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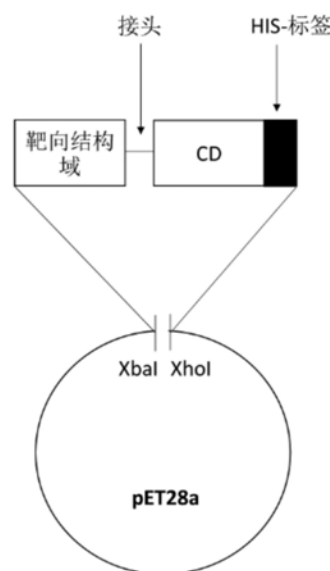
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(54) 发明名称

单域抗体-胞嘧啶脱氨酶融合蛋白

(57) 摘要

本公开涉及融合蛋白、制备融合蛋白的方法以及使用融合蛋白的方法,其中所述融合蛋白包含:单域抗体(sdAb)或其功能性变体、和胞嘧啶脱氨酶(CD)蛋白或其功能性变体,二者可选地经肽接头连接。本公开的融合蛋白还具有CD活性。本公开还涉及包含所述融合蛋白和药学可接受的赋形剂的药物组合物或制剂、以及这些融合蛋白的医药用途。



1. 一种包含式I或式II的融合蛋白, 其中:
式I为 $N-(L)_n-C$; 且
式II为 $C-(L)_n-N$;
其中, N为单域抗体(sdAb)或其功能性变体, L为肽接头, $n=0-50$, 且C为胞嘧啶脱氨酶(CD)蛋白或其功能性变体。
2. 如权利要求1所述的融合蛋白, 其中, $n=0$ 。
3. 如权利要求1所述的融合蛋白, 其中, $n=1$ 。
4. 如权利要求1所述的融合蛋白, 其中, $n=2$ 。
5. 如权利要求1至4中任一项所述的融合蛋白, 其中, 所述融合蛋白基本由式I或式II组成。
6. 如权利要求1至5中任一项所述的融合蛋白, 其中, 所述融合蛋白由式I或式II组成。
7. 如权利要求1至6中任一项所述的融合蛋白, 其中, 所述sdAb或其功能性变体可结合靶标, 其中所述靶标可选地选自由细胞膜分子、分泌的分子和细胞内分子组成的组。
8. 如权利要求7所述的融合蛋白, 其中, 所述靶标是肿瘤相关抗原或肿瘤特异性抗原。
9. 如权利要求7或8所述的融合蛋白, 其中, 所述靶标选自由以下组成的组: EGFR、5T4、A33、AFP、 β -连环蛋白、BRCA1、BRCA2、C242、CCR4、CD152、CD19、CD20、CD200、CD22、CD221、CD23、CD30、CD3、CD37、CD40、CD44、CD5、CD51、CD52、CD56、CD64、CD74、CD80、CDCP1、c-KIT、COX-2、cMET、CSF1R、CTLA-4、EGF2、ErbB2、ErbB3、FGFR1、FGFR2、FGFR3、FLT3、HER2、HER3、HIF-1 α 、HLA-DR、IGF-1R、mTOR、NPC-1C、P53、PDGFR α 、PDGFR β 、PLGF、PSA、RGMa、RoN、TNF、TP53、TPD52、VEGFR1、VEGFR2、VEGFR3、CA-IX、 α v β 3、 α 5 β 1、FAP、糖蛋白75、TAG-72、MUC16、NR-LU-13、SLAMF7、EGP40、BAFF、PRL-3、癌胚抗原(CEA)、前列腺特异性膜抗原、MART-1、gp100、癌-睾丸(CT)抗原(例如, NY-ESO-1、MAGE-A3、MAGE-A1)、hTERT、间皮素、MCC、Mum-1、ERBB2IP、EpCAM、TfR、整合素 α 6 β 4、HGFR、PTP-LAR、CD147、CDCP1、CEACAM6、JAM1、整合素 α 3 β 1、整合素 α v β 3、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体(nAChR)。
10. 如权利要求7或8所述的融合蛋白, 其中, 所述靶标选自由以下组成的组: EGFR、c-KIT、cMET、HER2、HER3、FGFR1、FGFR2、FGFR3、IGF-1R、P53、PDGFR α 、VEGFR1、VEGFR2、VEGFR3、CA-IX、 α v β 3、 α 5 β 1、MUC16、癌胚抗原(CEA)、前列腺特异性膜抗原、癌-睾丸(CT)抗原(例如, NY-ESO-1、MAGE-A3、MAGE-A1)、间皮素、EpCAM、整合素 α 6 β 4、CEACAM6、整合素 α 3 β 1、整合素 α v β 3、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体(nAChR)。
11. 如权利要求7至10中任一项所述的融合蛋白, 其中, 所述靶标为VEGFR2、EGFR、CEA、HER2或HER3。
12. 如权利要求11所述的融合蛋白, 其中, 所述靶标为VEGFR2。
13. 如权利要求11所述的融合蛋白, 其中, 所述靶标为EGFR。
14. 如权利要求11或12所述的融合蛋白, 其中, 所述sdAb或其功能性变体包含: 选自由SEQ ID NO:28、SEQ ID NO:31和SEQ ID NO:34组成的组的互补决定区1(CDR1); 选自由SEQ

ID NO:29、SEQ ID NO:32和SEQ ID NO:35组成的组的互补决定区2 (CDR2) ;和选自由SEQ ID NO:30、SEQ ID NO:33和SEQ ID NO:36组成的组的互补决定区3 (CDR3) 。

15. 如权利要求14所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:23 (3VGR19) 的氨基酸序列。

16. 如权利要求14所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:24 (4VGR17) 的氨基酸序列。

17. 如权利要求14所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:25 (4VGR38) 的氨基酸序列。

18. 如权利要求11或13所述的融合蛋白,其中,所述sdAb或其功能性变体包含选自由SEQ ID NO:37和SEQ ID NO:40组成的组的CDR1、选自由SEQ ID NO:38和SEQ ID NO:41组成的组的CDR2以及选自由SEQ ID NO:39和SEQ ID NO:42组成的组的CDR3。

19. 如权利要求18所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:26 (VHH122) 的氨基酸序列。

20. 如权利要求18所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:27 (7D12) 的氨基酸序列。

21. 如权利要求11所述的融合蛋白,其中,所述sdAb或其功能性变体包含:选自由SEQ ID NO:199、SEQ ID NO:202和SEQ ID NO:205组成的组的CDR1;选自由SEQ ID NO:200、SEQ ID NO:203和SEQ ID NO:206组成的组的CDR2;和选自由SEQ ID NO:201、SEQ ID NO:204和SEQ ID NO:207组成的组的CDR3。

22. 如权利要求21所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:69 (2D3) 的氨基酸序列。

23. 如权利要求21所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:70 (5F7) 的氨基酸序列。

24. 如权利要求21所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:71 (47D5) 的氨基酸序列。

25. 如权利要求11所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:208的CDR1、SEQ ID NO:209的CDR2和SEQ ID NO:210的CDR3。

26. 如权利要求25所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:75 (BCD090-M2) 的氨基酸序列。

27. 如权利要求11所述的融合蛋白,其中,所述sdAb或其功能性变体包含:选自由SEQ ID NO:211和SEQ ID NO:214组成的组的CDR1;选自由SEQ ID NO:212和SEQ ID NO:215组成的组的CDR2;和选自由SEQ ID NO:213和SEQ ID NO:216组成的组的CDR3。

28. 如权利要求27所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:77 (ABS29544.1) 的氨基酸序列。

29. 如权利要求27所述的融合蛋白,其中,所述sdAb或其功能性变体包含SEQ ID NO:79 (NbCEA5) 的氨基酸序列。

30. 如权利要求1或3-29中任一项所述的融合蛋白,其中,至少一个肽接头包含SEQ ID NO:1、SEQ ID NO:4、SEQ ID NO:5或SEQ ID NO:188的氨基酸序列。

31. 如权利要求1-30中任一项所述的融合蛋白,其中,所述CD蛋白或其功能性变体是:

(i) 细菌CD蛋白或其功能性变体、或者(ii) 酵母菌CD蛋白或其功能性变体。

32. 如权利要求31所述的融合蛋白, 其中, 所述CD蛋白或其功能性变体包含与选自由SEQ ID NO:21、SEQ ID NO:22、SEQ ID NO:186和SEQ ID NO:187组成的组的氨基酸序列具有至少90%同一性、至少91%同一性、至少92%同一性、至少93%同一性、至少94%同一性、至少95%同一性、至少96%同一性、至少97%同一性、至少98%同一性、至少99%同一性或100%同一性的氨基酸序列。

33. 如权利要求32所述的融合蛋白, 其中, 所述CD蛋白或其功能性变体包含选自由SEQ ID NO:21、SEQ ID NO:22、SEQ ID NO:186和SEQ ID NO:187组成的组的氨基酸序列。

34. 如权利要求32所述的融合蛋白, 其中, 所述CD蛋白或其功能性变体由选自由SEQ ID NO:21、SEQ ID NO:22、SEQ ID NO:186和SEQ ID NO:187组成的组的氨基酸序列组成。

35. 如权利要求31或32所述的融合蛋白, 其中, 所述CD蛋白或其功能性变体是选自由SEQ ID NO:21、SEQ ID NO:22、SEQ ID NO:186和SEQ ID NO:187组成的组的起始氨基酸序列的功能性变体; 其中, 当起始氨基酸序列是SEQ ID NO:21或SEQ ID NO:22时, 功能性变体包含选自由Y84A、Y84H、T85D、T86E、M92N、M92A、M92K、M92Q、V128A、V128T、V129A、V129L、V129I、V129T、V130A和V130T组成的组的至少一个突变; 并且其中, 当起始氨基酸序列是SEQ ID NO:186或SEQ ID NO:187时, 功能性变体包含选自由Y85A、Y85H、T86D、T87E、M93N、M93A、M93K、M93Q、V129A、V129T、V130A、V130L、V130I、V130T、V131A和V131T组成的组的至少一个突变。

36. 如权利要求1-12中任一项所述的融合蛋白, 其中, 所述融合蛋白包含: 抗-VEGFR2 sdAb或其功能性变体、和CD蛋白或其功能性变体。

37. 如权利要求36所述的融合蛋白, 其中, 所述融合蛋白包含选自由以下组成的组的氨基酸序列:

- (i) SEQ ID NO:7,
- (ii) SEQ ID NO:7的第1-297位氨基酸,
- (iii) SEQ ID NO:9,
- (iv) SEQ ID NO:9的第1-297位氨基酸,
- (v) SEQ ID NO:11, 和
- (vi) SEQ ID NO:11的第1-297位氨基酸。

38. 如权利要求1-11中任一项或权利要求13所述的融合蛋白, 其中, 所述融合蛋白包含: 抗-EGFR sdAb或其功能性变体、和CD蛋白或其功能性变体。

39. 如权利要求38所述的融合蛋白, 其中, 所述融合蛋白包含选自由以下组成的组的氨基酸序列:

- (i) SEQ ID NO:13,
- (ii) SEQ ID NO:13的第1-297位氨基酸,
- (iii) SEQ ID NO:15,
- (iv) SEQ ID NO:15的第1-297位氨基酸,
- (v) SEQ ID NO:17, 和
- (vi) SEQ ID NO:19。

40. 如权利要求1-11中任一项所述的融合蛋白, 其中, 所述融合蛋白包含: 抗-HER2

sdAb或其功能性变体、和CD蛋白或其功能性变体。

41. 如权利要求40所述的融合蛋白,其中,所述融合蛋白包含选自由以下组成的组的氨基酸序列:

- (i) SEQ ID NO:72,
- (ii) SEQ ID NO:72的第1-297位氨基酸,
- (iii) SEQ ID NO:73,
- (iv) SEQ ID NO:73的第1-291位氨基酸,
- (v) SEQ ID NO:74,和
- (vi) SEQ ID NO:74的第1-292位氨基酸。

42. 如权利要求1-11中任一项所述的融合蛋白,其中,所述融合蛋白包含:抗-HER3 sdAb或其功能性变体、和CD蛋白或其功能性变体。

43. 如权利要求42所述的融合蛋白,其中,所述融合蛋白包含选自由以下组成的组的氨基酸序列:

- (i) SEQ ID NO:76,和
- (ii) SEQ ID NO:76的第1-300位氨基酸。

44. 如权利要求1-11中任一项所述的融合蛋白,其中,所述融合蛋白包含:抗-CEA sdAb或其功能性变体、和CD蛋白或其功能性变体。

45. 如权利要求44所述的融合蛋白,其中,所述融合蛋白包含选自由以下组成的组的氨基酸序列:

- (i) SEQ ID NO:78,
- (ii) SEQ ID NO:78的第1-293位氨基酸,
- (iii) SEQ ID NO:80,和
- (iv) SEQ ID NO:80的第1-296位氨基酸。

46. 如前述权利要求中任一项所述的融合蛋白,其中,所述融合蛋白包含在至少一个T细胞表位中的至少一个去免疫化突变,其中所述至少一个T细胞表位选自由表位1 (SEQ ID NO:63)、表位2 (SEQ ID NO:64)、表位3 (SEQ ID NO:65)、表位4 (SEQ ID NO:66)、表位5 (SEQ ID NO:67) 和表位6 (SEQ ID NO:68) 组成的组。

47. 如权利要求1所述的融合蛋白,其中,所述融合蛋白基本由SEQ ID NO:17、SEQ ID NO:19、SEQ ID NO:93-185中的任一个的氨基酸序列组成,或者基本由SEQ ID NO:93-181中的任一个的第1-297位氨基酸组成。

48. 如权利要求47所述的融合蛋白,其中,所述融合蛋白基本由选自由SEQ ID NO:19、SEQ ID NO:182、SEQ ID NO:183、SEQ ID NO:184和SEQ ID NO:185组成的组的氨基酸序列组成。

49. 一种药物组合物,所述药物组合物包含:有效量的前述权利要求中任一项所述的至少一种融合蛋白、以及至少一种药学可接受的载剂或赋形剂。

50. 一种治疗有需要的受试者中的癌症的方法,所述方法包括对所述受试者施用权利要求1-48中任一项所述的至少一种融合蛋白或者权利要求49所述的药物组合物。

51. 如权利要求50所述的方法,其中,所述至少一种融合蛋白或所述药物组合物于胃肠外施用。

52. 如权利要求50或51所述的方法,该方法还包括对所述受试者施用有效量的胞嘧啶脱氨酶的底物。

53. 如权利要求52所述的方法,其中,所述底物包含5-氟尿嘧啶的前药。

54. 如权利要求53所述的方法,其中,所述5-氟尿嘧啶的前药选自5-氟胞嘧啶(5-FC)、Toca FC、5-FC类似物、以及它们的光活化性化合物、盐或酯组成的组。

55. 如权利要求54所述的方法,其中,所述前药是5-FC。

56. 如权利要求50-55中任一项所述的方法,其中,所述癌症选自结肠癌、胃癌、胰腺癌、乳癌、基底细胞癌、鲍温病、宫颈癌、眼表鳞状瘤、黑色素瘤、肾细胞癌、肺癌、膀胱癌、胆囊癌、喉癌、肝癌、甲状腺癌、唾液腺癌、前列腺癌、结直肠癌、头颈癌、胆管癌、食道癌、骨癌、子宫内膜癌、卵巢癌、软组织肉瘤和Merkel细胞癌组成的组。

57. 如权利要求50-56中任一项所述的方法,其中,所述癌症是实体肿瘤。

58. 如权利要求57所述的方法,其中,所述实体肿瘤是结肠癌、结直肠癌、胰腺癌或头颈癌。

59. 一种核酸分子,所述核酸分子包含编码权利要求1-48中任一项所述的融合蛋白的核酸序列,其中,所述核酸分子可选地包含经密码子优化的核酸序列。

60. 如权利要求59所述的核酸分子,其中,所述核酸分子基本由选自SEQ ID NO:8、10、12、14、16、18、20、195、196、197和198组成的组的核酸序列组成。

61. 一种载体,所述载体包含权利要求59或60所述的核酸分子。

62. 一种宿主细胞,所述宿主细胞包含权利要求61所述的载体。

63. 如权利要求62所述的宿主细胞,其中,所述宿主细胞是非哺乳动物细胞。

64. 如权利要求63所述的宿主细胞,其中,所述宿主细胞是酵母菌细胞或细菌细胞。

65. 如权利要求64所述的宿主细胞,其中,所述宿主细胞是大肠杆菌细胞、古细菌细胞或放线菌细胞。

66. 如权利要求65所述的宿主细胞,其中,所述宿主细胞是提供形成二硫键的细胞质环境的大肠杆菌菌株。

67. 如权利要求66所述的宿主细胞,其中,所述大肠杆菌菌株组成型地表达胞浆二硫键异构酶的染色体拷贝。

68. 如权利要求67所述的宿主细胞,其中,所述胞浆二硫键异构酶是DsbC。

69. 如权利要求66所述的宿主细胞,其中,所述大肠杆菌菌株是 SHuffle® T7、SHuffle® T7Express、SHuffle® Express、Origami™或Rosetta-gami™。

70. 一种制备融合蛋白的方法,所述方法包括在宿主细胞中表达权利要求59或60所述的核酸。

71. 如权利要求70所述的方法,其中,所述宿主细胞经工程化以改善所述融合蛋白的活性、细胞质生产和/或稳定性。

72. 如权利要求71所述的方法,其中,所述方法产生了具有二硫键的融合蛋白,该融合蛋白的活性、细胞质生产和/或稳定性与相同宿主细胞的非工程化形式产生的融合蛋白相比增加了2倍、5倍、10倍、20倍、50倍或100倍。

单域抗体-胞嘧啶脱氨酶融合蛋白

[0001] 相关申请

[0002] 本申请要求提交于2018年01月04日的美国临时申请第62/613,653号的优先权。

[0003] 电子提交的序列表的援引

[0004] 以创建于2019年1月3日的大小为385,759字节的文件名为13075_0003_SL.txt的ASCII格式序列表经EFS-Web电子提交了序列表的官方副本。该ASCII格式文件所包含的序列表是说明书的一部分,且在本文通过援引以其整体并入。

技术领域

[0005] 本公开涉及融合蛋白、制备融合蛋白的方法和使用融合蛋白的方法。更具体地,本公开涉及包含:针对细胞蛋白的功能性单域抗体(sdAb)(例如,VHH或纳米抗体)或其功能性变体;和胞嘧啶脱氨酶(CD)蛋白或其功能性变体的融合蛋白,二者可选地经肽接头连接。所述sdAb或其功能性变体可连接(可选地经肽接头)至CD蛋白或其功能性变体的N端或C端。本公开的融合蛋白还具有CD活性。本公开还涉及包含这类融合蛋白和药学可接受的赋形剂的药物组合物或制剂,以及这些融合蛋白的医药用途。

背景技术

[0006] 化疗药5-氟尿嘧啶(5-FU)广泛用于癌症治疗中,但采用5-FU的全身性治疗与严重毒性副作用相关。该试剂通过干扰转录而抑制细胞生长,且可以用在癌症和其它增殖性疾病的治疗中。胞嘧啶脱氨酶(CD)将非毒性前药5-氟胞嘧啶(5-FC)转化为细胞毒性剂5-氟尿嘧啶。5-FC因人类细胞中缺乏CD而对人体细胞无毒性。与5-氟胞嘧啶前药共同施用的胞嘧啶脱氨酶基因是癌症基因疗法中最广泛测试的自杀体系中的一种。在对受试者的5-FC治疗后,CD基因在肿瘤内的表达能够诱导5-氟尿嘧啶的局部生成,从而产生肿瘤内化疗。将5-FC的施用和CD相组合往往与全身性毒性相关。因此,需要在增殖性疾病的治疗中利用CD/5-FC组合策略的替代性手段。

[0007] 已开发了抗体导向的酶-前药疗法(ADEPT)来克服该限制。与肿瘤特异性抗体缀合的活化性酶被递送至肿瘤细胞内,随后施用前药,该前药在被所述酶活化前是惰性的。因此,可以避免全身性毒性。

[0008] Park等公开了含有TSG-6(Link)的透明质酸结合域和酵母菌胞嘧啶脱氨酶(CD)的重组融合蛋白。在他们的研究中,在BL21-Codon Plus®(DE3)RIPL大肠杆菌细胞中表达了各种Link-CD构建体,例如GST-标签、(Gly4Ser)₃(SEQ ID NO:188)接头。虽然努力增加可溶性蛋白的积累,但大多数表达的蛋白在包涵体(inclusion body)内聚集。平均而言,从每升培养基的可溶性级分中回收了约500μg/L的纯化蛋白(Mol Pharm.2009;6(3):801-812)。

[0009] Deckert等公开了A33scFv-胞嘧啶脱氨酶重组蛋白并证明了其抗原结合特异性及酶活性。利用BL21大肠杆菌λDE3溶源体(lysogen)通过T7-RNA聚合酶控制的细菌体系表达A33scFv-CD。融合蛋白作为包涵体以约100μg/L最终培养物产量表达(British Journal of Cancer(2003)88,937-939)。

[0010] 在单一表达体系中表达由人抗体序列和细菌酶组成的异种蛋白是困难的。Coelho 等试图在毕赤酵母 (*Pichia pastoris*) 中产生 A33scFv-胞嘧啶脱氨酶重组蛋白以选择高产量克隆进行生产。在其研究中,选择了 pPICZαA-转殖的高产量毕赤酵母克隆,且目标蛋白可以分泌至培养上清液中。纯化后的总产量为约 1.0mg/L (International Journal of Oncology 31:951-957,2007)。

[0011] 这些结果均指明,肿瘤特异性抗体或抗原结合片段与 CD 的融合不适合工业生产。因此,需要对于工业用途具有可观的生产产量并且展示出抗原结合特异性和酶活性的 CD 融合蛋白。

发明内容

[0012] 本公开提供了融合蛋白、制备融合蛋白的方法以及使用融合蛋白的方法。以下是本公开的非限制性实施方式。

[0013] 在本公开的某些实施方式中,融合蛋白包含式 I 或式 II:

[0014] N-(L)_n-C (式 I);

[0015] C-(L)_n-N (式 II);

[0016] 其中,N 为单域抗体 (sdAb) 或其功能性变体,L 为肽接头且 n=0-50,并且 C 为胞嘧啶脱氨酶 (CD) 蛋白或其功能性变体。

[0017] 在这些实施方式的某些方面,融合蛋白包含式 I 并且肽接头的 C 端或 sdAb 或其功能性变体的 C 端与 CD 蛋白或其功能性变体的 N 端融合。例如,在某些方面,不存在肽接头,且 sdAb 或其功能性变体的 C 端与 CD 蛋白或其功能性变体的 N 端融合。在某些方面,存在至少一个肽接头,且 sdAb 或其功能性变体的 C 端与肽接头的 N 端融合,而肽接头的 C 端与另一个肽接头的 N 端或者 CD 蛋白或其功能性变体的 N 端融合。

[0018] 在这些实施方式的其它方面,融合蛋白包含式 II 并且肽接头的 C 端或 CD 蛋白或其功能性变体的 C 端与 sdAb 或其功能性变体的 N 端融合。例如,在某些方面,不存在肽接头,且 CD 蛋白或其功能性变体的 C 端与 sdAb 或其功能性变体的 N 端融合。在某些方面,存在至少一个肽接头,且 CD 蛋白或其功能性变体的 C 端与肽接头的 N 端融合,而肽接头的 C 端与另一个肽接头的 N 端或者 sdAb 或其功能性变体的 N 端融合。

[0019] 在某些实施方式中,融合蛋白基本由式 I 组成。在某些实施方式中,融合蛋白是式 I。

[0020] 在某些实施方式中,融合蛋白基本由式 II 组成。在某些实施方式中,融合蛋白是式 II。

[0021] 在某些实施方式中,sdAb 或其功能性变体与靶标结合,其中所述靶标选自由细胞膜分子、分泌的分子和细胞内分子组成的组。在某些实施方式中,所述靶标是肿瘤相关抗原或肿瘤特异性抗原。

[0022] 在某些实施方式中,所述靶标选自由以下组成的组:EGFR、5T4、A33、AFP、β-连环蛋白、BRCA1、BRCA2、C242、CCR4、CD152、CD19、CD20、CD200、CD22、CD221、CD23、CD30、CD3、CD37、CD40、CD44、CD5、CD51、CD52、CD56、CD64、CD74、CD80、CD133、CD134、CD136、CD137、CD138、CD147、CD151、CD152、CD153、CD154、CD155、CD156、CD157、CD158、CD159、CD160、CD161、CD162、CD163、CD164、CD165、CD166、CD167、CD168、CD169、CD170、CD171、CD172、CD173、CD174、CD175、CD176、CD177、CD178、CD179、CD180、CD181、CD182、CD183、CD184、CD185、CD186、CD187、CD188、CD189、CD190、CD191、CD192、CD193、CD194、CD195、CD196、CD197、CD198、CD199、CD200、CD201、CD202、CD203、CD204、CD205、CD206、CD207、CD208、CD209、CD210、CD211、CD212、CD213、CD214、CD215、CD216、CD217、CD218、CD219、CD220、CD221、CD222、CD223、CD224、CD225、CD226、CD227、CD228、CD229、CD230、CD231、CD232、CD233、CD234、CD235、CD236、CD237、CD238、CD239、CD240、CD241、CD242、CD243、CD244、CD245、CD246、CD247、CD248、CD249、CD250、CD251、CD252、CD253、CD254、CD255、CD256、CD257、CD258、CD259、CD260、CD261、CD262、CD263、CD264、CD265、CD266、CD267、CD268、CD269、CD270、CD271、CD272、CD273、CD274、CD275、CD276、CD277、CD278、CD279、CD280、CD281、CD282、CD283、CD284、CD285、CD286、CD287、CD288、CD289、CD290、CD291、CD292、CD293、CD294、CD295、CD296、CD297、CD298、CD299、CD300、CD301、CD302、CD303、CD304、CD305、CD306、CD307、CD308、CD309、CD310、CD311、CD312、CD313、CD314、CD315、CD316、CD317、CD318、CD319、CD320、CD321、CD322、CD323、CD324、CD325、CD326、CD327、CD328、CD329、CD330、CD331、CD332、CD333、CD334、CD335、CD336、CD337、CD338、CD339、CD340、CD341、CD342、CD343、CD344、CD345、CD346、CD347、CD348、CD349、CD350、CD351、CD352、CD353、CD354、CD355、CD356、CD357、CD358、CD359、CD360、CD361、CD362、CD363、CD364、CD365、CD366、CD367、CD368、CD369、CD370、CD371、CD372、CD373、CD374、CD375、CD376、CD377、CD378、CD379、CD380、CD381、CD382、CD383、CD384、CD385、CD386、CD387、CD388、CD389、CD390、CD391、CD392、CD393、CD394、CD395、CD396、CD397、CD398、CD399、CD400、CD401、CD402、CD403、CD404、CD405、CD406、CD407、CD408、CD409、CD410、CD411、CD412、CD413、CD414、CD415、CD416、CD417、CD418、CD419、CD420、CD421、CD422、CD423、CD424、CD425、CD426、CD427、CD428、CD429、CD430、CD431、CD432、CD433、CD434、CD435、CD436、CD437、CD438、CD439、CD440、CD441、CD442、CD443、CD444、CD445、CD446、CD447、CD448、CD449、CD450、CD451、CD452、CD453、CD454、CD455、CD456、CD457、CD458、CD459、CD460、CD461、CD462、CD463、CD464、CD465、CD466、CD467、CD468、CD469、CD470、CD471、CD472、CD473、CD474、CD475、CD476、CD477、CD478、CD479、CD480、CD481、CD482、CD483、CD484、CD485、CD486、CD487、CD488、CD489、CD490、CD491、CD492、CD493、CD494、CD495、CD496、CD497、CD498、CD499、CD500、CD501、CD502、CD503、CD504、CD505、CD506、CD507、CD508、CD509、CD510、CD511、CD512、CD513、CD514、CD515、CD516、CD517、CD518、CD519、CD520、CD521、CD522、CD523、CD524、CD525、CD526、CD527、CD528、CD529、CD530、CD531、CD532、CD533、CD534、CD535、CD536、CD537、CD538、CD539、CD540、CD541、CD542、CD543、CD544、CD545、CD546、CD547、CD548、CD549、CD550、CD551、CD552、CD553、CD554、CD555、CD556、CD557、CD558、CD559、CD560、CD561、CD562、CD563、CD564、CD565、CD566、CD567、CD568、CD569、CD570、CD571、CD572、CD573、CD574、CD575、CD576、CD577、CD578、CD579、CD580、CD581、CD582、CD583、CD584、CD585、CD586、CD587、CD588、CD589、CD590、CD591、CD592、CD593、CD594、CD595、CD596、CD597、CD598、CD599、CD600、CD601、CD602、CD603、CD604、CD605、CD606、CD607、CD608、CD609、CD610、CD611、CD612、CD613、CD614、CD615、CD616、CD617、CD618、CD619、CD620、CD621、CD622、CD623、CD624、CD625、CD626、CD627、CD628、CD629、CD630、CD631、CD632、CD633、CD634、CD635、CD636、CD637、CD638、CD639、CD640、CD641、CD642、CD643、CD644、CD645、CD646、CD647、CD648、CD649、CD650、CD651、CD652、CD653、CD654、CD655、CD656、CD657、CD658、CD659、CD660、CD661、CD662、CD663、CD664、CD665、CD666、CD667、CD668、CD669、CD670、CD671、CD672、CD673、CD674、CD675、CD676、CD677、CD678、CD679、CD680、CD681、CD682、CD683、CD684、CD685、CD686、CD687、CD688、CD689、CD690、CD691、CD692、CD693、CD694、CD695、CD696、CD697、CD698、CD699、CD700、CD701、CD702、CD703、CD704、CD705、CD706、CD707、CD708、CD709、CD710、CD711、CD712、CD713、CD714、CD715、CD716、CD717、CD718、CD719、CD720、CD721、CD722、CD723、CD724、CD725、CD726、CD727、CD728、CD729、CD730、CD731、CD732、CD733、CD734、CD735、CD736、CD737、CD738、CD739、CD740、CD741、CD742、CD743、CD744、CD745、CD746、CD747、CD748、CD749、CD750、CD751、CD752、CD753、CD754、CD755、CD756、CD757、CD758、CD759、CD760、CD761、CD762、CD763、CD764、CD765、CD766、CD767、CD768、CD769、CD770、CD771、CD772、CD773、CD774、CD775、CD776、CD777、CD778、CD779、CD780、CD781、CD782、CD783、CD784、CD785、CD786、CD787、CD788、CD789、CD790、CD791、CD792、CD793、CD794、CD795、CD796、CD797、CD798、CD799、CD800、CD801、CD802、CD803、CD804、CD805、CD806、CD807、CD808、CD809、CD810、CD811、CD812、CD813、CD814、CD815、CD816、CD817、CD818、CD819、CD820、CD821、CD822、CD823、CD824、CD825、CD826、CD827、CD828、CD829、CD830、CD831、CD832、CD833、CD834、CD835、CD836、CD837、CD838、CD839、CD840、CD841、CD842、CD843、CD844、CD845、CD846、CD847、CD848、CD849、CD850、CD851、CD852、CD853、CD854、CD855、CD856、CD857、CD858、CD859、CD860、CD861、CD862、CD863、CD864、CD865、CD866、CD867、CD868、CD869、CD870、CD871、CD872、CD873、CD874、CD875、CD876、CD877、CD878、CD879、CD880、CD881、CD882、CD883、CD884、CD885、CD886、CD887、CD888、CD889、CD890、CD891、CD892、CD893、CD894、CD895、CD896、CD897、CD898、CD899、CD900、CD901、CD902、CD903、CD904、CD905、CD906、CD907、CD908、CD909、CD910、CD911、CD912、CD913、CD914、CD915、CD916、CD917、CD918、CD919、CD920、CD921、CD922、CD923、CD924、CD925、CD926、CD927、CD928、CD929、CD930、CD931、CD932、CD933、CD934、CD935、CD936、CD937、CD938、CD939、CD940、CD941、CD942、CD943、CD944、CD945、CD946、CD947、CD948、CD949、CD950、CD951、CD952、CD953、CD954、CD955、CD956、CD957、CD958、CD959、CD960、CD961、CD962、CD963、CD964、CD965、CD966、CD967、CD968、CD969、CD970、CD971、CD972、CD973、CD974、CD975、CD976、CD977、CD978、CD979、CD980、CD981、CD982、CD983、CD984、CD985、CD986、CD987、CD988、CD989、CD990、CD991、CD992、CD993、CD994、CD995、CD996、CD997、CD998、CD999、CD1000。

VEGFR2、VEGFR3、CA-IX、 $\alpha v\beta 3$ 、 $\alpha 5\beta 1$ 、FAP、糖蛋白75、TAG-72、MUC16、NR-LU-13、SLAMF7、EGP40、BAFF、PRL-3、癌胚抗原 (CEA)、前列腺特异性膜抗原、MART-1、gp100、癌-睾丸 (CT) 抗原 (例如, NY-ESO-1、MAGE-A3、MAGE-A1)、hTERT、间皮素、MCC、Mum-1、ERBB2IP、EpCAM、TfR、整合素 $\alpha 6\beta 4$ 、HGFR、PTP-LAR、CD147、CDCP1、CEACAM6、JAM1、整合素 $\alpha 3\beta 1$ 、整合素 $\alpha v\beta 3$ 、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体 (nAChR)。

[0023] 在某些实施方式中, 所述靶标选自由以下组成的组: EGFR、c-KIT、cMET、HER2、HER3、FGFR1、FGFR2、FGFR3、IGF-IR、P53、PDGFR α 、VEGFR1、VEGFR2、VEGFR3、CA-IX、 $\alpha v\beta 3$ 、 $\alpha 5\beta 1$ 、MUC16、癌胚抗原 (CEA)、前列腺特异性膜抗原、癌-睾丸 (CT) 抗原 (例如, NY-ESO-1、MAGE-A3、MAGE-A1)、间皮素、EpCAM、整合素 $\alpha 6\beta 4$ 、CEACAM6、整合素 $\alpha 3\beta 1$ 、整合素 $\alpha v\beta 3$ 、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体 (nAChR)。

[0024] 在某些实施方式中, 所述靶标为VEGFR2、EGFR、CEA、HER2或HER3。

[0025] 在某些实施方式中, 所述靶标为VEGFR2。在某些实施方式中, 所述靶标为EGFR。

[0026] 在某些实施方式中, sdAb或其功能性变体包含: 选自由SEQ ID NO:28、SEQ ID NO:31和SEQ ID NO:34组成的组的互补决定区1 (CDR1); 选自由SEQ ID NO:29、SEQ ID NO:32和SEQ ID NO:35组成的组的CDR2; 和选自由SEQ ID NO:30、SEQ ID NO:33和SEQ ID NO:36组成的组的CDR3。在某些方面, sdAb或其功能性变体基本由以下组成: 选自由SEQ ID NO:28、SEQ ID NO:31和SEQ ID NO:34组成的组的CDR1; 选自由SEQ ID NO:29、SEQ ID NO:32和SEQ ID NO:35组成的组的CDR2; 和选自由SEQ ID NO:30、SEQ ID NO:33和SEQ ID NO:36组成的组的CDR3。在某些方面, sdAb或其功能性变体由以下组成: 选自由SEQ ID NO:28、SEQ ID NO:31和SEQ ID NO:34组成的组的CDR1; 选自由SEQ ID NO:29、SEQ ID NO:32和SEQ ID NO:35组成的组的CDR2; 和选自由SEQ ID NO:30、SEQ ID NO:33和SEQ ID NO:36组成的组的CDR3。

[0027] 在某些实施方式中, sdAb或其功能性变体包含SEQ ID NO:23 (3VGR19) 的氨基酸序列。在某些方面, sdAb或其功能性变体基本由SEQ ID NO:23 (3VGR19) 的氨基酸序列组成。在某些方面, sdAb或其功能性变体由SEQ ID NO:23 (3VGR19) 的氨基酸序列组成。

[0028] 在某些实施方式中, sdAb或其功能性变体包含SEQ ID NO:24 (4VGR17) 的氨基酸序列。在某些方面, sdAb或其功能性变体基本由SEQ ID NO:24 (4VGR17) 的氨基酸序列组成。在某些方面, sdAb或其功能性变体由SEQ ID NO:24 (4VGR17) 的氨基酸序列组成。在某些实施方式中, sdAb或其功能性变体包含SEQ ID NO:25 (4VGR38) 的氨基酸序列。在某些方面, sdAb或其功能性变体基本由SEQ ID NO:25 (4VGR38) 的氨基酸序列组成。在某些方面, sdAb或其功能性变体由SEQ ID NO:25 (4VGR38) 的氨基酸序列组成。

[0029] 在某些实施方式中, sdAb或其功能性变体包含选自由SEQ ID NO:37和SEQ ID NO:40组成的组的CDR1、选自由SEQ ID NO:38和SEQ ID NO:41组成的组的CDR2以及选自由SEQ ID NO:39和SEQ ID NO:42组成的组的CDR3。在某些方面, sdAb或其功能性变体基本由选自由SEQ ID NO:37和SEQ ID NO:40组成的组的CDR1、选自由SEQ ID NO:38和SEQ ID NO:41组

成的组的CDR2以及选自由SEQ ID NO:39和SEQ ID NO:42组成的组的CDR3组成。在某些方面,sdAb或其功能性变体由选自由SEQ ID NO:37和SEQ ID NO:40组成的组的CDR1、选自由SEQ ID NO:38和SEQ ID NO:41组成的组的CDR2以及选自由SEQ ID NO:39和SEQ ID NO:42组成的组的CDR3组成。

[0030] 在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:26 (VHH122) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:26 (VHH122) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:26 (VHH122) 的氨基酸序列组成。在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:27 (7D12) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:27 (7D12) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:27 (7D12) 的氨基酸序列组成。

[0031] 在某些实施方式中,sdAb或其功能性变体包含:选自由SEQ ID NO:199、SEQ ID NO:202和SEQ ID NO:205组成的组的CDR1;选自由SEQ ID NO:200、SEQ ID NO:203和SEQ ID NO:206组成的组的CDR2;和选自由SEQ ID NO:201、SEQ ID NO:204和SEQ ID NO:207组成的组的CDR3。在某些实施方式中,sdAb或其功能性变体基本由以下组成:选自由SEQ ID NO:199、SEQ ID NO:202和SEQ ID NO:205组成的组的CDR1;选自由SEQ ID NO:200、SEQ ID NO:203和SEQ ID NO:206组成的组的CDR2;和选自由SEQ ID NO:201、SEQ ID NO:204和SEQ ID NO:207组成的组的CDR3。在某些实施方式中,sdAb或其功能性变体由以下组成:选自由SEQ ID NO:199、SEQ ID NO:202和SEQ ID NO:205组成的组的CDR1;选自由SEQ ID NO:200、SEQ ID NO:203和SEQ ID NO:206组成的组的CDR2;和选自由SEQ ID NO:201、SEQ ID NO:204和SEQ ID NO:207组成的组的CDR3。

[0032] 在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:69 (2D3) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:69 (2D3) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:69 (2D3) 的氨基酸序列组成。在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:70 (5F7) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:70 (5F7) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:70 (5F7) 的氨基酸序列组成。在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:71 (47D5) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:71 (47D5) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:71 (47D5) 的氨基酸序列组成。

[0033] 在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:208的CDR1、SEQ ID NO:209的CDR2和SEQ ID NO:210的CDR3。在某些实施方式中,sdAb或其功能性变体基本由SEQ ID NO:208的CDR1、SEQ ID NO:209的CDR2和SEQ ID NO:210的CDR3组成。在某些实施方式中,sdAb或其功能性变体由SEQ ID NO:208的CDR1、SEQ ID NO:209的CDR2和SEQ ID NO:210的CDR3组成。

[0034] 在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:75 (BCD090-M2) 的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:75 (BCD090-M2) 的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:75 (BCD090-M2) 的氨基酸序列组成。

[0035] 在某些实施方式中,sdAb或其功能性变体包含选自由SEQ ID NO:211和SEQ ID NO:214组成的组的CDR1、选自由SEQ ID NO:212和SEQ ID NO:215组成的组的CDR2和选自由

SEQ ID NO:213和SEQ ID NO:216组成的组的CDR3。在某些实施方式中,sdAb或其功能性变体基本由选自SEQ ID NO:211和SEQ ID NO:214组成的组的CDR1、选自SEQ ID NO:212和SEQ ID NO:215组成的组的CDR2和选自SEQ ID NO:213和SEQ ID NO:216组成的组的CDR3组成。在某些实施方式中,sdAb或其功能性变体由选自SEQ ID NO:211和SEQ ID NO:214组成的组的CDR1、选自SEQ ID NO:212和SEQ ID NO:215组成的组的CDR2和选自SEQ ID NO:213和SEQ ID NO:216组成的组的CDR3组成。

[0036] 在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:77 (ABS29544.1)的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:77 (ABS29544.1)的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:77 (ABS29544.1)的氨基酸序列组成。在某些实施方式中,sdAb或其功能性变体包含SEQ ID NO:79 (NbCEA5)的氨基酸序列。在某些方面,sdAb或其功能性变体基本由SEQ ID NO:79 (NbCEA5)的氨基酸序列组成。在某些方面,sdAb或其功能性变体由SEQ ID NO:79 (NbCEA5)的氨基酸序列组成。

[0037] 在某些实施方式中,存在至少一个肽接头,且其包含氨基酸序列(GGGGS)_n(SEQ ID NO:1),其中n为1、2、3、4、5或6。在某些实施方式中,存在至少一个肽接头,且其包含SEQ ID NO:4或SEQ ID NO:5的氨基酸序列。在某些实施方式中,存在至少一个肽接头,且其包含氨基酸序列(GGGGS)₃(SEQ ID NO:188)。

[0038] 在某些实施方式中,CD蛋白或其功能性变体是细菌CD蛋白或其功能性变体或者酵母菌CD蛋白或其功能性变体。

[0039] 在某些实施方式中,CD蛋白或其功能性变体包含选自SEQ ID NO:21、22、186和187组成的组的氨基酸序列。在某些方面,CD蛋白或其功能性变体基本由选自SEQ ID NO:21、22、186和187组成的组的氨基酸序列组成。在某些方面,CD蛋白或其功能性变体由选自SEQ ID NO:21、22、186和187组成的组的氨基酸序列组成。在某些实施方式中,CD包含SEQ ID NO:22的氨基酸序列、基本由其组成或者由其组成。在某些方面,CD包含SEQ ID NO:187的氨基酸序列、基本由其组成或者由其组成。

[0040] 在某些实施方式中,CD蛋白或其功能性变体包含与SEQ ID NO:21、22、186和187中的任一个具有至少90%同一性、至少91%同一性、至少92%同一性、至少93%同一性、至少94%同一性、至少95%同一性、至少96%同一性、至少97%同一性、至少98%同一性、至少99%同一性或100%同一性的氨基酸序列。

[0041] 在某些实施方式中,融合蛋白包含具有SEQ ID NO:21或SEQ ID NO:22的起始氨基酸序列的CD蛋白的功能性变体,其中所述功能性变体包含选自Y84A、Y84H、T85D、T86E、M92N、M92A、M92K、M92Q、V128A、V128T、V129A、V129L、V129I、V129T、V130A和V130T组成的组的与起始序列相比的至少一个突变。在某些实施方式中,融合蛋白包含具有SEQ ID NO:186或SEQ ID NO:187的起始氨基酸序列的CD蛋白的功能性变体,其中所述功能性变体包含选自Y85A、Y85H、T86D、T87E、M93N、M93A、M93K、M93Q、V129A、V129T、V130A、V130L、V130I、V130T、V131A和V131T组成的组的与起始序列相比的至少一个突变。

[0042] 在某些实施方式中,CD的功能性变体包含选自SEQ ID NO:22、187、189、190、191、192、193和194的氨基酸序列。在某些实施方式中,CD的功能性变体基本由选自SEQ ID NO:22、187、189、190、191、192、193和194的氨基酸序列组成。在某些实施方式中,CD的功能性变体由选自SEQ ID NO:22、187、189、190、191、192、193和194的氨基酸序列组成。

[0043] 在某些实施方式中,融合蛋白包含抗-VEGFR2 sdAb或其功能性变体和CD蛋白或其功能性变体。在这些实施方式的某些方面,融合蛋白包含选自以下组成的组的氨基酸序列:SEQ ID NO:7、无HIS-标签的SEQ ID NO:7(即,SEQ ID NO:7的第1-297位氨基酸)、SEQ ID NO:9、无HIS-标签的SEQ ID NO:9(即,SEQ ID NO:9的第1-297位氨基酸)、SEQ ID NO:11和无HIS-标签的SEQ ID NO:11(即,SEQ ID NO:11的第1-297位氨基酸)。

