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(54) 发明名称

PD-1结合分子及其应用

(57) 摘要

本发明提供一种PD-1结合分子,包含抗PD-1单域抗体,所述单域抗体的互补决定区CDR包括SEQ ID NO:1所示的CDR1、SEQ ID NO:2所示的CDR2、和SEQ ID NO:3所示的CDR3。

1. 一种PD-1结合分子, 包含抗PD-1单域抗体, 所述单域抗体的互补决定区CDR包含CDR1、CDR2和CDR3, 其中:

CDR1如SEQ ID NO:19所示、CDR2如SEQ ID NO:73所示、和CDR3如SEQ ID NO:87所示,
CDR1如SEQ ID NO:37所示、CDR2如SEQ ID NO:75所示、和CDR3如SEQ ID NO:135所示,
或者

CDR1如SEQ ID NO:320所示、CDR2如SEQ ID NO:75所示、和CDR3如SEQ ID NO:135所示。

2. 如权利要求1所述的PD-1结合分子, 其特征在于, 所述单域抗体VHH如SEQ ID NO: 231、310-319中任一所示。

3. 如权利要求1或2所述的PD-1结合分子, 其特征在于, 所述PD-1结合分子是包含一条或多条所述单域抗体的单价或多价单域抗体、重链抗体或其抗原结合片段。

4. 如权利要求3所述的PD-1结合分子, 其特征在于, 所述PD-1结合分子是重链抗体, 所述重链抗体还包含重链恒定区。

5. 如权利要求4所述的PD-1结合分子, 其特征在于, 所述重链恒定区如SEQ ID NO: 321所示。

6. 一种多核苷酸, 其特征在于, 所述多核苷酸选自:

(1) 权利要求1-5中任一项所述的PD-1结合分子的编码序列;

(2) (1)的互补序列。

7. 一种核酸构建物, 其特征在于, 所述核酸构建物包含权利要求6所述的多核苷酸。

8. 如权利要求7所述的核酸构建物, 其特征在于, 所述核酸构建物是重组载体。

9. 如权利要求8所述的核酸构建物, 其特征在于, 所述核酸构建物是表达载体。

10. 包含权利要求1-5中任一项所述的PD-1结合分子的噬菌体。

11. 如权利要求10所述的噬菌体, 其特征在于, 所述PD-1结合分子展示于所述噬菌体表面。

12. 一种宿主细胞, 其特征在于, 所述宿主细胞:

(1) 表达和/或分泌权利要求1-5中任一项所述的PD-1结合分子; 和/或

(2) 包含权利要求6所述的多核苷酸; 和/或

(3) 包含权利要求7-9中任一项所述的核酸构建物。

13. 一种产生PD-1结合分子的方法, 包括: 在适合产生PD-1结合分子的条件下培养权利要求12所述的宿主细胞。

14. 如权利要求13所述的方法, 其特征在于, 所述方法还包括步骤: 从培养物中纯化所述PD-1结合分子。

15. 一种检测PD-1的试剂盒, 所述的试剂盒包含权利要求1-5中任一项所述的PD-1结合分子、权利要求10或11所述的噬菌体。

16. 如权利要求15所述的试剂盒, 其特征在于, 所述试剂盒还包括用于检测PD-1与PD-1结合分子的结合的试剂。

17. 如权利要求15所述的试剂盒, 其特征在于, 所述试剂是通过酶联免疫反应法检测所述结合的试剂。

18. 一种检测样品中PD-1存在情况的非诊断性方法, 所述方法包括: 以权利要求1-5中任一项所述的PD-1结合分子与样品孵育, 和检测PD-1与PD-1结合分子的结合, 从而确定样

品中PD-1存在情况。

19. 权利要求1-5中任一项所述的PD-1结合分子在制备用于检测样品中PD-1的试剂盒中的用途。

PD-1结合分子及其应用

技术领域

[0001] 本发明涉及生物医学或生物制药技术领域,更具体地涉及一种PD-1结合分子及其应用。

背景技术

[0002] 程序性死亡受体-1蛋白,又称作PD-1(programmed death 1),是一种表达在T细胞表面并起免疫抑制作用的跨膜蛋白。PD-1有两个配体分子,分别为PD-L1和PD-L2,PD-L1和PD-L2在抗原呈递细胞上有较高水平的表达。当PD-L1和PD-L2与PD-1结合后会对T细胞的功能活性起到负调控的作用,肿瘤细胞通常能够高表达PD-L1或者PD-L2来实现“免疫逃逸”(Lee L等,J Clin Pharmacol.2016Feb;56(2):157-69)。所以,PD-1药物通过对免疫系统的正向调控作用来实现对肿瘤的杀伤。现在,PD-1也是免疫检查点抑制剂疗法的代名词。

[0003] 凭借在黑色素瘤治疗中的突出疗效,FDA在2014年和2015年先后批准两个PD-1单克隆抗体Pembrolizumab(Keytruda)和Nivolumab(Opdivo),目前适应症已经覆盖了近20种实体瘤(Prasad V等,Semin Oncol.2017Apr;44(2):132-135.)。目前国内已有4款PD-1单抗药物上市,分别是恒瑞的卡瑞利珠单抗(Camrelizumab)、百济神州的替雷利珠单抗(Tislelizumab)、信达的信迪利单抗(Sintilimab)和君实的特瑞普利单抗(Toripalimab)。

[0004] 研究发现,传统的scfv抗体在T细胞中表达量低,难以充分发挥PD-1抑制剂的效果,这主要是由于scfv抗体本身易聚集、折叠易错配、热稳定性低等性质导致的(Martin N等,Macromol Biosci.2017Feb;17(2))。而纳米抗体则具有易表达、稳定性高、亲和力高等天然优势,根据纳米抗体自身优势和PD-1生物学机制,开发PD-1纳米抗体具有非常广阔的应用前景。开发一种新型抗PD-1单域抗体,使其具有较好的特异性、阻断活性、临床药效,并且生产简便、成本低、减轻用药负担,已经成为亟待解决的问题。

发明内容

[0005] 本发明的目的在于提供一种新型抗PD-1结合分子及其应用。

[0006] 本发明第一方面提供一种PD-1结合分子,包含抗PD-1单域抗体,所述单域抗体的互补决定区CDR包含CDR1、CDR2和CDR3,其中CDR1包括SEQ ID NO:1所示的序列、CDR2包括SEQ ID NO:2所示的序列、和CDR3包括SEQ ID NO:3所示的序列。

[0007] 在一个或多个实施方案中,SEQ ID NO:1是GX₁X₂X₃X₄X₅X₆X₇,其中,X₁为D、F、G、H、L或R,X₂为P、S或T,X₃为A、F、I、L、N、R、S或V,X₄为D、F、G、L、M、N或S,X₅为A、D、F、G、I、N、R、S或T,X₆为D、F、H、I、L、S、V、W或Y,X₇为A、D、E、G、N、P、S或T。示例性地,CDR1包括SEQ ID NO:4-39、320中任一所示的序列。

[0008] 优选地,SEQ ID NO:1是GX₁X₂X₃X₄X₅X₆X₇,其中,X₁为D、F、G、H、L或R,X₂为P、S或T,X₃为F或S,X₄为F或S,X₅为G、I或T,X₆为S或Y,X₇为A或D。示例性地,CDR1包括SEQ ID NO:16、19、36-39、320中任一所示的序列。

[0009] 更优选地,SEQ ID NO:1是GX₁X₂X₃X₄IX₆X₇,其中,X₁为D或R,X₂为P或T,X₃为S或F,X₄

为F或S, X_6 为S或Y, X_7 为A或D。示例性地, CDR1包括SEQ ID NO:16或19所示的序列。

[0010] 或者更优选地, SEQ ID NO:1是 $GX_1X_2FSX_5YX_7$, 其中, X_1 为G、F、H、L或R, X_2 为P、S或T, X_5 为G、I或T, X_7 为A或D。示例性地, CDR1包括SEQ ID NO:19、36-39、320中任一所示的序列。

[0011] 在一个或多个实施方案中, SEQ ID NO:2是 $X_1X_2X_3X_4X_5X_6X_7X_8X_9$, 其中, X_1 为I、L、S、T或V, X_2 为A、N、S或T, X_3 为F、G、I、K、L、M、N、Q、R、S、T、W或Y, X_4 为A、D、G、H、N、R、S或T, X_5 为A、D、G、N、R、S或无, X_6 为G或R、S或T, X_7 为D、E、I、L、M、N、R、S、T或V, X_8 为A、K、M、Q或T, X_9 为A或无。示例性地, CDR2包括SEQ ID NO:40-75中任一所示的序列。

[0012] 优选地, SEQ ID NO:2是 $X_1X_2X_3X_4X_5GX_7TX_9$, 其中, X_1 为I或V, X_2 为N、S或T, X_3 为F、L或N, X_4 为A、G、S或T, X_5 为R或无, X_7 为D、N、I或T, X_9 为无。示例性地, CDR2包括SEQ ID NO:52、53、55、72-75中任一所示的序列。

[0013] 更优选地, SEQ ID NO:2是 $IX_2X_3X_4X_5GX_7TX_9$, X_2 为N、S或T, X_3 为L或N, X_4 为A、S或T, X_5 为R或无, X_7 为D、I或N, X_9 为无。示例性地, CDR2包括SEQ ID NO:52、53、55、72、73中任一所示的序列。

[0014] 或者更优选地, SEQ ID NO:2是 $X_1X_2X_3X_4RGX_7TX_9$, 其中, X_1 为I或V, X_2 为N、S或T, X_3 为F或L, X_4 为A、G或S, X_7 为D、N或T, X_9 为无。或者, CDR2包括SEQ ID NO:55或其变体, 所述变体包含选自以下的一个或多个氨基酸变化: X_1 的I突变为V, X_2 的N突变为S或T, X_3 的L突变为F, X_4 的S突变为A或G, X_7 的D突变为N或T。示例性地, CDR2包括SEQ ID NO:53、55、72-75中任一所示的序列。

[0015] 在一个或多个实施方案中, SEQ ID NO:3是 $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}$, 其中, X_1 是A、E、G、N、R、S、T或V, X_2 是A、G、I、K、L、P、R、T或V, X_3 是A、D、E、G、K、N、P、R、S、V或Y, X_4 是A、C、D、E、G、I、K、L、R、S、T、V或Y, X_5 是A、C、D、F、G、H、I、K、L、N、P、Q、R、S、W或Y, X_6 是A、C、D、E、G、I、K、L、M、P、Q、R、S或Y, X_7 是A、C、D、F、G、H、I、N、P、R、S、T、V或Y, X_8 是A、C、D、E、G、I、R、S、T、V、W、Y或无, X_9 是A、D、E、F、G、I、L、P、R、S、V、W、Y或无, X_{10} 是C、D、F、G、K、L、N、P、R、S、T、V、W、Y或无, X_{11} 是D、F、G、H、I、K、L、N、P、S、T、V、Y或无, X_{12} 是A、D、G、H、I、L、M、P、R、S、T、V、Y或无, X_{13} 是C、D、E、H、P、R、S、T、V、Y或无, X_{14} 是A、D、E、F、H、I、L、P、R、T、Y或无, X_{15} 是A、D、E、G、N、Q、R、S、T、V、Y或无, X_{16} 是A、D、E、F、G、H、M、P、S、V、Y或无, X_{17} 是A、D、E、H、N、Q、R、T、Y或无, X_{18} 是D、E、R、S、Y或无, X_{19} 是N、S、Y或无, X_{20} 是D、E、Y或无, X_{21} 是E、N、Y或无, X_{22} 是Y或无。示例性地, CDR3包括SEQ ID NO:76-183中任一所示的序列。

[0016] 优选地, SEQ ID NO:3是 $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}$, 其中, X_1 是E、G、N或V, X_2 是A、G、I、L或V, X_3 是A、D、E、G、N、V或Y, X_4 是A、G、I、K、R或S, X_5 是C、I、L、P、Q、R或W, X_6 是E、K、P、Q或R, X_7 是C、D、H、N、P或Y, X_8 是E、G、R、V或W, X_9 是F、G、L、S、V或W, X_{10} 是C、D、G、L、R、S或V, X_{11} 是F、G、I、L、N、S、T或V, X_{12} 是H、L、P、R、S、T或Y, X_{13} 是D、H、P、S、T或V, X_{14} 是E、F、H、I、L、P或R, X_{15} 是A、S或V, X_{16} 是A、D、E、G、H或V, X_{17} 是H、N、Q、R或Y, X_{18} - X_{22} 是无。示例性地, CDR3包括SEQ ID NO:76、87、108-183中任一所示的序列。

[0017] 更优选地, SEQ ID NO:3是 $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}$, 其中, X_1 是E、G或V, X_2 是A、G、I、L或V, X_3 是A、D、E、G、N、V或Y, X_4 是G、I、K、R或S, X_5 是C、I、L、Q、R或W, X_6 是E、K、P、Q或R, X_7 是C、D、H、N或Y, X_8 是E、G、R、V或W, X_9 是F、L、S、V或W, X_{10} 是C、D、G、R、S或V, X_{11} 是F、I、L、N、S、T或V, X_{12} 是H、L、P、R、S或T, X_{13} 是H、P、S、T或V, X_{14} 是F、H、I、L、P或R, X_{15} 是A、S或V, X_{16} 是A、D、E、G、H或V, X_{17} 是H、N、Q、R或Y, X_{18} - X_{22} 是无。或者, CDR3包括SEQ ID NO:87

所示的序列或其变体,所述变体包含选自以下的一个或多个氨基酸变化: X_1 的G突变为E、G或V, X_2 的V突变为A、G、I或V, X_3 的D突变为A、E、G、N、V或Y, X_4 的R突变为G、I、K或S, X_5 的R突变为C、I、L、Q或W, X_6 的Q突变为E、K、P或R, X_7 的Y突变为C、D、H或N, X_8 的G突变为E、R、V或W, X_9 的L突变为F、S、V或W, X_{10} 的G突变为C、D、R、S或V, X_{11} 的I突变为F、L、N、S、T或V, X_{12} 的P突变为H、L、R、S或T, X_{13} 的P突变为H、S、T或V, X_{14} 的L突变为F、H、I、P或R, X_{15} 的A突变为S或V, X_{16} 的D突变为A、E、G、H或V, X_{17} 的H突变为N、Q、R或Y。示例性地,CDR3包括SEQ ID NO:87、108-183中任一所示的序列。

[0018] 在一个或多个实施方案中,CDR1包括SEQ ID NO:4-39、320中任一所示的序列,CDR2包括SEQ ID NO:40-75中任一所示的序列,CDR3包括SEQ ID NO:76-183中任一所示的序列。

[0019] 在一个或多个实施方案中,CDR1包括SEQ ID NO:16、19、36-39、320中任一所示的序列,CDR2包括SEQ ID NO:52、53、55、72-75中任一所示的序列,CDR3包括SEQ ID NO:76、87、108-183中任一所示的序列。

[0020] 在一个或多个实施方案中,CDR1包括SEQ ID NO:16或19所示的序列,CDR2包括SEQ ID NO:52、53、55、72、73中任一所示的序列,CDR3包括SEQ ID NO:87、108-111、113-134、136-146、148-154、156-163、165-168、172、173、177-183中任一所示的序列。

[0021] 在一个或多个实施方案中,CDR1包括SEQ ID NO:19、36-39、320中任一所示的序列,CDR2包括SEQ ID NO:53、55、72-75中任一所示的序列,CDR3包括SEQ ID NO:87、108-183中任一所示的序列。

[0022] 在一个或多个实施方案中,CDR1包括SEQ ID NO:5、7、10、14-16、19、26、27、29、30、33中任一所示的序列,CDR2包括SEQ ID NO:41、47、50-52、55、56、61-66中任一所示的序列,CDR3包括SEQ ID NO:76、77、85-87、93、94、97、99-101、104中任一所示的序列。

[0023] 在一个或多个实施方案中,所述单域抗体含有以下组a1到组a136中任一组所示的CDR1、CDR2和CDR3:

[0024]

CDR1	CDR2	CDR3	组
4	40	76	a1
5	41	77	a2
6	42	78	a3
7	43	76	a4
8	44	79	a5
9	45	80	a6
10	46	81	a7
11	47	82	a8
12	48	83	a9
13	49	84	a10
10	50	85	a11
14	47	76	a12
15	51	86	a13
16	52	76	a14
17	53	87	a15
18	54	88	a16
19	55	87	a17
20	56	82	a18
21	57	89	a19
22	58	90	a20
23	59	91	a21
14	47	76	a22
24	60	92	a23
25	40	76	a24
26	61	93	a25
27	62	94	a26
24	60	95	a27
28	41	96	a28
10	63	97	a29
5	41	98	a30
29	64	99	a31
7	65	100	a32
30	66	101	a33
31	67	102	a34

[0025]

32	68	103	a35
33	56	104	a36
34	69	105	a37
35	70	106	a38
7	71	107	a39
16	52	76	a40
16	52	76	a41
16	52	76	a42
16	52	76	a43
16	52	76	a44
19	72	87	a45
19	72	87	a46
19	72	87	a47
19	73	87	a48
19	53	87	a49
19	53	87	a50
19	53	108	a51
19	53	109	a52
19	53	110	a53
19	53	111	a54
36	74	112	a55
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19	53	114	a57
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19	53	133	a76
19	53	134	a77
37	75	135	a78
19	53	136	a79
19	53	137	a80

[0026]

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19	53	143	a86
19	53	144	a87
19	53	145	a88
19	53	146	a89
38	53	147	a90
19	53	148	a91
19	53	149	a92
19	53	150	a93
19	53	151	a94
19	53	152	a95
19	53	153	a96
19	53	154	a97
39	53	155	a98
19	53	156	a99
19	53	157	a100
19	53	158	a101
19	53	159	a102
19	53	160	a103
19	53	161	a104
19	53	162	a105
19	53	163	a106
37	53	164	a107
19	53	165	a108
19	53	166	a109
19	53	167	a110
19	53	168	a111
36	74	169	a112
38	53	170	a113
37	53	171	a114
19	53	172	a115
19	53	173	a116
38	53	174	a117
38	53	175	a118
36	74	176	a119
19	53	177	a120
19	53	178	a121
19	53	179	a122
19	53	180	a123
19	53	181	a124
19	53	182	a125
19	53	183	a126

[0027]

