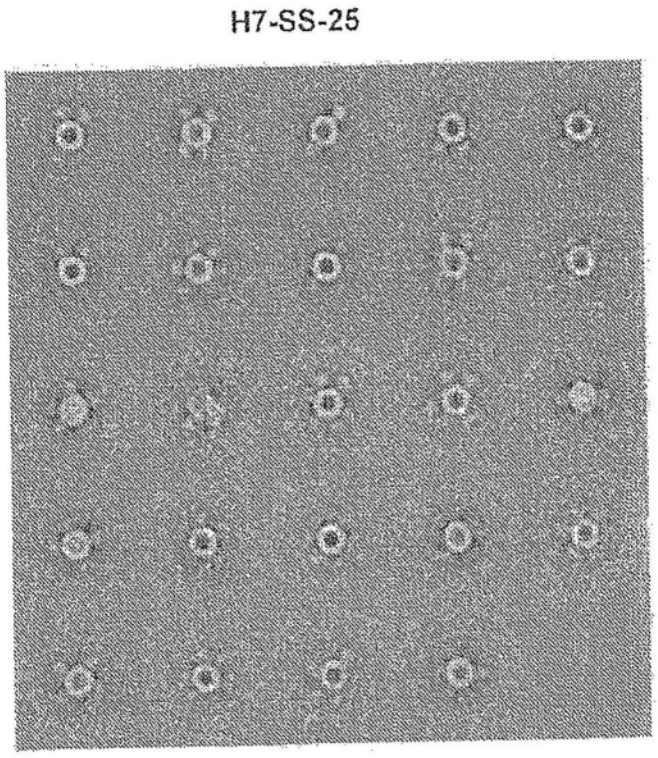


图25G

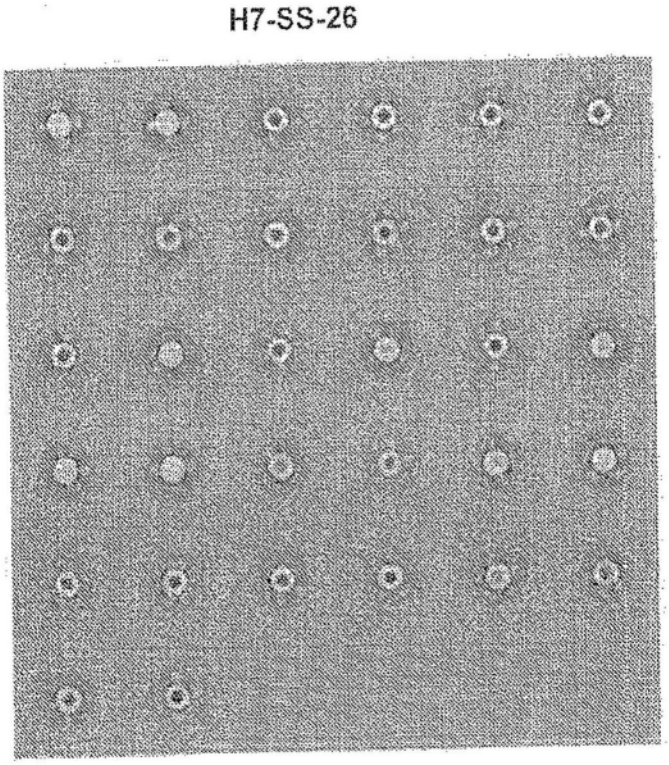


图25H

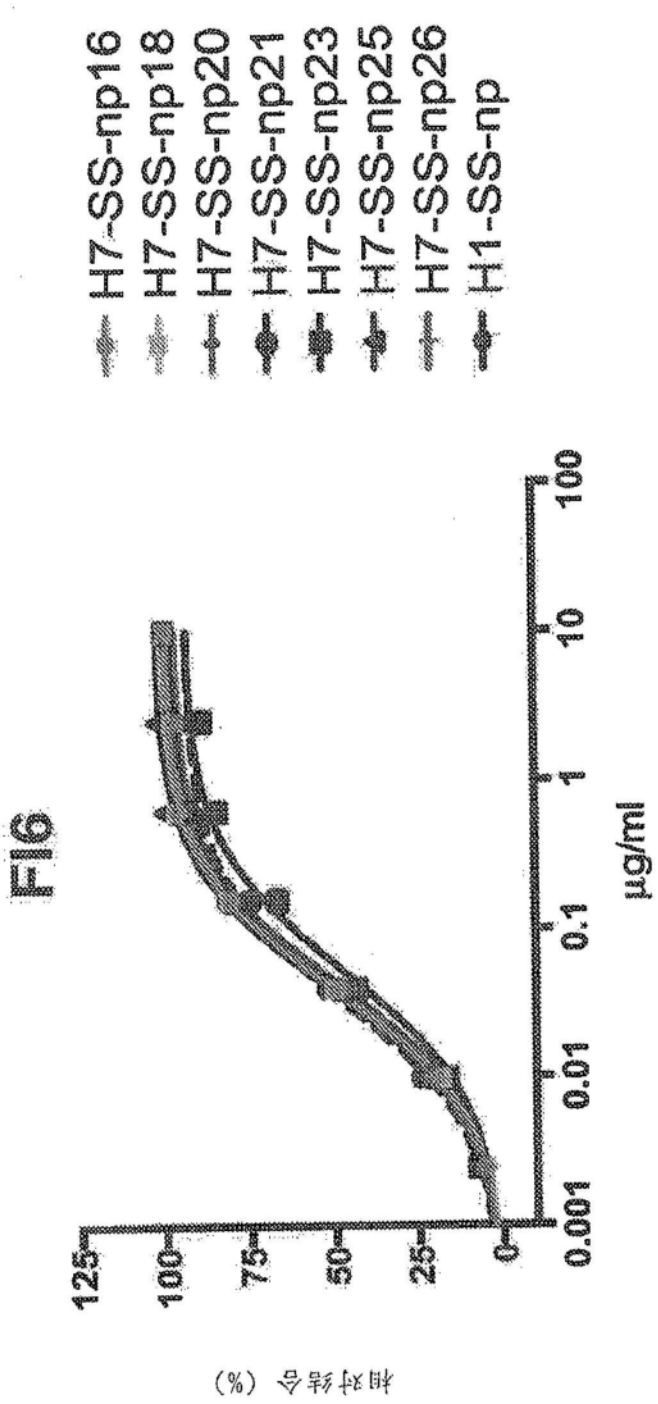

H7-SS-np16
H7-SS-np18
H7-SS-np20
H7-SS-np21
H7-SS-np23
H7-SS-np25
H7-SS-np26
H1-SS-np
FI6
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
μg/ml
相对结合 (%)

图26A

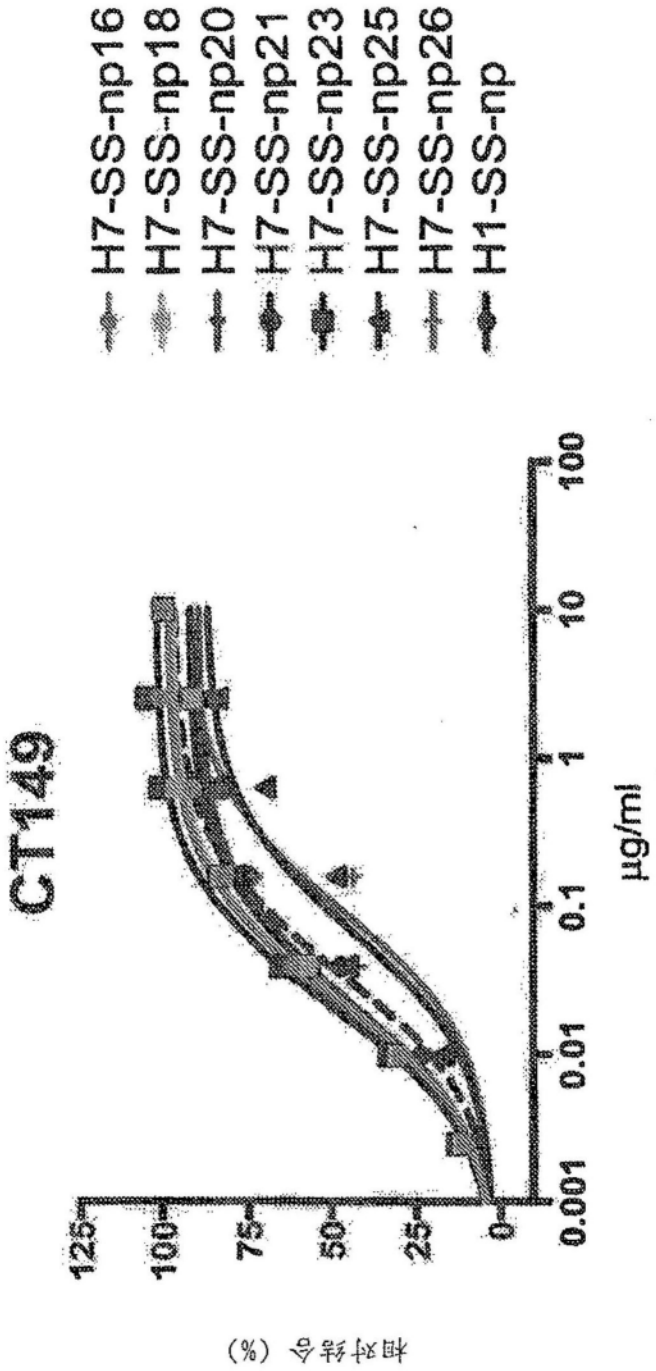

H7-SS-np16
H7-SS-np18
H7-SS-np20
H7-SS-np21
H7-SS-np23
H7-SS-np25
H7-SS-np26
H1-SS-np
CT149
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
μg/ml
相对结合（%）

图26B

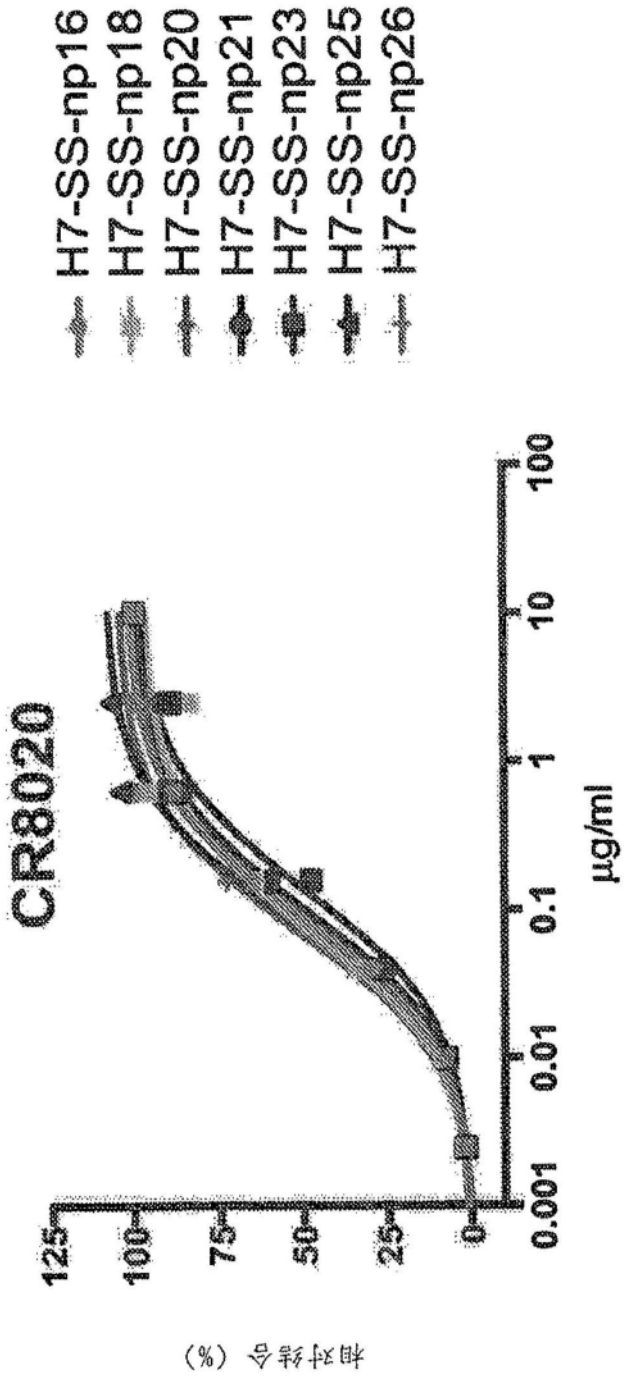

H7-SS-np16
H7-SS-np18
H7-SS-np20
H7-SS-np21
H7-SS-np23
H7-SS-np25
H7-SS-np26
CR8020
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
μg/ml
相对结合（%）

图26C

设计	抗体 IC_{50} (μg/ml)		
	FI6	CT149	CR8020
H7-SS-np16	0.039	0.024	0.089
H7-SS-np18	0.039	0.024	0.069
H7-SS-np20	0.045	0.024	0.084
H7-SS-np21	0.038	0.024	0.101
H7-SS-np23	0.052	0.022	0.135
H7-SS-np25	0.039	0.070	0.086
H7-SS-np26	0.038	0.096	0.071
H1-SS-np	0.032	0.037	ND

