(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 111148757 B
(45)授权公告日 2024.06.21

(21)申请号 201880063660.0
(22)申请日 2018.08.10
(65)同一申请的已公布的文献号
申请公布号 CN 111148757 A
(43)申请公布日 2020.05.12
(30)优先权数据
62/543,658 2017.08.10 US
62/583,314 2017.11.08 US
PCT/US2018/018371 2018.02.15 US
(85)PCT国际申请进入国家阶段日
2020.03.30
(86)PCT国际申请的申请数据
PCT/US2018/046199 2018.08.10
(87)PCT国际申请的公布数据
WO2019/032955 EN 2019.02.14
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(51)Int.Cl.
C07K 14/79(2006.01)
C07K 14/705(2006.01)
A61K 39/00(2006.01)
A61K 38/40(2006.01)
(56)对比文件
CN 101516907 A,2009.08.26
US 2017051071 A1,2017.02.23
审查员 戎晓媛

权利要求书7页 说明书127页
序列表320页 附图70页

(54)发明名称

工程改造的转铁蛋白受体结合多肽

(57)摘要

本文提供结合至转铁蛋白受体的多肽、包含此类多肽的Fc二聚体和融合蛋白,以及使用所述多肽以使组合物靶向转铁蛋白受体表达细胞的方法。

CN 111148757 B

1.一种包含特异性地结合至转铁蛋白受体的修饰的CH3结构域的Fc多肽,其中所述修饰的CH3结构域由SEQ ID NO:83、84、191、43和82中任一个的第114-220位的氨基酸组成。

2.如权利要求1所述的Fc多肽,其由SEQ ID NO:83、84、191、43和82中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:83、84、191、43和82中任一个的序列组成。

3.Fc多肽,其由SEQ ID NO:133、134、135、260、261、139、140、141、263和264中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:133、134、135、260、261、139、140、141、263和264中任一个的序列组成。

4.Fc多肽,所述多肽由SEQ ID NO:145、146、147、267、268、151、152、153、270和271中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:145、146、147、267、268、151、152、153、270和271中任一个的序列组成。

5.Fc多肽,其由SEQ ID NO:232、233、234、309、310、238、239、240、312和313中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:232、233、234、309、310、238、239、240、312和313中任一个的序列组成。

6.Fc多肽,其由SEQ ID NO:169、170、171、281、282、175、176、177、284和285中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:169、170、171、281、282、175、176、177、284和285中任一个的序列组成。

7.Fc多肽,其由SEQ ID NO:121、122、123、253、254、127、128、129、256和257中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:121、122、123、253、254、127、128、129、256和257中任一个的序列组成。

8.一种多肽,所述多肽从N末端至C末端包含:抗体重链可变区、CH1结构域、铰链区和如权利要求1至7中任一项所述的Fc多肽。

9.一种Fc多肽二聚体或其二聚体片段,所述Fc多肽二聚体或其二聚体片段包含:

(a)第一Fc多肽,所述第一Fc多肽由如权利要求1至7中任一项所述的Fc多肽组成;以及

(b)第二Fc多肽,所述第二Fc多肽能够与(a)的所述第一Fc多肽二聚化。

10.如权利要求9所述的Fc多肽二聚体或其二聚体片段,其中所述二聚体对于TfR结合为单价。

11.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第二Fc多肽由SEQ ID NO:351-356中任一个的序列组成。

12.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:133、134和260中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:133、134和260中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:354-356中任一个的序列组成。

13.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:145、146和267中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:145、146和267中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:354-356中任一个的序列组成。

14.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:232、233和309中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸

“PCP”的SEQ ID NO:232、233和309中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:354-356中任一个的序列组成。

15.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:169、170和281中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:169、170和281中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:354-356中任一个的序列组成。

16.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:121、122和253中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:121、122和253中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:354-356中任一个的序列组成。

17.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:139、140和263中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:139、140和263中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:351-353中任一个的序列组成。

18.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:151、152和270中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:151、152和270中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:351-353中任一个的序列组成。

19.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:238、239和312中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:238、239和312中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:351-353中任一个的序列组成。

20.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:175、176和284中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:175、176和284中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:351-353中任一个的序列组成。

21.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽由SEQ ID NO:127、128和256中任一个的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:127、128和256中任一个的序列组成;并且所述第二Fc多肽由SEQ ID NO:351-353中任一个的序列组成。

22.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中:

(a)所述第一Fc多肽由SEQ ID NO:134的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:134的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:134的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:134的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:260的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:260的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组

成;或

(d)所述第一Fc多肽由SEQ ID NO:260的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:260的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(e)所述第一Fc多肽由SEQ ID NO:140的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:140的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(f)所述第一Fc多肽由SEQ ID NO:140的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:140的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成;或

(g)所述第一Fc多肽由SEQ ID NO:263的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:263的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(h)所述第一Fc多肽由SEQ ID NO:263的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:263的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成。

23.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中:

(a)所述第一Fc多肽由SEQ ID NO:146的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:146的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:146的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:146的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:267的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:267的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(d)所述第一Fc多肽由SEQ ID NO:267的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:267的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(e)所述第一Fc多肽由SEQ ID NO:152的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:152的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(f)所述第一Fc多肽由SEQ ID NO:152的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:152的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成;或

(g)所述第一Fc多肽由SEQ ID NO:270的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:270的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(h)所述第一Fc多肽由SEQ ID NO:270的序列组成,或由在氨基末端处不包含前三个氨

基酸“PCP”的SEQ ID NO:270的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成。

24.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中:

(a)所述第一Fc多肽由SEQ ID NO:233的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:233的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:233的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:233的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:309的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:309的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(d)所述第一Fc多肽由SEQ ID NO:309的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:309的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(e)所述第一Fc多肽由SEQ ID NO:239的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:239的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(f)所述第一Fc多肽由SEQ ID NO:239的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:239的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成;或

(g)所述第一Fc多肽由SEQ ID NO:312的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:312的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(h)所述第一Fc多肽由SEQ ID NO:312的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:312的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成。

25.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中:

(a)所述第一Fc多肽由SEQ ID NO:170的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:170的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:170的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:170的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:281的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:281的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(d)所述第一Fc多肽由SEQ ID NO:281的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:281的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组

成;或

(e)所述第一Fc多肽由SEQ ID NO:176的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:176的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(f)所述第一Fc多肽由SEQ ID NO:176的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:176的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成;或

(g)所述第一Fc多肽由SEQ ID NO:284的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:284的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(h)所述第一Fc多肽由SEQ ID NO:284的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:284的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成。

26.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中:

(a)所述第一Fc多肽由SEQ ID NO:122的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:122的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:122的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:122的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:253的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:253的序列组成;并且所述第二Fc多肽由SEQ ID NO:355的序列组成;或

(d)所述第一Fc多肽由SEQ ID NO:253的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:253的序列组成;并且所述第二Fc多肽由SEQ ID NO:356的序列组成;或

(e)所述第一Fc多肽由SEQ ID NO:128的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:128的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(f)所述第一Fc多肽由SEQ ID NO:128的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:128的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成;或

(g)所述第一Fc多肽由SEQ ID NO:256的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:256的序列组成;并且所述第二Fc多肽由SEQ ID NO:352的序列组成;或

(h)所述第一Fc多肽由SEQ ID NO:256的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:256的序列组成;并且所述第二Fc多肽由SEQ ID NO:353的序列组成。

27.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中

(a)所述第一Fc多肽由SEQ ID NO:260的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:260的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:253的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:253的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:267的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:267的序列组成。

28.如权利要求27所述的Fc多肽二聚体或其二聚体片段,其中所述第二Fc多肽由SEQ ID NO:356的序列组成。

29.如权利要求9或10所述的Fc多肽二聚体或其二聚体片段,其中

(a)所述第一Fc多肽由SEQ ID NO:134的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:134的序列组成;或

(b)所述第一Fc多肽由SEQ ID NO:122的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:122的序列组成;或

(c)所述第一Fc多肽由SEQ ID NO:146的序列组成,或由在氨基末端处不包含前三个氨基酸“PCP”的SEQ ID NO:146的序列组成。

30.如权利要求29所述的Fc多肽二聚体或其二聚体片段,其中所述第二Fc多肽由SEQ ID NO:355的序列组成。

31.如权利要求9所述的Fc多肽二聚体或其二聚体片段,其中所述二聚体对于TfR结合为二价。

32.如权利要求31所述的Fc多肽二聚体或其二聚体片段,其中所述第一Fc多肽和所述第二Fc多肽包含相同的TfR结合位点。

33.一种Fc多肽二聚体-Fab融合蛋白,所述Fc多肽二聚体-Fab融合蛋白包含:

(a)能够结合抗原的抗体可变区,或其抗原结合片段;以及

(b)如权利要求9至32中任一项所述的Fc多肽二聚体或其二聚体片段。

34.如权利要求33所述的Fc多肽二聚体-Fab融合蛋白,其中所述抗体可变区形成Fab结构域的一部分。

35.如权利要求33或34所述的Fc多肽二聚体-Fab融合蛋白,其中所述抗体可变区包含两个抗体重链可变区和两个抗体轻链可变区,或它们各自的片段。

36.一种多核苷酸,所述多核苷酸包含编码如权利要求1至7中任一项所述的Fc多肽的核酸序列。

37.一种载体,所述载体包含如权利要求36所述的多核苷酸。

38.一种宿主细胞,所述宿主细胞包含如权利要求36所述的多核苷酸。

39.一种用于产生特异性地结合至转铁蛋白受体的多肽的方法,所述方法包括在表达由如权利要求36所述的多核苷酸编码的Fc多肽的条件下培养宿主细胞。

40.一种药物组合物,所述药物组合物包含:如权利要求1至7中任一项所述的Fc多肽、如权利要求9至32中任一项所述的Fc多肽二聚体或其二聚体片段、或如权利要求33至35中任一项所述的Fc多肽二聚体-Fab融合蛋白;以及药学上可接受的载体。

41.包含如权利要求1至7中任一项所述的Fc多肽、如权利要求9至32中任一项所述的Fc多肽二聚体或其二聚体片段、或如权利要求33至35中任一项所述的Fc多肽二聚体-Fab融合

蛋白的组合物在制备用于跨内皮转胞吞的药物中的用途。

42.如权利要求41所述的用途,其中所述内皮是血脑屏障(BBB)。

工程改造的转铁蛋白受体结合多肽

[0001] 相关申请的交叉引用

[0002] 本申请要求2017年8月10日提交的美国临时专利申请号62/543,658、2017年11月8日提交的美国临时专利申请号62/583,314和2018年2月15日提交的国际专利申请号PCT/US2018/018371的优先权,所述专利申请的公开内容出于所有目的以引用的方式整体并入本文。

背景技术

[0003] 已开发出将蛋白质工程改造成结合至所述蛋白质通常不结合的靶标的各种技术。举例而言,可产生文库以筛选具有所需结合或酶活性的工程改造的蛋白质。

[0004] 转铁蛋白受体是转铁蛋白的载体蛋白,转铁蛋白是将铁输入细胞中和其他功能所需的且响应于细胞内铁浓度进行调控。转铁蛋白受体在包括血脑屏障内皮在内的内皮上表达,并且在各种癌细胞和炎性细胞上的表达水平较高。转铁蛋白受体是介导同源受体跨血脑屏障转胞吞的受体之一。因此,转铁蛋白受体可以是将剂引入细胞中以内吞于细胞中或跨细胞转胞吞的理想靶标。

发明内容

[0005] 已经开发出包括能够结合转铁蛋白受体(TfR)的CH3结构域的多肽。这些多肽被工程改造成在CH3结构域中具有产生新颖TfR结合位点的取代。TfR在血脑屏障(BBB)上大量表达,并且TfR天然地将转铁蛋白从血液移至脑中。因为这些多肽结合TfR,所以它们还可跨BBB转运且进一步可用于跨BBB转运所附接的治疗剂(例如治疗性多肽、抗体可变区诸如Fab和小分子)。这种方法可基本上改善治疗剂的脑吸收且因此特别适用于治疗其中脑递送有利的病症和疾病。

[0006] 在一个方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含与SEQ ID NO:83、84、191、43和82中任一个的序列具有至少85%、90%或95%序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Tyr或Phe、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Val、Ser或Ala、在163位的Asn、在186位的Thr或Ser、在188位的Glu、在189位的Glu以及在194位的Phe。

[0007] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala以及在180位的Val。在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。

[0008] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸“PCP”(例如,所述多肽包含与SEQ ID NO:83、84、191、43和82中任一个的序列具有至少85%、90%或95%序列同一性的序列并且不含在氨基末端处的前三个氨基酸”PCP”)。

[0009] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0010] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含与SEQ ID NO:83的序列具有至少85%、90%或95%序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Tyr、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Val、在163位的Asn、在186位的Thr、在188位的Glu、在189位的Glu以及在194位的Phe。

[0011] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:133的序列。

[0012] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:134的序列。

[0013] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:260的序列。

[0014] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:139的序列。

[0015] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala以及在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:140的序列。

[0016] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:263的序列。

[0017] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸”PCP”(例如,所述多肽包含与SEQ ID NO:83、133、134、260、139、140和263中任一个的序列具有至少85%、90%或95%序列同一性的序列且不含在氨基末端处的前三个氨基酸”PCP”)。

[0018] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0019] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含与SEQ ID NO:84的序列具有至少85%、90%或95%序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Tyr、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Ser、在163位的Asn、在186位的Ser、在188位的Glu、在189位的Glu以及在194位的Phe。

[0020] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:145的序列。

[0021] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:146的序列。

[0022] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包

含SEQ ID NO:267的序列。

[0023] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:151的序列。

[0024] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala以及在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:152的序列。

[0025] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:270的序列。

[0026] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸"PCP"(例如,所述多肽包含与SEQ ID NO:84、145、146、267、151、152和270中任一个的序列具有至少85%、90%或95%序列同一性的序列且不含在氨基末端处的前三个氨基酸"PCP")。

[0027] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0028] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含与SEQ ID NO:191的序列具有至少85%、90%或95%序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Phe、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Ser、在163位的Asn、在186位的Ser、在188位的Glu、在189位的Glu以及在194位的Phe。

[0029] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:232的序列。

[0030] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:233的序列。

[0031] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:309的序列。

[0032] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:238的序列。

[0033] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala以及在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:239的序列。

[0034] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:312的序列。

[0035] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸"PCP"(例如,所述多肽包含与SEQ ID NO:191、232、233、309、238、239和312中任一个的序列具有至少85%、90%或95%序列同一性的序列且不含在氨基末端处的前三个氨基酸"PCP")。

[0036] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0037] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所

述多肽包含与SEQ ID NO:43的序列具有至少85％、90％或95％序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Tyr、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Ser、在163位的Asn、在186位的Thr、在188位的Glu、在189位的Glu以及在194位的Phe。

[0038] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:169的序列。

[0039] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:170的序列。

[0040] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:281的序列。

[0041] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:175的序列。

[0042] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala以及在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:176的序列。

[0043] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:284的序列。

[0044] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸"PCP"(例如,所述多肽包含与SEQ ID NO:43、169、170、281、175、176和284中任一个的序列具有至少85％、90％或95％序列同一性的序列且不含在氨基末端处的前三个氨基酸"PCP")。

[0045] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0046] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含与SEQ ID NO:82的序列具有至少85％、90％或95％序列同一性的序列,其中如参照SEQ ID NO:1所编号,所述多肽包含在153位的Glu、在157位的Tyr、在159位的Thr、在160位的Glu、在161位的Trp、在162位的Ala、在163位的Asn、在186位的Thr、在188位的Glu、在189位的Glu以及在194位的Phe。

[0047] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:121的序列。

[0048] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala和在139位的Trp。在某些实施方案中,所述多肽包含SEQ ID NO:122的序列。

[0049] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Trp、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:253的序列。

[0050] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含SEQ ID NO:127的序列。

[0051] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala和在180位的Val。在某些实施方案中,所述多肽包含

SEQ ID NO:128的序列。

[0052] 在一些实施方案中,如参照SEQ ID NO:1所编号,所述多肽还包含在7位的Ala、在8位的Ala、在139位的Ser、在141位的Ala、在180位的Val、在201位的Leu以及在207位的Ser。在某些实施方案中,所述多肽包含SEQ ID NO:256的序列。

[0053] 在一些实施方案中,所述多肽不包含在所述序列的氨基末端处的前三个氨基酸"PCP"(例如,所述多肽包含与SEQ ID NO:82、121、122、253、127、128和256中任一个的序列具有至少85%、90%或95%序列同一性的序列且不含在氨基末端处的前三个氨基酸"PCP")。

[0054] 在一些实施方案中,所述多肽还包含抗体重链可变区。

[0055] 在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含SEQ ID NO:347的序列。在另一方面中,本公开的特征在于一种特异性地结合至转铁蛋白受体的多肽,所述多肽包含SEQ ID NO:348的序列。在一些实施方案中,所述多肽还包含抗体重链可变区。

[0056] 在另一方面中,本公开的特征在于一种多肽,所述多肽从N末端至C末端包含:抗体重链可变区、CH1结构域、铰链区和本文所述的多肽。

[0057] 在另一方面中,本公开的特征在于一种Fc多肽二聚体或其二聚体片段,所述Fc多肽二聚体或其二聚体片段包含:

[0058] (a)第一Fc多肽,所述第一Fc多肽包含本文所述的多肽;以及

[0059] (b)第二Fc多肽,所述第二Fc多肽能够与(a)的所述第一Fc多肽二聚化。

[0060] 在一些实施方案中,所述二聚体对于TfR结合为单价。在一些实施方案中,所述第二Fc多肽包含SEQ ID NO:351-356中任一个的序列。

[0061] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:133、134和260中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:354-356中任一个的序列。

[0062] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:145、146和267中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:354-356中任一个的序列。

[0063] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:232、233和309中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:354-356中任一个的序列。

[0064] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:169、170和281中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:354-356中任一个的序列。

[0065] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:121、122和253中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:354-356中任一个的序列。

[0066] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:139、140和263中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:351-353中任一个的序列。

[0067] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:151、152和270中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:351-353中任一个的序列。

[0068] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:238、239和312中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:351-353中任一个的序列。

[0069] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:175、176和284中任一个的序列;并且所述第二Fc多肽包含SEQ ID NO:351-353中任一个的序列。

[0070] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:127、128和256中任一个的序

列;并且所述第二Fc多肽包含SEQ ID NO:351-353中任一个的序列。

[0071] 在某些实施方案中,所述二聚体中的第一Fc多肽和第二Fc多肽包含以下序列:

[0072] (a)所述第一Fc多肽包含SEQ ID NO:134的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0073] (b)所述第一Fc多肽包含SEQ ID NO:134的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0074] (c)所述第一Fc多肽包含SEQ ID NO:260的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0075] (d)所述第一Fc多肽包含SEQ ID NO:260的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0076] (e)所述第一Fc多肽包含SEQ ID NO:140的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0077] (f)所述第一Fc多肽包含SEQ ID NO:140的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列;或

[0078] (g)所述第一Fc多肽包含SEQ ID NO:263的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0079] (h)所述第一Fc多肽包含SEQ ID NO:263的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列。

[0080] 在某些实施方案中,所述二聚体中的第一Fc多肽和第二Fc多肽包含以下序列:

[0081] (a)所述第一Fc多肽包含SEQ ID NO:146的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0082] (b)所述第一Fc多肽包含SEQ ID NO:146的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0083] (c)所述第一Fc多肽包含SEQ ID NO:267的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0084] (d)所述第一Fc多肽包含SEQ ID NO:267的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0085] (e)所述第一Fc多肽包含SEQ ID NO:152的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0086] (f)所述第一Fc多肽包含SEQ ID NO:152的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列;或

[0087] (g)所述第一Fc多肽包含SEQ ID NO:270的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0088] (h)所述第一Fc多肽包含SEQ ID NO:270的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列。

[0089] 在某些实施方案中,所述二聚体中的第一Fc多肽和第二Fc多肽包含以下序列:

[0090] (a)所述第一Fc多肽包含SEQ ID NO:233的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0091] (b)所述第一Fc多肽包含SEQ ID NO:233的序列并且所述第二Fc多肽包含SEQ ID

NO:356的序列;或

[0092] (c)所述第一Fc多肽包含SEQ ID NO:309的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0093] (d)所述第一Fc多肽包含SEQ ID NO:309的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0094] (e)所述第一Fc多肽包含SEQ ID NO:239的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0095] (f)所述第一Fc多肽包含SEQ ID NO:239的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列;或

[0096] (g)所述第一Fc多肽包含SEQ ID NO:312的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0097] (h)所述第一Fc多肽包含SEQ ID NO:312的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列。

[0098] 在某些实施方案中,所述二聚体中的第一Fc多肽和第二Fc多肽包含以下序列:

[0099] (a)所述第一Fc多肽包含SEQ ID NO:170的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0100] (b)所述第一Fc多肽包含SEQ ID NO:170的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0101] (c)所述第一Fc多肽包含SEQ ID NO:281的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0102] (d)所述第一Fc多肽包含SEQ ID NO:281的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0103] (e)所述第一Fc多肽包含SEQ ID NO:176的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0104] (f)所述第一Fc多肽包含SEQ ID NO:176的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列;或

[0105] (g)所述第一Fc多肽包含SEQ ID NO:284的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0106] (h)所述第一Fc多肽包含SEQ ID NO:284的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列。

[0107] 在某些实施方案中,所述二聚体中的第一Fc多肽和第二Fc多肽包含以下序列:

[0108] (a)所述第一Fc多肽包含SEQ ID NO:122的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0109] (b)所述第一Fc多肽包含SEQ ID NO:122的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0110] (c)所述第一Fc多肽包含SEQ ID NO:253的序列并且所述第二Fc多肽包含SEQ ID NO:355的序列;或

[0111] (d)所述第一Fc多肽包含SEQ ID NO:253的序列并且所述第二Fc多肽包含SEQ ID NO:356的序列;或

[0112] (e)所述第一Fc多肽包含SEQ ID NO:128的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0113] (f)所述第一Fc多肽包含SEQ ID NO:128的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列;或

[0114] (g)所述第一Fc多肽包含SEQ ID NO:256的序列并且所述第二Fc多肽包含SEQ ID NO:352的序列;或

[0115] (h)所述第一Fc多肽包含SEQ ID NO:256的序列并且所述第二Fc多肽包含SEQ ID NO:353的序列。

[0116] 在一些实施方案中,所述第一Fc多肽不包含在所述序列的氨基末端处的前三个氨基酸"PCP"(例如,所述第一Fc多肽包含所述序列且不含在氨基末端处的前三个氨基酸"PCP")。

[0117] 在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:347的序列并且所述第二Fc多肽包含SEQ ID NO:350的序列。在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:348的序列并且所述第二Fc多肽包含SEQ ID NO:349的序列。

[0118] 在一些实施方案中,所述二聚体对于TfR结合为二价。在一些实施方案中,所述第二Fc多肽包含SEQ ID NO:347或348的序列。在某些实施方案中,所述第一Fc多肽包含SEQ ID NO:347的序列并且所述第二Fc多肽包含SEQ ID NO:348的序列。在一些实施方案中,所述第一Fc多肽和第二Fc多肽包含相同TfR结合位点。