37	75	135	a127
37	75	135	a128
37	75	135	a129
37	75	135	a130
37	75	135	a131
37	75	135	a132
37	75	135	a133
37	75	135	a134
320	75	135	a135
37	75	135	a136

[0028] 在一个或多个实施方案中,所述单域抗体VHH的FR1可选自表1中各抗体编号的VHH的FR1,VHH的FR2可选自表1中各抗体编号的VHH的FR2,VHH的FR3可选自表1中各抗体编号的VHH的FR3,VHH的FR4可选自表1中各抗体编号的VHH的FR4。

[0029] 在一个或多个实施方案中,所述单域抗体的FR区为选自SEQ ID NO:184-319的任一VHH的FR区。

[0030] 在一个或多个实施方案中,所述单域抗体VHH如SEQ ID NO:184-319中任一所示。优选地,所述单域抗体如SEQ ID NO:197、200、223-319中任一所示。

[0031] 在一个或多个实施方案中,所述PD-1结合分子是包含一条、两条或多条本文所述的抗PD-1单域抗体的单价或多价单域抗体、多特异性单域抗体、重链抗体或其抗原结合片段、抗体或其抗原结合片段。

[0032] 在一个或多个实施方案中,所述多价单域抗体或多特异性单域抗体通过连接子连接多个单域抗体。所述连接子由选自G和S的1-15个氨基酸组成。

[0033] 在一个或多个实施方案中,所述重链抗体的抗原结合片段是单链重链抗体。

[0034] 在一个或多个实施方案中,所述重链抗体是骆驼重链抗体或软骨鱼重链抗体。

[0035] 在一个或多个实施方案中,所述重链抗体还包含重链恒定区。

[0036] 在一个或多个实施方案中,所述重链恒定区是骆驼重链抗体的恒定区,包含CH2和CH3。在一个或多个实施方案中,所述CH2和CH3是人IgG Fc的CH2和CH3,例如IgG4的CH2和CH3。优选地,所述重链恒定区如SEQ ID NO:321所示。

[0037] 在一个或多个实施方案中,所述重链恒定区是软骨鱼重链抗体的恒定区,包含CH1、CH2、CH3、CH4和CH5。

[0038] 在一个或多个实施方案中,所述抗体是包含所述抗PD-1单域抗体作为重链可变结构域的抗体。

[0039] 在一个或多个实施方案中,所述抗体还包含轻链可变结构域、重链恒定域和轻链恒定域。

[0040] 在一个或多个实施方案中,抗体的抗原结合片段选自Fab、F(ab')₂、Fv、scFv。

[0041] 在一个或多个实施方案中,本发明任一实施方案所述的结合分子为嵌合抗体或完全人抗体;优选为完全人抗体。

[0042] 本发明还提供多核苷酸,选自:

[0043] (1) 本文任一实施方案所述单域抗体或本文所述抗体或其抗原结合片段的编码序列;

[0044] (2) (1)的互补序列;

- [0045] (3) (1) 或 (2) 中任一序列的5-50bp的片段。
- [0046] 在一个或多个实施方案中,所述片段是引物。
- [0047] 在一个或多个实施方案中,所述多核苷酸的序列如SEQ ID NO:322或323所示。
- [0048] 本发明还提供一种核酸构建物,包含本文所述的多核苷酸。
- [0049] 在一个或多个实施方案中,所述核酸构建物是重组载体或表达载体。
- [0050] 本发明还提供含本文任一实施方案所述PD-1结合分子的噬菌体。
- [0051] 在一个或多个实施方案中,所述PD-1结合分子展示于所述噬菌体表面。
- [0052] 本发明还提供一种宿主细胞,选自:
- [0053] (1) 表达和/或分泌本文任一实施方案所述PD-1结合分子;
- [0054] (2) 包含本文所述的多核苷酸;和/或
- [0055] (3) 包含本文所述的核酸构建物。
- [0056] 本发明还提供一种产生PD-1结合分子的方法,包括:在适合产生PD-1结合分子(例如单价或多价单域抗体、多特异性单域抗体、重链抗体、抗体或其抗原结合片段)的条件下培养本文所述的宿主细胞,和任选的从培养物中纯化所述PD-1结合分子。
- [0057] 本发明还提供一种药物组合物,包含本文任一实施方案所述PD-1结合分子、多核苷酸、核酸构建物、噬菌体或宿主细胞,和药学上可接受的辅料。
- [0058] 在一个或多个实施方案中,所述药物组合物用于治疗癌症。
- [0059] 在一个或多个实施方案中,所述癌症是PD-1相关癌症。优选地,所述癌症选自:黑色素瘤、肺癌、头颈部癌、肾细胞癌、泌尿道上皮癌、非霍奇金淋巴瘤等。
- [0060] 本发明还提供本文任一实施方案所述PD-1结合分子在制备用于预防或治疗癌症的药物中的用途。
- [0061] 在一个或多个实施方案中,所述癌症是PD-1相关癌症。优选地,所述癌症选自:黑色素瘤、肺癌、头颈部癌、肾细胞癌、泌尿道上皮癌、非霍奇金淋巴瘤等。
- [0062] 本发明还提供一种治疗或预防癌症的方法,所述方法包括给予需要的患者治疗有效量的本发明任一实施方案所述的PD-1结合分子,或含有本发明任一实施方案所述的PD-1结合分子的药物组合物。
- [0063] 在一个或多个实施方案中,所述癌症是PD-1相关癌症。优选地,所述癌症选自:黑色素瘤、肺癌、头颈部癌、肾细胞癌、泌尿道上皮癌、非霍奇金淋巴瘤等。
- [0064] 本发明还提供一种检测PD-1的试剂盒,用于评估药物治疗效果或诊断癌症,所述的试剂盒包含本文任一实施方案所述PD-1结合分子、多核苷酸、核酸构建物、噬菌体或宿主细胞。
- [0065] 在一个或多个实施方案中,所述试剂盒还包括用于检测PD-1与单域抗体、抗体或其抗原结合片段的结合的试剂。例如通过酶联免疫反应法检测所述结合的试剂。
- [0066] 在一个或多个实施方案中,所述检测结合的试剂是能与PD-1结合分子连接的可检测标记物,例如生物素。所述的可检测标记物被连接于所述PD-1结合分子或分离地存在于试剂盒中。
- [0067] 本发明还提供一种检测样品中PD-1存在情况的非诊断性方法,所述方法包括:以本文任一实施方案所述PD-1结合分子与样品孵育,和检测PD-1与单域抗体、抗体或其抗原结合片段的结合,从而确定样品中PD-1存在情况。所述检测是酶联免疫反应法检测。

[0068] 本发明还提供本文任一实施方案所述PD-1结合分子在制备用于检测样品中PD-1、评估药物治疗效果或诊断癌症的试剂盒中的用途。

附图说明

[0069] 图1为针对PD-1蛋白的羊驼抗血清效价检测。

[0070] 图2为针对PD-1过表达细胞株的羊驼抗血清效价检测。

[0071] 图3抗PD-1抗体对荧光素酶报告基因激活作用。同型对照(阴性对照)的氨基酸序列如CN106046152A中的SEQ ID NO.:2所示。

[0072] 图4在混合淋巴细胞反应(MLR)中PD-1抗体对IFN- γ 分泌量的影响。同型对照同图3。

[0073] 图5在混合淋巴细胞反应(MLR)中PD-1抗体对IL-2分泌量的影响。同型对照同图3。

[0074] 图6为NB182抗体与5300种膜蛋白交叉反应结果。

[0075] 图7为NB194抗体与5300种膜蛋白交叉反应结果。

[0076] 图8显示NB194突变体的亲和力和功能活性也有提升。EC50的单位为nM。。

具体实施方式

[0077] 本发明人经过广泛而深入地研究,经过大量的筛选,发现一类包含抗PD-1单域抗体的PD-1结合分子,实验结果表明,本发明结合分子能够特异性识别PD-1,以高亲和力与PD-1结合,具有良好的功能活性,能促进T细胞分泌细胞因子,并且无组织交叉反应。本发明单域抗体生成简便。

[0078] 具体地,本发明利用人源的PD-1蛋白免疫羊驼,获得高质量的免疫单域抗体基因文库。然后将PD-1蛋白偶联在酶标板上,利用噬菌体展示技术筛选免疫单域抗体基因库,从而获得了PD-1特异性的单域抗体基因。再将此基因转至哺乳动物细胞中,从而获得了能在哺乳动物细胞中高效表达的、且特异性高的单域抗体株。然后通过ELISA、流式细胞术、膜蛋白交叉反应、表位竞争试验等方法鉴定出高亲和力、高特异性、高功能活性、低组织交叉反应的单域抗体。

[0079] 抗体

[0080] 本文中,“PD-1结合分子”是特异性结合PD-1的蛋白质,包括但不限于,抗体、抗体的抗原结合片段、重链抗体、纳米抗体、微型抗体、亲和体、受体的靶结合区、细胞粘附分子、配体、酶、细胞因子、和趋化因子。

[0081] 本文中,术语“抗体”包括单克隆抗体(包括全长抗体,其具有免疫球蛋白Fc区),具有多表位特异性的抗体组合物,多特异性抗体(例如,双特异性抗体),双抗体和单链分子,以及抗体片段,尤其是抗原结合片段,例如,Fab,F(ab')₂和Fv。本文中,术语“免疫球蛋白”(Ig)和“抗体”可互换地使用。

[0082] 基本的4链抗体单元是由两条相同的轻链(L)和两条相同的重链(H)构成的异四聚体糖蛋白。IgM抗体由5个基本的异四聚体单元及称作J链的另外多肽组成,包含10个抗原结合位点;而IgA抗体包含2-5个基本的4链单元,其可与J链组合聚合形成多价装配物。在IgG的情况下,4链单元通常约150,000道尔顿。每条轻链通过一个共价二硫键与重链相连,而两条重链通过一个或多个二硫键彼此相连,二硫键的数目取决于重链的同种型。每条重链和

轻链还具有间隔规律的链内二硫桥。每条重链在N-末端具有可变结构域(VH),接着是三个(对于每种 α 和 γ 链,CH1、CH2和CH3)和四个(对于 μ 和 ϵ 同种型,CH1、CH2、CH3和CH4)恒定结构域(CH)以及位于CH1结构域与CH2结构域之间的绞链区(Hinge)。每条轻链在N-末端具有可变结构域(VL),接着是其另一端的恒定结构域(CL)。VL与VH排列在一起,而CL与重链的第一恒定结构域(CH1)排列在一起。特定的氨基酸残基被认为在轻链和重链可变结构域之间形成界面。成对的VH和VL一起形成一个抗原结合位点。关于不同类别抗体的结构和性质,参见如Basic and Clinical Immunology,第八版,Daniel P.Sties,Abba I.Terr和Tristram G.Parslow编辑,Appleton&Lange,Norwalk,CT,1994,第71页和第6章。来自任何脊椎动物物种的轻链,根据其恒定结构域氨基酸序列,可归入两种称作 κ 和 λ 的截然不同型中的一种。根据其重链恒定结构域(CH)氨基酸序列,免疫球蛋白可归入不同的类或同种型。有五类免疫球蛋白:IgA、IgD、IgE、IgG和IgM,分别具有称作 α 、 δ 、 ϵ 、 γ 和 μ 的重链。根据CH序列和功能的相对较小差异, γ 和 α 类可进一步分为亚类,例如人表达下列亚类:IgG1、IgG2A、IgG2B、IgG3、IgG4、IgA1和IgA2。

[0083] 本文所述“重链抗体”是源自骆驼科生物或软骨鱼科生物的抗体。相比上述4链抗体,重链抗体缺失轻链和重链恒定区1(CH1),仅包含2条由可变区(VHH)和其他恒定区组成重链,可变区通过类似绞链区结构与恒定区相连。骆驼科重链抗体的每条重链包含1个可变区(VHH)和2个恒定区(CH2和CH3),软骨鱼科重链抗体的每条重链含有1个可变区和5个恒定区(CH1-CH5)。重链抗体的抗原结合片段包括VHH和单链重链抗体。通过与人IgG Fc的恒定区融合,重链抗体可以具有人IgG Fc的CH2和CH3。

[0084] 如本文所用,术语“单域抗体”、“抗PD-1单域抗体”、“重链抗体的重链可变区结构域”、“VHH”、“纳米抗体”可互换使用,均指特异性识别和结合于PD-1的单域抗体。单域抗体是重链抗体的可变区。通常,单域抗体含有三个CDR和四个FR。优选地,本发明的单域抗体具有SEQ ID NO:1所示的CDR1、SEQ ID NO:2所示的CDR2、和SEQ ID NO:3所示的CDR3。单域抗体是最小的功能性抗原结合片段。通常先获得天然缺失轻链和重链恒定区1(CH1)的抗体后,再克隆抗体重链的可变区,构建仅由一个重链可变区组成的单域抗体。

[0085] 包含两条或多条单域抗体的结合分子是多价单域抗体;包含两条或多条不同特异性单域抗体的结合分子是多特异性单域抗体。多价单域抗体或多特异性单域抗体通过连接子连接多个单域抗体。所述连接子通常由选自G和S的1-15个氨基酸组成。

[0086] 本文中,重链抗体和抗体旨在区分抗体的不同组合方式。由于二者的结构具有相似性,下述针对抗体的结构描述除涉及轻链外也均适用于重链抗体。

[0087] 抗体的“可变区”或“可变结构域”是指抗体的重链或轻链的氨基末端结构域。重链和轻链的可变结构域可分别称为“VH”和“VL”。这些结构域通常是抗体的最可变的部位(相对于相同类型的其它抗体)并含有抗原结合位点。

[0088] 术语“可变的”指可变结构域中的某些区段在抗体序列中差异广泛的情况。可变结构域介导抗原结合并限定特定抗体对其特定抗原的特异性。然而,变异性并非均匀分布于可变结构域跨越的全部氨基酸。相反,其集中在三个称为高变区(HVR)的区段(在轻链和重链可变结构域中均有),即分别为重链可变区的HCDR1、HCDR2、HCDR3(重链抗体中可简称为CDR1、CDR2、CDR3)以及轻链可变区的LCDR1、LCDR2和LCDR3。可变结构域中更为高度保守的部分称为构架区(FR)。天然重链和轻链的可变结构域各自包含四个FR区(FR1、FR2、FR3和

FR4), 它们大多采取 β -折叠构象, 通过形成环状连接且在有些情况中形成 β -折叠结构一部分的三个HVR连接。每条链中的HVR通过FR区非常接近的保持在一起, 并与另一条链的HVR一起促成抗体的抗原结合位点的形成。通常, 轻链可变区的结构为FR1-LCDR1-FR2-LCDR2-FR3-LCDR3-FR4, 重链可变区的结构为FR1-HCDR1-FR2-HCDR2-FR3-HCDR3-FR4。恒定结构域不直接参与抗体与抗原的结合, 但展现出多种效应子功能, 如在抗体依赖性细胞介导的细胞毒性中抗体的参与。

[0089] “Fc区”(可结晶片段区域)或“Fc结构域”或“Fc”是指抗体重链的C-末端区域, 其介导免疫球蛋白与宿主组织或因子的结合, 包括与位于免疫系统的各种细胞(例如, 效应细胞)上的Fc受体的结合, 或者与经典补体系统的第一组分(C1q)的结合。在IgG, IgA和IgD抗体同种型中, Fc区由来自抗体两条重链的CH2结构域和CH3结构域的两个相同的蛋白片段构成; IgM和IgE的Fc区在每个多肽链中包含三个重链恒定结构域(CH结构域2-4)。虽然免疫球蛋白重链的Fc区的边界可以变化, 但是人IgG重链Fc区通常定义为从重链位置C226或P230的氨基酸残基到羧基端的序列段, 其中该编号是根据EU索引, 如在Kabat中一样。如本文所使用的, Fc区可以是天然序列Fc或变体Fc。

[0090] “抗体片段”包含完整抗体的一部分, 优选完整抗体的抗原结合区和/或可变区。抗体片段优选为抗体的抗原结合片段。抗体片段的例子包括Fab、Fab'、F(ab')₂和Fv片段; 双抗体; 线性抗体; 单链抗体分子; scFv-Fc片段; 由抗体片段形成的多特异性抗体; 以及通过化学修饰或通过掺入脂质体中应能够增加半衰期的任何片段。用木瓜蛋白酶消化抗体产生称作“Fab”片段的两个相同的抗原结合片段, 和一个残余“Fc”片段, 其名称反映了它易于结晶的能力。Fab片段由完整轻链及重链可变结构域(VH)和一条重链第一恒定结构域(CH1)组成。每个Fab片段在抗原结合方面是单价的, 即其具有单个抗原结合位点。胃蛋白酶处理抗体产生一个较大F(ab')₂片段, 它粗略相当于两个通过二硫键相连的Fab片段, 具有不同抗原结合活性且仍能够交联抗原。Fab'片段因在CH1结构域的羧基末端增加了一些另外的残基(包括来自抗体铰链区的一个或多个半胱氨酸)而与Fab片段有所不同。F(ab')₂抗体片段最初是作为成对Fab'片段生成的, 在Fab'片段之间具有铰链半胱氨酸。抗体片段的其它化学偶联也是已知的。Fc片段包含通过二硫键保持在一起的两条重链的羧基末端部分。抗体的效应子功能是由Fc区中的序列决定的, 该区还是由在某些类型细胞上发现的Fc受体(FcR)所识别的区。

[0091] “Fv”是含有完整抗原识别和结合位点的最小抗体片段。该片段由紧密、非共价结合的一个重链可变结构域和一个轻链可变结构域的二聚体组成。从这两个结构域的折叠中突出了六个高变环(重链和轻链各3个环), 贡献出抗原结合的氨基酸残基并赋予抗体以抗原结合特异性。然而, 即使是单个可变结构域(或只包含对抗原特异的三个HVR的半个Fv)也具有识别和结合抗原的能力, 尽管亲和力低于完整结合位点。“单链Fv”也可缩写为“sFv”或“scFv”, 是包含抗体VH和VL结构域的连接成一条多肽链的抗体片段。优选的是, sFv多肽在VH和VL结构域之间还包含多肽接头, 使得sFv形成期望的抗原结合结构。

[0092] 本文中, 术语“单克隆抗体”指从一群基本上同质的抗体中获得的抗体, 即除了可能以少量存在的可能的天然出现的突变和/或翻译后修饰(例如异构化、酰胺化)之外, 构成群体的各个抗体是相同的。单克隆抗体是高度特异性的, 针对单个抗原位点。与多克隆抗体制剂(其典型地包括针对不同决定簇(表位)的不同抗体)相比, 每个单克隆抗体针对抗原上