图26D

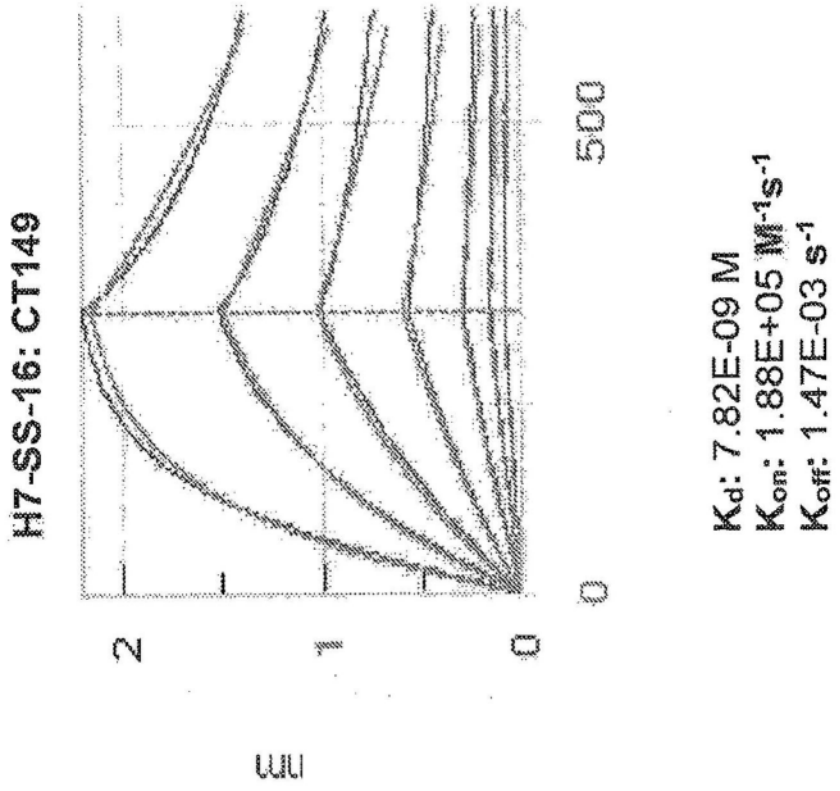


图27A

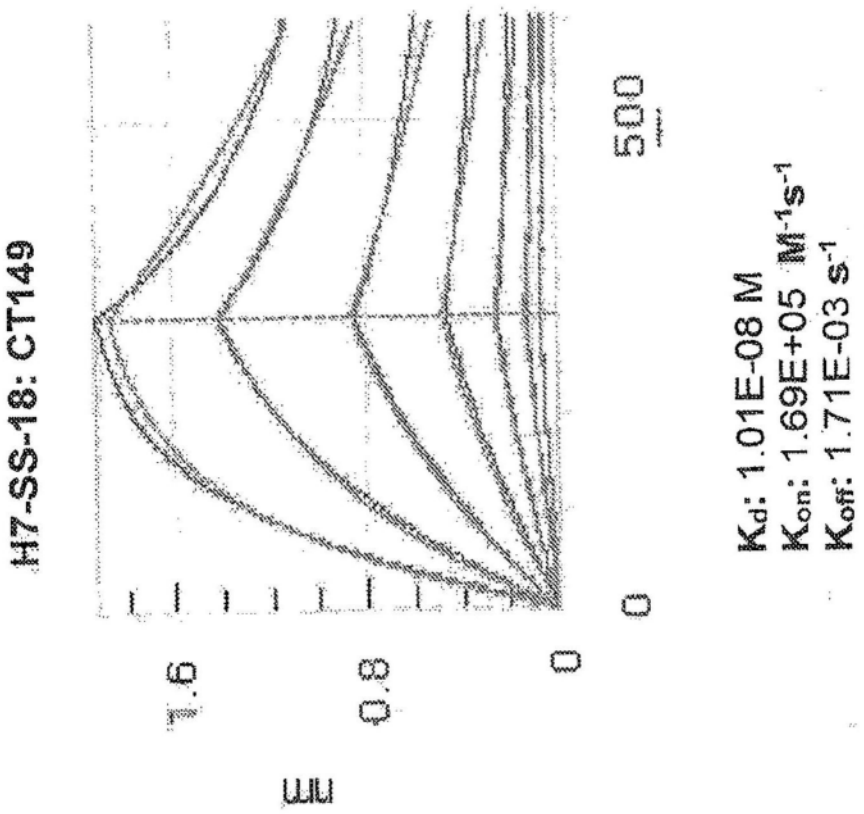

H7-SS-18: CT149
nm
1.6
0.8
0
0
500
K_d: 1.01E-08 M
K_{on}: 1.69E+05 $M^{-1}s^{-1}$
K_{off}: 1.71E-03 s^{-1}

图27B

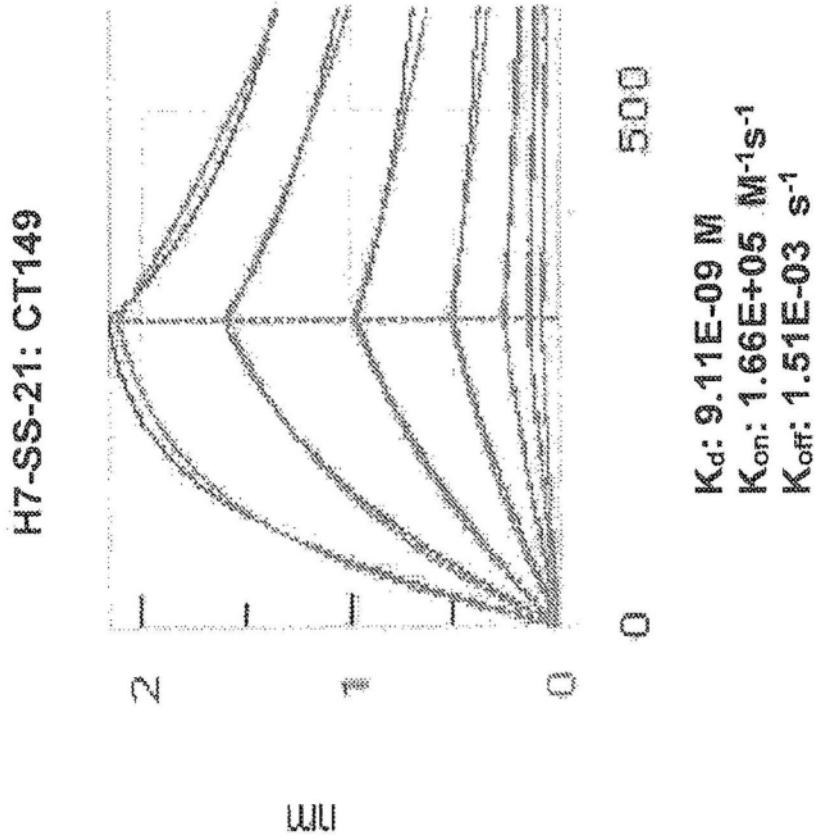

H7-SS-21: CT149
Kd: 9.11E-09 M
Kon: 1.66E+05 M-1s-1
Koff: 1.51E-03 s-1
500
0
2
0
nm

图27C

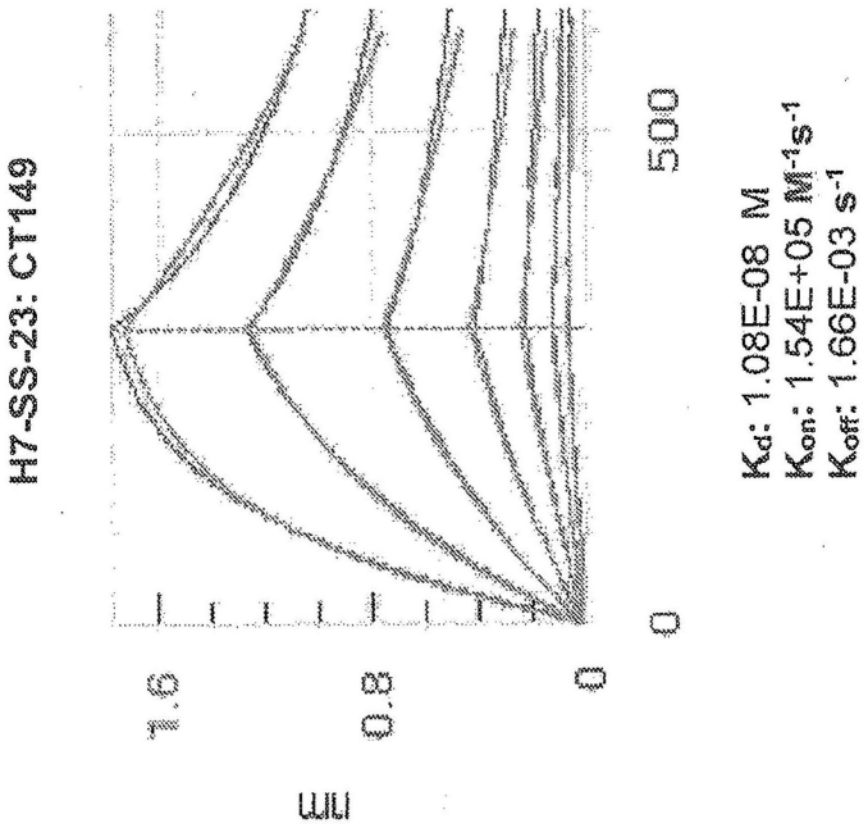

H7-SS-23: CT149
nm
1.6
0.8
0
0
500
K_d: 1.08E-08 M
K_{on}: 1.54E+05 $M^{-1}s^{-1}$
K_{off}: 1.66E-03 s^{-1}

图27D

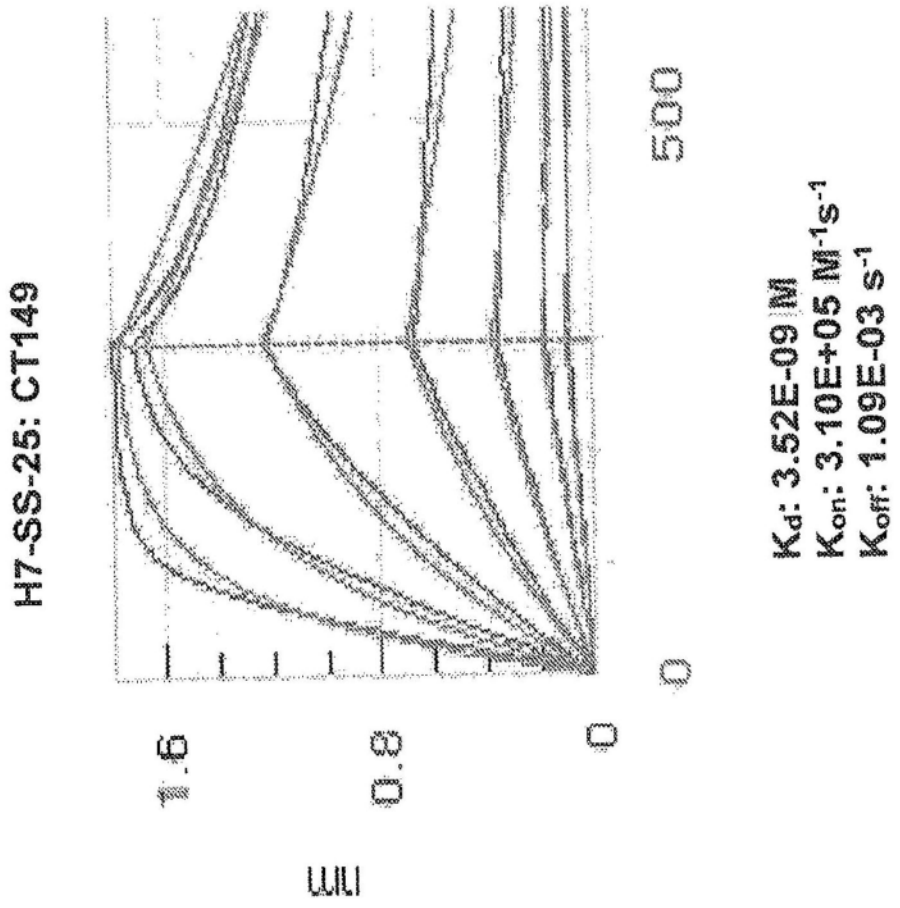

H7-SS-25: CT149
nm
1.6
0.8
0
0
500
K_d: 3.52E-09 M
K_{on}: 3.10E+05 $M^{-1}s^{-1}$
K_{off}: 1.09E-03 s^{-1}