[0119] 在另一方面中,本公开的特征在于一种Fc多肽二聚体-Fab融合蛋白,所述Fc多肽二聚体-Fab融合蛋白包含:

[0120] (a)能够结合抗原的抗体可变区,或其抗原结合片段;以及

[0121] (b)本文所述的Fc多肽二聚体。

[0122] 在一些实施方案中,所述抗体可变区形成Fab结构域的一部分。在某些实施方案中,所述抗体可变区包含两个抗体重链可变区和两个抗体轻链可变区,或它们各自的片段。

[0123] 在另一方面中,本公开的特征在于一种多核苷酸,所述多核苷酸包含编码本文所述的多肽的核酸序列。在一些实施方案中,提供一种包含所述多核苷酸的载体。在一些实施方案中,提供一种包含所述多核苷酸的宿主细胞。在另一方面中,本公开的特征在于一种用于产生特异性地结合至转铁蛋白受体的多肽的方法,所述方法包括在表达由所述多核苷酸编码的多肽的条件下培养宿主细胞。

[0124] 在另一方面中,本公开的特征在于一种药物组合物,所述药物组合物包含:本文所述的多肽、Fc多肽二聚体和/或Fc多肽二聚体-Fab融合蛋白;以及药学上可接受的载体。

[0125] 在另一方面中,本公开的特征在于一种用于跨内皮转胞吞组合物的方法,所述方法包括使所述内皮与包含本文所述的多肽、Fc多肽二聚体和/或Fc多肽二聚体-Fab融合蛋白的组合物接触。

[0126] 在一些实施方案中,所述内皮是血脑屏障(BBB)。

附图说明

[0127] 图1示出在酵母上CH3C克隆选择的FACS图,显示在3轮分选后结合群体的富集。在第1轮和第2轮分选中,将生物素化的TfR预先负载于链霉抗生物素蛋白-Alexa Fluor® 647

上,随后与酵母一起孵育。在第3轮分选中,首先将生物素化的TfR与酵母一起孵育,并且添加链霉抗生物素蛋白-Alexa Fluor® 647进行二次检测。在所有数轮分选中,均使用针对酵母展示构建体上的C末端Myc标签的鸡抗c-Myc抗体(从Thermo Fisher获得)监测表达。

[0128] 图2A-2C示出在存在或不存在铁饱和Tf下CH3C克隆与TfR的结合。所述克隆以Fc-Fab融合物形式测定。在此测定中使用Ab204(一种具有结合至TfR的可变区的标准抗体)作为阳性对照。图2A示出CH3C变体与包被于ELISA板上的人TfR的结合。图2B示出在5μM铁饱和Tf存在下,CH3C变体与包被于ELISA板上的人TfR的结合。图2C示出CH3C变体与包被于ELISA板上的食蟹猴TfR的结合。

[0129] 图3示出CH3C克隆与内源性表达人TfR的293F细胞的结合。将细胞分配于96孔V形底板上,并且添加不同浓度的呈Fc-Fab融合结合蛋白形式的CH3C克隆。在4℃下孵育1小时后,将所述板离心并洗涤,且然后与山羊抗人IgG-Alexa Fluor® 647第二抗体一起在4℃下孵育30分钟。再洗涤细胞后,在FACSCanto™II流式细胞仪上读取板,并且使用FlowJo®软件测定APC(647nm)通道中的中值荧光度值。

[0130] 图4A和4B示出在内源性表达人TfR的HEK293细胞中CH3C.3的内化。在37℃和8%CO_2浓度下,添加1μM浓度的CH3C.3或对照,保持30分钟,然后洗涤细胞,使所述细胞透化并用抗人IgG-Alexa Fluor® 488第二抗体染色。再次洗涤后,通过荧光显微术对细胞成像并定量斑点的数量。图4A示出显微镜检查数据。图4B示出每孔斑点的数量的图。

[0131] 图5示出CH3C软文库(soft library)的选择方案。通过MACS针对人(H)或食蟹猴(C)TfR分选初始文库。然后将所得酵母汇集物分离并如第一轮FACS分选中一样针对人或食蟹猴TfR分别进行分选。再次将所得汇集物分离以进行另一轮FACS分选。最后,将HHH和CCC汇集物保持分离并最终汇集具有两种靶标物种的其他汇集物。

[0132] 图6A和6B示出从第一软随机突变文库鉴定的CH3C克隆与人和食蟹猴TfR的结合。阳性对照是Ab204(一种高亲和力抗TfR抗体)和Ab084(一种低亲和力抗TfR抗体)。图6A示出与人TfR的结合。图6B示出与食蟹猴TfR的结合。

[0133] 图7A和7B示出在存在或不存在铁饱和Tf下,从第一软随机突变文库鉴定的CH3C克隆与人TfR的结合。克隆是呈Fc-Fab融合物形式。在此测定中使用Ab204(一种高亲和力抗TfR抗体)作为阳性对照。图7A示出CH3C变体与包被于ELISA板上的人TfR的结合。图7B示出在5μM铁饱和Tf存在下,CH3C变体与包被于ELISA板上的人TfR的结合。

[0134] 图8示出从第一软随机突变文库鉴定的CH3C克隆与293F细胞的结合。将细胞分配于96孔V形底板上,并且添加不同浓度的呈Fc-Fab融合蛋白形式的CH3C克隆。在4℃下孵育1小时后,将所述板离心并洗涤,且然后与山羊抗人IgG-Alexa Fluor® 647第二抗体一起在4℃下孵育30分钟。再洗涤细胞后,在FACSCanto™II流式细胞仪上读取板,并使用FlowJo®软件测定APC(647nm)通道中的中值荧光度值。

[0135] 图9A-9C示出从第一软随机突变文库鉴定的CH3C克隆与CHO-K1细胞的结合。将细胞分配于96孔V形底板上,并且添加不同浓度的呈Fc-Fab融合物形式的CH3C克隆。在4℃下孵育1小时后,将所述板离心并洗涤,且然后与山羊抗人IgG-Alexa Fluor® 647第二抗体一起在4℃下孵育30分钟。再洗涤细胞后,在FACSCanto™II流式细胞仪上读取板,并使用

FlowJo®软件测定APC(647nm)通道中的中值荧光度值。图9A示出过表达人TfR的CHO-K1细胞。图9B示出过表达食蟹猴TfR的CHO-K1细胞。图9C示出不表达人TfR的CHO-K1亲本细胞。

[0136] 图10A和10B示出TfR顶端结构域。图10A示出顶端结构域在人TfR蛋白质上的位置。插图示出在人与食蟹猴TfR之间不同的七个残基的近视图。图10B示出含有在人(SEQ ID NO:30)与食蟹猴(SEQ ID NO:31)TfR之间不同的七个残基的序列比对。共有序列是SEQ ID NO:342。

[0137] 图11A-11E示出CH3C克隆与展示于噬菌体上的顶端结构域的结合。图11A示出各种TfR顶端结构域突变体的Myc表达,表明所述突变体的表达水平类似且标准化。图11B示出CH3C.18与野生型和突变型人TfR顶端结构域的结合,表明与R208G突变体的结合减少。图11C示出CH3C.35与野生型和突变人TfR顶端结构域的结合,显示与R208G突变体的结合减少。图11D示出CH3C.18与野生型人和食蟹猴TfR顶端结构域以及G208R突变型食蟹猴顶端结构域的结合,表明与所述突变体的结合恢复。图11E示出CH3C.35与野生型人和食蟹猴TfR顶端结构域以及G208R突变型食蟹猴顶端结构域的结合,表明与所述突变体的结合恢复。

[0138] 图12A-12D示出通过将突变位置复原成野生型残基进行的CH3C变体的互补位定位。图12A示出通过ELISA进行的结合至人TfR的CH3C.35的回复突变体的互补位定位。图12B示出通过ELISA进行的结合至食蟹猴TfR的CH3C.35的回复突变体的互补位定位。图12C示出通过ELISA进行的结合至人TfR的CH3C.18的回复突变体的互补位定位。图12D示出通过ELISA进行的结合至食蟹猴TfR的CH3C.18的回复突变体的互补位定位。

[0139] 图13A-13D示出CH3C共有成熟文库的设计。图13A示出基于CH3C.35样序列的共有文库。图13B示出基于CH3C.18样序列的共有文库。图13C示出基于CH3C.18和CH3C.35的空位文库。图13D示出基于CH3C.18芳族化合物文库。

[0140] 图14A-14E示出来自共有成熟文库的CH3C变体与人或食蟹猴TfR的结合ELISA。新变体(即,CH3C.3.2-1、CH3C.3.2-5和CH3C.3.2-19)对于食蟹猴和人TfR具有类似结合EC_{50}值,而亲本克隆CH3C.18和CH3C.35对人TfR的EC_{50}值显著优于对食蟹猴TfR的EC_{50}值。图14A示出CH3C.3.2-1的数据。图14B示出CH3C.3.2-19的数据。图14C示出CH3C.3.2-5的数据。图14D示出CH3C.18的数据。图14E示出CH3C.35的数据。

[0141] 图15示出在人(HEK293)和猴(LLC-MK2)细胞中来自共有成熟文库的CH3C变体的内化。相较于与人TfR的结合更好的克隆CH3C.35,具有类似人和食蟹猴TfR亲和力的克隆CH3C.3.2-5和CH3C3.2-19在猴细胞中的吸收显著改善。使用Ab107(一种抗BACE1抗体)作为阴性对照。(BACE1在HEK293或MK2细胞上不表达)。使用Ab204(一种抗TfR抗体)作为阳性对照。

[0142] 图16示出描绘于CH3结构(改编自PDB 4W4O)上的NNK步行残基的图谱。黑色表面示出原始CH3C定位区,灰色表面示出并入NNK步行结构中的44个残基,且条带示出野生型主链。

[0143] 图17示出在三轮分选NNK步行文库之后富集的酵母群体。将酵母用抗c-Myc染色以监测表达(x轴)以及与TfR顶端结构域(200nM食蟹猴或200nM人)的结合(y轴)。此处呈现的数据清楚地表明与两种TfR顶端结构域直系同源物的结合增强。

[0144] 图18A和18B示出CH3C.35.21突变体的FACS数据。将酵母用抗c-Myc染色以监测表达(x轴)以及与人TfR顶端结构域(200nM)的结合(y轴)。图18A示出克隆CH3C.35.21的FACS

数据。图18B示出突变体的FACS数据,其中克隆CH3C.35.21中的11个位置回复突变成野生型(FACS图的上面一列)或表达为全部20个氨基酸的NNK文库(FACS图的下面一列,在任何分选之前)。

[0145] 图19A-19D示出二价和单价CH3C多肽与人和食蟹猴TfR的结合的ELISA比较。图19A示出二价CH3C多肽与人TfR的结合。图19B示出二价CH3C多肽与食蟹猴TfR的结合。图19C示出单价CH3C多肽与人TfR的结合。图19D示出单价CH3C多肽与食蟹猴TfR的结合。

[0146] 图20A-20E示出单价CH3C多肽的细胞结合。图20A示出293F细胞。图20B示出与图20A中所描绘的293F细胞的结合的放大。图20C示出用人TfR稳定转染的CHO-K1细胞。图20D示出与图20C中所描绘的用人TfR稳定转染的CHO-K1细胞的结合的放大。图20E示出用食蟹猴TfR稳定转染的CHO-K1细胞。

[0147] 图21示出在HEK293细胞中单价和二价CH3C多肽的内化。

[0148] 图22A-22H示出CH3C多肽的结合动力学。图22A示出CH3C.35.N163与人TfR的结合的数据。图22B示出CHC3.35与人TfR的结合的数据。图22C示出CHC3.35.N163与人TfR单价结合的数据。图22D示出CHC3.35与人TfR单价结合的数据。图22E示出CH3C.35.N163与食蟹猴TfR的结合的数据。图22F示出CHC3.35与食蟹猴TfR的结合的数据。图22G示出CHC3.35.N163与食蟹猴TfR单价结合的数据。图22H示出CHC3.35与食蟹猴TfR单价结合的数据。

[0149] 图23A-23F示出CH3C多肽的结合动力学。图23A示出CH3C.3.2-1与人TfR的结合的数据。图23B示出CH3C.3.2-5与人TfR的结合的数据。图23C示出CH3C.3.2-19与人TfR的结合的数据。图23D示出CH3C.3.2-1与食蟹猴TfR的结合的数据。图23E示出CH3C.3.2-5与食蟹猴TfR的结合的数据。图23F示出CH3C.3.2-19与食蟹猴TfR的结合的数据。

[0150] 图24A-24E示出在存在(下部迹线)或不存在(上部迹线)人TfR细胞外结构域的情况下,在pH 5.5下多肽-Fab融合物与FcRn的结合。图24A示出克隆CH3C.35的数据。图24B示出克隆CH3C.35.19的数据。图24C示出克隆CH3C.35.20的数据。图24D示出克隆CH3C.35.21的数据。图24E示出克隆CH3C.35.24的数据。

[0151] 图25示出在野生型小鼠中CH3C多肽的药物动力学(PK)分析。除CH3C.3.2-5具有较快清除率外,所有多肽-Fab融合物均具有与野生型Fc-Fab融合物(即,Ab122(一种抗RSV抗体)和Ab153(一种抗BACE1抗体))相当的清除率。

[0152] 图26示出在小鼠脑组织中的脑药物动力学/药效学(PK/PD)数据。向嵌合huTfR杂合小鼠(n＝4只/组)静脉内给与42mg/kg Ab153或单价CH3C.35.N163(标记为"CH3C.35.N163_mono"),且向野生型小鼠(n＝3)静脉内给与50mg/kg对照人IgG1(标记为"huIgG1")。条形图表示平均值+/-SD。

[0153] 图27A和27B示出在用50mg/kg多肽处理后24小时,hTfR$^{顶端结构域+/+}$小鼠中所发现的IgG的浓度。图27A示出血浆中的IgG浓度。图27B示出脑组织中的IgG浓度。

[0154] 图28A和28B示出如通过淀粉样β-蛋白40(Aβ40)减少所测量,在24小时后hTfR$^{顶端结构域+/+}$小鼠中给与的多肽的靶接合。图28A示出血浆中的Aβ40浓度。图28B示出脑组织中的Aβ40浓度。

[0155] 图29示出CH3C.18Fc和TfR顶端结构域(AD)复合物的不同大小部分的SDS-PAGE凝胶。泳道1:分子量标记物。泳道2:在尺寸排阻色谱法后减少的CH3C.18Fc-AD复合物。

[0156] 图30A和30B描绘本发明的多肽与转铁蛋白受体之间的结合。图30A描绘克隆

CH3C.18与转铁蛋白受体的顶端结构域之间的结合界面。图30B示出图30A中所描绘的结合界面的放大图。

[0157] 图31A和31B描绘CH3C.18与TfR顶端结构域之间的相互作用。图31A描绘TfR顶端结构域和CH3C.18Fc的结构架构(顶图)以及TfR顶端结构域与CH3C.18Fc的结合表面(在5埃内)(底图)。共复合物结构以3.6Å分辨率解析。所述结构揭示在TfR顶端结构域上结合至CH3C.18的表位。特别地,所述顶端结构域的N末端区参与CH3C Fc结合,并且所述结构与CH3C.18Fc和TfR顶端结构域诱变数据相符。另外,CH3C.18文库侧链都接触TfR(在5Å内)。CH3C.18文库残基:L157、H159、V160、W161、A162、V163、P186、T189以及W194。非文库残基:F196和S156。图31B描绘CH3C.18Fc与TfR顶端结构域的关键相互作用。CH3C.18Fc上的W161与顶端结构域上的R208之间的阳离子-π相互作用是重要的结合相互作用。CH3C.18W388或顶端结构域R208的突变破坏CH3C.18Fc与顶端结构域的结合。与此相符,从人至食蟹猴的R208G突变解释了食蟹猴亲和力降低的原因。此外,人顶端结构域中的非保守残基(N292和E294(食蟹猴中的K292和D294))是邻近的。因此,CH3C.18中的Q192可突变以相对于人结合选择性地改善食蟹猴结合。

[0158] 图32A和32B描绘本发明多肽与转铁蛋白受体之间的结合。图32A描绘克隆CH3C.18(A链)中的残基与转铁蛋白受体(D链)的顶端结构域之间的氢键和非键合接触。图32B描绘克隆CH3C.18(B链)中的残基与转铁蛋白受体(C链)的顶端结构域之间的氢键和非键合接触。

[0159] 图33示出人IgG1、IgG2、IgG3和IgG4氨基酸序列(SEQ ID NO:343-346)的比对。

[0160] 图34A-34C描绘本发明的多肽与转铁蛋白受体之间的结合。图34A描绘TfR顶端结构域和CH3C.35Fc的结构架构(顶图)以及TfR顶端结构域与CH3C.35Fc的结合表面(在5 Å内)(底图)。共复合物结构以3.4Å分辨率解析。所述结构揭示在TfR顶端结构域上结合至CH3C.35的表位。CH3C.35文库侧链都接触TfR(在5Å内)。CH3C.35文库残基:Y157、T159、E160、W161、S162、T186、E189以及W194。非文库残基:F196、S156、Q192。图34B和34C示出图34A中所描绘的克隆CH3C.35与转铁蛋白受体的顶端结构域之间的结合界面的放大图。

[0161] 图35A描绘CH3C.35Fc与TfR-AD复合物以及CH3C.18Fc与TfR-AD复合物之间的覆盖结构。

[0162] 图35B描绘图35A中的覆盖结构的放大图。

[0163] 图36A和36B描绘本发明的多肽与转铁蛋白受体之间的结合。图36A描绘克隆CH3C.35(A链)中的残基与转铁蛋白受体(D链)的顶端结构域之间的氢键和非键合接触。图36B描绘克隆CH3C.35(B链)中的残基与转铁蛋白受体(C链)的顶端结构域之间的氢键和非键合接触。

[0164] 图37A和37B描绘食蟹猴中包含融合至Ab153 Fab结构域的CH3C变体的Fc-Fab融合多肽的血浆PK和Aβ40减少。图37A示出,Ab210和CH3C.35.9:Ab153由于TfR介导的清除而展现与对照IgG(Ab122)和Ab153相比更快的清除率。图37B示出,全部结合并抑制BACE1的Ab153、Ab210和CH3C.35.9:Ab153展现血浆中的显著Aβ40减少。

[0165] 图38A和38B描绘在食蟹猴中利用包含融合至Ab153 Fab结构域的CH3C变体的Fc-Fab融合多肽使脑脊髓液(CSF)Aβ和sAPPβ/sAPPα显著减少。图38A示出,给与Ab210和

CH3C.35.9:Ab153的动物显示CSF Aβ40相较于Ab153和对照IgG(Ab122)减少约70％。图38B示出,给与Ab210和CH3C.35.9:Ab153的动物显示sAPPβ/sAPPα比率相较于Ab153和对照IgG(Ab122)降低约75％。n＝4只/组。线图表示平均值±SEM。

[0166] 图39A和39B描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C35.21:Ab153、CH3C35.20:Ab153或CH3C35:Ab153多肽融合物之后hTfR顶端结构域$^{+/+}$基因敲入(KI)小鼠的血浆(图39A)和脑溶解产物(图39B)中的huIgG1浓度(平均值±SEM,n＝5只/组)。

[0167] 图39C描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C35.21:Ab153、CH3C35.20:Ab153或CH3C35:Ab153多肽融合物之后hTfR顶端结构域$^{+/+}$KI小鼠的脑溶解产物中的内源性小鼠Aβ浓度(平均值±SEM,n＝5只/组)。

[0168] 图39D描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C35.21:Ab153、CH3C35.20:Ab153或CH3C35:Ab153多肽融合物之后hTfR顶端结构域$^{+/+}$KI小鼠的脑溶解产物中针对肌动蛋白标准化的脑TfR蛋白质的蛋白质印迹(Western blot)定量(平均值±SEM,n＝5只/组)。

[0169] 图40A和40B描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C.35.23:Ab153或CH3C.35.23.3:Ab153多肽融合物之后hTfR$^{顶端结构域+/+}$KI小鼠的血浆(图40A)和脑溶解产物(图40B)中的huIgG1浓度(平均值±SEM,n＝5只/组)。

[0170] 图40C描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C.35.23:Ab153或CH3C.35.23.3:Ab153多肽融合物之后hTfR$^{顶端结构域+/+}$KI小鼠的脑溶解产物中的内源性小鼠Aβ浓度(平均值±SEM,n＝5只/组)。

[0171] 图40D描绘在单次全身注射50mg/kg抗BACE1_Ab153、CH3C.35.23:Ab153或CH3C.35.23.3:Ab153多肽融合物之后hTfR$^{顶端结构域+/+}$KI小鼠的脑溶解产物中针对肌动蛋白标准化的脑TfR蛋白质的蛋白质印迹定量(平均值±SEM,n＝4只/组)。

[0172] 图41A-41D描绘在给与单次30mg/kg剂量的指定蛋白质之后在食蟹猴中进行的28天PKPD研究。图41A和41B描绘血清中的血清huIgG1和血浆中的血浆Aβ浓度,示出所给与的化合物的周围暴露和由此引起的随时间推移对血浆Aβ水平的影响。图41C和41D描绘在给药后食蟹猴的CSF中的Aβ和sAPPβ/sAPPα(平均值±SEM,n＝4-5只/组)。

[0173] 图42A-42C描绘在单次30mg/kg剂量的指定蛋白质之后食蟹猴的外周血中的血液网织红细胞相对于给药前水平(图42A)、绝对血清铁水平(图42B)和绝对红细胞计数(图42C)(平均值±SEM,n＝4-5只/组)。

[0174] 图43A和43B描绘在14天内单次10mg/kg静脉内注射之后hFcRn基因敲入小鼠中指定蛋白质的周围PK分析(血浆huIgG1浓度(图43A)和清除率值(图43B))(平均值±SEM,n＝3只/组)。

[0175] 图44描绘TfR结合CH3C.18变体的中值荧光强度。

具体实施方式

[0176] I.引言

[0177] 本文描述结合转铁蛋白受体(TfR)的多肽。本发明是部分基于发现Fc区中的某些氨基酸可被修饰以在Fc多肽中产生对TfR具有特异性的新颖结合位点。利用TfR在血脑屏障(BBB)上大量表达和TfR天然地将转铁蛋白从血液移动至脑中的事实,这些多肽可用于跨

BBB转运治疗剂(例如治疗性多肽、抗体可变区诸如Fab,和小分子)。这种方法可大体上改善治疗剂的脑吸收且因此特别适用于治疗得益于脑递送的病症和疾病。

[0178] 在一个方面中,本发明是部分基于发现CH3结构域多肽中的几组氨基酸可被取代以产生结合转铁蛋白受体的多肽。因此,在一个方面中,本文提供转铁蛋白受体结合多肽,所述转铁蛋白受体结合多肽在包含如参照SEQ ID NO:1编号的位置157、159、160、161、162、163、186、189以及194的一组氨基酸处具有多个取代。所述组中从四个至全部氨基酸位置不等可被取代。出于本公开的目的,取代是参照SEQ ID NO:1确定。因此,如果一个氨基酸不同于SEQ ID NO:1位置中的相应氨基酸,则认为所述胺基酸为取代,即使所述氨基酸存在于天然存在的CH3结构域多肽中的所述位置处。