的单个决定簇。除它们的特异性外,单克隆抗体的优势在于它们通过杂交瘤培养合成,未受到其它免疫球蛋白的污染。修饰语“单克隆”表明抗体从基本上同质的抗体群获得的特征,不应解释为要求通过任何特定方法来生产抗体。例如,将根据本发明使用的单克隆抗体可通过多种技术来生成,包括例如杂交瘤法、噬菌体展示法、重组DNA法、及用于从具有部分或整个人免疫球蛋白基因座或编码人免疫球蛋白序列的基因的动物生成人或人样抗体的技术、单细胞测序法。

[0093] 单克隆抗体在本文中也包括“嵌合”抗体,其中重链和/或轻链的一部分与衍生自特定物种或属于特定抗体类别或亚类的抗体中的相应序列相同或同源,而链的剩余部分与衍生自另一物种或属于另一抗体类别或亚类的抗体中的相应序列相同或同源,以及此类抗体的片段,只要它们展现出期望的生物学活性。

[0094] 非人(例如鼠)抗体的“人源化”形式指最低限度包含衍生自非人免疫球蛋白的序列的嵌合抗体。因此,“人源化抗体”通常指可变结构域构架区与在人抗体中发现的序列交换的非人抗体。通常在人源化抗体中,整个抗体(除CDR以外)由人来源的多核苷酸编码或与这种抗体相同(除CDR以外)。CDR(其中一些或全部由源自非人生物体的核酸编码)被移植到人抗体可变区的 β -折叠骨架中以产生抗体,其特异性由被移植的CDR来决定。这类抗体的产生方法本领域周知,例如使用具有基因工程免疫系统的小鼠而产生。本发明中,抗体、单域抗体、重链抗体等均包括各所述抗体的经人源化的变体。

[0095] “人抗体”指这样的抗体,其具有与由人生成的抗体的氨基酸序列对应的氨基酸序列和/或使用本文所公开的用于生成成人抗体的任何技术产生。人抗体的这种定义明确排除包含非人抗原结合残基的人源化抗体。人抗体可使用本领域已知的多种技术来生成,包括噬菌体展示文库。

[0096] 在一些实施方案中,本发明还提供与本发明的任何抗PD-1单域抗体结合人PD-1上相同表位的单域抗体、重链抗体、抗体或其抗原结合片段,即能够与本发明的任何单域抗体交叉竞争与PD-1的结合的单域抗体、重链抗体、抗体或其抗原结合片段。

[0097] 本发明中,抗PD-1单域抗体的CDR1包括SEQ ID NO:1所示的序列,SEQ ID NO:1是GX₁X₂X₃X₄X₅X₆X₇,其中,X₁为D、F、G、H、L或R,X₂为P、S或T,X₃为A、F、I、L、N、R、S或V,X₄为D、F、G、L、M、N或S,X₅为A、D、F、G、I、N、R、S或T,X₆为D、F、H、I、L、S、V、W或Y,X₇为A、D、E、G、N、P、S或T。示例性地,CDR1包括SEQ ID NO:4-39、320中任一所示的序列。

[0098] 抗PD-1单域抗体的CDR2包括SEQ ID NO:2所示的序列,SEQ ID NO:2是X₁X₂X₃X₄X₅X₆X₇X₈X₉,其中,X₁为I、L、S、T或V,X₂为A、N、S或T,X₃为F、G、I、K、L、M、N、Q、R、S、T、W或Y,X₄为A、D、G、H、N、R、S或T,X₅为A、D、G、N、R、S或无,X₆为G或R、S或T,X₇为D、E、I、L、M、N、R、S、T或V,X₈为A、K、M、Q或T,X₉为A或无。示例性地,CDR2包括SEQ ID NO:40-75中任一所示的序列。

[0099] 抗PD-1单域抗体的CDR3包括SEQ ID NO:3所示的序列,SEQ ID NO:3是X₁X₂X₃X₄X₅X₆X₇X₈X₉X₁₀X₁₁X₁₂X₁₃X₁₄X₁₅X₁₆X₁₇X₁₈X₁₉X₂₀X₂₁X₂₂,其中,X₁是A、E、G、N、R、S、T或V,X₂是A、G、I、K、L、P、R、T或V,X₃是A、D、E、G、K、N、P、R、S、V或Y,X₄是A、C、D、E、G、I、K、L、R、S、T、V或Y,X₅是A、C、D、F、G、H、I、K、L、N、P、Q、R、S、W或Y,X₆是A、C、D、E、G、I、K、L、M、P、Q、R、S或Y,X₇是A、C、D、F、G、H、I、N、P、R、S、T、V或Y,X₈是A、C、D、E、G、I、R、S、T、V、W、Y或无,X₉是A、D、E、F、G、I、L、P、R、S、V、W、Y或无,X₁₀是C、D、F、G、K、L、N、P、R、S、T、V、W、Y或无,X₁₁是D、F、G、H、I、K、L、N、P、S、T、V、Y或无,X₁₂是A、D、G、H、I、L、M、P、R、S、T、V、Y或无,X₁₃是C、D、E、H、P、R、S、T、V、Y或无,X₁₄是A、D、E、F、H、I、

L、P、R、T、Y或无, X_{15} 是A、D、E、G、N、Q、R、S、T、V、Y或无, X_{16} 是A、D、E、F、G、H、M、P、S、V、Y或无, X_{17} 是A、D、E、H、N、Q、R、T、Y或无, X_{18} 是D、E、R、S、Y或无, X_{19} 是N、S、Y或无, X_{20} 是D、E、Y或无, X_{21} 是E、N、Y或无, X_{22} 是Y或无。示例性地, CDR3包括SEQ ID NO:76-183中任一所示的序列。

[0100] 在一个或多个实施方案中, 单域抗体是NB182、NB194或其变体, CDR1包括SEQ ID NO:16、19、36-39、320中任一所示的序列, CDR2包括SEQ ID NO:52、53、55、72-75所示的序列, CDR3包括SEQ ID NO:76、87、108-183中任一所示的序列。或者, CDR1包括SEQ ID NO:16或19所示的序列, CDR2包括SEQ ID NO:52、53、55、72、73所示的序列, CDR3包括SEQ ID NO:87、108-111、113-134、136-146、148-154、156-163、165-168、172、173、177-183中任一所示的序列。或者CDR1包括SEQ ID NO:19、36-39、320中任一所示的序列, CDR2包括SEQ ID NO:53、55、72-75中任一所示的序列, CDR3包括SEQ ID NO:87、108-183中任一所示的序列。

[0101] 在一个或多个实施方案中, 所述单域抗体含有表1中组a1到组a136中任一组所示的CDR1、CDR2和CDR3:

[0102] 表1

[0103]

抗体名称	CDR1	CDR2	CDR3	VHH	组
NB139	4	40	76	184	a1
NB147	5	41	77	185	a2
NB148	6	42	78	186	a3
NB153	7	43	76	187	a4
NB154	8	44	79	188	a5
NB159	9	45	80	189	a6
NB164	10	46	81	190	a7
NB166	11	47	82	191	a8
NB169	12	48	83	192	a9
NB170	13	49	84	193	a10
NB171	10	50	85	194	a11
NB172	14	47	76	195	a12
NB173	15	51	86	196	a13
NB182	16	52	76	197	a14

[0104]

NB189	17	53	87	198	a15
NB192	18	54	88	199	a16
NB194	19	55	87	200	a17
NB195	20	56	82	201	a18
NB196	21	57	89	202	a19
NB197	22	58	90	203	a20
NB200	23	59	91	204	a21
NB202	14	47	76	205	a22
NB205	24	60	92	206	a23
NB209	25	40	76	207	a24
NB211	26	61	93	208	a25
NB215	27	62	94	209	a26
NB216	24	60	95	210	a27
NB218	28	41	96	211	a28
NB220	10	63	97	212	a29
NB221	5	41	98	213	a30
NB222	29	64	99	214	a31
NB223	7	65	100	215	a32
NB532	30	66	101	216	a33
NB548	31	67	102	217	a34
NB733	32	68	103	218	a35
NB734	33	56	104	219	a36
NB735	34	69	105	220	a37
NB754	35	70	106	221	a38
NB755	7	71	107	222	a39
NB182-z1	16	52	76	223	a40
NB182-z2	16	52	76	224	a41
NB182-z3	16	52	76	225	a42
NB182-z4	16	52	76	226	a43
NB182-z5	16	52	76	227	a44
NB194-z1	19	72	87	228	a45
NB194-z2	19	72	87	229	a46
NB194-z3	19	72	87	230	a47
NB194-z4	19	73	87	231	a48
NB194-z5	19	53	87	232	a49
NB194-P01	19	53	87	233	a50
NB194-P02	19	53	108	234	a51
NB194-P03	19	53	109	235	a52
NB194-P04	19	53	110	236	a53
NB194-P05	19	53	111	237	a54
NB194-P06	36	74	112	238	a55
NB194-P07	19	53	113	239	a56
NB194-P08	19	53	114	240	a57
NB194-P09	19	53	115	241	a58
NB194-P10	19	53	116	242	a59
NB194-P11	19	53	117	243	a60

[0105]

NB194-P12	19	53	118	244	a61
NB194-P13	19	53	119	245	a62
NB194-P14	19	53	120	246	a63
NB194-P15	19	53	121	247	a64
NB194-P16	19	53	122	248	a65
NB194-P17	19	53	123	249	a66
NB194-P18	19	53	124	250	a67
NB194-P19	19	53	125	251	a68
NB194-P20	19	53	126	252	a69
NB194-P21	19	53	127	253	a70
NB194-P22	19	53	128	254	a71
NB194-P23	19	53	129	255	a72
NB194-P24	19	53	130	256	a73
NB194-P25	19	53	131	257	a74
NB194-P26	19	53	132	258	a75
NB194-P27	19	53	133	259	a76
NB194-P28	19	53	134	260	a77
NB194-P29	37	75	135	261	a78
NB194-P30	19	53	136	262	a79
NB194-P31	19	53	137	263	a80
NB194-P32	19	53	138	264	a81
NB194-P33	19	53	139	265	a82
NB194-P34	19	53	140	266	a83
NB194-P35	19	53	141	267	a84
NB194-P36	19	53	142	268	a85
NB194-P37	19	53	143	269	a86
NB194-P38	19	53	144	270	a87
NB194-P39	19	53	145	271	a88
NB194-P40	19	53	146	272	a89
NB194-P41	38	53	147	273	a90
NB194-P42	19	53	148	274	a91
NB194-P43	19	53	149	275	a92
NB194-P44	19	53	150	276	a93
NB194-P45	19	53	151	277	a94
NB194-P46	19	53	152	278	a95
NB194-P47	19	53	153	279	a96
NB194-P48	19	53	154	280	a97
NB194-P49	39	53	155	281	a98
NB194-P50	19	53	156	282	a99
NB194-P51	19	53	157	283	a100
NB194-P52	19	53	158	284	a101
NB194-P53	19	53	159	285	a102
NB194-P54	19	53	160	286	a103
NB194-P55	19	53	161	287	a104
NB194-P56	19	53	162	288	a105
NB194-P57	19	53	163	289	a106

[0106]

NB194-P58	37	53	164	290	a107
NB194-P59	19	53	165	291	a108
NB194-P60	19	53	166	292	a109
NB194-P61	19	53	167	293	a110
NB194-P62	19	53	168	294	a111
NB194-P63	36	74	169	295	a112
NB194-P64	38	53	170	296	a113
NB194-P65	37	53	171	297	a114
NB194-P66	19	53	172	298	a115
NB194-P67	19	53	173	299	a116
NB194-P68	38	53	174	300	a117
NB194-P69	38	53	175	301	a118
NB194-P70	36	74	176	302	a119
NB194-P71	19	53	177	303	a120
NB194-P72	19	53	178	304	a121
NB194-P73	19	53	179	305	a122
NB194-P74	19	53	180	306	a123
NB194-P75	19	53	181	307	a124
NB194-P76	19	53	182	308	a125
NB194-P77	19	53	183	309	a126
NB194-P29-z1	37	75	135	310	a127
NB194-P29-z2	37	75	135	311	a128
NB194-P29-z3	37	75	135	312	a129
NB194-P29-z4	37	75	135	313	a130
NB194-P29-z5	37	75	135	314	a131
NB194-P29-z6	37	75	135	315	a132
NB194-P29-z7	37	75	135	316	a133
NB194-P29-z8	37	75	135	317	a134
NB194-P29-z9	320	75	135	318	a135
NB194-P29-z10	37	75	135	319	a136

[0107] 优选含有选自以下的任一组所示的CDR1、CDR2和CDR3:a14、a17、a40-a136,或者优选含有选自以下的任一组所示的CDR1、CDR2和CDR3:a14、a40-a44,或者优选含有选自以下的任一组所示的CDR1、CDR2和CDR3:a17、a45-a136。

[0108] 在一个或多个实施方案中,所述单域抗体VHH的FR1可选自表1中各抗体编号的VHH的FR1,VHH的FR2可选自表1中各抗体编号的VHH的FR2,VHH的FR3可选自表1中各抗体编号的VHH的FR3,VHH的FR4可选自表1中各抗体编号的VHH的FR4。

[0109] 在优选的实施方案中,所述单域抗体的FR区为选自SEQ ID NO:184-319的任一VHH的FR区。进一步优选地,这类抗体的CDR选自前述组a1到组a136中的任一组所示的CDR。在一个或多个实施方案中,所述单域抗体VHH如SEQ ID NO:184-319中任一所示。优选地,所述单域抗体如SEQ ID NO:197、200、223-319中任一所示。

[0110] 本文所述PD-1结合分子可以是包含一条、两条或多条本文所述的抗PD-1单域抗体的单价或多价单域抗体、多特异性单域抗体、重链抗体或其抗原结合片段、抗体或其抗原结合片段。所述重链抗体还包含重链恒定区,例如骆驼重链抗体或软骨鱼重链抗体的恒定区。优选地,所述重链恒定区如SEQ ID NO:321所示。

[0111] 本发明还包括所述抗体衍生物和类似物。“衍生物”和“类似物”是指基本上保持本

发明抗体相同的生物学功能或活性的多肽。本发明的衍生物或类似物可以是 (i) 在一个或多个氨基酸残基中具有取代基团的多肽, 或 (ii) 成熟多肽与另一个化合物 (比如延长多肽半衰期的化合物, 例如聚乙二醇) 融合所形成的多肽, 或 (iii) 附加的氨基酸序列融合到此多肽序列而形成的多肽 (如前导序列或分泌序列或用来纯化此多肽的序列或蛋白原序列, 或与6His标签形成的融合蛋白)。根据本文的教导, 这些衍生物和类似物属于本领域技术人员公知的范围。

[0112] 在不实质性影响抗体活性的前提下, 本领域技术人员可以对本发明的序列改变一个或更多个 (例如1、2、3、4、5、6、7、8、9或10个或更多个) 氨基酸, 以获得所述抗体或其功能性片段序列的变体。这些变体包括 (但并不限于): 一个或多个 (通常为1-50个, 较佳地1-30个, 更佳地1-20个, 最佳地1-10个) 氨基酸的缺失、插入和/或取代, 以及在C末端和/或N末端添加一个或数个 (通常为20个以内, 较佳地为10个以内, 更佳地为5个以内) 氨基酸。在本领域中, 用性能相近或相似的氨基酸进行保守性取代时, 通常不会改变蛋白质的功能。如在可变区的FR和/或CDR区中将具有类似性质的氨基酸进行取代。可进行保守性取代的氨基酸残基为本领域所周知。这样的取代的氨基酸残基可以是也可以不是由遗传密码编码的。又比如, 在C末端和/或N末端添加一个或数个氨基酸通常也不会改变蛋白质的功能。它们都被视为包括在本发明保护的范围内。

[0113] 本文所述抗体的变异形式包括: 同源序列、保守性变异体、等位变异体、天然突变体、诱导突变体、在高或低的严紧度条件下能与本发明抗体的编码DNA杂交的DNA所编码的蛋白、以及利用抗本发明抗体的抗血清获得的多肽或蛋白。

[0114] 在一些实施方案中, 本发明所述变体的序列可以与其来源序列有至少有95%、96%、97%、98%或99%的一致性。本发明所述的序列一致性可以使用序列分析软件测量。例如使用缺省参数的计算机程序BLAST, 尤其是BLASTP或TBLASTN。本发明还包括那些具有带CDR的抗体重链可变区的分子, 只要其CDR与此处鉴定的CDR具有90%以上 (较佳地95%以上, 最佳地98%以上) 的同源性。

[0115] 可采用本领域常规的方法制备本发明的抗体, 如本领域熟知的杂交瘤技术。可采用本领域常规的方法制备本发明的重链抗体, 如本领域熟知的噬菌体展示技术。或者, 本发明的抗体或重链抗体可在其他细胞系中表达。可用编码本发明抗体的序列转化合适的哺乳动物宿主细胞。转化可采用任何已知的方法进行, 例如包括将多核苷酸包装在病毒 (或病毒载体中) 并用病毒 (或载体) 转导宿主细胞。所用的转化程序取决于将转化的宿主。用于将异源多核苷酸引入哺乳动物细胞中的方法为本领域所熟知, 包括葡聚糖介导的转染、磷酸钙沉淀、聚凝胺介导的转染、原生质体融合、电穿孔、将多核苷酸囊封在脂质体中和将DNA直接微注射至核中等。可用作用于表达的宿主的哺乳动物细胞系为本领域所熟知, 包括但不限于可从美国典型培养物保藏中心 (ATCC) 获得的多种永生化细胞系, 包括但不限于中国仓鼠卵巢 (CHO) 细胞、HeLa细胞、幼仓鼠肾 (BHK) 细胞、猴肾细胞 (COS)、人肝细胞癌细胞 (例如, HepG2) 等。尤其优选的细胞系通过确定哪些细胞系具有高表达水平并产生具有基本PD-1结合特性的抗体来进行选择。

[0116] 核酸

[0117] 本发明还提供了编码上述抗体或其片段的多核苷酸。本文提供编码重链可变区、轻链可变区、重链、轻链以及各CDR的多核苷酸。本发明的多核苷酸可以是DNA形式或RNA形