[0044] 在某些实施方式中,融合蛋白包含抗-EGFR sdAb或其功能性变体和CD蛋白或其功能性变体。在这些实施方式的某些方面,融合蛋白包含选自以下组成的组的氨基酸序列:SEQ ID NO:13、无HIS-标签的SEQ ID NO:13(即,SEQ ID NO:13的第1-297位氨基酸)、SEQ ID NO:15、无HIS-标签的SEQ ID NO:15(即,SEQ ID NO:15的第1-297位氨基酸)、SEQ ID NO:17和无HIS-标签的SEQ ID NO:17(即,SEQ ID NO:17的第1-297位氨基酸,即SEQ ID NO:19)。

[0045] 在某些实施方式中,融合蛋白包含抗-HER2 sdAb或其功能性变体和CD蛋白或其功能性变体。在这些实施方式的某些方面,融合蛋白包含选自以下组成的组的氨基酸序列:SEQ ID NO:72、无HIS-标签的SEQ ID NO:72(即,SEQ ID NO:72的第1-297位氨基酸)、SEQ ID NO:73、无HIS-标签的SEQ ID NO:73(即,SEQ ID NO:73的第1-291位氨基酸)、SEQ ID NO:74和无HIS-标签的SEQ ID NO:74(即,SEQ ID NO:74的第1-292位氨基酸)。

[0046] 在某些实施方式中,融合蛋白包含抗-HER3 sdAb或其功能性变体和CD蛋白或其功能性变体。在这些实施方式的某些方面,融合蛋白包含SEQ ID NO:76和无HIS-标签的SEQ ID NO:76(即,SEQ ID NO:76的第1-300位氨基酸)氨基酸序列。

[0047] 在某些实施方式中,融合蛋白包含抗-CEA sdAb或其功能性变体和CD蛋白或其功能性变体。在这些实施方式的某些方面,融合蛋白包含选自以下组成的组的氨基酸序列:SEQ ID NO:78、无HIS-标签的SEQ ID NO:78(即,SEQ ID NO:78的第1-293位氨基酸)、SEQ ID NO:80和无HIS-标签的SEQ ID NO:80(即,SEQ ID NO:80的第1-296位氨基酸)。

[0048] 在某些实施方式中,融合蛋白包含去免疫化(de-immunized)的sdAb(例如,具有一个或多个去免疫化突变的sdAb的功能性变体)和/或去免疫化的CD(例如,具有一个或多个去免疫化突变的CD的功能性变体)。例如,在某些实施方式中,融合蛋白包含在至少一个T细胞表位中的至少一个去免疫化突变,所述至少一个T细胞表位选自表位1(SEQ ID NO:63)、表位2(SEQ ID NO:64)、表位3(SEQ ID NO:65)、表位4(SEQ ID NO:66)、表位5(SEQ ID NO:67)和表位6(SEQ ID NO:68)组成的组。在某些实施方式中,融合蛋白包含选自SEQ ID NO:93-185的氨基酸序列。在某些实施方式中,融合蛋白基本由选自SEQ ID NO:93-185的氨基酸序列组成。在某些实施方式中,融合蛋白由选自SEQ ID NO:93-185的氨基酸序列组成。

[0049] 在某些实施方式中,融合蛋白包含选自SEQ ID NO:93-181的氨基酸序列的第1-297位氨基酸。在某些实施方式中,融合蛋白基本由选自SEQ ID NO:93-181的氨基酸序列的第1-297位氨基酸组成。在某些实施方式中,融合蛋白由选自SEQ ID NO:93-181的氨基酸序列的第1-297位氨基酸组成。

[0050] 在某些实施方式中,融合蛋白基本由选自SEQ ID NO:182-185的氨基酸序列组成。

[0051] 在某些实施方式中,融合蛋白包含SEQ ID NO:19的氨基酸序列。在某些实施方式中,融合蛋白基本由SEQ ID NO:19的氨基酸序列组成。在某些实施方式中,融合蛋白由SEQ ID NO:19的氨基酸序列组成。

[0052] 在某些实施方式中,融合蛋白基本由选自SEQ ID NO:19、182、183、184和185的氨基酸序列组成。

[0053] 在某些方面,本公开涉及包含本公开的至少一种融合蛋白的药物组合物或药物制剂。在某些方面,所述药物组合物或药物制剂包含本公开的至少一种融合蛋白和至少一种药学可接受载剂或赋形剂。

[0054] 在某些方面,本公开涉及治疗有需要的受试者中的癌症的方法,所述方法包括对所述受试者施用有效量的本公开的至少一种融合蛋白或药物组合物。在某些实施方式中,所述至少一种融合蛋白或药物组合物于胃肠外施用。

[0055] 在某些实施方式中,治疗有需要的受试者中的癌症的方法还包括对所述受试者施用有效量的胞嘧啶脱氨酶底物。在某些实施方式中,所述底物包括5-氟尿嘧啶前药。在某些实施方式中,5-氟尿嘧啶前药选自由5-氟胞嘧啶(5-FC)、Toca FC、5-FC类似物以及它们的光活化性(photoactivatable)化合物、盐或酯组成的组。在某些实施方式中,对受试者施用的前药是5-FC。

[0056] 在某些实施方式中,癌症选自由结肠癌、胃癌、胰腺癌、乳腺癌、基底细胞癌、Bowen病、宫颈癌、眼表鳞状瘤、黑色素瘤、肾细胞癌、肺癌、膀胱癌、胆囊癌、喉癌、肝癌、甲状腺癌、唾液腺癌、前列腺癌、结直肠癌、头颈癌、胆管癌、食道癌、骨癌、子宫内膜癌、卵巢癌、软组织肉瘤和Merkel细胞癌组成的组。在某些实施方式中,癌症是实体肿瘤。在某些实施方式中,所述实体肿瘤是结肠癌、结直肠癌、胰腺癌或头颈癌。

[0057] 在某些方面,本公开涉及包含编码前述实施方式中任一个的融合蛋白的核酸序列的核酸分子。

[0058] 在某些方面,本公开涉及包含经密码子优化的核酸序列的核酸分子,该经密码子优化的核酸序列编码前述实施方式中任一个的任何融合蛋白的sdAb或其功能性变体。在某些方面,本公开涉及包含经密码子优化的核酸序列的核酸分子,该经密码子优化的核酸序列编码前述实施方式中任一个的任何融合蛋白的CD或其功能性变体。

[0059] 在某些实施方式中,核酸分子包含SEQ ID NO:8的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:10的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:12的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:14的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:16的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:18的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:20的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:195的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:196的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:197的核酸序列。在某些实施方式中,核酸分子包含SEQ ID NO:198的核酸序列。

[0060] 在某些方面,本公开涉及包含编码前述实施方式中任一个的融合蛋白的核酸的载体。

[0061] 在某些方面,本公开涉及包含编码前述实施方式中任一个的融合蛋白的载体或核酸的宿主细胞。

[0062] 在某些方面,本公开涉及制备前述实施方式中任一个所述的融合蛋白的方法,所述方法包括在宿主细胞中表达编码所述融合蛋白的核酸。在某些实施方式中,宿主细胞经工程化以改善具有二硫键的蛋白的活性、细胞质生产和/或稳定性。

[0063] 在某些实施方式中,所公开的制备融合蛋白的方法产生了具有二硫键的融合蛋白,该融合蛋白的活性、细胞质生产和/或稳定性与通过相同宿主细胞的非工程化形式产生的融合蛋白相比增加了选自2倍、5倍、10倍、20倍、50倍和100倍的量。

[0064] 在某些实施方式中,宿主细胞是非哺乳动物细胞。在某些实施方式中,宿主细胞是酵母菌细胞或细菌细胞。在某些实施方式中,宿主细胞是大肠杆菌细胞、古细菌细胞或放线菌细胞。在某些实施方式中,宿主细胞是提供二硫键形成的细胞质环境的大肠杆菌菌株。在某些方面,细胞质环境通过优化硫氧化蛋白和/或谷胱甘肽途径以及/或者表达胞浆二硫键异构酶来实现。在某些实施方式中,宿主细胞是组成型地表达胞浆二硫键异构酶的染色体拷贝的大肠杆菌菌株。在这些实施方式的某些方面,所述胞浆二硫键异构酶是DsbC。在某些方面,所述大肠杆菌菌株是SHuffle® T7、SHuffle® T7Express、SHuffle® Express、Origami™或Rosetta-gami™。

附图说明

[0065] 附图仅描绘本公开的示例性实施方式,且因此不限制其范围。

[0066] 图1A显示了全抗体-CD-CD融合蛋白的蛋白设计。图1B显示了在哺乳动物细胞中表达的全抗体-CD融合蛋白的蛋白设计和表达情形。

[0067] 图2A显示了抗原-靶向结构域-CD融合蛋白的载体设计。图2B总结了所测试的融合蛋白的表达谱和功能性分析结果;v=经验证;N/D=未经检测;N/A=无相关数据。图2C和2D显示了本公开的几种VHH-CD融合蛋白的表达情形。I0:诱导前的大肠杆菌培养物。I5:诱导后5小时的大肠杆菌培养物。胞浆(C):破菌液的可溶性部分。包涵体(I):破菌液的不溶性部分。M:标志物。

[0068] 图3显示了经小规模纯化的几种sdAb-CD融合蛋白的SDS-PAGE分析。M=标志物。

[0069] 图4A和图4B显示了几种sdAb-CD融合蛋白的尺寸排阻色谱分析。

[0070] 图5A和图5B显示了几种sdAb-CD融合蛋白的胞嘧啶脱氨酶(CDase)活性。

[0071] 图6A和图6B显示了展示sdAb-CD融合蛋白与人类VEGFR2和人类EGFR(图6A)以及人类HER2、HER3和CEA(图6B)的结合能力的ELISA测定。OD=光密度。

[0072] 图7A和图7B显示了经大规模纯化的adAb-CD融合蛋白3VGR19-CD-H(图7A)和7D12-CDome3(图7B)的纯化情形。LS=低速上清液;F1=镍琼脂糖凝胶管柱的流通液(flow through)1;F2=镍琼脂糖凝胶管柱的流通液2;M=标志物;Q1=第1离子交换管柱;Q2=第2离子交换管柱;QF1=第1离子交换管柱的流通液;QF2=第2离子交换管柱的流通液;X1=分离液1;X2=分离液2。

[0073] 图8显示了sdAb-CD(3VGR19-CD)融合蛋白在SHuffle® T7 Express和T7Express细胞中的表达谱。S=上清液(胞浆);P=沉淀(包涵体);M=标志物;I0=诱导前的大肠杆菌培养物;I5=诱导后5小时的大肠杆菌培养物。与融合蛋白对应的亮带以箭头标示。

[0074] 图9A(MDA-MB-231)和图9B(A431)显示了以本发明的几种融合蛋白在表达抗原的细胞中的细胞层级细胞毒性测定的结果。

[0075] 图10A显示了以融合蛋白CDoem3-H和7D12-CDoem3-H在表达EGFR的细胞中的细胞层级细胞毒性测定的结果。图10B显示了以融合蛋白CDoem3和7D12-CDoem3在表达EGFR的细胞中的细胞层级细胞毒性测定的结果。NP=阴性蛋白对照(CDoem3-H)。

[0076] 图11A显示了以7D12-CDom3-H和7D12-CDom3与5-氟胞嘧啶(5-FC)组合治疗后的A431异种移植模型的肿瘤生长曲线;图11B显示了以7D12-CDom3-H和7D12-CDom3与5-FC组合治疗后的A431异种移植模型的肿瘤重量。

[0077] 图12显示了7D12-CDom3-H的单突变变体的表达情形和功能性分析结果。

[0078] 图13A和图13B显示了7D12-CDom3-H的多突变变体的表达情形和功能性分析结果。

[0079] 图14显示了7D12-CDom3和7D12-CDom3变体的T细胞增殖和IL-2 ELISpot反应的总结果。

[0080] 图15显示了7D12-CDom3和7D12-CDom3变体的胞嘧啶脱氨酶活性和对人类EGFR的结合能力。

具体实施方式

[0081] 本公开提供了包含单域抗体(sdAb)或其功能性变体与胞嘧啶脱氨酶(CD)或其功能性变体的双功能融合蛋白。使用本文描述的方法制备了具有良好的生物学活性和优异产量(例如,约1g/L)、适于商业用途的融合蛋白。本公开的融合蛋白可以作为胞浆蛋白在大肠杆菌中以高产量表达,且在经工程化以优化胞浆中的二硫键形成的大肠杆菌菌株中能够进一步改善蛋白稳定性。本文还提供了在癌症和其它增殖性疾病的治疗中使用本公开的融合蛋白的组合物和方法。

[0082] 本公开表明根据本公开的各种sdAb-CD融合蛋白稳定且具有对癌细胞的细胞毒性效果。通过SDS-PAGE检测到可溶性蛋白,且通过SEC-HPLC显示出融合蛋白的相对高纯度。融合蛋白的CD和sdAb部分在生产的所有融合蛋白中均维持了其原有功能。CD活性通过5-FC向5-FU转化测定而证明,而融合蛋白与人VEGFR2、EGFR、HER3、HER2或CEA的结合通过ELISA显示。通过在癌细胞系上的细胞毒性测试,sdAb-CD融合蛋白证明了其能够靶向并结合VEGFR2和EGFR并且将无毒性的5-FC转化为毒性的5-FU从而杀死表达抗原的癌细胞。在A431小鼠异种移植模型中,sdAb-CD融合蛋白证实通过抑制和阻遏肿瘤生长而具功能性。

[0083] 利用本文所述的方法表达本公开的数种融合蛋白产生了具有良好的生物学活性和优异产量(例如,约1g/L)、适于商业用途的融合蛋白。

[0084] 本公开还提供了对于生产稳定且展示出CD活性和抗原结合活性的去免疫化sdAb-CD融合蛋白。

[0085] 除非具体说明或从上下文显而易见,如本文所用,术语“或”应理解为包含性。除非具体说明或从上下文显而易见,如本文所用,术语“一个/一种”(“a”,“an”)和“所述/该”(“the”)理解为单数或复数。

[0086] 此外,“和/或”在本文使用时应被当作两个指定的特征或成分的每一个与另一个同时或不与另一个同时具体公开。因此,在本文诸如“A和/或B”等短语中所用的术语“和/或”意在包括“A和B”、“A或B”、“A”(仅)和“B”(仅)。

[0087] 除非具体说明或从上下文显而易见,本文使用时,术语“约”应理解为处于本领域正常容许范围内,例如在平均值(例如,声明值)的两个标准偏差内。“约”可以理解为声明值的10%、9%、8%、7%、6%、5%、4%、3%、2%、1%、0.5%、0.1%、0.05%或0.01%以内。除非由上下文显而易见,本文提供的所有数值由术语“约”修饰。

[0088] 本文提供的任何组合物或方法可以与本文提供的任何一种或多种其它组合物或

方法进行组合。

[0089] 酶的“活性”是对其催化反应的能力(即,“发挥功能”)的量度,且可以表达为反应的产物产生的速率。例如,酶活性可表示为每单位时间或每单位的酶产生的产物的量(例如,浓度或重量),或者以亲和力或解离常数来表示。“胞嘧啶脱氨酶活性”、“胞嘧啶脱氨酶的生物活性”或“胞嘧啶脱氨酶的功能性活性”在本文中可互换使用,其是指根据标准技术在体内或体外确定的CD或其功能性变体或者本公开的融合蛋白所发挥的对于CD底物的活性。测量CD活性的测定是本领域已知的。例如,CD活性可以通过确定5-FC向5-FU或者胞嘧啶向尿嘧啶转化的速率来测量。5-FC、5-FU、胞嘧啶和尿嘧啶的检测可以通过“实施例”章节中描述的方法、通过色谱和/或通过本领域已知的其它方法来进行。

[0090] 在本公开中,“基本由…组成”或“基本以…组成”允许存在多于所叙述的内容,条件是所叙述的内容的基本特性或新特性不被多于所叙述内容的存在所改变,但是现有技术实施方式排除在外。例如,“基本由”所叙述的序列“组成”的多肽/蛋白或核酸序列可以分别包括不破坏所叙述序列的生物学活性的一个或多个额外的氨基酸或核酸。

[0091] 如本文所用,“融合多肽”或“融合蛋白”是指包含并非天然存在于同一蛋白中的两个或多个不同多肽或其活性片段的蛋白。融合蛋白具有单个连续多肽骨架,其可选地具有在两个或多个不同多肽中的任两者之间的肽接头。可以利用分子生物学的常规技术将两个或多个基因在框架内连接在单个核酸序列内,然后将该核酸在产生融合蛋白的条件下在适当的宿主细胞中表达,从而制备该融合蛋白。

[0092] 如本文所用,“功能性变体”是指与多肽或蛋白具有实质性或显着的序列同一性并且保留该多肽或蛋白的至少一种生物学活性的多肽或蛋白的变体。多肽或蛋白的功能性变体可以通过本领域已知手段基于本公开来制备。功能性变体可以包括对多肽或蛋白的氨基酸序列的一个或多个修饰。在某些实施方式中,所述修饰改变多肽或蛋白的一种或多种物化性质,例如,通过改善多肽或蛋白的热稳定性、改变底物特异性、改变最优pH和减少免疫原性等。在某些实施方式中,所述修饰改变多肽或蛋白的一种或多种生物学性质,条件是其不会破坏或损毁多肽或蛋白的所有生物学性质即可。

[0093] 根据本发明的某些实施方式,多肽或蛋白的功能性变体包含对多肽或蛋白的一个或多个氨基酸取代,该取代不会显着影响多肽或蛋白的生物学活性,优选为保守性氨基酸取代。保守性氨基酸取代包括但不限于:碱性氨基酸组(精氨酸、赖氨酸和组氨酸)内的氨基酸取代、极性氨基酸组(谷氨酸和天冬氨酸)内的氨基酸取代、疏水性氨基酸(亮氨酸、异亮氨酸和缬氨酸)组内的氨基酸取代、芳香性氨基酸(苯丙氨酸、色氨酸和酪氨酸)组内的氨基酸取代以及小氨基酸(甘氨酸、丙氨酸、丝氨酸、苏氨酸和甲硫氨酸)组内的氨基酸取代。非标准或非天然氨基酸(例如,4-羟基脯氨酸、6-N-甲基赖氨酸、2-氨基异丁酸和 α -甲基丝氨酸)也可以或者作为另选使用来取代多肽或蛋白中的标准氨基酸残基。

[0094] 根据本发明的某些实施方式,多肽或蛋白的功能性变体包含对该多肽或蛋白的一个或多个氨基酸的缺失和/或插入。例如,CD的功能性变体可以包括对CD的1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30或更多个氨基酸的缺失和/或插入。例如,sdAb的功能性变体可以包括对sdAb的1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30或更多个氨基酸的缺失和/或插入。在某些实施方式中,sdAb的功能性变体可以包括对sdAb的框架(FR)区的

1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30或更多个氨基酸的缺失和/或插入。在某些实施方式中,多肽或蛋白的功能性变体包括第一个甲硫氨酸的缺失。

[0095] 根据本发明的某些实施方式,多肽或蛋白的功能性变体包含对亲本蛋白的取代和缺失和/或插入。在某些方面,取代是保守性取代,并且/或者缺失和/或插入是小缺失和/或小插入。

[0096] 如本文所用,“单域抗体”、“sdAb”、“sdAb蛋白”、“VHH”(重链抗体的可变域)和“纳米抗体(nanobody)”可互换使用。如本文所用,“CD”、“CDase”和“CD蛋白”可互换使用。

[0097] 术语“同一”或百分比“同一性”在两个或多个核酸或多肽的背景下是指两个或多个序列或亚序列在针对最大对应性进行比较并比对(必要时引入空位)时相同或者具有有所指明的百分比的相同核苷酸或氨基酸残基(不将任何保守氨基酸取代认为是序列同一性的一部分)。术语“基本同一”是指两个或多个序列或亚序列具有与采用下文所述的默认参数使用BLAST或BLAST 2.0序列比较算法或者通过手动比对并目视检查所测定相同的所指明百分比的氨基酸残基或核苷酸(即,在比较窗或者指定的区域中针对最大对应性进行比较并比对(必要时引入空位)时,在所指明区域的至少约60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高的同一性)。该定义包括具有缺失和/或添加的序列,以及具有取代的那些序列。如下文所述,算法能将空位等计算在内。当未指明时,同一性或基本同一性在参比序列的整个长度上确定。当指明时,同一性可以在长度为至少约10个氨基酸或核苷酸的区域、长度为至少约25个氨基酸或核苷酸的区域或者在长度为50-100个氨基酸或核苷酸的区域中进行确定。

[0098] 同一性百分比可以采用序列比较软件或算法或者通过目视检查来测定。可以用来获得氨基酸或核苷酸序列的比对的各种算法和软件在本领域中已知(例如参见,Karlin等,1990,Proc.Natl.Acad.Sci.USA,87:2264-2268,如Karlin等,1993,Proc.Natl.Acad.Sci.USA,90:5873-5877中所改良),且并入NBLAST和XBLAST程序(Altschul等,1991,Nucleic Acids Res.,25:3389-3402)。在某些实施方式中,可以使用如Altschul等,1997,Nucleic Acids Res.25:3389-3402所述的Gapped BLAST、BLAST-2、WU-BLAST-2(Altschul等,1996,Methods in Enzymology,266:460-480)、ALIGN、ALIGN-2(Genentech,South San Francisco,Calif.)或MegAlign(DNASTAR)。

[0099] 术语“分离的”在用来描述蛋白或核酸时是指基本不含存在于其天然环境中的其它要素的分子。例如,分离的蛋白基本不含来自其所源自的细胞或组织来源的细胞物质或其他蛋白。术语“分离的”也指其中的分离的蛋白足够纯而足以作为药物组合物施用的制剂,或至少70%-80%(w/w)纯、更优选至少80%-90%(w/w)纯、甚至更优选至少90%-95%(w/w)纯、且最优选至少95%、96%、97%、98%、99%或100%(w/w)纯。

[0100] 如本文所用,在比较数据的上下文中的“参比”是指比较的标准物。

[0101] 如本文所用,“特异性结合”是指试剂(例如,sdAb或其功能性变体)可识别并结合分子(例如,VEGFR2、EGFR),但基本不会识别和结合样品中的其它分子(例如,生物样品中的其它分子)。例如,特异性结合的两种分子形成在生理学条件下相对稳定的复合体。特异性结合的特征在于高亲和力和低至中等的结合位点数,这区别于非特异性结合,后者通常具有低的亲和力以及中等至高的结合位点数。如本文所用,“特异性结合至”或“对…具有特异

性”是指靶标和抗体(例如,sdAb或其功能性变体)之间的可测定且可再现的相互作用,例如结合,该结合取决于在一个混杂的分子群体(包含生物学分子)中,存在着靶标。例如,特异性结合靶标(可以是表位)的sdAb或其功能性变体是以比其结合其它靶标更大的亲和力、亲合力、更容易和/或持续时间更长而与该靶标结合的sdAb或其功能性变体。在一个实施方式中,sdAb或其功能性变体与不相关靶标的结合程度低于该sdAb或其功能性变体与所测定(例如,通过放射免疫测定(RIA))的靶标的结合的约10%。在某些实施方式中,特异性结合靶标的sdAb或其功能性变体的解离常数(K_D) $<1 \times 10^{-6}M$ 、 $<1 \times 10^{-7}M$ 、 $<1 \times 10^{-8}M$ 、 $<1 \times 10^{-9}M$ 或者 $<1 \times 10^{-10}M$ 、 $<1 \times 10^{-11}M$ 、 $<1 \times 10^{-12}M$ 。在某些实施方式中,sdAb或其功能性变体特异性结合在蛋白上来自不同物种的蛋白间保守的表位。在另一个实施方式中,特异性结合可以包括专一性结合(即,其仅结合一个蛋白),但这并非必须。

[0102] 如本文所用,“受试者”是指哺乳动物,包括但不限于人或非人哺乳动物,例如牛、马、犬、羊或猫。

[0103] 本文所提供的范围应理解为简略表达且因此涵盖该范围内的所有值。例如,1至50的范围应理解为包括选自1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49或50(包括其非整数)的任何数字、数字的组合或者亚范围。

[0104] 术语“肿瘤”或“赘生物(neoplasm)”是指含有赘生性细胞的异常组织团块。赘生物和肿瘤可以是良性的、恶化前的和恶性的。

[0105] 术语“癌症”或“恶性赘生物”是指表现出不受控的生长、侵入临近组织且常常转移至身体的其它部位的细胞。这包括血液学和淋巴的癌症。

[0106] 术语“结合亲和力”一般指分子(例如,sdAb)的单个结合位点与其结合对象(例如,抗原)之间的非共价相互作用的总和的强度。除非另外指出,如本文所用,“结合亲和力”、“结合至”、“结合”或“与...结合”是指反映出结合对的成员(例如,抗体Fab片段和抗原)之间的1:1相互作用的内在结合亲和力。分子X对其伴侣Y的亲和力一般可以通过解离常数(K_D)表示。亲和力可以通过本领域已知的普通方法(包括本文所述的那些方法)来测定。低亲和力抗体通常缓慢地与抗原结合,且倾向于容易解离,而高亲和力抗体通常与抗原结合更快,且倾向于更长久地维持结合。测定结合亲和力的各种方法是本领域已知的,且出于本发明的目的可以使用其中任何一种。测定结合亲和力(例如,结合强度)的具体说明性和示例性实施方式在下文描述。

[0107] 在“背景技术”和整个说明书中引用或描述了各种出版物、文献和专利;这些参考文献的每一个在本文通过援引以其整体并入。对包括在本说明书中的文件、法案、材料、装置或文献等的讨论是出于提供本发明的背景的目的。这些讨论并非承认这些材料的任一种或所有构成了关于所公开或要求保护的发明的现有技术的一部分。

[0108] 本公开提供了包含式I或式II的融合蛋白,其中:

[0109] $N-(L)_n-C$ (式I);

[0110] $C-(L)_n-N$ (式II);

[0111] 其中,N为单域抗体(sdAb)或其功能性变体,L为肽接头, $n=0-50$,且C为胞嘧啶脱氨酶(CD)蛋白或其功能性变体。在某些实施方式中,融合蛋白基本由式I组成。在某些实施方式中,融合蛋白由式I组成。在某些实施方式中,融合蛋白基本由式II组成。在某些实施方

式中,融合蛋白由式II组成。

[0112] 在某些实施方式中,融合蛋白包含式I从而肽接头的C端或sdAb或其功能性变体的C端与CD蛋白或其功能性变体的N端融合。例如,在某些方面,不存在肽接头,sdAb或其功能性变体的C端与CD蛋白或其功能性变体的N端融合。在某些方面,存在肽接头,且sdAb或其功能性变体的C端与肽接头的N端融合,而肽接头的C端与CD蛋白或其功能性变体的N端融合。

[0113] 在其他实施方式中,融合蛋白包含式II从而肽接头的C端或CD蛋白或其功能性变体的C端与sdAb或其功能性变体的N端融合。例如,在某些方面,不存在肽接头,CD蛋白sdAb或其功能性变体的C端与sdAb或其功能性变体的N端融合。在某些方面,存在肽接头,且CD蛋白或其功能性变体的C端与肽接头的N端融合,而肽接头的C端与sdAb或其功能性变体的N端融合。

[0114] 本公开的融合蛋白的示例性单域抗体

[0115] sdAb包含具有3个互补决定区(CDR)的单个可变域。单域抗体传统上包含骆驼类(camelid)仅有重链的抗体(HcAb)的可变片段,即,重链抗体的重链的可变域VHH。某些VHH多肽也以商标名 **Nanobody®** (Nb;Ablynx) 指称。然而,在本公开中,使用术语纳米抗体(nanobody)不是将单域抗体限制为由Ablynx所提供的 **Nanobody®**。在某些实施方式中,sdAb或其功能性变体选自骆驼、驼羊(alpacas)或羊驼(llamas)的仅有重链IgG类抗体。在某些实施方式中,sdAb或其功能性变体是通过CDR嫁接产生的工程化多肽。例如,sdAb或其功能性变体通过将源自骆驼类的sdAb的CDR区域的全部或某一些替代为具有所需靶标的其它已知抗体的CDR区域而产生。在某些实施方式中,sdAb或其功能性变体是见于鲨鱼中的仅有重链的抗体的重组衍生物。在某些实施方式中,sdAb或其功能性变体利用本领域公知的技术通过合成生成。在某些实施方式中,sdAb或其功能性变体是人sdAb(Domantis, Inc., Waltham, Mass.; 参见例如,美国专利第6,248,516B1号)。

[0116] 在某些实施方式中,sdAb或其功能性变体是来自骆驼类的人源化VHH。如本文所用,术语“人源化”sdAb是指在天然存在的VHH序列的氨基酸序列中的一个或多个氨基酸残基被存在于来自人的常规四链抗体的VH结构域的对应位置处的一个或多个氨基酸残基所替换的sdAb。这种替换可以通过本领域公知的方法来进行,例如,sdAb的框架区(FR)可以由人可变FR替换。

[0117] CDR对于sdAb或其功能性变体的表位识别极为重要。在不干扰sdAb或其功能性变体识别并结合其同源表位的情况下可以对构成CDR的氨基酸残基进行改变。例如,可以进行不会影响靶标表位识别然而增加sdAb或其功能性变体对该表位的结合亲和力的改变。在某些实施方式中,这些改变是保守氨基酸取代和/或小的缺失或小的插入。

[0118] 在某些实施方式中,sdAb或其功能性变体包含任一种仅有重链IgG类抗体的可变结构域。单可变结构域包含3个互补决定区(CDR)。sdAb或其功能性变体可以为具有(通式)结构FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4的免疫球蛋白和/或多肽,其中FR1、FR2、FR3和FR4分别指框架区1、2、3和4,且其中CDR1、CDR2和CDR3分别指互补决定区1、2和3。sdAb或其功能性变体的氨基酸残基的编号根据Kabat等(“Sequence of proteins of immunological interest,”US Public Health Services,NIH Bethesda,Md.,Publication No.91)给出的对VH结构域的通用编号。根据该编号,sdAb的FR1包含在1-30位的氨基酸残基,sdAb或其功能性变体的互补决定区1(CDR1)包含在31-35位的氨基酸残基,sdAb或其功能性变体的FR2

包含在36-49位的氨基酸残基, sdAb或其功能性变体的互补决定区2 (CDR2) 包含在50-65位的氨基酸残基, sdAb或其功能性变体的FR3包含在66-94位的氨基酸残基, sdAb或其功能性变体的互补决定区3 (CDR3) 包含在95-102位的氨基酸残基, 且sdAb或其功能性变体的FR4包含在103-113位的氨基酸残基。

[0119] 在某些实施方式中, sdAb或其功能性变体是半衰期延长的sdAb。增加多肽的半衰期的方法是本领域公知的。

[0120] 本公开的融合蛋白作为治疗剂的有效性取决于适当的sdAb靶标的选择。靶标可以是目前已知或者正在被认知的任何种类,并且包括肽和非肽(例如,细胞表面脂质、聚糖或其他转译后修饰)。

[0121] 在一个实施方式中,本公开的sdAb或其功能性变体与癌细胞表面上的胞外靶标结合。在一个实施方式中,sdAb或其功能性变体与靶标结合,其中所述靶标选自细胞膜分子、分泌的分子和细胞内分子。

[0122] 在某些实施方式中,靶标选自自由以下组成的组:EGFR、5T4、A33、AFP、 β -连环蛋白、BRCA1、BRCA2、C242、CCR4、CD152、CD19、CD20、CD200、CD22、CD221、CD23、CD30、CD3、CD37、CD40、CD44、CD5、CD51、CD52、CD56、CD64、CD74、CD80、CDCP1、c-KIT、COX-2、cMET、CSF1R、CTLA-4、EGF2、ErbB2、ErbB3、FGFR1、FGFR2、FGFR3、FLT3、HER2、HER3、HIF-1 α 、HLA-DR、IGF-1R、mTOR、NPC-1C、P53、PDGFR α 、PDGFR β 、PLGF、PSA、RGMa、RoN、TNF、TP53、TPD52、VEGFR1、VEGFR2、VEGFR3、CA-IX、 α v β 3、 α 5 β 1、FAP、糖蛋白75、TAG-72、MUC16、NR-LU-13、SLAMF7、EGP40、BAFF、PRL-3、癌胚抗原(CEA)、前列腺特异性膜抗原、MART-1、gp100、癌-睾丸(CT)抗原(例如,NY-ESO-1、MAGE-A3、MAGE-A1)、hTERT、MCC、Mum-1、ERBB2IP、EpCAM、TfR、整合素 α 6 β 4、HGFR、PTP-LAR、CD147、CDCP1、CEACAM6、JAM1、整合素 α 3 β 1、整合素 α v β 3、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、间皮素、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体(nAChR)。

[0123] 在某些实施方式中,靶标选自由以下组成的组:EGFR、c-KIT、cMET、HER2、HER3、FGFR1、FGFR2、FGFR3、IGF-IR、P53、PDGFR α 、VEGFR1、VEGFR2、VEGFR3、CA-IX、 α v β 3、 α 5 β 1、MUC16、癌胚抗原(CEA)、前列腺特异性膜抗原、癌-睾丸(CT)抗原(例如,NY-ESO-1、MAGE-A3、MAGE-A1)、间皮素、EpCAM、整合素 α 6 β 4、CEACAM6、整合素 α 3 β 1、整合素 α v β 3、PD-L1、AXL、CDH6、DLL3、EDNRB、EFNA4、NEPP3、EPHA2、FOLR1、LewisY、GPNMB、GUCY2C、HAVCR1、整合素 α 、LYPD3、MUC1、NECTIN4、NOTCH3、PTK7、SLC34A2、SLC39A6、SLC44A4、SLITRK6、STEAP1、TACSTD2、TPBG、TIM-1、GD2和烟碱型乙酰胆碱受体(nAChR)。

[0124] 在某些实施方式中,所述靶标为VEGFR2、EGFR、CEA、HER2或HER3。

[0125] 在某些实施方式中,本公开的融合蛋白的sdAb或其功能性变体靶向EGFR。在某些实施方式中,sdAb或其功能性变体源自J.Biomol.Screen.2009Jan;14(1):77-85中所描述的VHH122。在某些实施方式中,sdAb或其功能性变体源自Structure 21,1214-1224,July 2,2013.PDB:4KRM I和美国专利公开第US2009/0252681号所描述的7D12。

[0126] 在某些实施方式中,本公开的融合蛋白的sdAb或其功能性变体靶向VEGFR2。在某些实施方式中,sdAb或其功能性变体源自Mol.Immunol.2012Feb;50(1-2):35-41中所描述的3VGR19。在某些实施方式中,sdAb或其功能性变体源自Mol.Immunol.2012Feb;50(1-2):

35-41 所描述的 4VGR17。在某些实施方式中, sdAb 或其功能性变体源自 Mol. Immunol. 2012Feb; 50 (1-2) :35-41 所描述的 4VGR38。

[0127] 在某些实施方式中, 本公开的融合蛋白的 sdAb 或其功能性变体靶向 HER2。在某些实施方式中, sdAb 或其功能性变体源自美国专利公开 US 2011/0059090 中所描述的 2D3、5F7 或 47D5。

[0128] 在某些实施方式中, 本公开的融合蛋白的 sdAb 或其功能性变体靶向 HER3。在某些实施方式中, sdAb 或其功能性变体源自 Version 2.F1000Res. 2018; 7:57 中所描述的 BCD090-M2 (PDB ID: 6EZW)。

[0129] 在某些实施方式中, 本公开的融合蛋白的 sdAb 或其功能性变体结合 CEA。在某些实施方式中, sdAb 或其功能性变体源自于 US20160280795A1、FEBS J. 2009Jul; 276 (14) :3881-93 和 J. Nucl. Med. 2010Jul; 51 (7) :1099-106 中描述的 ABS29544.1 或 NbCEA5。

[0130] 本公开的融合蛋白的 sdAb 或其功能性变体的生物学活性能通过确定其与靶标或其表位的结合亲和力来评估。在某些实施方式中, 融合蛋白的 sdAb 或其功能性变体对靶标或其表位的亲和力可以为例如约 1 皮摩尔 (pM) 至约 100 微摩尔 (μM) (例如, 约 1 皮摩尔 (pM) 至约 1 纳摩尔 (nM)、约 1 nM 至约 1 微摩尔 (μM)、或约 1 μM 至约 100 μM)。在某些实施方式中, 融合蛋白的 sdAb 或其功能性变体能以小于或等于 1 纳摩尔 (例如, 0.9 nM、0.8 nM、0.7 nM、0.6 nM、0.5 nM、0.4 nM、0.3 nM、0.2 nM、0.1 nM、0.05 nM、0.025 nM、0.01 nM、0.001 nM, 或者前述值的任意两个所限定的范围) 的 K_D 与靶标 (例如, VEGFR2、EGFR、HER2、HER3 或 CEA) 结合。在某些实施方式中, 本公开的融合蛋白的 sdAb 或其功能性变体能以小于或等于 200 pM (例如, 190 pM、175 pM、150 pM、125 pM、110 pM、100 pM、90 pM、80 pM、75 pM、60 pM、50 pM、40 pM、30 pM、25 pM、20 pM、15 pM、10 pM、5 pM、1 pM, 或者前述值的任意两个所限定的范围) 的 K_D 与靶标结合。本文公开的融合蛋白的 sdAb 或其功能性变体对所关注的抗原或表位的亲和力可以使用任何现有技术认可的测定来检测。这些方法包括例如荧光活化细胞分选 (FACS)、可分离珠 (例如, 磁珠)、表面等离子共振 (SPR)、溶液相竞争 (KINEXA.TM.)、抗原筛选 (antigen panning) 和/或 ELISA (参见例如, Janeway 等 (编), Immunobiology, 第 5 版, Garland Publishing, New York, N.Y., 2001)。

[0131] 用于制备本公开的融合蛋白的 sdAb (或其功能性变体) 和核酸可以如下文实施例所描述的或者通过本领域技术人员已知的任何方法来制备。

[0132] 在某些实施方式中, sdAb 或其功能性变体包含选自由 SEQ ID NO: 28、31 和 34 组成的组的 CDR1、选自由 SEQ ID NO: 29、32 和 35 组成的组的 CDR2 以及选自由 SEQ ID NO: 30、33 和 36 组成的组的 CDR3, 基本由上述组成或者由上述组成。

[0133] 在某些实施方式中, sdAb 或其功能性变体包含选自由 SEQ ID NO: 37 和 40 组成的组的 CDR1、选自由 SEQ ID NO: 38 和 41 组成的组的 CDR2 以及选自由 SEQ ID NO: 39 和 42 组成的组的 CDR3, 基本由上述组成或者由上述组成。

[0134] 在某些实施方式中, sdAb 或其功能性变体包含选自由 SEQ ID NO: 199、202 和 205 组成的组的 CDR1、选自由 SEQ ID NO: 200、203 和 206 组成的组的 CDR2 以及选自由 SEQ ID NO: 201、204 和 207 组成的组的 CDR3, 基本由上述组成或者由上述组成。

[0135] 在某些实施方式中, sdAb 或其功能性变体包含 SEQ ID NO: 208 的 CDR1、SEQ ID NO: 209 的 CDR2 以及 SEQ ID NO: 210 的 CDR3、基本由上述组成或者由上述组成。

[0136] 在某些实施方式中,sdAb或其功能性变体包含选自由SEQ ID NO:211和214组成的组的CDR1、选自由SEQ ID NO:212和215组成的组的CDR2以及选自由SEQ ID NO:213和216组成的组的CDR3,基本由上述组成或者由上述组成。

[0137] 在某些实施方式中,sdAb或其功能性变体选自实施例中所公开的抗-VEGFR2sdAb组,即3VGR19 (SEQ ID NO:23)、4VGR17 (SEQ ID NO:24) 和4VGR38 (SEQ ID NO:25)。在某些实施方式中,sdAb或其功能性变体选自实施例中所公开的抗-EGFR sdAb组,即VHH122 (SEQ ID NO:26) 和7D12 (SEQ ID NO:27)。在某些实施方式中,sdAb或其功能性变体选自实施例中所公开的抗-HER2 sdAb组,即2D3 (SEQ ID NO:69)、5F7 (SEQ ID NO:70) 和47D5 (SEQ ID NO:71)。在某些实施方式中,sdAb或其功能性变体选自实施例中所公开的抗-HER3 sdAb组,即BCD090-M2 (SEQ ID NO:75)。在某些实施方式中,sdAb或其功能性变体选自实施例中所公开的抗-CEAsdAb,即抗-CEA sdAb (ABS29544.1) (SEQ ID NO:77) 和NbCEA5 (SEQ ID NO:79)。

[0138] 在某些实施方式中,本文公开的任何sdAb或其功能性变体与酵母菌CD蛋白或其功能性变体融合,所述酵母菌CD蛋白或其功能性变体包含SEQ ID NO:21 (野生型CD,无N端甲硫氨酸)、SEQ ID NO:22 (具有点突变A22L/V107I/I139的SEQ ID NO:21变体)、SEQ ID NO:186 (野生型CD,包括N端甲硫氨酸)、SEQ ID NO:187 (具有点突变A23L/V108I/I140L的SEQ ID NO:186变体) 或者任何前述氨基酸序列的功能性变体。

[0139] 在某些实施方式中,融合蛋白包含处于C端的组氨酸标签 (HIS-标签),例如6-HIS标签 (SEQ ID NO:6)。在某些实施方式中,融合蛋白经肽接头 (例如,GSS) 与HIS-标签连接。

[0140] 在某些实施方式中,本公开的融合蛋白的sdAb或其功能性变体可以经部分或完全人源化以用于预防和/或治疗与sdAb的靶标的存在有正相关性的病况。一般而言,人源化涉及将sdAb或其功能性变体的源自骆驼类的框架区和可变区的所有或一部分用人类对应序列替换,其目的是减少sdAb在治疗应用中的免疫原性。在某些情形中,骆驼类免疫球蛋白的FR残基被相应人类残基所替换。

[0141] 在某些实施方式中,sdAb或其功能性变体包含在以下T细胞表位上的一个或多个突变:

[0142]	表位	HLA-DR限制表位	SEQ ID NO
	表位1	SVQTGGSLRL	63
	表位2	LKPEDTAIY	64
	表位3	IYYCAAAAGS	65

[0143] 在某些实施方式中,sdAb或其功能性变体包含从表位1 (SEQ ID NO:63) 修饰的序列X₁X₂QX₃X₄GX₅LRL,其中,X₁可以被V取代,X₂可以被A取代,X₃可以被V取代,X₄可以被D取代,和/或X₅可以被D或E取代。在某些实施方式中,sdAb或其功能性变体包含从表位2 (SEQ ID NO:64) 修饰的序列LX₁X₂EDX₃X₄X₅Y,其中,X₁可以被R、A、D、S或T取代;X₂可以被A、D或E取代;X₃可以被D、E、G、H或Q取代;X₄可以被D或E取代;和/或X₅可以被V、A、T、R、Q或N取代。在某些实施方式中,sdAb或其功能性变体包含从表位3 (SEQ ID NO:65) 修饰的序列X₁IYYCAAAAGS,其中X₁可以被V、A、T、R、Q或N取代。

[0144] 在某些实施方式中,sdAb或其功能性变体包含从表位1 (SEQ ID NO:63) 修饰的序列X₁X₂QX₃X₄GSLRL,其中,X₁可以被V取代,X₂可以被A取代,X₃可以被V取代,和/或X₄可以被D取代。在某些实施方式中,sdAb或其功能性变体包含从表位2 (SEQ ID NO:64) 修饰的序列

LX₁X₂EDTAX₅Y, 其中, X₁可以被R或T取代; X₂可以被A取代; 和/或X₅可以被V或R取代。在某些实施方式中, sdAb或其功能性变体包含从表位3 (SEQ ID NO:65) 修饰的序列X₁YYCAAAGS, 其中X₁可以被V、A或R取代。

[0145] 在某些实施方式中, sdAb或其功能性变体包含具有序列ESGGGX₁X₂QX₃GGSL的FR1序列, 其中, X₁为S或V, X₂为V或A, 且X₃为A、T或V。在某些实施方式中, sdAb或其功能性变体包含具有修饰序列MNSLX₁X₂EDTAX₃YYCAA的FR3序列, 其中X₁为K、R或T; X₂为P或A; 和X₃为R或V。