图27E

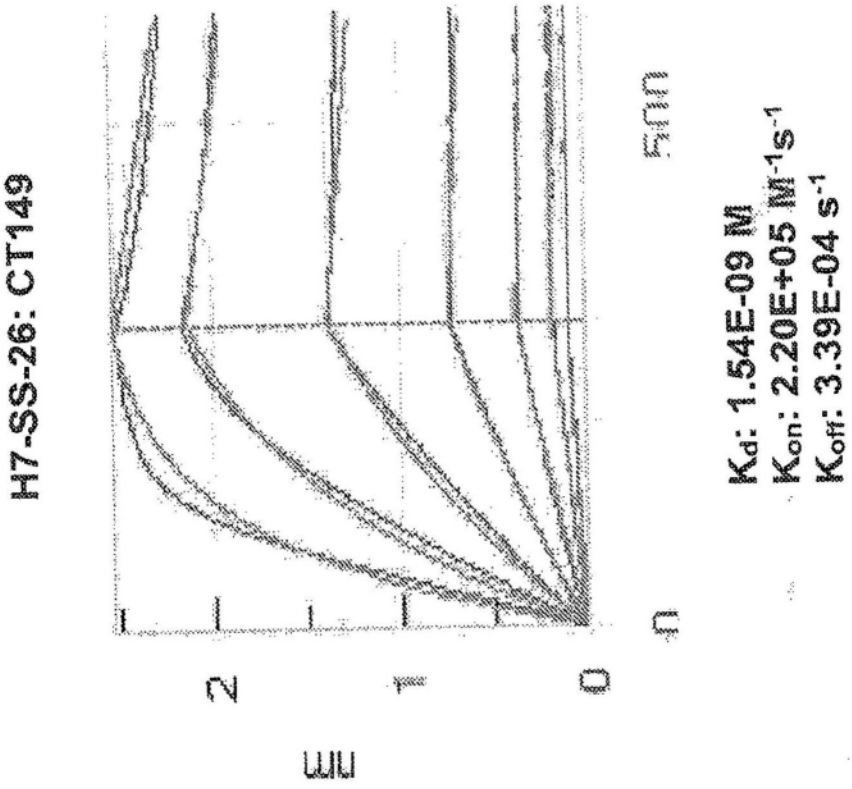

H7-SS-26: CT149
Kd: 1.54E-09 M
Kon: 2.20E+05 M-1s-1
Koff: 3.39E-04 s-1
nm
0
1
2

图27F

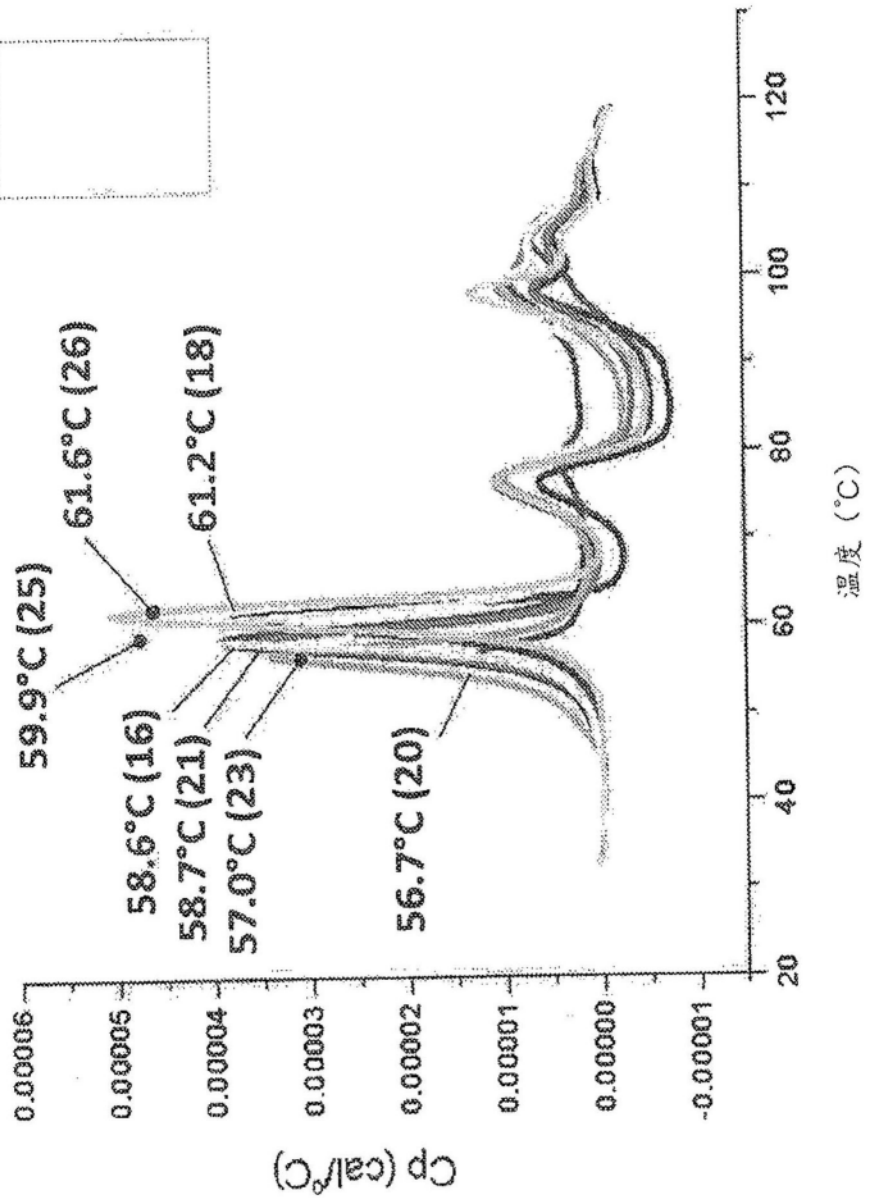

59.9°C (25)
61.6°C (26)
61.2°C (18)
58.6°C (16)
58.7°C (21)
57.0°C (23)
56.7°C (20)
0.00006
0.00005
0.00004
0.00003
0.00002
0.00001
0.00000
-0.00001
Cp (cal/°C)
20
40
60
80
100
120
温度（°C）

图28

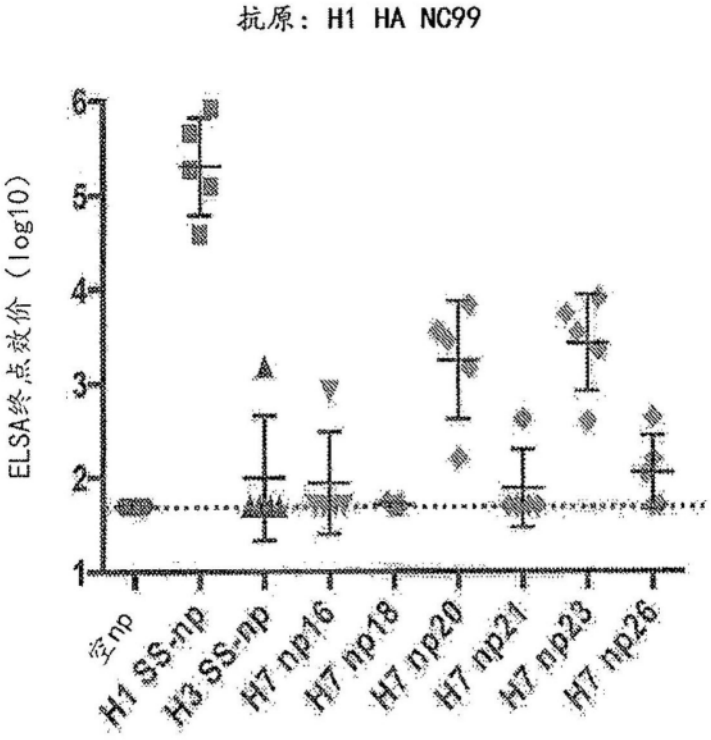

抗原：H1 HA NC99
ELSA终点效价（log10）
6
5
4
3
2
1
空np
H1 SS-np
H3 SS-np
H7 np16
H7 np18
H7 np20
H7 np21
H7 np23
H7 np26

图29A

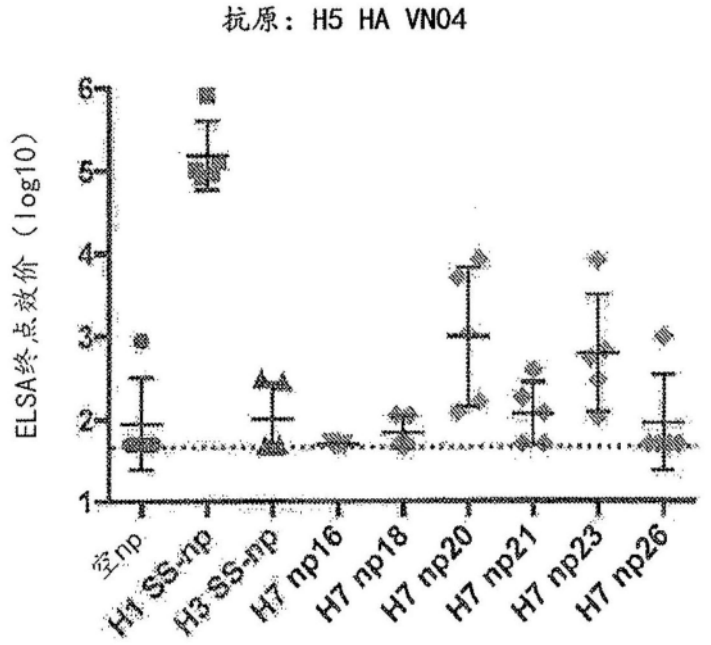

抗原：H5 HA VN04
ELSA终点效价（log10）
6
5
4
3
2
1
空np
H1 SS-np
H3 SS-np
H7 np16
H7 np18
H7 np20
H7 np21
H7 np23
H7 np26

图29B

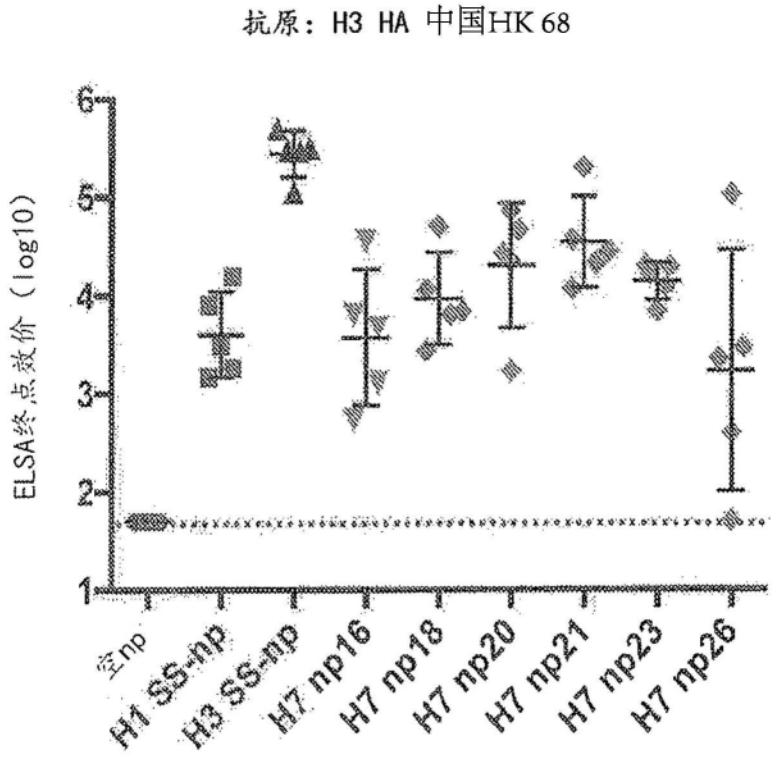

抗原：H3 HA 中国HK 68
ELSA终点效价（log10）
1
2
3
4
5
6
空np
H1 SS-np
H3 SS-np
H7 np16
H7 np18
H7 np20
H7 np21
H7 np23
H7 np26

图29C

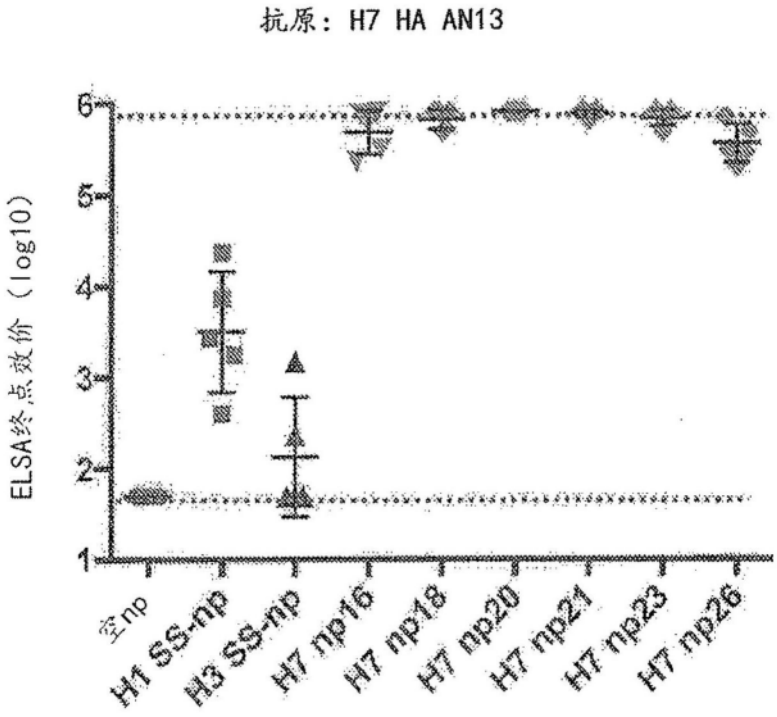

抗原：H7 HA AN13
ELSA终点效价（log10）
1
2
3
4
5
6
空np
H1 SS-np
H3 SS-np
H7 np16
H7 np18
H7 np20
H7 np21
H7 np23
H7 np26

图29D

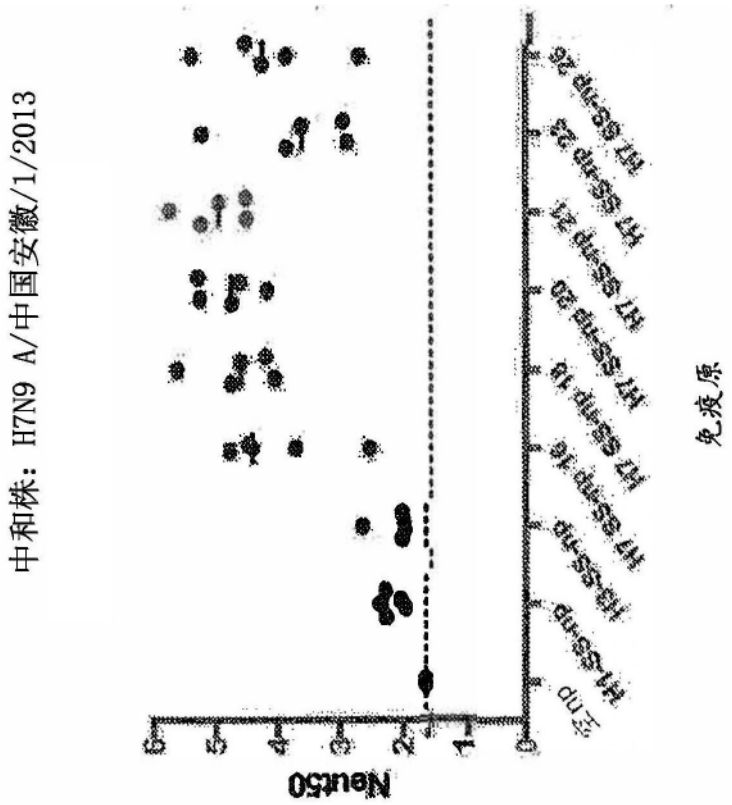

中和株：H7N9 A/中国安徽/1/2013
NeuT50
6
5
4
3
2
1
0
空NP
HA-SS-NP
H3 SS-NP
H7 SS-NP 16
H7 SS-NP 18
H7 SS-NP 20
H7 SS-NP 21
H7 SS-NP 23
H7 SS-NP 26
免疫原