[0179] 在另一方面中,本文提供治疗方法和使用转铁蛋白受体结合多肽来使组合物靶向转铁蛋白受体表达细胞,例如将所述组合物递送至所述细胞,或跨内皮、诸如跨血脑屏障递送组合物的方法。

[0180] II.定义

[0181] 除非上下文另作清楚规定,否则如本文所使用,单数形式“一个(种)”和“所述”包括多个(种)指示物。因此,例如,提及“多肽”可包括两个或更多个此类分子等。

[0182] 如本文所使用,术语“约”和“大约”当用于修饰以数字值或范围指定的量时指示,所述数字值以及本领域技术人员已知的与所述值的合理偏差,例如±20%、±10%或±5%在所述值的预定含义内。

[0183] 如本发明上下文中所使用,术语“转铁蛋白受体”或“TfR”是指转铁蛋白受体蛋白质1。人转铁蛋白受体1多肽序列在SEQ ID NO:38中列出。还已知来自其他物种的转铁蛋白受体蛋白质1(例如,黑猩猩,登录号XP_003310238.1;猕猴,NP_001244232.1;狗,NP_001003111.1;牛,NP_001193506.1;小鼠,NP_035768.1;大鼠,NP_073203.1;以及鸡,NP_990587.1)。术语“转铁蛋白受体”还涵盖由位于转铁蛋白受体蛋白质1染色体基因座处的基因编码的示例性参考序列,例如人序列的等位基因变体。全长转铁蛋白受体蛋白质包括短N末端细胞内区域、跨膜区和大细胞外结构域。所述细胞外结构域以三个结构域表征:蛋白酶样结构域、螺旋结构域和顶端结构域。人转铁蛋白受体1的顶端结构域序列在SEQ ID NO:30中列出。

[0184] 如本文所使用,术语“CH3结构域”和“CH2结构域”是指免疫球蛋白恒定区结构域多肽。在IgG抗体的情况下,CH3结构域多肽是指如根据EU编号方案编号从约341位至约447位的氨基酸的区段,并且CH2结构域多肽是指如根据EU编号方案编号从约231位至约340位的氨基酸的区段。CH2和CH3结构域多肽还可通过IMGT(ImMunoGeneTics)编号方案编号,其中根据IMGT Scientific图表编号(IMGT网站),CH2结构域编号是1-110且CH3结构域编号是1-107。CH2和CH3结构域是免疫球蛋白的Fc区的一部分。在IgG抗体的情况下,Fc区是指如根据EU编号方案编号,从约231位至约447位的氨基酸的区段。如本文所使用,术语“Fc区”还可包括抗体的铰链区的至少一部分。说明性铰链区序列在SEQ ID NO:37中列出。

[0185] 关于CH3或CH2结构域的术语“野生型”、“天然”和“天然存在”在本文中用于指具有自然界中存在的序列的结构域。

[0186] 在本发明的上下文中,关于突变多肽或突变多核苷酸的术语“突变体”可与“变体”互换使用。关于给定野生型CH3或CH2结构域参考序列的变体可包括天然存在的等位基因变

体。“非天然”存在的CH3或CH2结构域是指在自然界中不存在于细胞中且由通过例如使用基因工程改造技术或诱变技术遗传修饰天然CH3结构域或CH2结构域多核苷酸或多肽产生的变体或突变结构域。“变体”包括相对于野生型敖合至少一个氨基酸突变的任何结构域。突变可包括取代、插入和缺失。

[0187] 术语“氨基酸”是指天然存在和合成的氨基酸以及以类似于天然存在的氨基酸的方式起作用的氨基酸类似物和氨基酸模拟物。

[0188] 天然存在的氨基酸是由遗传密码编码的氨基酸,以及随后修饰的氨基酸,例如羟脯氨酸、γ-羧基谷氨酸和O-磷酸丝氨酸。“氨基酸类似物”是指具有与天然存在的氨基酸相同的基本化学结构(即,结合至氢、羧基、氨基和R基团的α碳)的化合物,例如高丝氨酸、正亮氨酸、甲硫氨酸亚砜、甲硫氨酸甲基锍。此类类似物具有修饰的R基团(例如正亮氨酸)或修饰的肽主链,但保留与天然存在的氨基酸相同的基本化学结构。“氨基酸模拟物”是指具有不同于氨基酸的一般化学结构的结构、但以类似于天然存在的氨基酸的方式作用的化合物。

[0189] 天然存在的α-氨基酸包括但不限于,丙氨酸(Ala)、半胱氨酸(Cys)、天冬氨酸(Asp)、谷氨酸(Glu)、苯丙氨酸(Phe)、甘氨酸(Gly)、组氨酸(His)、异亮氨酸(Ile)、精氨酸(Arg)、赖氨酸(Lys)、亮氨酸(Leu)、甲硫氨酸(Met)、天冬酰胺(Asn)、脯氨酸(Pro)、谷氨酰胺(Gln)、丝氨酸(Ser)、苏氨酸(Thr)、缬氨酸(Val)、色氨酸(Trp)、酪氨酸(Tyr)和它们的组合。天然存在的α-氨基酸的立体异构体包括但不限于,D-丙氨酸(D-Ala)、D-半胱氨酸(D-Cys)、D-天冬氨酸(D-Asp)、D-谷氨酸(D-Glu)、D-苯丙氨酸(D-Phe)、D-组氨酸(D-His)、D-异亮氨酸(D-Ile)、D-精氨酸(D-Arg)、D-赖氨酸(D-Lys)、D-亮氨酸(D-Leu)、D-甲硫氨酸(D-Met)、D-天冬酰胺(D-Asn)、D-脯氨酸(D-Pro)、D-谷氨酰胺(D-Gln)、D-丝氨酸(D-Ser)、D-苏氨酸(D-Thr)、D-缬氨酸(D-Val)、D-色氨酸(D-Trp)、D-酪氨酸(D-Tyr)以及它们的组合。

[0190] 氨基酸在本文中可以其通常已知的三字母符号或由IUPAC-IUB生物化学命名委员会(IUPAC-IUB Biochemical Nomenclature Commission)所推荐的单字母符号提及。

[0191] 术语“多肽”、“肽”与“蛋白质”在本文中可互换使用,是指氨基酸残基的聚合物。所述术语适用于一个或多个氨基酸残基是相应天然存在的氨基酸的人工化学模拟物的氨基酸聚合物,并且还适用于天然存在的氨基酸聚合物和非天然存在的氨基酸聚合物。氨基酸聚合物可仅包含L-氨基酸、仅包含D-氨基酸,或包含L和D氨基酸的混合物。

[0192] 术语“保守取代”、“保守突变”或“保守修饰的变体”是指用可归类为具有类似特征的一个氨基酸取代另一氨基酸的改变。以此方式定义的保守氨基酸群组的类别的实例可以包括:“带电/极性组”,包括Glu(谷氨酸或E)、Asp(天冬氨酸或D)、Asn(天冬酰胺或N)、Gln(谷氨酰胺或Q)、Lys(赖氨酸或K)、Arg(精氨酸或R)和His(组氨酸或H);“芳族氨基酸组”,包括Phe(苯丙氨酸或F)、Tyr(酪氨酸或Y)、Trp(色氨酸或W)和(组氨酸或H);和“脂族氨基酸组”,包括Gly(甘氨酸或G)、Ala(丙氨酸或A)、Val(缬氨酸或V)、Leu(亮氨酸或L)、Ile(异亮氨酸或I)、Met(甲硫氨酸或M)、Ser(丝氨酸或S)、Thr(苏氨酸或T)和Cys(半胱氨酸或C)。在各组内,还可鉴别出亚组。举例来说,带电或极性氨基酸组可细分成数个亚组,包括:“带正电亚组”,包括Lys、Arg和His;“带负电亚组”,包括Glu和Asp;和“极性亚组”,包括Asn和Gln。在另一实例中,芳族或环状氨基酸组可细分成包括以下的亚组:“氮环亚组”,包括Pro、His和Trp;和“苯基亚组”,包括Phe和Tyr。在又一实例中,脂族氨基酸组可细分成数个亚组,例

如“脂族非极性亚组”,包括Val、Leu、Gly和Ala;和“脂族低极性亚组”,包括Met、Ser、Thr和Cys。保守突变的类别的实例包括在以上亚组内的氨基酸的氨基酸取代,诸如但不限于:Lys取代Arg或反之亦然,由此可维持正电荷;Glu取代Asp或反之亦然,由此可维持负电荷;Ser取代Thr或反之亦然,由此可维持游离-OH;以及Gln取代Asn或反之亦然,由此可维持游离-NH_2。在一些实施方案中,用疏水性氨基酸取代例如活性位点中的天然存在的疏水性氨基酸,以保持疏水性。

[0193] 在两个或更多个多肽序列的背景下,术语“同一”或“同一性”百分比是指当在比较窗或指定区域内比较和比对以达到最大对应性时,如使用序列比较算法或通过手动比对和目测检查所测量的相同或在指定区域内具有指定百分比的氨基酸残基同一性,例如至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%或至少95%或更高百分比同一性的两个或更多个序列或子序列。

[0194] 对于多肽的序列比较,通常一个序列充当参考序列,用以与候选序列相比较。比对可使用本领域技术人员可用的各种方法,例如目测比对或使用公开可用的软件,使用已知算法进行,以实现最大比对性。此类程序包括BLAST程序、ALIGN、ALIGN-2(Genentech,South San Francisco,Calif.)或Megalign(DNASTAR)。用于比对达到最大比对性的参数可由本领域技术人员决定。出于本申请的目的,对于多肽序列的序列比较,使用以默认参数比对两个蛋白质序列的BLASTP算法标准蛋白质BLAST。

[0195] 当用于鉴定多肽序列中的给定氨基酸残基时,术语“对应于”、“参照……确定”或“参照……编号”是指当将给定氨基酸序列与指定参考序列最大程度地比对并进行比较时,所述参考序列中残基的位置。因此,例如,当与SEQ ID NO:1最优选地比对时,在多肽中的氨基酸残基与SEQ ID NO:1中的氨基酸比对的情况下,所述残基“对应于”SEQ ID NO:1中氨基酸114-220的区域中的氨基酸。与参考序列比对的多肽的长度无需与参考序列相同。

[0196] 如本文所使用,“结合亲和力”是指两个分子,例如多肽上的单一结合位点与其所结合的靶标(例如转铁蛋白受体)之间的非共价相互作用的强度。因此,除非另外指示或从上下文清楚可见,否则例如,所述术语可指多肽与其靶标之间的1:1相互作用。结合亲和力可通过测量平衡解离常数(K_D)定量,平衡解离常数是指解离速率常数(k_d,时间$^{-1}$)除以缔合速率常数(k_a,时间$^{-1}M^{-1}$)。K_D可通过例如使用表面等离子体共振(SPR)法,例如Biacore™系统;动力学排除测定,诸如KinExA®;和生物层干涉测量法(例如使用ForteBio® Octet®平台)测量复合物形成和解离的动力学确定。如本文所使用,“结合亲和力”不仅包括形式上的结合亲和力,诸如反映多肽与其靶标之间的1:1相互作用的结合亲和力,而且还包括表观亲和力,对于表观亲和力,计算的K_D可反映所希望的结合。

[0197] 如本文所用,当提及如本文所述的包含修饰的CH3结构域的多肽时,术语“特异性地结合”或“选择性地结合”至靶标(例如TfR)是指使所述多肽以比其结合至结构不同的靶标更高的亲和力、更高的亲合力和/或更长的持续时间结合质所述靶标的结合反应。在典型实施方案中,当在相同亲和力测定条件下测定时,与对不相关靶标的亲和力相比,所述多肽对特定靶标(例如,TfR)的亲和力大至少5倍、6倍、7倍、8倍、9倍、10倍、20倍、25倍、50倍、100倍、1000倍、10,000倍或更多倍。如本文所用,术语“特异性结合”、”特异性地结合至”特定靶标(例如TfR)或“对特定靶标(例如TfR)具有特异性”可例如由对其所结合的靶标具有例如10^{-4}M或更小,例如10^{-5}M、10^{-6}M、10^{-7}M、10^{-8}M、10^{-9}M、10^{-10}M、10^{-11}M或10^{-12}M的平衡解离常数K_D

的分子展现。在一些实施例中,经修饰的CH3的结构域多肽特异性地结合至TfR上各物种间保守(例如在各物种间在结构上保守),例如在非人灵长类动物与人物种之间保守(例如在非人灵长类动物与人物种之间在结构上保守)的表位。在一些实施方案中,多肽只能结合至人TfR。

[0198] 术语“受试者”、“个体”和“患者”在本文中可互换使用,是指哺乳动物,包括但不限于人、非人灵长类动物、啮齿动物(例如大鼠、小鼠和天竺鼠)、兔、牛、猪、马和其他哺乳动物物种。在一个实施方案中,患者是人。

[0199] 术语“治疗(treatment)”、“治疗(treating)”和类似表述在本文中一般用于指获得所需药理学和/或生理学作用。“治疗(treating)”或“治疗(treatment)”可指在治疗或改善损伤、疾病或疾患方面的任何成功指标,包括任何客观或主观参数,诸如消除、缓解、患者存活期的延长、存活时间或存活率增加、减轻症状或使患者更易忍受所述损伤、疾病或疾患、减慢退化或减退的速率,或改善患者的身体或精神健康。症状的治疗或改善可基于客观或主观参数。治疗效果可与未接受所述治疗的一位个体或一组个体,或与同一患者在治疗前或在治疗期间的不同时间的状况相比较。

[0200] 术语“药学上可接受的赋形剂”是指在生物学上或药理学上适合用于人或动物的非活性药物成分,诸如但不限于缓冲剂、载体或防腐剂。

[0201] 如本文所使用,剂的“治疗量”或“治疗有效量”是治疗、减轻、消除受试者疾病,或降低疾病的症状的严重程度的剂的量。“治疗量”或“治疗有效量”的剂可改善患者存活状况;增加存活时间或存活率;减轻症状;使损伤、疾病或病症更易忍受;减慢退化或减退的速率;或改善患者的身体或精神健康。

[0202] 术语“施用”是指将剂、化合物或组合物递送至所希望的生物作用部位的方法。这些方法包括但不限于,表面递送、胃肠外递送、静脉内递送、皮内递送、肌肉内递送、鞘内递送、结肠递送、直肠递送或腹膜内递送。在一个实施方案中,静脉内施用本文所述的多肽。

[0203] III.转铁蛋白受体结合多肽

[0204] 本章节描述结合至转铁蛋白受体且能够跨血脑屏障(BBB)转运的根据本发明的多肽的产生。

[0205] 在一个方面中,提供包含CH3结构域的多肽,所述CH3结构域具有允许所述多肽特异性地结合至转铁蛋白受体的修饰。所述修饰引入在CH3结构域的表面处存在的指定组的氨基酸中。在一些实施方案中,包含经修饰的CH3结构域的多肽特异性地结合至转铁蛋白受体的顶端结构域中的表位。

[0206] 本领域的技术人员应理解,可通过鉴定其他免疫球蛋白同种型,例如IgM、IgA、IgE、IgD等的CH3结构域中对应于本文所述的指定组的氨基酸,以类似方式修饰所述结构域。还可对来自其他物种,例如非人灵长类动物、猴、小鼠、大鼠、兔、狗、猪、鸡和类似物种的免疫球蛋白中的相应结构域进行修饰。

[0207] CH3转铁蛋白受体结合多肽

[0208] 在一些实施方案中,经修饰的结构域是人Ig CH3结构域,诸如IgG CH3结构域。所述CH3结构域可属于任何IgG亚型,即,来自IgG1、IgG2、IgG3或IgG4。在IgG抗体的情况下,CH3结构域是指如根据EU编号方案编号,从约341位至约447位的氨基酸的区段。除非另作说明,否则出于鉴定用于转铁蛋白受体结合的相应氨基酸位置组的目的,CH3结构域中的位置

是参照SEQ ID NO:3确定或参照SEQ ID NO:1的氨基酸114-220确定。取代还参照SEQ ID NO:1确定,即,相对于在SEQ ID NO:1中相应位置处的氨基酸,考虑待取代的氨基酸。SEQ ID NO:1包括部分铰链区序列,即PCP,作为氨基酸1-3。参照SEQ ID NO:1进行的CH3结构域中位置的编号包括前三个氨基酸。

[0209] 如以上所指示,CH3结构域中可根据本发明修饰的一组残基在本文中是参照SEQ ID NO:1编号。任何CH3结构域,例如IgG1、IgG2、IgG3或IgG4 CH3结构域可在对应于SEQ ID NO:1中所述位置处的残基的一组残基中具有修饰,例如氨基酸取代。SEQ ID NO:1的人IgG1氨基酸序列与人IgG2、IgG3和IgG4的比对在图33中示出。所述IgG2、IgG3和IgG4序列中的每一序列中对应于SEQ ID NO:1的任何给定位置的位置可容易地确定。

[0210] 在一个实施方案中,特异性地结合转铁蛋白受体的经修饰的CH3结构域多肽在包含全长人转铁蛋白受体序列(SEQ ID NO:38)的208位的表位处结合至所述转铁蛋白受体的顶端结构域,所述位置对应于SEQ ID NO:30中列出的人转铁蛋白受体顶端结构域序列的11位。SEQ ID NO:30对应于人转铁蛋白受体-1uniprotein序列P02786(SEQ ID NO:38)的氨基酸198-378。在一些实施方案中,经修饰的CH3结构域多肽在包含全长人转铁蛋白受体序列(SEQ ID NO:38)的位置158、188、199、207、208、209、210、211、212、213、214、215和/或294的表位处结合至转铁蛋白受体的顶端结构域。所述经修饰的CH3结构域多肽可结合至转铁蛋白受体,而不封闭或以其他方式抑制转铁蛋白与所述受体的结合。在一些实施方案中,转铁蛋白与TfR的结合基本上不受抑制。在一些实施方案中,转铁蛋白与TfR的结合被抑制低于约50%(例如低于约45%、40%、35%、30%、25%、20%、15%、10%或5%)。在一些实施方案中,转铁蛋白与TfR的结合被抑制低于约20%(例如低于约19%、18%、17%、16%、15%、14%、13%、12%、11%、10%、9%、8%、7%、6%、5%、4%、3%、2%或1%)。展现这种结合特异性的说明性CH3结构域多肽包括在如参照SEQ ID NO:1的氨基酸114-220所确定的位置157、159、160、161、162、163、186、189和194处具有氨基酸取代的多肽。

[0211] CH3转铁蛋白受体结合组:157、159、160、161、162、163、186、189和194

[0212] 在一些实施方案中,根据本发明的经修饰的CH3结构域多肽在包含157、159、160、161、162、163、186、189和194的一组氨基酸位置中包含至少三个或至少四个,且通常五个、六个、七个、八个或九个取代。可在这些位置处引入的说明性取代在表1中示出。在一些实施方案中,161位和/或194位的氨基酸是芳族氨基酸,例如Trp、Phe或Tyr。在一些实施方案中,161位的氨基酸是Trp。在一些实施方案中,161位的氨基酸是Gly。在一些实施方案中,194位的芳族氨基酸是Trp或Phe。

[0213] 在一些实施方案中,特异性地结合转铁蛋白受体的经修饰的CH3结构域多肽相对于SEQ ID NO:1,包含如下所示的至少一个具有取代的位置:在157位的Leu、Tyr、Met或Val;在159位的Leu、Thr、His或Pro;在160位的Val、Pro或酸性氨基酸;在161位的芳族氨基酸,例如Trp或Gly(例如Trp);在162位的Val、Ser或Ala;在186位的酸性氨基酸、Ala、Ser、Leu、Thr或Pro;在189位的Thr或酸性氨基酸;或在194位的Trp、Tyr、His或Phe。在一些实施方案中,经修饰的CH3结构域多肽可在所述组的一个或多个位置处包含特定氨基酸的保守取代,例如在同一带电分组、疏水性分组、侧链环结构分组(例如芳族氨基酸)或大小分组,和/或极性或非极性分组中的氨基酸。因此,例如,Ile可存在于157位、159位和/或186位。在一些实施方案中,在位置160、186和189中的一个、两个或每个位置处的酸性氨基酸是Glu。在其他

实施方案中,在位置160、186和189中的一个、两个或每个位置处的酸性氨基酸是Asp。在一些实施方案中,在位置157、159、160、161、162、186、189和194中的两个、三个、四个、五个、六个、七个或全部八个位置具有如本段中所说明的氨基酸取代。

[0214] 在一些实施方案中,经修饰的CH3结构域多肽包含163位的天然Asn。在一些实施方案中,经修饰的CH3结构域多肽在163位包含Gly、His、Gln、Leu、Lys、Val、Phe、Ser、Ala或Asp。在一些实施方案中,所述经修饰的CH3结构域多肽进一步在包含153、164、165和188的位置处包含一个、两个、三个或四个取代。在一些实施方案中,Trp、Tyr、Leu或Gln可存在于153位。在一些实施方案中,Ser、Thr、Gln或Phe可存在于164位。在一些实施方案中,Gln、Phe或His可存在于165位。在一些实施方案中,Glu可存在于188位。

[0215] 在一些实施方案中,经修饰的CH3结构域多肽包含选自以下的两个、三个、四个、五个、六个、七个、八个、九个或十个位置:在153位的Trp、Leu或Glu;在157位的Tyr或Phe;在159位的Thr;在160位的Glu;在161位的Trp;在162位的Ser、Ala、Val或Asn;在163位的Ser或Asn;在186位的Thr或Ser;在188位的Glu或Ser;在189位的Glu;和/或在194位的Phe。在一些实施方案中,经修饰的CH3结构域多肽包含如下全部十一个位置:在153位的Trp、Leu或Glu;在157位的Tyr或Phe;在159位的Thr;在160位的Glu;在161位的Trp;在162位的Ser、Ala、Val或Asn;在163位的Ser或Asn;在186位的Thr或Ser;在188位的Glu或Ser;在189位的Glu;和/或在194位的Phe。

[0216] 在一些实施方案中,经修饰的CH3结构域多肽包含在157位的Leu或Met;在159位的Leu、His或Pro;在160位的Val;在161位的Trp;在162位的Val或Ala;在186位的Pro;在189位的Thr;和/或在194位的Trp。在一些实施方案中,经修饰的CH3结构域多肽还包含在164位的Ser、Thr、Gln或Phe。在一些实施方案中,经修饰的CH3结构域多肽还包含在153位的Trp、Tyr、Leu或Gln和/或在165位的Gln、Phe或His。在一些实施方案中,Trp存在于153位和/或Gln存在于165位。在一些实施方案中,经修饰的CH3结构域多肽在153位不具有Trp。

[0217] 在其他实施方案中,经修饰的CH3结构域多肽包含在157位的Tyr;在159位的Thr;在160位的Glu或Val;在161位的Trp;在162位的Ser;在186位的Ser或Thr;在189位的Glu;和/或在194位的Phe。在一些实施方案中,经修饰的CH3结构域多肽包含在163位的天然Asn。在一些实施方案中,经修饰的CH3结构域多肽还包含在153位的Trp、Tyr、Leu或Gln;和/或在188位的Glu。在一些实施方案中,经修饰的CH3结构域多肽还包含在153位的Trp和/或在188位的Glu。