[0146] 单域抗体氨基酸序列与人类家族III VH氨基酸序列紧密相关。因此, 在某些实施方式中, 产生了“人源化”sdAb形式。在某些实施方式中, sdAbs或其功能性变体源自HCAb, 该HCAb通过用靶肽对其中已消除了内源性鼠科抗体表达并导入了人转基因的转基因小鼠进行免疫而产生。HCAb小鼠公开于美国专利8,883,150号、美国专利8,921,524号、美国专利8,921,522号、美国专利8,507,748号、美国专利8,502,014、US 2014/0356908、US2014/0033335、US2014/0037616、US2014/0356908、US2013/0344057、US2013/0323235、US2011/0118444和US2009/0307787中, 所有均通过援引并入本文, 因为它们都公开了关于仅有重链的抗体及其在转基因小鼠中的生产。HCAb小鼠经免疫且所得的免疫活化 (primed) 的脾细胞与鼠科骨髓瘤细胞融合以形成杂交瘤。然后所得HCAb可以通过用对应的人序列替换鼠科CH2和CH3区来完全人源化。

[0147] 用于制备本公开的融合蛋白的sdAb或其功能性变体的另外的方法是本领域公知的。例如, 一种获得sdAb或其功能性变体的方法包括: (a) 将骆驼类用一种或多种抗原免疫; (b) 从经免疫的骆驼类分离外周淋巴细胞, 获得总RNA并合成对应的cDNA; (c) 构建编码sdAb结构域的cDNA片段的基因库; (d) 使用PCR将步骤(c)中获得的编码sdAb结构域的cDNA转录为mRNA, 将mRNA转化为核糖体或噬菌体展示形式, 并通过核糖体展示或噬菌体展示筛选来选择sdAb结构域; 和(e) 在合适的载体中表达该sdAb结构域, 以及可选地将表达的sdAb结构域纯化。其他示例性方法在Revets等, 2015Expert Opin.Biol.Ther. (2005) 5 (1):111-124, “Generation and production of recombinant nanobodies.”中提供的任一篇参考文献中有描述。另外, Harbour Biomed提供了人类重链啮齿类技术和人类重链构建体的平台, 描述于美国专利9,353,179、9,346,877和8,921,522以及欧洲专利1776383和1864998中, 所有均通过援引并入本文。Ablynx还提供了可以用来制备本公开的化合物的纳米抗体的来源。

[0148] 关于纳米抗体的进一步描述, 可以参考以下参考文献 (其各自通过援引并入本文): Muyldermans的综述文章 (Reviews in Molecular Biotechnology 74:277-302, 2001), 以及作为一般背景技术提及的以下专利申请: Vrije Universiteit Brussel的W094/04678、W0 95/04079和W0 96/341031; Unilever的W0 94/25591、W0 99/37681、W0 00/40968、W0 00/43507、W0 00/65057、W0 01/40310、W0 01/44301、EP 1134231和W0 02/48193; Vlaams Instituut voor Biotechnologie (VIB) 的W0 97/49805、W001/21817、W0 03/035694、W0 03/054016和W0 03/055527; Algonomics N.V. 和Ablynx N.V. 的W0 03/050531; National Research Council of Canada的W0 01/90190; Institute of Antibodies的W0 03/025020 (对应于EP 1433793); 以及Ablynx N.V. 的W0 04/041867、W0 04/041862、W0 04/041865、W0 04/041863、W0 04/062551、W0 05/044858、W0 06/40153、W0 06/079372、W0 06/122786、W0 06/122787和W0 06/122825, 和Ablynx N.V. 的其它公布的专利申请。也参考这些申请中提及的其它技术, 特别是国际申请W0 06/040153的第41-43页提

到的参考文献列表,所述列表和参考文献通过援引并入本文。如这些参考文献中所述,纳米抗体(特别是VHH序列和部分人源化纳米抗体)的特征特别在于一个或多个框架序列中的“Hallmark残基”的存在。在例如WO 08/101985和WO 08/142164中可以看到对纳米抗体(包括纳米抗体的人源化和/或骆驼化)以及其他修饰、部分或片段、衍生物或者“纳米抗体融合物”、多价构建体(包括接头序列的某些非限制性实例)和增加纳米抗体的半衰期的不同修饰以及它们的制备。对于纳米抗体的其它一般性描述,参考WO 08/020079(第16页,第61页第24行至第98页第3行)。

[0149] 本公开的融合蛋白的示例性接头

[0150] 本文所用的术语“接头”、“肽接头”、“接头结构域”和“接头区”(简称为“L”)可互换使用并且指长度为约1至100个氨基酸的寡肽或多肽区,其将本公开的融合蛋白的多肽(例如,sdAb或其功能性变体和CD蛋白或其功能性变体)连接起来。本公开的融合蛋白可以包含一个或多于一个接头。接头可以由柔性残基如甘氨酸和苏氨酸组成,从而相邻蛋白结构域相对于彼此自由移动。在某些实施方式中,接头包含1至20、1至15、1至10或者1至9个氨基酸。在某些实施方式中,接头包含1至9个氨基酸,例如,1、2、3、4、5、6、7、8或9个氨基酸。在某些实施方式中,接头是长度为约6至约30个氨基酸的肽。在这些实施方式的各方面中,肽接头的长度可以为例如至少6、至少7、至少8、至少9、至少10、至少11、至少12、至少13、至少14、至少15、至少16、至少17、至少18、至少19、至少20、至少21、至少22、至少23、至少24、至少25、至少26、至少27、至少28、至少29或30个氨基酸。在这些实施方式的其它方面中,肽接头的长度可以为例如至多6、至多7、至多8、至多9、至多10、至多11、至多12、至多13、至多14、至多15、至多16、至多17、至多18、至多19、至多20、至多21、至多22、至多23、至多24、至多25、至多26、至多27、至多28、至多29或至多30个氨基酸。在这些实施方式的其它方面中,肽接头的长度可以为约6至约8、约6至约10、约6至约12、约6至约14、约6至约16、约6至约18、约6至约20、约6至约22、约6至约24、约6至约26、约6至约28、约6至约30、约8至约10、约8至约12、约8至约14、约8至约16、约8至约18、约8至约20、约8至约22、约8至约24、约8至约26、约8至约28、约8至约30、约10至约12、约10至约14、约10至约16、约10至约18、约10至约20、约10至约22、约10至约24、约10至约26、约10至约28、约10至约30、约12至约14、约12至约16、约12至约18、约12至约20、约12至约22、约12至约24、约12至约26、约12至约28、约12至约30、约14至约16、约14至约18、约14至约20、约14至约22、约14至约24、约14至约26、约14至约28、约14至约30、约16至约18、约16至约20、约16至约22、约16至约24、约16至约26、约16至约28、约16至约30、约18至约20、约18至约22、约18至约24、约18至约26、约18至约28、约18至约30、约20至约22、约20至约24、约20至约26、约20至约28、约20至约30、约22至约24、约22至约26、约22至约28、约22至约30、约24至约26、约24至约28、约24至约30、约26至约28、约26至约30或者约26至约30个氨基酸。在某些实施方式中,接头区包含1至50个氨基酸。

[0151] 接头可以包含天然或非天然氨基酸。在某些实施方式中,接头包含任何氨基酸、不同氨基酸的组合或者相同氨基酸。接头可以是不同种类互相连接的肽序列,其一次或多次地连续或者与其他序列交替。接头还可以是重复的肽序列。在某些实施方式中,整个肽序列重复了1至50次。在希望确保两个相邻结构域不会在空间位阻上彼此干扰时,也可以使用更长的接头。

[0152] 在某些实施方式中,接头是(GGGGS)_n,其中n=1、2、3、4、5或6(SEQ ID NO:1)。在某

些实施方式中,接头是一个或多个GSGG (SEQ ID NO:2),GGGSGGGS (SEQ ID NO:3)和/或一个或多个GSG。在某些实施方式中,接头是KESGSVSSEQLAQFRSLD (SEQ ID NO:4)或EGKSSGSGSESKST (SEQ ID NO:5)。在某些实施方式中,接头是(GGGGS)3 (SEQ ID NO:188)。用在接头中的示例性氨基酸包括甘氨酸、苏氨酸、精氨酸、丝氨酸、丙氨酸、天冬酰胺、谷氨酰胺、天冬氨酸、脯氨酸、谷氨酸和/或赖氨酸。可用于融合蛋白的其他接头的实例是本领域公知的,且某些可见于Chen,X等,Adv Drug Deliv.Rev.2013Oct 15;65(10):1357-1369中,本文通过援引以其整体并入。适于本公开的融合蛋白的另外的接头也可见于Klein等,Protein Eng.Des.Sel.2014Oct;27(10):325-330,本文通过援引以其整体并入。

[0153] 在某些实施方式中,本公开的融合蛋白在sdAb或其功能性变体和CD蛋白或其功能性变体之间包含一个接头。在某些实施方式中,所述融合蛋白在sdAb或其功能性变体和CD蛋白或其功能性变体之间包含至少一个接头。例如,在某些方面,所述融合蛋白在sdAb或其功能性变体和CD蛋白或其功能性变体之间包含两个接头。

[0154] 在某些实施方式中,sdAb或其功能性变体和CD蛋白或其功能性变体直接融合(例如,没有连接性接头)。

[0155] 本公开的融合蛋白的示例性胞嘧啶脱氨酶(CD)蛋白

[0156] 胞嘧啶脱氨酶(CD)是能够将相对无害的5-氟胞嘧啶(5-FC)前药转化为细胞毒性化合物5-尿嘧啶(5-FU)(特别是在其被转化为具有细胞毒性的5-氟尿苷5'-单磷酸(5-FdUMP)时)的酶。因此,本公开的融合蛋白将结合表达本公开的sdAb或其功能性变体的靶标的细胞,且所述融合蛋白的CD蛋白或其功能性变体会将5-FC转化为5-FU,由此杀死靶细胞。在某些实施方式中,靶细胞是癌细胞。在某些实施方式中,靶细胞通过旁观者效应被杀死。Anticancer Res.1998Sep-Oct;18(5A):3399-406;Am J Cancer Res.2015;5(9):2686-2696。

[0157] 在某些实施方式中,CD或其功能性变体可以是酵母菌CD或其功能性变体。在某些实施方式中,CD或其功能性变体可以是细菌CD或其功能性变体。在某些实施方式中,CD或其功能性变体是大肠杆菌胞嘧啶脱氨酶或其功能性变体。例如,在某些实施方式中,CD或其功能性变体是由NCBI参照序列:NP_414871.1表示的大肠杆菌胞嘧啶脱氨酶。在某些实施方式中,CD或其功能性变体是由GenBank登录号AAB67713.1表示的酵母菌胞嘧啶脱氨酶。酿酒酵母(*S.cerevisiae*)的FCY1基因和大肠杆菌的coda基因分别编码这两种生物体的CD,它们是已知的且其序列已公布(EP402108;Erbs等,1997,Curr.Genet.31,1-6;WO 93/01281)。

[0158] 在某些实施方式中,CD蛋白或其功能性变体包含SEQ ID NO:21的序列。在某些实施方式中,CD蛋白或其功能性变体包含SEQ ID NO:186的序列。在某些实施方式中,对应于胞嘧啶脱氨酶的序列含有一个或多个变化。某些实施方式中,所述变化产生了野生型CD的功能性变体。优选地,CD结构域中的变化是稳定性突变。例如,在某些实施方式中,CD的功能性变体包含SEQ ID NO:22的序列,其与SEQ ID NO:21相比具有A22L/V107I/I139L。在某些实施方式中,CD的功能性变体包含SEQ ID NO:187的序列,其与SEQ ID NO:186相比具有A23L/V108I/I140L。

[0159] 本公开还提供了包含CD多肽的融合蛋白,所述CD多肽包含与SEQ ID NO:21、22、186或187具有至少80%、90%、95%、98%或99%的同一性的序列,其中所述多肽具有胞嘧啶脱氨酶活性且因此被称为“功能性变体”。

[0160] 在某些实施方式中,CD蛋白的功能性变体可以是去免疫化形式以减少免疫原性。在某些实施方式中,CD蛋白或其功能性变体包含以下T细胞表位上的一个或多个突变:

[0161]	表位	HLA-DR限制表位	SEQ ID NO
	表位4	YTTLSPCDM	66
	表位5	MCTGAIIMY	67
	表位6	VVVVDDERCKK	68

[0162] 在某些实施方式中,CD蛋白或其功能性变体包含从表位4 (SEQ ID NO:66) 修饰的序列 $X_1X_2X_3LSPCD X_4$,其中 X_1 可以被A或H取代, X_2 可以被D取代, X_3 可以被E取代,且 X_4 可以被N、A、K或Q取代。在某些实施方式中,CD蛋白或其功能性变体包含从表位5 (SEQ ID NO:67) 修饰的序列 $X_1CTGAIIMY$,其中 X_1 可以被N、A、K或Q取代。在某些实施方式中,CD蛋白或其功能性变体包含从表位6 (SEQ ID NO:68) 修饰的序列 $X_1X_2X_3VDDERCKK$,其中 X_1 可以被A或T取代, X_2 可以被A、L、I或T取代,且 X_3 可以被A或T取代。

[0163] 在某些实施方式中,CD蛋白或其功能性变体包含从表位6 (SEQ ID NO:68) 修饰的序列 $X_1X_2VDDERCKK$,其中 X_1 可以被A取代, X_2 可以被T取代。

[0164] 在某些实施方式中,CD功能性变体是SEQ ID NO:21或22的变体,其中所述变体包含选自Y84A、Y84H、T85D、T86E、M92N、M92A、M92K、M92Q、V128A、V128T、V129A、V129L、V129I、V129T、V130A和V130T的至少一个突变。在某些实施方式中,CD功能性变体是SEQ ID NO:186或187的变体,其中所述变体包含选自Y85A、Y85H、T86D、T87E、M93N、M93A、M93K、M93Q、V129A、V129T、V130A、V130L、V130I、V130T、V131A和V131T的至少一个突变。

[0165] 在某些实施方式中,CD蛋白的功能性变体选自由SEQ ID NO:22、187、189、190、191、192、193和194组成的组。在某些实施方式中,CD蛋白的功能性变体选自由SEQ ID NO:22、189、191和193组成的组。

[0166] 用于检测胞嘧啶脱氨酶活性的测定是本领域已知的。例如,胞嘧啶脱氨酶活性可以通过确定5-FC向5-FU或者胞嘧啶向尿嘧啶转化的速率来检测。5-FC、5-FU、胞嘧啶和尿嘧啶的检测可以通过实施例章节中所述的方法、通过色谱和/或通过本领域中已知的其它方法来进行。

[0167] 本公开的示例性融合蛋白

[0168] 本公开提供了数种融合蛋白的实例,如下所述:

[0169] 本公开提供了包含式I或式II的融合蛋白,其中:

[0170] $N-(L)_n-C$ (式I);

[0171] $C-(L)_n-N$ (式II);

[0172] 其中,N为单域抗体(sdAb)或其功能性变体,L为肽接头, $n=0-50$,且C为胞嘧啶脱氨酶(CD)蛋白或其功能性变体。在某些实施方式中,融合蛋白基本由式I组成。在某些实施方式中,融合蛋白由式I组成。在某些实施方式中,融合蛋白基本由式II组成。在某些实施方式中,融合蛋白由式II组成。

[0173] 在某些实施方式中,融合蛋白包含式I从而肽接头的C端或sdAb或其功能性变体的C端与CD蛋白或其功能性变体的N端融合。例如,在某些方面,不存在肽接头,sdAb或其功能性变体的C端与CD蛋白或其功能性变体的N端融合。在某些方面,存在肽接头,且sdAb或其功能性变体的C端与肽接头的N端融合,而肽接头的C端与CD蛋白或其功能性变体的N端融合。

[0174] 在其他实施方式中,融合蛋白包含式II从而肽接头的C端或CD蛋白或其功能性变体的C端与sdAb或其功能性变体的N端融合。例如,在某些方面,不存在肽接头,CD蛋白或其功能性变体的C端与sdAb或其功能性变体的N端融合。在某些方面,存在肽接头,且CD蛋白或其功能性变体的C端与肽接头的N端融合,而肽接头的C端与sdAb或其功能性变体的N端融合。

[0175] 本公开还提供了包含sdAb(其针对胞外靶抗原,包括但不限于本文所述的任何靶抗原)与本文所述的任何胞嘧啶脱氨酶融合的融合蛋白。

[0176] 例如,在某些实施方式中,融合蛋白包含SEQ ID NO:7、9、11、13、15、17或者任何前述序列的第1-297位氨基酸的氨基酸序列。在某些实施方式中,融合蛋白基本由SEQ ID NO:7、9、11、13、15、17或者任何前述序列的第1-297位氨基酸的氨基酸序列组成。在某些实施方式中,融合蛋白由SEQ ID NO:7、9、11、13、15、17或者任何前述序列的第1-297位氨基酸的氨基酸序列组成。

[0177] 在某些实施方式中,融合蛋白包含选自由SEQ ID NO:17、19和93-185组成的组的氨基酸序列。在某些实施方式中,融合蛋白基本由选自由SEQ ID NO:17、19和93-185组成的组的氨基酸序列组成。在某些实施方式中,融合蛋白由选自由SEQ ID NO:17、19和93-185组成的组的氨基酸序列组成。

[0178] 在某些实施方式中,融合蛋白包含选自由SEQ ID NO:93-181组成的组的氨基酸序列的第1-297位氨基酸。在某些实施方式中,融合蛋白基本由选自由SEQ ID NO:93-181组成的组的氨基酸序列的第1-297位氨基酸组成。在某些实施方式中,融合蛋白由选自由SEQ ID NO:93-181组成的组的氨基酸序列的第1-297位氨基酸组成。

[0179] 在某些实施方式中,融合蛋白包含选自由SEQ ID NO:19、182、183、184和185组成的组的氨基酸序列。在某些实施方式中,融合蛋白基本由选自由SEQ ID NO:19、182、183、184和185组成的组的氨基酸序列组成。在某些实施方式中,融合蛋白由选自由SEQ ID NO:19、182、183、184和185组成的组的氨基酸序列组成。

[0180] 本公开还提供了包含多于一个sdAb或其功能性变体或者CD蛋白或其功能性变体的融合蛋白。例如,融合蛋白可以具有以下式III或IV:

[0181] $N1-(L1)_n-N2-(L2)_n-(C)-[(L3)_n-C]_{n2}$ (式III)

[0182] $(C)-[(L1)_n-C]_{n2}-(L2)_n-N1-[(L3)_n-N2]_{n1}$ (式IV)

[0183] 其中,N1和N2各自为sdAb或其功能性变体,其中N1和N2可以是相同或不同的sdAb或其功能性变体,且其中 $n1=0-10$;L1、L2和L3各自为肽接头,其中 $n=0-50$;C是胞嘧啶脱氨酶(CD)蛋白或其功能性变体,其中 $n2=0-10$ 。

[0184] 例如,融合蛋白可以具有以下式:

[0185] $N1-L1-N2-L2-C$;

[0186] $N1-L1-N2-L2-C-L3-C$;

[0187] $N1-N2-L-C$;

[0188] $N1-N2-L-C$;

[0189] $N1-L1-C-N2-L2-C$;

[0190] 其中,N1和N2可以相同和不同,且其中L1、L2和L3的任一个可以相同或不同。

[0191] 在某些实施方式中,融合蛋白是包含两种不同sdAb或其功能性变体(即,其结合两

个不同靶标或者同一靶标中的两个不同表位)的双价融合蛋白。在某些实施方式中,融合蛋白是单价融合蛋白。

[0192] 本公开的融合蛋白可以进一步与例如肽标签等部分融合以便纯化,参见例如,WO 93/21232;EP 439,095;Naramura等,Immunol Lett 39:91 (1994);U.S.Pat.No.5,474,981;Gillies等,Proc Natl Acad Sci USA 89:1428 (1992);和Fell等,J Immunol 146:2446 (1991)。在某些实施方式中,肽标签是组氨酸(HIS)标签。在某些实施方式中,肽标签是六组氨酸肽(SEQ ID NO:6)。六组氨酸标签可以是在pQE载体(QIAGEN, Inc., Chatsworth, 加利福尼亚州)或者另一种载体(许多可商购得到,Gentz等,Proc Natl Acad Sci USA 86:821 (1989))中提供的标签。可用于纯化的其它肽标签包括但不限于“HA”标签(其对应于源自流感血凝素蛋白的表位(Wilson等,Cell 37:767 (1984)))和“FLAGTM”标签。肽标签可以位于融合蛋白的N端、融合蛋白的C端或者处于融合蛋白的功能性结构域之间(例如,sdAb和CD或其功能性变体之间)。肽标签可以通过肽接头连接至融合蛋白。例如,连接融合蛋白和标签(例如,HIS-标签)的肽接头可以是GSS。

[0193] 本公开还涵盖与化学小分子缀合的融合蛋白,包括例如细胞毒性/化疗小分子和/或放射标签。本文所述用于与本公开的融合蛋白的组治疗的任何细胞毒性剂和化疗剂均可化学缀合至本公开的融合蛋白。在某些实施方式中,细胞毒性剂和化疗剂与融合蛋白共价缀合。在某些实施方式中,细胞毒性剂和化疗剂与融合蛋白非共价缀合。

[0194] 在某些实施方式中,本公开的融合蛋白与细胞毒性剂或化疗剂的缀合通过选自由二巯基、硫醚基、酸性不稳定基团、光不稳定基团、肽酶不稳定基团和酯酶不稳定基团组成的组的接头进行。

[0195] 在某些实施方式中,本公开的融合蛋白与细胞毒性和/或细胞生长抑制剂缀合。在这些实施方式的某些方面,细胞毒性和/或细胞生长抑制剂与融合蛋白的sdAb或其功能性变体缀合。在这些实施方式的某些方面,细胞毒性和/或细胞生长抑制剂与融合蛋白的CD蛋白或其功能性变体缀合。

[0196] 在其它实施方式中,融合蛋白与细胞因子、超抗原和/或毒素缀合(以化学方式或基因改造方式)或者偶联。

[0197] 在某些实施方式中,融合蛋白的药代动力学(包括融合蛋白的半衰期)可以通过化学修饰而改善,例如添加诸如聚乙二醇等聚(亚烷基)二醇(“聚乙二醇化(PEGylation)”、POLY PEG、PAS化(PASylation)或者通过加入脂质体中而改善。在某些实施方式中,融合蛋白(例如,sdAb或其功能性变体)包含允许聚乙二醇化和/或促进聚乙二醇化的一个或多个额外的氨基酸残基(例如,额外的半胱氨酸残基以便容易附接PEG基团)。在某些实施方式中,融合蛋白的半衰期通过如下增加:附接聚唾液酸(PSA)、羟乙基淀粉(HES)、白蛋白结合性配体或糖屏蔽体到融合蛋白上;与结合血清蛋白(诸如白蛋白、IgG、FcRn和/或转铁蛋白)的蛋白基因融合;与白蛋白或白蛋白的结构域或者与白蛋白结合性蛋白基因融合;将融合蛋白加入纳米载剂、缓释制剂或者医疗器械中。

[0198] 在某些实施方式中,融合蛋白可以通过糖基化、乙酰化、磷酸化、酰胺化、已知保护基/阻断基的衍生化和/或蛋白裂解切割来修饰。这些修饰可以通过已知技术进行,包括但不限于特异性化学切割、乙酰化、甲酰化和本领域已知的其它技术。另外,融合蛋白可以包含一个或多个非经典氨基酸。

[0199] 在某些实施方式中,例如出于诊断或测定目的(例如,为允许例如监测治疗或跟踪融合蛋白的分布而进行成像),融合蛋白可以包含可检测标签。合适的可检测标记和标记蛋白的方法是本领域公知的。合适的可检测标记包括例如放射性同位素(例如,铟-111、镓-99m或碘-131)、正电子发射性标记(例如,氟-19)、顺磁性离子(例如,钆(III)、锰(II))、表位标记(标签)、亲和性标记(例如,生物素、亲和素)、自旋标记、酶、荧光基团或者化学发光基团。当不采用标记时,复合物的形成(例如,所述融合蛋白与一靶间)可以通过表面等离子共振、ELISA、FACS或本领域已知的其它合适方法来确定。

[0200] 编码本公开的蛋白的核酸

[0201] 包括编码如本文所述的sdAb、接头、CD蛋白、sdAb和/或CD蛋白的功能性变体、融合蛋白或者任何前述物质的功能性等价物的核苷酸序列在内的核酸,是用于重组DNA分子中,以达到在适当的宿主细胞(例如细菌细胞)表达本公开的融合蛋白。如本文所用,术语“核酸分子”或“多核苷酸”意在包括DNA分子(例如,cDNA或基因组DNA)和RNA分子(例如,mRNA)以及使用核苷酸类似物生成的DNA或RNA的类似物。核酸分子可以是单链或双链的。

[0202] 在某些方面,本公开涉及编码胞嘧啶脱氨酶或突变体胞嘧啶脱氨酶多肽或其生物学活性部分的多核苷酸;编码sdAb或其生物学活性变体的多核苷酸;编码本公开的一个或多个接头的多核苷酸;以及编码本公开的融合蛋白的多核苷酸。

[0203] 在某些实施方式中,编码CD或其功能性变体的多核苷酸是经密码子优化的多核苷酸。在某些实施方式中,CD多核苷酸或经密码子优化的多核苷酸包含从生物体(例如,细菌或酵母菌株)分离的天然存在的核酸的重组、工程化或分离的形式。示例性CD多核苷酸包括编码SEQ ID NO:21、22、186或187所述的多肽的那些。本公开的实施例中所用的核酸落在所述实施方式的范围内。

[0204] 在某些实施方式中,CD或sdAb多核苷酸(包括经密码子优化的多核苷酸)通过将一个或多个天然存在的、分离的或者重组的CD或sdAb多核苷酸序列进行多样化(例如,重组和/或突变)而产生。如本文其他部分更详细所述,可以产生具有优异的功能属性(例如,与用作多样化过程中的底物或亲本的未经修饰的CD或sdAb多核苷酸相比,增加的催化功能、增加的稳定性或者更高的表达水平)的编码CD或sdAb多肽(例如,CD或sdAb的功能性变体)的多种CD或sdAb多核苷酸。由于遗传密码的简并性,编码基本相同或功能性等同氨基酸序列的不同核酸序列可以用于克隆和/或表达本公开的融合蛋白。

[0205] 本公开的多核苷酸具有各种用途,例如在本公开的融合蛋白的重组生产(即,表达)中,和作为产生进一步多样性的底物,例如产生新的和/或改进的变体的重组反应或突变反应;等等。

[0206] 本公开的CD和单域抗体多核苷酸的某些具体的、实质性和可靠的功用不要求该多核苷酸编码具有显着CD活性、或者变体CD活性或sdAb活性(例如,靶结合)的多肽。例如,不编码活性酶的CD多核苷酸可以是用于实现具有希望的功能性质(例如,高 k_{cat} 或 k_{cat}/K_m 、低 K_m 、对热或其它环境因素的高稳定性、高转录率或翻译率、对蛋白裂解切割的抗性、增加的抗原结合、增加的抗原特异性、降低的免疫原性)CD多核苷酸变体或非-CD多核苷酸的多样化程序中的宝贵资源。

[0207] 在某些实施方式中,编码sdAb或其功能性变体的多核苷酸是经密码子优化的多核苷酸。在某些实施方式中,sdAb多核苷酸或sdAb密码子优化的多核苷酸包含分离自生物体

(例如,单峰驼、骆驼、羊驼、驼羊或鲨鱼)的天然存在的氨基酸的重组、工程化或分离的形式。

[0208] 编码本公开的融合蛋白的示例性多核苷酸包括SEQ ID NO:8、10、12、14、16、18、20和195-198中所述的那些。

[0209] 本文所用的术语“宿主细胞”包括任何可接受核酸构建体的转化的细胞。术语“转化”是指将外来(即,外在或胞外)基因、DNA或RNA序列引入宿主细胞,从而该宿主细胞将表达所引入的基因或序列以产生所需物质,通常是所引入的基因或序列编码的蛋白或酶。引入的基因或序列可以包括调节序列或控制序列,例如细胞的遗传机制所利用的起始、终止、启动子、信号、分泌或其他序列。接受并表达引入的DNA或RNA的宿主细胞已被“转化”并且是“转化体”或“克隆”。引入宿主细胞的DNA或RNA可以来自任何来源,包括与该宿主细胞同一属或同一种的细胞,或者不同属或种的细胞,或者来自基因合成。

[0210] 术语“经密码子优化的序列”通常是指已通过替换使用频率低于约20%的任何密码子而针对特定宿主物种进行优化的核苷酸序列。对于在给定宿主物种中的表达已进行优化(例如,除密码子优化外,通过除去假多聚腺苷酸化序列、除去外显子/内含子剪接信号、除去转座子样重复、和/或优化GC含量)的核苷酸序列在本文称为“表达增强的序列”。

[0211] 本公开还提供了包含编码所公开的CD蛋白或其功能性变体、sdAb或其功能性变体、接头和/或融合蛋白的一个或多个核酸序列的载体。所述载体可以例如为质粒、附加体(episome)、粘粒、病毒载体(例如,逆转录病毒或腺病毒)或者噬菌体。合适的载体和载体制备方法是本领域公知的(参见例如,Sambrook等,Molecular Cloning,a Laboratory Manual,第4版,Cold Spring Harbor Press,Cold Spring Harbor,N.Y.(2012);和Ausubel等,Current Protocols in Molecular Biology,Green Publishing Associates and John Wiley&Sons,New York,N.Y.(1994,以及在线可获取的更新章节)。

[0212] 在某些实施方式中,包含编码本文公开的一个或多个氨基酸序列的一个或多个核酸的载体可以被引入能够表达由其所编码的多肽/蛋白的宿主细胞(包括任何合适的原核或真核细胞)内。因此,本公开提供了包含所公开的载体的细胞(包括分离的细胞)。优选的宿主细胞是能够容易且可靠地生长、具有足够快的生长速率、具有良好表征的表达体系并且能够容易且高效地转化或转染的那些宿主细胞。

[0213] 合适的原核宿主细胞的实例包括但不限于来自芽孢杆菌属(例如,枯草芽孢杆菌(*Bacillus subtilis*)和短芽孢杆菌(*Bacillus brevis*))、埃希氏菌属(如大肠杆菌)、假单胞菌属、链霉菌属、沙门氏菌属和欧文氏菌属的细胞。另外的合适的原核宿主细胞包括大肠杆菌的各种菌株(例如,K12、HB101(ATCC No.33694)、DH5、DH10、MC1061(ATCC No.53338)和CC102))。在某些实施方式中,宿主细胞是TunerTM(Novagen)、AD494(Novagen)、HMS174(Novagen)、NovaBlue(Novagen)、BLR(Novagen)、C41(Lucigen)、C43(Lucigen)、Lemo21(NEB)、NiCo21(NEB)、BL21、BL21(DE3)或T7 Express(NEB)。

[0214] 在某些实施方式中,宿主细胞是提供使二硫键形成的细胞质环境的大肠杆菌菌株。例如,所述细胞质环境通过优化硫氧还蛋白和/或谷胱甘肽途径和/或通过表达胞浆二硫键异构酶来实现。在某些实施方式中,宿主细胞是透过染色体基因套持续地表达胞浆二硫键异构酶(例如,DsbC)的染色体拷贝的大肠杆菌菌株。在某些实施方式中,原核宿主细胞是SHuffle[®] Express(NEB#C3028)细胞(New England Biolabs)。在某些实施方式中,原核宿

主细胞是SHuffle® T7 (NEB#C3026) 或 SHuffle® Express T7 LysY (NEB#C3030) 细胞。SHuffle®具有谷氧还蛋白还原酶和硫氧还蛋白还原酶的基因缺失($\Delta gor \Delta trxB$),这允许在细胞质中形成二硫键。该突变组合通常是致命的,但致死性通过编码过氧化物还原酶(ahpC*)的基因中的突变而受到抑制。另外,SHuffle®表达了缺乏其信号序列的周质二硫键异构酶DsbC形式,将DsbC保持在细胞质中。该酶据显示会作用于具有多个二硫键的蛋白以纠正被错误氧化的键并促进正确折叠。具有这些性质(例如,提供二硫键形成的细胞质环境)的任何其它细胞系可以用于制备被公开的化合物。在某些实施方式中,原核宿主细胞是Origami™或Rosetta-gami™。

[0215] 酵母菌真核表达体系的实例包括但不限于酵母属、毕赤酵母属、克鲁维酵母属、汉逊酵母属和耶氏酵母属。

[0216] 合适的昆虫宿主细胞描述于例如Kitts等,Biotechniques,14:810-817(1993); Lucklow,Curr.Opin.Biotechnol.,4:564-572(1993);和Lucklow等,J.Virol.,67:4566-4579(1993)中。示例性昆虫宿主细胞包括Sf-9和HI5 (Invitrogen,Carlsbad,加州)。

[0217] 体外蛋白表达的实例包括但不限于大肠杆菌裂解物、兔网织红细胞裂解物(RRL)、小麦胚芽提取物以及昆虫细胞裂解物(例如,SF9或SF21裂解物)。无细胞表达体系是其中蛋白合成在细胞裂解物中发生而不是在培养的细胞内发生的重组蛋白生产。无细胞表达体系可以提供对传统体内方法进行补充的数种优点和特性,例如更快的生产速度,因为其无需基因转染、细胞培养或者充分的蛋白纯化。

[0218] 与其他药物的组合治疗

[0219] 本公开的融合蛋白可以单独施用或与其他药物(例如,作为佐剂)组合施用。例如,多种化疗药、尤其是抗赘生药可用于与本公开的融合蛋白组合。大多数化疗药物可以分为烷基化剂、抗代谢药、蒽环类、植物生物碱、拓扑异构酶抑制剂、抗体和其他抗肿瘤剂。

[0220] 如本文所用,辅助或组合施用(共施用)包括以相同或不同剂型同时施用融合蛋白和另一种药物,或者分开施用融合蛋白和另一种药物(例如,依次施用)。

[0221] 在某些实施方式中,本公开的融合蛋白与损伤DNA或干扰DNA修复的抗赘生药物共施用。在某些实施方式中,本公开的融合蛋白和抗赘生药物协同性地起效。在某些实施方式中,本公开的融合蛋白增加了细胞对抗赘生药物的敏感性,例如增加了至少10%、15%、20%、25%、30%、35%、40%、45%或50%。损伤DNA或干扰DNA修复的抗赘生药物的非限制实例包括卡铂、卡莫司汀、苯丁酸氮芥、顺铂、环磷酰胺、达卡巴嗪、柔红霉素、多柔比星、表柔比星、伊达比星、异环磷酰胺、洛莫司汀、二氯甲基二乙胺(mechlorethamine)、米托蒽醌、奥沙利铂、丙卡巴肼、替莫唑胺和戊柔比星。在某些实施方式中,抗赘生药物是替莫唑胺,其为通常针对胶质母细胞瘤使用的损伤DNA的烷基化剂。在某些实施方式中,抗赘生药物是PARP抑制剂(例如,KU0058948、ABT-888(维利帕尼(veliparib))、奥拉帕尼(olaparib)、KU-59436、AZD-2281、AG-014699、BSI-201、BGP-15、INO-1001、ONO-2231),其抑制DNA损伤的碱基切除修复中的步骤。在某些实施方式中,抗赘生药物是组蛋白去乙酰化酶抑制剂(例如,伏立司他;罗米地新;西达本胺;帕比司他;丙戊酸;贝林司他(Belinostat);莫西司他(Mocetinostat);阿贝司他(Abexinostat);恩替司他(Entinostat);SB939(pracinostat);Resminostat(Resminostat);吉维司他(Givinostat);奎诺司他(Quisinostat);硫脲丁腈(Kevetrin™);CUDC-10;CHR-2845(特诺司他);CHR-3996;4SC-202;CG200745;ACY-1215(瑞

考司他);ME-344;莱蕨硫烷(sulforaphane)),其在转录层级抑制DNA修复并破坏染色质结构。在某些实施方式中,抗赘生药物是蛋白酶体抑制剂(例如,硼替佐米;卡非佐米;环氧酶素;伊沙佐米;Salinosporamide A),其通过破坏细胞中的泛素代谢来抑制DNA修复。泛素是调节DNA修复的信号传导分子。在某些实施方式中,抗赘生药物是激酶抑制剂(例如,ATM抑制剂(CP466722或KU-55933);CHK 1抑制剂(XL-844、UCN-01、AZD7762或PF00477736);或CHK 2抑制剂(XL-844、AZD7762或PF00477736)),其通过改变DNA损伤响应信号传导途径来抑制DNA修复。

[0222] 可以与本公开的融合蛋白组合的抗赘生药物的另外实例包括但不限于:烷基化剂(例如,替莫唑胺、顺铂、卡铂、奥沙利铂、二氯甲基二乙胺(mechlorethamine)、环磷酰胺、苯丁酸氮芥、达卡巴嗪、洛莫司汀、卡莫司汀、丙卡巴肼、苯丁酸氮芥和异环磷酰胺)、抗代谢药(例如,吉西他滨、甲氨蝶呤、阿糖胞苷、氟达拉滨和氟尿嘧啶)、抗有丝分裂剂、长春花生物碱如长春新碱、长春碱、长春瑞滨和长春地辛)、蒽环类(包括多柔比星、柔红霉素、戊柔比星、伊达比星和表柔比星,以及放线菌素如放线菌素D)、细胞毒性抗生素(包括丝裂霉素、普卡霉素和博来霉素)和拓扑异构酶抑制剂(包括喜树碱,诸如拓扑替康和表鬼臼毒素衍生物,如安吡啶、依托泊苷、磷酸依托泊苷和替尼泊苷)。

[0223] 可以与本公开的融合蛋白组合施用的其它化疗剂的实例包括:烷基化剂,例如塞替派和环磷酰胺;烷基磺酸盐,例如白消安、英丙舒凡(improsulfan)和哌泊舒凡(piposulfan);氮丙啶,例如苯左替派(benzodopa)、卡波醌、美妥替派(meturedopa)和乌瑞替派(uredopa);乙烯亚胺和甲基蜜胺(methylamelamine),包括六甲蜜胺(altretamine)、三亚乙基三聚氰胺、三亚乙基磷酰胺、三亚乙基硫代磷酰胺和三羟甲基蜜胺;乙酸原化合物(acetogenin)(例如,布拉它辛(bullatacin)和布拉它辛酮(bullatacinone)); δ -9-四氢大麻酚(屈大麻酚(dronabinol)); β -拉帕醌;拉帕醇;秋水仙碱;桦木酸;喜树碱(包括合成类似物托泊替康(CPT-11(伊立替康)、乙酰喜树碱、东莨菪素(scopolectin)和9-氨基喜树碱);苔藓抑素;培美曲塞;海洋抑素(callystatin);CC-1065(包括其阿多来新(adozelesin)、卡折来新(carzelesin)和比折来新(bizelesin)合成类似物);鬼臼毒素;鬼臼酸;替尼泊苷;念珠藻环肽(cryptophycin)(如克瑞托欣(cryptophycin)1和克瑞托欣8);海兔毒素;倍癌霉素(duocarmycin)(包括合成类似物,KW-2189和CB1-TM1),艾榴塞洛素(eleutherobin);潘可瑞斯汀(pancratistatin);TLK-286;CDP323,口服 α -4整合素抑制剂;匍枝珊瑚醇(sarcodictyin);海绵抑素(spongistatin);氮芥,例如苯丁酸氮芥、氯吡嗪、氯吡膦、雌莫司汀、异环磷酰胺、二氯甲基二乙胺、二氯甲基二乙胺氧化物盐酸盐、美法仑、新恩比兴、苯芥胆甾醇、松龙苯芥、曲磷胺和尿嘧啶氮芥;亚硝基脲类,如卡莫司汀、氯脲菌素、福莫司汀、洛莫司汀、尼莫司汀和雷尼莫司汀;抗生素,例如烯二炔类抗生素(如卡奇霉素,特别是卡奇霉素 γ 和卡奇霉素 ω (参见例如,Nicolaou等,Angew.Chem Intl.Ed.Engl.,33:183-186(1994);达米辛(dynemicin),包括达米辛A;埃斯培拉霉素(esperamicin);新制癌菌素生色团和相关的色素蛋白烯二炔抗生素生色团;阿克拉霉素(aclacinomysins);放线菌素;安曲霉素;重氮丝氨酸;博来霉素;放线菌素C(cactinomycin);卡柔比星;洋红霉素;嗜癌素;色霉素;放线菌素D;柔红霉素;地托比星(detorubicin);6-重氮-5-氧代-L-正亮氨酸;多柔比星(包括吗啉多柔比星素,氨基吗啉多柔比星,2-吡咯啉多柔比星,多柔比星HCl脂质体注射液和脱氧多柔比星);表柔比星;依索比星(esorubicin);伊达比星;麻西罗霉素

(marcellomycin); 丝裂霉素, 如丝裂霉素C, 霉酚酸, 诺加拉霉素, 橄榄霉素, 培洛霉素 (peplomycin), 泊非霉素 (potfiromycin), 嘌呤霉素, 古拉霉素 (guelamycin), 罗多比星 (rodorubicin), 链黑霉素 (streptonigrin), 链脲霉素, 杀结核菌素, 乌苯美司, 净司他丁和佐柔比星; 抗代谢药, 例如, 甲氨蝶呤、吉西他滨, 替加氟, 卡培他滨, 埃坡霉素和5-氟尿嘧啶 (5-FU); 叶酸类似物, 例如, 二甲叶酸 (denopterin)、甲氨蝶呤, 蝶罗呤 (pteropterin) 和三甲曲沙 (trimetrexate); 嘌呤类似物, 例如, 氟达拉滨, 6-巯基嘌呤, 硫胺素和硫鸟嘌呤; 嘧啶类似物, 例如, 安西他滨, 阿扎胞苷, 6-氮尿苷, 卡莫氟, 阿糖胞苷, 双脱氧尿苷, 多西氟尿苷, 依诺他滨, 氟尿苷和伊马替尼 (2-苯基氨基嘧啶衍生物), 以及其他c-Kit抑制剂; 抗肾上腺素, 例如, 氨鲁米特, 米托坦, 曲洛司坦; 叶酸补充剂, 例如亚叶酸 (frolinic acid); 醋葡醛内酯; 醛磷酸胺糖苷; 氨基乙酰丙酸; 恩尿嘧啶; 安吡啶; 贝斯布西 (bestrabucil); 比生群; 依达曲沙地磷酸胺 (defofamine); 美可辛; 地吡醌; 表鸟氨酸 (elfomithine); 依利醋铵 (elliptinium acetate); 依托格鲁 (etoglucid); 硝酸镓; 羟基脲; 香菇多糖; 氯尼达明 (lonidainine); 美登素类, 如美登素和安沙霉素; 米托胍脲; 米托蒽醌; 莫比达摩 (mopidanmol); 二胺硝吡啶 (nitraerine); 喷司他丁; 蛋氨酸芥; 吡柔比星; 洛索; 2-乙基酰肼; 甲基苄肼; PSK.RTM. 多糖复合物 (JHS Natural Products, Eugene, Oreg.); 雷佐生; 根霉素; 西佐; 螺环锗; 细交链孢菌酮酸 (tenuazonic acid), 三亚胺醌 (triaziquone); 2,2,2-三氯乙胺 (trichloroethethylamine); 单端孢霉烯 (例如T-2毒素, 疣孢菌素A, 杆孢菌素A和anguidine); 乌拉坦; 长春地辛; 达卡巴嗪; 甘露醇氮芥; 二溴甘露醇; 卫矛醇; 哌泊溴烷; 加西托星 (gacytosine); 阿拉伯糖苷 (“Ara-C”); 塞替派; 紫杉烷类, 例如紫杉醇、紫杉醇的白蛋白工程化纳米颗粒制剂和多西紫杉醇; 苯丁酸氮芥 (chloranbucil); 6-巯鸟嘌呤; 巯基嘌呤; 甲氨蝶呤; 铂类似物, 如顺铂和卡铂; 长春碱; 铂; 依托泊苷 (VP-16); 异环磷酸胺; 米托蒽醌; 长春新碱; 奥沙利铂; 甲酰四氢叶酸 (leucovorin); 长春瑞滨; 诺消灵; 依达曲沙; 柔红霉素; 氢嘌呤; 伊班膦酸盐; 拓扑异构酶抑制剂RFS 2000; 二氟甲基鸟氨酸 (DMFO); 类视色素, 例如视黄酸; 上述中的任一者的药学可接受盐、酸或衍生物; 以及上述中的两种或多种的组合, 例如CHOP (对环磷酸胺、阿霉素、长春新碱和泼尼松龙的组合疗法的缩写) 和FOLFOX (对采用奥沙利铂与5-FU和甲酰四氢叶酸 (leucovorin) 组合的治疗方案的缩写)。可以与本公开的融合蛋白组合使用的其它治疗剂包括: 二膦酸盐, 例如氯膦酸盐 (clodronate), NE-58095, 唑来膦酸/唑来膦酸盐, 阿仑膦酸盐, 帕米膦酸盐, 替鲁膦酸盐或利塞膦酸盐; 以及曲沙他滨 (1,3-二氧杂环戊烷核苷胞嘧啶类似物); 反义寡核苷酸、特别是抑制参与异常细胞增殖的信号传导途径中的表达或基因的那些, 例如, PKC- α 、Raf, H-Ras和表皮生长因子受体 (EGFR); 疫苗, 例如, Stimuvax疫苗、Theratope疫苗以及基因疗法疫苗 (例如, Allovectin疫苗、Leavectin疫苗和Vaxid疫苗); 拓扑异构酶1抑制剂; 抗雌激素, 例如氟维司群; Kit抑制剂, 例如伊马替尼或EXEL-0862 (酪氨酸激酶抑制剂); EGFR抑制剂, 例如, 厄洛替尼或西妥昔单抗; 抗VEGF抑制剂, 例如贝伐单抗; arinotecan; rmRH; 拉帕替尼和拉帕替尼二甲苯磺酸盐 (ErbB-2和EGFR双酪氨酸激酶小分子抑制剂, 也称为GW572016); 17AAG (格尔德霉素衍生物, 其为热休克蛋白 (Hsp) 90毒素) 以及上述中任一者的药学可接受盐、酸或衍生物。