式。DNA形式包括cDNA、基因组DNA或人工合成的DNA。DNA可以是单链的或是双链的。DNA可以是编码链或非编码链。

[0118] 如本领域技术人员将了解,由于遗传密码的简并性,可制得极大量的核酸,它们全部编码本发明的抗体或其抗原结合片段。因此,在已鉴定特定氨基酸序列的情况下,本领域技术人员可通过以不改变编码蛋白质的氨基酸序列的方式简单地修饰一个或多个密码子的序列来制得任何数量的不同的核酸。所以,本发明还涉及与上述多核苷酸序列杂交且两个序列之间具有至少50%,较佳地至少70%,更佳地至少80%相同性的多核苷酸。本发明特别涉及在严谨条件下与本发明所述多核苷酸可杂交的多核苷酸。在本发明中,“严谨条件”是指:(1)在较低离子强度和较高温度下的杂交和洗脱,如 $0.2 \times \text{SSC}$, $0.1\% \text{SDS}$, 60°C ;或(2)杂交时加有变性剂,如50% (v/v) 甲酰胺, 0.1% 小牛血清/ $0.1\% \text{Ficoll}$, 42°C 等;或(3)仅在两条序列之间的相同性至少在90%以上,更好是95%以上时才发生杂交。并且,可杂交的多核苷酸编码的多肽与成熟多肽有相同的生物学功能和活性。

[0119] 本发明的抗体的核苷酸全长序列或其片段通常可以用PCR扩增法、重组法或人工合成的方法获得。一种可行的方法是用人工合成的方法来合成有关序列,尤其是片段长度较短时。通常,通过先合成多个小片段,然后再进行连接可获得序列很长的片段。此外,还可将重链的编码序列和表达标签(如6His)融合在一起,形成融合蛋白。

[0120] 一旦获得了有关的序列,就可以用重组法来大批量地获得有关序列。这通常是将其克隆入载体,再转入细胞,然后通过常规方法从增殖后的宿主细胞中分离得到有关序列。本发明所涉及的生物分子(核酸、蛋白等)包括以分离的形式存在的生物分子。目前,已经可以完全通过化学合成来得到编码本发明蛋白(或其片段,或其衍生物)的DNA序列。然后可将该DNA序列引入本领域中已知的各种现有的DNA分子(或如载体)和细胞中。此外,还可通过化学合成将突变引入本发明蛋白序列中。

[0121] 所以,本发明还涉及包含上述的适当DNA序列以及适当启动子或者控制序列的核酸构建物,例如表达载体和重组载体。这些载体可以用于转化适当的宿主细胞,以使其能够表达蛋白质。载体通常含有用于质粒维系和用于克隆与表达外源性核苷酸序列的序列。所述序列(在某些实施方案中总称为“侧翼序列”)通常包括一个或多个以下核苷酸序列:启动子、一个或多个增强子序列、复制起点、转录终止序列、含有供体和受体剪接位点的完全内含子序列、编码用于多肽分泌的前导序列的序列、核糖体结合位点、聚腺苷酸化序列、用于插入编码将要表达的抗体的核酸的多连接子区和可选标记元件。示例性的载体可参见CN105154473A和CN111206043A,这些文献通过引用全文纳入本文。

[0122] 宿主细胞可以是原核细胞,如细菌细胞;或是低等真核细胞,如酵母细胞;或是高等真核细胞,如哺乳动物细胞。代表性例子有:大肠杆菌,链霉菌属;鼠伤寒沙门氏菌的细菌细胞;真菌细胞如酵母;果蝇S2或Sf9的昆虫细胞;CHO、COS7、293细胞的动物细胞等。

[0123] 在某些实施方案中,宿主细胞可以是本领域周知的各种功能细胞,例如各种杀伤性细胞,包括但不限于细胞因子诱导的杀伤细胞(CIK)、树突状细胞刺激的细胞因子诱导的杀伤细胞(DC-CIK)、细胞毒性T淋巴细胞(CTL)、 $\gamma \delta$ T细胞、自然杀伤细胞(NK)、肿瘤浸润淋巴细胞(TIL)、淋巴因子激活杀伤细胞(LAK)、CD3AK细胞(抗CD3单抗的杀伤细胞)和CAR-T/TCR-T细胞。在某些实施方案中,所述杀伤性细胞为T细胞或NK细胞。示例性的NK细胞包括但不限于原代NK细胞、NK细胞株(如NK92)和NKT细胞。在某些实施方案中,所述NK细胞为原代

NK细胞。示例性的T细胞包括但不限于外周血T淋巴细胞、细胞毒杀伤T细胞(CTL)、辅助T细胞、抑制/调节性T细胞、 $\gamma\delta$ T细胞以及细胞因子诱导的杀伤细胞(CIK)、肿瘤浸润淋巴细胞(TIL)等混合细胞群体的T细胞。在某些实施方案中,所述T细胞为外周血T淋巴细胞与源自TIL的T细胞。

[0124] 在某些实施方案中,宿主细胞含有表达嵌合抗原受体(CAR)的编码序列和/或表达嵌合抗原受体。

[0125] 用重组DNA转化宿主细胞可用本领域技术人员熟知的常规技术进行。当宿主为原核生物如大肠杆菌时,能吸收DNA的感受态细胞可在指数生长期后收获,用 CaCl_2 法处理,所用的步骤在本领域众所周知。另一种方法是使用 MgCl_2 。如果需要,转化也可用电穿孔的方法进行。当宿主是真核生物,可选用如下的DNA转染方法:磷酸钙共沉淀法,常规机械方法如显微注射、电穿孔,脂质体包装等。

[0126] 获得的转化子可以用常规方法培养,表达本发明的基因所编码的多肽。根据所用的宿主细胞,培养中所用的培养基可选自各种常规培养基。在适于宿主细胞生长的条件下进行培养。当宿主细胞生长到适当的细胞密度后,用合适的方法(如温度转换或化学诱导)诱导选择的启动子,将细胞再培养一段时间。

[0127] 在上面的方法中的多肽可在细胞内、或在细胞膜上表达、或分泌到细胞外。如果需要,可利用其物理的、化学的和其它特性通过各种分离方法分离和纯化重组的蛋白。这些方法是本领域技术人员所熟知的。这些方法的例子包括但不限于:常规的复性处理、用蛋白沉淀剂处理(盐析方法)、离心、渗透破菌、超处理、超离心、分子筛层析(凝胶过滤)、吸附层析、离子交换层析、高效液相层析(HPLC)和其它各种液相层析技术及这些方法的结合。

[0128] 治疗用途和药物组合物

[0129] 通过构建纳米抗体文库,发明人发现并表达纯化126个可以结合PD-1的纳米抗体及其变体。通过蛋白水平亲和力检测、细胞水平亲和力检测、肿瘤细胞PD-1结合检测、表位竞争实验和组织交叉反应验证了这些抗体的对抗原和细胞的结合能力和药物安全性。

[0130] 本文所述的抗体的所有方面都可用于制备用以预防或治疗本文所述各种病况和疾病的药物,所述病况和疾病尤其病况与表达PD-1的细胞相关的疾病或病况。在一些实施方案中,所述病况和疾病是癌症,包括但不限于:黑色素瘤、肺癌、头颈部癌、肾细胞癌、泌尿道上皮癌、非霍奇金淋巴瘤等。

[0131] 本文的药物组合物含有本文所述结合分子,以及药学上可接受的辅料,包括但不限于稀释剂、载剂、增溶剂、乳化剂、防腐剂和/或佐剂。辅料优选地在所采用的剂量和浓度下对接受者无毒。这类辅料包括(但不限于):盐水、缓冲液、葡萄糖、水、甘油、乙醇、及其组合。在某些实施方案中,药物组合物可含有用于改善、维持或保留例如组合物的pH、渗透性、粘度、澄清度、颜色、等渗性、气味、无菌性、稳定性、溶解或释放速率、吸收或渗透的物质。这些物质为现有技术已知。可视预期的施用途径、递送方式和所需的剂量来确定最佳的药物组合物。

[0132] 用于体内施用的药物组合物通常以无菌制剂的形式提供。通过经无菌过滤膜过滤来实现灭菌。在组合物冻干时,可在冻干和复水之前或之后使用此方法进行灭菌。可选择本发明的药物组合物用于肠胃外递送。用于肠胃外施用的组合物可以冻干形式或在溶液中储存。例如用生理盐水或含有葡萄糖和其他辅剂的水溶液通过常规方法进行制备。肠胃外组

合物通常放在具有无菌进入孔的容器中,例如具有皮下注射针可刺穿的塞子的静脉内溶液带或小瓶。或者,可选择组合物用于吸入或通过消化道(诸如经口)递送。所述药学上可接受的组合物的制备在本领域的技术内。其它药物组合物将为本领域技术人员显而易见,包括在持续或控制释放递送配制物中包含抗体的配制物。用于配制多种其它持续或可控传递方式的技术(诸如脂质体载剂、生物易蚀微粒或多孔珠粒和积存注射)也为本领域技术人员所知。

[0133] 药物组合物一经配制,就以溶液、悬浮液、凝胶、乳液、固体、晶体或以脱水或冻干粉末的形式储存在无菌小瓶中。所述配制物可储存成即用形式或在施用前复水的形式(例如,冻干)。本发明还提供用于产生单剂量施用单位的试剂盒。本发明的试剂盒可各自含有具有干燥蛋白的第一容器和具有含水配制物的第二容器。在本发明的某些实施方案中,提供含有单腔和多腔预填充注射器(例如,液体注射器和冻干注射器)的试剂盒。

[0134] 本发明也提供通过施用本发明任一实施方案所述的结合分子或其药物组合物来治疗患者(尤其是患者的PD-1相关疾病)的方法。本文中,术语“患者”、“受试者”、“个体”、“对象”在本文中可互换使用,包括任何生物体,优选动物,更优选哺乳动物(例如大鼠、小鼠、狗、猫、兔等),且最优选的是人。“治疗”指向受试者采用本文所述治疗方案以达到至少一种阳性治疗效果(比如,癌症细胞数目减少、肿瘤体积减小、癌细胞浸润至周边器官的速率降低或肿瘤转移或肿瘤生长的速率降低)。有效治疗患者的治疗方案可根据多种因素(比如患者的疾病状态、年龄、体重及疗法激发受试者的抗癌反应的能力)而变。

[0135] 将采用的含有本发明结合分子的药物组合物的治疗有效量将取决于例如治疗程度和目标。本领域技术人员将了解,用于治疗的适当剂量水平将部分取决于所递送的分子、适应症、施用途径和患者的大小(体重、体表或器官大小)和/或状况(年龄和一般健康状况)而变化。在某些实施方案中,临床医生可滴定剂量并改变施用途径来获得最佳的治疗效果。例如每天约10微克/千克体重-约50毫克/千克体重。

[0136] 给药频率将取决于所用配制物中结合分子的药物动力学参数。临床医生典型地施用组合物直到达到实现所需效果的剂量。组合物因此可作为单次剂量施用,或随时间以作为两次或多次剂量(可含有或不含有相同量的所需分子)施用,或通过植入装置或导管以连续输液的方式施用。

[0137] 药物组合物的施用途径是根据已知方法,例如经口、通过静脉内、腹膜内、脑内(脑实质内)、脑室内、肌肉内、眼内、动脉内、门静脉或病灶内途径注射;通过持续释放系统或通过植入装置。

[0138] 诊断、检测和试剂盒

[0139] 本发明的结合分子因其与PD-1的高亲合力可用于测定,例如结合测定来检测和/或定量在组织或细胞中表达的PD-1。结合分子例如单域抗体可用在进一步研究PD-1在疾病中的作用的研究中。检测PD-1的方法大致如下:获得细胞和/或组织样本;检测样本中PD-1的水平。

[0140] 本发明的PD-1结合分子可用于诊断目的,用来检测、诊断或监控与PD-1相关的疾病和/或病况。本发明提供使用本领域技术人员已知的经典免疫组织学方法检测样本中PD-1的存在。可以体内或体外进行PD-1的检测。适用于检测PD-1的存在的方法实例包括ELISA、FACS、RIA等。

[0141] 对于诊断应用来说,通常用可检测的标记基团来标记结合分子例如单域抗体。合适的标记基团包括(但不限于)以下:放射性同位素或放射性核素(例如,3H、14C、15N、35S、90Y、99Tc、111In、125I、131I)、荧光基团(例如,FITC、罗丹明、镧系元素磷光体)、酶促基团(例如,辣根过氧化物酶、 β 根半乳糖苷酶、荧光素酶、碱性磷酸酶)、化学发光基团、生物素基基团或由二级报导体识别的预定多肽表位(例如,亮氨酸拉链对序列、用于二级抗体的结合位点、金属结合结构域、表位标签)、MRI(磁共振成像)或CT(电子计算机X射线断层扫描技术)造影剂。用于标记蛋白质的各种方法在本领域中已知且可用来进行本发明。

[0142] 本发明的另一方面提供检测与本发明的抗体竞争结合PD-1的测试分子的存在的方法。一种所述测定的实例将涉及在存在或不存在测试分子的情形下检测含有一定量PD-1的溶液中的游离抗体的量。游离抗体(即,未结合PD-1的抗体)的量增加将表示测试分子能与该抗体竞争结合PD-1。在一个实施方案中,用标记基团标记抗体。或者,标记测试分子并在存在或不存在抗体的情形下监控游离测试分子的量。

[0143] 本发明还提供了用于检测PD-1水平的检测试剂盒,该试剂盒包括识别PD-1蛋白的抗体,用于溶解样本的裂解介质,检测所需的通用试剂和缓冲液,如各种缓冲液、检测标记、检测底物等。该检测试剂盒可以是体外诊断装置。

[0144] 下文将以具体实施例的方式阐述本发明。应理解,这些实施例仅仅是阐述性的,并非意图限制本发明的范围。实施例中所用到的方法和材料,除非另有说明,否则均为本领域常规的材料和方法。

[0145] 实施例

[0146] 实施例1,羊驼免疫

[0147] 1.1免疫原制备:

[0148] 根据NCBI上查询PD-1蛋白序列,与人IgG Fc片段序列进行融合,委托南京金斯瑞公司进行合成构建pCDNA3.4(Thermo)质粒的真核表达载体,将合成后的质粒利用EXpiCHO™(Thermo Fisher)表达系统表达,表达后用5mL的Protein A预装柱(GE)进行一步亲和纯化,将纯化后样品置换如PBS缓冲液中,经SDS-PAGE电泳凝胶与HPLC鉴定纯度,ELISA鉴定活性后,分装冻存于-80度冰箱用于后续免疫。

[0149] 1.2羊驼免疫:

[0150] 首次免疫抗原(PD-1.hFc)量为400 μ g,与佐剂(GERBU FAMA)混匀,选取羊驼背部皮下四点注射免疫,每点免疫量为1mL。第二至7次免疫:免疫抗原量为200 μ g,选取羊驼背部皮下四点注射免疫,每点免疫量为1mL。每次免疫间隔时间为一周。

[0151] 1.3免疫血清效价检测:

[0152] 1.3.1蛋白水平效价检测

[0153] 4度过夜包被PD-1.His抗原,封闭洗涤后,将梯度稀释的血清加入ELISA板进行孵育后,再使用anti-llama(抗羊驼)IgG HRP(Abcam)抗体进行孵育,洗涤后加入TMB显色液显色,用2M HCl终止反应,然后用酶标仪检测OD450纳米处吸光值。实验结果如图1所示,经过7次免疫后羊驼效价达到较高水平(>81000)。

[0154] 1.3.2细胞水平效价检测

[0155] 将PD-1转染的CHO-K1细胞铺于96孔板中,细胞量为 3×10^5 细胞/孔。然后用3倍梯度稀释的血清与细胞孵育。孵育、洗涤后,加入anti-llama IgG PE(Jackson)抗体孵育,洗

涤后用PBS重悬细胞,然后用流式细胞仪(Beckman)检测荧光强度(MFI)。经过7次免疫后,羊驼在细胞水平效价达到9000。结果如图2所示。

[0156] 实施例2,针对于PD-1的纳米抗体免疫文库的构建及筛选

[0157] (1)7次免疫结束后,提取骆驼外周血淋巴细胞100mL并提取总RNA。RNA的提取参照TAKARA公司RNAiso试剂说明书进行。

[0158] (2)以RNA为模板,oligo dT为引物,参照TAKARA公司反转录酶说明书合成cDNA第一链。

[0159] (3)采用PrimeSTAR高保真DNA聚合酶,经巢式PCR获得重链抗体的可变区编码基因。用巢式PCR扩增重链抗体的可变区片段:

[0160] 第一轮PCR:

[0161] 上游引物:GTCCTGGCTGCTCTTCTACAAGGC

[0162] 下游引物:GGTACGTGCTGTTGAACTGTTCC

[0163] 扩增重链抗体引导肽和抗体CH2之间的片段,55℃退火,30个循环;回收约600bp的DNA片段,作为第二轮PCR的模板。

[0164] 第二轮PCR:

[0165] 上游引物:GATGTGCAGCTGCAGGAGTCTGGRGGAGG

[0166] 下游引物:GGACTAGTGCGGCCGCTGGAGACGGTGACCTGGGT

[0167] 扩增重链抗体FR1区和长、短铰链区之间的片段(长片段和短片段),55℃退火,30个循环,回收目的片段,结果显示该片段的大小约为500bp,即纳米抗体基因电泳带约为500bp。

[0168] (4)将噬菌粒pME207和PCR扩增产物分别用Sfi I和Not I双酶切(NEB),回收、定量后,以1:3摩尔比,用T4 DNA连接酶(TaKaRa)连接两个片段,在16℃,过夜连接。

[0169] (5)连接产物经乙醇沉淀后,溶于100μL无菌水,分十次进行电穿孔转化大肠杆菌TG1。取100μL电击、培养后的菌液倍比稀释,涂布氨苄青霉素LB培养板,计算库容,其余部分全部涂布于氨苄青霉素2×YT培养板,37℃,倒置培养13~16h。用10mL,2×YT培养基将培养板上的菌苔刮洗后,加入终浓度25%甘油,分装,-80℃保存备用。库容的大小为 4.3×10^9 。为检测文库的插入率,随机选取48个克隆做菌落PCR,结果显示插入率已达到90%以上。