[0218] 在一些实施方案中,经修饰的CH3结构域多肽包含以下取代中的一个或多个:在153位的Trp;在159位的Thr;在161位的Trp;在162位的Val;在186位的Ser或Thr;在188位的Glu;和/或在194位的Phe。

[0219] 在另外的实施方案中,所述经修饰的CH3结构域多肽还包含选自以下的一个、两个或三个位置:187位是Lys、Arg、Gly或Pro;197位是Ser、Thr、Glu或Lys;并且199位是Ser、Trp或Gly。

[0220] 在一些实施方案中,特异性结合转铁蛋白受体的经修饰的CH3结构域多肽与SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸114-220具有至少70%同一性、至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,这种经修饰的CH3结构域多肽包含SEQ ID NO:4-29、39-102和182-195中任一个

的氨基酸157-163和/或186-194。在一些实施方案中,这种经修饰的CH3结构域多肽包含SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸153-163和/或186-194。在一些实施方案中,经修饰的CH3结构域多肽包含SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸153-163和/或186-199。

[0221] 在一些实施方案中,特异性结合转铁蛋白受体的经修饰的CH3结构域多肽与SEQ ID NO:1的氨基酸114-220具有至少70%同一性、至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性,其限制条件为同一性百分比不包括所述组位置157、159、160、161、162、163、186、189和194。在一些实施方案中,所述经修饰的CH3结构域多肽包含如SEQ ID NO:4-29、39-102和182-195中任一个中所列出的氨基酸157-163和/或氨基酸186-194。

[0222] 在一些实施方案中,经修饰的CH3结构域多肽与SEQ ID NO:4-29、39-102和182-195中的任一个具有至少70%同一性、至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性,其限制条件为对应于SEQ ID NO:4-29、39-102和182-195中的任一个的位置153、157、159、160、161、162、163、164、165、186、187、188、189、194、197和199的位置中的至少五个、六个、七个、八个、九个、十个、十一个、十二个、十三个、十四个、十五个或十六个未缺失或未被取代。

[0223] 在一些实施方案中,经修饰的CH3结构域多肽与SEQ ID NO:4-29、39-102和182-195中的任一个具有至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性,并且还包含如下位置中的至少五个、六个、七个、八个、九个、十个、十一个、十二个、十三个、十四个、十五个或十六个:在153位的Trp、Tyr、Leu、Gln或Glu;在157位的Leu、Tyr、Met或Val;在159位的Leu、Thr、His或Pro;在160位的Val、Pro或酸性氨基酸;在161位的芳族氨基酸,例如Trp;在162位的Val、Ser或Ala;在163位的Ser或Asn;在164位的Ser、Thr、Gln或Phe;在165位的Gln、Phe或His;在186位的酸性氨基酸、Ala、Ser、Leu、Thr或Pro;在187位的Lys、Arg、Gly或Pro;在188位的Glu或Ser;在189位的Thr或酸性氨基酸;在194位的Trp、Tyr、His或Phe;在197位的Ser、Thr、Glu或Lys;和在199位的Ser、Trp或Gly。

[0224] 在一些实施方案中,根据本发明的经修饰的CH3结构域多肽在包含153、157、159、160、162、163、186、188、189、194、197和199的一组氨基酸位置处包含一个或多个取代;并且其中所述取代和所述位置是参照SEQ ID NO:13的序列确定。在一些实施方案中,所述经修饰的CH3结构域包含在153位的Glu、Leu、Ser、Val、Trp或Tyr;在157位的芳族氨基酸(例如Tyr、Phe或Trp)、Met、Pro或Val;在159位的Thr、Asn或Val;在160位的Glu、Ile、Pro或Val;在162位的脂族氨基酸(例如Ala、Ile或Val)、Ser或Thr;在163位的Ser、Asn、Arg或Thr;在186位的Thr、His或Ser;在188位的Glu、Ser、Asp、Gly、Thr、Pro、Gln或Arg;在189位的Glu或Arg;在194位的Phe、His、Lys、Tyr或Trp;在197位的Ser、Thr或Trp;和在199位的Ser、Cys、Pro、Met或Trp。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:316的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:314的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:315的序列。

[0225] 在一些实施方案中,所述经修饰的CH3结构域多肽包含在153位的Glu、Leu或Trp;在157位的芳族氨基酸;在159位的Thr;在160位的Glu;在162位的脂族氨基酸或Ser;在163位的Ser或Asn;在186位的Thr或Ser;在188位的Glu或Ser;在189位的Glu;在194位的Phe、

His、Tyr或Trp;在197位的Ser;和在199位的Ser,其中所述取代和所述位置是参照SEQ ID NO:13的序列确定。在特定实施方案中,所述在157位的芳族氨基酸是Tyr或Phe,并且所述在162位的脂族氨基酸是Ala或Val。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:319的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:317的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:318的序列。

[0226] 在另外的实施方案中,所述经修饰的CH3结构域多肽可包含在153位的Glu、Leu或Trp;在157位的Tyr或Phe;在159位的Thr;在160位的Glu;在162位的Ala、Val或Ser;在163位的Ser或Asn;在186位的Thr或Ser;在188位的Glu或Ser;在189位的Glu;在194位的Phe;在197位的Ser;和在199位的Ser,其中所述取代和所述位置是参照SEQ ID NO:13的序列确定。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:322的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:320的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:321的序列。

[0227] 在一些实施方案中,根据本发明的经修饰的CH3结构域多肽在包含153、157、159、160、162、163、186、188、189、194、197和199的一组氨基酸位置中仅包含一个取代;并且其中所述取代和所述位置是参照SEQ ID NO:41的序列确定。在一些实施方案中,经修饰的CH3结构域多肽包含在153位的Glu、Leu、Ser、Val、Trp或Tyr。经修饰的CH3结构域多肽可包含在153位的Glu。经修饰的CH3结构域多肽可包含在153位的Leu。经修饰的CH3结构域多肽可包含在153位的Ser。经修饰的CH3结构域多肽可包含在153位的Val。经修饰的CH3结构域多肽可包含在153位的Trp。经修饰的CH3结构域多肽可包含在153位的Tyr。在一些实施方案中,经修饰的CH3结构域多肽包含在157位的Tyr、Phe、Trp、Met、Pro或Val。经修饰的CH3结构域多肽可包含在157位的Tyr。经修饰的CH3结构域多肽可包含在157位的Phe。经修饰的CH3结构域多肽可包含在157位的Trp。经修饰的CH3结构域多肽可包含在157位的Met。经修饰的CH3结构域多肽可包含在157位的Pro。经修饰的CH3结构域多肽可包含在157位的Val。在一些实施方案中,经修饰的CH3结构域多肽包含在159位的Thr、Asn或Val。经修饰的CH3结构域多肽可包含在159位的Thr。经修饰的CH3结构域多肽可包含在159位的Asn。经修饰的CH3结构域多肽可包含在159位的Val。在一些实施方案中,经修饰的CH3结构域多肽包含在160位的Glu、Ile、Pro或Val。经修饰的CH3结构域多肽可包含在160位的Glu。经修饰的CH3结构域多肽可包含在160位的Ile。经修饰的CH3结构域多肽可包含在160位的Pro。经修饰的CH3结构域多肽可包含在160位的Val。在一些实施方案中,经修饰的CH3结构域多肽包含在162位的Ala、Ile、Val、Ser或Thr。经修饰的CH3结构域多肽可包含在162位的Ala。经修饰的CH3结构域多肽可包含在162位的Ile。经修饰的CH3结构域多肽可包含在162位的Val。经修饰的CH3结构域多肽可包含在162位的Ser。经修饰的CH3结构域多肽可包含在162位的Thr。在一些实施方案中,经修饰的CH3结构域多肽包含在163位的Ser、Asn、Arg或Thr。经修饰的CH3结构域多肽可包含在163位的Ser。经修饰的CH3结构域多肽可包含在163位的Asn。经修饰的CH3结构域多肽可包含在163位的Arg。经修饰的CH3结构域多肽可包含在163位的Thr。在一些实施方案中,经修饰的CH3结构域多肽包含在186位的Thr、His或Ser。经修饰的CH3结构域多肽可包含在186位的Thr。经修饰的CH3结构域多肽可包含在186位的His。经修饰的CH3结构域多肽可包含在186位的Ser。在一些实施方案中,经修饰的CH3结构域多肽包含在188位的Glu、Ser、Asp、Gly、Thr、Pro、Gln或Arg。经修饰的CH3结构域多肽可包含在188位的Glu。经

修饰的CH3结构域多肽可包含在188位的Ser。经修饰的CH3结构域多肽可包含在188位的Asp。经修饰的CH3结构域多肽可包含在188位的Gly。经修饰的CH3结构域多肽可包含在188位的Thr。经修饰的CH3结构域多肽可包含在188位的Pro。经修饰的CH3结构域多肽可包含在188位的Gln。经修饰的CH3结构域多肽可包含在188位的Arg。在一些实施方案中,经修饰的CH3结构域多肽包含在189位的Glu或Arg。经修饰的CH3结构域多肽可包含在189位的Glu。经修饰的CH3结构域多肽可包含在189位的Arg。在一些实施方案中,经修饰的CH3结构域多肽包含在194位的Phe、His、Lys、Tyr或Trp。经修饰的CH3结构域多肽可包含在194位的Phe。经修饰的CH3结构域多肽可包含在194位的His。经修饰的CH3结构域多肽可包含在194位的Lys。经修饰的CH3结构域多肽可包含在194位的Tyr。经修饰的CH3结构域多肽可包含在194位的Trp。在一些实施方案中,经修饰的CH3结构域多肽包含在197位的Ser、Thr或Trp。经修饰的CH3结构域多肽可包含在197位的Ser。经修饰的CH3结构域多肽可包含在197位的Thr。经修饰的CH3结构域多肽可包含在197位的Trp。在一些实施方案中,经修饰的CH3结构域多肽包含在199位的Ser、Cys、Pro、Met或Trp。经修饰的CH3结构域多肽可包含在199位的Ser。经修饰的CH3结构域多肽可包含在199位的Cys。经修饰的CH3结构域多肽可包含在199位的Pro。经修饰的CH3结构域多肽可包含在199位的Met。经修饰的CH3结构域多肽可包含在199位的Trp。经修饰的CH3结构域多肽可具有SEQ ID NO:323-334中任一个的序列。

[0228] 在一些实施方案中,根据本发明的经修饰的CH3结构域多肽在包含153、157、159、160、162、163、164、186、189和194的一组氨基酸位置处包含一个或多个取代;并且其中所述取代和所述位置是参照SEQ ID NO:9的序列确定。在一些实施方案中,所述经修饰的CH3结构域包含在153位的Glu或Trp;在157位的Val、Trp、Leu或Tyr;在159位的Leu、Pro、Phe、Thr或His;在160位的Pro、Val或Glu;在162位的Ala、Ser、Val或Gly;在163位的Leu、His、Gln、Gly、Val、Ala、Asn、Asp、Thr或Glu;在164位的Thr、Phe、Gln、Val或Tyr;在186位的Leu、Ser、Glu、Ala或Pro;在189位的Glu、Asp、Thr或Asn;和在194位的Trp、Tyr、Phe或His。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:337的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:335的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:336的序列。

[0229] 在一些实施方案中,所述经修饰的CH3结构域多肽包含在153位的Glu或Trp;在157位的Trp、Leu或Tyr;在159位的Thr或His;在160位的Val;在162位的Ala、Ser或Val;在163位的Val、Asn或Thr;在164位的Gln或Tyr;在186位的Pro;在189位的Thr或Asn;和在194位的Trp、Tyr、Phe或His,其中所述取代和所述位置是参照SEQ ID NO:9的序列确定。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:340的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:338的序列。在某些实施方案中,经修饰的CH3结构域多肽可包含SEQ ID NO:339的序列。

[0230] 在另外的实施方案中,转铁蛋白结合多肽包含SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸157-194、氨基酸153-194或氨基酸153-199。在另外的实施方案中,所述多肽包含与SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸157-194,或与SEQ ID NO:4-29、39-102和182-195中任一个的氨基酸153-194或氨基酸153-199具有至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性的氨基酸序列。

[0231] 在一些实施方案中,所述多肽包含SEQ ID NO:4-29、39-102和182-195中的任一

个。在另外的实施方案中,所述多肽包含SEQ ID NO:4-29、39-102和182-195中的任一个,而无氨基末端处的前三个氨基酸"PCP"。在另外的实施方案中,所述多肽可与如在无氨基末端处的前三个氨基酸"PCP"情况下所测定的SEQ ID NO:4-29、39-102和182-195中的任一个具有至少75%同一性、至少80%同一性、至少85%同一性、至少90%同一性或至少95%同一性。

[0232] 包含经修饰的CH3结构域的说明性多肽

[0233] 本发明的经修饰的CH3结构域多肽可接合至Fc区的另一结构域。在一些实施方案中,本发明的经修饰的CH3结构域多肽接合至CH2结构域,所述CH2结构域可为天然存在的CH2结构域或变体CH2结构域,通常在所述CH2结构域的C末端处。在一些实施方案中,包含接合至CH2结构域的经修饰的CH3结构域的多肽还包含抗体的部分或完整铰链区,由此产生经修饰的CH3结构域多肽作为具有部分或完整铰链区的Fc区的一部分的形式。所述铰链区可来自任何免疫球蛋白亚类或同种型。说明性免疫球蛋白铰链是IgG铰链区,诸如IgG1铰链区,例如人IgG1铰链区氨基酸序列EPKSCDKTHTCPPCP(SEQ ID NO:37)。在另外的实施方案中,可以呈含有铰链区或部分铰链区的Fc形式的多肽进一步接合至另一部分,例如Fab片段,由此产生转铁蛋白受体结合Fc-Fab融合物。在一些实施方案中,所述转铁蛋白受体结合Fc-Fab融合物包含经修饰的CH3结构域多肽、铰链区和Fab片段。Fab片段可针对任何目标靶标,例如治疗性神经靶标,在这种情况下,通过经修饰的CH3结构域多肽与转铁蛋白受体的结合所介导的跨血脑屏障转胞吞将Fab递送至靶标。

[0234] 在一些实施方案中,接合至转铁蛋白受体结合多肽的Fab片段可结合至τ蛋白(例如人τ蛋白)或其片段。在一些实施方案中,Fab片段可结合至磷酸化τ蛋白、未磷酸化的τ蛋白、τ蛋白的剪接同工型、N末端截短的τ蛋白、C末端截短的τ蛋白和/或其片段。

[0235] 在一些实施方案中,接合至转铁蛋白受体结合多肽的Fab片段可结合至β-分泌酶1(BACE1)蛋白(例如人BACE1蛋白)或其片段。在一些实施方案中,Fab片段可结合至BACE1蛋白的一种或多种剪接同工型,或其片段。

[0236] 在一些实施方案中,接合至转铁蛋白受体结合多肽的Fab片段可结合至骨髓细胞上表达的触发受体2(TREM2)蛋白(例如人TREM2蛋白)或其片段。

[0237] 在一些实施方案中,接合至转铁蛋白受体结合多肽的Fab片段可结合至α-突触核蛋白(例如人α-突触核蛋白)或其片段。在一些实施方案中,Fab片段可结合至单体α-突触核蛋白、寡聚α-突触核蛋白、α-突触核蛋白原纤维、可溶性α-突触核蛋白和/或其片段。

[0238] 在一些实施方案中,包含本发明的经修饰的CH3结构域多肽的Fc-Fab融合物是二聚体的亚单位。在一些实施方案中,二聚体是异二聚体。在一些实施方案中,二聚体是同二聚体。在一些实施方案中,二聚体包含结合至转铁蛋白受体的单一多肽,即,对于转铁蛋白受体结合为单价。在一些实施方案中,二聚体包含结合至转铁蛋白受体的第二多肽。所述第二多肽可包含所述Fc-Fab融合物中存在的相同经修饰的CH3结构域多肽以提供二价结合同二聚体,或本发明的第二经修饰的CH3结构域多肽可提供第二转铁蛋白受体结合位点。在一些实施方案中,二聚体包含含有经修饰的CH3结构域多肽的第一亚单位,和含有CH2和CH3结构域的第二亚单位,所述CH2和CH3结构域均不结合转铁蛋白受体。

[0239] 转铁蛋白受体结合多肽还可与除Fab外的不同目标多肽融合。举例而言,在一些实施方案中,转铁蛋白受体结合多肽可与不同多肽融合,所述不同多肽是靶向转铁蛋白受体

表达细胞或通过转胞吞跨内皮,例如血脑屏障递送所需的。在一些实施方案中,转铁蛋白受体结合多肽与可溶性蛋白质,例如受体或生长因子、细胞因子或酶的细胞外结构域融合。

[0240] 在仍然其他实施方案中,转铁蛋白受体结合多肽可与可用于蛋白质纯化的肽或蛋白质(例如聚组氨酸)、表位标签(例如FLAG、c-Myc、血凝素标签等)、谷胱甘肽S转移酶(GST)、硫氧还蛋白、蛋白质A、蛋白质G或麦芽糖结合蛋白(MBP)融合。在一些情况下,与转铁蛋白受体结合多肽融合的肽或蛋白质可包含蛋白酶裂解位点,诸如因子Xa或凝血酶裂解位点。

[0241] 本发明的转铁蛋白受体结合多肽例如基于多肽的形式,可具有较宽范围的结合亲和力。举例而言,在一些实施方案中,包含经修饰的CH3结构域的多肽对转铁蛋白受体的结合亲和力在1pM至10μM的范围内。在一些实施方案中,亲和力可按单价形式测量。在其他实施方案中,亲和力可按二价形式,例如以包含多肽-Fab融合蛋白的二聚体形式测量。

[0242] 用于分析结合亲和力、结合动力学和交叉反应性的方法是本领域中已知的。所述方法包括但不限于,固相结合测定(例如ELISA测定)、免疫沉淀法、表面等离子体共振(例如Biacore™(GE Healthcare,Piscataway,NJ))、动力学排除测定(例如KinExA®)、流式细胞术、荧光活化细胞分选(FACS)、生物层干涉测量法(例如Octet® (FortéBio,Inc.,Menlo Park,CA))和蛋白质印迹分析。在一些实施方案中,使用ELISA来测定结合亲和力和/或交叉反应性。用于进行ELISA测定的方法是本领域中已知的,并且还在以下实施例部分中进行描述。在一些实施方案中,使用表面等离子体共振(SPR)来测定结合亲和力、结合动力学和/或交叉反应性。在一些实施方案中,使用动力学排除测定来测定结合亲和力、结合动力学和/或交叉反应性。在一些实施方案中,使用生物膜层干涉测定来测定结合亲和力、结合动力学和/或交叉反应性。

[0243] 包含经修饰的CH3结构域多肽的Fc区中的另外的突变

[0244] 如本文提供的被修饰成结合转铁蛋白受体且起始跨BBB转运的多肽还可包含另外的突变,例如以增加血清稳定性、调节效应子功能、影响糖基化、降低在人体中的免疫原性,和/或提供多肽的钮和孔异二聚化。

[0245] 在一些实施方案中,根据本发明的多肽与相应的野生型Fc区(例如人IgG1、IgG2、IgG3或IgG4 Fc区)具有至少约75%、76%、77%、78%、79%、80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%的氨基酸序列同一性。

[0246] 根据本发明的多肽还可具有在指定氨基酸组范围外引入的其他突变,例如以影响糖基化、增加血清半衰期,或对于CH3结构域,提供包含经修饰的CH3结构域的多肽的钮和孔异二聚化。一般而言,所述方法涉及在第一多肽的界面处引入突起(“钮”)且在第二多肽界面中引入相应空腔(“孔”),由此所述突起可安置于空腔中以促进异二聚体形成且阻碍同二聚体形成。突起通过用较大侧链(例如酪氨酸或色氨酸)替代来从第一多肽的界面的小氨基酸侧链来构建。通过用较小氨基酸侧链(例如丙氨酸或苏氨酸)替代较大氨基酸侧链,在第二多肽的界面中产生与所述突起相同或类似大小的补偿性空腔。此类另外的突变是在多肽中对经修饰的CH3结构域与转铁蛋白受体的结合不具有负面影响的位置。

[0247] 在钮和孔二聚化方法的一个示例性实施方案中,待二聚化的第一Fc多肽亚单位中对应于SEQ ID NO:1的139位的位置具有色氨酸替代天然苏氨酸,且二聚体的第二Fc多肽在

对应于SEQ ID NO:1的180位处具有缬氨酸替代天然酪氨酸。Fc多肽的第二亚单位还可包含取代,其中在对应于SEQ ID NO:1的139位的位置处的天然苏氨酸被丝氨酸取代且在对应于SEQ ID NO:1的141位的位置处的天然白氨酸被丙氨酸取代。

[0248] 如本文所述的多肽还可被工程改造成含有针对异二聚化的其他修饰,例如CH3-CH3界面内接触残基的静电工程改造,所述接触残基为天然地带电或疏水补丁(patch)修饰。

[0249] 在一些实施方案中,可引入增加血清半衰期的修饰。举例而言,在一些实施方案中,Fc区包含在对应于SEQ ID NO:1的25位的位置处包含Tyr、在对应于SEQ ID NO:1的27位的位置处包含Thr且在对应于SEQ ID NO:1的29位的位置处包含Glu的CH2结构域。

[0250] 在一些实施方案中,如参照SEQ ID NO:1所确定,在位置17-30、52-57、80-90、156-163和201-208中的一个或多个位置处引入突变,例如取代。在一些实施方案中,如参照SEQ ID NO:1所确定,在位置24、25、27、28、29、80、81、82、84、85、87、158、159、160、162、201、206、207或209处引入一个或多个突变。在一些实施方案中,如参照SEQ ID NO:1所确定,在25位、27位和29位中的一个、两个或三个中引入突变。在一些实施方案中,如参照SEQ ID NO:1所编号,所述突变是M25Y、S27T和T29E。在一些实施方案中,本文所述的多肽还包含突变M25Y、S27T和T29E。在一些实施方案中,如参照SEQ ID NO:1所确定,在201位和207位中的一个或两个中引入突变。在一些实施方案中,如参照SEQ ID NO:1所编号,所述突变是M201L和N207S。在一些实施方案中,本文所述的多肽还包含N207S且存在或不存在M201L。在一些实施方案中,如参照SEQ ID NO:1所编号,本文所述的多肽在位置T80、E153和N207中的一个、两个或全部三个处包含取代。在一些实施方案中,突变是T80Q和N207A。在一些实施方案中,本文所述的多肽包含突变T80A、E153A和N207A。在一些实施方案中,如参照SEQ ID NO:1所编号,本文所述的多肽在位置T23和M201处包含取代。在一些实施方案中,本文所述的多肽包含突变T23Q和M201L。在一些实施方案中,如参照SEQ ID NO:1所编号,本文所述的多肽在位置M201和N207处包含取代。在一些实施方案中,本文所述的多肽包含取代M201L和N207S。在一些实施方案中,本文所述的多肽包含N207S或N207A取代。