图30A

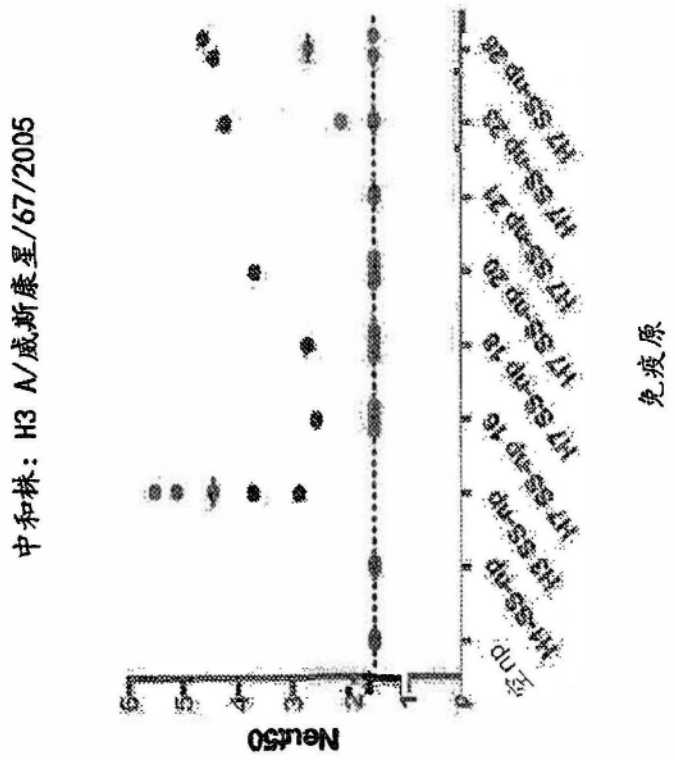

中和株：H3 A/威斯康星/67/2005
NeuT50
6
5
4
3
2
1
0
空NP
HA-SS-NP
H3 SS-NP
H7 SS-NP 16
H7 SS-NP 18
H7 SS-NP 20
H7 SS-NP 21
H7 SS-NP 23
H7 SS-NP 26
免疫原

图30B

>H10N8-SS-np_02 (H10ssF_2) (SEQ ID NO:103)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATELVFPGCVLMLATGMRNVPELIQGRGLFGAIAGFLENGWEGMVDGWY
GFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEM
CDDSCMESIRNNTYDHSQYREEALLNRLNINSGGDIIKLLNEQVNKEMKSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNEN
NVPVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFKDIIDKIELIGNENHGLYLADQYV
KGIAKSRKSGS

>H10N8-SS-np_03 (H10ssF_3) (SEQ ID NO:104)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATELVFPCGVLMLATGMRNVPELIQGRGLFGAIAGFLENGWEGMVDGWY
GFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDMTDSEM
CDDSCMESIRNNTYDHSQYREEALLNRLNINSGGDIIKLLNEQVNKEMKSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNEN
NVPVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFKDIIDKIELIGNENHGLYLADQYV
KGIAKSRKSGS

>H10N8-SS-np_04 (H10ssF_4) (SEQ ID NO:105)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATELVFPGCGVLMLATGMRNVPELIQGRGLFGAIAGFLENGWEGMVDGWY
GFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDMTDSEM
DDSCMESIRNNTYDHSQYREEALLNRLNITMSGGDIIKLLNEQVNKEMQSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNV
PVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVLFKDIIDKIELIGNENHGLYLADQYVKGI
AKSRKSGS

>H10N8-SS-np_05 (H10ssF_5) (SEQ ID NO:106)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATELVFPGCGVLMLATGMRNVPELIQGRGLFGAIAGFLENGWEGMVDGWY
GFRHQNAQGTGQAADYKSTQAAIDQITGKLNRLIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDMTDSEM
DDSCMESIRNNTYDHSQYREEALLNRLNITNSGGDIIKLLNEQVNKEMQSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIIFLNENNV
PVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKSKDHATFNFLQWYVAEQHEEEVTGFKDIIDKIELIGNENHGLYLADQYVKGI
AKSRKSGS