[0224] 在某些实施方式中, 本文公开的融合蛋白或药物组合物与5-氟尿嘧啶 (5-FU) 共施用。在某些实施方式中, 融合蛋白或其药物组合物与例如含有5-FU的以下方案共施用: FOLFUD (5-FU和甲酰四氢叶酸 (leucovorin)、sLV5FU2 (5-FU和甲酰四氢叶酸)、IFL (伊立替

康、甲酰四氢叶酸和5-FU)、FLOX(5-FU、甲酰四氢叶酸和奥沙利铂)、mFOLFOX6(奥沙利铂、甲酰四氢叶酸和5-FU)、FOLFOX4(奥沙利铂、甲酰四氢叶酸和5-FU)、FOLFOX7(奥沙利铂、甲酰四氢叶酸和5-FU)、FOLFIRI(伊立替康、甲酰四氢叶酸和5-FU)、FOLFOXIRI(伊立替康、奥沙利铂、甲酰四氢叶酸和5-FU)、FOLFIRINOX(甲酰四氢叶酸钙、氟尿嘧啶、盐酸伊立替康和奥沙利铂)或CMF(环磷酰胺、甲氨蝶呤和5-FU)。在某些实施方式中,融合蛋白或其药物组合物与含有5-FC的方案共施用。例如,在某些实施方式中,任何前述含有方案的5-FU的5-FU成分被5-FC所替代(例如,5-FC和甲酰四氢叶酸;5-FC、甲酰四氢叶酸和伊立替康;5-FC、甲酰四氢叶酸和奥沙利铂;5-FU、甲酰四氢叶酸、伊立替康和奥沙利铂;5-FU、甲酰四氢叶酸钙、盐酸伊立替康和奥沙利铂;5-FC、环磷酰胺和甲氨蝶呤)。

[0225] 在某些实施方式中,本文公开的融合蛋白或药物组合物可以与一种或多种增强5-FU的细胞毒性效应的物质组合施用或共施用。增强5-FU的细胞毒性效应的物质包括但不限于:抑制嘧啶的从头生物合成的酶的药物;和诸如甲酰四氢叶酸(Waxman等,1982, Eur. J. Cancer Clin. Oncol. 18, 685-692)等药物,甲酰四氢叶酸在5-FU的代谢产物(5-FdUMP)存在时增加对胸苷酸合成酶的抑制,从而导致复制所需的dTMP总量的减少;以及如甲氨蝶呤(Cadman等,1979, Science 250, 1135-1137)等药物,其通过抑制二氢叶酸还原酶并增加PRPP(磷酸核糖焦磷酸)总量使得细胞RNA内的5-FU的引入增加。在某些实施方式中,增强5-FU的细胞毒性效应的物质抑制5-FU的降解。例如,在某些实施方式中,所述物质是吉美嘧啶。在某些实施方式中,增强5-FU的细胞毒性效应的物质降低5-FU的副作用。例如,在某些实施方式中,所述物质是奥替拉西钾。在某些实施方式中,增强5-FU的细胞毒性效应的物质通过抑制二氢嘧啶脱氢酶来抑制5-FU的代谢。例如,在某些实施方式中,所述物质是尿嘧啶。

[0226] 施用方法

[0227] 本公开的融合蛋白或药物组合物的递送可以以不同方式进行,包括口服、皮下、静脉内、腹腔或肿瘤内施用。其它施用和递送途径包括关节内、动脉内、肌内、胃肠外、皮下、胸膜内、局部、皮肤、皮内、透皮、胃肠外,例如,透粘膜、颅内、椎管内、粘膜、呼吸道、鼻内、经插管、肺内、肺内灌注、颊部、舌下、静脉内、鞘内、腔内、离子电渗、眼内、眼部、腺内、器官内和淋巴管内。

[0228] 每种递送/施用途对于本公开的融合蛋白制剂具有不同要求,且所述制剂可以由本领域普通技术人员常规制备。例如,对于口服应用或腹腔内注射,sdAb-CD融合蛋白需要对极端条件(即,蛋白酶和/或酸性pH)的抗性。如果需要,如本领域所公知,可以通过改造序列或通过引入额外的二硫键来改善对肽酶和糜蛋白酶的抗性从而使融合蛋白具有蛋白酶抗性。对于静脉内施用,在血清中的稳定性可能很重要。大多数与效应结构区域或纳米颗粒组合的sdAb据描述在血清中都非常稳定。

[0229] 根据某些实施方式,治疗应用或治疗方法包括对受试者或细胞施用药学可接受量的前药(例如,胞嘧啶类似物,特别是5-FC)的额外步骤。以非限制性说明而言,可以使用50mg/kg/日至1000mg/kg/日的剂量,或者500mg/kg/day的剂量或者200mg/kg/day的剂量,一天一次或者一天多于一次。在某些实施方式中,所述方法包括足以在施用的1至2天内获得约1-200(例如,10-100) $\mu\text{g/ml}$ 的血清浓度的5-FC首次加载剂量。在某些实施方式中,前药根据标准疗法施用(例如,口服、全身性),且所述前药施用在施用本文公开的融合蛋白之后

进行。在某些实施方式中,前药口服施用。在某些实施方式中,前药以单次剂量施用。在某些实施方式中,前药以如下剂量施用:该剂量经反复足够的时间以使得能够在宿主生物体或细胞内产生毒性代谢物。

[0230] 在某些实施方式中,前药可以是在体内被转化以提供具生物学、药学或治疗上活性形式的5-FC的化合物。这类光活化性化合物可以包含可在用例如紫外光(包括能够远程或临时激活的植入肿瘤位点的光)照射时被切割的光敏接头。

[0231] 在某些实施方式中,胞嘧啶类似物代替5-FC施用。胞嘧啶类似物可以作为胞嘧啶脱氨酶的底物,包括卤代胞嘧啶和前药5-氟胞嘧啶(5-FC)(其被CD活化为5-氟尿嘧啶(5-FU))。另外,可以使用5-FC的延长释放制剂(例如,Toca FC)。

[0232] 药物组合物

[0233] 本公开提供了包含本文公开的一种或多种融合蛋白的药物组合物。在某些实施方式中,药物组合物包含本文公开的一种或多种融合蛋白的药物组合物和一种或多种药学可接受的赋形剂。包含本公开的融合蛋白及其任何转译后修饰物以及药学可接受的赋形剂的药物组合物也落在本公开范围内,并且可以使用本领域已知的方法制备。合适的赋形剂是本领域公知的。赋形剂的选择部分地取决于组合物可施用的特定位点以及用于施用组合物的特定方法。组合物可选地可以为无菌的。组合物可以冷冻或冻干以便储存,并在使用前在合适的无菌载剂中回溶。组合物可以根据例如Remington:The Science and Practice of Pharmacy,第22版,Lippincott Williams&Wilkins,Philadelphia,Pa.(2013)和任何其它版本中所描述的常规技术来生成。

[0234] 术语“赋形剂”宽泛地指除活性治疗成分以外的任何成分。赋形剂可以是惰性物质、非活性物质和/或非医药活性的物质。赋形剂可以起到各种目的,例如,作为载剂、空载剂、溶剂、片剂助剂,和/或用以改善活性物质的施用和/或吸收。

[0235] 在某些实施方式中,本公开的药物组合物经制备以具有某种稳定性(物理和/或化学稳定性)。术语“物理稳定性”是指多肽或蛋白由于暴露于热-机械压力和/或与不稳定界面或表面(例如,疏水性表面)相互作用而形成生物学上无活性和/或不溶性聚集沉淀倾向。水性蛋白制剂的物理稳定性可以在不同温度以各种时长暴露于机械/物理应力(例如,振摇)后借助目视检查和/或通过浑浊度测定来评估。作为另选,物理稳定性可以使用蛋白的构象状态的光谱学试剂或探针(例如,硫代黄素T或“疏水斑”探针)评估。

[0236] 术语“化学稳定性”是指多肽或蛋白结构中的化学(特别是共价)变化,该变化导致形成与无损蛋白相比具有降低的生物学价效和/或增加的免疫原性效果的化学降解产物。化学稳定性可以通过在暴露于不同的环境条件后在不同的时间点测定化学降解产物的量来评估,例如,通过SEC-HPLC和/或RP-HPLC。

[0237] 本公开的融合蛋白可以作为药物制剂治疗性使用。术语“药物制剂”是指处于允许活性成分的生物学活性起效的形式的制剂,其中所述制剂不含对于将要施用该制剂的受试者具有不可接受的毒性的额外成分。在某些实施方式中,药物制剂是无菌的。

[0238] 在某些实施方式中,药物组合物或药物制剂可以是溶液、乳化液或悬浮液(例如,加入微粒、脂质体或细胞内)。典型地,在组合物或制剂中施用适当量的药学可接受盐以使其等渗。药学可接受载剂的实例包括但不限于食盐水、林格氏溶液和葡萄糖溶液。溶液的pH优选为约5至约8,且更优选为约7至约7.5。药物组合物或制剂可以包含载剂、增稠剂、稀释

剂、缓冲剂、防腐剂和/或表面活性剂。合适的载剂包括持续释放制剂,例如含有本公开的融合蛋白的固体疏水性聚合物的半透性基质,该基质为成形的颗粒的形式,例如膜、脂质体或微粒。取决于例如施用途和待施用的组合物的浓度,某些载剂将更为优选,此为本领域技术人员显而易见的。药物组合物或制剂还可以包含一种或多种额外的活性成分例如细胞毒性剂、细胞生长抑制剂、化疗剂、抗微生物剂、抗炎剂和麻醉剂。

[0239] 为了辅助本公开的融合蛋白溶解在水性环境中,可以添加表面活性剂作为润湿剂。表面活性剂可以包括阴离子洗涤剂例如月桂基硫酸钠、磺基琥珀酸二辛基酯钠和二辛基磺酸钠。可以使用阳离子洗涤剂,其可包括苯扎氯铵或苄索氯铵(benzethonium chloride)。可以在制剂中作为表面活性剂使用的非离子洗涤剂包括但不限于:聚桂醇400;聚乙二醇40硬脂酸酯;聚氧乙烯氢化蓖麻油10、50或60;甘油单硬脂酸酯;聚山梨酯20、40、60、65或80;蔗糖脂肪酸酯;甲基纤维素;和羧甲基纤维素。这些表面活性剂可以单独地或者作为混合物以不同比例存在于融合蛋白的药物组合物或制剂中。可增强肽摄取的添加剂可以包含在本公开的组合物或制剂中。例如,在某些实施方式中,组合物或制剂包含脂肪酸油酸、亚油酸和亚麻酸中的一种或多种。

[0240] 使用方法

[0241] 本公开的融合蛋白可以用于治疗增殖性疾病(癌症/肿瘤、再狭窄、青光眼、瘢痕)。在某些方面,本公开涉及包含对患有癌症或本文公开的任何疾病的受试者施用融合蛋白或其药物组合物或制剂由此治疗该患者中的所述疾病的方法。除了治疗用途外,本文所述的融合蛋白、药物组合物和/或药物制剂可以用在诊断或研究应用中。

[0242] 在某些实施方式中,本公开的融合蛋白或其药物组合物或制剂可以用于治疗本领域已知的任何癌症,例如结肠癌、食管癌、胃癌、胰腺癌、乳腺癌、基底细胞癌、Bowen病和宫颈癌。在某些实施方式中,本公开的化合物可以用于治疗眼表鳞状瘤。在某些实施方式中,所公开的融合蛋白、药物组合物和/或药物制剂可以用于治疗黑色素瘤、肾细胞癌、肺癌、膀胱癌、乳腺癌、宫颈癌、结肠癌、胆囊癌、喉癌、肝癌、甲状腺癌、胃癌、唾液腺癌、前列腺癌、胰腺癌、胆管癌、食道癌、骨癌、子宫内膜癌、卵巢癌、软组织肉瘤或Merkel细胞癌。在某些实施方式中,所公开的融合蛋白、药物组合物和/或药物制剂可以用于治疗实体肿瘤。在某些实施方式中,所述实体肿瘤是结肠癌、结直肠癌、胰腺癌或头颈癌。

[0243] 在某些实施方式中,所公开的融合蛋白、药物组合物和/或药物制剂可以用于治疗光化性角化病。在某些实施方式中,所公开的融合蛋白、药物组合物和/或药物制剂可以用作眼部和/或眶周手术的辅助治疗。在某些实施方式中,所公开的融合蛋白、药物组合物和/或药物制剂恶意用于治疗肥厚性(HTS)瘢痕和/或瘢痕疙瘩。

[0244] 术语“治疗”是指意图在于治愈、缓解或稳定疾病的对患者的医学管理。该术语包括积极治疗,即具体针对改善疾病、病理状况或者病症的治疗,也包括病因治疗,即针对去除相关疾病、病理状况或者病症的成因的治疗。另外,该术语包括:姑息性治疗,即设计来缓解症状而非将疾病、病理状况或者病症治愈的治疗;预防性治疗,即针对最小化或者部分或完全地抑制相关疾病、病理状况或者病症的发展的治疗;和/或支持性治疗,即用来补充针对改善疾病、病理状况或者病症的另一种特定疗法的治疗。

[0245] 术语“治疗有效性”是指所用的蛋白、组合或制剂的量是足以缓解疾病或病症的一个或多个成因或症状的量。所述缓解仅要求减少或改变,并非必须消除。用于治疗癌症的蛋

白、组合物或制剂的治疗有效量优选为足以导致肿瘤消退或者使肿瘤对放疗或化疗敏化的量。用于治疗所需的所公开的融合蛋白、药物组合物和/或药物制剂的量不仅随所选的特定sdAb(或其功能性变体)和融合蛋白而有所变化,而且随施用途径、待治疗的病况的性质、以及患者的年龄和状况等等因素而变化,且最终由主治医师或临床医师斟酌决定。此外,所公开的融合蛋白、药物组合物和/或药物制剂的剂量可能根据靶细胞、肿瘤、组织、移植物或器官而有所变化。

[0246] 临床医师通常将根据本文提到的因素来确定合适剂量。此外还显而易见,在特定情况下,临床医师可以选择偏离这些量,例如基于上文引用的因素以及该医师的专业判断。一般地,由以基本相同的途径,针对相同靶标而施用的相当的常规抗体或抗体片段所通常施用的量可以获得对待施用的量的一定的指引,但要考虑亲和力/亲合力、效力、生物分布、半衰期和本领域技术人员公知的类似因素的差异。例如,本公开的融合蛋白通常可以连续地(例如,通过输注)作为单次每日剂量或者作为在当天中多次分开的剂量以1克/kg体重/天至0.01微克/kg体重/天施用,优选0.1克/kg体重/天至0.1微克/kg体重/天,例如约1、10、100、或1000微克/kg体重/天。在某些实施方式中,本公开的融合蛋白以约10mg/kg至约60mg/kg的剂量施用。在某些实施方式中,本公开的融合蛋白以约10mg/kg/天至约60mg/kg/天的剂量施用。

[0247] 本公开的融合蛋白的其它合适剂量可以例如为1pg/kg至60mg/kg动物或人体重的范围内;然而,低于或高于该示例性范围的剂量在本发明的范围之内。每日胃肠外剂量可以为:约0.00001μg/kg至约20或约40mg/kg总体重(例如,约0.001μg/kg、约0.1μg/kg、约1μg/kg、约5μg/kg、约10μg/kg、约100μg/kg、约500μg/kg、约1mg/kg、约5mg/kg、约10mg/kg,或前述值中任两者所限定的范围),优选为约0.1μg/kg至约10mg/kg总体重(例如,约0.5μg/kg、约1μg/kg、约50μg/kg、约150μg/kg、约300μg/kg、约750μg/kg、约1.5mg/kg、约5mg/kg,或前述值中任两者所限定的范围),更优选为约1μg/kg至5mg/kg总体重(例如,约3μg/kg、约15μg/kg、约75μg/kg、约300μg/kg、约900μg/kg、约2mg/kg、约4mg/kg,或前述值中任两者所限定的范围),甚至更优选为0.5至15mg/kg体重/天(例如,约1mg/kg、约2.5mg/kg、约3mg/kg、约6mg/kg、约9mg/kg、约11mg/kg、约13mg/kg,或前述值中任两者所限定的范围)。治疗性或预防性效力可以通过对受治疗患者的定期评估来监测。对于在数日或更长时间中的重复施用,根据病况,治疗可以重复进行直到发生对疾病症状的所需遏制。然而,其它剂量方案也可以使用,且落在本公开的范围内的。例如,可以通过组合物的单次快速施用、组合物的多次快速施用或者通过连续输注施用本公开的组合物来递送所需剂量。可以用于本文公开的融合蛋白的其它施用方法在本文件其它部分示例说明。

[0248] 实施例

[0249] 实施例1.哺乳动物表达质粒的构建

[0250] 通过本领域的重组DNA技术方法来构建CD融合蛋白的表达质粒。某些代表性的表达质粒的构建方法/设计如本文所述。

[0251] (1) Rituxan-CD-CD表达质粒

[0252] Rituxan-CD-CD融合蛋白的设计如图1A所示。Rituxan重链、Rituxan轻链和酵母菌胞嘧啶脱氨酶的核酸序列可通过基因合成来合成。包含SP-RituxanHC-CD-接头-CD(SEQ ID NO:89)和SP-RituxanLC(SEQ ID NO:90)的编码片段通过重叠PCR生成。然后将片段SP-

RituxanHC-CD-接头-CD和SP-RituxanLC分别经AvrII/BstZ171位点和EcoRV/PacI位点克隆至pCH01.0载体内(*SP:信号肽)。

[0253] (2) Herceptin-CD表达质粒

[0254] Herceptin-CD融合蛋白的设计如图1B所示。Herceptin可变区和酵母菌胞嘧啶脱氨酶的核酸序列可以通过基因合成来合成。含有SP-HerceptinHC-CD (SEQ ID NO:91) 和SP-HerceptinLC (SEQ ID NO:92) 的编码片段通过重叠PCR生成。然后将片段SP-HerceptinHC-CD和SP-HerceptinLC分别经AvrII/BstZ171位点和EcoRV/PacI位点克隆至pCH01.0载体内。

[0255] 实施例2. Rituxan-CD-CD和Herceptin-CD在哺乳动物细胞中的生产

[0256] 为产生哺乳动物表达蛋白, 将Rituxan-CD-CD和Herceptin-CD通过CHO-STM细胞(Thermo)利用FreeStyle MaxTM试剂根据FreeStyle MaxTM转染步骤进行暂时性表达。转染后72小时收集上清液。然后将上清液: (1) 通过ELISA定量以确定蛋白滴度, (2) 通过蛋白A纯化并通过非还原性PAGE检查表达情况, 和 (3) 浓缩以用于CD活性分析。

[0257] Rituxan-CD-CD和Herceptin CD的表达滴度分别为0.002μg/mL和0.5μg/mL。两种融合蛋白均具有CD活性。Rituxan-CD-CD即使在蛋白A纯化后通过PAGE也几乎检测不到(数据未示出)。据观察, 在通过非还原性PAGE分析时, Herceptin-CD作为多聚体聚集(图1B)。

[0258] 实施例3. 大肠杆菌表达质粒的构建

[0259] 每种融合蛋白的编码序列包含两个主要部分, 一个编码抗原识别片段(靶向结构域)的部分, 如sdAb、抗原结合片段或内皮抑素等; 以及一个编码酵母菌胞嘧啶脱氨酶片段的部分。编码接头肽序列的编码序列连接所述主要成分, 在表达时接头不会干扰靶向结构域蛋白成分或CD成分的任一个的功能。表达质粒简化示意性示出在图2A中。

[0260] (1) 单域抗体-CD表达质粒

[0261] sdAb和酵母菌胞嘧啶脱氨酶的核酸序列可以通过基因合成来合成。使用特定引物通过重叠PCR获得sdAb-CD融合蛋白的编码片段。sdAb和CD之间的接头肽序列为(GGGGS)₃ (SEQ ID NO:188)。将上述片段经XbaI和XhoI位点克隆至pET28a载体(Novagen)内(图2A)。具有CD突变或VHH突变的融合蛋白变体是通过重叠PCR生成。

[0262] (2) 抗原结合片段-CD表达质粒

[0263] 通过基因合成来合成酵母菌胞嘧啶脱氨酶的核酸序列。使用特定引物通过延伸PCR获得抗原结合片段-CD的编码片段(SEQ ID NO:81-84)。抗原结合片段和CD之间的接头肽序列是(GGGGS)₃ (SEQ ID NO:188)。将上述片段经XbaI和XhoI位点克隆至pET28a载体(Novagen)内(图2A)。

[0264] (3) 内皮抑素-CD表达质粒

[0265] 通过基因合成来合成内皮抑素和酵母菌胞嘧啶脱氨酶的核酸序列。使用特定引物通过重叠PCR获得内皮抑素-CD融合蛋白的编码片段(SEQ ID NO:85)。置于抗原结合片段和CD之间的接头肽序列是(GGGGS)₃ (SEQ ID NO:188)。然后将上述片段经XbaI和XhoI位点克隆至pET28a载体(Novagen)内(图2A)。

[0266] 实施例4. 大肠杆菌中的CD融合蛋白生产

[0267] 为进行生产, 通过标准转化步骤将表达质粒转化至SHuffle® T7 express或T7express感受态大肠杆菌细胞(New England Biolabs)内。

[0268] 为了测试估测蛋白特性, 将重组蛋白以约300mL生产规模表达并纯化。对于蛋白表

达,将新鲜的转化菌株以1:100稀释度接种至30℃ (SHuffle®T7 Express细胞) 或37℃ (T7 Express细胞) 的选择培养基中直到OD600达到0.4-0.8 (I_0)。将IPTG (Uni-region) 以0.4mM添加以诱导蛋白表达。对于T7 Express细胞,经诱导的培养物在37℃温育5小时。对于SHuffle®T7 Express细胞,在生产诱导温度为25℃或30℃时,生产温度为25℃,诱导温度为30℃。诱导后5小时 (I_5),收集培养物并在PBS中打散悬浮,以通过超声进行细胞裂解。分别从细胞裂解物收集可溶和不溶的部分。首先将细胞破菌液的可溶部分与Ni Sepharose珠 (GE Healthcare) 在室温共置1小时。共置后,以20mM、40mM和80mM咪唑 (分别为W1、W2和W3) 梯度洗涤Ni珠 (GE)。用含150mM和250mM咪唑的缓冲液 (E1和E2) 将每种融合蛋白洗脱。通过SDS-PAGE分析来自每个步骤的样品以评估表达和纯化情形。收集经纯化的重组蛋白并与具有5%甘油的PBS进行缓冲液交换,以便进行SDS-PAGE、SEC-HPLC、CD活性和抗原结合活性分析。所有重组蛋白的表达浓度、物化特性、CD活性和抗原结合活性经评估并总结在图2B中。表达谱在图2C和图2D中示例说明。纯化的sdAb-CD的SDS-PAGE、SEC-HPLC、CD活性和抗原结合活性分析在图3、4A、4B、5A、5B、6A和6B中示例说明。

[0269] 结果显示,sdAb-CD融合蛋白大多以可溶形式表达并且在SDS-PAGE和SEC-HPLC分析期间表现出可接受的纯度状态。小规模生产期间的sdAb-CD融合蛋白的滴度为约10 μ g/mL或大于10 μ g/mL,滴度可以在大规模生产中进一步增加至160-400mg/L,且可在过程优化后增加至>1g/L,这适合于工业生产。所有sdAb-CD融合蛋白的抗原结合活性和CD活性都得以保持。

[0270] 相比之下,内皮抑素-CD无法以可溶形式表达,因此不适合工业生产。虽然抗原结合片段-CD融合蛋白具有更小的分子量,其似乎以可溶形式表达。大多数抗原结合片段-CD融合蛋白以二聚体或多聚体形式聚集,且抗原结合片段在与CD融合时丧失了其抗原结合活性。

[0271] 测试了大于10种sdAb-CD融合蛋白和5种靶向抗原,数据显示sdAb是合适的与CD融合的抗原结合片段,且sdAb和CD均维持其生物学活性。

[0272] 实施例5. 由不同大肠杆菌菌株生产的sdAb-CD的稳定性研究

[0273] 3VGR19-CD-H的表达质粒被分别转化至SHuffle®T7Express和T7 Express感受态大肠杆菌中。数据表明3VGR19-CD-H在SHuffle®T7Express和T7 Express中的表达情形相似(图8)。

[0274] 从SHuffle®T7Express和T7 Express感受态大肠杆菌表达的3VGR19-CD-H融合蛋白经纯化并以3mg/mL在以下4种缓冲液中透析: (1) PBS, (2) 含1%甘油的PBS, (3) 含5%甘油的PBS, (4) 含3%甘露醇的PBS。在37℃温育3小时、37℃温育8小时和4℃温育1周后,观察每种缓冲液中的纯化蛋白的外观,并总结于表1中。“+”的数目指示浑浊度水平。“+/-”意味着观察到极少的聚集。结果显示出,在从T7 Express细胞表达的3VGR19-CD-H中观察到大量沉淀,但在SHuffle®T7Express细胞中没有。

[0275] 表1. 从T7 Express和SHuffle®T7 Express产生的sdAb-CD的稳定性

[0276]	浑浊度	T7 Express				SHuffle® T7 Express			
	缓冲液	1	2	3	4	1	2	3	4
	37°C, 3 hr	+++++	+++++	+++++	+++++	-	-	-	-
	37°C, 8 hr	+++++	+++++	+++++	+++++	-	-	-	-
	4°C, 1 周	+++	+++	+	++	+/-	+/-	+/-	+/-

[0277] 实施例6:sdAb-CD融合蛋白的5L补料分批发酵

[0278] 为了评估本公开的sdAb-CD融合蛋白在生物反应器条件下的产生,进行了5L给料-批次发酵。将冷冻细胞接种至2mL选择培养基中,在30°C以4-6小时,然后1:1000稀释接种至200mL选择培养基作为种培养物。次日,将种培养物接种至5-L发酵罐中。将温度设定在30°C,pH为 7.2 ± 0.1 ,D0为25%,气流为1-1.5vvm。在葡萄糖低于0.3g/L开始进料,且调节进料速率以将葡萄糖维持在0.5-1g/L。当OD600高于60时,添加0.4mM IPTG以诱导蛋白表达。在细胞达到稳定期后收获给料批次。最终,在发酵过程达到稳定期后停止发酵过程。纯化后的sdAb-CD的生产浓度为约160-400mg/L。在工序优化后TC4的生产滴度可以增加至1-1.3g/L。

[0279] 实施例7.单域抗体-CD融合蛋白的大规模纯化

[0280] 具有HIS-标签的融合蛋白

[0281] 将细胞沉淀以由20mM TrisHCl,0.5M NaCl,20mM咪唑和5%甘油,pH 8.0组成的缓冲液重悬,并通过均质器(APV2000)以850-950bar在10分钟内均质化两次。所得均质物通过在4°C于22000xg离心60分钟澄清并过滤。然后将细胞破菌液载入具有镍琼脂糖凝胶管柱和接续的离子交换Q-琼脂糖凝胶管柱的FPLC。将细胞破菌液用20mM TrisHCl,0.5M NaCl,20mM咪唑和5%甘油,pH 8.0载入至镍琼脂糖凝胶管柱上,然后用20mM TrisHCl,0.5M NaCl和5%甘油,pH 8.0中,以0-500mM咪唑梯度进行洗脱。将洗出液用20mM TrisHCl,170mM NaCl,5%甘油,pH 8.0加载至离子交换Q-琼脂糖凝胶管柱上,并收集流通液作为纯化产物,然后用20mM TrisHCl,1000mM NaCl,5%甘油,pH 8.0洗涤以除去杂质和聚集沉淀物。通过SDS-PAGE分析纯化的融合蛋白。结果显示所有sdAb-CD融合蛋白在纯化后都显示出高纯度(图7A)。

[0282] 无HIS-标签的融合蛋白

[0283] 将细胞沉淀重悬在pH 8.0的由5%甘油中的20mM Tris-HCl和150mM NaCl组成的缓冲液中,并通过均质器(APV2000)以850-950bar在10分钟内均质化两次。所得均质物通过在4°C于22000xg离心60分钟澄清并过滤。然后将过滤物通过rProteinA亲和柱(Repligen)并随后用离子交换柱阴离子交换Q-琼脂糖凝胶管柱(GE)纯化。用于rProteinA亲和柱的缓冲体系包含在pH 8.0的5%甘油、20mM Tris-HCL和150mM NaCl(用于结合和洗涤),然后用50mM甘氨酸,5%甘油,pH 3.0缓冲液洗脱,在洗脱后将产物用1M Tris-HCl,pH 9.0以1:25的比例中和。用于离子交换柱的缓冲液包含在5%甘油、20mM Tris-HCl和150mM NaCl的pH 8.0溶液。然后将纯化的产物通过5kDa(孔尺寸)TFF系统过滤以浓缩产物(切面流过滤)

(Merck Millipore), 然后通过10kDa Amicon过滤器 (Merck Millipore) 交换缓冲液 (图7B)。

[0284] 实施例8:sdAb-CD融合蛋白的尺寸排阻色谱分析

[0285] 为了检验每种融合蛋白的纯度, 使用BioSep SEC-s2000 (Phenomenex) 或Superdex 200Increase (GE Healthcare) 10/300管柱树脂进行SEC-HPLC色谱分析。将如上所述生产的蛋白的样品首先在含5%甘油的PBS中稀释至1或2mg/mL。使用注射过滤器 (PureTech) 将样品过滤, 并置于PP Insert (Thermo) 中进行SEC-HPLC分析。BioSep SEC-s2000的流动相为pH7.0的具有0.3M氯化钠的0.1M磷酸钠。Superdex 200的流动相为含有5%甘油的PBS。每个管柱的流速均为0.5mL/min。柱温设定在 $25 \pm 2^\circ\text{C}$, 且自动采样器温度设定在 $10 \pm 2^\circ\text{C}$ 。以UV280的吸光值检测蛋白。结果显示, 抗-VEGFR2 sdAb-CD融合蛋白3VGR19-CD-H、4VGR17-CD-H和4VGR38-CD-H的纯度分别为约71%、约74%和约71% (图4A)。抗-EGFR sdAb-CD融合蛋白VHH122-CD-H和7D12-CD-H的纯度分别为约83%和约87% (图4A)。对于7D12-CDom3-H和7D12-CDom3, 纯度分别为约88%和约93% (图4A)。在优化纯化过程后, 纯度可达到约95%或高于95% (图4B)。

[0286] 实施例9:sdAb-CD融合蛋白的胞嘧啶脱氨酶活性

[0287] 为了检验CD融合蛋白的胞嘧啶脱氨酶活性, 如上所述制备sdAb-CD融合蛋白, 将融合蛋白样品的连续稀释液在包含0.25%BSA和0.05%Tween 20的缓冲液中与20mM 5-FC混合, 并将混合物在 37°C 温育90分钟。然后用10%三氯乙酸终止反应, 并将混合物在 4°C 离心以收集上清。分别通过290nm和255nm处的吸亮度来检测5-FC和5-FU的存在。

[0288] 结果证明, 所测试的靶向VEGFR2的sdAb-CD融合蛋白可将5-FC转化为5-FU (图5A)。对靶向EGFR、HER2、HER3或CEA的sdAb-CD融合蛋白获得了类似结果 (图5A和图5B)。

[0289] 实施例10:sdAb-CD融合蛋白的抗原结合亲和力

[0290] 通过ELISA测试了本文公开的人VEGFR2和sdAb-CD融合蛋白之间的结合。对于VEGFR2结合测定, 将涂布抗体人VEGFR2-Fc (Sino Biological) 在涂布缓冲液 (100mM NaHCO_3 +32mM Na_2HCO_3) 中稀释至 $1\mu\text{g}/\text{ml}$ 。通过用封闭缓冲液 (0.25%BSA, 0.05%Tween-20, 0.05% NaN_3 , 1mM EDTA) 温育2小时进行封闭。将所测试的融合蛋白样品在封闭缓冲液中制备并添加至板孔以进行结合。将兔抗-His-HRP (abcam) 在含0.25%BSA和0.05%Tween 20的缓冲液中稀释5000倍以进行检测。

[0291] 对于EGFR结合检测, 将ELISA板用在涂布缓冲液中浓度为 $1\mu\text{g}/\text{mL}$ 的hEGFR-Fc (Sino Biological) 涂布。通过与封闭缓冲液 (0.25%BSA, 0.05%Tween-20, 0.05% NaN_3 , 1mM EDTA) 温育2小时进行封闭。封闭后, 将样品在封闭缓冲液中连续稀释并添加至板孔以结合1小时。最后, 将二抗 (兔抗-HIS-HRP) 在含0.25%BSA和0.05%Tween 20的缓冲液中稀释以进行检测。

[0292] 对于HER2、HER3和CEA结合测定, 用于各测定的涂布抗体分别为人ErbB2/Her2-Fc (Acro biosystem)、人ErbB3/Her3-Fc (Acro biosystem) 和人CEACAM5-Fc (novoprotein)。

[0293] 结果显示, 3VGR19-CD-H、4-VGR17-CD-H和4VGR38-CD-H结合VEGFR2; VHH122CD-H和7D12-CD-H结合EGFR; 5F7-CDom3-H、47D5-CDom3-H和2D3-CDom3-H结合HER2, NbCEA5-CDom3-H和AntiCEA-CDom3-H结合CEACAM5; 且BCD090-M2-CDom3-H结合HER3 (图6A和图6B)

[0294] 实施例11:对sdAb-CD融合蛋白的基于细胞的细胞毒性测定

[0295] 实验方法A:

[0296] 在MDA-MB-231 (人乳腺癌) 和A431 (人表皮样癌) EGFR表达性癌细胞系上测试与5-FC组合的数种抗-EGFR sdAb-CD融合蛋白的细胞毒性。首先将细胞以30,000细胞/孔接种至96-孔板中,并于37°C在生长培养基(DMEM(Gibco)+10%FBS)中过夜温育。在温育16至18小时后,将板孔用PBS洗涤一次。向各孔添加100微升的100 μ g/ml融合蛋白并在37°C温育1小时。在用PBS洗涤以除去过量融合蛋白后,将100 μ l的5-FC或5-FU以指定浓度添加至对应孔以进行72小时温育。最后,添加10 μ l/孔的细胞增殖试剂WST-1 (Roche) 并将细胞在37°C温育4小时。使用ELISA读板器在吸光度OD450 (WST-1) 和OD690 (参照波长) 测定细胞存活。结果证明,每种所测试的sdAb-CD融合蛋白和5-FC的组合都降低了MDA-MB-231和A431两种细胞系中的癌细胞存活(图9A和9B)。

[0297] 实验方法B:

[0298] 在作为另选的测定方法中,本公开的抗EGFR sdAb-CD融合蛋白与5-FC组合的细胞毒性在A431、Bx-PC3、Ca1-27和FaDu癌细胞系上进行了测试。使用具有C端His-标签的CD蛋白(CDoem3-H)作为阴性蛋白对照(NP)。首先,将细胞用4mL含有2 μ M NP或sdAb-CD的培养基重悬并在37°C温育1小时。各细胞系使用ATCC建议的生长培养基:A431:CRL-1555TM;FaDu:HTB-43TM;Ca1-27:CRL-2095TM;BxPC-3:CRL-1687TM。然后将细胞用PBS洗涤3次并以30,000细胞/孔重新接种到96孔板中。向板孔中添加指定浓度的5-FC并在37°C温育72小时。温育后,添加10 μ l细胞增殖试剂WST-1并将混合物在37°C温育3小时。使用ELISA测定仪在OD450和OD690测定细胞存活。结果表明,抗EGFR sdAb-CD融合蛋白降低了所有受测癌细胞系的存活率(图10A和图10B)。

[0299] 实施例12:在A431异种移植模型上的sdAb-CD蛋白测试

[0300] 采用在NOD-SCID雄性小鼠中的A431异种移植模型(LASCo)评估了7D12-CDoem3或7D12-CDoem3-H融合蛋白的治疗效果。将 2.5×10^6 A431肿瘤细胞皮下注射至体重为20-27g的小鼠的右肋。在肿瘤尺寸达到200-300mm³后(肿瘤移植后大约10天),将小鼠随机分配至不同治疗组(n=6)。在4周中每周2次施用所示量的空载剂(PBS)、5-FU(腹膜内)、5-FC(腹膜内)和sdAb-CD融合蛋白(静脉内)。测定肿瘤的固体团块并通过t-检验评估肿瘤体积的显著的显著性。

[0301] 静脉施用7D12-CDoem3-H或7D12-CDoem3的20mg/kg或40mg/kg,连同腹膜内施用剂量为500mg/kg的5-FC,可导致A431肿瘤生长的显著减少,如在肿瘤细胞移植后,在肿瘤体积和肿瘤肿瘤方面与空载剂处理的组相比均有减少(p<0.01)(图11A和图11B)。这证实7D12-CDoem3-H或7D12-CDoem3与5-FC的共施用对于体内A431癌细胞生长具有抑制性效应。

[0302] 实施例13.T细胞表位定位

[0303] 针对91个肽进行EpiScreenTMT细胞表位定位(epitope mapping),结果显示包含6个表位的六个肽对T细胞有阳性反应。使用iTopeTM,在可诱导T细胞阳性增殖反应的肽中,鉴定出9个潜在的HLA-DR限制的结合序列。

[0304] 总之,在7D12-CDoem3序列内鉴定出6个T细胞表位,表位1-3位于7D12 sdAb的框架区,而表位4-6位位于CD区。

[0305]

表位	HLA-DR限制表位	SEQ ID NO
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表位1	SVQTGGSLRL	63
表位2	LKPEDTAIY	64
表位3	IYYCAAAAGS	65
表位4	YTTLSPCDM	66
表位5	MCTGAIIMY	67
表位6	VVVVDDERCKK	68

[0306] 实施例14.sdAb-CD融合蛋白的单表位变体

[0307] 设计了7D12-CD_{oem3}-H的各个单表位变体来评估这些变体是否在保持其结构、溶解性、CDase活性和抗原结合活性的同时消除了免疫原性。

[0308] 通过重叠PCR生成了43个单表位变体的表达质粒。生成这些融合蛋白变体并评估其CD活性、EGFR-结合活性和表达情形。结果总结在图12中。

[0309] 数据表明,所有EGFR-结合结构域取代(TC3-001~TC3-027)对EGFR-结合能力都没有显著影响。所有具有修饰的表位4和表位5的8个变体(TC3-028~TC3-035)丧失其CDase活性。具有修饰的表位6的变体(TC3-036~TC3-043)受到的影响较小。

[0310] 基于表达浓度、生物学活性和与人种系的序列相似性(EGFR-结合结构域),选择以下变体用于多突变设计(相对于SEQ ID NO:17编号):

[0311] a.表位1:S12V、V13A、T15V、G16D和S18D

[0312] b.表位2:K88R、P89A、I94V、K88D、K88T

[0313] c.表位3:I94R、I94Q

[0314] d.表位4:Y224H

[0315] e.表位6:V268A、V268T、V269T

[0316] 实施例15.sdAb-CD融合蛋白的单表位变体

[0317] 通过重叠PCR生成了43个TC3多突变变体的表达质粒。生成这些融合蛋白变体并评估其CD活性、EGFR-结合活性和表达情形。结果总结在图13A和图13B中。

[0318] 基于表达浓度、生物学活性、生理学特性和消除T细胞表位的覆盖程度,进一步选择5个候选多变体来评估其免疫原性潜能。

[0319] 实施例16.免疫原性分析

[0320] 使用EpiScreen™时间进程T细胞测定评估了7D12-CD_{oem3}的5个变体的免疫原性潜能。使用移除CD8表现的PBMC建立基底培养细胞,添加样品后的不同时间点测定CD4+T细胞增殖是通过放射性[3H]-胸苷的嵌入量测定。在8天后还通过ELISpot测定了IL-2分泌。对TC4(样品1)和其它4种融合蛋白候选物进行了测试。

[0321]

样品	融合蛋白名称	SEQ ID NO
样品1	TC4-WT (7D12-CD _{oem3})	19
样品2	TC4_44 (S12V、T15V、K88R、P89A、I94V、V268A)	182
样品3	TC4_50 (V13A、K88T、I94R、V268A)	183
样品4	TC4_51 (G16D、K88T、I94R、V268A)	184
样品5	TC4_87 (S12V、T15V、K88R、P89A、I94V、V268A、V269T)	185

[0322] EpiScreen™时间进程T细胞增殖测定

[0323] 选择一组52个供体来最好地呈现欧洲人/北美人和世界人群表达的HLA-DR和HLA-

DQ同种异型 (allotype) 的数量和频率。来自每个供体的PBMC被重悬在 AIM-V® 中达 $4 \times 10^6 - 6 \times 10^6$ PBMC/mL。测定的重组蛋白的最终样品浓度为 $0.3 \mu\text{M}$ 。将培养物培养总共8天。在第5、6、7和8天,将各孔中的细胞用 $100 \mu\text{L}$ AIM-V® 培养基中的 $0.75 \mu\text{Ci}$ [3H]-胸苷 (Perkin Elmer®, Beaconsfield, 英国) 作为脉冲标记,并再培养18小时,其后使用 TomTec Mach III 细胞收集器收集至过滤垫上 (Perkin Elmer®, Beaconsfield, 英国)。以视差低背景计数在 1450 Microbeta Wallac Trilux Liquid Scintillation Counter (Perkin Elmer®, Beaconsfield, 英国) 上通过闪烁计数来测定各孔的每分钟计数 (cpm)。

[0324] EpiScreen™ IL-2 ELISpot测定

[0325] 使用来自同组供体的PBMC进行IL-2 ELISpot测定。将ELISpot板 (Millipore, Watford, 英国) 用IL-2捕获抗体 (R&D Systems, Abingdon, 英国) 预先润湿并涂布过夜。将各供体的细胞密度调节至在AIM-V® 培养基中为 $4 \times 10^6 - 6 \times 10^6$ PBMC/mL,并向各孔添加 $100 \mu\text{L}$ 细胞。向适当的孔内添加50微升样品和对照。在8天培养期之后,根据制造商说明 (R&D Systems) 将ELISpot板显影。简言之,洗涤反应板然后添加生物素标记的检测抗体 (R&D Systems, Abingdon, 英国)。在 37°C 温育1.5小时后,将板再用PBS洗涤 ($\times 3$),添加过滤后的AP标记的链霉亲和素- (R&D Systems, Abingdon, 英国) 1小时 (室温温育)。弃去AP标记的链霉亲和素-,并将板用PBS洗涤 ($\times 3$)。向各孔添加100微升BCIP/NBT底物 (R&D Systems, Abingdon, 英国) 并在室温温育30分钟。通过用dH2O洗涤孔和孔的背部3次而终止斑点显色。在 Immunoscan® 分析仪上扫描经干燥的板并使用 Immunoscan® 第5版软件确定每孔斑点 (spw)。