[0251] Fc效应子功能

[0252] 在一些实施方案中,包含经修饰的CH3结构域的Fc区具有效应子功能,即,所述Fc区能够在结合至介导效应子功能的效应细胞上表达的Fc受体时诱导某些生物功能。效应细胞包括但不限于,单核细胞、巨噬细胞、嗜中性粒细胞、树突状细胞、嗜酸性粒细胞、肥大细胞、血小板、B细胞、大颗粒淋巴细胞、朗格汉斯细胞(Langerhans'cell)、自然杀伤(NK)细胞和细胞毒性T细胞。

[0253] 抗体效应子功能的实例包括但不限于,C1q结合和补体依赖性细胞毒性(CDC)、Fc受体结合、抗体依赖性细胞介导的细胞毒性(ADCC)、抗体依赖性细胞介导的吞噬作用(ADCP)、细胞表面受体(例如B细胞受体)下调和B细胞活化。效应子功能可随抗体类别而变化。举例而言,天然人IgG1和IgG3抗体在结合至免疫系统细胞上存在的适当Fc受体时能够引发ADCC和CDC活性;并且天然人IgG1、IgG2、IgG3和IgG4在结合至免疫细胞上存在的适当Fc受体时能够引发ADCP功能。

[0254] 在一些实施方案中,如本文所述的多肽可包括调节效应子功能的另外的修饰。或者,在一些实施方案中,本发明的包含经修饰的CH3结构域的多肽可包括增强效应子功能的

另外的修饰。

[0255] 调节效应子功能的说明性Fc多肽突变包括但不限于,在CH2结构域中,例如对应于SEQ ID NO:1的7位和8位处的取代。在一些实施方案中,在CH2结构域中的取代包含在SEQ ID NO:1的7位和8位处的Ala。在一些实施方案中,在CH2结构域中的取代包含在SEQ ID NO:1的7位和8位处的Ala和在102位处的Gly。

[0256] 调节效应子功能的另外的Fc多肽突变包括但不限于,在位置238、265、269、270、297、327和329(EU编号方案,对应于如参照SEQ ID NO:1所编号的位置11、38、42、43、70、100和102)处的一个或多个取代。说明性取代(如根据EU编号方案编号)包括以下:329位可具有脯氨酸被甘氨酸或精氨酸或足够大以破坏Fc/Fcγ受体界面的氨基酸残基取代的突变,所述Fc/Fcγ受体界面形成于Fc的脯氨酸329与FcγRIII的色氨酸残基Trp 87和Trp 110之间。另外的示例性取代包括S228P、E233P、L235E、N297A、N297D和P331S。还可能存在多个取代,例如人IgG1 Fc区的L234A和L235A;人IgG1 Fc区的L234A、L235A和P329G;人IgG4 Fc区的S228P和L235E;人IgG1Fc区的L234A和G237A;人IgG1 Fc区的L234A、L235A和G237A;人IgG2 Fc区的V234A和G237A;人IgG4 Fc区的L235A、G237A和E318A;以及人IgG4 Fc区的S228P和L236E。在一些实施方案中,本发明的多肽可具有一个或多个调节ADCC的氨基酸取代,例如根据EU编号方案,在Fc区的位置298、333和/或334处的取代。

[0257] 在一些实施方案中,如本文所述的多肽可具有一个或多个增加或减弱ADCC的氨基酸取代或者可具有改变C1q结合和/或CDC的突变。

[0258] 包含另外的突变的说明性多肽

[0259] 如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可包含另外的突变,包括钮突变(例如,如参照SEQ ID NO:1编号的T139W)、孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A)),和/或增加血清稳定性的突变(例如,(i)如参照SEQ ID NO:1编号的M25Y、S27T和T29E,或(ii)如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)。

[0260] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有钮突变。

[0261] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有钮突变和调节效应子功

能的突变。

[0262] 在一些实施方案中,本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,(i)如参照SEQ ID NO:1编号的M25Y、S27T和T29E,或(ii)如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有钮突变和增加血清稳定性的突变。

[0263] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,(i)如参照SEQ ID NO:1编号的M25Y、S27T和T29E,或(ii)如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有钮突变、调节效应子功能的突变和增加血清稳定性的突变。

[0264] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有孔突变。

[0265] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有孔突变和调节效应子功能的突变。

[0266] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,(i)如参照SEQ ID NO:1编号的M25Y、S27T和T29E,或(ii)如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85%同一性、至少

90％同一性或至少95％同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有孔突变和增加血清稳定性的突变。

[0267] 在一些实施方案中,如本文所述的多肽(例如克隆CH3C.35.20.1、CH3C.35.23.2、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.21.17.2、CH3C.35.23、CH3C.35.21、CH3C.35.20.1.1、CH3C.23.2.1和CH3C.35.23.1.1中的任一个)可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,(i)如参照SEQ ID NO:1编号的M25Y、S27T和T29E,或(ii)如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:4-29、39-102和182-195中任一个的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有SEQ ID NO:4-29、39-102和182-195中任一个的序列的多肽可被修饰成具有孔突变、调节效应子功能的突变和增加血清稳定性的突变。

[0268] 克隆CH3C.35.20.1

[0269] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:109的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.20.1具有SEQ ID NO:109的序列。

[0270] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:110或111的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.20.1具有SEQ ID NO:110或111的序列。

[0271] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:112的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:112的序列。

[0272] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:245的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:245的序列。

[0273] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:113或114的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:113或114的序列。

[0274] 在一些实施方案中,克隆CH3C.35.20.1可具有钮突变(例如,如参照SEQ ID NO:1

编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:246或247的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:246或247的序列。

[0275] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:115的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.20.1具有SEQ ID NO:115的序列。

[0276] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:116或117的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.20.1具有SEQ ID NO:116或117的序列。

[0277] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:118的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:118的序列。

[0278] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:248的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:248的序列。

[0279] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:119或120的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:119或120的序列。

[0280] 在一些实施方案中,克隆CH3C.35.20.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:249或250的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1具有SEQ ID NO:249或250的序列。

[0281] 克隆CH3C.35.23.2

[0282] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:121的序列具有至少85%同一性、至少90%同一性或至少

95％同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23.2具有SEQ ID NO:121的序列。

[0283] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:122或123的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23.2具有SEQ ID NO:122或123的序列。

[0284] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:124的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:124的序列。

[0285] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:252的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:252的序列。

[0286] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:125或126的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:125或126的序列。

[0287] 在一些实施方案中,克隆CH3C.35.23.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:253或254的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:253或254的序列。

[0288] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:127的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23.2具有SEQ ID NO:127的序列。

[0289] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:128或129的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23.2具有SEQ ID NO:128或129的序列。

[0290] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1

编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:130的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:130的序列。

[0291] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:255的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:255的序列。

[0292] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:131或132的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:131或132的序列。

[0293] 在一些实施方案中,克隆CH3C.35.23.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:256或257的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2具有SEQ ID NO:256或257的序列。

[0294] 克隆CH3C.35.23.3

[0295] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:133的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23.3具有SEQ ID NO:133的序列。

[0296] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:134或135的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23.3具有SEQ ID NO:134或135的序列。

[0297] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:136的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:136的序列。

[0298] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:259的序列具有至少85%同一性、至少90%同一性或至少95%

同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:259的序列。

[0299] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:137或138的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:137或138的序列。

[0300] 在一些实施方案中,克隆CH3C.35.23.3可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:260或261的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:260或261的序列。

[0301] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:139的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23.3具有SEQ ID NO:139的序列。

[0302] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:140或141的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23.3具有SEQ ID NO:140或141的序列。

[0303] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:142的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:142的序列。

[0304] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:262的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:262的序列。

[0305] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:143或144的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:143或144的序列。

[0306] 在一些实施方案中,克隆CH3C.35.23.3可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:263或264的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.3具有SEQ ID NO:263或264的序列。

[0307] 克隆CH3C.35.23.4

[0308] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:145的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23.4具有SEQ ID NO:145的序列。

[0309] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:146或147的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23.4具有SEQ ID NO:146或147的序列。

[0310] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:148的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:148的序列。

[0311] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:266的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:266的序列。

[0312] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:149或150的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:149或150的序列。

[0313] 在一些实施方案中,克隆CH3C.35.23.4可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:267或268的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:267或268的序列。

[0314] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1

编号的T139S、L141A和Y180V)且与SEQ ID NO:151的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23.4具有SEQ ID NO:151的序列。

[0315] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:152或153的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23.4具有SEQ ID NO:152或153的序列。

[0316] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:154的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:154的序列。

[0317] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:269的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:269的序列。

[0318] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:155或156的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:155或156的序列。

[0319] 在一些实施方案中,克隆CH3C.35.23.4可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:270或271的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.4具有SEQ ID NO:270或271的序列。

[0320] 克隆CH3C.35.21.17.2

[0321] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:157的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.21.17.2具有SEQ ID NO:157的序列。

[0322] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:158或159的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克

隆CH3C.35.21.17.2具有SEQ ID NO:158或159的序列。

[0323] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:160的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:160的序列。

[0324] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:273的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:273的序列。

[0325] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:161或162的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:161或162的序列。

[0326] 在一些实施方案中,克隆CH3C.35.21.17.2可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:274或275的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:274或275的序列。

[0327] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:163的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.21.17.2具有SEQ ID NO:163的序列。

[0328] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:164或165的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:164或165的序列。

[0329] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:166的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:166的序列。

[0330] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号

的N207S且存在或不存在M201L)且与SEQ ID NO:276的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:276的序列。

[0331] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:167或168的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:167或168的序列。

[0332] 在一些实施方案中,克隆CH3C.35.21.17.2可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:277或278的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21.17.2具有SEQ ID NO:277或278的序列。

[0333] 克隆CH3C.35.23

[0334] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:169的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23具有SEQ ID NO:169的序列。

[0335] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:170或171的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23具有SEQ ID NO:170或171的序列。

[0336] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:172的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:172的序列。

[0337] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:280的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:280的序列。

[0338] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:173或174的序列具有至少85％同一性、至少90％同一性或至少95％

同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:173或174的序列。

[0339] 在一些实施方案中,克隆CH3C.35.23可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:281或282的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:281或282的序列。

[0340] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:175的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23具有SEQ ID NO:175的序列。

[0341] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:176或177的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23具有SEQ ID NO:176或177的序列。

[0342] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:178的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:178的序列。

[0343] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:283的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:283的序列。

[0344] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:179或180的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:179或180的序列。

[0345] 在一些实施方案中,克隆CH3C.35.23可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:284或285的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23具有SEQ ID NO:284或285的序列。

[0346] 克隆CH3C.35.21

[0347] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:196的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.21具有SEQ ID NO:196的序列。

[0348] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:197或198的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.21具有SEQ ID NO:197或198的序列。

[0349] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:199的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:199的序列。

[0350] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:287的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:287的序列。

[0351] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:200或201的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:200或201的序列。

[0352] 在一些实施方案中,克隆CH3C.35.21可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:288或289的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:288或289的序列。

[0353] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:202的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.21具有SEQ ID NO:202的序列。

[0354] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:203或204的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突

变的克隆CH3C.35.21具有SEQ ID NO:203或204的序列。

[0355] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:205的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:205的序列。

[0356] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:290的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:290的序列。

[0357] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:206或207的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:206或207的序列。

[0358] 在一些实施方案中,克隆CH3C.35.21可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:291或292的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.21具有SEQ ID NO:291或292的序列。

[0359] 克隆CH3C.35.20.1.1

[0360] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:208的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.20.1.1具有SEQ ID NO:208的序列。

[0361] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:209或210的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:209或210的序列。

[0362] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:211的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:211的序列。

[0363] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:

1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:294的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:294的序列。

[0364] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:212或213的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:212或213的序列。

[0365] 在一些实施方案中,克隆CH3C.35.20.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:295或296的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:295或296的序列。

[0366] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:214的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.20.1.1具有SEQ ID NO:214的序列。

[0367] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:215或216的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:215或216的序列。

[0368] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:217的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:217的序列。

[0369] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:297的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:297的序列。

[0370] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:218或219的序列具有至少85%同一性、至少90%

同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:218或219的序列。

[0371] 在一些实施方案中,克隆CH3C.35.20.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:298或299的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.20.1.1具有SEQ ID NO:298或299的序列。

[0372] 克隆CH3C.35.23.2.1

[0373] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:220的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23.2.1具有SEQ ID NO:220的序列。

[0374] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:221或222的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:221或222的序列。

[0375] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:223的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:223的序列。

[0376] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:301的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:301的序列。

[0377] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:224或225的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:224或225的序列。

[0378] 在一些实施方案中,克隆CH3C.35.23.2.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:302或303的序列具有至少85％同一性、至少90％同一性或至少95％同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清

稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:302或303的序列。

[0379] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:226的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23.2.1具有SEQ ID NO:226的序列。

[0380] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:227或228的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:227或228的序列。

[0381] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:229的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:229的序列。

[0382] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:304的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:304的序列。

[0383] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:230或231的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:230或231的序列。

[0384] 在一些实施方案中,克隆CH3C.35.23.2.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:305或306的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.2.1具有SEQ ID NO:305或306的序列。

[0385] 克隆CH3C.35.23.1.1

[0386] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)且与SEQ ID NO:232的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变的克隆CH3C.35.23.1.1具有SEQ ID NO:232的序列。

[0387] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或

P102G(例如L7A和L8A))且与SEQ ID NO:233或234的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和调节效应子功能的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:233或234的序列。

[0388] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:235的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:235的序列。

[0389] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:308的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:308的序列。

[0390] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:236或237的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:236或237的序列。

[0391] 在一些实施方案中,克隆CH3C.35.23.1.1可具有钮突变(例如,如参照SEQ ID NO:1编号的T139W)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:309或310的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有钮突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:309或310的序列。

[0392] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)且与SEQ ID NO:238的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变的克隆CH3C.35.23.1.1具有SEQ ID NO:238的序列。

[0393] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))且与SEQ ID NO:239或240的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和调节效应子功能的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:239或240的序列。

[0394] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:241的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:241的序列。

[0395] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:311的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:311的序列。

[0396] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的M25Y、S27T和T29E)且与SEQ ID NO:242或243的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:242或243的序列。

[0397] 在一些实施方案中,克隆CH3C.35.23.1.1可具有孔突变(例如,如参照SEQ ID NO:1编号的T139S、L141A和Y180V)、调节效应子功能的突变(例如,如参照SEQ ID NO:1编号的L7A、L8A和/或P102G(例如L7A和L8A))、增加血清稳定性的突变(例如,如参照SEQ ID NO:1编号的N207S且存在或不存在M201L)且与SEQ ID NO:312或313的序列具有至少85%同一性、至少90%同一性或至少95%同一性。在一些实施方案中,具有孔突变、调节效应子功能的突变和增加血清稳定性的突变的克隆CH3C.35.23.1.1具有SEQ ID NO:312或313的序列。

[0398] IV.缀合物

[0399] 在一些实施方案中,根据本发明的包含经修饰的CH3结构域的转铁蛋白受体结合多肽经由接头连接至剂,例如内化至细胞中和/或跨内皮,诸如血脑屏障转胞吞的剂。所述接头可为适合将剂接合至多肽的任何接头。在一些实施方案中,所述键联是酶可裂解的。在某些实施方案中,所述键联可通过中枢神经系统中存在的酶裂解。

[0400] 在一些实施方案中,接头是肽接头。肽接头可被构造成使得其允许所述剂和转铁蛋白受体结合多肽相对于彼此旋转,和/或对蛋白酶消化具有抗性。在一些实施方案中,所述接头可为柔性接头,例如含有诸如Gly、Asn、Ser、Thr、Ala等的氨基酸。此类接头使用已知参数设计。举例而言,所述接头可具有重复序列,诸如Gly-Ser重复序列。

[0401] 在各种实施方案中,缀合物可使用熟知的化学交联试剂和方案产生。举例而言,本领域的技术人员已知众多化学交联剂且可用于使多肽与目标剂交联。举例而言,交联剂是异双官能交联剂,其可用于以逐步方式连接分子。异双官能交联剂使得能够设计出更特异性的用于缀合蛋白质的偶联方法,由此减少不想要的副反应,诸如同源蛋白质聚合物的发生。本领域中已知多种异双官能交联剂,包括N-羟基琥珀酰亚胺(NHS)或其水溶性类似物N-羟基磺基琥珀酰亚胺(磺基-NHS)、4-(N-马来酰亚胺基甲基)环己烷-1-甲酸琥珀酰亚胺酯(SMCC)、间马来酰亚胺基苯甲酰基-N-羟基琥珀酰亚胺酯(MBS);(4-碘代乙酰基)氨基苯甲酸N-琥珀酰亚胺酯(SIAB)、4-(对马来酰亚胺基苯基)丁酸琥珀酰亚胺酯(SMPB)、1-乙基-3-(3-二甲基氨基丙基)碳化二亚胺盐酸盐(EDC);4-琥珀酰亚氨基氧基羰基-a-甲基-a-(2-吡啶基二硫代)-甲苯(SMPT)、3-(2-吡啶基二硫代)丙酸N-琥珀酰亚胺酯(SPDP)和6-[3-(2-吡啶基二硫代)丙酸酯]己酸琥珀酰亚胺酯(LC-SPDP)。具有N-羟基琥珀酰亚胺部分的所那些交联剂可呈N-羟基磺基琥珀酰亚胺类似物形式获得,其一般具有较高水溶性。此外,在连接链中具有二硫桥的你先交联剂可进而以烷基衍生物形式获得以便减少体内接头裂解的量。

除异双官能交联剂外,还存在多种其他交联剂,包括同双官能交联剂和光反应性交联剂。辛二酸双琥珀酰亚胺酯(DSS)、双马来酰亚胺基己烷(BMH)和庚二酰亚胺二甲酯.2HCl(DMP)是有用同双官能交联剂的实例,且双-[B-(4-叠氮基水杨基酰氨基)乙基]二硫化物(BASED)和6(4'-叠氮基-2'-硝基苯基氨基)己酸N-琥珀酰亚胺酯(SANPAH)是有用的光反应性交联剂的实例。

[0402] 目标试剂可为治疗剂,包括细胞毒性剂、DNA或RNA分子、化学部分等。在一些实施方案中,所述剂可为肽或小分子治疗剂或显像剂。在一些实施方案中,所述小分子小于1000Da、小于750Da或小于500Da.

[0403] 目标剂可连接至转铁蛋白受体结合多肽的N末端或C末端区域,或附接至多肽的任何区域,只要所述剂不干扰转铁蛋白受体结合多肽与转铁蛋白受体的结合即可。

[0404] V.核酸、载体和宿主细胞

[0405] 如本文所述的经修饰的转铁蛋白受体结合多肽通常使用重组方法制备。因此,在一些方面中,本发明提供分离的核酸,所述分离的核酸包含编码含有本文所述的多肽的任一多肽的核酸序列;和宿主细胞,所述核酸引入所述宿主细胞中以用于复制多肽编码核酸和/或表达所述多肽。在一些实施方案中,宿主细胞是真核细胞,例如人细胞。

[0406] 在另一方面中,提供包含编码本文所述的多肽的核苷酸的多核苷酸。所述多核苷酸可为单链或双链。在一些实施方案中,所述多核苷酸是DNA。在特定实施方案中,所述多核苷酸是cDNA。在一些实施方案中,所述多核苷酸是RNA。

[0407] 在一些实施方案中,所述多核苷酸是包含在核酸构建体内。在一些实施方案中,所述构建体是可复制的载体。在一些实施方案中,所述载体选自质粒、病毒载体、噬菌粒、酵母染色体载体和非游离型哺乳动物载体。

[0408] 在一些实施方案中,所述多核苷酸在表达构建体中可操作地连接至一个或多个调控核苷酸序列。在一系列实施方案中,核酸表达构建体适合用作表面表达文库。在一些实施方案中,所述文库适于在酵母中表面表达。在一些实施方案中,所述文库适于在噬菌体中表面表达。在另一系列实施方案中,核酸表达构建体适于在允许分离毫克或克量的多肽的系统中表达多肽。在一些实施方案中,所述系统是哺乳动物细胞表达系统。在一些实施方案中,所述系统是酵母细胞表达系统。

[0409] 用于产生重组多肽的表达媒介物包括质粒和其他载体。例如,适合载体包括以下类型的质粒:用于在原核细胞,诸如大肠杆菌中表达的pBR322源性质粒、pEMBL源性质粒、pEX源性质粒、pBTac源性质粒和pUC源性质粒。pcDNAI/amp、pcDNAI/neo、pRc/CMV、pSV2gpt、pSV2neo、pSV2-dhfr、pTk2、pRSVneo、pMSG、pSVT7、pko-neo和pHyg源性载体是适于转染真核细胞的哺乳动物表达载体的实例。或者,可使用病毒的衍生物,诸如牛乳头瘤病毒(BPV-1)或埃-巴二氏病毒(Epstein-Barr virus)(pHEBo、pREP源性和p205)在真核细胞中短暂表达多肽。在一些实施方案中,利用杆状病毒表达系统表达重组多肽可能是合乎需要的。此类杆状病毒表达系统的实例包括pVL源性载体(诸如pVL1392、pVL1393和pVL941)、pAcUW源性载体(诸如pAcUW1)和pBlueBac源性载体。另外的表达系统包括腺病毒、腺相关病毒和其他病毒表达系统。

[0410] 载体可转化至任何适合的宿主细胞中。在一些实施方案中,宿主细胞,例如细菌或酵母细胞,可能适于用作表面表达文库。在一些细胞中,载体在宿主细胞中表达以表达相对

较大量的多肽。此类宿主细胞包括哺乳动物细胞、酵母细胞、昆虫细胞和原核细胞。在一些实施方案中,细胞是哺乳动物细胞,诸如中国仓鼠卵巢(CHO)细胞、幼仓鼠肾(BHK)细胞、NSO细胞、YO细胞、HEK293细胞、COS细胞、Vero细胞或HeLa细胞。

[0411] 用编码转铁蛋白受体结合多肽的表达载体转染的宿主细胞可在允许多肽表达的适当条件下培养。所述多肽可从细胞分泌并且从含有所述多肽的细胞和培养基混合物分离。或者,所述多肽可保留在细胞质中或膜部分中并使用所需方法收集细胞、溶解并分离出多肽。

[0412] VI.治疗方法

[0413] 根据本发明的转铁蛋白受体结合多肽可用于治疗许多适应症。在一些实施方案中,转铁蛋白受体结合多肽用于将治疗剂递送至表达转铁蛋白受体的靶细胞类型。在一些实施方案中,转铁蛋白受体结合多肽可用于跨内皮,例如血脑屏障转运治疗部分以由脑吸收。