图31

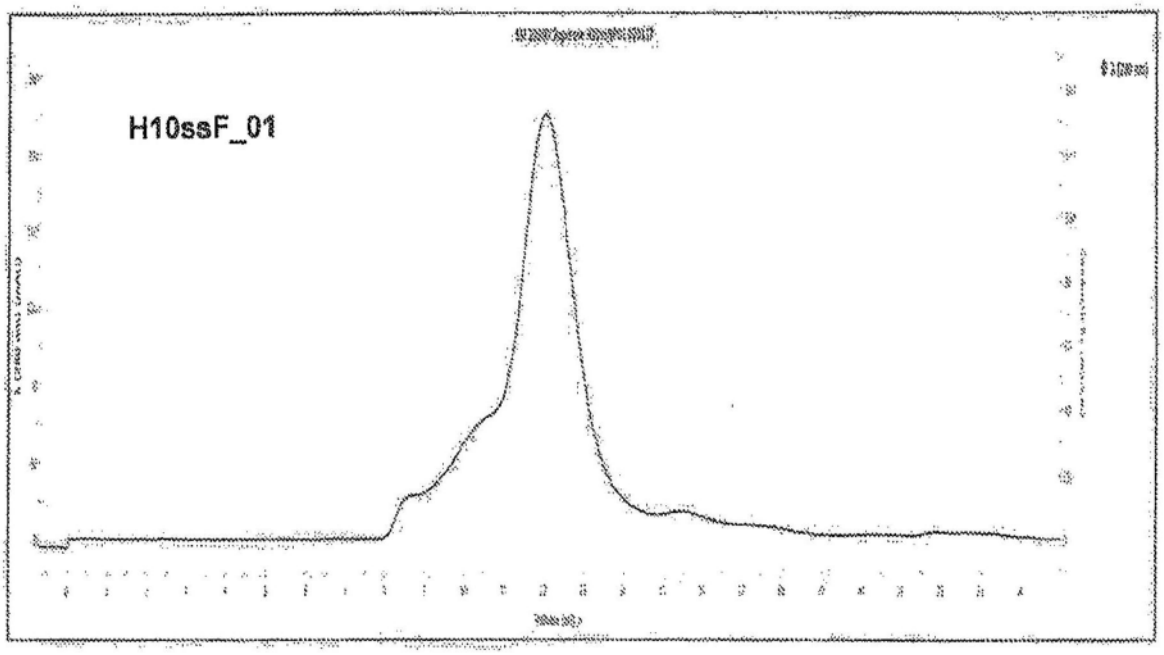


图32A

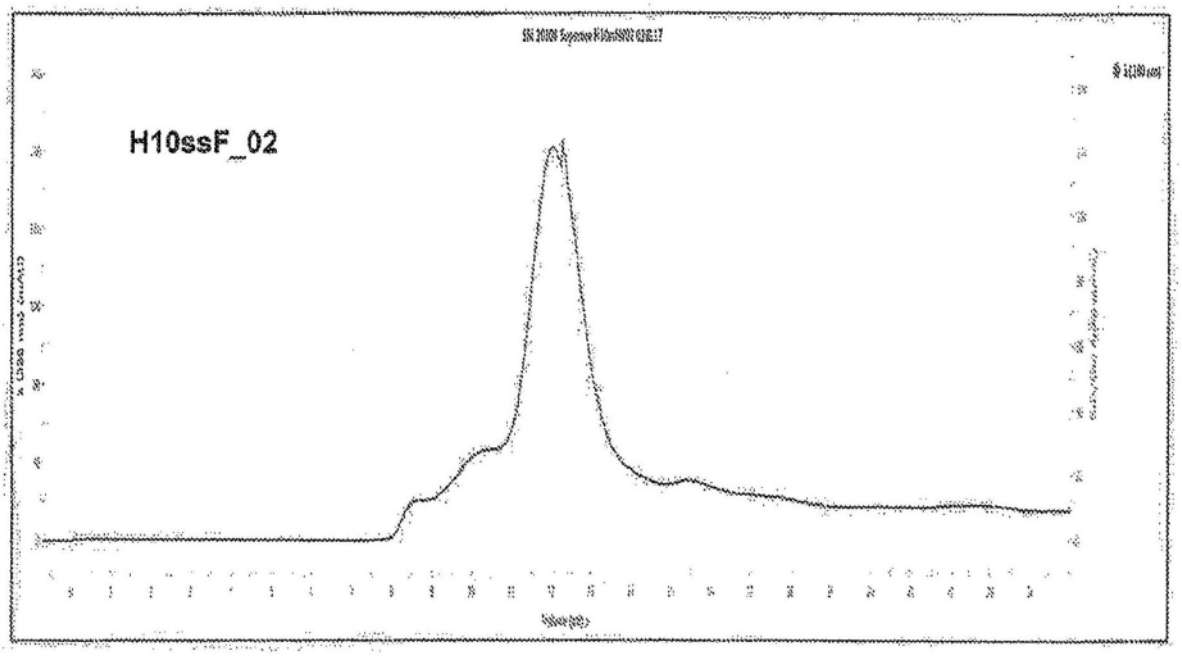


图32B

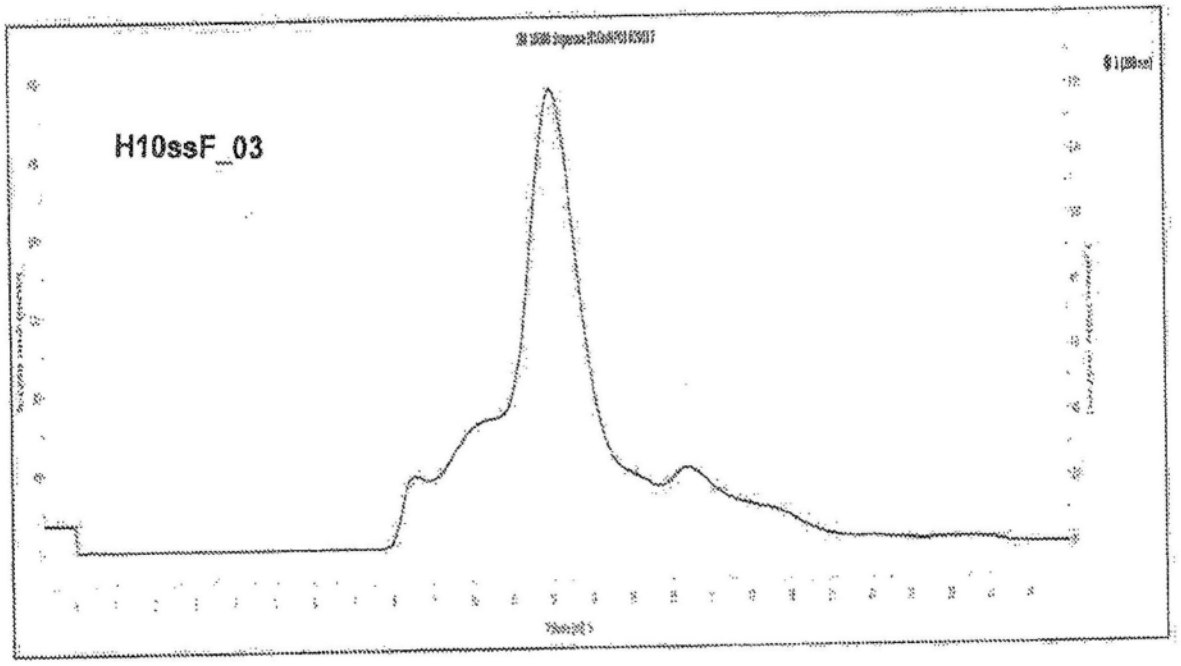


图32C

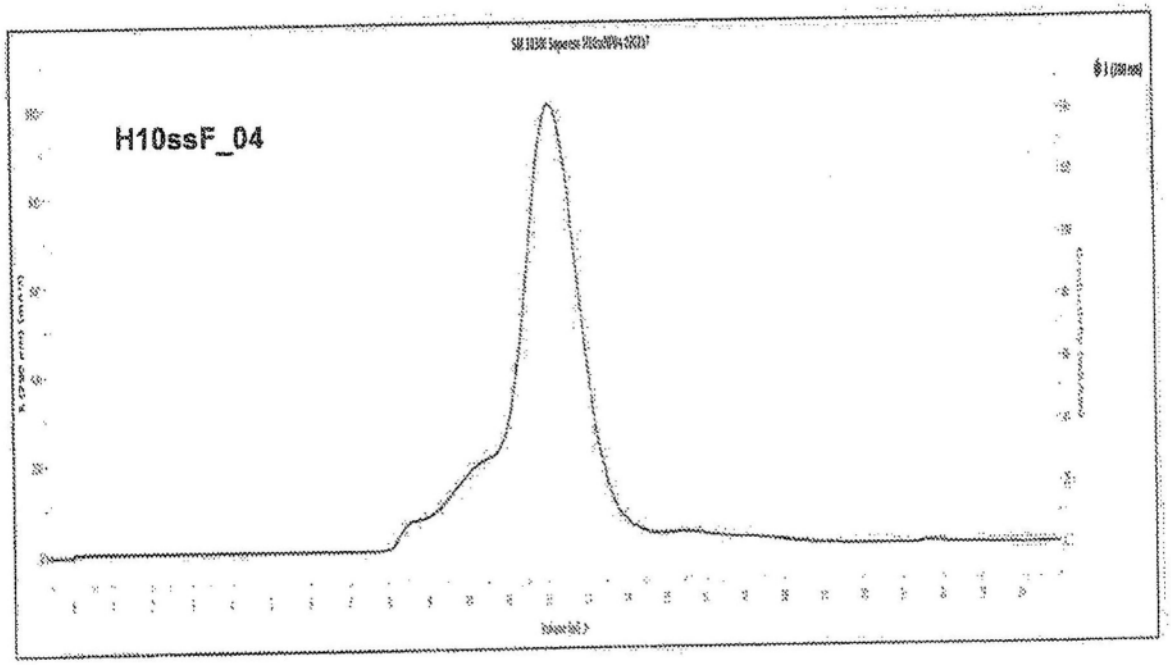


图32D

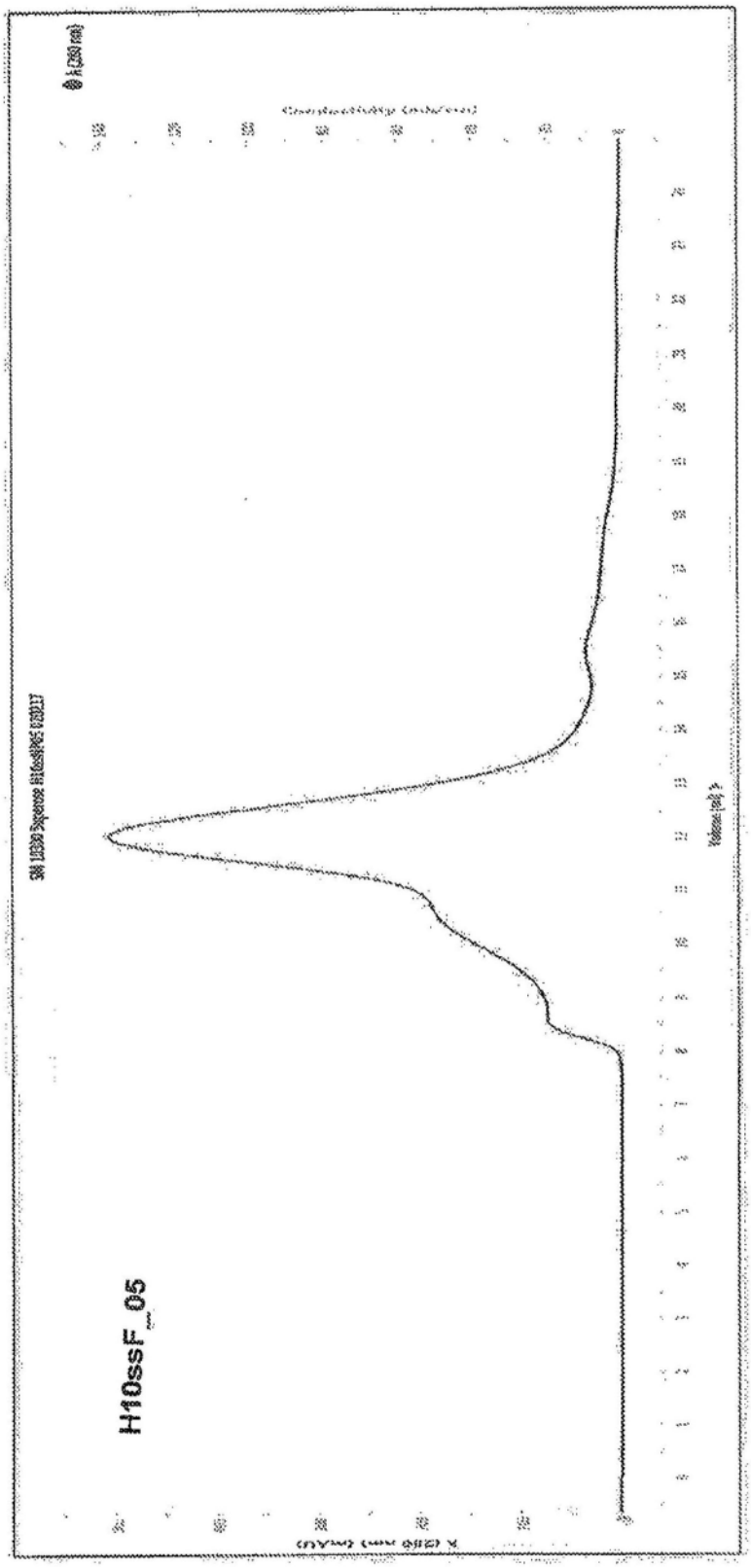
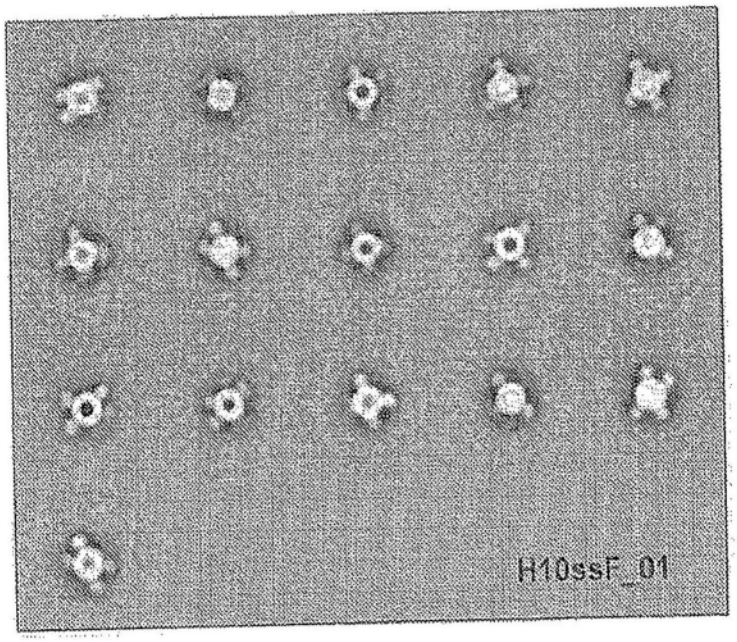
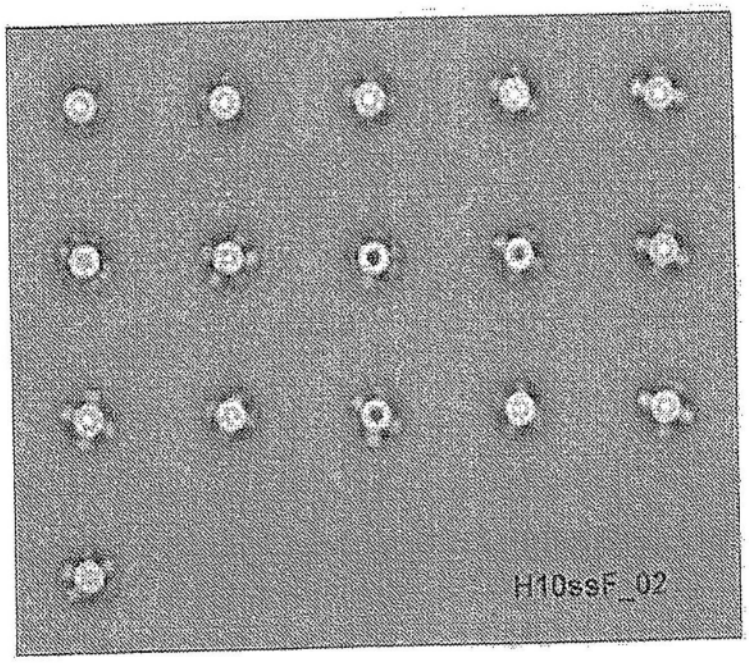


图32E



平均核尺寸: 13.5 ± 0.3 nm
平均刺突尺寸: 6.5 ± 0.4 nm

图33A



平均核尺寸: 13.5 ± 0.5 nm
平均刺突尺寸: 7.1 ± 0.8 nm

图33B

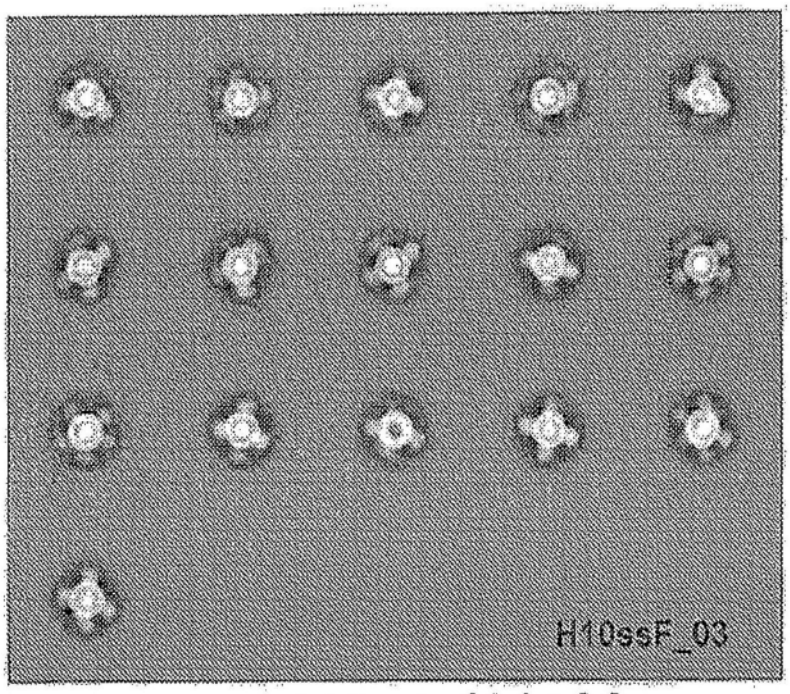

H10ssF_03
平均核尺寸: 14.4 ± 0.3 nm
平均刺突尺寸: 6.6 ± 0.5 nm

图33C

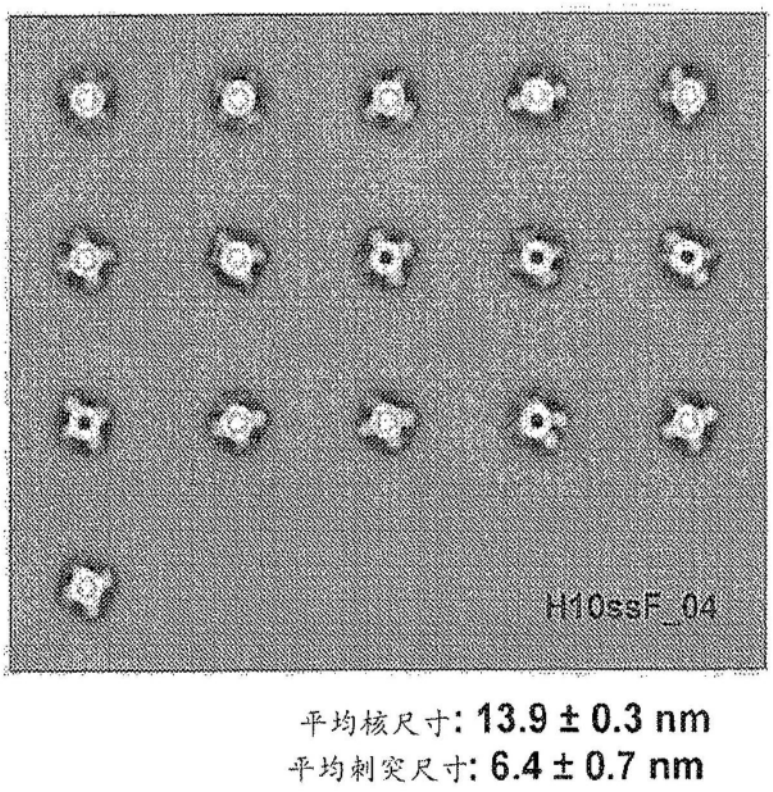
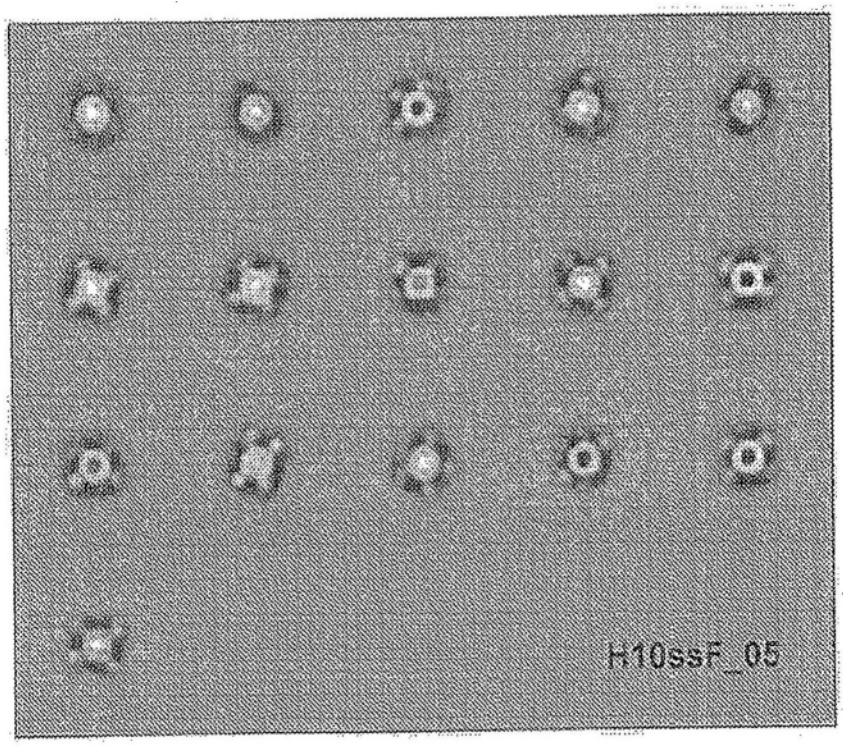