[0170] (6)根据计算的库容量结果,接种10倍库容量的活细胞于200mL的2×YT(含2%葡萄糖,100μg/mL氨苄青霉素),37℃,200r/min培养至OD600达0.5,按感染复数20:1加入辅助噬菌体,37℃静置30min后,37℃,200r/min,30min。将培养物离心,用200mL的2×YT(含100μg/mL氨苄青霉素和50μg/mL卡那霉素)重悬沉淀,37℃,250r/min过夜培养后,8000rpm离心取上清,加入5×PEG/NaCl溶液,冰上放置60min,8000rpm离心30min,重悬沉淀于5mL的PBS中,即得到抗PD-1的单域重链抗体(VHH)免疫文库,取10μL测定滴度,其余分装于-80℃保存备用。

[0171] (7)将PD-1蛋白按5μg/mL,100μL每孔包被在酶标板上,4℃放置过夜,同时设立负对照。第二天五个孔中分别加入200μL,3%BSA,室温封闭2小时。2小时后用PBST(PBS中含有0.05%吐温20)洗3遍。洗板后先在每个负筛孔加入100μL用5%脱脂牛奶预封闭的噬菌体($2 \sim 3 \times 10^{11}$ tfu免疫骆驼纳米抗体噬菌展示基因库),在室温下作用1.5小时,再将负筛后上清转移至目的抗原包被孔中,室温下作用1.5小时。用PBST(PBS中含有0.05%吐温20)洗12遍,

以洗掉不结合的噬菌体。用Glycine (SIGMA) 将与PD-1特异性结合的噬菌体解离下,洗脱的噬菌体经Tris(Invitrogen,1M,PH 8.0) 中和后感染处于对数期的TG1,经繁殖扩增,进行下一轮“吸附-洗脱”。最后洗脱下的噬菌体浸染TG1,利用IPTG (Thermo) 诱导TG1表达纳米抗体,取TG1表达的上清做ELISA结合检测与阻断PD-L1.hFc检测。ELISA结合检测使用二抗为 anti-c-myc Antibody HRP (抗c-myc抗体HRP) (Bethyl),阻断PD-L1结合检测使用二抗为 Goat anti-Human IgG-Fc Fragment Antibody HRP (羊抗人IgG-Fc片段抗体HRP) (Bethyl)。

[0172] (8) 通过序列分析后,总计得到39个可以结合PD-1蛋白的纳米抗体,如下表所示。

克隆编号	ELISA (OD450)		
	克隆与PD-1 结合	PD-L1 与PD-1 结合	阴性对照
NB139	3.122	2.394	0.026
NB147	2.627	0.994	0.027

[0174]	NB148	2.841	2.563	0.026
	NB153	3.293	2.052	0.025
	NB154	2.608	2.281	0.026
	NB159	1.837	2.104	0.065
	NB164	2.841	2.001	0.039
	NB166	3.388	2.293	0.026
	NB169	2.895	2.128	0.026
	NB170	2.701	2.015	0.026
	NB171	2.781	0.715	0.026
	NB172	3.052	2.168	0.027
	NB173	2.974	0.794	0.027
	NB182	3.081	0.213	0.028
	NB189	2.968	2.337	0.035
	NB192	2.647	2.240	0.026
	NB194	2.835	0.152	0.025
	NB195	3.131	2.237	0.027
	NB196	3.387	2.491	0.026
	NB197	2.659	2.274	0.025
	NB200	2.305	2.477	0.025
	NB202	3.040	0.723	0.025
	NB205	2.248	2.204	0.027
	NB209	3.219	2.041	0.026
	NB211	2.711	2.211	0.026
	NB215	3.289	1.275	0.027
	NB216	2.746	2.451	0.026
	NB218	2.615	2.318	0.026
	NB220	2.378	2.206	0.026
	NB221	2.623	2.250	0.026
	NB222	3.128	2.227	0.027
	NB223	1.298	2.254	0.027
	NB532	1.358	2.193	0.026
	NB548	2.127	2.429	0.026
	NB733	1.033	2.471	0.026
	NB734	2.173	1.421	0.026
	NB735	1.815	2.437	0.026
	NB754	2.036	2.371	0.026
	NB755	1.704	2.204	0.025

[0175] 实施例3, 候选抗体表达纯化

[0176] 将纳米抗体构建到pCDNA3.4-IgG4载体上, 然后经EXpiCHO™ (Thermo Fisher) 表达系统表达, 表达一周后收取上清进行Protein A (GE) 纯化。然后使用Nanodrop检测蛋白质质量, HPLC检测蛋白纯度。所得蛋白纯度及产量满足后续试验需要。Keytruda和Opdivo根据<https://www.drugbank.ca/>提供的序列制备IgG4抗体。

[0177] 实施例4, 候选抗体表征

[0178] 蛋白水平亲和力检测: 使用表面等离子共振技术 (SPR) 测定抗体对人PD-1.Fc抗原的结合动力学和亲和力。将纯化的抗体流经预先固定protein A的传感器芯片, 抗体被protein A捕获, 然后将5个不同浓度的PD-1.Fc蛋白作为流动相, 结合时间和解离时间分别

为30min和60min。使用Biacore Evaluation Software 2.0(GE)分析结合速率(ka)、解离速率(kd)和平衡常数(KD)。选择上市的PD-1抗体药物Keytruda和Opdivo为对照。结果如下表所示。

[0179]	样品	ka (1/Ms)	kd (1/s)	KD (M)
	NB147	5.58E+04	1.53E-04	2.75E-09
	NB171	4.97E+04	3.09E-04	6.21E-09
	NB173	2.15E+03	1.79E-04	8.31E-08
	NB182	7.38E+03	6.40E-05	8.67E-09
	NB202	2.06E+05	6.77E-05	3.28E-10
	NB211	2.26E+06	3.00E-03	1.33E-09
	NB215	4.90E+04	5.08E-04	1.04E-08
	NB223	1.35E+05	8.63E-04	6.39E-09
	NB194	1.13E+06	7.62E-05	5.62E-10
	NB220	1.48E+06	3.23E-04	2.19E-10
	NB222	2.05E+06	3.06E-04	1.49E-10
	NB532	1.31E+05	9.20E-04	7.03E-09
	NB734	2.36E+05	6.88E-05	2.92E-10
	其他抗体	2.31E+4 至 5.01E+6	8.11E-03 至 7.95E-5	2.74E-8 至 6.32E-10
	Keytruda	1.01E+06	3.33E-04	3.29E-10
	Opdivo	7.08E+05	9.48E-05	1.34E-10

[0180] 实施例5:不同种属PD-1结合

[0181] 分别将不同种属(人、食蟹猴、鼠科)PD-1蛋白(ACROBiosystems)包被酶标板,浓度为1 μ g/ml,4 $^{\circ}$ C放置过夜。封闭和洗涤后,将稀释好的抗体分别加入酶标板中,室温孵育2小时。洗涤后,加入Goat anti-Human IgG-Fc Fragment Antibody HRP(Bethyl)二抗,室温孵育1小时。洗涤后加入TMB显色液,然后用2M HCl终止反应,使用酶标仪读取OD450数值。

[0182] 实验结果如下表所示,候选抗体、Keytruda和Opdivo均结合人和食蟹猴PD-1,与鼠科PD-1蛋白不结合。

[0183]	样品	ELISA (OD 值)								
		包被人 PD-1 蛋白			包被食蟹猴 PD-1 蛋白			包被鼠科 PD-1 蛋白		
	NB182, 0.1 μ g	2.174	2.130	2.100	2.070	2.075	1.949	0.068	0.071	0.061
	NB194, 0.1 μ g	2.220	1.947	2.108	2.225	2.170	2.097	0.024	0.022	0.024
	其他抗体, 0.1 μ g	0.723-2.231			0.533-2.179			0.020-0.081		
	Keytruda, 0.1 μ g	2.254	2.336	2.184	2.222	2.340	2.319	0.079	0.088	0.090
	Opdivo, 0.1 μ g	2.112	2.144	2.248	1.888	1.795	1.834	0.024	0.023	0.023

[0184] 实施例6:CD28家族蛋白结合测试

[0185] 分别将CD28家族蛋白(CD28,CTLA-4,ICOS和PD-1)蛋白(ACROBiosystems)包被酶标板,浓度为1 μ g/ml,4 $^{\circ}$ C放置过夜。封闭和洗涤后,将稀释好的抗体分别加入酶标板中,室温孵育2小时。洗涤后,加入羊抗人IgG-Fc片段抗体HRP(Bethyl)二抗,室温孵育1小时。洗涤后加入TMB显色液,然后用2M HCl终止反应,使用酶标仪读取OD450数值。

[0186] 实验结果如下表所示,候选抗体、Keytruda和Opdivo均只与PD-1蛋白结合,与CD28家族其它蛋白均不结合。

样品	ELISA (OD 值)											
	CTLA-4			ICOS			CD28			PD-1		
NB182	0.191	0.186	0.185	0.110	0.134	0.111	0.053	0.049	0.047	2.055	2.093	2.287
NB194	0.033	0.028	0.026	0.022	0.021	0.023	0.022	0.022	0.020	2.034	1.957	2.272
其他抗体	0.011-0.108			0.017-0.141			0.019-0.046			0.821-2.346		
Keytruda	0.090	0.086	0.089	0.125	0.107	0.131	0.066	0.054	0.053	2.118	2.209	2.452
Opdivo	0.024	0.022	0.019	0.023	0.021	0.022	0.020	0.021	0.023	2.051	1.999	2.350

[0187] 实施例7:表位竞争实验

[0188] 使用仪器Biacore T200 (GE),检测温度25℃,缓冲液1×HBS-EP+ (10mM HEPES, 150mM NaCl, 3mM EDTA和0.05%v/v Surfactant P20,GE),流速30ul/min。PD-1-His溶于醋酸盐缓冲液,pH4.0(Biacore Amine Coupling Kit,GE),至终浓度10μg/ml,按照氨基偶联试剂盒产品说明,将PD-1-His固定于CM5芯片 (GE) 通道2 (FC-2),约21RU。通道1 (FC-1) 做空白对照。用1×HBS-EP+分别稀释抗体至目标浓度,向上述完成PD-1固定的芯片FC-1和FC-2注入其中一个抗体至饱和水平,随后再注入另外一个抗体至饱和,以评价两个抗体的竞争关系。第二个抗体注射完成后,复合物解离400s。最后采用50mM NaOH注射15s对芯片表面再生。数据处理采用Biacore Evaluation Software 2.0 (GE),传感图采用双参比扣除,记录FC2-1信号。

[0189] 实验结果如下表所示,NB194和NB182抗体结合的表位与Keytruda和Opdivo的表位有部分重合。其余抗体的结果与NB194和NB182抗体类似,均与Keytruda和Opdivo为表位部分竞争。

第一个抗体	第二个抗体			
	NB194	NB182	Keytruda	Opdivo
NB194	完全竞争	部分竞争	部分竞争	部分竞争
NB182	完全竞争	完全竞争	NA	NA
Keytruda	完全竞争	部分竞争	完全竞争	部分竞争
Opdivo	完全竞争	部分竞争	部分竞争	完全竞争

[0190] 实施例8:抗体功能活性测试

[0191] 1) 报告基因实验。先将GS/C2-PDL1 (金斯瑞) 靶细胞用无抗生素培养基调整密度至 5×10^5 个/mL, 20μL每孔铺到384孔板中培养16-20h。抗体用RMPI1640+10%FBS buffer进行梯度稀释,GS-J2/PD1 (金斯瑞) 效应细胞用无抗生素培养基调整密度至 2×10^6 个/mL;除去384孔板中旧培养基,每孔加入20μL抗体,20μL GS-J2/PD1效应细胞,培养6h。最后每孔加入40μL One-Glo底物反应10分钟后酶标仪检测。如图3所示,抗体在Reporter Gene Assay功能检测方法中具有良好的功能活性,其中NB182和NB194的EC50为16.3nM和7.0nM,Keytruda和Opdivo的EC50为3.3nM和7.3nM。其余抗体的EC50为1.7至75nM之间。

[0192] 2) 混合淋巴细胞反应。抽取100毫升健康人的外周血用来做PBMC的分离,获得的PBMC再做monocyte的分离,获得的monocyte在九天内被诱导成为成熟的树突细胞DC。第九天,将DC用流式细胞仪做质量检测,符合诱导成熟的标准后,再次取得100毫升人体外周血做PBMC的分离,然后把PBMC中的CD4+T细胞分离出来,使用5:1的E:T比值来孵育效应细胞和

刺激细胞,并加入待测样品,8浓度,3复孔,稀释倍数为10倍,首浓度为10-50ug/ml。孵育3天。收集细胞培养的上清,检测IL-2和IFN- γ 的释放量。

[0195] 检测结果如图4和图5所示,在一定范围内,NB182和NB194可以以剂量依赖的方式促进T细胞分泌IL-2和IFN- γ ,并且展现出与Keytruda和Opdivo相同的功能效果。其余抗体的结果与NB182和NB194类似,均可以以剂量依赖的方式促进T细胞分泌IL-2和IFN- γ :IL-2EC50在0.115nM至3.278nM之间,IFN- γ EC50在0.078nM至1.102nM之间。

[0196] 实施例9:抗体特异性验证

[0197] 1) 膜蛋白交叉反应

[0198] 利用美国Integral molecular公司开发的膜蛋白阵列筛选平台 (Membrane Proteome Array,MPA) 做膜蛋白交叉反应。将人的5300种不同膜蛋白通过转染HEK293细胞展示在细胞表面,通过FACS检测抗体在这些蛋白上的结合信号,以此评价待检测抗体的特异性。MPA筛选结果(图6和图7)显示,NB182和NB194抗体只与人的PD-1蛋白结合,与其它5000多种蛋白均不结合。除NB171抗体外,其余抗体也只与人的PD-1蛋白结合。

[0199] 2) 组织交叉反应

[0200] 选取34种组织做冰冻切片,常温晾干后使用丙酮固定。使用内源性生物素阻断试剂盒(生工,E674001)的试剂A和试剂B进行封闭,将生物素标记的抗体样品孵育30min,洗涤后加入辣根过氧化物酶标记的链霉亲和素(Abcam,ab7403)孵育15min。使用DAB显色和苏木素复染,中性塑胶封片,自然风干后待镜检。阳性对照为Anti-PD-1抗体(abcam),阴性对照为IgG4同型对照。

[0201] NB182和NB194抗体与正常人体淋巴细胞发生特异性结合,包括淋巴结、脾脏、胸腺。除NB171抗体外,其余抗体也只与正常人体淋巴细胞发生特异性结合。

[0202]

序号	器官	NB182	NB194	同型对照
1	肾上腺	-	-	-
2	乳腺	-	-	-
3	眼	-	-	-
4	肾脏	-	-	-
5	胰腺	-	-	-
6	脊髓	-	-	-
7	甲状腺	-	-	-

[0203]

8	主动脉	-	-	-
9	小脑	-	-	-
10	食管	-	-	-
11	肝脏	-	-	-
12	垂体	-	-	-
13	脾脏	淋巴细胞样阳性染色	淋巴细胞样阳性染色	-
14	输尿管	-	-	-
15	膀胱	-	-	-
16	大脑	-	-	-
17	输卵管	-	-	-
18	肺脏	-	-	-
19	胎盘	-	-	-
20	骨骼肌	-	-	-
21	子宫颈	-	-	-
22	血细胞	-	-	-
23	结肠	-	-	-
24	胃	-	-	-
25	淋巴结	淋巴细胞样阳性染色	淋巴细胞样阳性染色	-
26	前列腺	-	-	-
27	睾丸	-	-	-
28	子宫内膜	-	-	-
29	骨髓	-	-	-
30	十二指肠	-	-	-
31	心脏	-	-	-
32	卵巢	-	-	-
33	皮肤	-	-	-
34	胸腺	淋巴细胞样阳性染色	淋巴细胞样阳性染色	-

[0204] 实施例10:抗体人源化

[0205] 参考对纳米抗体做人源化的方法(J.Biol.Chem.2009;284:3273-3284),使用CDR区移植的方法对NB182和NB194做人源化。在IgBLAST(<http://www.ncbi.nlm.nih.gov/igblast/>)数据库筛选与NB182和NB194同源性较高的种系(germline)为模板。使用Biacore对将人源化前后的抗体做亲和力检测,将纯化的抗体流经预先固定protein A的传感器芯片,抗体被protein A捕获,然后将5个不同浓度的PD-1.His蛋白作为流动相,结合时间和解离时间分别为30min和60min。使用Biacore Evaluation Software 2.0(GE)分析结合速率(k_a)、解离速率(k_d)和平衡常数(KD)。NB182-z1和NB182-z2两个人源化分子与NB182亲和力一致,NB182-z3、NB182-z4、NB182-z5与NB182亲和力相似。NB194-z4和NB194-z5两个人源化分子与NB194亲和力一致,NB194-z1、NB194-z2、NB194-z3与NB194亲和力相似。

[0206]

样品	k_a (1/Ms)	k_d (1/s)	KD (M)
NB182	7.38E+03	6.40E-05	8.67E-09
NB182-z1	9.22E+03	7.61E-05	8.25E-09
NB182-z2	5.60E+03	4.59E-05	8.20E-09

NB182-z3	6.00E+03	7.11E-05	1.18E-08
NB182-z4	6.48E+03	9.73E-05	1.50E-08
NB182-z5	6.46E+03	9.07E-05	1.40E-08
NB194	2.12E+05	1.05E-04	4.94E-10
NB194-z1	1.28E+05	1.07E-04	8.37E-10
NB194-z2	9.76E+04	9.88E-05	1.01E-09
NB194-z3	1.41E+05	1.39E-04	9.87E-09
NB194-z4	1.33E+05	7.79E-05	5.86E-10
NB194-z5	1.33E+05	7.92E-05	5.98E-10

[0207] 实施例11:突变型抗体

[0208] 使用GeneMorph II试剂盒(安捷伦,200550)对NB194抗体进行点随机突变,然后构建噬菌体抗体库,经过筛选,获得了77个突变型抗体(NB194-P1至NB194-P77)。经验证,这些抗体的亲和力和抗体功能活性与NB194抗体相似。如下表和图8所示,NB194-P29突变的亲和力最高,相比于NB194,亲和力提高了5倍,功能活性也有提升。

[0209]

样品	ka (1/Ms)	kd (1/s)	KD (M)
NB194	1.39E+05	7.36E-05	5.31E-10
NB194-P29	2.43E+05	2.86E-05	1.18E-10