[0326] 对于增殖测定和IL-2 ELISpot测定,测前已确立了刺激指数 (SI, stimulation index) 的经验阈值大于或等于1.9 ($\text{SI} \geq 1.90$),因此能引起高于该阈值的反应的样品认为是阳性的。对于细胞增殖 (每时间点 $n=3$) 和ELISpot ($n=6$),如下通过统计和经验阈值定义阳性响应:

[0327] 1. 以独立样本t检验比较对照孔培养基与测试孔的cpm或spw值, $p < 0.05$ 反应认定为显着。

[0328] 2. $\text{SI} \geq 1.90$, 其中 $\text{SI} = \text{测试孔平均值 (cpm或spw)} / \text{基线 (cpm或spw)}$ 。

[0329] 图14显示了健康供体T细胞增殖和IL-2 ELISpot反应的总结。指出了对于在第5-8天时期期间皆具有阳性的T细胞反应者 ($\text{SI} \geq 1.90$, 显着 $p < 0.05$) 以“P”呈现, IL-2 ELISpot阳性反应者 ($\text{SI} \geq 1.90$, 显着 $p < 0.05$) 以“E”呈现。细胞增殖和IL-2 ELISpot测定的阳性反应的频率以百分比在表格底部表示。相关性代表在细胞增殖测定与ELISpot测定皆为阳性的百分比。

[0330] 由于IL-2 ELISpot测定中的阳性反应的频率低,仅基于细胞增殖反应对样品排序。样品4引起了较高的阳性反应 ($\text{SI} \geq 1.90$, $p < 0.05$),在本供体组有25%。样品1、3和5引起了本供体组12%至15%的阳性响应,而样品2对8%的供体组有阳性反应。样品2产生了最低的临床免疫原性风险。

[0331] 实施例17. 去免疫化sdAb-CD的功能分析

[0332] 分析了去免疫化TC4变体的CD活性和EGFR结合活性并显示在图15中。

[0333] CD活性通过实施例8所述的方法进行评估。

[0334] 通过表面等离子共振 (SPR) 测定了TC4相关蛋白和EGFR-Fc之间的结合亲和力。SPR测定通过Biacore T100 (GE Healthcare) 进行。将抗人IgG (Fc) 抗体以25 μ g/mL稀释在固定缓冲液 (10mM NaOAc, pH 5.0) 中。根据制造商步骤将抗体经标准胺基偶联化学反应在CM5芯片 (Series S Sensor Chip CM5, GE; 目录号: 29104988) 上固定。过程应产生约9000RU的结合量水平。流动相为PBST且流动池中的温度维持在25 $^{\circ}$ C。固定后, 将配体溶液 (人EGFR-Fc蛋白, 在流动相中为2 μ g/mL) 注射至系统, 接触时间120s, 流速10 μ L/min。其后, 将TC4-wt或TC4-突变体在PBST中稀释为0.74nM、2.22nM、6.67nM、20nM和60nM, 并以低浓度至高浓度注射至系统。分析物注射的条件为: 对各浓度的接触时间为120秒, 在最终步骤解离样品600秒。用Biacore T100评估软件进行分析。各样品的单次循环动力学分析物的分析结果以二级反应拟合以确定 K_D 值。结果标准为最大结合量 (R_{max}) 应在50~250RU范围内。

[0335] 数据表明, 与野生型TC4相比, TC4变体TC4-44、50、51和87的EGFR-结合能力和CD活性类似 (图15)。

序列表

<110> 上海晟顺生物科技有限公司

顺天医药生技股份有限公司

<120> 单域抗体-胞嘧啶脱氨酶融合蛋白

<130> 13075.0003-00304

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			20					25					30		
Asn	Ser	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Gly
		35					40					45			
Val	Ala	Gly	Ile	Asn	Glu	Gly	Gly	Thr	Ala	Thr	Tyr	Tyr	Ala	Asn	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Tyr	Leu	Gln	Met	Asn	Thr	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Gly	Ser	Pro	Asp	Pro	Pro	Pro	Leu	Ile	Glu	Ser	Val	Val
			100					105					110		
Lys	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115					120					125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
			130				135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Val	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245					250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Ile	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
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gcaccgggta aagaacgtga aggtgttgca ggtattaatg aaggtggcac cgcaacctat 180		
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ggcattccca ggtgtgtggt gggagagaat gtcaacttca agtcaaaagg agagaagtac 780		
ctccagacca ggggccatga ggtggttgtg gtggatgatg agaggtgcaa gaagattatg 840		
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20 25 30		
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35 40 45		

Val	Ala	Gly	Ile	Asn	Tyr	Gly	Gly	Thr	Ala	Thr	Tyr	Tyr	Ala	Asn	Ser
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Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Tyr	Leu	Gln	Met	Asn	Thr	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
			85					90					95		
Cys	Ala	Ala	Gly	Ser	Pro	Asp	Pro	Pro	Pro	Leu	Ile	Glu	Gly	Val	Val
		100					105					110			
Lys	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
	115					120					125				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130					135					140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150					155					160
Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
	195						200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Val	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245					250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Ile	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
		275					280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
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<223> 对“未知”的描述:编码4VGR17-CD-H的多核苷酸序列

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ctgagctgtg ttgcaagcgg ttatagcgtt agcaaaaatt caatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga aggtgttgca ggtattaatt atggtggcac cgcaacctat 180
tatgccaaata gcgttaaagg tcgtttttacc attagccagg ataatgccaa aaataccgtt 240
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gatggcagtg tcctgggcag gggccacaac atgaggttcc agaagggcag tgccaccctg 600
catggggaga tcagcaccct ggagaactgt ggcaggctgg agggcaaggt ctacaaggac 660
accactctgt acaccaccct cagcccttgt gacatgtgca caggggccat catcatgtat 720
ggcattccca ggtgtgtggt gggagagaat gtcaacttca agtcaaaagg agagaagtac 780
ctccagacca ggggccatga ggtggtttgt gtggatgatg agaggtgcaa gaagattatg 840
aagcagttca ttgatgagag accccaggac tggtttgagg acattgggga gggcagcagc 900
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Gly Ser Leu Thr Leu Ser Cys Glu Val Ser Gly Tyr Ser Val Asn Ser
20           25           30
Asn Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly
35           40           45
Val Ala Gly Ile Asn Glu Gly Gly Val Ser Thr Tyr Tyr Ala Asn Phe
50           55           60
Val Gln Gly Arg Phe Thr Ile Ser Gln Asp Asn Ala Lys Asn Met Val
65           70           75           80
Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
85           90           95
Cys Ala Ala Gly Ala Pro Asp Pro Pro Pro Leu Ile Glu Ser Ile Val
100          105          110
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Lys Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro		
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His His

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<212> DNA

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gcaccgggta aagaacgtga aggtgttgca ggtattaatg aaggtggtgt tagcacctat 180
tatgccaaatt ttgttcaggg tcgttttacc attagccagg ataatgcaaa aaacatggtt 240
tacctgcaga tgaatagcct gaaaccggaa gataccgcaa tctattattg tgcagcgggt 300
gcaccggatc cgcctccgct gattgaaagc attgtgaaat attggggtca gggcacccag 360

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gttaccgta gctcaggtag tggtaggcagc ggtggcggtg gttctggggg tggtaggtca 420
 gtcacaggag gcatggcttc aaagtgggac cagaaggga tggacattgc ctatgaggag 480
 gctgctctgg gctacaagga gggaggggtc ccaattggtg gctgcctcat caacaacaag 540
 gatggcagtg tcctgggcag gggccacaac atgaggttcc agaagggcag tgccaccctg 600
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			20					25					30		
Tyr	Thr	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35				40					45				
Val	Ala	Ala	Ile	Leu	Trp	Ser	Gly	Pro	Thr	Thr	Tyr	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70					75					80	
Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
			85					90						95	
Cys	Ala	Ala	Ala	Leu	Gly	Val	Leu	Val	Leu	Ala	Pro	Gly	Asn	Val	Tyr
			100					105					110		
Ser	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115				120							125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130				135						140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150					155					160	
Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300

His His

305

<210> 14

<211> 921

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码VHH122-CD-H的多核苷酸序列

<400> 14

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atggaagttc agctgcaaga aagcgggtgt ggtctggttc aggcaggcga tagcctgcgt 60
ctgagctgtc tggtagcgg tcgtagcttt aatagctata ccatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttggtgca gcaattctgt ggtcaggtcc gaccacctat 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgccaa aaataccgtt 240
tacctgcaga tgaatagcct gaaaccggaa gataccgcag tgtattattg tgcagcagca 300
ctgggtgttc tggtagctgc tccgggtaat gtttatagtt attgggggtca gggcaccag 360
gttaccgtta gctcaggtgg tggtagctgc ggtggcggtg gctctggtgg tggcggttca 420
gtcacaggag gcatggcttc aaagtgggac cagaagggca tggacattgc ctatgaggag 480
gctgctctgg gctacaagga gggaggggtc ccaattggtg gctgcctcat caacaacaag 540
gatggcagtg tcctgggcag gggccacaac atgaggttcc agaagggcag tgccaccctg 600
catggggaga tcagcaccct ggagaactgt ggcaggctgg agggcaaggt ctacaaggac 660
accactctgt acaccaccct cagcccttgt gacatgtgca caggggccat catcatgtat 720
ggcattccca ggtgtgtggt gggagagaat gtcaacttca agtcaaaagg agagaagtac 780
ctccagacca ggggccatga ggtggttgtg gtggatgatg agaggtgcaa gaagattatg 840

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aagcagttca ttgatgagag accccaggac tggtttgagg acattgggga gggcagcagc 900

catcatcatc atcatcacta a 921

<210> 15

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:7D12-CD-H的蛋白序列

<400> 15

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35				40					45				
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70					75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
			85					90						95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
		100						105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
	115					120						125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130					135						140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150					155					160	
Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
			165					170					175		
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
	180							185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
	195					200						205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225				230					235					240	

Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 16

<211> 921

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码7D12-CD-H的多核苷酸序列

<400> 16

atgcaggatga aactggaaga aagcggatgt ggtagcgttc agaccggtgg tagcctgcgt 60
 ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
 gcaccgggta aagaacgtga atttgttagc ggtattagct ggcgtggtga tagcaccggt 180
 tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgccaa aaataccgtt 240
 gacctgcaga tgaatagcct gaaaccggaa gataccgcaa tctattattg tgcagcagca 300
 gccggtagcg cctgggtatgg caccctgtat gaatatgatt attgggggtca gggcaccag 360
 gttaccgtta gctcagggtg tgggtggcagc ggtggcgggtg gttcagggtg cggaggtagc 420
 gtcacaggag gcatggcttc aaagtgggac cagaagggca tggacattgc ctatgaggag 480
 gctgctcttg gctacaagga gggaggggtc ccaattgggtg gctgcctcat caacaacaag 540
 gatggcagtg tcctgggcag gggccacaac atgaggttcc agaagggcag tgccaccctg 600
 catggggaga tcagcaccct ggagaactgt ggcaggctgg agggcaaggt ctacaaggac 660
 accactctgt acaccaccct cagcccttgt gacatgtgca caggggccat catcatgtat 720
 ggcatcccca ggtgtgtgtg gggagagaat gtcaacttca agtcaaaagg agagaagtac 780
 ctccagacca ggggccatga ggtggtttgt gtggatgatg agaggtgcaa gaagattatg 840
 aagcagttca ttgatgagag accccaggac tggtttgagg acattgggga gggcagcagc 900
 catcatcatc atcatcacta a 921

<210> 17

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:7D12-CDom3-H的蛋白序列

<400> 17

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
			85					90					95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
		100						105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
	115					120					125				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130					135					140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
			165					170				175			
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
	180							185				190			
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
	195					200					205				
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245					250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
	260							265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275					280					285				
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
	290					295					300				

His His

305

<210> 18

<211> 921

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码7D12-CDoem3-H的多核苷酸序列

<400> 18

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atgcaggtga aactggaaga aagcggtagt ggtagcggtc agaccggtag tagcctgcgt 60
ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgttagc ggtattagct ggctgggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgcca aaataccgtt 240
gacctgcaga tgaatagcct gaaaccggaa gataccgcaa tctattattg tgcagcagca 300
gccggtagcg cctggtagtg caccctgtat gaatatgatt attgggggtc gggcaccag 360
gttaccgtta gctcaggttg tggtagcagc ggtggcggtg gttcaggttg cggaggtagc 420
gttaccggtg gtatggcaag caaatgggat cagaaaggta tggatattgc atatgaagaa 480
gcactgctgg gttataaaga aggtggcggt ccgattggtg gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cggtcataat atgcgttttc agaaaggcag cgcaaccctg 600
catggtgaaa ttagcacctt ggaaaattgt ggtcgtcttg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccgtgt gatatgtgta ccggtgccat tattatgtat 720
ggtattccgc gttgtgtgat tggcgaaaac gttacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtggtcatga agttgttgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga aggcagcagc 900
catcatcatc atcatcacta a 921

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<210> 19

<211> 297

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 7D12-CDoem3的蛋白序列

<400> 19

```

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
           20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
           35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser

```

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

<210> 20

<211> 894

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码7D12-CDoem3的多核苷酸序列

<400> 20

atgcagggtga aactggaaga aagcgggtggt ggtagcggttc agaccggtgg tagcctgcgt 60

ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgtagc ggtattagct ggcgtggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgccaa aaataccgtt 240
gacctgcaga tgaatagcct gaaaccggaa gataccgcaa tctattattg tgcagcagca 300
gccggtagcg cctgggtatgg caccctgtat gaatatgatt attgggggtca gggcaccag 360
gttaccgtta gctcaggtgg tgggtggcagc ggtggcggtg gttcaggtgg cggaggtagc 420
gttaccggtg gtatggcaag caaatgggat cagaaaggta tggatattgc atatgaagaa 480
gcaactgctgg gttataaaga aggtggcggt ccgattgggt gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cggtcataat atgcgttttc agaaaggcag cgcaaccctg 600
catggtgaaa ttagcaccct ggaaaattgt ggtcgtctgg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccgtgt gatatgtgta ccggtgccat tattatgtat 720
ggtattccgc gttgtgtgat tggcgaaaac gttaacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtggcatga agttgttgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga ataa 894

<210> 21

<211> 157

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:酵母菌胞嘧啶脱氨酶的蛋白序列

<400> 21

Val	Thr	Gly	Gly	Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile
1				5					10					15	
Ala	Tyr	Glu	Glu	Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile
				20					25					30	
Gly	Gly	Cys	Leu	Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly
				35					40					45	
His	Asn	Met	Arg	Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile
				50					55					60	
Ser	Thr	Leu	Glu	Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp
65				70					75					80	
Thr	Thr	Leu	Tyr	Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala
				85					90					95	
Ile	Ile	Met	Tyr	Gly	Ile	Pro	Arg	Cys	Val	Val	Gly	Glu	Asn	Val	Asn
				100					105					110	
Phe	Lys	Ser	Lys	Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val
				115					120					125	
Val	Val	Val	Asp	Asp	Glu	Arg	Cys	Lys	Lys	Ile	Met	Lys	Gln	Phe	Ile
				130					135					140	

Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155

<210> 22

<211> 157

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:突变体酵母菌胞嘧啶脱氨酶的蛋白序列

<400> 22

Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile
1 5 10 15
Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile
 20 25 30
Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly
 35 40 45
His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile
 50 55 60
Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp
65 70 75 80
Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala
 85 90 95
Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn
 100 105 110
Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val
 115 120 125
Val Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile
 130 135 140
Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155

<210> 23

<211> 124

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 3VGR19的蛋白序列

<400> 23

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Tyr Ser Val Ser Lys Asn

20	25	30
Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val		
35	40	45
Ala Gly Ile Asn Glu Gly Gly Thr Ala Thr Tyr Tyr Ala Asn Ser Val		
50	55	60
Lys Gly Arg Phe Thr Ile Ser Gln Asp Asn Ala Lys Asn Thr Val Tyr		
65	70	75
Leu Gln Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys		
85	90	95
Ala Ala Gly Ser Pro Asp Pro Pro Pro Leu Ile Glu Ser Val Val Lys		
100	105	110
Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
115	120	

<210> 24

<211> 124

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR17的蛋白序列

<400> 24

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly		
1	5	10
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Tyr Ser Val Ser Lys Asn		
20	25	30
Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val		
35	40	45
Ala Gly Ile Asn Tyr Gly Gly Thr Ala Thr Tyr Tyr Ala Asn Ser Val		
50	55	60
Lys Gly Arg Phe Thr Ile Ser Gln Asp Asn Ala Lys Asn Thr Val Tyr		
65	70	75
Leu Gln Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys		
85	90	95
Ala Ala Gly Ser Pro Asp Pro Pro Pro Leu Ile Glu Gly Val Val Lys		
100	105	110
Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
115	120	

<210> 25

<211> 124

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR38的蛋白序列

<400> 25

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Ala	Gly	Gly
1				5					10					15	
Ser	Leu	Thr	Leu	Ser	Cys	Glu	Val	Ser	Gly	Tyr	Ser	Val	Asn	Ser	Asn
			20						25				30		
Ser	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Gly	Val
		35					40					45			
Ala	Gly	Ile	Asn	Glu	Gly	Gly	Val	Ser	Thr	Tyr	Tyr	Ala	Asn	Phe	Val
		50				55					60				
Gln	Gly	Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Met	Val	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys
				85						90					95
Ala	Ala	Gly	Ala	Pro	Asp	Pro	Pro	Pro	Leu	Ile	Glu	Ser	Ile	Val	Lys
			100						105					110	
Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
			115						120						

<210> 26

<211> 124

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122的蛋白序列

<400> 26

Glu	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	Asp
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Leu	Val	Ser	Gly	Arg	Ser	Phe	Asn	Ser	Tyr
			20						25				30		
Thr	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
		35					40					45			
Ala	Ala	Ile	Leu	Trp	Ser	Gly	Pro	Thr	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
		50				55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85						90					95

Ala Ala Ala Leu Gly Val Leu Val Leu Ala Pro Gly Asn Val Tyr Ser
 100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120

<210> 27

<211> 124

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：7D12的蛋白序列

<400> 27

Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly Gly
 1 5 10 15

Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser Tyr
 20 25 30

Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
 35 40 45

Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr Asp
 100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120

<210> 28

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：3VGR19 CDR1序列

<400> 28

Lys Asn Ser Met Gly
 1 5

<210> 29

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:3VGR19 CDR2序列

<400> 29

Gly Ile Asn Glu Gly Gly Thr Ala Thr Tyr Tyr Ala Asn Ser Val Lys

1

5

10

15

Gly

<210> 30

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:3VGR19 CDR3序列

<400> 30

Gly Ser Pro Asp Pro Pro Pro Leu Ile Glu Ser Val Val Lys Tyr

1

5

10

15

<210> 31

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:4VGR17 CDR1序列

<400> 31

Lys Asn Ser Met Gly

1

5

<210> 32

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:4VGR17 CDR2序列

<400> 32

Gly Ile Asn Tyr Gly Gly Thr Ala Thr Tyr Tyr Ala Asn Ser Val Lys

1

5

10

15

Gly

<210> 33

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

4VGR17 CDR3序列

<400> 33

Gly Ser Pro Asp Pro Pro Pro Leu Ile Glu Gly Val Val Lys Tyr

1 5 10 15

<210> 34

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 4VGR38 CDR1序列

<400> 34

Ser Asn Ser Met Gly

1 5

<210> 35

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 4VGR38 CDR2序列

<400> 35

Gly Ile Asn Glu Gly Gly Val Ser Thr Tyr Tyr Ala Asn Phe Val Gln

1 5 10 15

Gly

<210> 36

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 4VGR38 CDR3序列

<400> 36

Gly Ala Pro Asp Pro Pro Pro Leu Ile Glu Ser Ile Val Lys Tyr

1 5 10 15

<210> 37

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122 CDR1序列

<400> 37

Ser Tyr Thr Met Gly

1 5

<210> 38

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122 CDR2序列

<400> 38

Ala Ile Leu Trp Ser Gly Pro Thr Thr Tyr Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 39

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：

VHH122 CDR3序列

<400> 39

Ala Leu Gly Val Leu Val Leu Ala Pro Gly Asn Val Tyr Ser Tyr

1 5 10 15

<210> 40

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：7D12 CDR1序列

<400> 40

Ser Tyr Gly Met Gly

1 5

<210> 41

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：7D12 CDR2序列

<400> 41

Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 42

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：

7D12 CDR3序列

<400> 42

Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr Asp Tyr

1 5 10 15

<210> 43

<211> 30

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：3VGR19 FR1序列

<400> 43

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Tyr Ser Val Ser

20 25 30

<210> 44

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：3VGR19 FR2序列

<400> 44

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ala

1 5 10

<210> 45

<211> 32

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

3VGR19 FR3序列

<400> 45

Arg Phe Thr Ile Ser Gln Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln

1 5 10 15

Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ala Ala

20 25 30

<210> 46

<211> 11

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 3VGR19 FR4序列

<400> 46

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser

1 5 10

<210> 47

<211> 30

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 4VGR17 FR1序列

<400> 47

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Tyr Ser Val Ser

20 25 30

<210> 48

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述: 4VGR17 FR2序列

<400> 48

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ala

1 5 10

<210> 49

<211> 32

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR17 FR3序列

<400> 49

Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr	Leu	Gln
1				5					10					15	
Met	Asn	Thr	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	Ala	Ala
			20					25					30		

<210> 50

<211> 11

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR17 FR4序列

<400> 50

Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser
1				5					10	

<210> 51

<211> 30

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR38 FR1序列

<400> 51

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Ala	Gly	Gly
1				5					10					15	
Ser	Leu	Thr	Leu	Ser	Cys	Glu	Val	Ser	Gly	Tyr	Ser	Val	Asn		
			20					25					30		

<210> 52

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR38 FR2序列

<400> 52

Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Gly	Val	Ala
1				5					10				

<210> 53

<211> 32

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR38 FR3序列

<400> 53

Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Met	Val	Tyr	Leu	Gln
1				5					10					15	
Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	Ala	Ala
			20					25					30		

<210> 54

<211> 11

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：4VGR38 FR4序列

<400> 54

Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser
1				5					10	

<210> 55

<211> 30

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122 FR1序列

<400> 55

Glu	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	Asp
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Leu	Val	Ser	Gly	Arg	Ser	Phe	Asn		
			20					25					30		

<210> 56

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122 FR2序列

<400> 56

Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val	Ala
1				5					10				

<210> 57

<211> 32

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：VHH122 FR3序列

<400> 57

Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr	Leu	Gln
1				5					10					15	
Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Ala
			20					25					30		

<210> 58

<211> 11

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：

VHH122 FR4序列

<400> 58

Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser
1				5					10	

<210> 59

<211> 30

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：7D12 FR1序列

<400> 59

Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg		
			20					25					30		

<210> 60

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：7D12 FR2序列

<400> 60

Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val	Ser
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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<210> 65
<211> 10
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述：T细胞表位3序列
<400> 65
Ile Tyr Tyr Cys Ala Ala Ala Ala Gly Ser
1 5 10
<210> 66
<211> 9
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述：T细胞表位4序列
<400> 66
Tyr Thr Thr Leu Ser Pro Cys Asp Met
1 5
<210> 67
<211> 9
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述：T细胞表位5序列
<400> 67
Met Cys Thr Gly Ala Ile Ile Met Tyr
1 5
<210> 68
<211> 11
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述：T细胞表位6序列
<400> 68
Val Val Val Val Asp Asp Glu Arg Cys Lys Lys
1 5 10
<210> 69
<211> 124
<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：2D3的蛋白序列

<400> 69

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Ser	Leu	Val	Gln	Pro	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
			20					25					30		
Ala	Met	Ser	Trp	Val	Arg	Gln	Val	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Ser	Ile	Asn	Trp	Ser	Gly	Thr	His	Thr	Asp	Tyr	Ala	Asp	Ser	Val
	50					55				60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asn	Asn	Ala	Asn	Asn	Thr	Leu	Tyr
65					70					75				80	
Leu	Gln	Met	Asn	Ser	Leu	Lys	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90				95	
Ala	Lys	Asn	Trp	Arg	Asp	Ala	Gly	Thr	Thr	Trp	Phe	Glu	Lys	Ser	Gly
					100					105				110	
Ser	Ala	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
					115					120					

<210> 70

<211> 118

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：5F7的蛋白序列

<400> 70

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Ile	Thr	Phe	Ser	Ile	Asn
			20					25					30		
Thr	Met	Gly	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Gln	Arg	Glu	Leu	Val
		35					40					45			
Ala	Leu	Ile	Ser	Ser	Ile	Gly	Asp	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
		50					55				60				
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr	Leu
65					70					75				80	
Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Lys
					85					90				95	

Arg Phe Arg Thr Ala Ala Gln Gly Thr Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

Gln Val Thr Val Ser Ser
 115

<210> 71

<211> 119

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：47D5的蛋白序列

<400> 71

Lys Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Gly Phe Asn
 20 25 30

Asp Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
 35 40 45

Ala Leu Ile Ser Arg Val Gly Val Thr Ser Ser Ala Asp Ser Val Lys
 50 55 60

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

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
 85 90 95

Met Asp Gln Arg Leu Asp Gly Ser Thr Leu Ala Tyr Trp Gly Gln Gly
 100 105 110

Thr Gln Val Thr Val Ser Ser
 115

<210> 72

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：2D3-CDoem3-H序列

<400> 72

Met Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Gln Pro Gly
 1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp
 20 25 30

Tyr Ala Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp

35	40	45
Val Ser Ser Ile Asn Trp	Ser Gly Thr His Thr	Asp Tyr Ala Asp Ser
50	55	60
Val Lys Gly Arg Phe Thr	Ile Ser Arg Asn Asn	Ala Asn Asn Thr Leu
65	70	75
Tyr Leu Gln Met Asn Ser	Leu Lys Ser Glu Asp	Thr Ala Val Tyr Tyr
85	90	95
Cys Ala Lys Asn Trp Arg	Asp Ala Gly Thr Thr	Trp Phe Glu Lys Ser
100	105	110
Gly Ser Ala Gly Gln Gly	Thr Gln Val Thr Val	Ser Ser Gly Gly Gly
115	120	125
Gly Ser Gly Gly Gly Gly	Ser Gly Gly Gly Gly	Ser Val Thr Gly Gly
130	135	140
Met Ala Ser Lys Trp Asp	Gln Lys Gly Met Asp	Ile Ala Tyr Glu Glu
145	150	155
Ala Leu Leu Gly Tyr Lys	Glu Gly Gly Val Pro	Ile Gly Gly Cys Leu
165	170	175
Ile Asn Asn Lys Asp Gly	Ser Val Leu Gly Arg	Gly His Asn Met Arg
180	185	190
Phe Gln Lys Gly Ser Ala	Thr Leu His Gly Glu	Ile Ser Thr Leu Glu
195	200	205
Asn Cys Gly Arg Leu Glu	Gly Lys Val Tyr Lys	Asp Thr Thr Leu Tyr
210	215	220
Thr Thr Leu Ser Pro Cys	Asp Met Cys Thr Gly	Ala Ile Ile Met Tyr
225	230	235
Gly Ile Pro Arg Cys Val	Ile Gly Glu Asn Val	Asn Phe Lys Ser Lys
245	250	255
Gly Glu Lys Tyr Leu Gln	Thr Arg Gly His Glu	Val Val Val Val Asp
260	265	270
Asp Glu Arg Cys Lys Lys	Leu Met Lys Gln Phe	Ile Asp Glu Arg Pro
275	280	285
Gln Asp Trp Phe Glu Asp	Ile Gly Glu Gly Ser	Ser His His His His
290	295	300
His His		
305		
<210> 73		
<211> 300		
<212> PRT		
<213> 未知		

<220>

<223> 对“未知”的描述:

5F7-CDom3-H序列

<400> 73

Met	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Ile	Thr	Phe	Ser	Ile
			20					25					30		
Asn	Thr	Met	Gly	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Gln	Arg	Glu	Leu
		35					40					45			
Val	Ala	Leu	Ile	Ser	Ser	Ile	Gly	Asp	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55				60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
65					70					75				80	
Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90					95	
Lys	Arg	Phe	Arg	Thr	Ala	Ala	Gln	Gly	Thr	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
		115					120					125			
Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly	Met	Ala	Ser	Lys	Trp	Asp
	130					135					140				
Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu	Ala	Leu	Leu	Gly	Tyr	Lys
145				150						155				160	
Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu	Ile	Asn	Asn	Lys	Asp	Gly
			165					170					175		
Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg	Phe	Gln	Lys	Gly	Ser	Ala
			180				185						190		
Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu	Asn	Cys	Gly	Arg	Leu	Glu
		195					200					205			
Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr	Thr	Thr	Leu	Ser	Pro	Cys
	210					215					220				
Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr	Gly	Ile	Pro	Arg	Cys	Val
225				230					235					240	
Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys	Gly	Glu	Lys	Tyr	Leu	Gln
			245					250					255		
Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp	Asp	Glu	Arg	Cys	Lys	Lys
		260					265					270			
Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro	Gln	Asp	Trp	Phe	Glu	Asp

275	280	285
Ile Gly Glu Gly Ser Ser His His His His His His		
290	295	300
<210> 74		
<211> 301		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
47D5-CDem3-H序列		
<400> 74		
Met Lys Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Gly Phe		
20 25 30		
Asn Asp Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu		
35 40 45		
Val Ala Leu Ile Ser Arg Val Gly Val Thr Ser Ser Ala Asp Ser Val		
50 55 60		
Lys Gly Arg Phe Thr Ile Ser Arg Val Asn Ala Lys Asp Thr Val Tyr		
65 70 75 80		
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys		
85 90 95		
Tyr Met Asp Gln Arg Leu Asp Gly Ser Thr Leu Ala Tyr Trp Gly Gln		
100 105 110		
Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly Met Ala Ser Lys Trp		
130 135 140		
Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Leu Leu Gly Tyr		
145 150 155 160		
Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp		
165 170 175		
Gly Ser Val Leu Gly Arg Gly His Asn Met Arg Phe Gln Lys Gly Ser		
180 185 190		
Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu		
195 200 205		
Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro		
210 215 220		

$\langle 220 \rangle$

<223> 对“未知”的描述:

BCD090-M2-CDoem3-H序列

<400> 76

Met	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	1	5	10	15
Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Phe	Ser	Gly	Arg	Thr	Phe	Ser	Met	20	25	30	
Tyr	Thr	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	35	40	45	
Val	Ala	Ala	Asn	Arg	Gly	Arg	Gly	Leu	Ser	Pro	Asp	Ile	Ala	Asp	Ser	50	55	60	
Val	Asn	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Leu	65	70	75	80
Tyr	Leu	Gln	Met	Asp	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	85	90	95	
Cys	Ala	Ala	Asp	Leu	Gln	Tyr	Gly	Ser	Ser	Trp	Pro	Gln	Arg	Ser	Ser	100	105	110	
Ala	Glu	Tyr	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	115	120	125	
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	130	135	140	
Thr	Gly	Gly	Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	145	150	155	160
Tyr	Glu	Glu	Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	165	170	175	
Gly	Cys	Leu	Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	180	185	190	
Asn	Met	Arg	Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	195	200	205	
Thr	Leu	Glu	Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	210	215	220	
Thr	Leu	Tyr	Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	225	230	235	240
Ile	Met	Tyr	Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	245	250	255	
Lys	Ser	Lys	Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	260	265	270	
Val	Val	Asp	Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	275	280	285	

Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His
 290 295 300

His His His His His
 305

<210> 77

<211> 120

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

抗-CEA vhh (ABS29544.1) 序列

<400> 77

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Ala Gly Glu
 1 5 10 15

Ser Leu Thr Leu Ser Cys Thr Ser Ser Thr Leu Thr Phe Thr Pro Tyr
 20 25 30

Arg Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Asp Leu Val
 35 40 45

Ala Asp Ile Ser Ser Gly Asp Gly Arg Thr Thr Asn Tyr Ala Asp Phe
 50 55 60

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

Phe Leu Arg Met Thr Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Asn Thr Phe Val Ser Phe Val Gly Ile Ala Arg Ser Trp Gly Gln
 100 105 110

Gly Thr Gln Val Thr Val Ser Ser
 115 120

<210> 78

<211> 302

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

抗-CEA (ABS29544.1)-CDoem3-H序列

<400> 78

Met Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Ala Gly
 1 5 10 15

Glu Ser Leu Thr Leu Ser Cys Thr Ser Ser Thr Leu Thr Phe Thr Pro

20	25	30
Tyr Arg Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Asp Leu		
35	40	45
Val Ala Asp Ile Ser Ser Gly Asp Gly Arg Thr Thr Asn Tyr Ala Asp		
50	55	60
Phe Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ile Lys Asn Thr		
65	70	75
Val Phe Leu Arg Met Thr Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr		
85	90	95
Tyr Cys Asn Thr Phe Val Ser Phe Val Gly Ile Ala Arg Ser Trp Gly		
100	105	110
Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly		
115	120	125
Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly Met Ala Ser Lys		
130	135	140
Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Leu Leu Gly		
145	150	155
Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn Asn Lys		
165	170	175
Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg Phe Gln Lys Gly		
180	185	190
Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys Gly Arg		
195	200	205
Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr Leu Ser		
210	215	220
Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr Gly Ile Pro Arg		
225	230	235
Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys Gly Glu Lys Tyr		
245	250	255
Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp Asp Glu Arg Cys		
260	265	270
Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro Gln Asp Trp Phe		
275	280	285
Glu Asp Ile Gly Glu Gly Ser Ser His His His His His His		
290	295	300

<210> 79

<211> 123

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

NbCEA5序列

<400> 79

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Ala	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Asp	Thr	Tyr	Gly	Ser	Tyr
			20					25					30		
Trp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Gly	Val
		35					40					45			
Ala	Ala	Ile	Asn	Arg	Gly	Gly	Gly	Tyr	Thr	Val	Tyr	Ala	Asp	Ser	Val
		50				55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ala	Lys	Asn	Thr	Val	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Asp	Asp	Thr	Ala	Asp	Tyr	Tyr	Cys
				85					90					95	
Ala	Ala	Ser	Gly	Val	Leu	Gly	Gly	Leu	His	Glu	Asp	Trp	Phe	Asn	Tyr
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser					
			115					120							

<210> 80

<211> 305

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

NbCEA5-CDoem3-H序列

<400> 80

Met	Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Ala	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Asp	Thr	Tyr	Gly	Ser
			20					25					30		
Tyr	Trp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Gly
		35					40					45			
Val	Ala	Ala	Ile	Asn	Arg	Gly	Gly	Gly	Tyr	Thr	Val	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ala	Lys	Asn	Thr	Val
65					70					75					80
Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Asp	Asp	Thr	Ala	Asp	Tyr	Tyr

				85					90					95		
Cys	Ala	Ala	Ser	Gly	Val	Leu	Gly	Gly	Leu	His	Glu	Asp	Trp	Phe	Asn	
			100						105					110		
Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	
			115						120					125		
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly	Met	
			130						135					140		
Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu	Ala	
145						150					155					160
Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu	Ile	
						165					170				175	
Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg	Phe	
				180						185				190		
Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu	Asn	
				195						200				205		
Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr	Thr	
							215					220				
Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr	Gly	
225						230					235					240
Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys	Gly	
						245					250				255	
Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp	Asp	
						260					265				270	
Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro	Gln	
						275						285				
Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His	His	
						290						300				
His																
305																
<210>	81															
<211>	194															
<212>	PRT															
<213>	未知															
<220>																
<223>	对“未知”的描述：															
GE10-CD-H序列																
<400>	81															
Met	Leu	His	Leu	Trp	Val	Pro	Glu	Pro	Trp	Thr	Gln	Thr	Gly	Gly	Gly	
1					5				10				15			

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

His His

<210> 82

<211> 194

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

GE11-CD-H序列

<400> 82

Met Tyr His Trp Tyr Gly Tyr Thr Pro Gln Asn Val Ile Gly Gly Gly
 1 5 10 15
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly
 20 25 30
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 35 40 45
 Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 50 55 60

Met	Met	Leu	Tyr	Asn	Pro	Thr	Thr	Tyr	Gln	Met	Asp	Val	Asn	Pro	Glu
1				5					10					15	
Gly	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
				20					25					30	
Ser	Val	Thr	Gly	Gly	Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp
				35					40					45	
Ile	Ala	Tyr	Glu	Glu	Ala	Ala	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro
				50					55					60	
Ile	Gly	Gly	Cys	Leu	Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg
65						70				75					80
Gly	His	Asn	Met	Arg	Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu
				85						90				95	
Ile	Ser	Thr	Leu	Glu	Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys
				100					105					110	

Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
 115 120 125
 Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val
 130 135 140
 Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
 145 150 155 160
 Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe
 165 170 175
 Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser
 180 185 190
 Ser His His His His His His
 195

<210> 84

<211> 199

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述：

Inherbin3-CD-H序列

<400> 84

Met Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu Glu Pro Asn Pro His
 1 5 10 15
 Thr Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 20 25 30
 Ser Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
 35 40 45
 Ile Ala Tyr Glu Glu Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro
 50 55 60
 Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
 65 70 75 80
 Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
 85 90 95
 Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
 100 105 110
 Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
 115 120 125
 Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val
 130 135 140
 Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu

145	150	155	160
Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe			
	165	170	175
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser			
	180	185	190
Ser His His His His His His			
195			
<210> 85			
<211> 357			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
Endo-CD序列			
<400> 85			
Met His Ser His Arg Asp Phe Gln Pro Val Leu His Leu Val Ala Leu			
1 5 10 15			
Asn Ser Pro Leu Ser Gly Gly Met Arg Gly Ile Arg Gly Ala Asp Phe			
20 25 30			
Gln Cys Phe Gln Gln Ala Arg Ala Val Gly Leu Ala Gly Thr Phe Arg			
35 40 45			
Ala Phe Leu Ser Ser Arg Leu Gln Asp Leu Tyr Ser Ile Val Arg Arg			
50 55 60			
Ala Asp Arg Ala Ala Val Pro Ile Val Asn Leu Lys Asp Glu Leu Leu			
65 70 75 80			
Phe Pro Ser Trp Glu Ala Leu Phe Ser Gly Ser Glu Gly Pro Leu Lys			
85 90 95			
Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Lys Asp Val Leu Arg His			
100 105 110			
Pro Thr Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro Asn Gly			
115 120 125			
Arg Arg Leu Thr Glu Ser Tyr Cys Glu Thr Trp Arg Thr Glu Ala Pro			
130 135 140			
Ser Ala Thr Gly Gln Ala Ser Ser Leu Leu Gly Gly Arg Leu Leu Gly			
145 150 155 160			
Gln Ser Ala Ala Ser Cys His His Ala Tyr Ile Val Leu Cys Ile Glu			
165 170 175			
Asn Ser Phe Met Thr Ala Ser Lys Ser Gly Gly Gly Gly Ser Gly Gly			
180 185 190			

Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly Met Ala Ser Lys
 195 200 205
 Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Ala Leu Gly
 210 215 220
 Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn Asn Lys
 225 230 235 240
 Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg Phe Gln Lys Gly
 245 250 255
 Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys Gly Arg
 260 265 270
 Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr Leu Ser
 275 280 285
 Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr Gly Ile Pro Arg
 290 295 300
 Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys Gly Glu Lys Tyr
 305 310 315 320
 Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp Asp Glu Arg Cys
 325 330 335
 Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro Gln Asp Trp Phe
 340 345 350
 Glu Asp Ile Gly Glu
 355

<210> 86

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

3VGR10-CD-H序列

<400> 86

Met Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Tyr Ser Val Ser Lys
 20 25 30
 Asn Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly
 35 40 45
 Val Ala Gly Ile Asn Glu Gly Gly Thr Ala Thr Tyr Tyr Ala Asn Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Gln Asp Asn Ala Arg Asn Thr Val

65	70	75	80
Tyr Leu Gln Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr			
	85	90	95
Cys Ala Ala Gly Ser Pro Asp Pro Pro Pro Leu Ile Glu Ser Val Val			
	100	105	110
Lys Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly			
	115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly			
	130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu			
145	150	155	160
Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 87			
<211> 304			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
3VGR17-CD-H序列			
<400> 87			

Met	Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Ala	Gly
1			5						10					15	
Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Tyr	Thr	Tyr	Cys	Ser
			20					25					30		
Tyr	Asp	Met	Gly	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Ala	Ile	Asp	Asn	Tyr	Gly	Arg	Thr	Gly	Tyr	Ala	Asp	Ser	Val
		50				55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Gln	Asp	Asn	Ala	Lys	Asn	Thr	Ser	Tyr
65					70				75					80	
Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys
			85					90					95		
Lys	Val	Asp	Val	Cys	Pro	Asp	Pro	Ser	Arg	Pro	Gly	Arg	Pro	Gly	Tyr
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser
			115				120						125		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly	Met	Ala
			130				135				140				
Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu	Ala	Ala
145					150				155					160	
Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu	Ile	Asn
			165					170					175		
Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg	Phe	Gln
			180					185					190		
Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu	Asn	Cys
			195				200					205			
Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr	Thr	Thr
			210				215					220			
Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr	Gly	Ile
225					230				235					240	
Pro	Arg	Cys	Val	Val	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys	Gly	Glu
			245					250					255		
Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp	Asp	Glu
			260				265						270		
Arg	Cys	Lys	Lys	Ile	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro	Gln	Asp
			275				280					285			
Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His	His	His
			290				295					300			

<210> 88

<211> 290

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

DOM-16-39-CD-H序列

<400> 88

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Met Asp Ile Gln Met Thr Gln Ser Pro Thr Ser Leu Ser Ala Ser Val
1           5           10           15
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Asn
          20           25           30
Leu Leu Asp Trp Tyr Gln Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu
          35           40           45
Ile Tyr Tyr Ala Ser Phe Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
          50           55           60
Gly Gly Gly Phe Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65           70           75           80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Pro Ala Pro
          85           90           95
Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly
          100          105          110
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly
          115          120          125
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
          130          135          140
Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          145          150          155          160
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          165          170          175
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          180          185          190
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          195          200          205
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
          210          215          220
Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys
          225          230          235          240
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
          245          250          255

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Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro
 260 265 270
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 275 280 285
 His His
 290
 <210> 89
 <211> 802
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 SP-RituxanHC-CD-L-CD序列
 <400> 89
 Met Lys Lys Asn Ile Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser
 1 5 10 15
 Ile Ala Thr Asn Ala Tyr Ala Gln Val Gln Leu Gln Gln Pro Gly Ala
 20 25 30
 Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser
 35 40 45
 Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro
 50 55 60
 Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp
 65 70 75 80
 Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
 85 90 95
 Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu
 100 105 110
 Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp
 115 120 125
 Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala
 130 135 140
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 145 150 155 160
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 165 170 175
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 180 185 190
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

195	200	205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser	Leu Gly Thr Gln Thr	
210	215	220
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys		
225	230	235
Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys		
245	250	255
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro		
260	265	270
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys		
275	280	285
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp		
290	295	300
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu		
305	310	315
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu		
325	330	335
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn		
340	345	350
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly		
355	360	365
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu		
370	375	380
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr		
385	390	395
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn		
405	410	415
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe		
420	425	430
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn		
435	440	445
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr		
450	455	460
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Val Thr Gly Gly Met Ala		
465	470	475
Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Ala		
485	490	495
Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn		
500	505	510

Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg Phe Gln		
515	520	525
Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys		
530	535	540
Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr		
545	550	555
560		
Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr Gly Ile		
565	570	575
Pro Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys Gly Glu		
580	585	590
Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp Asp Glu		
595	600	605
Arg Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro Gln Asp		
610	615	620
Trp Phe Glu Asp Ile Gly Glu Gly Ser Thr Ser Gly Ser Gly Lys Ser		
625	630	635
640		
Ser Glu Gly Lys Gly Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln		
645	650	655
Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Ala Leu Gly Tyr Lys Glu		
660	665	670
Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser		
675	680	685
Val Leu Gly Arg Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr		
690	695	700
Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly		
705	710	715
720		
Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp		
725	730	735
Met Cys Thr Gly Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Val		
740	745	750
Gly Glu Asn Val Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr		
755	760	765
Arg Gly His Glu Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Ile		
770	775	780
Met Lys Gln Phe Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile		
785	790	795
800		
Gly Glu		
<210> 90		
<211> 236		