H10ssF_04
平均核尺寸: 13.9 ± 0.3 nm
平均刺突尺寸: 6.4 ± 0.7 nm

图33D



平均核尺寸：13.2 ± 0.7 nm
平均刺突尺寸：6.8 ± 0.5 nm

图33E

FI6

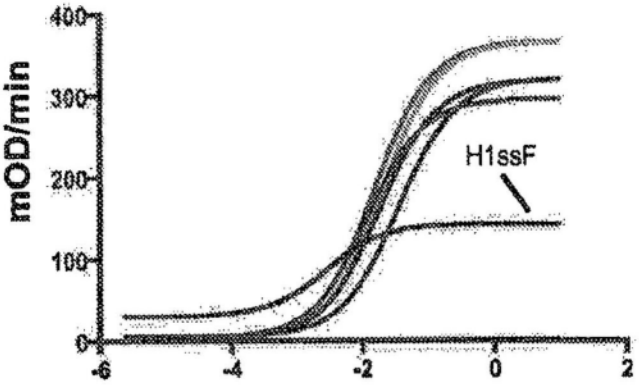


图34A

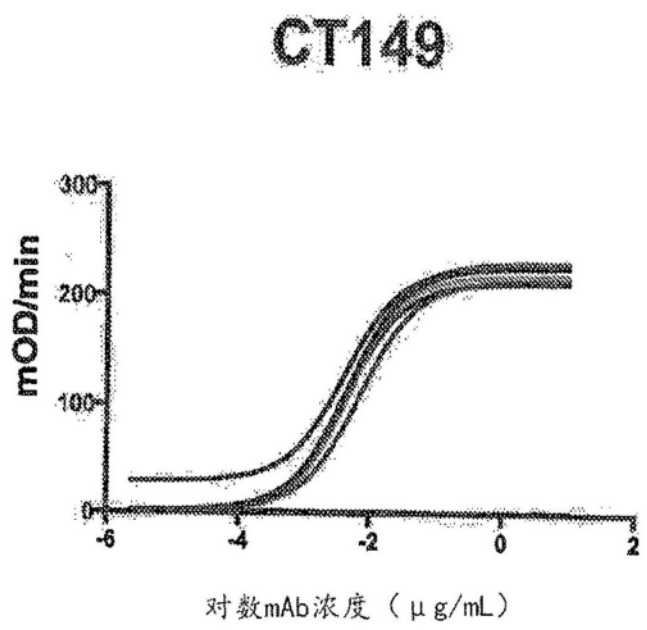

CT149
mOD/min
300
200
100
0
-6
-4
-2
0
2
对数mAb浓度（μg/mL）

图34B

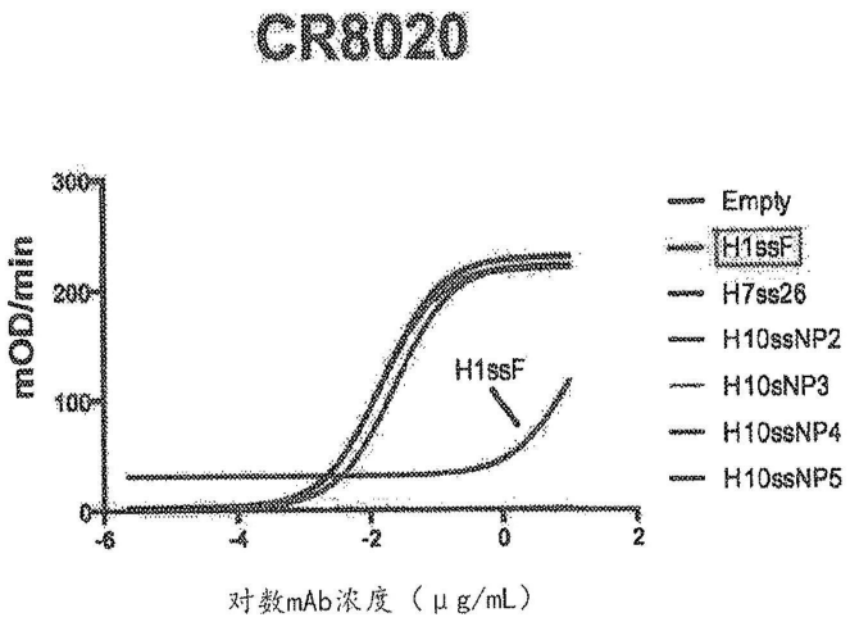

CR8020
mOD/min
300
200
100
0
-6
-4
-2
0
2
H1ssF
Empty
H1ssF
H7ss26
H10ssNP2
H10sNP3
H10ssNP4
H10ssNP5
对数mAb浓度（μg/mL）

图34C

纳米颗粒	抗体IC_{50} (mg/ml)		
	FI6	CT149	CR8020
Empty	ND	ND	ND
H1ssF	0.002	0.004	ND
H7ssF26	0.01	0.007	0.02
H10ssF2	0.02	0.004	0.01
H10ssF3	0.02	0.004	0.01
H10ssF4	0.01	0.005	0.01
H10ssF5	0.02	0.004	0.01

ND，未检测到

图34D

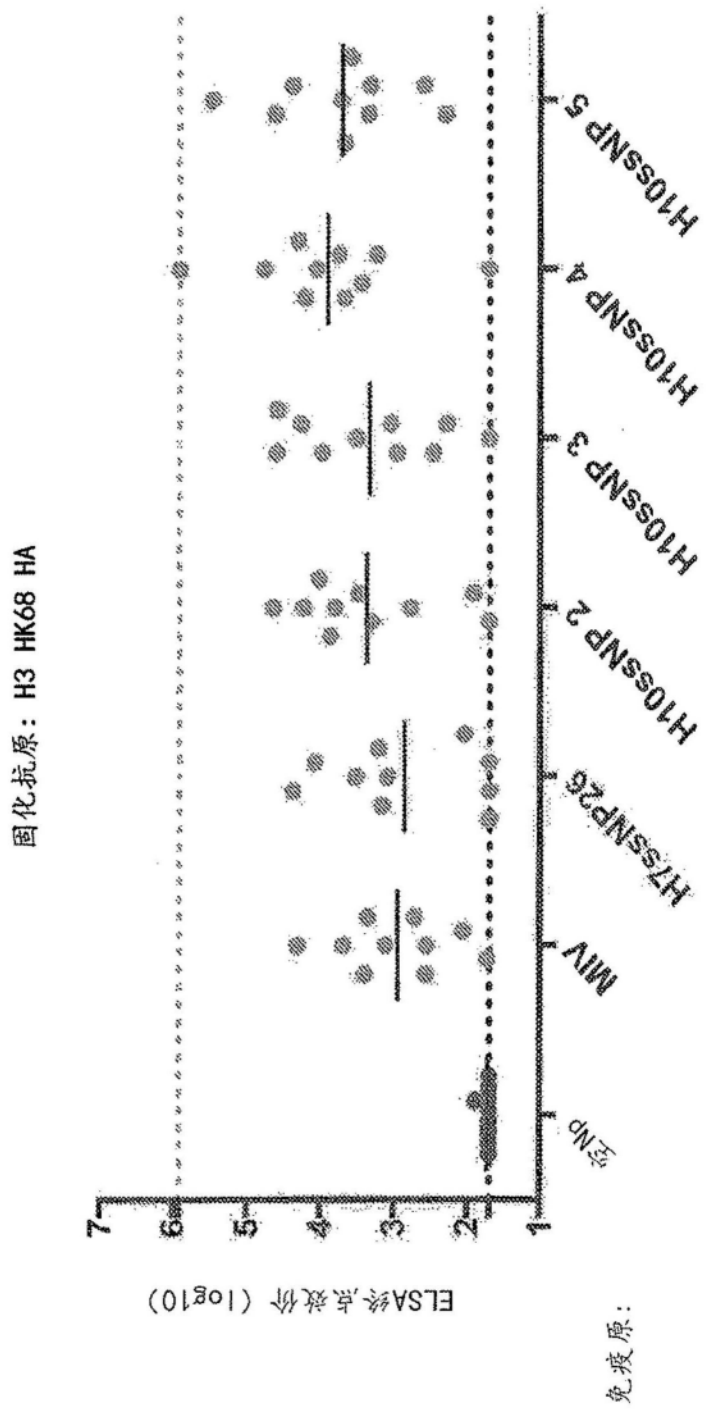

固化抗原：H3 HK68 HA
ELSA终点效价（log10）
7
6
5
4
3
2
1
免疫原：
空NP
MIV
H7SSNP26
H10SSNP 2
H10SSNP 3
H10SSNP 4
H10SSNP 5

图35A

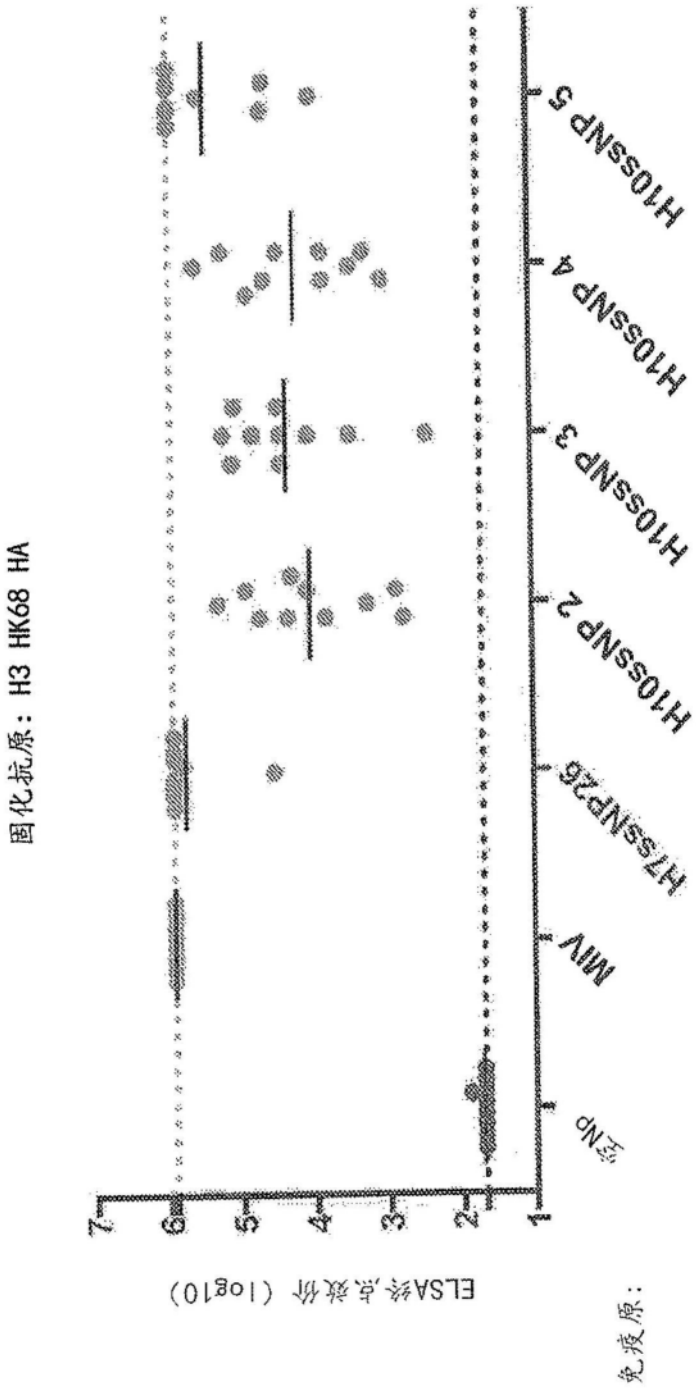

固化抗原：H3 HK68 HA
ELSA终点效价（log10）
7
6
5
4
3
2
1
免疫原：
空NP
MIV
H7SSNP26
H10SSNP2
H10SSNP3
H10SSNP4
H10SSNP5