[0210] 实施例12:NB194-P29人源化

[0211] 采用实施例10中所述的人源化方式,对NB194-P29抗体进行人源化,获得了10个人源化分子,所有分子的亲和力均和NB194-P29亲和力相近。

[0212]

样品	ka (1/Ms)	kd (1/s)	KD (M)
NB194-P29	2.90E+05	4.37E-05	1.51E-10

[0213]

NB194-P29-z1	1.17E+05	3.06E-05	2.63E-10
NB194-P29-z2	1.29E+05	1.66E-05	1.29E-10
NB194-P29-z3	1.86E+05	3.75E-05	2.02E-10
NB194-P29-z4	1.17E+05	2.61E-05	2.22E-10
NB194-P29-z5	1.21E+05	2.43E-05	2.00E-10
NB194-P29-z6	1.13E+05	3.02E-05	2.68E-10
NB194-P29-z7	1.45E+05	2.18E-05	1.50E-10
NB194-P29-z8	1.08E+05	2.54E-05	2.35E-10
NB194-P29-z9	1.24E+05	5.03E-05	4.06E-10
NB194-P29-z10	9.68E+04	1.74E-05	1.79E-10

[0001] 序列表

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[1419]	Ala Gly Ala Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr	
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[1457]	Lys Asp Arg Phe Thr Ile Ala Arg Asp Asn Ala Lys Asn Thr Val Tyr	
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[1459]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys	
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[1461]	Ala Ala Gly Leu Arg Ala Tyr Tyr Gly Asp Ser Tyr Val Asp Thr Met	
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[1479]	Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Thr Val Tyr Leu	
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[1518]	Ser Met Gly Trp Phe Arg Gln Ala Ser Gly Lys Glu Arg Glu Phe Val					
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[1562]	Ala Ala Ile Thr Asn Ser Gly Leu Thr Tyr Tyr Pro Asp Ser Val Lys
[1563]	50 55 60
[1564]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
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[1567]	85 90 95
[1568]	Ala Gly Gly Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr
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[1602]	Glu Thr Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val			
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[1604]	Ala Ala Ile Ser Trp Asp Gly Glu Thr Ser Tyr Ala Asp Ser Val Lys			
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[1606]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Ala Leu			
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[1608]	Gln Met Asn Arg Leu Thr Pro Glu Asp Thr Ala Val Tyr Phe Cys Ala			
[1609]	85	90	95	
[1610]	Ala Arg Val Ile Leu Arg Ala Tyr Lys Tyr Trp Gly Gln Gly Thr Gln			
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[1612]	Val Thr Val Ser Ser			
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[1621]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr			
[1622]	20	25	30	
[1623]	Ala Met Gly Trp Phe Arg Gln Ala Leu Gly Lys Glu Arg Glu Trp Ile			
[1624]	35	40	45	
[1625]	Ala Gly Val Ser Met Ser Gly Arg Thr Thr Tyr Tyr Ala Ala Pro Val			
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[1627]	Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Thr			
[1628]	65	70	75	80
[1629]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys			
[1630]	85	90	95	
[1631]	Ala Ala Gly Arg Ala Gln Ala Glu Ile Pro Ile Met Arg Ala Gln Glu			
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[1633]	Tyr Asp Ser Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
[1634]	115	120	125	
[1635]	<210> 195			
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[1643]				20						25					30	
[1644]	Ala	Met	Gly	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Leu	Val
[1645]				35						40				45		
[1646]	Ala	Val	Ile	Thr	Asn	Ser	Gly	Leu	Thr	His	Tyr	Ala	Asp	Ser	Val	Glu
[1647]				50						55				60		
[1648]	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr	Leu
[1649]	65						70					75				80
[1650]	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Asn
[1651]						85					90				95	
[1652]	Ala	Gly	Ala	Pro	Pro	Pro	Gly	Gly	Leu	Gly	Tyr	Asp	Glu	Ser	Asp	Tyr
[1653]							100				105				110	
[1654]	Trp	Asp	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser					
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[1657]	<211> 128															
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[1662]	1				5						10				15	
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[1664]											25				30	
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[1667]	Ala	Ala	Ile	Ser	Gln	Asn	Gly	Gly	Thr	Gln	Gly	Tyr	Ala	Glu	Ala	Val
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[1670]	65														80	
[1671]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Ala	Tyr	Tyr	Cys
[1672]															95	
[1673]	Ala	Ala	Asp	Gly	Asp	Ala	Ser	Asp	Ile	Ser	Tyr	Ala	Pro	Pro	Arg	Asp
[1674]															110	
[1675]	Tyr	Glu	Tyr	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser
[1676]															125	

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[1679]	<212>	PRT
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[1681]	<400>	197
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[1684]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Thr Ser Phe Ile Ser	
[1685]	20 25 30	
[1686]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val	
[1687]	35 40 45	
[1688]	Ala Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys	
[1689]	50 55 60	
[1690]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu	
[1691]	65 70 75 80	
[1692]	Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn	
[1693]	85 90 95	
[1694]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr	
[1695]	100 105 110	
[1696]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser	
[1697]	115 120	
[1698]	<210>	198
[1699]	<211>	124
[1700]	<212>	PRT
[1701]	<213>	Artificial Sequence
[1702]	<400>	198
[1703]	Gln Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly	
[1704]	1 5 10 15	
[1705]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Gly Thr Phe Asn Ser Tyr	
[1706]	20 25 30	
[1707]	Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val	
[1708]	35 40 45	
[1709]	Ala Ala Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val	
[1710]	50 55 60	
[1711]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr	
[1712]	65 70 75 80	
[1713]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys	
[1714]	85 90 95	
[1715]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp	

[1716]	100	105	110
[1717]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
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[1725]	1 5 10 15		
[1726]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Asn Gly Tyr		
[1727]	20 25 30		
[1728]	Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val		
[1729]	35 40 45		
[1730]	Ala Ala Ile Ser Trp Arg Asp Ser Ser Lys Tyr Tyr Ala Asp Ser Val		
[1731]	50 55 60		
[1732]	Arg Asp Arg Phe Thr Ala Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr		
[1733]	65 70 75 80		
[1734]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys		
[1735]	85 90 95		
[1736]	Arg Pro Tyr Ser Asp Tyr Val Thr Tyr Asp Pro Tyr Asp Tyr Asp Ala		
[1737]	100 105 110		
[1738]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[1739]	115 120		
[1740]	<210> 200		
[1741]	<211> 124		
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[1744]	<400> 200		
[1745]	Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Arg Ala Gly Gly		
[1746]	1 5 10 15		
[1747]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
[1748]	20 25 30		
[1749]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val		
[1750]	35 40 45		
[1751]	Ala Val Ile Asn Leu Ser Arg Gly Asp Thr Tyr Tyr Ala Asp Ser Val		
[1752]	50 55 60		
[1753]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[1754]	65 70 75 80		

[1755]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
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[1757]	Gly	Val	Asp	Arg	Arg	Gln	Tyr	Gly	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
[1758]				100					105					110		
[1759]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
[1760]				115					120							
[1761]	<210>	201														
[1762]	<211>	123														
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[1766]	Glu	Val	Gln	Val	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	Gly
[1767]	1			5					10					15		
[1768]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Asp	Thr	Ile	Leu	Ile	Ser
[1769]				20					25					30		
[1770]	Ala	Ile	Gly	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Val	Arg	Glu	Leu	Val
[1771]				35					40					45		
[1772]	Ala	Ala	Ile	Thr	Asn	Ser	Gly	Val	Thr	Tyr	Tyr	Thr	Asp	Ser	Val	Lys
[1773]				50					55					60		
[1774]	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr	Leu
[1775]	65					70					75				80	
[1776]	Gln	Met	Asp	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Asn
[1777]					85					90					95	
[1778]	Ala	Gly	Gly	Pro	Pro	Pro	Gly	Gly	Leu	Gly	Tyr	Asp	Glu	Ser	Asp	Tyr
[1779]				100					105					110		
[1780]	Trp	Gly	Pro	Gly	Thr	His	Val	Thr	Val	Ser	Ser					
[1781]				115					120							
[1782]	<210>	202														
[1783]	<211>	123														
[1784]	<212>	PRT														
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[1789]	Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Asp	Thr	Asn	Leu	Phe	Ser
[1790]				20					25					30		
[1791]	Ala	Met	Gly	Trp	His	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Leu	Val
[1792]				35					40					45		
[1793]	Ala	Ala	Ile	Thr	Asn	Ser	Gly	Met	Thr	Tyr	Tyr	Ala	Asp	Val	Val	Lys

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[1795]	Gly Arg Phe Thr Leu Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu		
[1796]	65	70	75 80
[1797]	Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn		
[1798]	85	90	95
[1799]	Ala Gly Ala Pro Pro Pro Gly Gly Phe Gly Tyr Asp Glu Ser Asp Tyr		
[1800]	100	105	110
[1801]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[1802]	115	120	
[1803]	<210> 203		
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[1805]	<212> PRT		
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[1807]	<400> 203		
[1808]	Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly		
[1809]	1	5	10 15
[1810]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Asp His		
[1811]	20	25	30
[1812]	Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Pro Val		
[1813]	35	40	45
[1814]	Ser Cys Ile Ser Thr Ser Asp Gly Arg Thr Tyr Tyr Glu Asp Ser Val		
[1815]	50	55	60
[1816]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys Ala Lys Asn Thr Val Tyr		
[1817]	65	70	75 80
[1818]	Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys		
[1819]	85	90	95
[1820]	Thr Thr Asp Val Ala Cys Tyr Ser Asp Tyr Asp Pro Ser Phe Arg Phe		
[1821]	100	105	110
[1822]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[1823]	115	120	
[1824]	<210> 204		
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[1828]	<400> 204		
[1829]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly		
[1830]	1	5	10 15
[1831]	Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Asn Ser Tyr		
[1832]	20	25	30

[1833]	Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
[1834]	35 40 45
[1835]	Ala Ala Ile Ser Gln Asn Gly Gly Ser Gln Gly Tyr Ala Glu Ala Val
[1836]	50 55 60
[1837]	Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Thr Asn Lys Val Val Ala
[1838]	65 70 75 80
[1839]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ala Tyr Tyr Cys
[1840]	85 90 95
[1841]	Ala Ala Asp Gly Asp Ala Ser Asp Arg Ser Tyr Ala Pro Pro Arg Asp
[1842]	100 105 110
[1843]	Tyr Glu Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[1844]	115 120 125
[1845]	<210> 205
[1846]	<211> 123
[1847]	<212> PRT
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[1849]	<400> 205
[1850]	Glu Val Gln Val Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
[1851]	1 5 10 15
[1852]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Asp Thr Arg Leu Ala Ser
[1853]	20 25 30
[1854]	Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
[1855]	35 40 45
[1856]	Ala Ala Ile Thr Asn Ser Gly Leu Thr Tyr Tyr Ala Asp Ser Val Glu
[1857]	50 55 60
[1858]	Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Thr Val Tyr Leu
[1859]	65 70 75 80
[1860]	Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
[1861]	85 90 95
[1862]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr
[1863]	100 105 110
[1864]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[1865]	115 120
[1866]	<210> 206
[1867]	<211> 123
[1868]	<212> PRT
[1869]	<213> Artificial Sequence
[1870]	<400> 206
[1871]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Val Gly Asp

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[1873]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Val			
[1874]	20	25	30	
[1875]	Pro Met Gly Trp Phe Arg Gln Ala Pro Gly Asn Gln Arg Glu Phe Val			
[1876]	35	40	45	
[1877]	Ala Ala Ile Ser Lys Ser Gly Gly Ser Ala Gly Tyr Ala Asp Ser Val			
[1878]	50	55	60	
[1879]	Lys Asp Arg Ser Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Ile Tyr			
[1880]	65	70	75	80
[1881]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys			
[1882]	85	90	95	
[1883]	Ala Ala Ser Ser Phe Asp Phe Cys Ser Thr His Gly Cys Tyr Asp Tyr			
[1884]	100	105	110	
[1885]	Trp Gly Gln Gly Thr Gln Val Thr Ile Ser Ser			
[1886]	115	120		
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[1893]	1	5	10	15
[1894]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Thr Ala Leu Phe Ser			
[1895]	20	25	30	
[1896]	Ala Val Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val			
[1897]	35	40	45	
[1898]	Ala Ala Leu Thr Asn Thr Gly Ile Thr Tyr Tyr Ala Asp Ser Val Glu			
[1899]	50	55	60	
[1900]	Gly Arg Phe Thr Ile Phe Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu			
[1901]	65	70	75	80
[1902]	Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn			
[1903]	85	90	95	
[1904]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr			
[1905]	100	105	110	
[1906]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
[1907]	115	120		
[1908]	<210> 208			
[1909]	<211> 125			
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[1915]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Phe	Ser	Gly	Tyr
[1916]				20					25					30		
[1917]	Thr	Val	Gly	Trp	Tyr	Arg	Gln	Ser	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
[1918]			35					40					45			
[1919]	Ala	Ala	Ile	Ser	Tyr	Ser	Gly	Gly	Ser	Thr	Asp	Tyr	Ala	Asp	Ser	Val
[1920]		50					55				60					
[1921]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Asn	Asn	Thr	Val	Tyr
[1922]	65					70				75					80	
[1923]	Leu	Gln	Met	Gly	Ser	Leu	Lys	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[1924]					85					90				95		
[1925]	Asn	Arg	Val	Ile	Arg	Gly	Thr	Arg	Asp	Pro	Ser	Ile	Tyr	Tyr	Val	Met
[1926]			100						105					110		
[1927]	Asp	Tyr	Trp	Gly	Lys	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser			
[1928]			115					120					125			
[1929]	<210> 209															
[1930]	<211> 129															
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[1936]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Gly	Thr	Ile	Ser	Gly	Tyr
[1937]				20					25					30		
[1938]	Glu	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
[1939]			35					40					45			
[1940]	Ala	Gly	Ile	Ser	Arg	Asn	Gly	Arg	Ser	Thr	Gly	Tyr	Ser	Asp	Ser	Ala
[1941]		50					55				60					
[1942]	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
[1943]	65					70				75					80	
[1944]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[1945]				85						90				95		
[1946]	Ala	Ala	Gly	Leu	Lys	Ala	Asp	Tyr	Gly	Asp	Ser	Tyr	Val	Asp	Thr	Ser
[1947]			100						105					110		
[1948]	Thr	Arg	Asn	Tyr	Asn	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser
[1949]			115					120					125			

[1950]	Ser
[1951]	<210> 210
[1952]	<211> 123
[1953]	<212> PRT
[1954]	<213> Artificial Sequence
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[1958]	Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Val
[1959]	20 25 30
[1960]	Pro Met Gly Trp Phe Arg Gln Ala Pro Gly Asn Gln Arg Glu Phe Val
[1961]	35 40 45
[1962]	Ala Ala Ile Ser Lys Ser Gly Gly Ser Ala Gly Tyr Ala Asp Ser Val
[1963]	50 55 60
[1964]	Lys Asp Arg Ser Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Ile Tyr
[1965]	65 70 75 80
[1966]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
[1967]	85 90 95
[1968]	Ala Ala Ser Ser Tyr Asp Phe Cys Ser Thr His Gly Cys Tyr Asp Tyr
[1969]	100 105 110
[1970]	Trp Gly Gln Gly Thr Gln Val Thr Ile Ser Ser
[1971]	115 120
[1972]	<210> 211
[1973]	<211> 123
[1974]	<212> PRT
[1975]	<213> Artificial Sequence
[1976]	<400> 211
[1977]	Gln Leu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
[1978]	1 5 10 15
[1979]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Ile
[1980]	20 25 30
[1981]	Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
[1982]	35 40 45
[1983]	Ala Ala Ile Ser Arg Ser Gly Gly Ser Ala Gly Tyr Ala Asp Ser Val
[1984]	50 55 60
[1985]	Lys Asp Arg Ser Thr Ile Val Arg Asp Asn Thr Lys Asn Thr Val Tyr
[1986]	65 70 75 80
[1987]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys
[1988]	85 90 95

[1989]	Ala	Ala	Ser	Asp	Tyr	Asp	Phe	Cys	Ser	Thr	His	Gly	Cys	Tyr	Asp	Tyr
[1990]				100				105						110		
[1991]	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Ile	Ser	Ser					
[1992]			115					120								
[1993]	<210>	212														
[1994]	<211>	125														
[1995]	<212>	PRT														
[1996]	<213>	Artificial Sequence														
[1997]	<400>	212														
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[1999]	1			5				10						15		
[2000]	Ser	Leu	Arg	Leu	Ser	Cys	Ile	Val	Ser	Gly	Arg	Thr	Phe	Ser	Ser	Tyr
[2001]			20					25						30		
[2002]	Ala	Ile	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
[2003]			35					40						45		
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[2005]		50					55					60				
[2006]	Lys	Asp	Arg	Phe	Thr	Val	Ser	Ile	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
[2007]	65					70					75				80	
[2008]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[2009]				85				90						95		
[2010]	Ala	Ala	Glu	Arg	His	Leu	Gly	Val	Pro	Thr	Val	Arg	Asp	Asp	Glu	Tyr
[2011]			100					105						110		
[2012]	Asp	Asp	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser			
[2013]			115					120						125		
[2014]	<210>	213														
[2015]	<211>	123														
[2016]	<212>	PRT														
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[2021]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Arg	Thr	Phe	Ser	Ser	Val
[2022]			20					25						30		
[2023]	Ala	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
[2024]			35					40						45		
[2025]	Ala	Ala	Ile	Ser	Arg	Ser	Gly	Gly	Ser	Ala	Gly	Tyr	Ala	Asp	Ser	Val
[2026]		50					55					60				
[2027]	Lys	Asp	Arg	Ser	Thr	Ile	Ala	Arg	Asp	Asn	Thr	Lys	Asn	Thr	Val	Tyr