[0414] 在一些实施方案中,本发明的转铁蛋白受体结合多肽可用于,例如缀合至治疗剂,递送治疗剂以治疗神经病症,诸如脑或中枢神经系统(CNS)的疾病。说明性疾病包括阿尔茨海默氏病、帕金森氏病、肌萎缩性脊髓侧索硬化、额颞叶痴呆、血管性痴呆、路易体痴呆(Lewy body dementia)、皮克氏病(Pick's disease)、原发性年龄相关性τ蛋白病或进行性核上麻痹。在一些实施方案中,所述疾病可为τ蛋白病、朊病毒病(诸如牛海绵状脑病、痒病、克-雅二氏综合征(Creutzfeldt-Jakob syndrome)、库鲁病(kuru)、杰茨曼-斯脱司勒-史茵克病(Gerstmann-Straussler-Scheinker disease)、慢性消耗性疾病和致死性家族性失眠症)、延髓性麻痹、运动神经元疾病或神经系统异变性病症(诸如卡纳万病(Canavan disease)、亨廷顿氏病(Huntington's disease)、神经元蜡样脂褐质沉积症、亚历山大氏病(Alexander's disease)、图雷特综合征(Tourette's syndrome)、门克斯卷发综合征(Menkes kinky hair syndrome)、柯凯因综合征(Cockayne syndrome)、哈勒沃登-施帕茨综合征(Halervorden-Spatz syndrome)、拉福拉病(lafora disease)、雷特氏综合征(Rett syndrome)、肝豆状核变性、莱施-奈恩综合征(Lesch-Nyhan syndrome)、弗里德希氏共济失调(Friedreich's ataxia)、脊髓性肌肉萎缩症和尤-兰二氏综合征(Unverricht-Lundborg syndrome))。在一些实施方案中,所述疾病系中风或多发性硬化。在一些实施方案中,患者可为无症状的,但具有与脑或CNS疾病相关的标记物。在一些实施方案中,提供本发明的转铁蛋白受体结合多肽在制造用于治疗神经病症的药物中的用途。

[0415] 在一些实施方案中,本发明的转铁蛋白受体结合多肽用于治疗癌症。在一些实施方案中,所述癌症是原发性CNS癌症,诸如神经胶质瘤、多形性成胶质细胞瘤、脑膜瘤、星形细胞瘤、听神经瘤、软骨瘤、少突神经胶质瘤、成神经管细胞瘤、神经节神经胶质瘤、神经鞘瘤(Schwannoma)、神经纤维瘤、成神经细胞瘤,或硬膜外、髓鞘内或硬膜内肿瘤。在一些实施方案中,所述癌症是实体肿瘤,或在其他实施方案中,所述癌症是非实体肿瘤。实体肿瘤癌症包括中枢神经系统肿瘤、乳腺癌、前列腺癌、皮肤癌(包括基底细胞癌、细胞癌、鳞状细胞癌和黑素瘤)、子宫颈癌、子宫癌、肺癌、卵巢癌、睾丸癌、甲状腺癌、星形细胞瘤、神经胶质瘤、胰腺癌、间皮瘤、胃癌、肝癌、结肠癌、直肠癌、肾癌(包括肾母细胞瘤)、膀胱癌、食道癌、喉癌、腮腺癌、胆道癌、子宫内膜癌、腺癌、小细胞癌、成神经细胞瘤、肾上腺皮质癌、上皮癌、韧带样瘤、促纤维增生性小圆细胞肿瘤、内分泌肿瘤、尤文氏肉瘤家族肿瘤(Ewing sarcoma

family tumor)、生殖细胞肿瘤、肝母细胞瘤、肝细胞癌、非横纹肌肉瘤软组织肉瘤、骨肉瘤、外周原始神经外胚层肿瘤、成视网膜细胞瘤和横纹肌肉瘤。在一些实施方案中,提供本发明的转铁蛋白受体结合多肽在制造用于治疗癌症的药物中的用途。

[0416] 在一些实施方案中,本发明的转铁蛋白受体结合多肽可用于治疗自身免疫性或炎性疾病。此类疾病的实例包括但不限于,强直性脊柱炎、关节炎、骨关节炎、类风湿性关节炎、银屑病性关节炎、哮喘、硬皮病、中风、动脉粥样硬化、克罗恩氏病(Crohn's disease)、结肠炎、溃疡性结肠炎、皮炎、憩室炎、纤维化、特发性肺纤维化、纤维肌痛、肝炎、肠易激综合征(IBS)、狼疮、全身性红斑狼疮(SLE)、肾炎、多发性硬化和溃疡性结肠炎。在一些实施方案中,提供本发明的转铁蛋白受体结合多肽在制造用于治疗自身免疫性或炎性疾病的药物中的用途。

[0417] 在一些实施方案中,本发明的转铁蛋白受体结合多肽可用于治疗心血管疾病,诸如冠状动脉疾病、心脏病发作、心律失常或心律不齐、心脏衰竭、心脏瓣膜疾病、充血性心脏病、心肌疾病、心肌病、心包疾病、主动脉疾病、马凡氏综合征(marfan syndrome)、血管疾病(vascular disease)和血管疾病(blood vessel disease)。在一些实施方案中,提供本发明的转铁蛋白受体结合多肽在制造用于治疗心血管疾病的药物中的用途。

[0418] 在一些实施方案中,所述方法还包括向受试者施用一种或多种另外的治疗剂。例如,在用于治疗脑或中枢神经系统疾病的一些实施方案中,所述方法可包括向受试者施用神经保护剂,例如抗胆碱剂、多巴胺能剂、谷氨酸能剂、组蛋白去乙酰化酶(HDAC)抑制剂、大麻素、半胱天冬酶抑制剂、褪黑激素、抗炎剂、激素(例如雌激素或孕酮)或维生素。在一些实施方案中,所述方法包括向受试者施用用于治疗神经病症的认知或行为症状的剂(例如抗抑郁剂、多巴胺激动剂或抗精神病剂)。

[0419] 本发明的转铁蛋白受体结合多肽以治疗有效量或剂量施用至受试者。可使用的说明性剂量包括约0.01mg/kg至约500mg/kg,或约0.1mg/kg至约200mg/kg,或约1mg/kg至约100mg/kg,或约10mg/kg至约50mg/kg的每日剂量范围。然而,剂量可根据若干因素而变化,包括所选施用途径、组合物的制剂、患者应答、疾患的严重程度、受试者的体重和处方医师的判断。根据个别患者的要求,所述剂量可随时间增加或减少。在一些实施方案中,患者最初给予较低剂量,然后将剂量增加至患者耐受的有效剂量。有效剂量的确定在本领域技术人员的能力范围内。

[0420] 在各种实施方案中,胃肠外施用本发明的转铁蛋白受体结合多肽。在一些实施方案中,静脉内施用所述多肽。静脉内施用可通过例如经约10至约30分钟时间,或经至少1小时、2小时或3小时的时间输注进行。在一些实施方案中,静脉内推注施用所述多肽。还可使用输注与推注施用的组合。

[0421] 在一些胃肠外实施方案中,腹膜内、皮下、皮内或肌肉内施用转铁蛋白受体结合多肽。在一些实施方案中,皮内或肌肉内施用所述多肽。在一些实施方案中,鞘内施用所述多肽,诸如通过硬膜外施用或脑室内施用。

[0422] 在其他实施方案中,可经口施用、肺部施用、鼻内施用、眼内施用或局部施用转铁蛋白受体结合多肽。还可采用肺部施用,例如通过使用吸入器或雾化器施用,并且与气雾剂一起配制。

[0423] VII.药物组合物和药盒

[0424] 在另一方面中,提供包含根据本发明的转铁蛋白受体结合多肽的药物组合物和药盒。

[0425] 药物组合物

[0426] 有关制备用于本发明中的制剂的指导可见于本领域的技术人员已知的有关药物制备和配制的多种手册中。

[0427] 在一些实施方案中,药物组合物包含如本文所述的转铁蛋白受体结合多肽,并且还包含一种或多种药学上可接受的载体和/或赋形剂。药学上可接受的载体包括在生理学上相容且优选不干扰或以其他方式抑制活性剂的活性的任何溶剂、分散介质或包衣剂。各种药学上可接受的赋形剂是熟知的。

[0428] 在一些实施方案中,所述载体适于静脉内、鞘内、脑室内、肌肉内、经口、腹膜内、经皮、局部或皮下施用。药学上可接受的载体可含有一种或多种用于例如使组合物稳定,或者增加或减少多肽的吸收的生理学上可接受的化合物。生理学上可接受的化合物可包括例如碳水化合物,诸如葡萄糖、蔗糖或葡聚糖;抗氧化剂,诸如抗坏血酸或谷胱甘肽;螯合剂;低分子量蛋白质;减少活性剂的清除或水解的组合物;或赋形剂,或其他稳定剂和/或缓冲剂。其他药学上可接受的载体及其制剂也可用于本领域中。

[0429] 本文所述的药物组合物可以本领域的技术人员已知的方式,例如借助于常规混合、溶解、制粒、制糖衣丸、乳化、囊封、包封或冻干方法制造。以下方法和赋形剂仅为示例性的且决不作为限制。

[0430] 对于经口施用,转铁蛋白受体结合多肽可通过与本领域中熟知的药学上可接受的载体组合来配制。此类载体能够将所述化合物配制为片剂、丸剂、糖衣丸、胶囊、乳液、亲脂性和亲水性悬浮液、液体、凝胶、糖浆、浆液、悬浮液等,以便供待治疗的患者口服。可通过将多肽与固体赋形剂混合,任选地研磨所得混合物,并且如果需要,在添加适合的佐剂后加工颗粒混合物,以获得片剂或糖衣丸核心,来得到用于口服使用的药物制剂。适合的赋形剂包括例如填充剂,诸如糖,包括乳糖、蔗糖、甘露糖醇或山梨糖醇;纤维素制剂,诸如玉米淀粉、小麦淀粉、大米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠,和/或聚乙烯吡咯烷酮。如果需要,可添加崩解剂,诸如交联聚乙烯吡咯烷酮、琼脂,或者海藻酸或其盐,诸如海藻酸钠。

[0431] 如上文所公开,如本文所述的转铁蛋白受体结合多肽可配制用于通过注射,例如通过推注或连续输注胃肠外施用。对于注射,可通过在水性或非水性溶剂,诸如植物油或其他类似油、合成脂肪酸甘油酯、高级脂肪酸或丙二醇酯中溶解、悬浮或乳化所述多肽;并且如果需要,添加常规添加剂,诸如增溶剂、等渗剂、悬浮剂、乳化剂、稳定剂和防腐剂来将所述多肽配制成制剂。在一些实施方案中,可在水溶液中,优选在生理学上相容的缓冲液,诸如汉克斯溶液(Hanks's solution)、林格氏溶液或生理盐水缓冲液中配制多肽。注射用制剂可以单位剂型提供于例如加有防腐剂的安瓿或多剂量容器中。所述组合物可呈诸如于油性或水性媒介物中的悬浮液、溶液或乳液的形式,并且可含有配制剂,诸如悬浮剂、稳定剂和/或分散剂。

[0432] 在一些实施方案中,转铁蛋白受体结合多肽被制备成例如于含有活性剂的固体疏水性聚合物的半渗透基质中的持续释放、控制释放、延长释放、定时释放或延迟释放制剂形式递送。已经确定且本领域的技术人员熟知各种类型的持续释放材料。延长释放制剂包括

膜包衣的片剂、多颗粒或丸粒系统、使用亲水性或亲脂性材料的基质技术和含有成孔赋形剂的基于蜡的片剂。取决于设计,持续释放递送系统可在数小时或数天时间内,例如经4、6、8、10、12、16、20、24小时或更长时间释放化合物。通常,持续释放制剂可使用天然存在或合成聚合物,例如聚合乙烯吡咯烷酮,诸如聚乙烯吡咯烷酮;羧基乙烯基亲水性聚合物;疏水性和/或亲水性水胶体,诸如甲基纤维素、乙基纤维素、羟丙基纤维素和羟丙基甲基纤维素;以及羧基聚甲烯制备。

[0433] 通常,用于体内施用的药物组合物是无菌的。灭菌可根据本领域中已知的方法,例如热灭菌、蒸汽灭菌、无菌过滤或照射实现。

[0434] 本发明的药物组合物的剂量和所需药物浓度可取决于预期的特定用途而变化。适当施用剂量或途径的确定在本领域技术人员的技能范围内。适合剂量还在以上第VII部分中进行了描述。

[0435] 药盒

[0436] 在一些实施方案中,提供包括如本文所述的转铁蛋白受体结合多肽的药盒。在一些实施方案中,所述药盒用于预防或治疗神经病症,诸如脑或中枢神经系统(CNS)疾病。

[0437] 在一些实施方案中,所述药盒还包括一种或多种另外的治疗剂。举例而言,在一些实施方案中,所述药盒包括如本文所述的转铁蛋白受体结合多肽,并且还包括一种或多种用于治疗神经病症的另外的治疗剂。在一些实施方案中,所述药盒还包括说明材料,所述说明材料含有关于实践本文所述的方法的指导(即,方案)(例如有关使用所述药盒跨血脑屏障施用组合物的说明书)。尽管所述说明材料通常包括书面或印刷材料,但其不限于此。能够储存此类说明书并将它们传达给终端用户的任何介质均涵盖在本发明中。此类介质包括但不限于,电子存储介质(例如磁盘、磁带、磁片盒、芯片)、光学介质(例如,CD-ROM)等。此类介质可包括提供此类说明材料的互联网网站的地址。

[0438] VIII.实施例

[0439] 本发明将借助于具体实施例更详细地描述。提供以下实施例仅用于说明性目的,并且不意图以任何方式限制本发明。本领域的技术人员将易于认识到,可改变或修改多种非关键参数以得到基本上相同的结果。已作出大量努力来确保所用数值(例如量、温度等)的准确性,但仍可能存在一些实验误差和偏差。除非另外指示,否则本发明的实践将采用本领域技能范围内的蛋白质化学、生物化学、重组DNA技术和药理学的常规方法。此类技术将于文献中完整地阐述。另外,本领域的技术人员应显而易见,适用于某些文库的工程改造方法还可用于本文所述的其他文库。

[0440] 实施例1.TfR靶标的产生

[0441] 将编码转铁蛋白受体(TfR)胞外结构域(ECD)(人(SEQ ID NO:38)或食蟹猴(SEQ ID NO:103)TfR的残基121-760)的DNA克隆至带有C末端可裂解His和Avi标签的哺乳动物表达载体中。将质粒转染至HEK293细胞中并使其表达。使用Ni-NTA色谱法,随后尺寸排阻色谱法以移除任何聚集的蛋白质,从收获的上清液纯化胞外结构域。产率为每升培养物约5mg。将蛋白质储存于10mM K_3PO_4(pH 6.7)、100mM KCl、100mM NaCl和20%甘油中并在-20℃下冷冻。

[0442] 将编码改变的TfR顶端结构域(SEQ ID NO:104)(人或食蟹猴TfR的残基326-379和194-296)的DNA克隆至带有供纯化的N末端His标签和供体外生物素化的Avi标签的pET28载

体中。将所述质粒与BirA表达载体一起共转化至BL21(DE3)细胞中。在37℃下,使细胞在LB培养基中生长至对数期,且然后用1mM异丙基1-硫代-β-D-吡喃半乳糖苷(IPTG)诱导,随后在18℃下培养过夜。将细胞溶解并将可溶性部分施加至Ni-NTA柱上进行亲和纯化,随后进行尺寸排阻色谱法以移除任何聚集的蛋白质。产率为每升培养物约10mg。将蛋白质储存于50mM HEPES(pH 7.5)、150mM NaCl和1mM DTT中并在-20℃下冷冻。

[0443] 使用EZ-link磺基-NHS-LC-生物素药盒(从Thermo Scientific获得)使纯化的TfR ECD生物素化。使用五倍摩尔过量的生物素进行反应。通过针对PBS充分透析来移除过量的生物素。

[0444] 使用BirA-500(来自Avidity有限公司的BirA生物素-蛋白质连接酶标准反应药盒)使Avi标记的TfR ECD和顶端结构域生物素化。反应后,通过尺寸排阻色谱法进一步纯化标记的蛋白质以移除过量的BirA酶。将最终的材料储存于10mM K_3PO_4(pH 6.7)、100mM KCl、100mM NaCl和20%甘油中并在-20℃下冷冻。

[0445] 实施例2.工程改造的转铁蛋白受体结合多肽的设计和表征

[0446] 本实施例描述本发明多肽的设计、产生和表征。出于本实施例和比较在克隆序列中相同的氨基酸的目的,认为"保守"突变施在所有鉴定的克隆中存在的突变(非保守氨基酸取代),而"半保守"突变是在>50%克隆中存在的突变。

[0447] 除非另外指示,否则本章节中氨基酸残基的位置是基于SEQ ID NO:1编号,人IgG1野生型Fc区在氨基末端具有来自铰链的三个残基,即PCP。

[0448] 多肽Fc区结构域文库的设计

[0449] 通过选择某些溶剂暴露表面补丁进行修饰,构建所选补丁的氨基酸组成因随机突变而改变的表面展示文库,且然后使用标准表达展示技术,针对所需功能筛选表面展示的序列变体,将新分子识别位点工程改造至多肽Fc区中。如本文所使用,术语"随机突变"包括部分随机突变以及具有预定核苷酸或氨基酸混合比的序列变化。选择用于随机突变的典型表面暴露补丁具有在600至1500 $Å^2$之间的面积,且包含约7至15个氨基酸。

[0450] 克隆定位区

[0451] 根据本文所述的方法,设计并产生以下定位区。如本文所使用,术语"定位区"是指形成连续表面的一系列表面暴露的氨基酸残基,所述氨基酸残基可改变(例如通过将突变引入多肽编码基因序列中以在定位区中所列位置处产生氨基酸取代、插入和/或缺失)。

[0452] CH3定位区C

[0453] CH3C定位区(表1)包括如参照SEQ ID NO:1中列出的人IgG1 Fc区氨基酸序列编号的氨基酸位置157、159、160、161、162、163、186、189和194。CH3C定位区位置通过包括来自远离FcγR和FcRn结合位点的两个环的溶剂暴露残基而形成连续表面。

[0454] 噬菌体展示文库的产生

[0455] 合成用于编码野生型人Fc序列(SEQ ID NO:1)的DNA模板并将其并入噬菌粒载体中。噬菌粒载体含有ompA或pelB前导序列、与c-Myc和6×His表位标签融合的Fc插入序列,以及琥珀终止密码子,后接M13外壳蛋白pIII。

[0456] 产生在随机突变的相应位置处含有"NNK"三密码子的引物,其中N是任何DNA碱基(即,A、C、G或T)且K是G或T。或者,使用进行"软"随机突变的引物,其中在每一随机突变位置使用对应于70%野生型碱基和10%其他三个碱基中的每一个的碱基混合物。通过进行Fc区

中对应于随机突变区域的片段的PCR扩增,且然后使用含SfiI限制性位点的末端引物组装,随后用SfiI消化并连接至噬菌粒载体中来产生文库。或者,使用所述引物进行Kunkel诱变。本领域的技术人员将已知进行Kunkel诱变的方法。将连接的产物或Kunkel产物转化至电感受态大肠杆菌TG1细胞株(从Lucigen®获得)中。在回收并生长过夜后,用M13KO7辅助噬菌体感染大肠杆菌细胞,之后用5%PEG/NaCl使文库噬菌体沉淀,将其再悬浮于含15%甘油的PBS中,并冷冻待用。典型文库大小在约10^9至约10^{11}个转化体范围内。经由pIII融合的Fc与未连接至pIII的可溶性Fc(所述可溶性Fc由于琥珀终止密码子而在pIII之前而产生)之间配对,将Fc二聚体展示于噬菌体上。

[0457] 酵母展示文库的产生

[0458] 合成编码野生型人Fc序列的DNA模板并将其并入酵母展示载体中。对于CH3文库,将Fc多肽展示于Aga2p细胞壁蛋白上。两种载体均含有具有Kex2裂解序列的前原前导肽,以及与Fc末端融合的c-Myc表位标签。

[0459] 使用与关于噬菌体文库所描述的方法类似的方法,除了用含所述载体的同源末端的引物进行片段扩增来组装酵母展示文库。用线性化载体和组装的文库插入序列对新鲜制备的电感受态酵母(即,EBY100菌株)进行电穿孔。电穿孔方法使本领域技术人员已知的。在选择性SD-CAA培养基中回收之后,使酵母生长至汇合并分裂两次,然后通过转移至SG-CAA培养基中诱导蛋白质表达。典型文库大小在约10^7至约10^9个转化体范围内。通过相邻展示的Fc单体配对来形成Fc二聚体。

[0460] 用于噬菌体选择的通用方法

[0461] 噬菌体方法改编自Phage Display:A Laboratory Manual(Barbas,2001)。另外的方案细节可从所述参考文献获得。

[0462] 板分选法

[0463] 将人TfR靶标包被于MaxiSorp®微量滴定板上(通常1-10μg/mL于PBS中,200μL),在4℃下保持过夜。所有结合均在室温下进行,除非另外说明。将噬菌体文库添加至各孔中并孵育过夜进行结合。用含0.05% Tween® 20的PBS(PBST)充分洗涤微量滴定孔并通过将所述孔与酸(通常为含500mM KCl的50mM HCl,或100mM甘氨酸,pH 2.7)一起孵育30分钟来洗脱结合的噬菌体。用1M Tris(pH 8)中和经洗脱的噬菌体,并使用TG1细胞和M13/KO7辅助噬菌体扩增,并使其在37℃下于含50μg/mL羧苄青霉素和50ug/mL卡那霉素的2YT培养基中生长过夜。将从含靶标的孔洗脱的噬菌体的效价与从不含靶标的孔回收的噬菌体的效价相比较来评估富集。随后通过缩短结合期间的孵育时间以及增加洗涤时间和洗涤次数来增加选择严格度。

[0464] 珠粒分选法

[0465] 使用NHS-PEG4-生物素(从Pierce™获得),通过游离胺使人TfR靶标生物素化。对于生物素化反应,在PBS中使用3倍至5倍摩尔过量的生物素试剂。用Tris淬灭反应,随后在PBS中充分透析。将生物素化的靶标固定于用链霉抗生物素蛋白包被的磁珠(即,从Thermo Fisher获得的M280-链霉抗生物素蛋白珠粒)上。将噬菌体展示文库与用靶标包被的珠粒一起在室温下孵育1小时。然后移除未结合的噬菌体并用PBST洗涤珠粒。通过与含500mM KCl的50mM HCl(或0.1M甘氨酸,pH 2.7)一起孵育30分钟来洗脱结合的噬菌体,且然后如上文

关于板分选所描述进行中和和繁殖。

[0466] 在三轮至五轮淘选后,通过在噬菌体上表达Fc或在大肠杆菌周质中可溶性表达Fc来筛选单一克隆。此类表达方法是本领域技术人员已知的。使单独噬菌体上清液或周质提取物暴露于用靶标或阴性对照包被的封闭的ELISA板且随后,对于周质提取物使用HRP缀合的山羊抗Fc(从Jackson Immunoresearch获得)或对于噬菌体使用抗M13(GE Healthcare)进行检测,然后用TMB试剂(从Thermo Fisher获得)显色。将OD_{450}值为背景值约5倍的孔视为阳性克隆并测序,之后,将一些克隆表达为可溶性Fc片段或与Fab片段融合。

[0467] 用于酵母选择的通用方法

[0468] 珠粒分选(磁性辅助的细胞分选(MACS))方法

[0469] 以与Ackerman等人,2009Biotechnol.Prog.25(3),774中所描述类似的方法进行MACS和FACS选择。用生物素化的靶标记链霉抗生物素蛋白磁珠(例如来自ThermoFisher的M-280链霉抗生物素蛋白珠粒)并将其与酵母(通常5-10×文库多样性)一起孵育。移除未结合的酵母,洗涤珠粒,并使结合的酵母在选择性培养基中生长并诱导用于后续数轮选择。