图35B

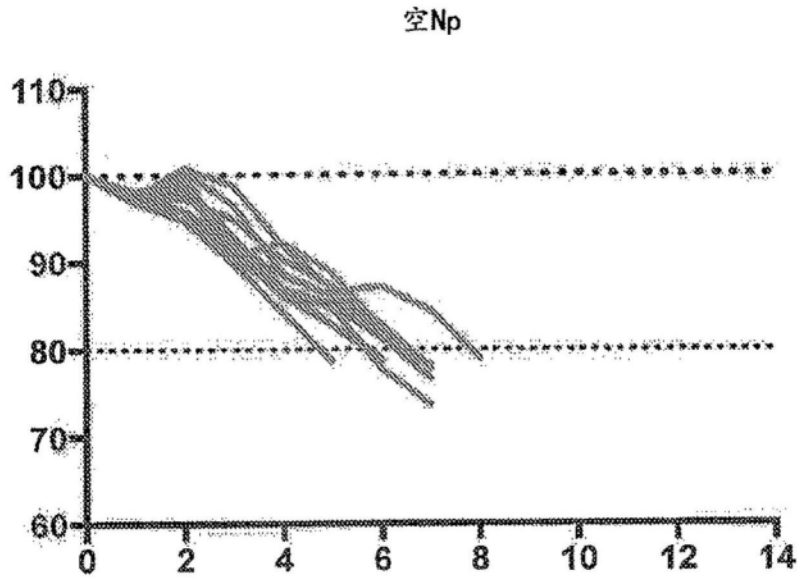

空Np
110
100
90
80
70
60
0
2
4
6
8
10
12
14

图36A

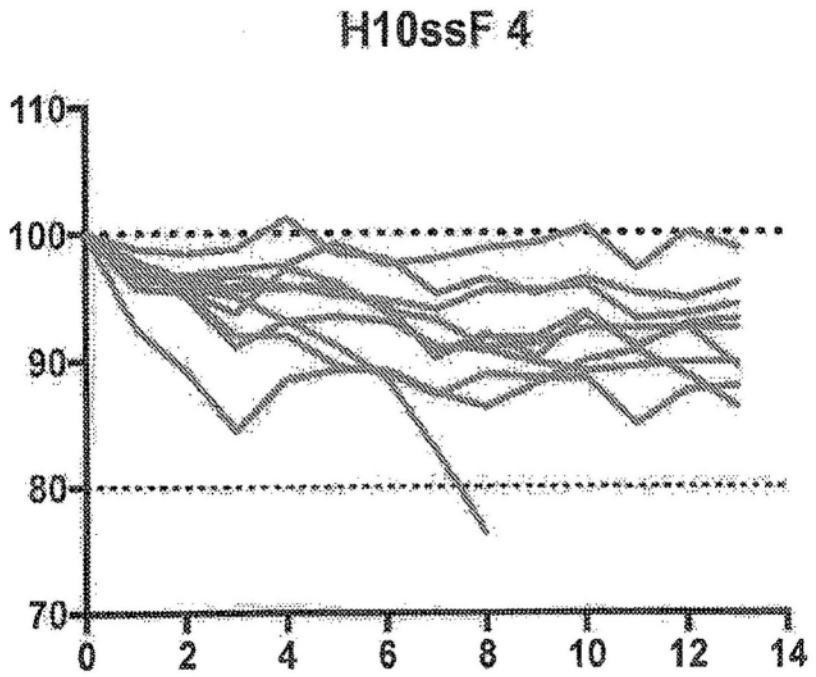

H10ssF 4
110
100
90
80
70
0
2
4
6
8
10
12
14

图36B

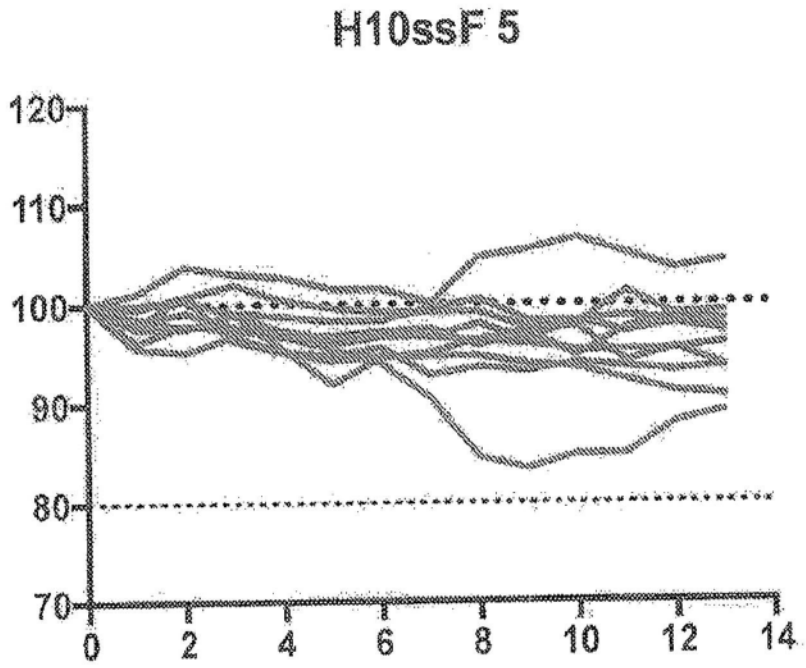

H10ssF 5
120
110
100
90
80
70
0
2
4
6
8
10
12
14

图36C

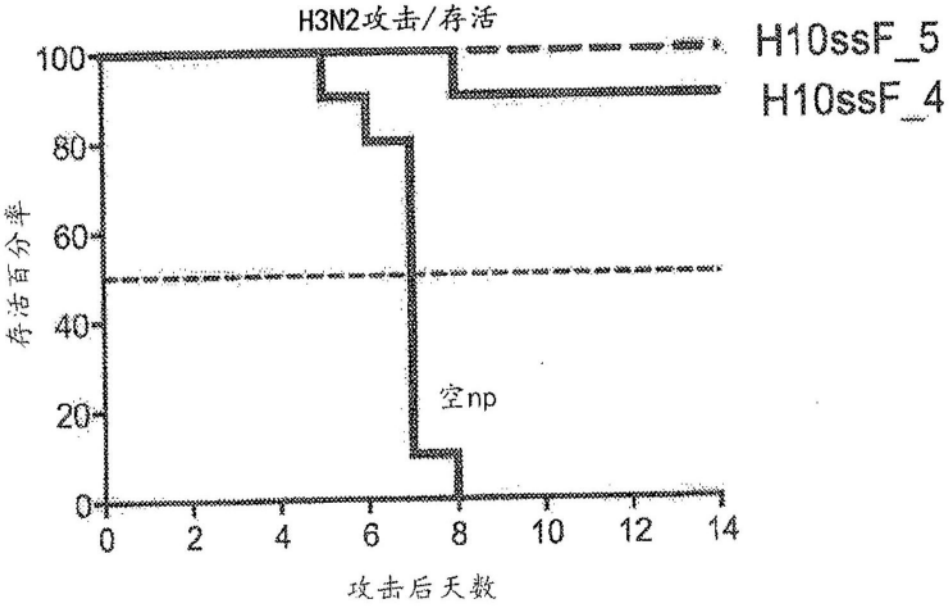

H3N2攻击/存活
H10ssF_5
H10ssF_4
存活百分率
100
80
60
40
20
0
空np
0
2
4
6
8
10
12
14
攻击后天数

图36D

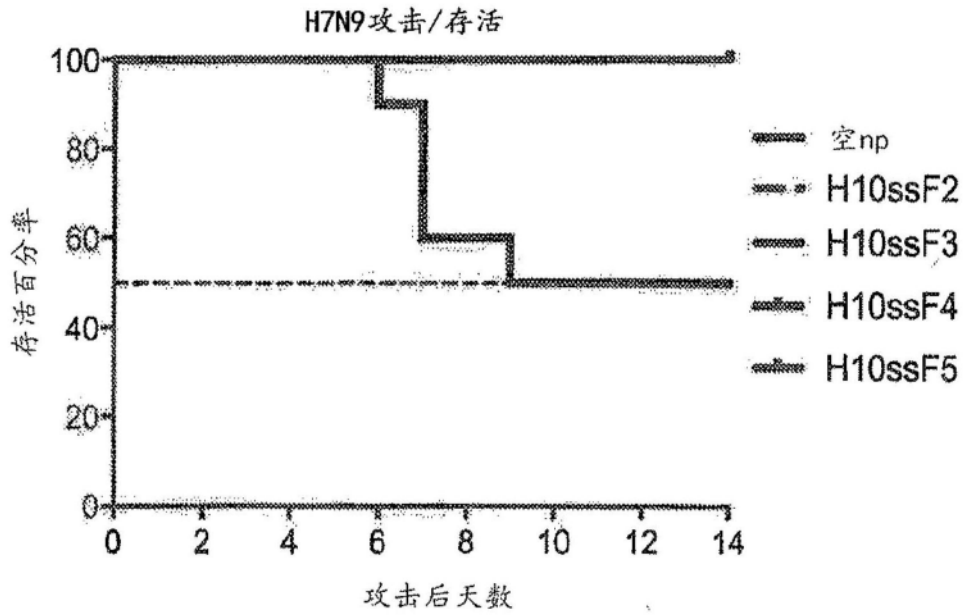

H7N9攻击/存活
存活百分率
100
80
60
40
20
0
0
2
4
6
8
10
12
14
攻击后天数
空np
H10ssF2
H10ssF3
H10ssF4
H10ssF5