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

SP-RituxanLC序列

<400> 90

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Met Lys Lys Asn Ile Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser
1           5           10           15
Ile Ala Thr Asn Ala Tyr Ala Gln Ile Val Leu Ser Gln Ser Pro Ala
           20           25           30
Ile Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala
           35           40           45
Ser Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser
           50           55           60
Ser Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val
65           70           75           80
Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr
           85           90           95
Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
           100          105          110
Trp Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
           115          120          125
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
           130          135          140
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145          150          155          160
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
           165          170          175
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
           180          185          190
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
           195          200          205
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
           210          215          220
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225          230          235

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<210> 91

<211> 630

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

SP-HerceptinHC-CD序列

<400> 91

Met	Lys	Lys	Asn	Ile	Ala	Phe	Leu	Leu	Ala	Ser	Met	Phe	Val	Phe	Ser
1				5					10					15	
Ile	Ala	Thr	Asn	Ala	Tyr	Ala	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly
			20					25					30		
Gly	Leu	Val	Gln	Pro	Gly	Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser
		35					40					45			
Gly	Phe	Asn	Ile	Lys	Asp	Thr	Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro
		50				55				60					
Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr
65				70					75					80	
Thr	Arg	Tyr	Ala	Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp
				85					90					95	
Thr	Ser	Lys	Asn	Thr	Ala	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu
			100					105					110		
Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr
		115				120						125			
Ala	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala
		130				135						140			
Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser
145				150					155					160	
Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe
				165					170					175	
Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly
			180					185					190		
Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu
			195					200					205		
Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr
		210				215						220			
Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys
225				230					235					240	
Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
				245					250					255	
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
			260					265						270	

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
275	280	285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
290	295	300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
305	310	315
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
	325	330
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
	340	345
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
	355	360
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met		
	370	375
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
385	390	395
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
	405	410
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
	420	425
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val		
	435	440
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
	450	455
Lys Ser Leu Ser Leu Ser Pro Gly Lys Val Thr Gly Gly Met Ala Ser		
465	470	475
Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu Ala Ala Leu		
	485	490
Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu Ile Asn Asn		
	500	505
Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg Phe Gln Lys		
	515	520
Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu Asn Cys Gly		
	530	535
Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr Thr Thr Leu		
545	550	555
Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr Gly Ile Pro		
	565	570
Arg Cys Val Val Gly Glu Asn Val Asn Phe Lys Ser Lys Gly Glu Lys		

580	585	590
Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp Asp Glu Arg		
595	600	605
Cys Lys Lys Ile Met Lys Gln Phe Ile Asp Glu Arg Pro Gln Asp Trp		
610	615	620
Phe Glu Asp Ile Gly Glu		
625	630	
<210> 92		
<211> 237		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
SP-HerceptinLC序列		
<400> 92		
Met Lys Lys Asn Ile Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser		
1 5 10 15		
Ile Ala Thr Asn Ala Tyr Ala Asp Ile Gln Met Thr Gln Ser Pro Ser		
20 25 30		
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala		
35 40 45		
Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly		
50 55 60		
Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly		
65 70 75 80		
Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu		
85 90 95		
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln		
100 105 110		
Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu		
115 120 125		
Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser		
130 135 140		
Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn		
145 150 155 160		
Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala		
165 170 175		
Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys		
180 185 190		

Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
 195 200 205
 Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
 210 215 220
 Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235
 <210> 93
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述:
 TC3-001 S12V序列
 <400> 93
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Val Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 94		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-002 V13A序列		
<400> 94		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		

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

His His

305

<210> 95

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-003 T15V序列

<400> 95

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Val Gly			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			

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

His His

305

<210> 96

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-004 G16D序列

<400> 96

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Asp
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135				140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260				265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 97		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-005 S18D序列		
<400> 97		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 98

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-006 S18E序列

<400> 98

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Glu Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 99			
<211> 306			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
TC3-007 K88R序列			
<400> 99			
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
	50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115				120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
			130				135						140		
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150					155					160
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
					165				170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
			195				200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
			210				215						220		
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235					240
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
					245				250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265						270	
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
			275				280						285		
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
			290				295					300			
His	His														
305															
<210>	100														
<211>	306														
<212>	PRT														
<213>	未知														
<220>															
<223>	对“未知”的描述:														
TC3-008	P89A序列														
<400>	100														
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly

1	5	10	15
Gly Ser Leu Arg	Leu Thr Cys Ala	Ala Ser Gly Arg	Thr Ser Arg Ser
20	25	30	
Tyr Gly Met Gly	Trp Phe Arg Gln	Ala Pro Gly Lys	Glu Arg Glu Phe
35	40	45	
Val Ser Gly Ile	Ser Trp Arg Gly	Asp Ser Thr Gly	Tyr Ala Asp Ser
50	55	60	
Val Lys Gly Arg	Phe Thr Ile Ser	Arg Asp Asn Ala	Lys Asn Thr Val
65	70	75	80
Asp Leu Gln Met	Asn Ser Leu Lys	Ala Glu Asp Thr	Ala Ile Tyr Tyr
85	90	95	
Cys Ala Ala Ala	Ala Gly Ser Ala	Trp Tyr Gly Thr	Leu Tyr Glu Tyr
100	105	110	
Asp Tyr Trp Gly	Gln Gly Thr Gln	Val Thr Val Ser	Ser Gly Gly Gly
115	120	125	
Gly Ser Gly Gly	Gly Gly Ser Gly	Gly Gly Ser Val	Thr Gly Gly
130	135	140	
Met Ala Ser Lys	Trp Asp Gln Lys	Gly Met Asp Ile	Ala Tyr Glu Glu
145	150	155	160
Ala Leu Leu Gly	Tyr Lys Glu Gly	Gly Val Pro Ile	Gly Gly Cys Leu
165	170	175	
Ile Asn Asn Lys	Asp Gly Ser Val	Leu Gly Arg Gly	His Asn Met Arg
180	185	190	
Phe Gln Lys Gly	Ser Ala Thr Leu	His Gly Glu Ile	Ser Thr Leu Glu
195	200	205	
Asn Cys Gly Arg	Leu Glu Gly Lys	Val Tyr Lys Asp	Thr Thr Leu Tyr
210	215	220	
Thr Thr Leu Ser	Pro Cys Asp Met	Cys Thr Gly Ala	Ile Ile Met Tyr
225	230	235	240
Gly Ile Pro Arg	Cys Val Ile Gly	Glu Asn Val Asn	Phe Lys Ser Lys
245	250	255	
Gly Glu Lys Tyr	Leu Gln Thr Arg	Gly His Glu Val	Val Val Val Asp
260	265	270	
Asp Glu Arg Cys	Lys Lys Leu Met	Lys Gln Phe Ile	Asp Glu Arg Pro
275	280	285	
Gln Asp Trp Phe	Glu Asp Ile Gly	Glu Gly Ser Ser	His His His His
290	295	300	
His His			
305			

<210> 101

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-009 K88A序列

<400> 101

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
          20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
          35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
          50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Ala Pro Glu Asp Thr Ala Ile Tyr Tyr
          85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
          130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

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				245				250				255					
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp		
				260				265				270					
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro		
				275				280				285					
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His		
				290				295				300					
His	His																
305																	
<210> 102																	
<211> 306																	
<212> PRT																	
<213> 未知																	
<220>																	
<223> 对“未知”的描述:																	
TC3-010 K88D序列																	
<400> 102																	
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly		
				5				10				15					
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser		
				20				25				30					
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe		
				35				40				45					
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser		
				50				55				60					
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val		
				70				75				80					
Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr		
				85				90				95					
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr		
				100				105				110					
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly		
				115				120				125					
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly		
				130				135				140					
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu		
				145				150				155				160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu		
				165				170				175					

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 103

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-011 K88S序列

<400> 103

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Ser Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 104		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-012 K88T序列		
<400> 104		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
35				40				45							
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
50				55				60							
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70				75				80			
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
100				105				110							
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
115				120				125							
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
130				135				140							
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
180				185				190							
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
195				200				205							
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
210				215				220							
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225				230				235				240			
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
260				265				270							
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
275				280				285							
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
290				295				300							
His	His														
305															
<210> 105															
<211> 306															
<212> PRT															

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-013 P89D序列

<400> 105

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Asp	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245					250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300
 His His
 305
 <210> 106
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-014 P89E序列
 <400> 106
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Glu Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		

305

<210> 107

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-015 T92D序列

<400> 107

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Asp Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125

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

His His

305

<210> 108

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-016 T92E序列

<400> 108

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser

50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Glu Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 109		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		

TC3-017 T92G序列

<400> 109

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Gly	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135				140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260				265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 110		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-018 T92H序列		
<400> 110		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp His Ala Ile Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 111

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-019 T92Q序列

<400> 111

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Gln Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 112			
<211> 306			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
TC3-020 A93D序列			
<400> 112			
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
	50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Asp	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115				120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
			130				135						140		
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145						150					155				160
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
						165				170				175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
			195					200					205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
			210				215					220			
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225						230					235				240
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
						245				250				255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
			275					280					285		
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
			290				295					300			
His	His														
305															
<210>	113														
<211>	306														
<212>	PRT														
<213>	未知														
<220>															
<223>	对“未知”的描述:														
TC3-022	I94V序列														
<400>	113														
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly

1	5	10	15
Gly Ser Leu Arg	Leu Thr Cys Ala	Ala Ser Gly Arg	Thr Ser Arg Ser
20	25	30	
Tyr Gly Met Gly	Trp Phe Arg Gln	Ala Pro Gly Lys	Glu Arg Glu Phe
35	40	45	
Val Ser Gly Ile	Ser Trp Arg Gly	Asp Ser Thr Gly	Tyr Ala Asp Ser
50	55	60	
Val Lys Gly Arg	Phe Thr Ile Ser	Arg Asp Asn Ala	Lys Asn Thr Val
65	70	75	80
Asp Leu Gln Met	Asn Ser Leu Lys	Pro Glu Asp Thr	Ala Val Tyr Tyr
85	90	95	
Cys Ala Ala Ala	Ala Gly Ser Ala	Trp Tyr Gly Thr	Leu Tyr Glu Tyr
100	105	110	
Asp Tyr Trp Gly	Gln Gly Thr Gln	Val Thr Val Ser	Ser Gly Gly Gly
115	120	125	
Gly Ser Gly Gly	Gly Gly Ser Gly	Gly Gly Ser Val	Thr Gly Gly
130	135	140	
Met Ala Ser Lys	Trp Asp Gln Lys	Gly Met Asp Ile	Ala Tyr Glu Glu
145	150	155	160
Ala Leu Leu Gly	Tyr Lys Glu Gly	Gly Val Pro Ile	Gly Gly Cys Leu
165	170	175	
Ile Asn Asn Lys	Asp Gly Ser Val	Leu Gly Arg Gly	His Asn Met Arg
180	185	190	
Phe Gln Lys Gly	Ser Ala Thr Leu	His Gly Glu Ile	Ser Thr Leu Glu
195	200	205	
Asn Cys Gly Arg	Leu Glu Gly Lys	Val Tyr Lys Asp	Thr Thr Leu Tyr
210	215	220	
Thr Thr Leu Ser	Pro Cys Asp Met	Cys Thr Gly Ala	Ile Ile Met Tyr
225	230	235	240
Gly Ile Pro Arg	Cys Val Ile Gly	Glu Asn Val Asn	Phe Lys Ser Lys
245	250	255	
Gly Glu Lys Tyr	Leu Gln Thr Arg	Gly His Glu Val	Val Val Val Asp
260	265	270	
Asp Glu Arg Cys	Lys Lys Leu Met	Lys Gln Phe Ile	Asp Glu Arg Pro
275	280	285	
Gln Asp Trp Phe	Glu Asp Ile Gly	Glu Gly Ser Ser	His His His His
290	295	300	
His His			
305			

<210> 114

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-023 I94A序列

<400> 114

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
           20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
           35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
           50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ala Tyr Tyr
           85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
           100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
           115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
           130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
           165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
           180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
           195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
           210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

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				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
				260				265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
				275				280				285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
				290				295				300			
His	His														
305															
<210> 115															
<211> 306															
<212> PRT															
<213> 未知															
<220>															
<223> 对“未知”的描述:															
TC3-024 I94T序列															
<400> 115															
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5				10				15			
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
				20				25				30			
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
				35				40				45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
				50				55				60			
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70				75				80			
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
				100				105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
				115				120				125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
				130				135				140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 116

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-025 I94R序列

<400> 116

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr

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

His His

305

<210> 117

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-026 I94Q序列

<400> 117

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Gln Tyr Tyr		
	85	90
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
	100	105
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
	115	120
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly		
	130	135
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
	165	170
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
	180	185
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
	195	200
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
	210	215
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
	245	250
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
	260	265
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
	275	280
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
	290	295
His His		300
305		
<210> 118		
<211> 306		
<212> PRT		

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-027 I94N序列

<400> 118

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Asn	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
			165						170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245						250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300
 His His
 305
 <210> 119
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-028 Y224A序列
 <400> 119
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Ala		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 120		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-029 Y224H序列		
<400> 120		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		

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

His His

305

<210> 121

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-030 T225D序列

<400> 121

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser

50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Asp Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 122		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		

TC3-031 T226E序列

<400> 122

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85				90					95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135				140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170					175		
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
		180						185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Glu	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245					250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
		260					265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 123		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-032 M232N序列		
<400> 123		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Asn Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 124

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-033 M232A序列

<400> 124

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Ala Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 125			
<211> 306			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
TC3-034 M232K序列			
<400> 125			
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
	50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115				120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
			130				135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150					155					160
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
					165				170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
			195				200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
			210				215					220			
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Lys	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235					240
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
					245				250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
			275				280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
			290				295					300			
His	His														
305															
<210>	126														
<211>	306														
<212>	PRT														
<213>	未知														
<220>															
<223>	对“未知”的描述:														
TC3-035	M232Q序列														
<400>	126														
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly

1	5	10	15
Gly Ser Leu Arg	Leu Thr Cys Ala	Ala Ser Gly Arg	Thr Ser Arg Ser
20	25	30	
Tyr Gly Met Gly	Trp Phe Arg Gln	Ala Pro Gly Lys	Glu Arg Glu Phe
35	40	45	
Val Ser Gly Ile	Ser Trp Arg Gly	Asp Ser Thr Gly	Tyr Ala Asp Ser
50	55	60	
Val Lys Gly Arg	Phe Thr Ile Ser	Arg Asp Asn Ala	Lys Asn Thr Val
65	70	75	80
Asp Leu Gln Met	Asn Ser Leu Lys	Pro Glu Asp Thr	Ala Ile Tyr Tyr
85	90	95	
Cys Ala Ala Ala	Ala Gly Ser Ala	Trp Tyr Gly Thr	Leu Tyr Glu Tyr
100	105	110	
Asp Tyr Trp Gly	Gln Gly Thr Gln	Val Thr Val Ser	Ser Gly Gly Gly
115	120	125	
Gly Ser Gly Gly	Gly Gly Ser Gly	Gly Gly Ser Val	Thr Gly Gly
130	135	140	
Met Ala Ser Lys	Trp Asp Gln Lys	Gly Met Asp Ile	Ala Tyr Glu Glu
145	150	155	160
Ala Leu Leu Gly	Tyr Lys Glu Gly	Gly Val Pro Ile	Gly Gly Cys Leu
165	170	175	
Ile Asn Asn Lys	Asp Gly Ser Val	Leu Gly Arg Gly	His Asn Met Arg
180	185	190	
Phe Gln Lys Gly	Ser Ala Thr Leu	His Gly Glu Ile	Ser Thr Leu Glu
195	200	205	
Asn Cys Gly Arg	Leu Glu Gly Lys	Val Tyr Lys Asp	Thr Thr Leu Tyr
210	215	220	
Thr Thr Leu Ser	Pro Cys Asp Gln	Cys Thr Gly Ala	Ile Ile Met Tyr
225	230	235	240
Gly Ile Pro Arg	Cys Val Ile Gly	Glu Asn Val Asn	Phe Lys Ser Lys
245	250	255	
Gly Glu Lys Tyr	Leu Gln Thr Arg	Gly His Glu Val	Val Val Val Asp
260	265	270	
Asp Glu Arg Cys	Lys Lys Leu Met	Lys Gln Phe Ile	Asp Glu Arg Pro
275	280	285	
Gln Asp Trp Phe	Glu Asp Ile Gly	Glu Gly Ser Ser	His His His His
290	295	300	
His His			
305			

<210> 127

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-036 V268A序列

<400> 127

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
          20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
          35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
          50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
          85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
          130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

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				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
				260				265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
				275				280				285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
				290				295				300			
His	His														
305															
<210> 128															
<211> 306															
<212> PRT															
<213> 未知															
<220>															
<223> 对“未知”的描述:															
TC3-037 V268T序列															
<400> 128															
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5				10				15			
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
				20				25				30			
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
				35				40				45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
				50				55				60			
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70				75				80			
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
				100				105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
				115				120				125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
				130				135				140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300

His His

305

<210> 129

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-038 V269A序列

<400> 129

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Ala Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 130		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-039 V269L序列		
<400> 130		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Leu Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 131		
<211> 306		
<212> PRT		

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-040 V269I序列

<400> 131

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
			165						170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245						250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Ile	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300
 His His
 305
 <210> 132
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-041 V269T序列
 <400> 132
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		

305

<210> 133

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-042 V270A序列

<400> 133

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125

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

His His

305

<210> 134

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-043 V270T序列

<400> 134

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			

50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Thr Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 135		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		

TC3-044 S12V, T15V, K88R, P89A, I94V, V268A序列

<400> 135

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Val	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250						255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
			260				265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 136		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-045 S12V, T15V, K88R, P89A, I94V, V268T序列		
<400> 136		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Val Val Gln Val Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 137

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-046 S12V, T15V, K88R, P89A, I94V, V269T序列

<400> 137

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Val Val Gln Val Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
290	295	300	

His His

305

<210> 138

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-047 V13A, K88D, I94R, V268A序列

<400> 138

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
	20	25
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
	35	40
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
	50	55
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
		80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
				100				105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
				115				120				125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
				130				135				140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
				180				185				190			
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
				195				200				205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
210				215				220							
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225				230				235				240			
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
				260				265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
275				280				285							
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
290				295				300							
His His															
305															
<210> 139															
<211> 306															
<212> PRT															
<213> 未知															
<220>															
<223> 对“未知”的描述:															
TC3-048 G16D, K88D, I94R, V268A序列															
<400> 139															
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp															

1	5	10	15
Gly Ser Leu Arg	Leu Thr Cys Ala	Ala Ser Gly Arg	Thr Ser Arg Ser
20	25	30	
Tyr Gly Met Gly	Trp Phe Arg Gln	Ala Pro Gly Lys	Glu Arg Glu Phe
35	40	45	
Val Ser Gly Ile	Ser Trp Arg Gly	Asp Ser Thr Gly	Tyr Ala Asp Ser
50	55	60	
Val Lys Gly Arg	Phe Thr Ile Ser	Arg Asp Asn Ala	Lys Asn Thr Val
65	70	75	80
Asp Leu Gln Met	Asn Ser Leu Asp	Pro Glu Asp Thr	Ala Arg Tyr Tyr
85	90	95	
Cys Ala Ala Ala	Ala Gly Ser Ala	Trp Tyr Gly Thr	Leu Tyr Glu Tyr
100	105	110	
Asp Tyr Trp Gly	Gln Gly Thr Gln	Val Thr Val Ser	Ser Gly Gly Gly
115	120	125	
Gly Ser Gly Gly	Gly Gly Ser Gly	Gly Gly Ser Val	Thr Gly Gly
130	135	140	
Met Ala Ser Lys	Trp Asp Gln Lys	Gly Met Asp Ile	Ala Tyr Glu Glu
145	150	155	160
Ala Leu Leu Gly	Tyr Lys Glu Gly	Gly Val Pro Ile	Gly Gly Cys Leu
165	170	175	
Ile Asn Asn Lys	Asp Gly Ser Val	Leu Gly Arg Gly	His Asn Met Arg
180	185	190	
Phe Gln Lys Gly	Ser Ala Thr Leu	His Gly Glu Ile	Ser Thr Leu Glu
195	200	205	
Asn Cys Gly Arg	Leu Glu Gly Lys	Val Tyr Lys Asp	Thr Thr Leu Tyr
210	215	220	
Thr Thr Leu Ser	Pro Cys Asp Met	Cys Thr Gly Ala	Ile Ile Met Tyr
225	230	235	240
Gly Ile Pro Arg	Cys Val Ile Gly	Glu Asn Val Asn	Phe Lys Ser Lys
245	250	255	
Gly Glu Lys Tyr	Leu Gln Thr Arg	Gly His Glu Ala	Val Val Val Asp
260	265	270	
Asp Glu Arg Cys	Lys Lys Leu Met	Lys Gln Phe Ile	Asp Glu Arg Pro
275	280	285	
Gln Asp Trp Phe	Glu Asp Ile Gly	Glu Gly Ser Ser	His His His His
290	295	300	
His His			
305			

<210> 140

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-049 S18D, K88D, I94R, V268A序列

<400> 140

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
1           5           10           15
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
          20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
          35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
          50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Arg Tyr Tyr
          85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
          130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

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	245		250		255										
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
	260							265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275							280					285		
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
	290						295					300			
His	His														

305

<210> 141

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-050 V13A, K88T, I94R, V268A序列

<400> 141

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Ala	Gln	Thr	Gly
1			5					10					15		
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
		20						25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
	35						40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70					75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
			85					90					95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
		100						105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135				140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150					155				160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 142

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-051 G16D, K88T, I94R, V268A序列

<400> 142

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 143		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-052 S18D, K88T, I94R, V268A序列		
<400> 143		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1	5	10
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
35				40				45							
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
50				55				60							
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70				75				80			
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
100				105				110							
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
115				120				125							
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
130				135				140							
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
180				185				190							
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
195				200				205							
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
210				215				220							
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225				230				235				240			
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
260				265				270							
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
275				280				285							
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
290				295				300							
His	His														
305															
<210> 144															
<211> 306															
<212> PRT															

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-053 V13A, K88D, I94Q, V268A序列

<400> 144

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Ala	Gln	Thr	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Gln	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
			165						170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245						250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300
 His His
 305
 <210> 145
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-054 G16D, K88D, I94Q, V268A序列
 <400> 145
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 146		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-055 S18D, K88D, I94Q, V268A序列		
<400> 146		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		

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

His His

305

<210> 147

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-056 V13A, K88T, I94Q, V268A序列

<400> 147

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser

50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 148		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		

TC3-057 G16D, K88T, I94Q, V268A序列

<400> 148

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Asp
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Gln	Tyr	Tyr
				85					90				95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170				175		
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245					250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
			260				265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 149		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-058 S18D, K88T, I94Q, V268A序列		
<400> 149		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly		
1 5 10 15		
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 150

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-059 V13A, K88D, I94R, V268T序列

<400> 150

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 151			
<211> 306			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
TC3-060 G16D, K88D, I94R, V268T序列			
<400> 151			
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp			
1	5	10	15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
	50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
			115				120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
			130				135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150					155					160
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
					165				170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
			195				200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
			210				215					220			
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235					240
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
					245				250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Thr	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
			275				280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
			290				295					300			
His	His														
305															
<210>	152														
<211>	306														
<212>	PRT														
<213>	未知														
<220>															
<223>	对“未知”的描述:														
TC3-061	S18D, K88D, I94R, V268T	序列													
<400>	152														
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly

1	5	10	15
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
20	25	30	
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
35	40	45	
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
50	55	60	
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Arg Tyr Tyr			
85	90	95	
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr			
100	105	110	
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly			
115	120	125	
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly			
130	135	140	
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu			
145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
165	170	175	
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
180	185	190	
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
195	200	205	
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
210	215	220	
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
245	250	255	
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp			
260	265	270	
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
275	280	285	
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
290	295	300	
His His			
305			

<210> 153

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-062 V13A, K88T, I94R, V268T序列

<400> 153

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
          20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
          35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
          50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Arg Tyr Tyr
          85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
          130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

```

				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Thr	Val	Val	Val	Asp
				260				265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
				275				280				285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
				290				295				300			
His	His														
305															
<210> 154															
<211> 306															
<212> PRT															
<213> 未知															
<220>															
<223> 对“未知”的描述:															
TC3-063 G16D, K88T, I94R, V268T序列															
<400> 154															
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Asp
1				5				10				15			
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
				20				25				30			
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
				35				40				45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
50				55				60							
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65				70				75				80			
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
				100				105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
				115				120				125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
130				135				140							
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 155

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-064 S18D, K88T, I94R, V268T序列

<400> 155

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 156		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-065 V13A, K88D, I94Q, V268T序列		
<400> 156		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 157		
<211> 306		
<212> PRT		

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-066 G16D, K88D, I94Q, V268T序列

<400> 157

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Asp
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Gln	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245					250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Thr	Val	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300
 His His
 305
 <210> 158
 <211> 306
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-067 S18D, K88D, I94Q, V268T序列
 <400> 158
 Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly
 1 5 10 15
 Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Thr Val Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		

305

<210> 159

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-068 V13A, K88T, I94Q, V268T序列

<400> 159

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125

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

His His

305

<210> 160

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-069 G16D, K88T, I94Q, V268T序列

<400> 160

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser

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

His His

305

<210> 161

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-070 S18D, K88T, I94Q, V268T序列

<400> 161

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Asp	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Gln	Tyr	Tyr
				85					90				95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130					135					140				
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170				175		
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
		180						185				190			
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245					250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Thr	Val	Val	Val	Asp
		260					265				270				
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280				285				
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His

290	295	300
His His		
305		
<210> 162		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-071 V13A, K88D, I94R, V269T序列		
<400> 162		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Arg Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130 135 140		
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145 150 155 160		
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165 170 175		
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180 185 190		
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195 200 205		
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210 215 220		

Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 163

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-072 G16D, K88D, I94R, V269T序列

<400> 163

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu

145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
290	295	300	

His His

305

<210> 164

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-073 S18D, K88D, I94R, V269T序列

<400> 164

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			
	50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val			
65	70	75	80

Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85				90				95			
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
				100				105				110			
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
				115				120				125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
				130				135				140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145				150				155				160			
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165				170				175			
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
				180				185				190			
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
				195				200				205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
				210				215				220			
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225				230				235				240			
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250				255			
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Thr	Val	Val	Asp
				260				265				270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
				275				280				285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
290				295				300							
His His															
305															
<210> 165															
<211> 306															
<212> PRT															
<213> 未知															
<220>															
<223> 对“未知”的描述:															
TC3-074 V13A, K88T, I94R, V269T序列															
<400> 165															
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly															

1	5	10	15
Gly Ser Leu Arg	Leu Thr Cys Ala	Ala Ser Gly Arg	Thr Ser Arg Ser
20	25	30	
Tyr Gly Met Gly	Trp Phe Arg Gln	Ala Pro Gly Lys	Glu Arg Glu Phe
35	40	45	
Val Ser Gly Ile	Ser Trp Arg Gly	Asp Ser Thr Gly	Tyr Ala Asp Ser
50	55	60	
Val Lys Gly Arg	Phe Thr Ile Ser	Arg Asp Asn Ala	Lys Asn Thr Val
65	70	75	80
Asp Leu Gln Met	Asn Ser Leu Thr	Pro Glu Asp Thr	Ala Arg Tyr Tyr
85	90	95	
Cys Ala Ala Ala	Ala Gly Ser Ala	Trp Tyr Gly Thr	Leu Tyr Glu Tyr
100	105	110	
Asp Tyr Trp Gly	Gln Gly Thr Gln	Val Thr Val Ser	Ser Gly Gly Gly
115	120	125	
Gly Ser Gly Gly	Gly Gly Ser Gly	Gly Gly Ser Val	Thr Gly Gly
130	135	140	
Met Ala Ser Lys	Trp Asp Gln Lys	Gly Met Asp Ile	Ala Tyr Glu Glu
145	150	155	160
Ala Leu Leu Gly	Tyr Lys Glu Gly	Gly Val Pro Ile	Gly Gly Cys Leu
165	170	175	
Ile Asn Asn Lys	Asp Gly Ser Val	Leu Gly Arg Gly	His Asn Met Arg
180	185	190	
Phe Gln Lys Gly	Ser Ala Thr Leu	His Gly Glu Ile	Ser Thr Leu Glu
195	200	205	
Asn Cys Gly Arg	Leu Glu Gly Lys	Val Tyr Lys Asp	Thr Thr Leu Tyr
210	215	220	
Thr Thr Leu Ser	Pro Cys Asp Met	Cys Thr Gly Ala	Ile Ile Met Tyr
225	230	235	240
Gly Ile Pro Arg	Cys Val Ile Gly	Glu Asn Val Asn	Phe Lys Ser Lys
245	250	255	
Gly Glu Lys Tyr	Leu Gln Thr Arg	Gly His Glu Val	Thr Val Val Asp
260	265	270	
Asp Glu Arg Cys	Lys Lys Leu Met	Lys Gln Phe Ile	Asp Glu Arg Pro
275	280	285	
Gln Asp Trp Phe	Glu Asp Ile Gly	Glu Gly Ser Ser	His His His His
290	295	300	
His His			
305			

<210> 166

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-075 G16D, K88T, I94R, V269T序列

<400> 166

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Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp
1           5           10           15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
          20           25           30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
          35           40           45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
          50           55           60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65           70           75           80
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Arg Tyr Tyr
          85           90           95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
          130          135          140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145          150          155          160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
          165          170          175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
          180          185          190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
          195          200          205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
          210          215          220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
225          230          235          240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys

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				245				250				255					
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Thr	Val	Val	Asp		
				260				265				270					
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro		
				275				280				285					
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His		
				290				295				300					
His	His																
305																	
<210> 167																	
<211> 306																	
<212> PRT																	
<213> 未知																	
<220>																	
<223> 对“未知”的描述:																	
TC3-076 S18D, K88T, I94R, V269T序列																	
<400> 167																	
Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly		
				5				10				15					
Gly	Asp	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser		
				20				25				30					
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe		
				35				40				45					
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser		
				50				55				60					
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val		
				70				75				80					
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr		
				85				90				95					
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr		
				100				105				110					
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly		
				115				120				125					
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly		
				130				135				140					
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu		
				145				150				155				160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu		
				165				170				175					

Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240
 Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 168

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-077 V13A, K88D, I94Q, V269T序列

<400> 168

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 169		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-078 G16D, K88D, I94Q, V269T序列		
<400> 169		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp		
1	5	10
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20	25	30

Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Asp Pro Glu Asp Thr Ala Gln Tyr Tyr		
	85	90
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
	100	105
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
	115	120
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Val Thr Gly Gly		
	130	135
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
	165	170
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
	180	185
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
	195	200
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
	210	215
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
	245	250
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp		
	260	265
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
	275	280
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
	290	295
His His		300
305		
<210> 170		
<211> 306		
<212> PRT		

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-079 S18D, K88D, I94Q, V269T序列

<400> 170

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Gly
1				5					10					15	
Gly	Asp	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Asp	Pro	Glu	Asp	Thr	Ala	Gln	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
		210					215					220			
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230					235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245					250					255	
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Thr	Val	Val	Asp
			260					265						270	

Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
275 280 285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
290 295 300
His His
305
<210> 171
<211> 306
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述:
TC3-080 V13A, K88T, I94Q, V269T序列
<400> 171
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
1 5 10 15
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
20 25 30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
35 40 45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
65 70 75 80
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr
85 90 95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
130 135 140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
145 150 155 160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
165 170 175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
180 185 190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu

195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 172		
<211> 306		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		
TC3-081 G16D, K88T, I94Q, V269T序列		
<400> 172		
Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Asp		
1 5 10 15		
Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser		
20 25 30		
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35 40 45		
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50 55 60		
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65 70 75 80		
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr		
85 90 95		
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100 105 110		
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115 120 125		

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

His His

305

<210> 173

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-082 S18D, K88T, I94Q, V269T序列

<400> 173

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Val Gln Thr Gly			
1	5	10	15
Gly Asp Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser			
	20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe			
	35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser			

50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val		
65	70	75
Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Gln Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly		
115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly		
130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu		
145	150	155
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu		
165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg		
180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu		
195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr		
210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr		
225	230	235
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys		
245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Thr Val Val Asp		
260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro		
275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His		
290	295	300
His His		
305		
<210> 174		
<211> 291		
<212> PRT		
<213> 未知		
<220>		
<223> 对“未知”的描述:		

TC3-084 h7D12v2-CDoem3-H序列

<400> 174

Met	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Thr	Gly
1				5				10					15		
Arg	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Val
65					70				75					80	
Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Val	Thr	Gly
		115					120					125			
Gly	Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu
	130						135				140				
Glu	Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys
145					150					155				160	
Leu	Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met
				165					170					175	
Arg	Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu
			180					185					190		
Glu	Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu
		195					200					205			
Tyr	Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met
	210					215					220				
Tyr	Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser
225					230				235					240	
Lys	Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Val	Val	Val	Val
				245					250					255	
Asp	Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg
			260					265					270		
Pro	Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His
		275					280					285			
His	His	His													

290
 <210> 175
 <211> 291
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-083 h7D12v1-CDoem3-H序列
 <400> 175
 Met Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly
 1 5 10 15
 Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val
 65 70 75 80
 Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Val Thr Gly
 115 120 125
 Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu
 130 135 140
 Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys
 145 150 155 160
 Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met
 165 170 175
 Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu
 180 185 190
 Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu
 195 200 205
 Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met
 210 215 220
 Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser
 225 230 235 240

Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val
 245 250 255
 Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg
 260 265 270
 Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His
 275 280 285
 His His His
 290
 <210> 176
 <211> 291
 <212> PRT
 <213> 未知
 <220>
 <223> 对“未知”的描述：
 TC3-085 h7D12v3-CDoem3-H序列
 <400> 176
 Met Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15
 Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
 65 70 75 80
 Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Val Thr Gly
 115 120 125
 Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu
 130 135 140
 Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys
 145 150 155 160
 Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met
 165 170 175
 Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu

180	185	190
Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu		
195	200	205
Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met		
210	215	220
Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser		
225	230	235
Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val		
245	250	255
Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg		
260	265	270
Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His		
275	280	285
His His His		
290		

<210> 177

<211> 291

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-086 h7D12v4-CDoem3-H序列

<400> 177

Met Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly		
1	5	10
Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser Arg Ser		
20	25	30
Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe		
35	40	45
Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser		
50	55	60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu		
65	70	75
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr		
85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Val Thr Gly		
115	120	125

Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu
 130 135 140
 Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys
 145 150 155 160
 Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met
 165 170 175
 Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu
 180 185 190
 Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu
 195 200 205
 Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met
 210 215 220
 Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser
 225 230 235 240
 Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val Val Val Val
 245 250 255
 Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg
 260 265 270
 Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His
 275 280 285
 His His His
 290

<210> 178

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-087 S12V, T15V, K88R, P89A, I94V, V268A序列

<400> 178

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Val Val Gln Val Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val

65	70	75	80
Asp Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr			
	85	90	95
Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr			
	100	105	110
Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly			
	115	120	125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly			
	130	135	140
Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu			
145	150	155	160
Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu			
	165	170	175
Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg			
	180	185	190
Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu			
	195	200	205
Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr			
	210	215	220
Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr			
225	230	235	240
Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys			
	245	250	255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Thr Val Val Asp			
	260	265	270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro			
	275	280	285
Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His			
	290	295	300
His His			
305			
<210> 179			
<211> 306			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:			
TC3-088 S12V, T15V, K88R, P89A, I94V, Y224H, V268A序列			
<400> 179			

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Val	Gly
1			5					10					15		
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
		50				55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
				85					90					95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120						125		
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
		130					135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170					175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200						205		
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	His
		210					215				220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
			245					250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
			260					265					270		
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
		275					280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His
	290					295					300				
His	His														

305

<210> 180

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-089 V13A, K88T, I94R, V268A, V269T序列

<400> 180

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Ala	Gln	Thr	Gly	1	5	10	15
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser	20	25	30	
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	35	40	45	
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser	50	55	60	
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	65	70	75	80
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr	85	90	95	
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr	100	105	110	
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	115	120	125	
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly	130	135	140	
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu	145	150	155	160
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu	165	170	175	
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg	180	185	190	
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu	195	200	205	
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr	210	215	220	
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr	225	230	235	240

Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
 245 250 255
 Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Thr Val Val Asp
 260 265 270
 Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
 275 280 285
 Gln Asp Trp Phe Glu Asp Ile Gly Glu Gly Ser Ser His His His His
 290 295 300

His His

305

<210> 181

<211> 306

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC3-090 V13A, K88T, I94R, Y224H, V268A序列

<400> 181

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Ser Ala Gln Thr Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Thr Pro Glu Asp Thr Ala Arg Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu

165								170				175					
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg		
180								185				190					
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu		
195								200				205					
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	His		
210								215				220					
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr		
225								230				235				240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys		
245								250				255					
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp		
260								265				270					
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro		
275								280				285					
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu	Gly	Ser	Ser	His	His	His	His		
290								295				300					

His His

305

⟨210⟩ 182

<211> 297

<212> PRT

〈213〉 未知

 $\langle 220 \rangle$

〈223〉 对“未知”的描述:

TC4 44 (S12V, T15V, K88R, P89A, I94V, V268A) 序列

<400> 182

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Val	Gly
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
				85					90					95	

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

<210> 183

<211> 297

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC4_50 (V13A, K88T, I94R, V268A) 序列

<400> 183

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Ala	Gln	Thr	Gly
1	5			10			15								
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
20					25					30					
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe

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

<210> 184

<211> 297

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC4_51 (G16D, K88T, I94R, V268A) 序列

<400> 184

Met	Gln	Val	Lys	Leu	Glu	Glu	Ser	Gly	Gly	Gly	Ser	Val	Gln	Thr	Asp
1				5					10					15	
Gly	Ser	Leu	Arg	Leu	Thr	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Ser	Arg	Ser
			20					25					30		
Tyr	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe
		35					40					45			
Val	Ser	Gly	Ile	Ser	Trp	Arg	Gly	Asp	Ser	Thr	Gly	Tyr	Ala	Asp	Ser
	50					55					60				
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val
65					70				75					80	
Asp	Leu	Gln	Met	Asn	Ser	Leu	Thr	Pro	Glu	Asp	Thr	Ala	Arg	Tyr	Tyr
				85					90				95		
Cys	Ala	Ala	Ala	Ala	Gly	Ser	Ala	Trp	Tyr	Gly	Thr	Leu	Tyr	Glu	Tyr
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly
		115					120					125			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Val	Thr	Gly	Gly
	130						135					140			
Met	Ala	Ser	Lys	Trp	Asp	Gln	Lys	Gly	Met	Asp	Ile	Ala	Tyr	Glu	Glu
145					150				155					160	
Ala	Leu	Leu	Gly	Tyr	Lys	Glu	Gly	Gly	Val	Pro	Ile	Gly	Gly	Cys	Leu
				165					170				175		
Ile	Asn	Asn	Lys	Asp	Gly	Ser	Val	Leu	Gly	Arg	Gly	His	Asn	Met	Arg
			180					185					190		
Phe	Gln	Lys	Gly	Ser	Ala	Thr	Leu	His	Gly	Glu	Ile	Ser	Thr	Leu	Glu
		195					200					205			
Asn	Cys	Gly	Arg	Leu	Glu	Gly	Lys	Val	Tyr	Lys	Asp	Thr	Thr	Leu	Tyr
	210					215					220				
Thr	Thr	Leu	Ser	Pro	Cys	Asp	Met	Cys	Thr	Gly	Ala	Ile	Ile	Met	Tyr
225					230				235					240	
Gly	Ile	Pro	Arg	Cys	Val	Ile	Gly	Glu	Asn	Val	Asn	Phe	Lys	Ser	Lys
				245				250					255		
Gly	Glu	Lys	Tyr	Leu	Gln	Thr	Arg	Gly	His	Glu	Ala	Val	Val	Val	Asp
			260				265					270			
Asp	Glu	Arg	Cys	Lys	Lys	Leu	Met	Lys	Gln	Phe	Ile	Asp	Glu	Arg	Pro
	275						280					285			
Gln	Asp	Trp	Phe	Glu	Asp	Ile	Gly	Glu							

290 295

<210> 185

<211> 297

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

TC4_87 (S12V, T15V, K88R, P89A, I94V, V268A, V269T)序列

<400> 185

Met Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Val Val Gln Val Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Thr Cys Ala Ala Ser Gly Arg Thr Ser Arg Ser
 20 25 30
 Tyr Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
 35 40 45
 Val Ser Gly Ile Ser Trp Arg Gly Asp Ser Thr Gly Tyr Ala Asp Ser
 50 55 60
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
 65 70 75 80
 Asp Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Ala Ala Ala Gly Ser Ala Trp Tyr Gly Thr Leu Tyr Glu Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Val Thr Gly Gly
 130 135 140
 Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile Ala Tyr Glu Glu
 145 150 155 160
 Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile Gly Gly Cys Leu
 165 170 175
 Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly His Asn Met Arg
 180 185 190
 Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile Ser Thr Leu Glu
 195 200 205
 Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp Thr Thr Leu Tyr
 210 215 220
 Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala Ile Ile Met Tyr
 225 230 235 240

Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn Phe Lys Ser Lys
245 250 255
Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala Thr Val Val Asp
260 265 270
Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile Asp Glu Arg Pro
275 280 285
Gln Asp Trp Phe Glu Asp Ile Gly Glu
290 295
<210> 186
<211> 158
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述:具有甲硫氨酸的酵母菌胞嘧啶脱氨酶的蛋白序列
<400> 186
Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
1 5 10 15
Ile Ala Tyr Glu Glu Ala Ala Leu Gly Tyr Lys Glu Gly Gly Val Pro
20 25 30
Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
35 40 45
Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
50 55 60
Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
65 70 75 80
Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
85 90 95
Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Val Gly Glu Asn Val
100 105 110
Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
115 120 125
Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Ile Met Lys Gln Phe
130 135 140
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155
<210> 187
<211> 158
<212> PRT
<213> 未知

<220>

<223> 对“未知”的描述:具有甲硫氨酸的酵母菌胞嘧啶脱氨酶的蛋白序列

<400> 187

```

Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
1           5           10           15
Ile Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro
           20           25           30
Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
           35           40           45
Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
           50           55           60
Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
65           70           75           80
Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
           85           90           95
Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val
           100          105          110
Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
           115          120          125
Val Val Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe
           130          135          140
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145          150          155

```

<210> 188

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 人工序列的描述:合成肽

<400> 188

```

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1           5           10           15

```

<210> 189

<211> 157

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:没有甲硫氨酸的Cdoem V128A的蛋白序列

<400> 189

Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile
 1 5 10 15
 Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile
 20 25 30
 Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly
 35 40 45
 His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile
 50 55 60
 Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp
 65 70 75 80
 Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala
 85 90 95
 Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn
 100 105 110
 Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala
 115 120 125
 Val Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile
 130 135 140
 Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
 145 150 155

<210> 190

<211> 158

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:具有甲硫氨酸的蛋白序列Cdoem V129A

<400> 190

Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
 1 5 10 15
 Ile Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro
 20 25 30
 Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
 35 40 45
 Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
 50 55 60
 Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
 65 70 75 80
 Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
 85 90 95

Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val
100 105 110
Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
115 120 125
Ala Val Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe
130 135 140
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155
<210> 191
<211> 157
<212> PRT
<213> 未知
<220>
<223> 对“未知”的描述:没有甲硫氨酸的Cdoem V129T的蛋白序列
<400> 191
Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile
1 5 10 15
Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile
20 25 30
Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly
35 40 45
His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile
50 55 60
Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp
65 70 75 80
Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala
85 90 95
Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn
100 105 110
Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Val
115 120 125
Thr Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile
130 135 140
Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145 150 155
<210> 192
<211> 158
<212> PRT
<213> 未知

<220>

<223> 对“未知”的描述:蛋白序列Cdoem V130T WITH methionine

<400> 192

```

Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp
1           5           10           15
Ile Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro
           20           25           30
Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg
           35           40           45
Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu
           50           55           60
Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys
65           70           75           80
Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly
           85           90           95
Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val
           100          105          110
Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu
           115          120          125
Val Thr Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe
           130          135          140
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu
145          150          155

```

<210> 193

<211> 157

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:没有甲硫氨酸的Cdoem V128A, V129T的蛋白序列

<400> 193