[0470] 荧光活化细胞分选(FACS)方法

[0471] 用抗c-Myc抗体标记酵母以监测表达和生物素化靶标(浓度随分选次数而变化)。在一些实验中,为增强相互作用的亲合力,将靶标与链霉抗生物素蛋白-Alexa Fluor® 647预混合。在其他实验中,在与链霉抗生物素蛋白-Alexa Fluor® 647结合并洗涤后,检测生物素化靶标。使用FACS Aria III细胞分选仪分选具有结合的单一酵母。使分选的酵母在选择性培养基中生长,然后诱导用于后续数轮选择。

[0472] 在获得富集的酵母群体后,将酵母接种于SD-CAA琼脂板上并使单一集落生长并诱导表达,然后如上文所描述进行标记以确定其结合至靶标的倾向。随后对结合靶标的阳性单一克隆进行测序,之后,使一些克隆表达为可溶性Fc片段或与Fab片段融合。

[0473] 用于筛选的通用方法

[0474] 通过ELISA筛选

[0475] 从淘选输出物选择克隆且使其在96孔深孔板各孔中生长。所述克隆使用自动诱导培养基(从EMD Millipore获得)诱导周质表达,或用辅助噬菌体感染以将单独Fc变体经噬菌体展示于噬菌体上。使培养物生长过夜且离心以使大肠杆菌沉淀。对于噬菌体ELISA,直接使用含噬菌体的上清液。对于周质表达,将沉淀物再悬浮于20%蔗糖中,随后用水以4:1稀释,并在4℃下振荡1小时。将板离心以使固体沉淀且上清液用于ELISA中。

[0476] 用通常0.5mg/mL靶包被ELISA板过夜,然后用1%BSA封闭,随后添加噬菌体或周质提取物。在孵育1小时并洗掉结合的蛋白质之后,添加HRP缀合的第二抗体(即,抗Fc或抗M13,分别针对可溶性Fc或噬菌体展示的Fc)并孵育30分钟。再次洗涤板,且然后用TMB试剂显色并用2N硫酸淬灭。使用酶标仪(BioTek®)定量在450nm下的吸光度并在适用时,使用Prism软件绘制结合曲线。将测试克隆的吸光度信号与阴性对照(不含Fc的噬菌体或周质提取物)相比较。在一些测定中,在结合步骤期间添加通常大量摩尔过量(大于10倍过量)的可溶性铁饱和转铁蛋白。

[0477] 通过流式细胞术筛选

[0478] 将Fc变体多肽(在噬菌体上、周质提取物中或以与Fab片段的融合物形式可溶性地

表达)添加至96孔V形底板(每孔约100,000个细胞于PBS+1％BSA(PBSA)中)中,并在4℃下孵育1小时。随后将板离心并移除培养基,且然后用PBSA洗涤细胞一次。将细胞再悬浮于含第二抗体(山羊抗人IgG-Alexa Fluor® 647(从Thermo Fisher获得))的PBSA中。30分钟后,将板离心并移除培养基,用PBSA洗涤细胞1-2次,且然后在流式细胞仪(即,FACSCanto™II流式细胞仪)上读取板。使用FlowJo软件计算每种条件下的中值荧光度值并用Prism软件绘制结合曲线。

[0479] CH3C克隆产生和表征

[0480] 用CH3C文库针对转铁蛋白受体(TfR)进行选择

[0481] 如上文所描述,针对TfR淘选并分选针对CH3C的酵母文库。前三轮分选的群体富集FACS图显示于图1中。在另两轮分选后,对单一克隆测序并鉴定出四个独特序列(即,克隆CH3C.1(SEQ ID NO:4)、CH3C.2(SEQ ID NO:5)、CH3C.3(SEQ ID NO:6)和CH3C.4(SEQ ID NO:7))。这些序列在161位具有保守Trp,且在194位都具有芳族残基(即,Trp、Tyr或His)。在其他位置存在较大多样性。

[0482] 第一代CH3C克隆的表征

[0483] 在CHO或293细胞中将选自CH3C文库的四个克隆表达为Fc与Fab片段的融合物形式,并通过蛋白质A和尺寸排阻色谱法纯化,且然后在存在或不存在铁饱和Tf下,通过ELISA针对与食蟹猴和人TfR的结合进行筛选。如图2中所示,所述克隆均结合至人TfR且添加过量(5μM)铁饱和Tf不影响所述结合。然而,所述克隆不明显结合至食蟹猴TfR。还测试了克隆与内源性表达人TfR的293F细胞的结合。图3示出,所述克隆结合至293F细胞,但总体结合基本上弱于高亲和力阳性对照。

[0484] 接下来,测试克隆CH3C.3是否能够内化于表达TfR的细胞中。使粘附HEK 293细胞在96孔板中生长至约80％汇合,移除培养基且添加1μM浓度样品:CH3C.3、抗TfR基准阳性对照抗体(Ab204)、抗BACE1基准阴性对照抗体(Ab107)和人IgG同种型对照(从Jackson Immunoresearch获得)。在37℃和8％CO_2浓度下孵育所述细胞30分钟,然后洗涤,用0.1％Triton™X-100透化,并用抗人IgG-Alexa Fluor® 488第二抗体染色。再次洗涤后,在高含量荧光显微镜(即,Opera Phenix™系统)下对细胞进行成像,并定量每个细胞的斑点数,如图4中所示。在1μM下,克隆CH3C.3显示与阳性抗TfR对照类似的内化倾向,而阴性对照不显示内化作用。

[0485] CH3C克隆的二次工程改造

[0486] 产生另外的文库以改善初始CH3C命中针对人TfR的亲和力,并尝试引入与食蟹猴TfR的结合。使用软随机突变方法,其中基于原始四个命中中的每一个,产生DNA寡聚物以引入软诱变。经由独立片段构建定位区的第一部分(WESXGXXXXXYK;SEQ ID NO:34)和定位区的第二部分(TVXKSXWQQGXV;SEQ ID NO:35),因此,软随机突变的定位区在PCR扩增期间改组(例如,来自克隆CH3C.1的定位区的第一部分与来自克隆CH3C.1、CH3C.2、CH3C.3和CH3C.4的定位区的第二部分混合等等)。混合所有片段且然后将其引入酵母中以实现表面表达和选择。

[0487] 选择方案显示于图5中。在一轮MACS和三轮FACS后,对单独克隆测序(克隆CH3C.17(SEQ ID NO:8)、CH3C.18(SEQ ID NO:9)、CH3C.21(SEQ ID NO:10)、CH3C.25(SEQ ID NO:11)、CH3C.34(SEQ ID NO:12)、CH3C.35(SEQ ID NO:13)、CH3C.44(SEQ ID NO:14)和

CH3C.51(SEQ ID NO:15))。所选克隆分为两个常见序列组。第1组克隆(即,克隆CH3C.18、CH3C.21、CH3C.25和CH3C.34)分别具有在157位半保守的Leu、在159位的Leu或His以及在160位和162位分别保守和半保守的Val,以及在186位、189位和194位半保守的P-T-W基序。第2组克隆分别具有在157位的保守Tyr、在位置159-163处的基序TXWSX(SEQ ID NO:341)以及在186位、189位和194位的保守基序S/T-E-F。在另外的研究中,使用克隆CH3C.18和CH3.35作为各序列组的代表性成员。应注意,克隆CH3C.51具有来自第1组的其定位区的第一部分和来自第2组的其定位区的第二部分。

[0488] 来自软诱变文库的CH3C克隆的结合表征

[0489] 使来从软诱变文库的克隆形式改换为Fc-Fab融合物多肽且如上文所述进行表达和纯化。如图7中所示,这些变体相较于来自初始文库选择的首位克隆(CH3C.3)具有改善的与人TfR的ELISA结合,并且此外不与铁饱和Tf竞争。如下表2中所示,铁饱和Tf的存在或不存在不明显影响EC_{50}值而超出实验误差范围。

[0490] 表2.在存在或不存在铁饱和Tf下CH3C变体与TfR的ELISA结合的EC_{50}值(nM)

[0491]

克隆	-Tf	+Tf
CH3C.3	8.1	6.3
CH3C.17	5.3	17
CH3C.18	6.9	3.5
CH3C.25	51	48
CH3C.35	0.49	0.61
CH3C.51	160	36
Ab204	1.6	0.24

[0492] 值得注意的是,克隆CH3C.35与人TfR的结合与高亲和力抗TfR对照抗体Ab204大致相当。如图8中所示,选自软随机突变文库的克隆还具有改善的与293F细胞的细胞结合。在类似细胞结合测定中,测试这些克隆与在表面上高水平稳定表达人或食蟹猴TfR的CHO-K1细胞的结合。选自软随机突变文库的克隆结合至表达人TfR(图9A)以及食蟹猴TfR(图9B)的细胞且不结合至亲本CHO-K1细胞(图9C)。相较于人TfR,针对食蟹猴TfR的幅值和结合EC_{50}值明显较低。数据概述于下表3中。

[0493] 表3.CH3C克隆与细胞结合的EC_{50}和最大MFI(中值荧光强度)值

[0494]

克隆	**293F EC50 (nM)**	**293F MFI 200 nM**	**CHO-huTfR EC_{50} (nM)**	**CHO-huTf MFI 200 nM**	**CHO-cyTfR EC_{50} (nM)**	**CHO-cyTfR MFI 200 nM**
CH3C.3	n.d.	1385	6.5	10296	n.d.	941
CH3C.17	n.d.	1556	4.2	13933	> 50	8205
CH3C.18	22	2100	2.3	22997	6.6	9614
CH3C.25	n.d.	314	17	11434	> 50	12515

[0495]

克隆	293F EC50 (nM)	293F MFI 200 nM	CHO-huTfR EC_{50} (nM)	CHO-huTf MFI 200 nM	CHO-cyTfR EC_{50} (nM)	CHO-cyTfR MFI 200 nM
CH3C.35	0.67	1481	2.6	22059	11	8292
CH3C.51	n.d.	784	27	11892	> 50	14455
Ab204	0.25	3404	1.8	35744	2.4	41041

[0496] 表位定位

[0497] 为了确定工程改造的CH3C Fc区是否结合至TfR的顶端结构域,在噬菌体表面上表达TfR顶端结构域(人和食蟹猴分别为SEQ ID NO:30和31)。为了正确折叠并展示顶端结构域,须截短一个环且需要将序列环形布置;鉴定出噬菌体上表达的人和食蟹猴的序列分别为SEQ ID NO:32和33。将克隆CH3C.18和CH3C.35包被于ELISA板上并遵循先前描述的噬菌体ELISA方案。简言之,在用1%PBSA洗涤并封闭后,添加噬菌体展示的稀释液并在室温下孵育1小时。随后洗涤板并且添加抗M13-HRP,且再次洗涤之后,用TMB底物使板显色并用2N H_2SO_4淬灭。在此测定中,CH3C.18和CH3C.35均结合至顶端结构域。

[0498] 由于已知与食蟹猴TfR的结合比与人TfR的结合要弱得多,故假定在食蟹猴与人顶端结构域之间存在的一个或多个氨基酸差异可能引起结合差异。因此,在人TfR顶端结构域中作出一系列六个点突变,其中人残基被相应食蟹猴残基置换。使所述突变体展示于噬菌体上且通过OD_{268}使噬菌体浓度标准化并通过噬菌体ELISA滴定测试与CH3C.18和CH3C.35的结合(图11B和11C)。捕获于抗Myc抗体9E10上显示,所有突变体的展示水平是类似的(图11A)。与人TfR突变的结合清楚显示出R208G突变的显著影响,其表明此残基是表位的关键部分且受此位置处食蟹猴残基的负面影响。对噬菌体展示的食蟹猴顶端结构域进行G208R突变且显示,这种突变显著改善与食蟹猴顶端结构域的结合(图11D和11E)。这些结果表明,CH3C克隆结合至TfR的顶端结构域且208位对于结合很重要,而位置247、292、364、370和372明显不那么重要。

[0499] 互补位定位

[0500] 为了解Fc结构域中对于TfR结合最重要的残基,产生一系列突变体克隆CH3C.18和CH3C.35,其中各突变体在TfR结合定位区中具有一个位置回复突变成野生型。所得变体重组表达为CH3C Fc-Fab融合物形式且测试其与人或食蟹猴TfR的结合(图12)。对于CH3C.35,位置161和194对于结合很重要;这些位置中的任一个回复突变成野生型完全消除与人TfR的结合。出人意料地,163位回复突变成野生型使得与食蟹猴TfR的结合明显增强,同时对人结合具有极少影响。相反,残基163回复突变成野生型在CH3C.18中具有极少影响,但在这种变体中,189位和194位回复突变使得与人TfR的结合完全消除。在两种变体中,其他单一回复突变对人TfR结合具有中等(不利)影响,同时在许多情况下,使得与食蟹猴TfR的结合消除。

[0501] 另外工程改造以改善与食蟹猴TfR的结合

[0502] 制备另外的文库以进一步增加CH3C变体对食蟹猴TfR的亲和力。这些文库被设计成就理论多样性而言少于约10^7个克隆,由此可使用酵母表面展示研究整个多样性空间。这些文库的设计显示于图13A-13D中。使用四个文库设计;所有文库均使用含NNK或其他简并密码子位置的简并寡核苷酸产生,并通过重叠PCR扩增,如上文所述。

[0503] 第一个文库是基于CH3C.35样序列的共有序列(图13A)。此处,位置157-161恒定保持为YGTEW(SEQ ID NO:36),而位置162、163、186、189和194则使用饱和诱变进行突变。

[0504] 第二个文库是基于CH3C.18样序列的共有序列(图13B)。此处,157位限于Leu和Met,159位限于Leu和His,160位恒定保持为Val,161位限于Trp和Gly,162位限于Val和Ala,163位完全随机突变,164位添加至定位区中且完全随机突变,186位软随机突变,189位完全随机突变,且194位限于芳族氨基酸和Leu。

[0505] 第三个文库添加新随机突变的位置至所述文库中(图13C)。产生两种型式,各自具有CH3C.18和CH3C.35作为起始定位区,且然后通过饱和诱变使其他位置随机突变:E153、E155、Y164、S188和Q192。

[0506] 第四个文库对于CH3C.18保持某些位置恒定,但允许在其他位置存在变化,相较于共有序列文库偏差较少(图13D)。位置160、161和186固定不变,且位置157、159、162、163和189通过饱和诱变随机突变;194位突变但限于芳族氨基酸和Leu。

[0507] 在酵母中针对食蟹猴TfR对所述文库进行四至五轮选择,且对单一克隆测序并将其转化成多肽-Fab融合物,如上文所述。从第二个文库(即,CH3.18亲本克隆的衍生物)观察到最丰富的食蟹猴TfR结合,但是在huTfR结合方面还存在一定损失。

[0508] CH3C成熟克隆的结合表征

[0509] 如上文所述,利用纯化的CH3C Fc-Fab融合物和包被于板上的人或食蟹猴TfR进行结合ELISA。来自CH3C.18成熟文库、CH3C3.2-1、CH3C.3.2-5和CH3C.3.2-19的变体以大致相等的EC_{50}值结合人和食蟹猴TfR,而亲本克隆CH3C.18和CH3C.35与人TfR的结合比与食蟹猴TfR的结合强10倍(图14)。

[0510] 接下来,测试新多肽是否内化于人和猴细胞中。使用先前上文在题为“第一代CH3C克隆的表征”部分中所描述的方案,测试于人HEK293细胞和恒河猴LLC-MK2细胞中的内化。如图15中所示,类似地结合人和食蟹猴TfR的变体,即CH3C.3.2-5和CH3C.3.2-19相较于CH3C.35在LLC-MK2细胞中具有显著改善的内化作用。

[0511] CH3C克隆的另外工程改造

[0512] 针对其他亲和力成熟克隆CH3C.18和CH3C.35的另外工程改造涉及添加另外的突变至通过直接相互作用、第二壳相互作用或结构稳定化增强结合的主链(即,非定位区)位置。此目的经由产生“NNK步行”或“NNK补丁”文库并进行选择来实现。NNK步行文库涉及使互补位附近的残基逐一发生NNK突变。通过观察结合至FcgRI(PDB ID:4W4O)的Fc的结构,鉴定出如图16中所示的原始文库位置附近的44个残基为询问的候选物。具体言之,将以下残基作为靶标进行NNK诱变:K21、R28、Q115、R117、E118、Q120、T132、K133、N134、Q135、S137、K143、E153、E155、S156、G158、Y164、K165、T166、D172、S173、D174、S176、K182、L183、T184、V185、K187、S188、Q191、Q192、G193、V195、F196、S197、S199、Q211、S213、S215、L216、S217、P218、G219和K220。使用Kunkel诱变技术产生44个单点NNK文库,且汇集产物并如以上关于其他酵母文库所描述,经由电穿孔将其引入酵母中。

[0513] 组合这些微型文库(其各自具有一个位置突变,产生20种变体)产生一个小型文库,所述文库使用酵母表面展示针对引起较高亲和力结合的任何位置进行选择。如上文所述,使用TfR顶端结构域蛋白质进行选择(图17)。在三轮分选之后,对来自富集酵母文库的克隆进行测序,并鉴定出若干”热点”位置,其中某些点突变显著改善与顶端结构域蛋白质

的结合。对于CH3C.35,这些突变包括E153(突变成Trp、Tyr、Leu或Gln)和S188(突变成Glu)。CH3C.35单突变体和组合突变体的序列在SEQ ID NO:21-23、39-44和100-102中列出。对于CH3C.18,这些突变包括E153(突变成Trp、Tyr或Leu)和K165(突变成Gln、Phe或His)。CH3C.18单一突变体的序列在SEQ ID NO:45-50中列出。

[0514] “NNK补丁”方法类似于以上关于CH3B文库所描述的方法,但利用直接邻近CH3C定位区的补丁。使用克隆CH3C.35作为起点并产生以下文库:

[0515] CH3C-补丁1:氨基酸位置:K21、R28、Y164、K165和T166;

[0516] CH3C-补丁2:氨基酸位置:Q115、R117、E118、Q120和K143;

[0517] CH3C-补丁3:氨基酸位置:T132、K133、N134、Q135和S137;

[0518] CH3C-补丁4:氨基酸位置:E153、E155、S156和G158;

[0519] CH3C-补丁5:氨基酸位置:D172、S173、D174、S176和K182;

[0520] CH3C-补丁6:氨基酸位置:L183、T184、V185、K187和S188;

[0521] CH3C-补丁7:氨基酸位置:Q191、Q192、G193、V195和F196;

[0522] CH3C-补丁8:氨基酸位置:S197、S199、Q211、S213和S215;和

[0523] CH3C-补丁9:氨基酸位置:L216、S217、P218、G219和K220。

[0524] 如上文所述,使用TfR顶端结构域蛋白质进行选择。不过,未鉴定出结合增强的克隆。

[0525] 改善CH3C.35亲和力的另外成熟文库

[0526] 如关于先前的酵母文库所描述,产生另一文库,以鉴定NNK步行文库中的突变组合,同时在其周围添加若干另外的位置。在此文库中,YxTEWSS和TxxExxxxF基序保持不变,且有六个位置完全随机突变:E153、K165、K187、S188、S197和S199。包括位置E153和S188是因为其是NNK步行文库中的”热点”。包括位置K165、S197和S199系因为其构成可定位结合区的核心的一部分,而选择K187是因为其邻近188位。

[0527] 如先前所描述,仅用食蟹猴TfR顶端结构域分选所述文库。五轮分选后,对富集的汇集物进行测序,且所鉴定的独特克隆的CH3区的序列在SEQ ID NO:51-68中列出。

[0528] 有关CH3C.35.21的原始定位区和热点内可接受的多样性的研究

[0529] 设计新一批文库以研究主要结合互补位中的整个可接受的多样性。所用方法类似于NNK步行文库。用NNK密码子使原始定位区位置(157、159、160、161、162、163、186、189和194)加两个热点(153和188)各自独立地随机突变以在酵母上产生一系列单位置饱和诱变文库。此外,使每个位置单独地回复突变成野生型残基,并将这些单独克隆展示于酵母上。图18显示与野生型回复突变和单位置NNK文库相比,亲本克隆CH3C.35.21的结合。注意到,位置153、162、163和188在回复突变成野生型残基后与TfR保持显著结合的唯一位置(关于186回复突变成野生型观察到有一些残留但明显减弱的结合)。

[0530] 针对人TfR顶端结构域对单位置NNK文库进行三轮分选以收集约前5%的结合物,且然后对来自各文库的至少16个克隆进行测序。结果指示在CH3C.35克隆的背景下各位置处可接受而不会明显减弱与人TfR的结合的氨基酸。概述于下:

[0531] 153位:Trp、Leu或Glu;

[0532] 157位:Tyr或Phe;

[0533] 159位:仅Thr;

[0534] 160位:仅Glu;

[0535] 161位:仅Trp;

[0536] 162位:Ser、Ala或Val(应注意,尽管野生型Asn残基看来保持一定结合,但其未出现在后续文库分选中);

[0537] 163位:Ser或Asn;

[0538] 186位:Thr或Ser;

[0539] 188位:Glu或Ser;

[0540] 189位:仅Glu;和

[0541] 194位:仅Phe。

[0542] 以上残基当作为单一变化或组合变化取代至克隆CH3C.35中时,表示保持与TfR顶端结构域的结合的互补位多样性。在这些位置具有突变的克隆显示于表4中,且这些克隆的CH3结构域的序列在SEQ ID NO:40-44、67和69-99中列出。

[0543] 单价多肽-Fab融合物

[0544] 单价TfR结合多肽-Fab融合物的产生

[0545] 尽管Fc结构域天然地形成同二聚体,但称为"钮入孔"的一系列不对称突变可能使两个Fc片段优先异二聚体化,其中一个Fc单元具有T139W钮突变(使用EU编号方案,所述突变对应于366位)且另一个Fc单元具有T139S、L141A和Y180V孔突变(使用EU编号方案,分别对应于位置366、368和407)。在一些实施方案中,本发明的经修饰的CH3结构域包含在139位的Trp。在一些实施方案中,本发明的经修饰的CH3结构域包含在139位的Ser、在141位的Ala和在180位的Val。异二聚体TfR结合多肽通过两个质粒(即,钮-Fc和孔-Fc)的短暂共转染在293或CHO细胞中表达,而多肽-Fab融合物通过三个质粒(即,钮-Fc-Fab重链、孔-Fc-Fab和共同轻链)的短暂共转染表达。以与同二聚体相同的方式纯化所分泌的异二聚体多肽或多肽-Fab融合物(即,使用蛋白质A随后尺寸排阻色谱进行两柱纯化,如果需要,然后进行浓缩和缓冲液交换)。使用质谱法或疏水相互作用色谱法测定所形成的异二聚体对比同二聚体(例如钮-钮或孔-孔配对的Fc)的量。由典型制备型色谱法测定超过95%多肽且通常超过98%为异二聚体。为清楚起见,以此方式产生的所有单价TfR结合物(Fc同二聚体)均称为"ZZ.mono",其中ZZ是多肽的名称且".mono"指示单价TfR结合。对于异二聚体多肽和多肽-Fab融合物,除非另外指示,否则赋予TfR结合的突变包括"钮"突变,而非TfR结合Fc区与"孔"区一起使用。在一些情况下,在这些构建体中还包括改变Fc特性的另外突变,诸如对于经修饰的FcγR或FcRn结合分别为L7A/L8A、M25Y/S27T/T29E、N207S或N207S/M201L。