[2028]	65	70	75	80
[2029]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys			
[2030]	85	90	95	
[2031]	Ala Ala Ser Glu Tyr Asp Phe Cys Ser Thr His Gly Cys Tyr Asp Tyr			
[2032]	100	105	110	
[2033]	Trp Gly Gln Gly Thr Gln Val Thr Ile Ser Leu			
[2034]	115	120		
[2035]	<210> 214			
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[2037]	<212> PRT			
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[2039]	<400> 214			
[2040]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly			
[2041]	1	5	10	15
[2042]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Thr Phe Ser Asn Phe			
[2043]	20	25	30	
[2044]	Asn Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val			
[2045]	35	40	45	
[2046]	Ala Ala Ser Asn Trp Ser Ala Gly Thr Thr His Tyr Ser Asp Ser Val			
[2047]	50	55	60	
[2048]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Ala Asn Thr Ala Tyr			
[2049]	65	70	75	80
[2050]	Leu Gln Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val Tyr Tyr Cys			
[2051]	85	90	95	
[2052]	Asn Arg Val Ile Arg Gly Thr Thr Tyr Pro Asp Val Tyr Tyr Gly Met			
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[2054]	Asp Tyr Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser			
[2055]	115	120	125	
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[2063]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr			
[2064]	20	25	30	
[2065]	Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val			
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[2067]	Ala Ala Val Asn Trp Ser Asn Ser Ser Ala Tyr Tyr Ala Asp Ser Val
[2068]	50 55 60
[2069]	Lys Asp Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Ser Thr Ile Tyr
[2070]	65 70 75 80
[2071]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
[2072]	85 90 95
[2073]	Arg Pro Tyr Ser Asp Tyr Val Thr Tyr Asp Pro Asp Asp Tyr Asp Tyr
[2074]	100 105 110
[2075]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2076]	115 120
[2077]	<210> 216
[2078]	<211> 128
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[2080]	<213> Artificial Sequence
[2081]	<400> 216
[2082]	Gln Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Ala Gly Gly
[2083]	1 5 10 15
[2084]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
[2085]	20 25 30
[2086]	Asn Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
[2087]	35 40 45
[2088]	Ala Ala Ile Ser Trp Ser Gly Gly Ser Gln Gly Tyr Ala Ala Ala Val
[2089]	50 55 60
[2090]	Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
[2091]	65 70 75 80
[2092]	Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2093]	85 90 95
[2094]	Ala Ala Lys Tyr His Ser Gly Ser Tyr Tyr Tyr Thr Ser Ile Arg Pro
[2095]	100 105 110
[2096]	Glu Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2097]	115 120 125
[2098]	<210> 217
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[2102]	<400> 217
[2103]	Gln Leu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2104]	1 5 10 15
[2105]	Ser Leu Arg Leu Ser Cys Thr Ala Asn Gly Phe Ser Val Gly Asp Tyr

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[2107]	Ser	Met	Ser	Trp	His	Arg	Gln	Pro	Pro	Gly	Lys	Glu	Arg	Glu	Val	Val				
[2108]	35						40						45							
[2109]	Ala	Thr	Thr	Ala	Arg	Asp	Ser	Gly	Ser	Thr	Phe	Tyr	Ala	Ala	Ser	Val				
[2110]	50						55						60							
[2111]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr				
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[2113]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Gly	Val	Tyr	Tyr	Cys				
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[2115]	Arg	Val	Asn	Ser	Gln	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val				
[2116]	100						105						110							
[2117]	Ser	Ser																		
[2118]	<210> 218																			
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[2125]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ala	Gly	Phe	Thr	Phe	Ser	Ser	Trp				
[2126]	20						25						30							
[2127]	Ala	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val				
[2128]	35						40						45							
[2129]	Ser	Ala	Ile	Ser	Ser	Gly	Ser	Gly	Glu	Met	Ala	Asp	Tyr	Ala	Asp	Ser				
[2130]	50						55						60							
[2131]	Val	Lys	Gly	Arg	Phe	Ala	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Leu				
[2132]	65						70						75						80	
[2133]	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Gln	Pro	Glu	Asp	Thr	Ala	Met	Tyr	Tyr				
[2134]	85						90						95							
[2135]	Cys	Ala	Lys	Gly	Gly	Tyr	Leu	Thr	Tyr	Ala	Asn	Leu	Gly	Pro	Gly	Thr				
[2136]	100						105						110							
[2137]	Gln	Val	Thr	Val	Ser	Ser														
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[2146]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Thr Ile Leu Phe Ser			
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[2148]	Ala Val Gly Trp His Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val			
[2149]	35	40	45	
[2150]	Ala Ala Ile Thr Asn Ser Gly Val Thr Tyr Tyr Ala Asp Ser Val Lys			
[2151]	50	55	60	
[2152]	Gly Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu			
[2153]	65	70	75	80
[2154]	Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn			
[2155]	85	90	95	
[2156]	Ala Gly Ala Pro Pro Pro Gly Glu Phe Gly Tyr Asp Glu Ser Asp Tyr			
[2157]	100	105	110	
[2158]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
[2159]	115	120		
[2160]	<210> 220			
[2161]	<211> 122			
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[2164]	<400> 220			
[2165]	Glu Val Gln Val Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly			
[2166]	1	5	10	15
[2167]	Ser Leu Thr Leu Ser Cys Ala Val Ser Gly Phe Thr Leu Asp Asp Tyr			
[2168]	20	25	30	
[2169]	Ser Ile Gly Trp Phe Arg Gln Ala Pro Gly Arg Ala Arg Glu Ala Val			
[2170]	35	40	45	
[2171]	Ser Cys Thr Ser Asn Arg Asp Gly Ser Thr Tyr Tyr Glu Asp Ser Val			
[2172]	50	55	60	
[2173]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr			
[2174]	65	70	75	80
[2175]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Arg Cys			
[2176]	85	90	95	
[2177]	Ser Thr Asp Cys Ser Leu Tyr Gly Ser Thr Tyr Ser Pro Asp Tyr Trp			
[2178]	100	105	110	
[2179]	Gly Gln Gly Thr Gln Val Ile Val Ser Ser			
[2180]	115	120		
[2181]	<210> 221			
[2182]	<211> 120			
[2183]	<212> PRT			

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[2185]	<400> 221															
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[2189]					20					25					30	
[2190]	Ala	Met	Asn	Trp	Tyr	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Leu	Val
[2191]					35					40					45	
[2192]	Ala	Ser	Ile	Thr	Ile	Asp	Gly	Gly	Ser	Thr	Asn	Tyr	Ala	Asp	Ser	Val
[2193]					50					55					60	
[2194]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Leu	Tyr
[2195]	65									70					75	
[2196]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[2197]																
[2198]					85					90					95	
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[2199]																
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[2200]	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser								
[2201]																
[2201]					115					120						
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[2203]	<211> 123															
[2204]	<212> PRT															
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[2206]	<400> 222															
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[2208]	1				5					10					15	
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[2210]																
[2210]					20					25					30	
[2211]	Gly	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Phe	Val
[2212]																
[2212]					35					40					45	
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[2214]																
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[2215]	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Ser	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
[2216]	65															
[2216]										70					75	
[2217]	Leu	Gln	Met	Ala	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Gly	Val	Tyr	Tyr	Cys
[2218]																
[2218]																
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[2220]																
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[2220]					100					105					110	
[2221]	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser					
[2222]																
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[2224]	<211>	123
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[2227]	<400>	223
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[2230]	Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Asp Thr Ser Phe Ile Ser	
[2231]	20	25 30
[2232]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val	
[2233]	35	40 45
[2234]	Ser Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys	
[2235]	50	55 60
[2236]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu	
[2237]	65	70 75 80
[2238]	Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Asn	
[2239]	85	90 95
[2240]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr	
[2241]	100	105 110
[2242]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser	
[2243]	115	120
[2244]	<210>	224
[2245]	<211>	123
[2246]	<212>	PRT
[2247]	<213>	Artificial Sequence
[2248]	<400>	224
[2249]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
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[2251]	Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Asp Thr Ser Phe Ile Ser	
[2252]	20	25 30
[2253]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val	
[2254]	35	40 45
[2255]	Ser Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys	
[2256]	50	55 60
[2257]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu	
[2258]	65	70 75 80
[2259]	Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Asn	
[2260]	85	90 95
[2261]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr	

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[2263]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
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[2272]	Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Asp Thr Ser Phe Ile Ser		
[2273]	20 25 30		
[2274]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val		
[2275]	35 40 45		
[2276]	Ser Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys		
[2277]	50 55 60		
[2278]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu		
[2279]	65 70 75 80		
[2280]	Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Asn		
[2281]	85 90 95		
[2282]	Ala Gly Ala Pro Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr		
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[2284]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[2285]	115 120		
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[2293]	Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Asp Thr Ser Phe Ile Ser		
[2294]	20 25 30		
[2295]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val		
[2296]	35 40 45		
[2297]	Ser Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys		
[2298]	50 55 60		
[2299]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu		
[2300]	65 70 75 80		

[2301]	Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Asn
[2302]	85 90 95
[2303]	Ala Gly Ala Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr
[2304]	100 105 110
[2305]	Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2306]	115 120
[2307]	<210> 227
[2308]	<211> 123
[2309]	<212> PRT
[2310]	<213> Artificial Sequence
[2311]	<400> 227
[2312]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2313]	1 5 10 15
[2314]	Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Asp Thr Ser Phe Ile Ser
[2315]	20 25 30
[2316]	Ala Ala Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
[2317]	35 40 45
[2318]	Ala Ala Ile Thr Asn Thr Gly Ile Thr Tyr Tyr Pro Asp Ser Val Lys
[2319]	50 55 60
[2320]	Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
[2321]	65 70 75 80
[2322]	Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Asn
[2323]	85 90 95
[2324]	Ala Gly Ala Pro Pro Gly Gly Leu Gly Tyr Asp Glu Ser Asp Tyr
[2325]	100 105 110
[2326]	Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[2327]	115 120
[2328]	<210> 228
[2329]	<211> 124
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[2332]	<400> 228
[2333]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2334]	1 5 10 15
[2335]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Pro Phe Ser Ile Tyr
[2336]	20 25 30
[2337]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val
[2338]	35 40 45
[2339]	Ala Val Ile Ser Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val

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[2341]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr		
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[2343]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys		80
[2344]	85	90	95
[2345]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
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[2347]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[2348]	115	120	
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[2357]	20	25	30
[2358]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val		
[2359]	35	40	45
[2360]	Ala Val Ile Ser Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2361]	50	55	60
[2362]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Thr Val Tyr		
[2363]	65	70	75
[2364]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys		80
[2365]	85	90	95
[2366]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
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[2369]	115	120	
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[2375]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly		
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[2377]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		15
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[2379]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val
[2380]	35 40 45
[2381]	Ala Val Ile Ser Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2382]	50 55 60
[2383]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[2384]	65 70 75 80
[2385]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys
[2386]	85 90 95
[2387]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[2388]	100 105 110
[2389]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2390]	115 120
[2391]	<210> 231
[2392]	<211> 124
[2393]	<212> PRT
[2394]	<213> Artificial Sequence
[2395]	<400> 231
[2396]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2397]	1 5 10 15
[2398]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Pro Phe Ser Ile Tyr
[2399]	20 25 30
[2400]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val
[2401]	35 40 45
[2402]	Ala Val Ile Asn Leu Ala Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2403]	50 55 60
[2404]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
[2405]	65 70 75 80
[2406]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys
[2407]	85 90 95
[2408]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[2409]	100 105 110
[2410]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2411]	115 120
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[2421]	Asp Met Gly Trp Phe Arg Gln Ala Pro Asp Lys Glu Arg Glu Ser Val			
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[2423]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[2425]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr			
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[2427]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Ser Cys			
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[2429]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp			
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[2442]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
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[2444]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[2446]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
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[2469]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
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[2471]	Gly	Val	Asp	Arg	Arg	Gln	Tyr	Gly	Trp	Gly	Ile	Pro	Pro	Leu	Ala	Asp
[2472]					100						105					110
[2473]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[2485]					35					40					45	
[2486]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[2487]					50					55					60	
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[2489]	65					70					75					80
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[2492]	Gly	Val	Asp	Arg	Arg	Gln	Tyr	Gly	Leu	Cys	Ile	Pro	Pro	Leu	Ala	Asp
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[2505]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[2506]			35					40					45			
[2507]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[2508]		50					55					60				
[2509]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr
[2510]	65					70				75						80
[2511]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
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[2514]				100					105					110		
[2515]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[2532]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
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[2547]	Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[2548]	35 40 45		
[2549]	Ala Ala Val Thr Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2550]	50 55 60		
[2551]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Phe Tyr		
[2552]	65 70 75 80		
[2553]	Leu Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys		
[2554]	85 90 95		
[2555]	Gly Leu Asp Arg Ile Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
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[2557]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[2558]	115 120		
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[2566]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
[2567]	20 25 30		
[2568]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[2569]	35 40 45		
[2570]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2571]	50 55 60		
[2572]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[2573]	65 70 75 80		

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[2577]					100					105					110	
[2578]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[2596]					85					90					95	
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[2610]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
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[2612]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val

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[2616]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		80
[2617]		85	90
[2618]	Gly Val Gly Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		95
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[2620]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		110
[2621]		115	120
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[2631]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		30
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[2633]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		45
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[2635]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[2637]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		80
[2638]		85	90
[2639]	Gly Val Asp Arg Arg Lys Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		95
[2640]		100	105
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[2651]		20	25
			30

[2652]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
[2653]	35 40 45
[2654]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2655]	50 55 60
[2656]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[2657]	65 70 75 80
[2658]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[2659]	85 90 95
[2660]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Pro Ala Asp
[2661]	100 105 110
[2662]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2663]	115 120
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[2669]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Ala Gln Ala Gly Gly
[2670]	1 5 10 15
[2671]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
[2672]	20 25 30
[2673]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
[2674]	35 40 45
[2675]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2676]	50 55 60
[2677]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[2678]	65 70 75 80
[2679]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[2680]	85 90 95
[2681]	Gly Val Glu Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[2682]	100 105 110
[2683]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2684]	115 120
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[2694]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
[2695]	35	40	45	
[2696]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[2698]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
[2699]	65	70	75	80
[2700]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
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[2702]	Gly Val Asp Arg Arg Gln Tyr Gly Phe Gly Ile Pro Pro Leu Ala Asp			
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[2704]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
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[2713]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr			
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[2715]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
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[2717]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[2719]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
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[2721]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
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[2723]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Leu Pro Pro Leu Ala Asp			
[2724]	100	105	110	
[2725]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
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[2736]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[2737]					35					40					45	
[2738]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[2739]					50					55					60	
[2740]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr
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[2757]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[2758]					35					40					45	
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[2760]					50					55					60	
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 [2776] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
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 [2778] Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
 [2779] 35 40 45
 [2780] Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
 [2781] 50 55 60
 [2782] Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
 [2783] 65 70 75 80
 [2784] Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
 [2785] 85 90 95
 [2786] Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Thr Pro Pro Leu Ala Asp
 [2787] 100 105 110
 [2788] His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 [2789] 115 120
 [2790] <210> 250
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 [2796] 1 5 10 15
 [2797] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
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 [2801] Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
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 [2803] Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
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 [2805] Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
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 [2807] Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Thr Pro Leu Ala Asp

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[2820]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[2821]	35 40 45		
[2822]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2823]	50 55 60		
[2824]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[2825]	65 70 75 80		
[2826]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[2827]	85 90 95		
[2828]	Gly Val Asp Arg Arg Gln Tyr Arg Leu Gly Ile Pro Pro Leu Ala Asp		
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[2841]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[2842]	35 40 45		
[2843]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2844]	50 55 60		
[2845]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[2846]	65 70 75 80		

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[2850]				100					105					110		
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[2860]	Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Arg	Pro	Phe	Ser	Ile	Tyr
[2861]				20					25					30		
[2862]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[2863]				35					40					45		
[2864]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[2865]				50					55					60		
[2866]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr
[2867]	65					70					75				80	
[2868]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
[2869]				85					90					95		
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[2871]				100					105					110		
[2872]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[2875]	<211> 124															
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[2881]	Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Arg	Pro	Phe	Ser	Ile	Tyr
[2882]				20					25					30		
[2883]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[2884]				35					40					45		
[2885]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val

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[2889]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[2890]	85	90	95
[2891]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Leu Pro Leu Ala Asp		
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[2893]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
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[2902]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
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[2904]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[2905]	35	40	45
[2906]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[2907]	50	55	60
[2908]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[2909]	65	70	75 80
[2910]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[2911]	85	90	95
[2912]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile His Pro Leu Ala Asp		
[2913]	100	105	110
[2914]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[2915]	115	120	
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[2923]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
[2924]	20	25	30

[2925]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
[2926]	35 40 45
[2927]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2928]	50 55 60
[2929]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[2930]	65 70 75 80
[2931]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[2932]	85 90 95
[2933]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Val Pro Pro Leu Ala Asp
[2934]	100 105 110
[2935]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2936]	115 120
[2937]	<210> 257
[2938]	<211> 124
[2939]	<212> PRT
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[2942]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Ala Gln Ala Gly Gly
[2943]	1 5 10 15
[2944]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
[2945]	20 25 30
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[2947]	35 40 45
[2948]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2949]	50 55 60
[2950]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[2951]	65 70 75 80
[2952]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[2953]	85 90 95
[2954]	Gly Val Val Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[2955]	100 105 110
[2956]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[2957]	115 120
[2958]	<210> 258
[2959]	<211> 124
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[2963]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Ala Gln Ala Gly Gly

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[2965]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr			
[2966]	20	25	30	
[2967]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
[2968]	35	40	45	
[2969]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
[2970]	50	55	60	
[2971]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
[2972]	65	70	75	80
[2973]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
[2974]	85	90	95	
[2975]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Ser Pro Leu Ala Asp			
[2976]	100	105	110	
[2977]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
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[2986]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr			
[2987]	20	25	30	
[2988]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
[2989]	35	40	45	
[2990]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
[2991]	50	55	60	
[2992]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
[2993]	65	70	75	80
[2994]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
[2995]	85	90	95	
[2996]	Glu Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp			
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[2998]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
[2999]	115	120		
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[3009]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[3010]					35					40					45	
[3011]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[3012]					50					55					60	
[3013]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr
[3014]	65									70					75	
[3015]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
[3016]																
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[3017]	Gly	Val	Asp	Lys	Arg	Gln	Tyr	Gly	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
[3018]																
[3018]					100					105					110	
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[3028]	Ser	Leu	Thr	Leu	Ser	Cys	Thr	Ala	Ser	Gly	His	Ser	Phe	Ser	Ile	Tyr
[3029]																
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[3031]																
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[3037]																
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[3038]	Gly	Ile	Asp	Arg	Arg	Gln	Tyr	Gly	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
[3039]																
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[3041]						115				120						