图37A

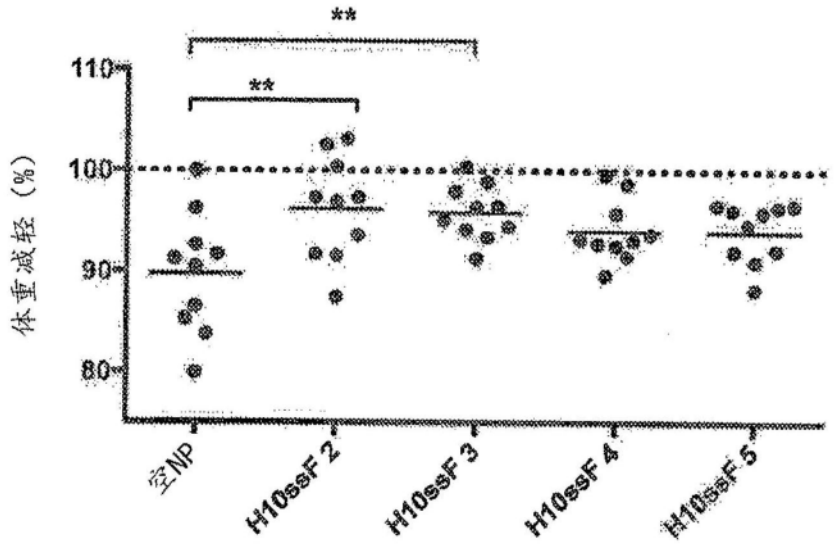

**
**
体重减轻（%）
110
100
90
80
空NP
H10ssF 2
H10ssF 3
H10ssF 4
H10ssF 5

图37B

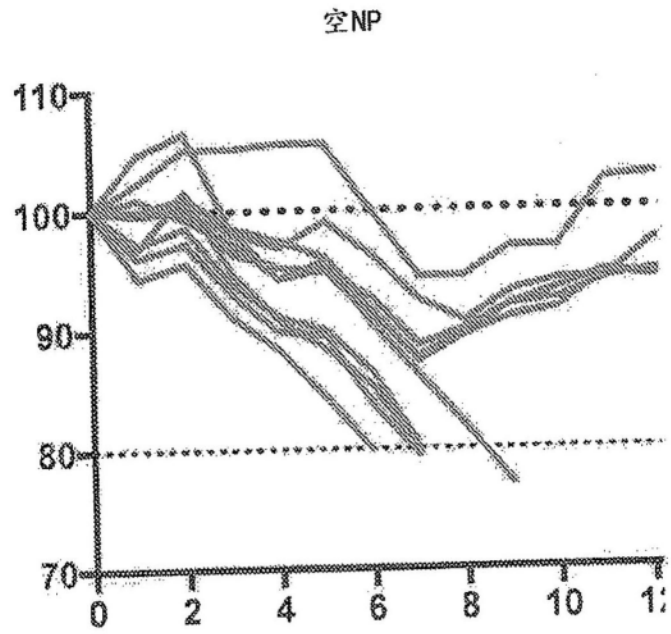


图37C

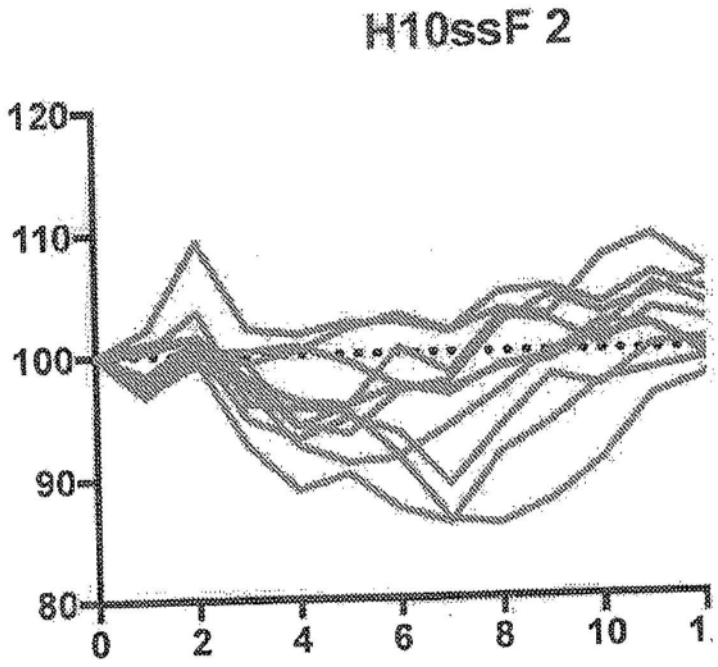


图37D

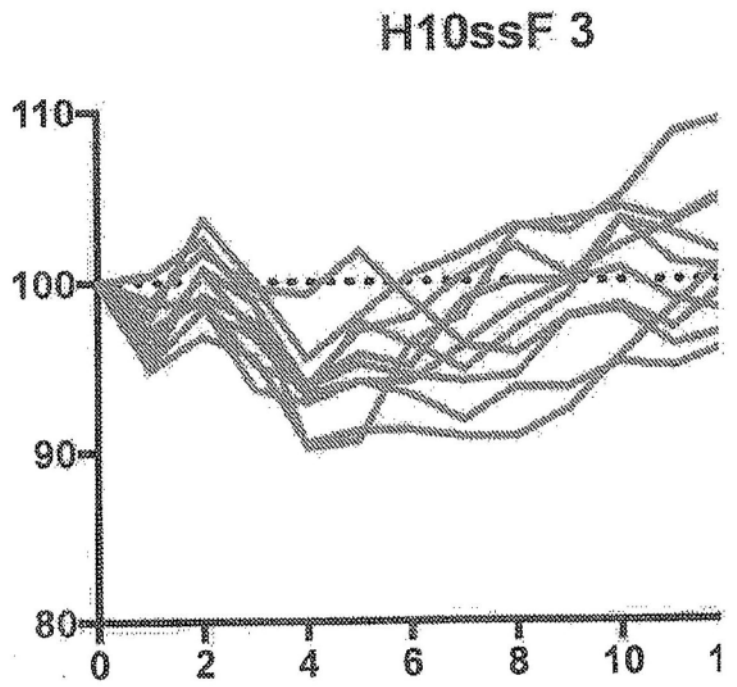

H10ssF 3
110
100
90
80
0
2
4
6
8
10
1

图37E

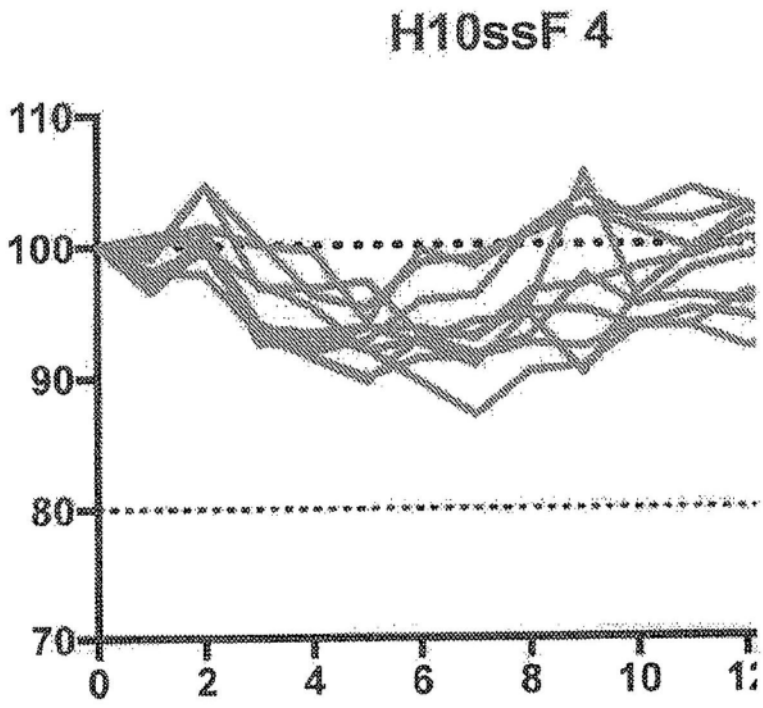

H10ssF 4
110
100
90
80
70
0
2
4
6
8
10
1

图37F

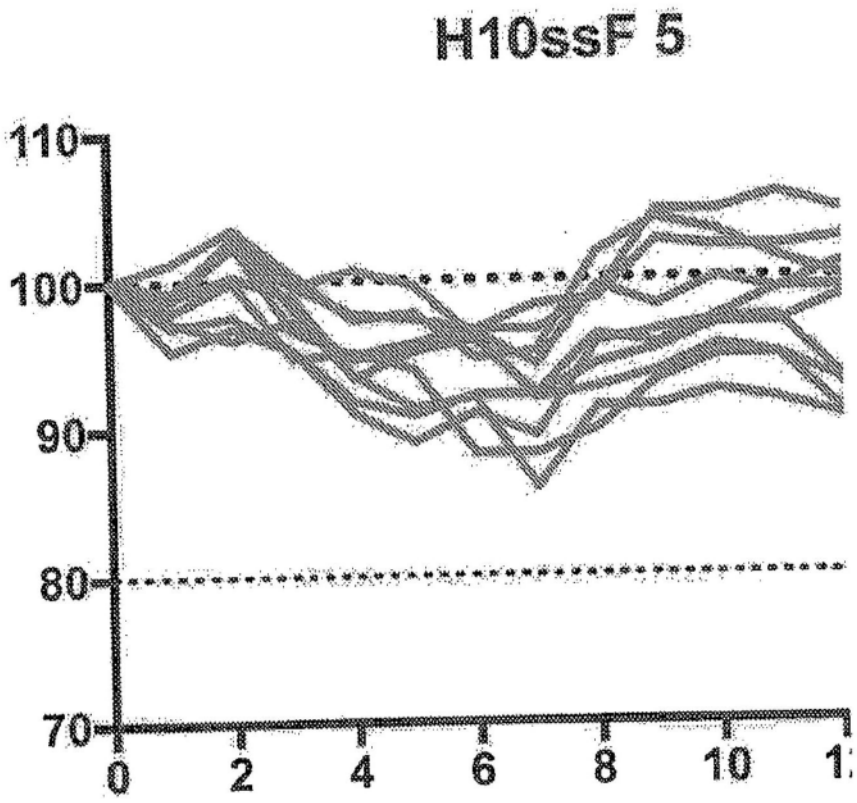


图37G

>H3-SS-np_231 SEQ ID NO:46
>H3-SS-np_249 SEQ ID NO:47
>H3-SS-np_256 SEQ ID NO:48
>H3-SS-np_258 SEQ ID NO:49

图38

>H7-SS-np_020 (H7ssF_20) SEQ ID NO:93
>H7-SS-np_023 (H7ssF_23) SEQ ID NO:95
>H7-SS-np_025 (H7ssF_25) SEQ ID NO:96
>H7-SS-np_026 (H7ssF_26) SEQ ID NO:97

图39

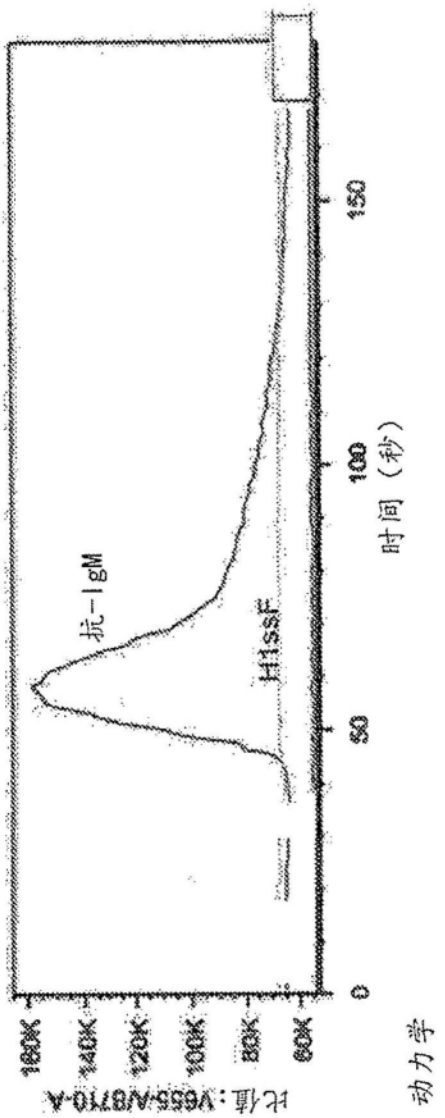

抗-IgM
H1ssF
0
50
100
150
时间（秒）
动力学
180K
140K
120K
100K
80K
60K
RL值：V655-A/8710-A

图40A

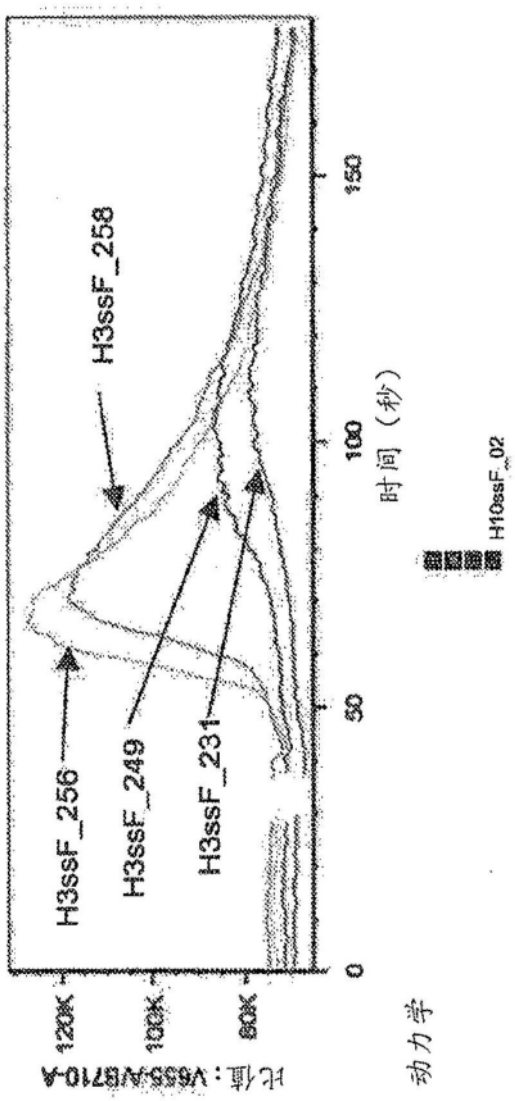

H3ssF_258
H3ssF_256
H3ssF_249
H3ssF_231
H10ssF_02
时间（秒）
动力学
比值：V655/V671-A
120K
100K
80K
0
50
100
150

图40B

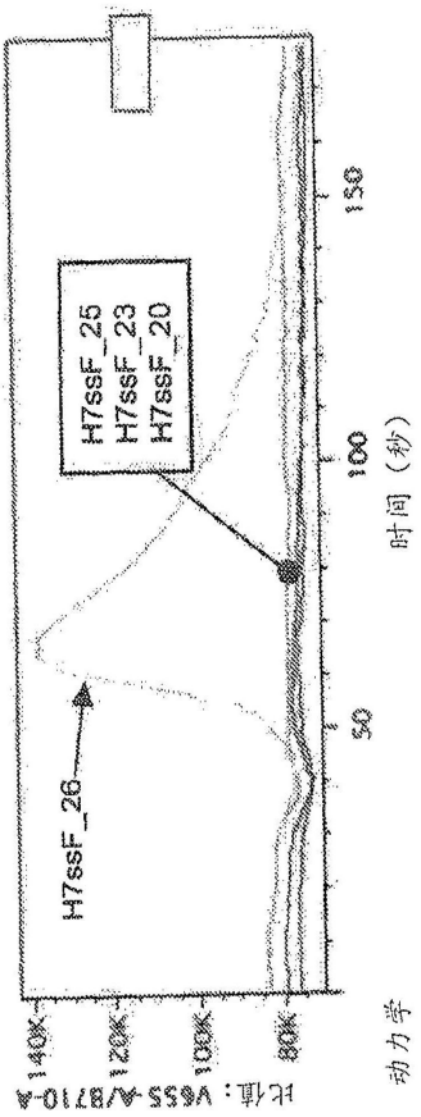

H7ssF_25
H7ssF_23
H7ssF_20
H7ssF_26
150
100
50
时间（秒）
140K
120K
100K
80K
比值：V655-A/B710-A
动力学

图40C

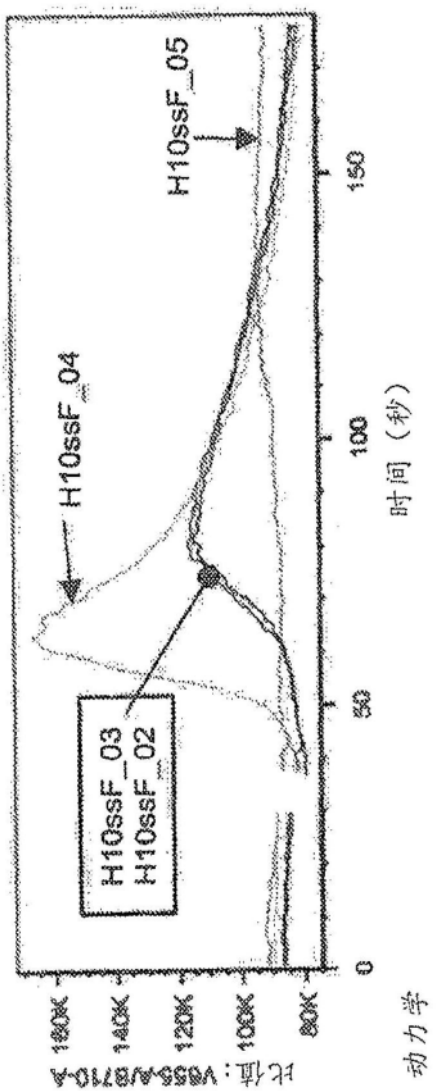

H10ssF_05
H10ssF_04
H10ssF_03
H10ssF_02
150
100
50
0
时间（秒）
160K
140K
120K
100K
80K
比值：V055A/V871O-A
动力学

图40D

>H3-SS-np_256 (H3ssF_256) SEQ ID NO:48
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTNATE
GFRHQNSEGIGQAADLKSTQAAINQITG
RNGTYDHDVYRDEALNNRFQIK
>H3-SS-np_258 (H3ssF_258) SEQ ID NO:49
MKTIIALSYILCLVFAQKLPGNDNSTATLCLGHHAVPN
GFRHQNSEGIGQAADLKSTQAAINQITG
RNGTYDHDVYRDEALNNRFQIK
>H7-SS-np_026 (H7ssF_26) SEQ ID NO:97
MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATE
GFRHQNAQGEGTAADYKSTQSAIDQITG
DDCMASIRNNTYDHSKYREEAMQNRIQID
>H10N8-SS-np_02 (H10ssF_2) (SEQ ID NO:103)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATE
GFRHQNAQGTGQAADYKSTQAAIDQITG
CDDSCMESIRNNTYDHSQYREEALLNRLNIN
>H10N8-SS-np_03 (H10ssF_3) (SEQ ID NO:104)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATE
GFRHQNAQGTGQAADYKSTQAAIDQITG
CDDSCMESIRNNTYDHSQYREEALLNRLNIN
>H10N8-SS-np_04 (H10ssF_4) (SEQ ID NO:105)
MYKIVVIIALLGAVKGLDKICLGHHAVANGTIVKTLTNEQEEVTNATE
GFRHQNAQGTGQAADYKSTQAAIDQITG
DDSCMESIRNNTYDHSQYREEALLNRLNIN

图41