```

Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp Ile
1           5           10           15
Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro Ile
           20           25           30
Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg Gly
           35           40           45
His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu Ile
           50           55           60
Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys Asp

```

65	70	75	80
Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly Ala			
	85	90	95
Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val Asn			
	100	105	110
Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu Ala			
	115	120	125
Thr Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe Ile			
	130	135	140
Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu			
145	150	155	
<210> 194			
<211> 158			
<212> PRT			
<213> 未知			
<220>			
<223> 对“未知”的描述:具有甲硫氨酸的Cdoem V129A, V130T的蛋白序列			
<400> 194			
Met Val Thr Gly Gly Met Ala Ser Lys Trp Asp Gln Lys Gly Met Asp			
1	5	10	15
Ile Ala Tyr Glu Glu Ala Leu Leu Gly Tyr Lys Glu Gly Gly Val Pro			
	20	25	30
Ile Gly Gly Cys Leu Ile Asn Asn Lys Asp Gly Ser Val Leu Gly Arg			
	35	40	45
Gly His Asn Met Arg Phe Gln Lys Gly Ser Ala Thr Leu His Gly Glu			
	50	55	60
Ile Ser Thr Leu Glu Asn Cys Gly Arg Leu Glu Gly Lys Val Tyr Lys			
65	70	75	80
Asp Thr Thr Leu Tyr Thr Thr Leu Ser Pro Cys Asp Met Cys Thr Gly			
	85	90	95
Ala Ile Ile Met Tyr Gly Ile Pro Arg Cys Val Ile Gly Glu Asn Val			
	100	105	110
Asn Phe Lys Ser Lys Gly Glu Lys Tyr Leu Gln Thr Arg Gly His Glu			
	115	120	125
Ala Thr Val Val Asp Asp Glu Arg Cys Lys Lys Leu Met Lys Gln Phe			
	130	135	140
Ile Asp Glu Arg Pro Gln Asp Trp Phe Glu Asp Ile Gly Glu			
145	150	155	
<210> 195			

<211> 897

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码TC4_44 (S12V, T15V, K88R, P89A, I94V, V268A)的多核苷酸序列

<400> 195

```
atgcaggtga aactggaaga aagcggtagt ggtgttggtc aggttggtgg tagcctgcgt 60
ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgttagc ggtattagct ggctgggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgccaa aaataccgtt 240
gacctgcaga tgaatagcct gcgtgcagaa gataccgcag tttattattg tgcagcagca 300
gccggtagcg cctggtagtg caccctgtat gaatatgatt attgggttca gggcaccag 360
gttaccgtta gctcaggtgg tggtagcagc ggtggcgggt gttcaggtgg cggaggtagc 420
gttaccggtg gtatggcaag caaatgggat cagaaaggta tggatattgc atatgaagaa 480
gcactgctgg gttataaaga aggtggcggt ccgattgggt gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cggtcataat atgcgctttc agaaaggcag cgcaaccctg 600
catggtgaaa ttagcaccct ggaaaattgt ggtcgtctgg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccggtg gatattgtga ccggtgccat tattatgtat 720
ggtattccgc gttgtgtgat tggcgaaaac gttacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtgggtcatga agcagttgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga ataataa 897
```

<210> 196

<211> 897

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码TC4_50 (V13A, K88T, I94R, V268A)的多核苷酸序列

<400> 196