111

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[3091]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
[3092]	20 25 30		
[3093]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[3094]	35 40 45		
[3095]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3096]	50 55 60		
[3097]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[3098]	65 70 75 80		
[3099]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[3100]	85 90 95		
[3101]	Gly Val Asp Gly Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
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[3103]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[3104]	115 120		
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[3111]	1 5 10 15		
[3112]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
[3113]	20 25 30		
[3114]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[3115]	35 40 45		
[3116]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3117]	50 55 60		
[3118]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[3119]	65 70 75 80		

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[3122]	Gly	Val	Asp	Arg	Arg	Gln	His	Gly	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
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[3135]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[3136]				35					40					45		
[3137]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[3138]				50					55					60		
[3139]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Asn	Thr	Val	Tyr
[3140]	65					70					75					80
[3141]	Leu	Gln	Met	Asn	Ser	Leu	Lys	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Ser	Cys
[3142]				85					90					95		
[3143]	Gly	Val	Asp	Arg	Arg	Gln	Tyr	Trp	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
[3144]				100					105					110		
[3145]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
[3146]				115					120							
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[3149]	<212> PRT															
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[3154]	Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Arg	Pro	Phe	Ser	Ile	Tyr
[3155]				20					25					30		
[3156]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
[3157]				35					40					45		
[3158]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val

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[3162]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[3163]	85	90	95
[3164]	Gly Val Asp Arg Gln Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
[3165]	100	105	110
[3166]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
[3167]	115	120	
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[3175]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr		
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[3177]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[3178]	35	40	45
[3179]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3180]	50	55	60
[3181]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
[3182]	65	70	75
[3183]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
[3184]	85	90	95
[3185]	Gly Val Asp Arg Trp Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
[3186]	100	105	110
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[3198]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
[3199]	35 40 45
[3200]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[3201]	50 55 60
[3202]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[3203]	65 70 75 80
[3204]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[3205]	85 90 95
[3206]	Gly Gly Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[3207]	100 105 110
[3208]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[3209]	115 120
[3210]	<210> 270
[3211]	<211> 124
[3212]	<212> PRT
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[3216]	1 5 10 15
[3217]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
[3218]	20 25 30
[3219]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
[3220]	35 40 45
[3221]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[3222]	50 55 60
[3223]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[3224]	65 70 75 80
[3225]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[3226]	85 90 95
[3227]	Gly Val Asn Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp
[3228]	100 105 110
[3229]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[3230]	115 120
[3231]	<210> 271
[3232]	<211> 124
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[3236]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Ala Gln Ala Gly Gly

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[3238]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr			
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[3240]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
[3241]	35	40	45	
[3242]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[3246]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
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[3269]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Arg Ile Pro Pro Leu Ala Asp			
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[3283]					35					40					45	
[3284]	Ala	Val	Ile	Asn	Leu	Ser	Arg	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
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[3313]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
[3314]					115											120

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[3366]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[3367]	35 40 45		
[3368]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
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[3374]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Phe Pro Pro Leu Ala Asp		
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[3386]	20 25 30		
[3387]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val		
[3388]	35 40 45		
[3389]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3390]	50 55 60		
[3391]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3411]					50					55				60		
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[3428]					20					25					30	
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[3450]	Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Asn Glu Arg Glu Ser Val		
[3451]	35 40 45		
[3452]	Ala Ala Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3453]	50 55 60		
[3454]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr		
[3455]	65 70 75 80		
[3456]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys		
[3457]	85 90 95		
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[3472]	35 40 45
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[3475]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[3476]	65 70 75 80
[3477]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[3478]	85 90 95
[3479]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Arg Ala Asp
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[3481]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[3482]	115 120
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[3484]	<211> 124
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[3488]	Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Ala Gln Ala Gly Gly
[3489]	1 5 10 15
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[3493]	35 40 45
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[3495]	50 55 60
[3496]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
[3497]	65 70 75 80
[3498]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[3499]	85 90 95
[3500]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Phe Ala Asp
[3501]	100 105 110
[3502]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
[3503]	115 120
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[3515]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
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[3517]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
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[3519]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
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[3523]	Arg Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser			
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[3532]	Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr			
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[3534]	Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val			
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[3536]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val			
[3537]	50	55	60	
[3538]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr			
[3539]	65	70	75	80
[3540]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys			
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[3542]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Gly			
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[3545]	115	120		
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 [3553] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
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 [3555] Asp Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
 [3556] 35 40 45
 [3557] Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
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 [3559] Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
 [3560] 65 70 75 80
 [3561] Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
 [3562] 85 90 95
 [3563] Gly Val Asp Arg Arg Gln Tyr Gly Val Gly Ile Pro Pro Leu Ala Asp
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 [3565] His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 [3566] 115 120
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 [3573] 1 5 10 15
 [3574] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Pro Phe Ser Ile Tyr
 [3575] 20 25 30
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 [3577] 35 40 45
 [3578] Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val
 [3579] 50 55 60
 [3580] Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr
 [3581] 65 70 75 80
 [3582] Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
 [3583] 85 90 95
 [3584] Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro His Ala Asp
 [3585] 100 105 110
 [3586] His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
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125

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[3664]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3669]						100				105					110	
[3670]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[3681]	Asp	Met	Gly	Trp	Phe	Arg	Gln	Ala	Pro	Gly	Lys	Glu	Arg	Glu	Ser	Val
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[3690]						100				105					110	
[3691]	His	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr	Val	Ser	Ser				
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[3703]					35					40				45		
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[3706]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3708]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
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[3710]	Gly Val Asp Arg Arg Pro Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		
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[3712]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
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[3725]	Ala Val Ile Asn Leu Ser Arg Gly Asn Thr Tyr Tyr Ala Asp Ser Val		
[3726]	50 55 60		
[3727]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3733]	Asn Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		
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 [3750] Leu Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys
 [3751] 85 90 95
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[3857]	Gly	Val	Asp	Arg	Arg	Gln	Tyr	Val	Leu	Gly	Ile	Pro	Pro	Leu	Ala	Asp
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[3874]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3876]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys		
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[3899]	Gly Ile Asp Arg Ile Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp		

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[3916]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3936]	50 55 60		
[3937]	Lys Gly Arg Phe Thr Ile Ser Leu Asp Ser Ala Lys Asn Thr Val Tyr		
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[3983]	Gly Val Asp Arg Arg Gln Asn Gly Leu Gly Ile Pro Pro Leu Ala Asp		95
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[3985]	His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser		110
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[4004]	Gly Val Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Val		95
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			30

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[4023]	Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
[4024]	85 90 95
[4025]	Gly Val Asp Arg Arg Gln Tyr Gly Trp Cys Ile Pro Pro Leu Ala Asp
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[4088]	Gly Ile Asp Arg Arg Gln Tyr Gly Leu Gly Ile Pro Pro Leu Ala Asp			
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[4102]					35					40					45	
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[4104]					50					55					60	
[4105]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Thr	Val	Tyr
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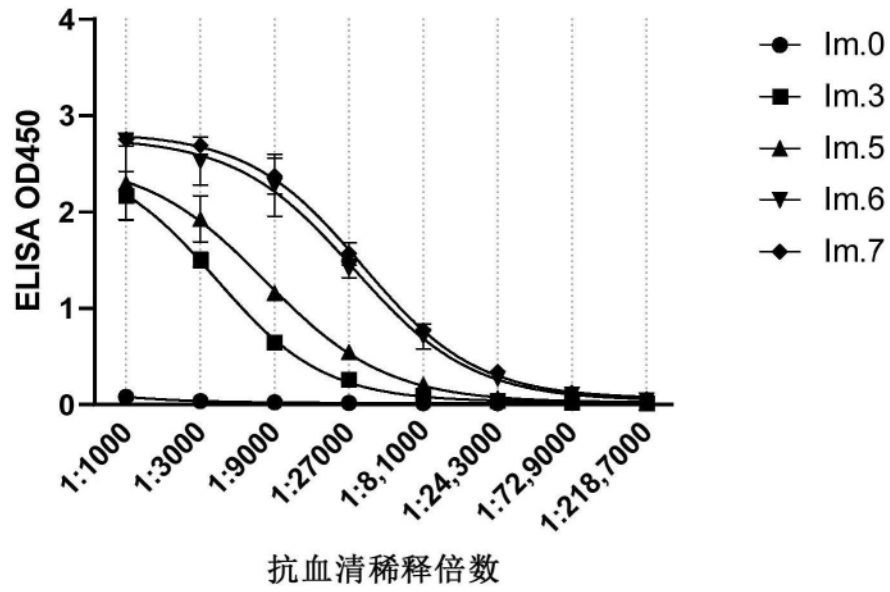


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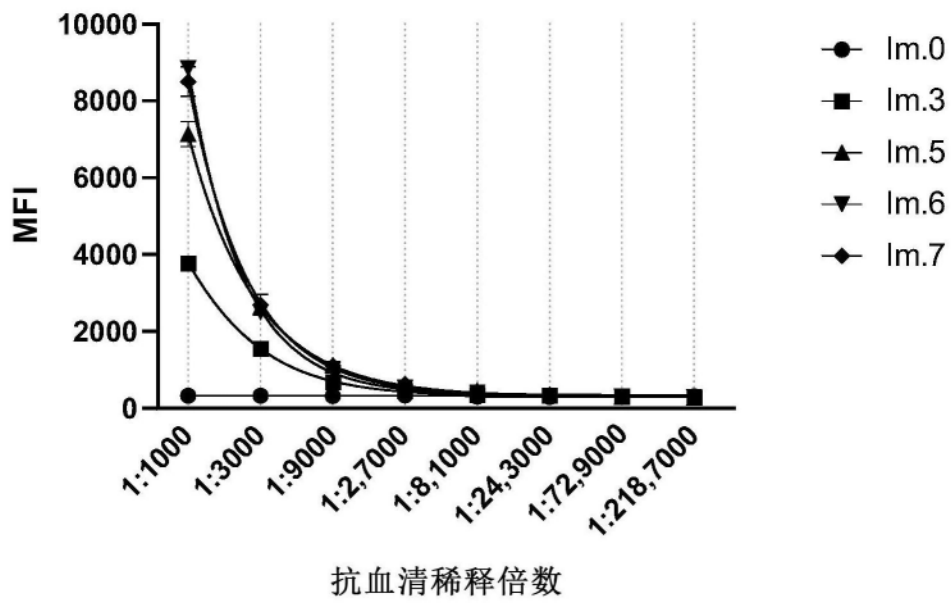


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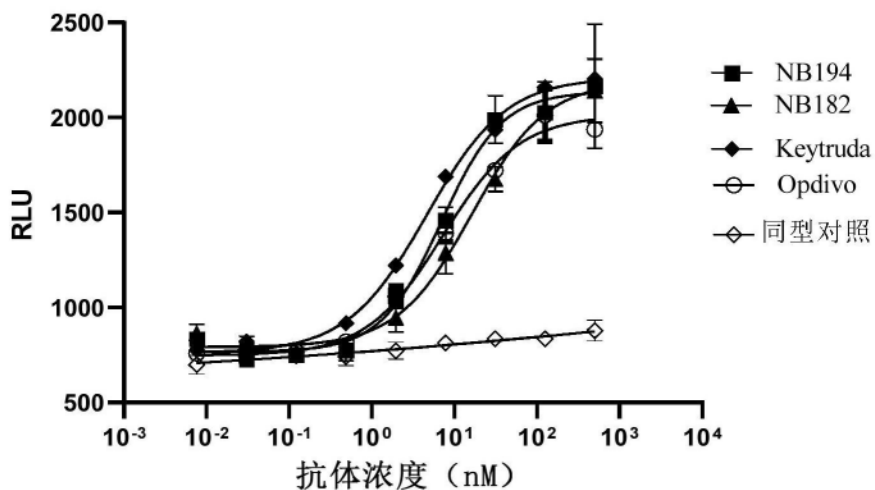


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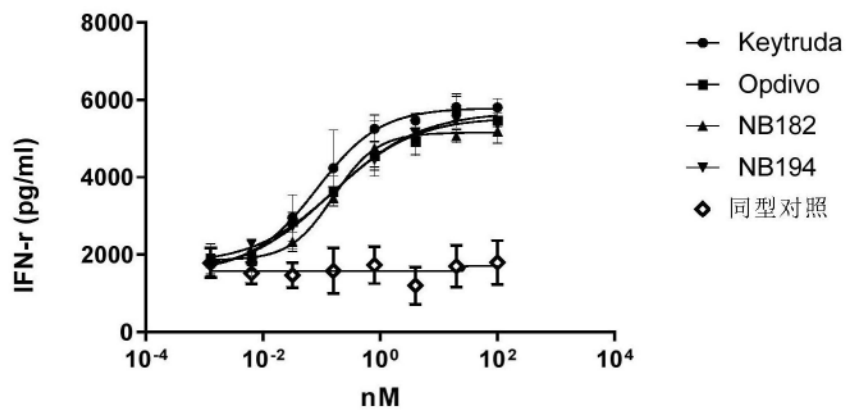


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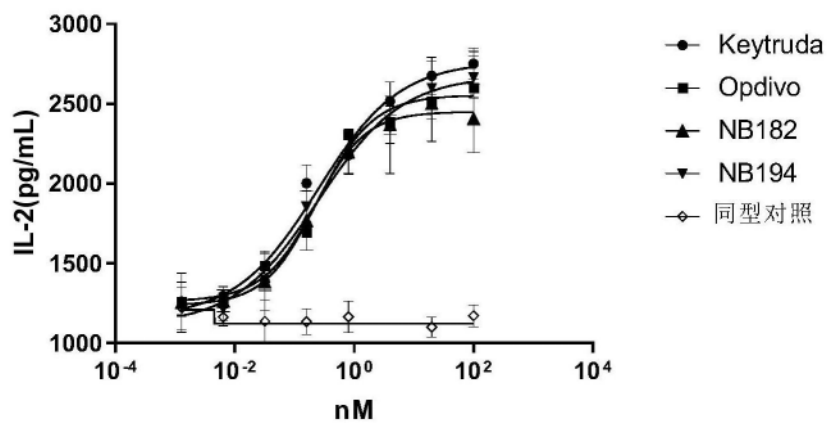


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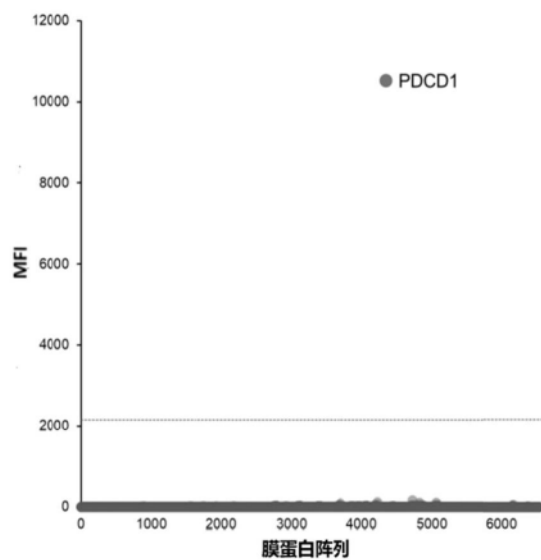


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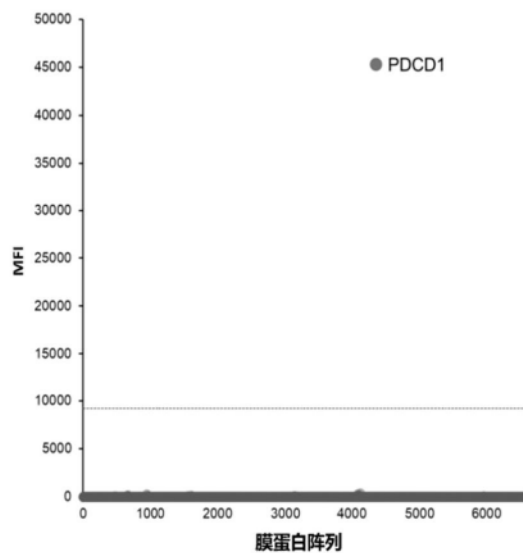


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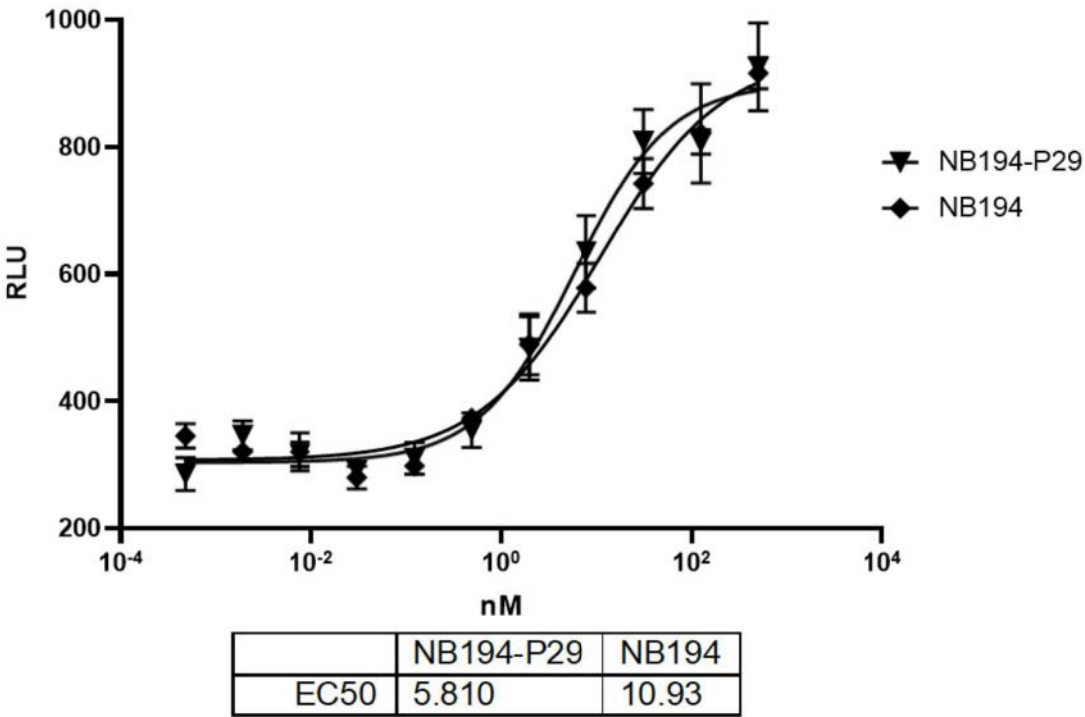


图8