```
atgcaggtga aactggaaga aagcggtagt ggtagcgcac agaccggtgg tagcctgcgt 60
ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgttagc ggtattagct ggctgggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgccaa aaataccgtt 240
gacctgcaga tgaatagcct gaccccgga gataccgcac gttattattg tgcagcagca 300
gccggtagcg cctggtagtg caccctgtat gaatatgatt attgggttca gggcaccag 360
gttaccgtta gctcaggtgg tggtagcagc ggtggcgggt gttcaggtgg cggaggtagc 420
gttaccggtg gtatggcaag caaatgggat cagaaaggta tggatattgc atatgaagaa 480
gcactgctgg gttataaaga aggtggcggt ccgattgggt gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cggtcataat atgcgctttc agaaaggcag cgcaaccctg 600
```

catggtgaaa ttagcaccct ggaaaattgt ggtcgtcttg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccgtgt gatatgtgta ccggtgccat tattatgtat 720
ggtattccgc gttgtgtgat tggcgaaaac gttacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtggtcatga agcagttgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga ataataa 897

<210> 197

<211> 897

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码TC4_51 (G16D, K88T, I94R, V268A)的多核苷酸序列

<400> 197

atgcaggtag aactggaaga aagcggtagt ggtagcgttc agaccgatgg tagcctgcgt 60
ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgtagc ggtattagct ggcgtggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgcaa aaataccgtt 240
gacctgcaga tgaatagcct gaccccgaa gataccgcac gttattattg tgcagcagca 300
gccggtagcg cctggtatgg caccctgtat gaatatgatt attgggttca gggcaccag 360
gttaccgtta gctcaggtag tggtagcagc ggtggcgggt gttcaggtag cgaggttagc 420
gttaccggtg gtatggcaag caaatgggat cagaaagga tggatattgc atatgaagaa 480
gcaactgctg gttataaaga aggtggcgtt ccgattggtg gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cgtcataat atgcgctttc agaaaggcag cgcaaccctg 600
catggtgaaa ttagcaccct ggaaaattgt ggtcgtcttg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccgtgt gatatgtgta ccggtgccat tattatgtat 720
ggtattccgc gttgtgtgat tggcgaaaac gttacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtggtcatga agcagttgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga ataataa 897

<210> 198

<211> 897

<212> DNA

<213> 未知

<220>

<223> 对“未知”的描述:编码TC4_87 (S12V, T15V, K88R, P89A, I94V, V268A, V269T)的多核苷酸序列

<400> 198

atgcaggtag aactggaaga aagcggtagt ggtgttgttc aggttggttg tagcctgcgt 60
ctgacctgtg cagcaagcgg tcgtaccagc cgtagctatg gtatgggttg gtttcgtcag 120
gcaccgggta aagaacgtga atttgtagc ggtattagct ggcgtggtga tagcaccggt 180
tatgcagata gcgttaaagg tcgttttacc attagccgtg ataatgcaa aaataccgtt 240

gacctgcaga tgaatagcct gcgtgcagaa gataccgcag tttattattg tgcagcagca 300
gccggtagcg cctgggtatgg caccctgtat gaatatgatt attgggggtca gggcaccag 360
gttaccgtta gctcagggtg tggtggcagc ggtggcggtg gttcagggtg cggaggtagc 420
gttaccggtg gtatggcaag caaatgggat cagaaaggta tggatattgc atatgaagaa 480
gcactgctgg gttataaaga aggtggcggtt ccgattgggtg gttgtctgat taataacaaa 540
gatggtagcg ttctgggtcg cggtcataat atgcgctttc agaaaggcag cgcaaccctg 600
catggtgaaa ttagcaccct ggaaaattgt ggtcgtctgg aaggtaaagt gtataaagat 660
accaccctgt ataccacact gagcccgtgt gatatgtgta ccggtgccat tattatgtat 720
ggatttccgc gttgtgtgat tggcgaaaac gttaacttta aaagcaaagg cgagaaatat 780
ctgcagaccc gtggtcatga agcaaccgtt gtggatgatg aacgttgcaa aaaactgatg 840
aaacagttta tcgatgaacg tccgcaggat tggtttgaag atattggtga ataataa 897

<210> 199

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

2D3 CDR1序列

<400> 199

Asp Tyr Ala Met Ser

1 5

<210> 200

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

2D3 CDR2序列

<400> 200

Ser Ile Asn Trp Ser Gly Thr His Thr Asp Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 201

<211> 15

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

2D3 CDR3序列

<400> 201

Asn Trp Arg Asp Ala Gly Thr Thr Trp Phe Glu Lys Ser Gly Ser
1 5 10 15

<210> 202

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

5F7 CDR1序列

<400> 202

Ile Asn Thr Met Gly
1 5

<210> 203

<211> 16

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

5F7 CDR2序列

<400> 203

Leu Ile Ser Ser Ile Gly Asp Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 204

<211> 10

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

5F7 CDR3序列

<400> 204

Phe Arg Thr Ala Ala Gln Gly Thr Asp Tyr
1 5 10

<210> 205

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

47D5 CDR1序列

<400> 205

Phe Asn Asp Met Ala

1 5

<210> 206

<211> 16

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

47D5 CDR2序列

<400> 206

Leu Ile Ser Arg Val Gly Val Thr Ser Ser Ala Asp Ser Val Lys Gly

1 5 10 15

<210> 207

<211> 11

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

47D5 CDR3序列

<400> 207

Asp Gln Arg Leu Asp Gly Ser Thr Leu Ala Tyr

1 5 10

<210> 208

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

BCD090-M2 CDR1序列

<400> 208

Met Tyr Thr Met Gly

1 5

<210> 209

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

BCD090-M2 CDR2序列

<400> 209

Ala Asn Arg Gly Arg Gly Leu Ser Pro Asp Ile Ala Asp Ser Val Asn

1 5 10 15

Gly

<210> 210

<211> 18

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

BCD090-M2 CDR3序列

<400> 210

Asp Leu Gln Tyr Gly Ser Ser Trp Pro Gln Arg Ser Ser Ala Glu Tyr

1 5 10 15

Asp Tyr

<210> 211

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

anti-CEA vhh (ABS29544.1) CDR1序列

<400> 211

Pro Tyr Arg Met Ala

1 5

<210> 212

<211> 18

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

anti-CEA vhh (ABS29544.1) CDR2序列

<400> 212

Asp Ile Ser Ser Gly Asp Gly Arg Thr Thr Asn Tyr Ala Asp Phe Ala

1 5 10 15

Lys Gly

<210> 213

<211> 10

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:

抗-CEA vhh (ABS29544.1) CDR3序列

<400> 213

Phe Val Ser Phe Val Gly Ile Ala Arg Ser

1 5 10

<210> 214

<211> 5

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:NbCEA5 CDR1序列

<400> 214

Ser Tyr Trp Met Gly

1 5

<210> 215

<211> 17

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:NbCEA5 CDR2序列

<400> 215

Ala Ile Asn Arg Gly Gly Gly Tyr Thr Val Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 216

<211> 14

<212> PRT

<213> 未知

<220>

<223> 对“未知”的描述:NbCEA5 CDR3序列

<400> 216

Ser Gly Val Leu Gly Gly Leu His Glu Asp Trp Phe Asn Tyr

1 5 10

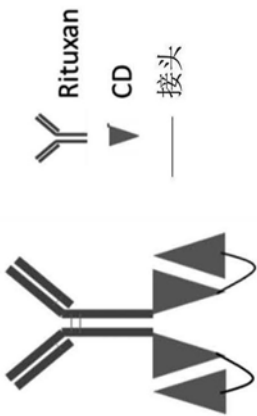


图1A

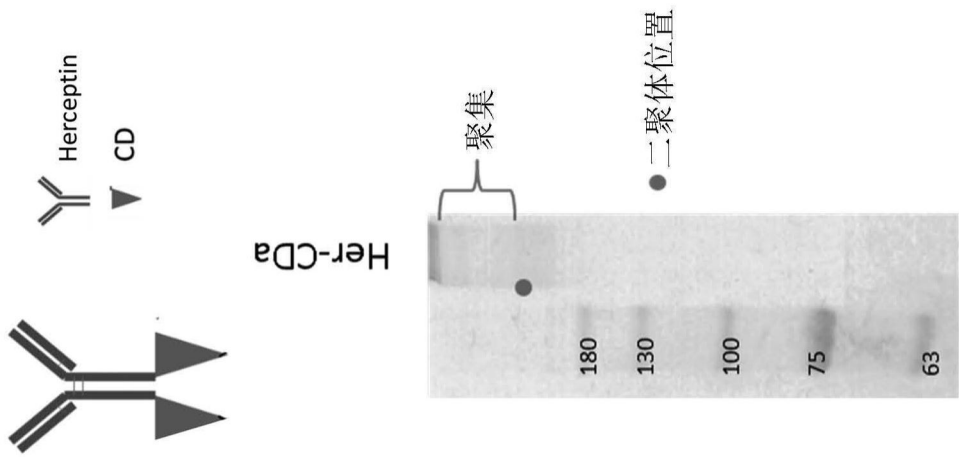


图1B

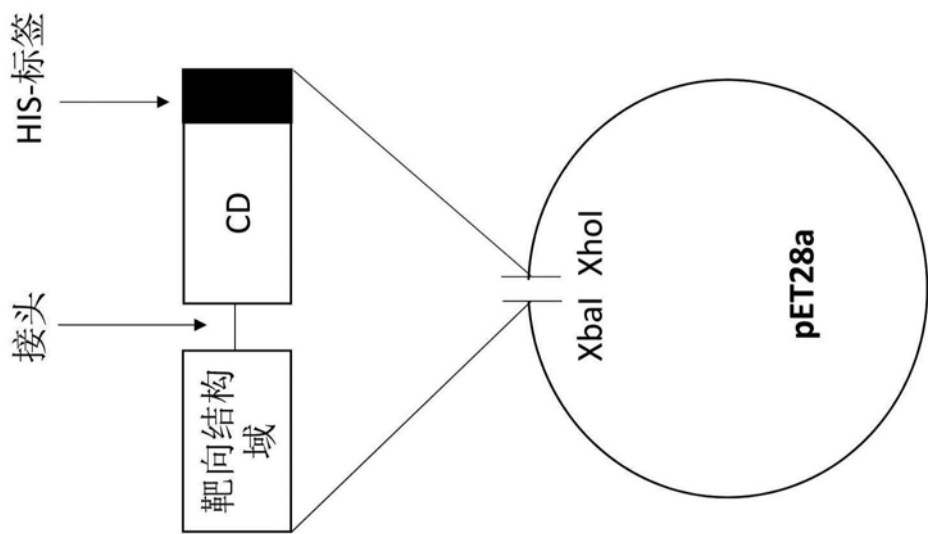


图2A

抗原	靶向结构域	靶向结构域的类型	融合蛋白名称	SEQ ID NO	表达体系	物化表征		5L发酵浓度	CD活性	抗原结合活性
						溶解性/小规模浓度 (µg/mL)	纯度			
VEGFR2	3VGR19	sdAb (VHH)	3VGR19-CD-H	7	SHuffle® T7 express	可溶 / ~19	v	375 mg/L	v	v
	3VGR10		3VGR10-CD-H	86		可溶 / ~6.2	v		v	v
	3VGR17		3VGR17-CD-H	87		可溶 / ~10	v		v	v
	4VGR17		4VGR17-CD-H	9		可溶 / ~19	v	405 mg/L	v	v
	4VGR38		4VGR38-CD-H	11		可溶 / ~20	v		v	v
EGFR	DOM-16-39		DOM-16-39-CD-H	88		可溶 / N/A	v		v	v
	V122		VH122-CD-H	13		可溶 / 9.2	v		v	v
	7D12		7D12-CD-H	15		可溶 / 7.5	v	211 mg/L	v	v
	7D12		7D12-CDDoem3-H	17		可溶 / 8.1	v	259 mg/L	v	v
	7D12		7D12-CDDoem3	19		可溶 / 7.8	v	163 mg/L	v	v
Her2	5F7		5F7-CDDoem3-H	73		可溶 / 39	v		v	v
	47D5		47D5-CDDoem3-H	74		可溶 / 4.5	v		v	v
	2D3		2D3-CDDoem3-H	72		可溶 / 38	v		v	v
CEA	NbCEA5		NbCEA5-CDDoem3-H	80		可溶 / 15.2	v		v	v
	AntiCEA		Anti-CEA-CDDoem3-H	78		可溶 / 11.3	v		v	v
Her3	BCD0090-M2		BCD090-M2-CDDoem3-H	76		可溶 / 29	v		v	v
EGFR	GE10	抗原结合片段	GE10-CD-H	81	T7 express	可溶	聚集, 降解		v	低
	GE11		GE11-CD-H	82		可溶	v		v	无活性
	Inherbin1		Inherbin1-CD-H	83		可溶	二聚体或多聚体		v	无活性
	Inherbin3		Inherbin3-CD-H	84		可溶	聚集, 二聚体或多聚体		v	低
α5整合素	内皮抑素	成熟蛋白	Endo-CD	85		不溶	N/D		v	N/D

图2B

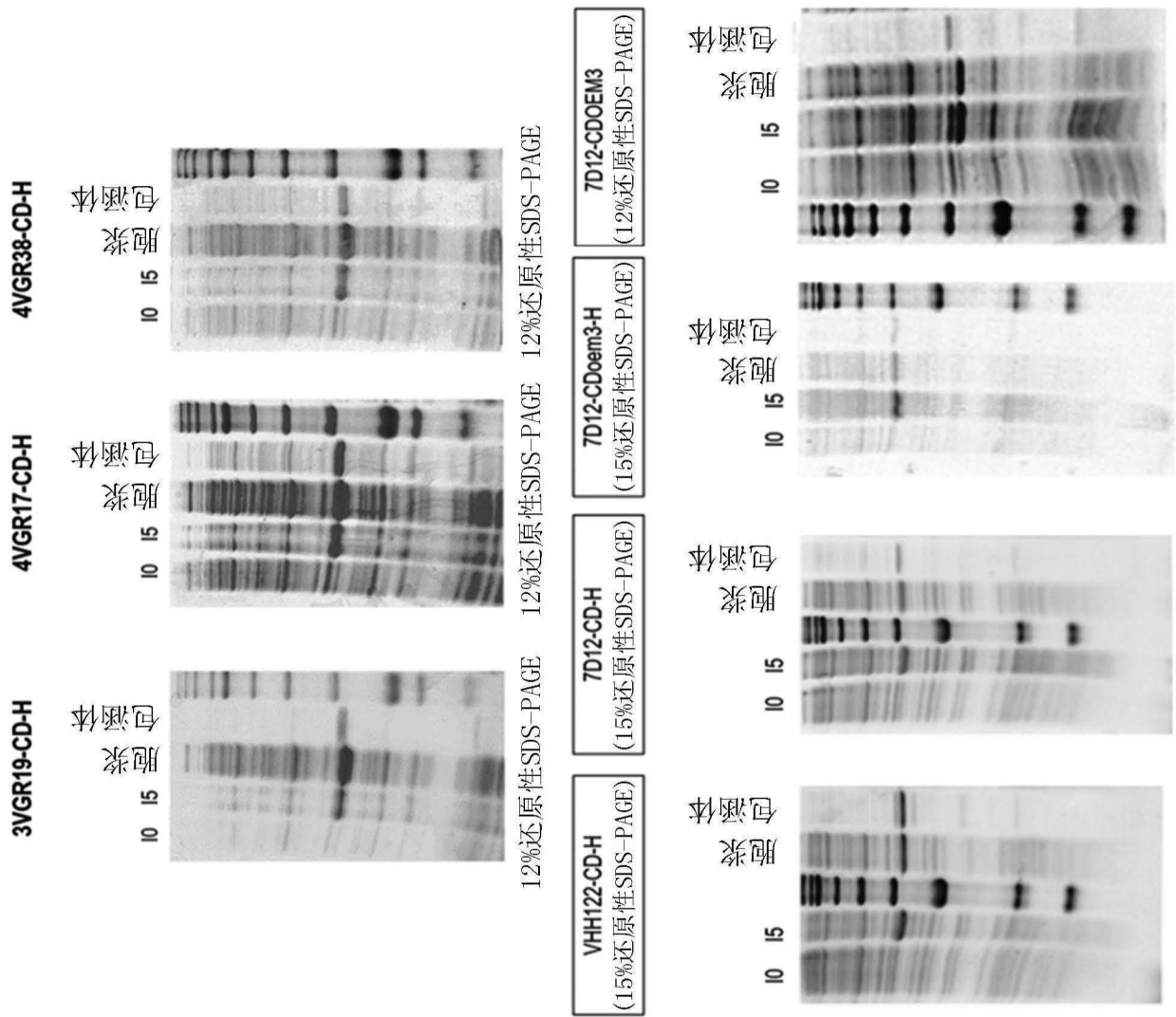


图2C

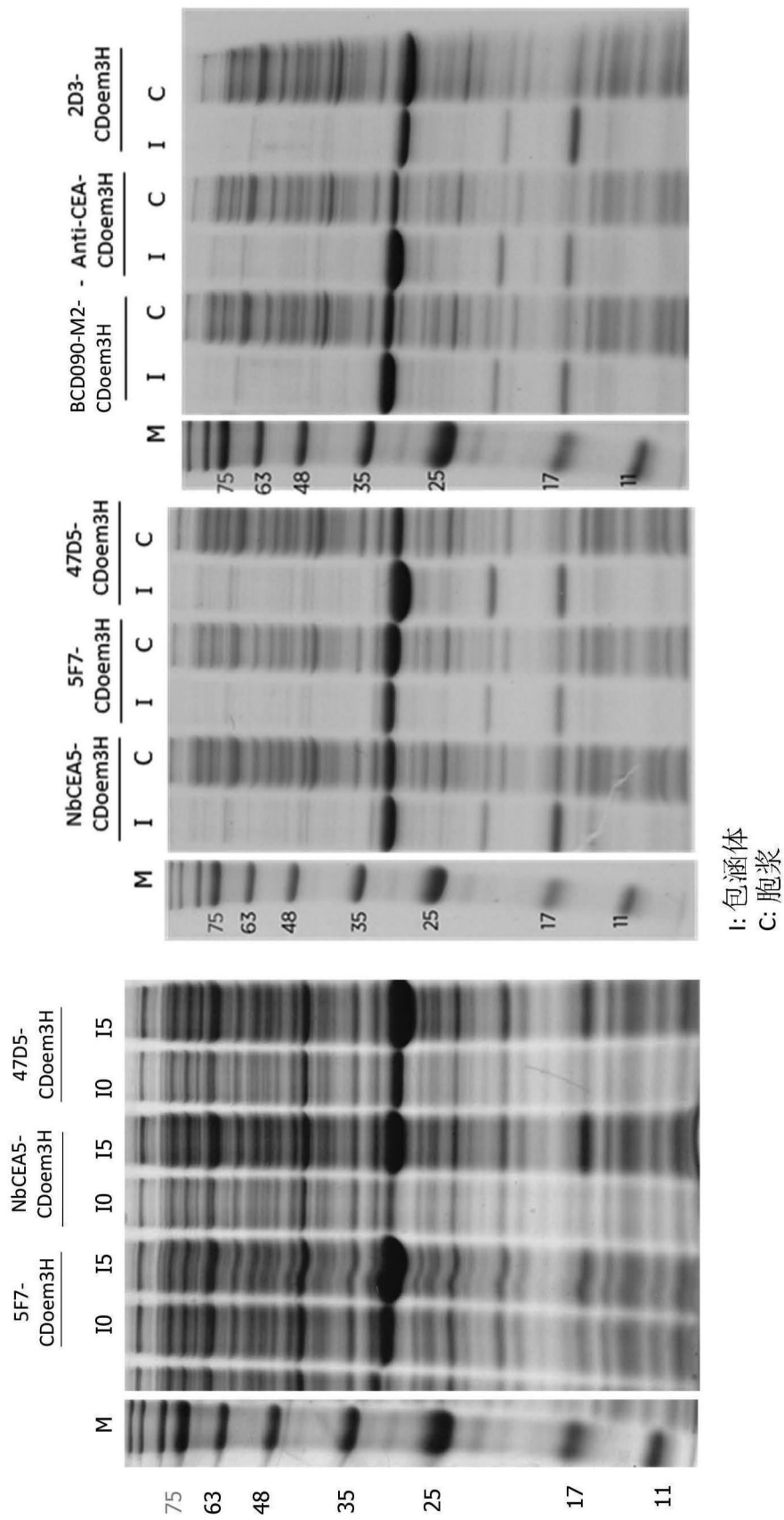
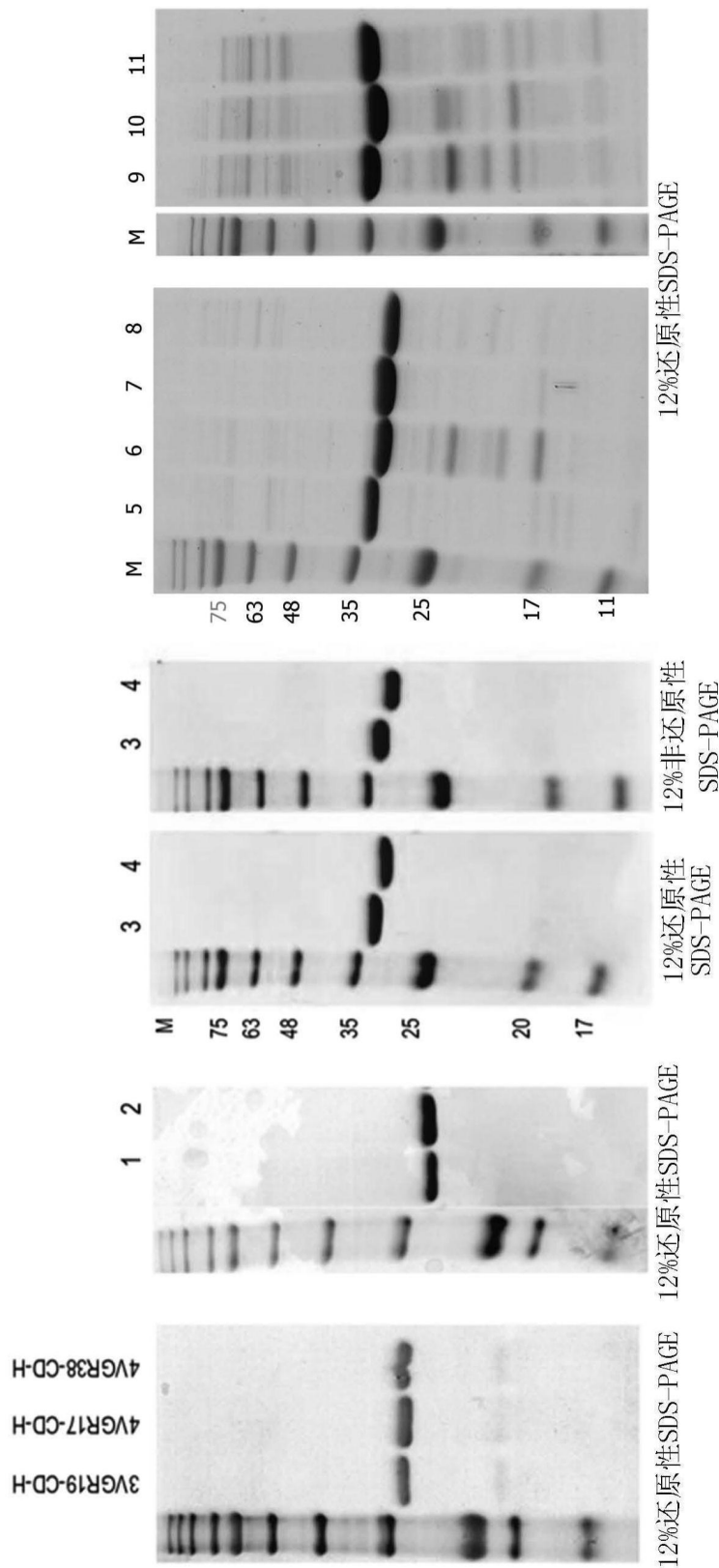


图2D



No.	样品
1	VHH12-CD-H
2	7D12-CD-H
3	7D12-CDom3-H (TC3)
4	7D12-CDom3 (TC4)
5	TC3
6	NbCEA5-CDom3H
7	5F7-CDom3H
8	47D5-CDom3H
9	BCD090-M2-CDom3H
10	2D3-CDom3H
11	AntiCEA-CDom3H

图3

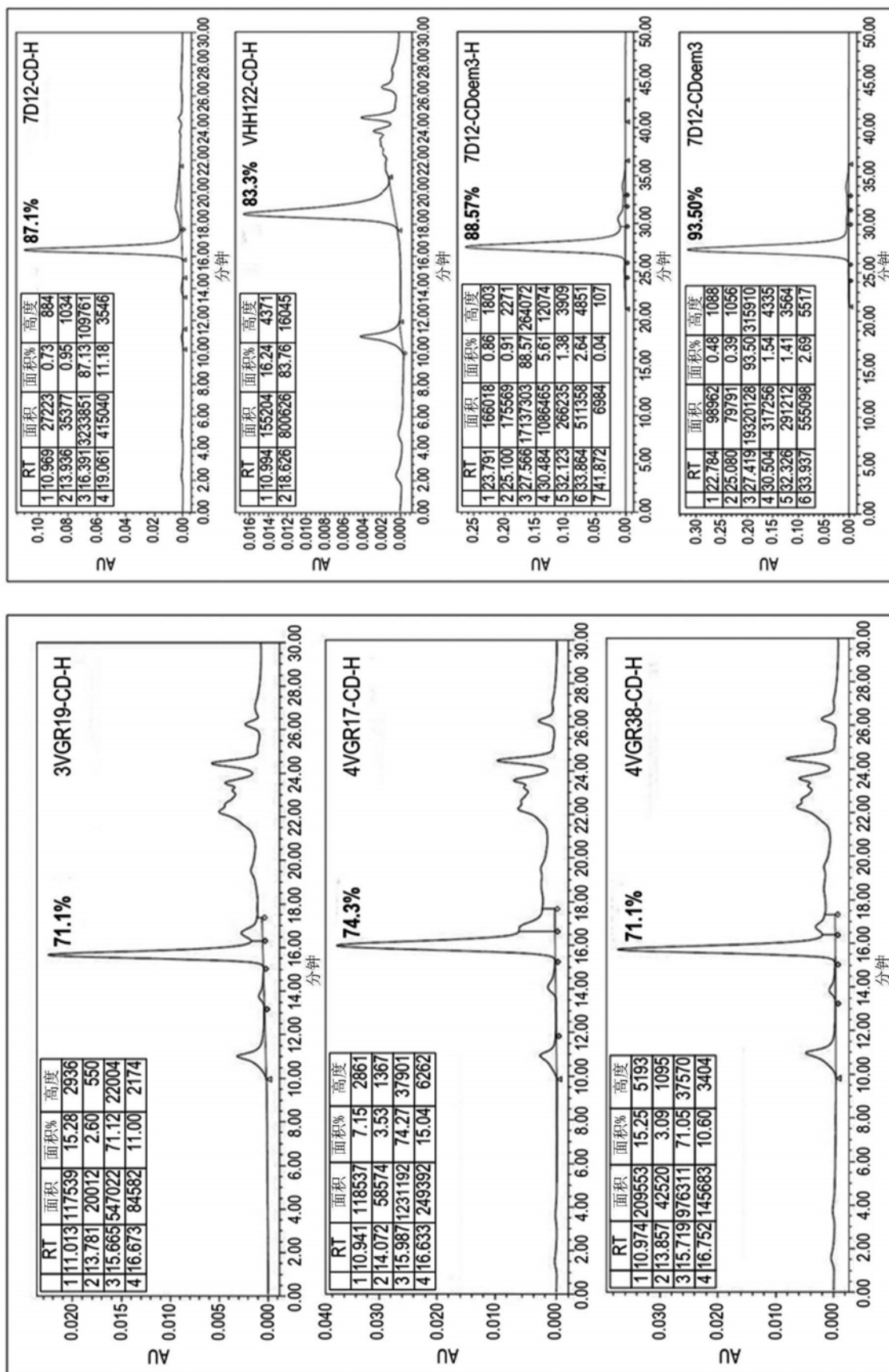


图4A

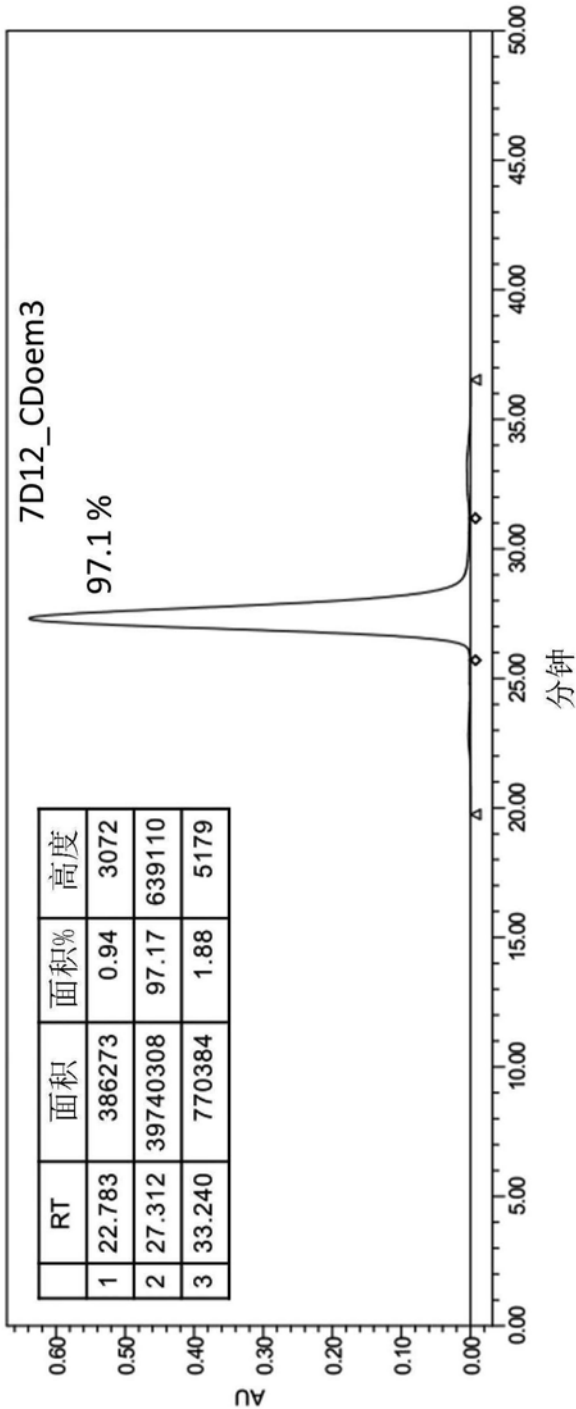


图4B

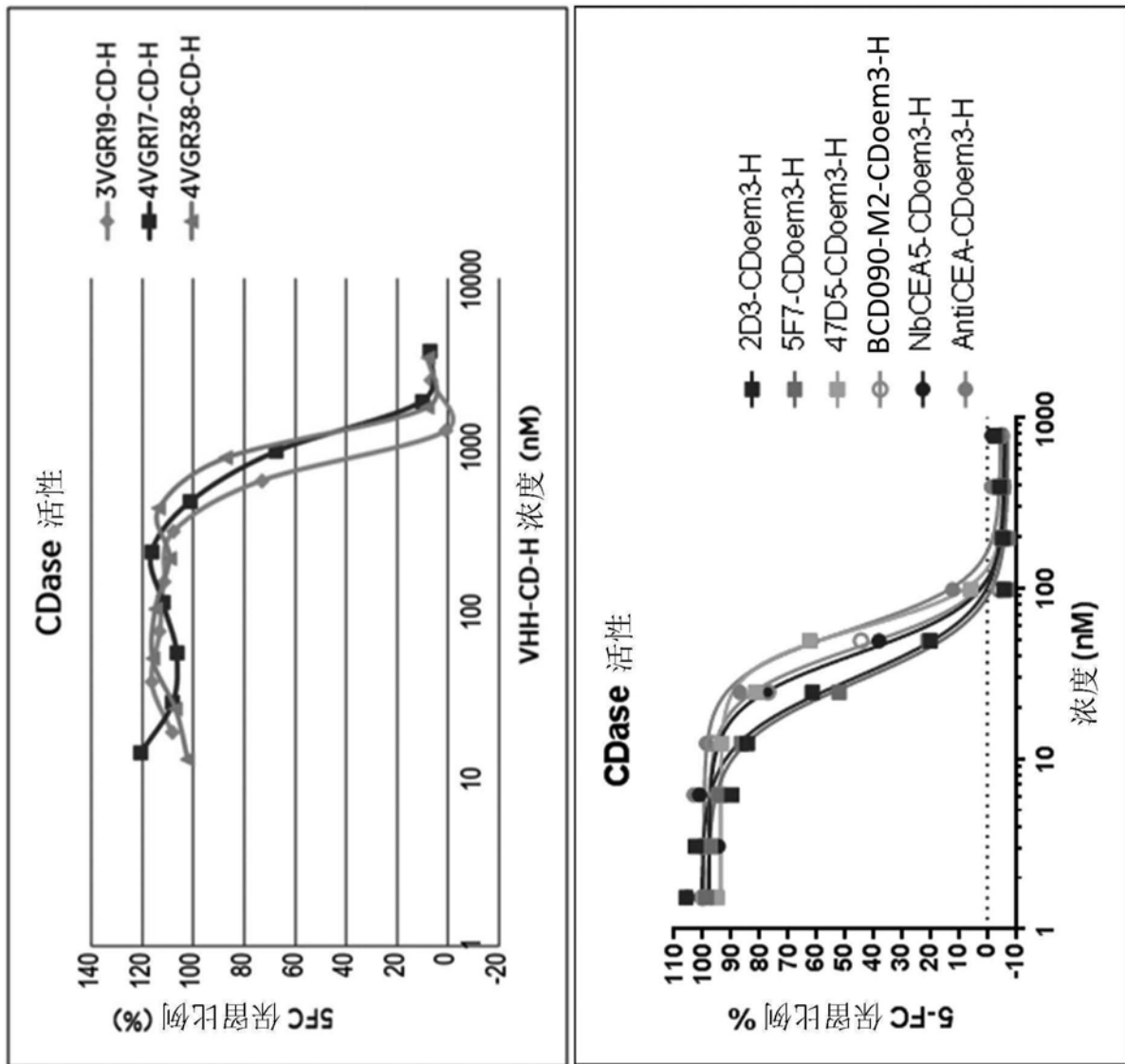


图5A

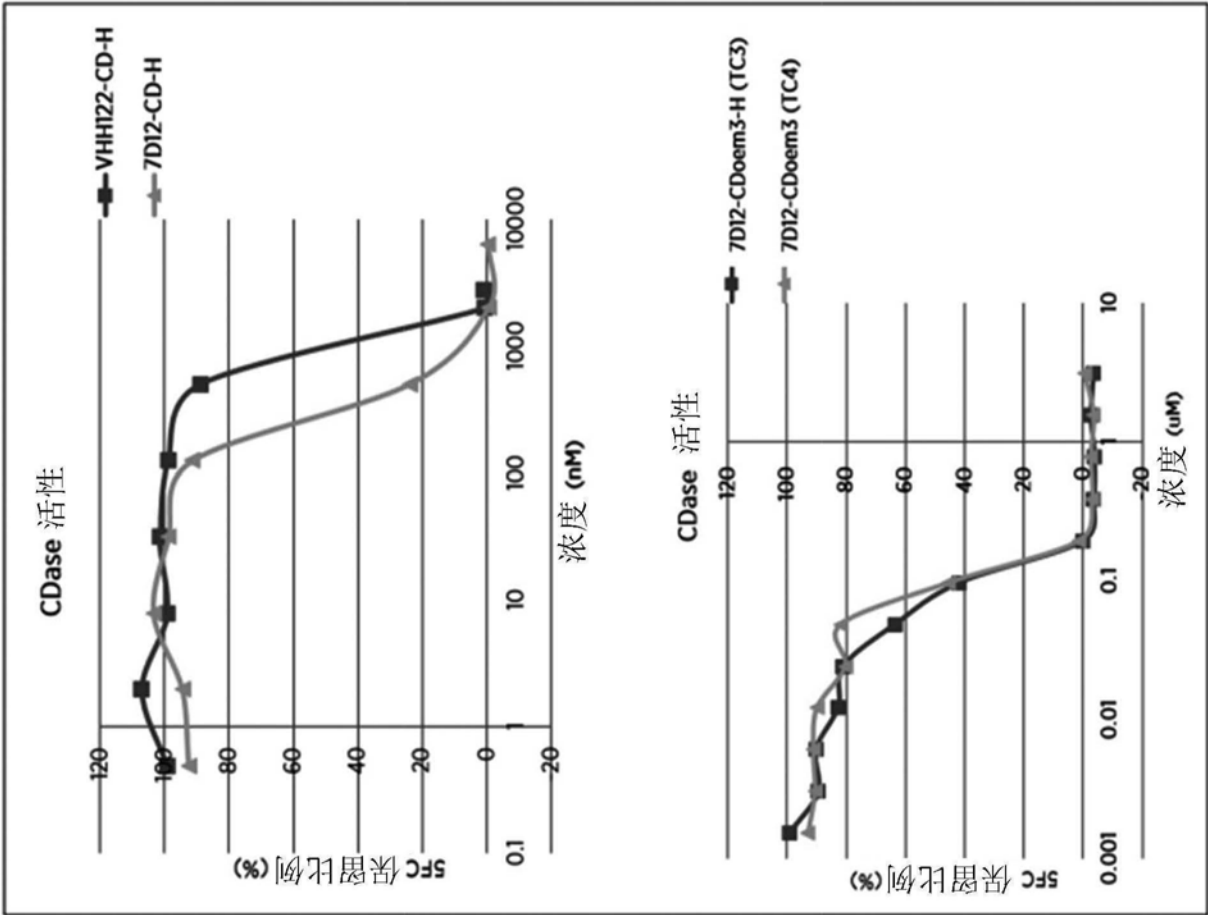


图5B

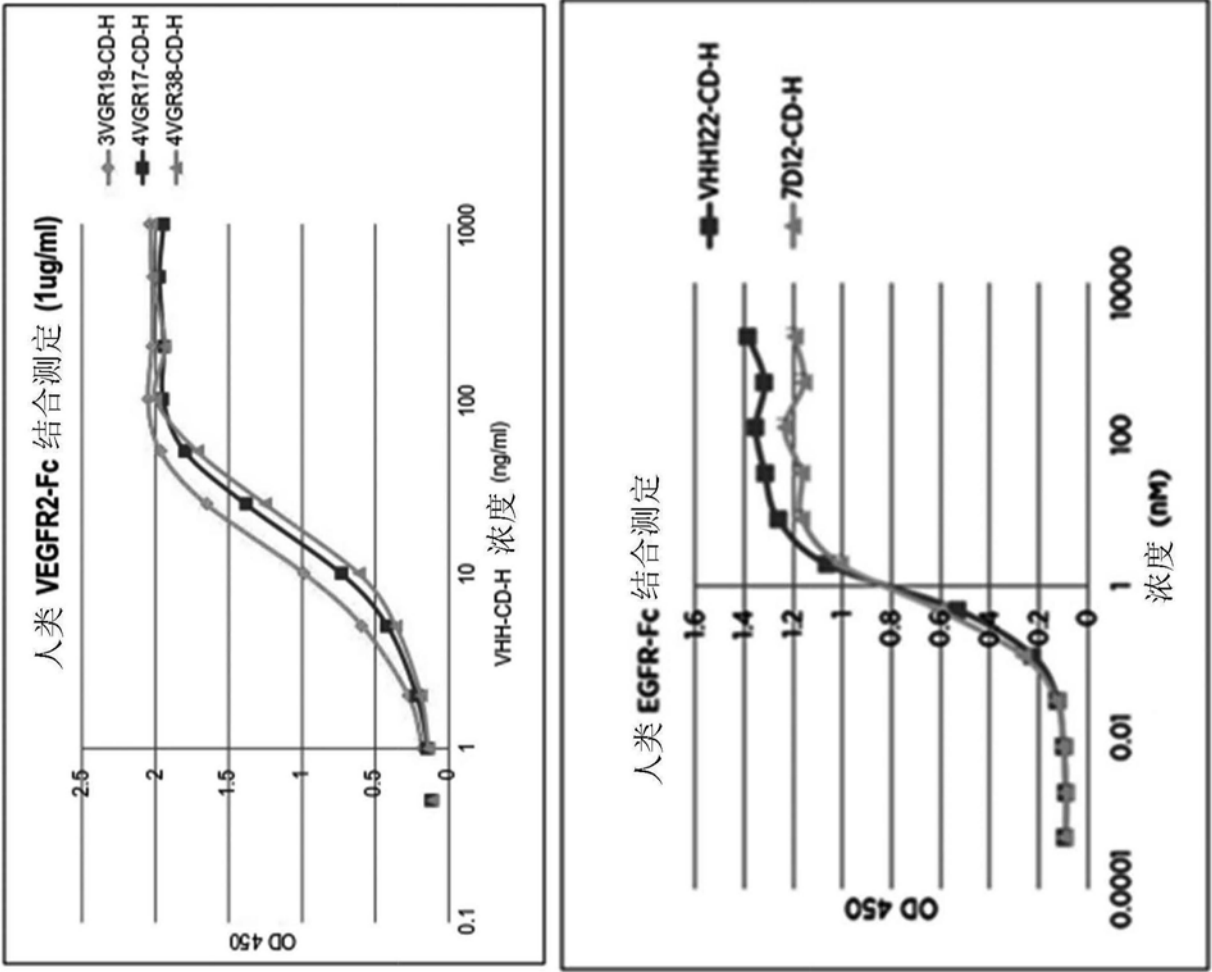


图6A

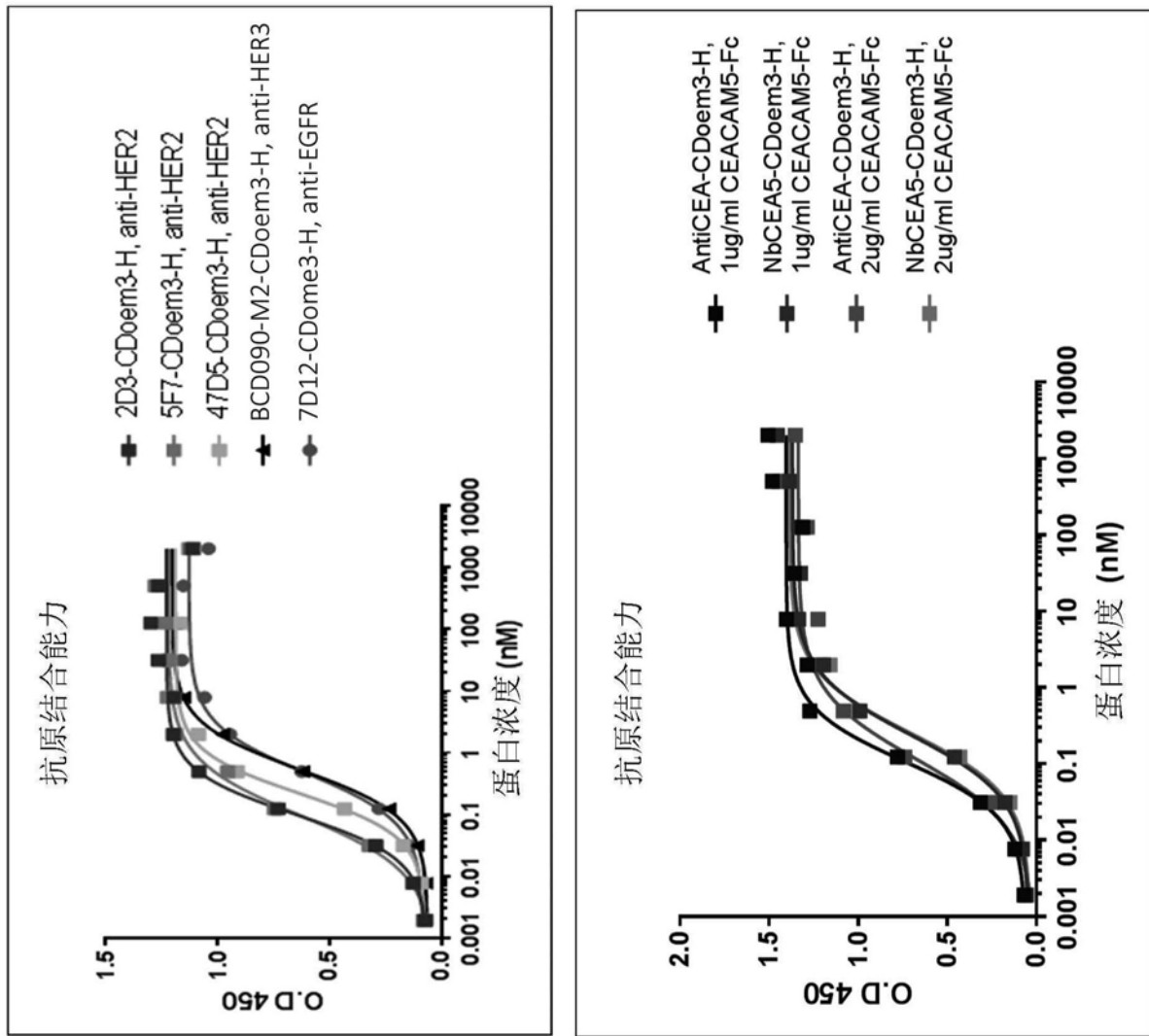


图6B

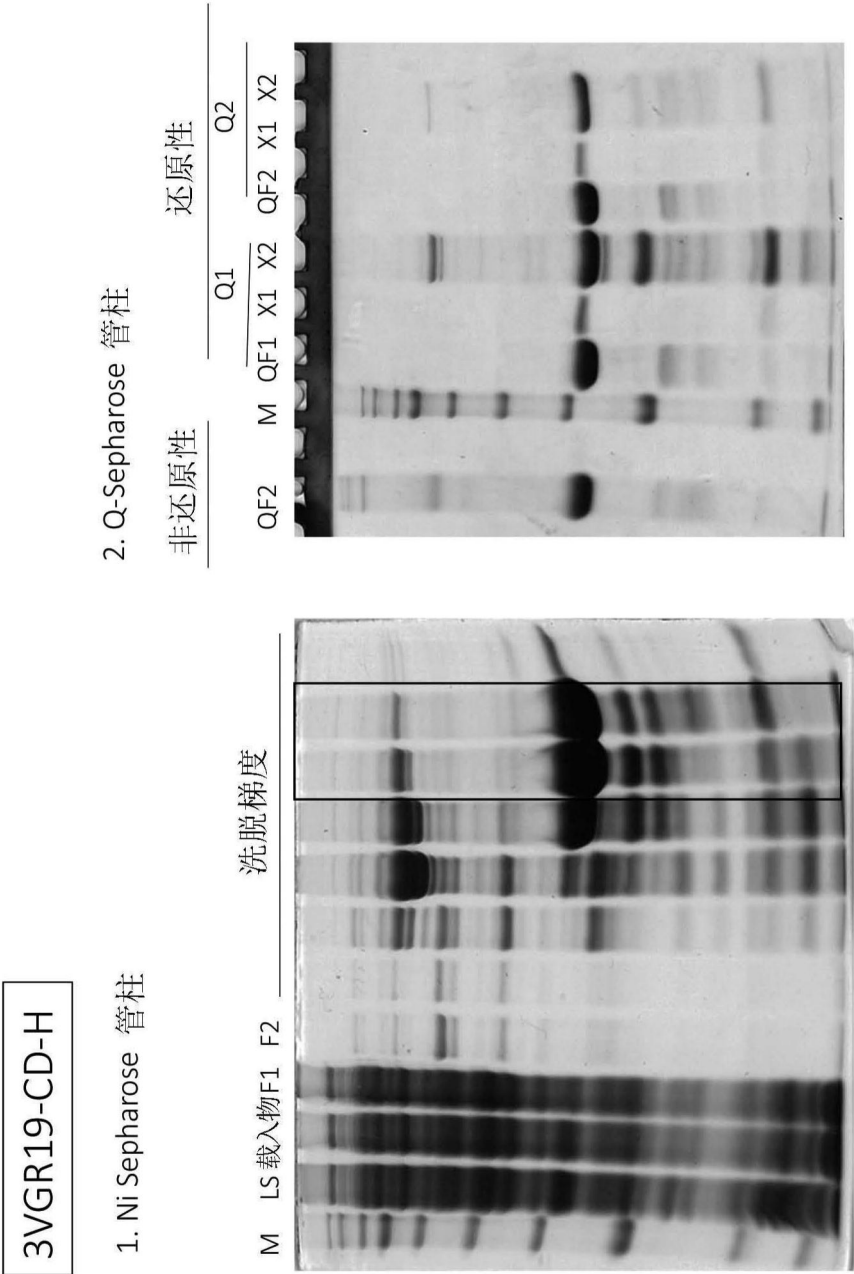


图7A

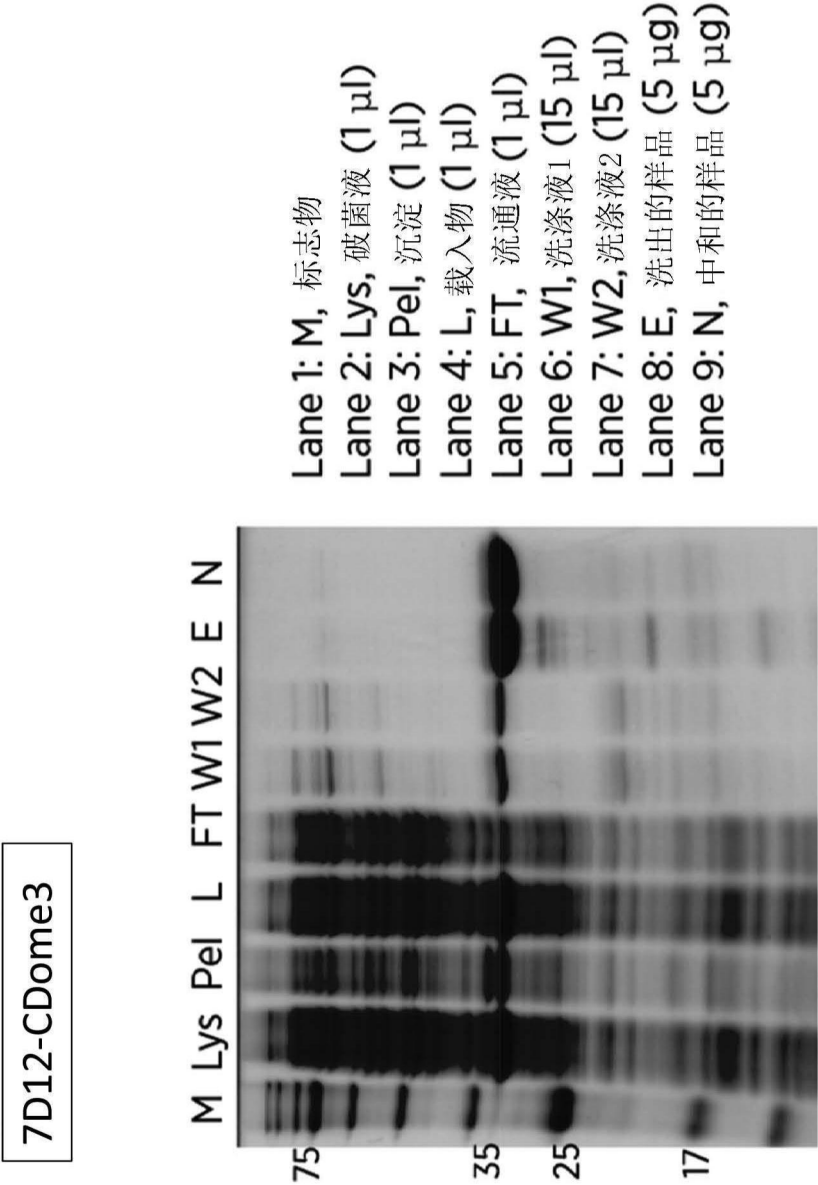


图7B

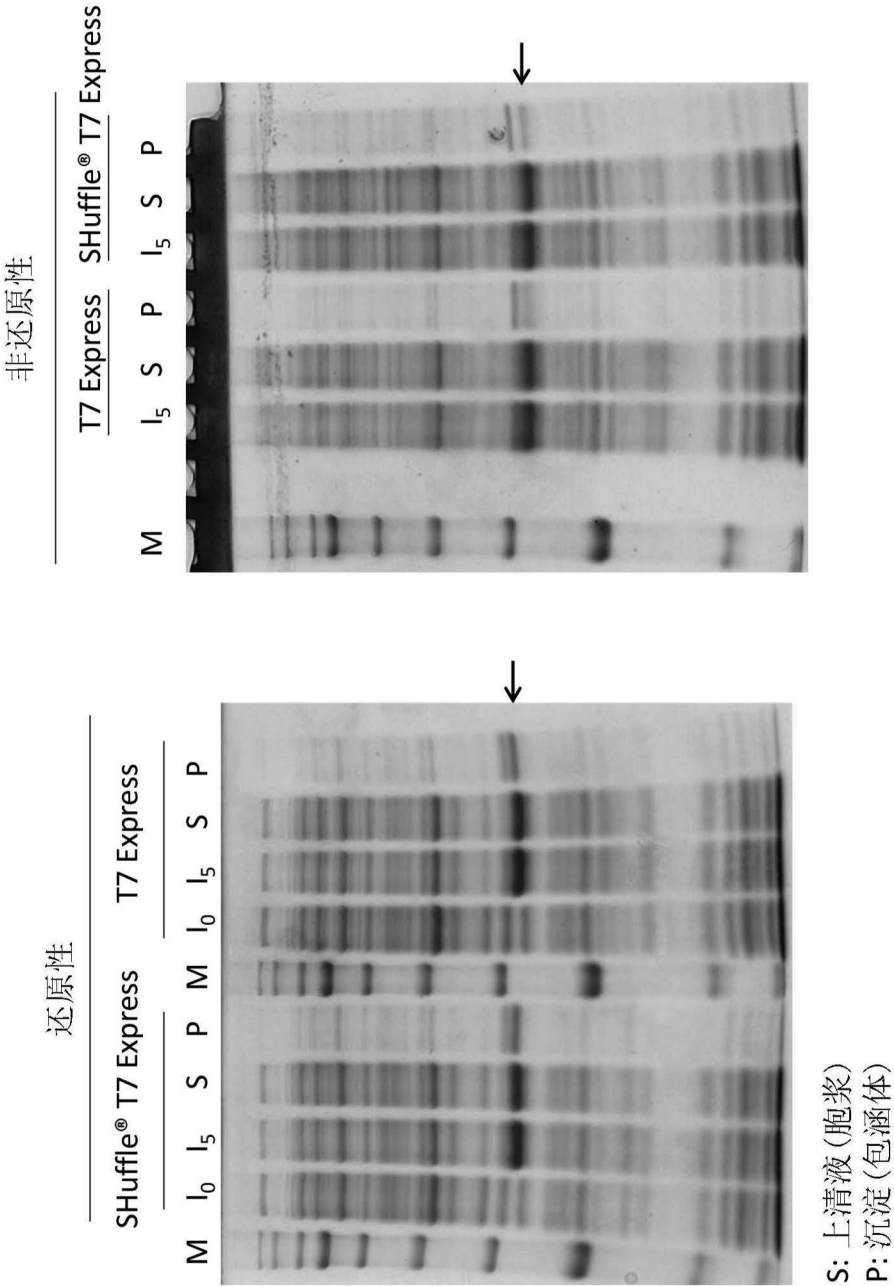


图8

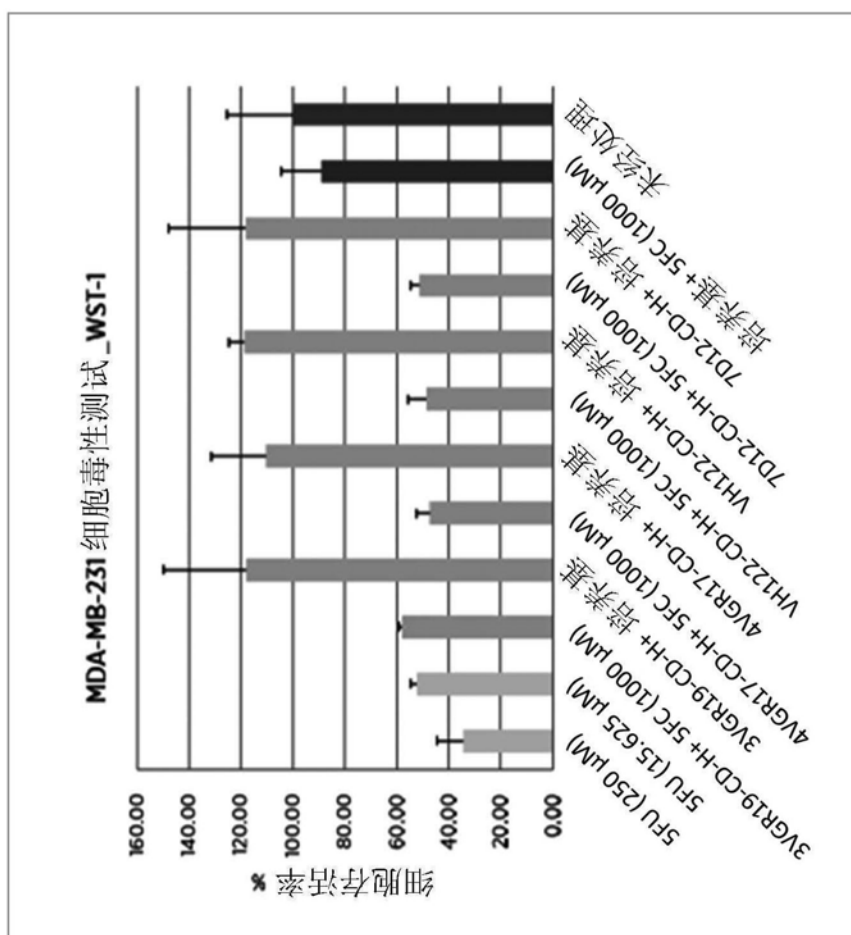


图9A

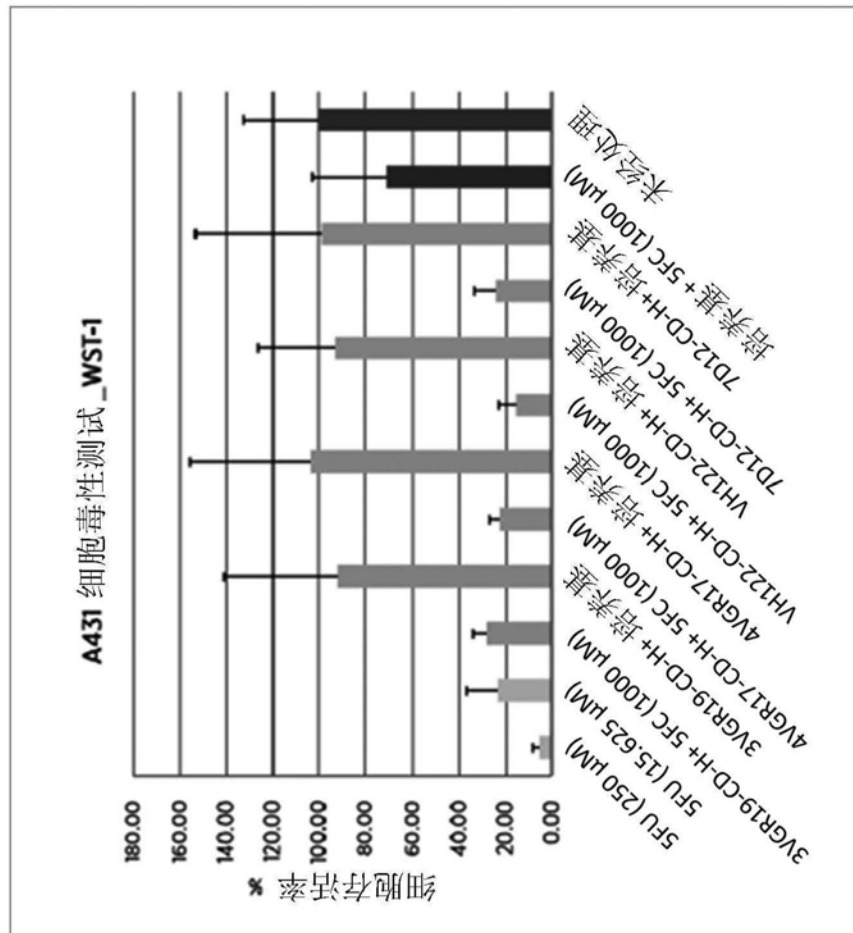


图9B

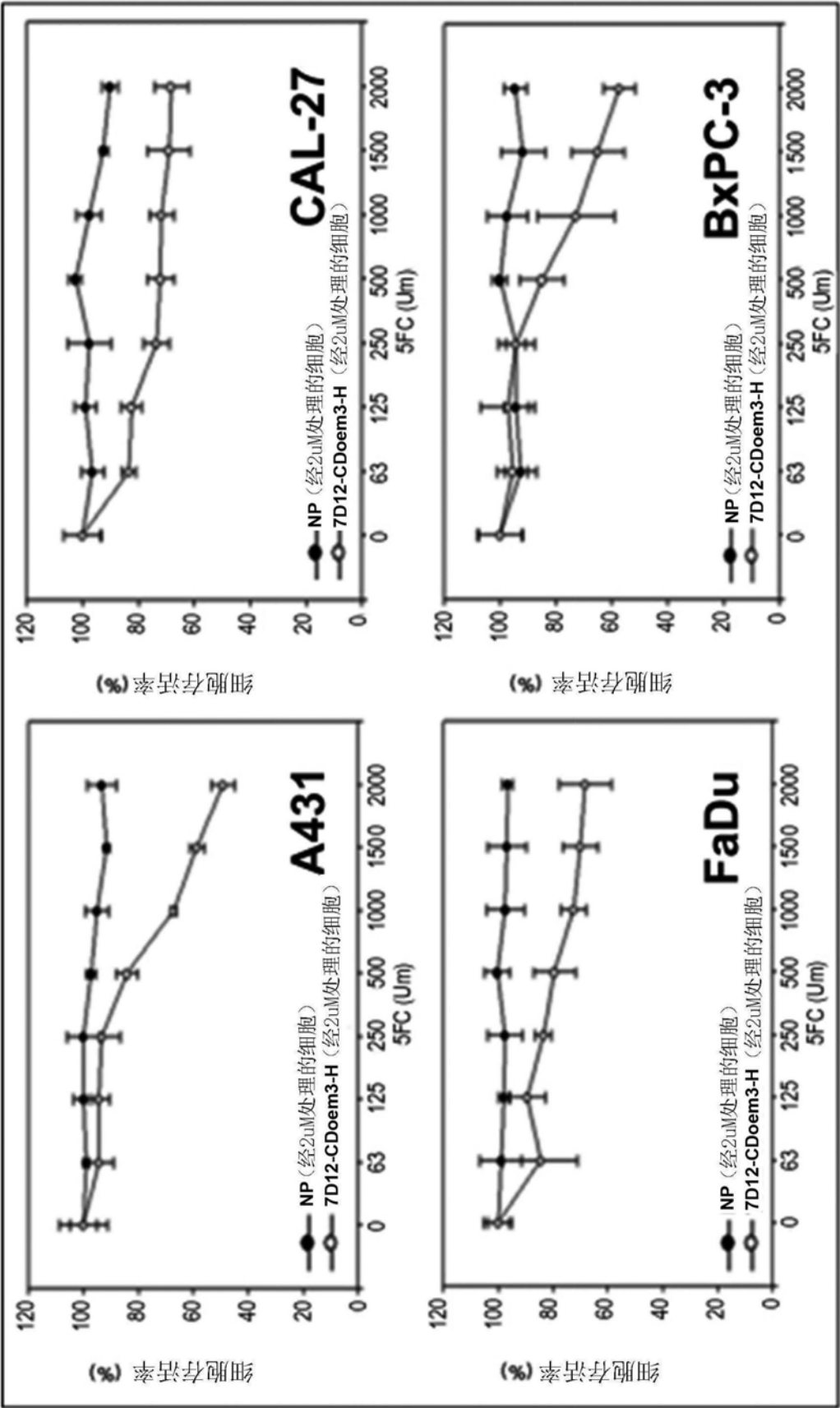


图10A

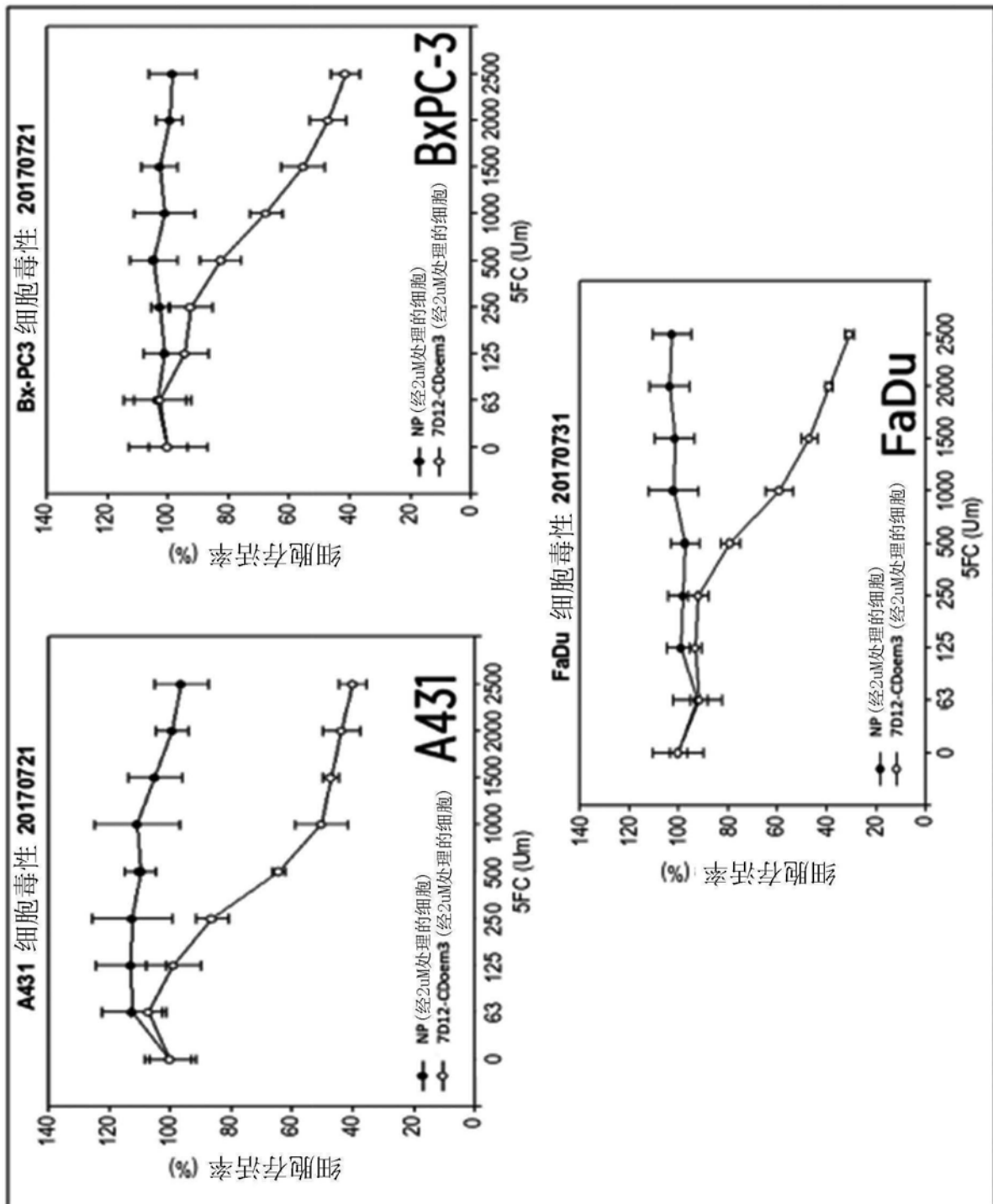


图10B

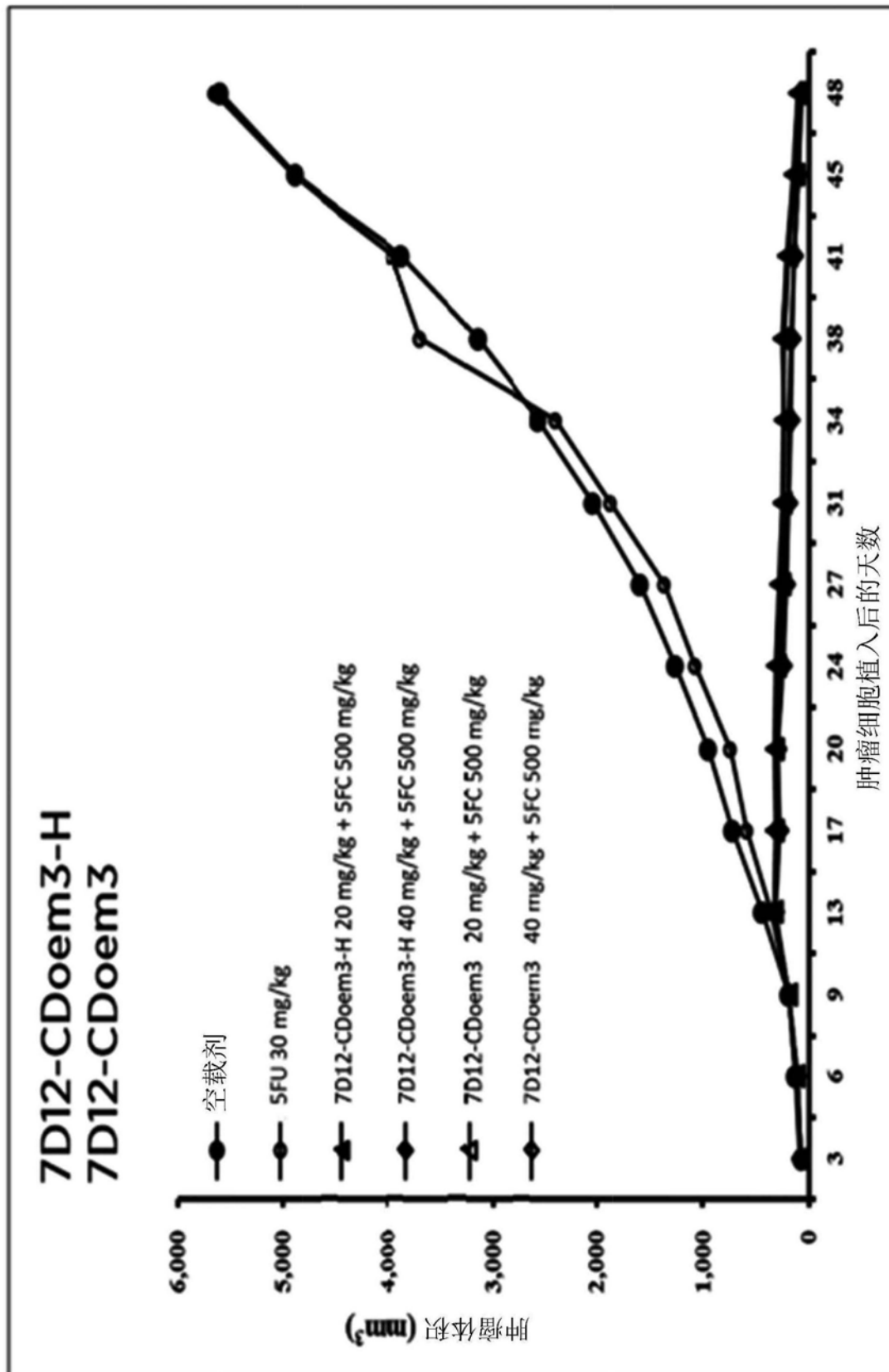


图11A

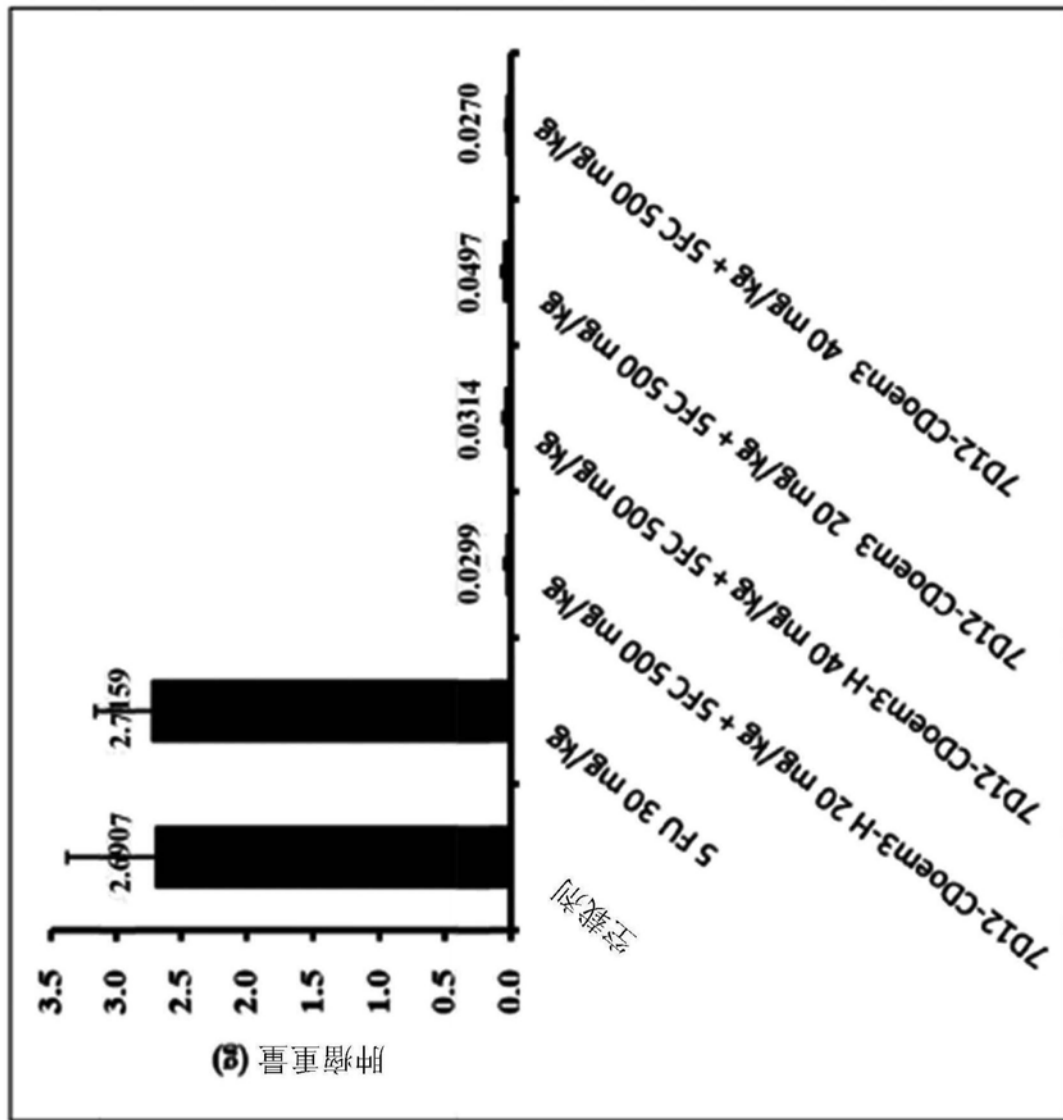


图11B

代码	纯化产量 (mg/mL)	CDase活性 (EC50, μM)	EGFR结合能力 (EC50, nM)		
			0.115	0.118	0.115
TC3-001, S12V	2.356	NT	0.115	0.118	NT
TC3-002, V13A	1.085	NT	0.122	NT	NT
TC3-003, T15V	2.538	NT	0.129	NT	NT
TC3-004, G16D	0.884	NT	0.146	NT	NT
TC3-005, S18D	0.437	NT	0.154	NT	NT
TC3-006, S18E	0.414	NT	0.14	NT	NT
TC3-007, K88R	0.464	NT	0.152	NT	NT
TC3-008, P89A	0.554	NT	0.12	NT	NT
TC3-009, K88A	0.357	NT	0.084	0.168	NT
TC3-010, K88D	0.692	NT	0.083	0.138	NT
TC3-011, K88S	0.74	NT	0.094	0.172	NT
TC3-012, K88T	1.034	NT	0.08	0.115	NT
TC3-013, P89D	0.082	NT	0.089	0.388	0.062
	0.377				
TC3-014, P89E	0.322	NT	0.13	NT	NT
TC3-015, T92D	0.379	NT	0.095	0.149	NT
TC3-016, T92E	0.672	NT	0.094	0.144	NT
TC3-017, T92G	0.489	NT	0.105	0.125	NT
TC3-018, T92H	0.293	NT	0.109	0.143	NT
TC3-019, T92Q	0.443	NT	0.116	NT	NT
TC3-020, A93D	0.105	NT	0.081	0.175	0.205
	0.1				
TC3-021, A93E	NT	NT	NT	NT	NT
TC3-022, I94V	0.801	NT	0.056	0.083	NT
TC3-023, I94A	0.447	NT	0.103	0.096	NT
TC3-024, I94T	0.627	NT	0.129	NT	NT
TC3-025, I94R	0.783	NT	0.12	NT	NT
TC3-026, I94Q	0.636	NT	0.094	0.1	NT
TC3-027, I94N	0.635	NT	0.124	NT	NT
TC3-028, Y224A	0.351	1.49	NT		
TC3-029, Y224H	0.176	0.29	NT		
TC3-030, T225D	0.433	-	NT		
TC3-031, T226E	0.379	-	NT		
TC3-032, M232N	0.431	-	NT		
TC3-033, M232A	0.543	-	NT		
TC3-034, M232K	0.547	-	NT		
TC3-035, M232Q	0.259	-	NT		
TC3-036, V268A	1.21	0.07	NT		
TC3-037, V268T	1.388	0.07	NT		
TC3-038, V269A	1.085	0.11	NT		
TC3-039, V269L	0.984	0.1	NT		
TC3-040, V269I	0.656	0.09	NT		
TC3-041, V269T	0.88	0.08	NT		
TC3-042, V270A	0.574	0.24	NT		
TC3-043, V270T	0.734	0.12	NT		
TC3	0.691	0.05	0.072 0.109	0.104	0.078
	0.763	0.07			
	0.607				

图12

代码	表位1	表位2	表位3	表位6	纯化产量 (mg/mL)	rhEGFR结合		CDase活性 (EC50: nM)
						(EC50: nM)		
TC3-044	S12V, T15V	K88R, P89A, I94V		V268A	1.081	0.02	0.02	0.06
	S12V, T15V	K88R, P89A, I94V		V268T	0.125	0.16	0.16	0.5
TC3-046	S12V, T15V	K88R, P89A, I94V		V269T	0.518	0.07	0.07	0.11
	V13A	K88D	I94R	V268A	0.355	0.05	0.05	0.05
TC3-048	G16D	K88D	I94R	V268A	0.019	NT	NT	NT
TC3-049	S18D	K88D	I94R	V268A	0.026	NT	NT	NT
TC3-050	V13A	K88T	I94R	V268A	0.399	0.04	0.04	0.05
TC3-051	G16D	K88T	I94R	V268A	0.118	0.08	0.08	0.14
TC3-052	S18D	K88T	I94R	V268A	0.043	NT	NT	NT
TC3-053	V13A	K88D	I94Q	V268A	0.104	0.16	0.16	0.28
TC3-054	G16D	K88D	I94Q	V268A	0.032	NT	NT	NT
TC3-055	S18D	K88D	I94Q	V268A	0.033	NT	NT	NT
TC3-056	V13A	K88T	I94Q	V268A	0.274	0.04	0.04	0.07
TC3-057	G16D	K88T	I94Q	V268A	0.127	0.08	0.08	0.14
TC3-058	S18D	K88T	I94Q	V268A	0.017	NT	NT	NT
TC3-059	V13A	K88D	I94R	V268T	0.223	0.1	0.1	0.14
TC3-060	G16D	K88D	I94R	V268T	0.052	NT	NT	NT
TC3-061	S18D	K88D	I94R	V268T	0.026	NT	NT	NT
TC3-062	V13A	K88T	I94R	V268T	0.182	0.12	0.12	0.15
TC3-063	G16D	K88T	I94R	V268T	0.174	0.1	0.1	0.14
TC3-064	S18D	K88T	I94R	V268T	0.07	NT	NT	NT
TC3-065	V13A	K88D	I94Q	V268T	0.107	0.2	0.2	1.42
TC3-066	G16D	K88D	I94Q	V268T	0.013	NT	NT	NT
TC3-067	S18D	K88D	I94Q	V268T	0.021	NT	NT	NT
TC3-068	V13A	K88T	I94Q	V268T	0.341	0.09	0.09	0.12
TC3-069	G16D	K88T	I94Q	V268T	0.014	NT	NT	NT
TC3-070	S18D	K88T	I94Q	V268T	0.023	NT	NT	NT
TC3-071	V13A	K88D	I94R	V269T	0.168	0.16	0.16	0.55
TC3-072	G16D	K88D	I94R	V269T	0.019	NT	NT	NT
TC3-073	S18D	K88D	I94R	V269T	0.017	NT	NT	NT
TC3-074	V13A	K88T	I94R	V269T	0.343	0.14	0.14	0.14
TC3-075	G16D	K88T	I94R	V269T	0.114	0.15	0.15	1.7
TC3-076	S18D	K88T	I94R	V269T	0.101	0.34	0.34	NA
TC3-077	V13A	K88D	I94Q	V269T	0.019	NT	NT	NT
TC3-078	G16D	K88D	I94Q	V269T	0.044	NT	NT	NT
TC3-079	S18D	K88D	I94Q	V269T	0.043	NT	NT	NT
TC3-080	V13A	K88T	I94Q	V269T	0.21	0.1	0.1	0.29
TC3-081	G16D	K88T	I94Q	V269T	0.051	NT	NT	NT
TC3-082	S18D	K88T	I94Q	V269T	0.018	NT	NT	NT
TC_WT					0.212	0.09	0.09	0.15
					0.301			0.17

图13A

代码	表位1	表位2	表位3	表位4	表位6	纯化后的 产量 (mg/200mL 批量)	rhEGFR结合 (EC50:nM)	CDase 活性 (EC50:nM)	S2000 SEC-HPLC RT (27min) 主峰
TC3-044	S12V, T15V	K88R, P89A, I94V			V268A	7.5	0.07	10.35	89.34
TC3-087	S12V, T15V	K88R, P89A, I94V			V268A, V269T	5.6	0.07	10.32	81.37
TC3-088	S12V, T15V	K88R, P89A, I94V			V268A	5.9	0.08	11.95	72.9
TC3-047	V13A	K88D	I94R		V268A	0.9	0.1	11.27	83.98
TC3-050	V13A	K88T	I94R		V268A	3.3	0.13	13.42	78.38
TC3-089	V13A	K88T	I94R		V268A, V269T	1.5	0.12	15.62	66.2
TC3-090	V13A	K88T	I94R	Y224H	V268A	2.3	0.11	12.17	72.09
TC3-051	G16D	K88T	I94R		V268A	1.9	0.11	12.13	88.35
TC3-052	S18D	K88T	I94R		V268A	1.9	0.1	10.77	93.97
TC3-056	V13A	K88T	I94Q		V268A	0.9	0.1	11.59	81.39
TC3 WT						2.1	0.14	13.44	86.94

图13B

	样品1	样品2	样品3	样品4	样品5	Exenatide	KLH
供体1							PE
供体2				P			PE
供体3							PE
供体4							PE
供体5							PE
供体6							PE
供体7				P		P	PE
供体8							PE
供体9						P	PE
供体10	PE	P	P	P	PE		PE
供体11							PE
供体12							PE
供体13	P					P	PE
供体14				P	P	P	PE
供体15		P	P	P			PE
供体16				P	P	P	PE
供体17							E
供体18							PE
供体19							PE
供体20							PE
供体21							PE
供体22	P			P	P		PE
供体23					P		PE
供体24							PE
供体25				P		P	PE
供体26						P	PE
供体27							PE
供体28						P	P
供体29							PE
供体30	PE			PE		PE	PE
供体31	P					PE	PE
供体32			P		P	P	PE
供体33						P	PE
供体34			E			P	PE
供体35						P	PE
供体36					E	PE	PE
供体37				P			PE
供体38				P		P	PE
供体39						PE	PE
供体40							P
供体41						P	PE
供体42				E			PE
供体43							P
供体44						P	PE
供体45		E			P		
供体46							P
供体47	P	P	P			P	PE
供体48	P	PE	P	PE		P	P
供体49						P	PE
供体50	PE	E	P	PE	PE	P	PE
供体51						P	PE
供体52							PE
细胞增殖%	15	8	12	25	15	46	96
ELISpot %	6	6	2	8	6	8	88
细胞增殖和 ELISpot %	6	2	0	6	4	8	87
相关性%	38	25	0	23	25	17	90

图14

CD活性	TC4-WT	TC4-44	TC4-50	TC4-51	TC-87
EC50 (nM)	33.3	23.43	19.67	16.35	24.45

样品	ka1(1/Ms)	kd1(1/s)	ka2(1/s)	kd2(1/s)	KD(M)
TC4-WT	2.15E+06	0.04414	0.009098	2.71E-04	5.93E-10
TC4-WT	1.22E+06	0.03604	0.007203	2.71E-04	1.07E-09
TC4-44	1.05E+06	0.05938	0.01108	1.86E-04	9.35E-10
TC4-50	6.90E+05	0.08054	0.01145	2.01E-04	2.02E-09
TC4-51	6.96E+05	0.07411	0.01099	2.13E-04	2.03E-09
TC4-87	7.63E+05	0.05579	0.008993	1.58E-04	1.27E-09

图15