[0546] CH3C.mono Fc多肽的结合表征

[0547] 在ELISA中,使用上述程序的修改,测量单价CH3C多肽的结合。将含1μg/mL链霉抗生物素蛋白的PBS包被于96孔ELISA板上,保持过夜。洗涤后,用含1%BSA的PBS封闭所述板,然后添加1μg/mL生物素化的人或食蟹猴TfR,并孵育30分钟。再次洗涤后,将多肽的连续稀释液添加至板中并孵育1小时。洗涤板并且添加第二抗体(即,抗κ-HRP,1:5,000),保持30分钟,并再次洗涤板。用TMB底物使板显色并用2N H_2SO_4淬灭,且然后在BioTek®酶标仪上读取在450nm下的吸光度。结果显示于图19中,其中直接比较了标准(即,二价TfR结合)与单价TfR结合多肽。Ab204是高亲和力抗TfR对照抗体。

[0548] 进一步测试与内源性表达人TfR的293F细胞以及用人TfR或食蟹猴TfR稳定转染的

CHO-K1的结合(图20)。

[0549] 一般而言,相较于二价多肽,观察到单价多肽与人TfR的结合明显减少,且在这些测定中,单价多肽与食蟹猴的结合太弱而无法检测。

[0550] 接下来,测试CH3C多肽的单价形式是否能内化于表达人TfR的HEK293细胞中。使用以上关于内化测定所描述的方法。如比较二价与单价多肽的图21中所示,单价多肽还可内化,但总体信号比对应二价形式要弱,此可能归因于结合亲和力/亲合力的损失。

[0551] 通过生物层干涉测量法测量CH3C多肽的结合动力学

[0552] 使用生物层干涉测量法(即,使用Octet® RED系统)测定与抗BACE1 Fab融合的若干单价和二价CH3C多肽变体的结合动力学,并将其与其二价等效物相比较。将TfR捕获于链霉抗生物素蛋白传感器上,然后使CH3C多肽与其结合并洗涤。将传感器图谱与1:1结合模型拟合;二价多肽的K_D(app)值表示所希望的与TfR二聚体的结合。结果示于表5以及图22和23中。

[0553] 表5.使用Octet®Red测定的CH3C多肽的动力学

[0554]

多肽	K_D (app) (nM) [人 TfR]	K_D (app) (nM) [食蟹猴 TfR]
CH3C.35.N163	67	374
CH3C.35.N163.mono	251	n.d.
CH3C.35	59	934
CH3C.35.mono	483	n.d.
CH3C.3.2-1	337	367
CH3C.3.2-5	270	385
CH3C.3.2-19	367	454

[0555] n.d.=因结合信号太弱而无法测定

[0556] 转化成单价形式的多肽因亲合力损失而具有明显较弱的K_D(app)值。先前通过ELISA示出具有类似人和食蟹猴TfR结合的克隆CH3C.3.2-1、CH3C.3.2-5和CH3C.3.2-19在人与食蟹猴TfR之间也具有极其类似的K_D(app)值。尝试测试这些多肽的单价形式,但在此测定中结合太弱而无法计算动力学参数。

[0557] 实施例3.使用Biacore™测定的另外CH3C变体的结合表征

[0558] 使用Biacore™T200仪器,通过表面等离子体共振测定克隆变体对重组TfR顶端结构域的亲和力。Biacore™S系列CM5传感器芯片用抗人Fab(来自GE Healthcare的人Fab捕获药盒)固定。将5μg/mL多肽-Fab融合物捕获于各流动池上,保持1分钟,并在室温下,以30μL/分钟流速注入人或食蟹猴顶端结构域的连续3倍稀释液。用45分钟缔合和3分钟解离分析各样品。每次注射后,使用10mM盐酸甘氨酸(pH 2.1)使芯片再生。通过用以类似密度捕获不相关IgG的流动池减去RU来校正结合反应。通过使用Biacore™T200评价软件v3.1,针对浓度拟合平衡时的反应来获得稳态亲和力。

[0559] 为了测定克隆变体对重组TfR胞外结构域(ECD)的亲和力,用链霉抗生物素蛋白固定Biacore™S系列CM5传感器芯片。将生物素化的人或食蟹猴TfR ECD捕获于各流动池上,保持1分钟,并在室温下,以30μL/分钟流速注入克隆变体的连续3倍稀释液。用45分钟缔合和3

分钟解离分析各样品。通过用类似密度的不含TfR ECD的流动池减去RU来校正结合反应。通过使用Biacore™T200评价软件v3.1,针对浓度拟合平衡时的反应来获得稳态亲合力。

[0560] 结合亲和力概述于表6中。通过稳态拟合获得亲和力。

[0561] 表6.另外CH3C变体的结合亲和力

[0562]

克隆	人 TfR (μM)	食蟹猴 TfR (μM)	人顶端 TfR (μM)	食蟹猴顶端 TfR (μM)
CH3C.35.19.mono	0.4	5.9	0.37	5.6
CH3C.35.20.mono	0.25	6.7	0.17	8
CH3C.35.21.mono	0.1	2.1	0.12	2.2
CH3C.35.24.mono	0.29	3.3	0.23	3
CH3C.35.21.11.mono	0.24	4	0.13	2.2
CH3C.35.21.16.mono	0.18	1.8	0.12	1.9
CH3C.35.21.17.mono	0.3	2.9	0.13	2.6
CH3C.35.mono	0.61	>10	0.61	>10
CH3C.35.N153.mono	0.42	>10	0.95	>10
CH3C.35.bi	0.22	>2	未测试	未测试
CH3C.35.N153.bi	0.37	3.3	未测试	未测试
CH3C.3.2-19.bi	5.2	5.6	未测试	未测试
CH3C.35.19.bi	0.074	1.5	未测试	未测试
CH3C.35.20.bi	0.054	1.7	未测试	未测试
CH3C.35.21.bi	0.049	0.7	未测试	未测试
CH3C.35.24.bi	0.061	0.65	未测试	未测试

[0563] 产生另外的CH3C变体CH3C.35.20.1.1、CH3C.35.23.2.1、CH3C.35.23.1.1、CH3C.35.S413、CH3C.35.23.3.1、CH3C.35.N390.1和CH3C.35.23.6.1并遵循与先前所描述相同的方法,测量其与人TfR的结合亲和力。CH3C.35.20.1.1、CH3C.35.23.2.1、CH3C.35.23.1.1、CH3C.35.S413、CH3C.35.23.3.1、CH3C.35.N390.1和CH3C.35.23.6.1的结合亲和力分别为620nM、690nM、750nM、1700nM、1900nM、2000nM和2100nM。

[0564] 实施例4.CH3C变体与FcRn的结合表征

[0565] 使用ForteBio® Octet® RED384仪器,使用ForteBio®链霉抗生物素蛋白生物传感器进行FcRn结合测定。在动力学缓冲液(从ForteBio®获得)中将生物素化的重组BACE1稀释至10μg/mL浓度并将其捕获至单独生物传感器上,保持1分钟。然后在动力学缓冲液中保持1分钟以确定基线。在存在或不存在1uM人TfR ECD下,使10μg/mL多肽-Fab融合物(包含抗BACE1 Fab臂)结合至传感器尖端。利用3分钟缔合和3分钟解离来分析重组人FcRn(pH5.5)与固定的多肽-Fab融合物的结合。

[0566] 从这些实验(图24)获得的传感器图谱指示,多肽-Fab融合物变体在酸性pH(pH 5.5)下结合至FcRn且TfR结合不会明显干扰FcRn结合。

[0567] 实施例5.CH3C变体的药物动力学/药效学表征

[0568] 此实施例描述本发明的CH3C变体多肽在小鼠血浆和脑组织中的药物动力学/药效学(PK/PD)特征。

[0569] CH3C变体在野生型小鼠血浆中的药物动力学

[0570] 由于多肽-Fab融合物仅结合人TfR且不结合鼠类TfR,因此测试若干CH3C变体在野

生型小鼠中的药物动力学(PK)以展示在缺乏TfR介导的清除的模型中的体内稳定性。研究设计显示于下表7中。对6-8周龄的C57B16小鼠静脉内给药并在表7中所指示的时间点,经由下颌下抽血取得活体血液。将血液收集于EDTA血浆管中,以14,000rpm离心5分钟且然后分离血浆以供后续分析。

[0571] 表7.PK研究设计

[0572]

组	多肽	时间点	N	剂量(IV)
1A/1B	Ab122	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	12.3 mg/kg
2A/2B	Ab153	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	11.4 mg/kg
3A/3B	CH3C.35.163 mono (Ab153 融合物)	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	11.4 mg/kg
4A/4B	CH3C.3.2-19 (Ab153 融合物)	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	11.0 mg/kg
5A/5B	CH3C.3.2-5 (Ab153 融合物)	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	10.5 mg/kg
6A/6B	CH3C.3.2-1 (Ab153 融合物)	A = 30 分钟、24 小时、4 天 B = 4 小时、2 天、7 天	A=2 B=3	10.0 mg/kg

[0573] Ab122用作抗RSV对照,其在小鼠中具有标准PK。Ab153用作抗BACE1对照,其在小鼠中具有标准PK。在此研究中Ab153的Fab臂与多肽融合。

[0574] 使用普通人IgG测定(MSD®人IgG药盒#K150JLD-4),遵循制造商的方案定量小鼠血浆中的多肽浓度。简言之,用MSD®封闭剂A封闭预包被板30分钟。使用Hamilton® NIMBUS液体处理器以1:2,500稀释血浆样品,并一式两份添加至封闭的板中。还在同一板上分析给药溶液以确认正确剂量。使用四参数逻辑回归(four-parameter logistic regression)拟合标准曲线0.78-200ng/mL IgG。图25和表8显示这些数据的分析。除CH3C.3.2-5具有明显较快的清除率和较短半衰期外,所有CH3C多肽变体均具有与标准Ab122相当的清除率和半衰期值。值得注意的是,这种变体是CH3C.3.2-19的点突变体(N163D),而CH3C.3.2-19具有标准PK概况。

[0575] 表8.CH3C多肽-Fab融合物的PK参数

[0576]

多肽	清除率(mg/天/kg)	半衰期(天)
Ab122	6.12	9.12
Ab153	9.11	4.74
CH3C.35.N163 mono (Ab153 融合物)	8.44	5.35
CH3C.3.2-19 (Ab153 融合物)	10.3	5.42
CH3C.3.2-5 (Ab153 融合物)	21.0	1.90
CH3C.3.2-1 (Ab153 融合物)	9.25	4.65

[0577] 在野生型小鼠中进行的另外PK研究

[0578] 根据下表9中的研究设计(所有多肽-Fab融合物均针对Ab153Fab),在野生型小鼠中进行第二PK研究。

[0579] 表9

[0580]

多肽	剂量(mg/kg)	时间点	n/组
Ab153	10	0.5小时、1天、4天、7天	3
CH3C.35.21.mono	10	0.5小时、1天、4天、7天	3
CH3C.35.24.mono	10	0.5小时、1天、4天、7天	3
CH3C.35.21.16.mono	10	0.5小时、1天、4天、7天	3
CH3C.35.21.17.mono	10	0.5小时、1天、4天、7天	3
CH3C.35.20.bi	10	0.5小时、1天、4天、7天	3
CH3C.35.21.bi	10	0.5小时、1天、4天、7天	3

[0581] 如先前的研究中所描述,加工小鼠和样品。数据提供于表10中。

[0582] 表10.CH3C.35多肽-Fab融合物的清除率值

[0583]

测试多肽	清除率(mL/天/kg)
Ab153	9.53
CH3C.35.21.mono	8.99
CH3C.35.24.mono	9.00
CH3C.35.21.16.mono	11.6
CH3C.35.21.17.mono	10.9
CH3C.35.20.bi	7.13

[0584]

测试多肽	清除率(mL/天/kg)
CH3C.35.21.bi	11.6

[0585] 从清除率值显而易见,这些多肽-Fab融合物在野生型小鼠中展现与标准对照抗体类似的清除率。

[0586] 单价CH3C.35.N163在野生型小鼠脑组织中的PK/PD的评价

[0587] 使用CRISPR/Cas9技术产生在鼠类Tfrc基因内表达人Tfrc顶端结构域的转基因小

鼠。在内源启动子控制下在体内表达所得嵌合TfR。

[0588] 向嵌合huTfR^{顶端结构域}杂合小鼠(n＝4只/组)静脉内给与42mg/kg Ab153或单价CH3C.35.N163,且野生型小鼠(n＝3)静脉内给与50mg/kg对照人IgG1。Ab153用作对照,其在小鼠中具有标准PK。给药后24小时,对所有小鼠灌注PBS。灌注之前,经由心脏穿刺将血液收集于EDTA血浆管中,并以14,000rpm离心5分钟。然后分离血浆用于后续PK和PD分析。在灌注后,提取脑并分离半脑以在10倍组织重量的含1％NP-40的PBS(对于PK)或5M GuHCl(对于PD)中均质化。

[0589] 图26显示脑PK研究的结果。单价CH3C.35.N163组的吸收高于Ab153和对照人IgG1组中的吸收。

[0590] 多肽-Fab融合物在hTfR$^{顶端结构域+/+}$小鼠中的脑和血浆PKPD:CH3C.35.21和CH3C.35.N153

[0591] 如表11的研究设计中所示,对纯合hTfR$^{顶端结构域+/+}$小鼠静脉内注射50mg/kg抗BACE1抗体Ab153、抗TfR/BACE1双特异性抗体Ab116、与Ab153 Fab融合的CH3C.35.21.mono或与Ab153 Fab融合的CH3C.35.N153.bi。在此研究中,所有Fc均具有LALAPG突变以移除效应子功能。

[0592] 表11.单时间点脑和血浆PKPD研究的研究设计

[0593]

多肽	hTfR 亲和力(nM)	剂量(mg/kg)	时间点(天)	n/组
Ab153	n/a	50	1	8
Ab116	330	50	1	8
CH3C.35.21.mono	160	50	1	8
CH3C.35.N153.bi	370	50	1	8

[0594] 24小时后,经由心脏穿刺收集血液并对小鼠灌注PBS。在10倍组织重量的含1％NP-40于PBS中的溶解缓冲液中使脑组织均质化。将血液收集于EDTA管中以防止凝血并以14,000rpm离心7分钟以分离血浆。使用普通人IgG测定(MSD人IgG药盒#K150JLD),遵循制造商的说明书定量小鼠血浆和脑溶解产物中的多肽浓度。简言之,用MSD封闭剂A封闭预包被板30分钟。使用Hamilton Nimbus液体处理器以1:10,000稀释血浆样品,并一式两份添加至封闭的板中。在1％NP40溶解缓冲液中使血液样品均质化且溶解产物以1:10稀释以用于PK分析。还在同一板上分析给药溶液以确定正确剂量。使用四参数逻辑回归拟合标准曲线0.78-200ng/mL IgG。

[0595] 24小时后,TfR结合多肽的血浆水平低于抗BACE1的水平,这可能归因于此抗体经由结合至周围表达的hTfR^{顶端结构域}而清除(图27A)。在脑中,抗TfR/BACE1的浓度相较于抗BACE1明显增加(图27B)。关于CH3C.35.21.mono观察到最大幅度增加,而且脑吸收也相较于含CH3C35.N153.bi的抗BACE显著改善。工程改造的TfR结合多肽在血脑屏障处因TfR介导的转胞吞而显著累积,由此验证工程改造的TfR结合至Fc区中的效用。

[0596] 使用BACE1抑制淀粉样前体APP裂解作为抗体在血浆和脑中的活性的药效学读出。在10倍组织重量的5M盐酸胍中使脑组织均质化且然后在含0.25％酪蛋白缓冲液的PBS中以1:10稀释。使用夹心ELISA测量血浆和脑溶解产物中的小鼠Aβ40水平。用对Aβ40肽的C末端

具有特异性的多克隆捕获抗体(Millipore#ABN240)包被384孔MaxiSorp板。在ELISA板上以1:2对酪蛋白稀释的胍脑溶解产物进一步稀释且同时添加检测抗体,即生物素化的M3.2。分析1:5稀释的血浆。在4℃下孵育样品过夜,随后依序添加链霉抗生物素蛋白-HRP和TMB底物。使用四参数逻辑回归拟合标准曲线0.78-50pg/mL msAβ40。

[0597] 由于所有多肽上均存在抗BACE1 Fab,使得所有多肽的血浆淀粉样β蛋白(Aβ)降低至与未处理的野生型小鼠类似的程度(图28A)。相较于抗BACE1,用TfR结合多肽处理使hTfR$^{顶端结构域+/+}$小鼠中的Aβ降低有所增加,从而表明在脑中实现BACE1靶标接合(图28B)。工程改造的多肽融合物和抗TfR/BACE1双特异性抗体在脑中的靶标接合水平类似。

[0598] 多肽-Fab融合物在hTfR$^{顶端结构域+/+}$小鼠中的脑和血浆PKPD:CH3C.35.21、CH3C.35.20、CH3C.35、CH3C.35.23、CH3C.35.23.3

[0599] 为了评价TfR结合亲和力对PK和脑吸收的影响,产生了抗BACE1 Ab153和TfR结合多肽融合物(CH3C.35.21:Ab153、CH3C.35.20:Ab153、CH3C.35:Ab153融合物),如通过Biacore所测量,所述融合物对顶端人TfR的结合亲和力不同。CH3C.35.21:Ab153、CH3C.35.20:Ab153、CH3C.35:Ab153融合物与人TfR的结合亲和力分别为100nM、170nM和620nM。对hTfR顶端结构域$^{+/+}$基因敲入小鼠全身性施用50mg/kg Ab153或多肽-Fab融合物,并在给药后1天、3天和7天,评价血浆PK和脑PKPD。如前一部分中所述,进行脑和血浆PKPD分析。由于TfR在周围组织上表达,CH3C.35.21:Ab153、CH3C.35.20:Ab153和CH3C.35:Ab153融合物在血浆中展现的清除率比单独Ab153快,符合靶标介导的清除率且指示体内TfR结合(图39A)。值得关注的是,脑中CH3C.35.21:Ab153、CH3C.35.20:Ab153和CH3C.35:Ab153融合物的浓度相较于Ab153明显增加,在给药后1天时达到超过30nM的最大脑浓度,与在此相同时间点时仅为约3nM的Ab153脑浓度形成对比(图39B)。CH3C.35.21:Ab153、CH3C.35.20:Ab153和CH3C.35:Ab153融合物的脑暴露量增加使得小鼠脑中内源性小鼠Aβ水平相较于给与Ab153的小鼠中的Aβ水平降低约55-60%(图39C)。当CH3C.35.21:Ab153、CH3C.35.20:Ab153和CH3C.35:Ab153融合物在脑中保持较高浓度时,仍保持较低的脑Aβ水平,且到第7天,暴露量降低时回到与Ab153处理小鼠类似的水平。脑暴露量随时间降低与CH3C.35.21:Ab153、CH3C.35.20:Ab153和CH3C.35:Ab153融合物的周围暴露量降低有关,展示明确的体内PK/PD关系(比较图39A与39C)。另外,在这种单次高剂量之后,Ab153处理的小鼠与多肽-Fab融合物处理的小鼠的总脑TfR水平相当,从而表明多肽-Fab融合物的脑暴露量增加对脑中TfR的表达无显著影响(图39D)。

[0600] 为了进一步评价PK和脑吸收与较宽亲和力范围的TfR结合多肽-Fab融合物之间的关系,产生对hTfR结合具有较宽亲和力范围的其他融合物。CH3C.35.23:Ab153和CH3C.35.23.3:Ab153融合物对人TfR的结合亲和力分别为420nM和1440nM。如上文所述,对hTfR顶端结构域$^{+/+}$基因敲入小鼠给药。在给药后1天、4天、7天和10天,评价血浆PK和脑PKPD。多肽-Fab融合物的周围PK与hTfR亲和力相关,其中亲和力较高的CH3C.35.23:Ab153融合物展现的清除率比亲和力明显较低的CH3C.35.23.3:Ab153融合物快(图40A)。CH3C.35.23:Ab153和CH3C.35.23.3:Ab153融合物均具有明显高于单独Ab153的脑暴露量,且CH3C.35.23:Ab153在给药后1天时在脑中达到约36nM(图40B)。尽管血浆浓度类似,但所述CH3C.35.23.3:Ab153融合物可能由于对hTfR的亲和力比CH3.35.23:Ab153融合物低约3.5倍而使其最大脑吸收低于CH3.35.23:Ab153融合物。值得关注的是,由于亲和力较低的

融合物到第10天时提供较为持续的周围暴露量,因此其脑暴露量也高于亲和力较高的CH3C.35.23:Ab153融合物的脑暴露量。由此说明对于较低亲和力的TfR结合多肽-Fab融合物,较低脑C_{max}但随时间较高的持续PK存在平衡。相较于单独抗BACE1,在给与抗BACE1多肽融合物的小鼠的脑中观察到明显较低浓度的Aβ40(图40C)。这种Aβ40减少的持续时间与脑中huIgG1暴露量随时间的变化一致(图40B)。值得注意的是,给与CH3C.35:Ab153融合物的小鼠在单次剂量后7-10天仍展现持续的脑Aβ40减少。在给药后1天时,给与Ab153的小鼠与给与CH3C.35:Ab153融合物的小鼠之间的总脑TfR水平相当(图40D)。总体而言,这些数据展示,TfR结合多肽融合物在单次剂量后可增加抗BACE1的脑暴露量,由此明显减少脑Aβ40。

[0601] 实施例6.CH3C.18Fc和转铁蛋白受体顶端结构域结晶

[0602] 此实施例描述CH3C.18与转铁蛋白受体顶端结构域(TfR-AD)之间的结合界面的结晶和分析。

[0603] 表达

[0604] 在初始细胞密度为2.5×10^6个细胞/mL的Expi293细胞中表达人转铁蛋白受体顶端结构域(TfR-AD)和工程改造的人Fc(CH3C.18Fc)(分别为SEQ ID NO:104和105)。如果需要,以200mL或更高体积进行表达。转染后20小时,添加糖基化抑制剂Kifunensine,其最终浓度为25μM。转染后3至4天,当细胞活力明显降低时,收集表达培养物。

[0605] 纯化

[0606] 分别用蛋白质A和Ni-NTA树脂纯化表达的TfR-AD和CH3C.18Fc,随后在Superdex200 26/60凝胶过滤柱上进行尺寸排阻色谱法。

[0607] 使用以下缓冲液:

[0608] 蛋白质A洗涤缓冲液:20mM Hepes pH 7.4、100mM NaCl;

[0609] 蛋白质A洗脱缓冲液:30mM甘氨酸pH 2.5(洗脱物收集于含有1M Tris pH 9.0的管中以立即中和洗脱物);

[0610] Ni-NTA洗涤缓冲液:30mM Tris pH 8.0、10mM咪唑和200mM NaCl;

[0611] Ni-NTA洗脱缓冲液:30mM Tris pH 8.0、200mM NaCl和250mM咪唑;以及

[0612] 尺寸排阻缓冲液(SEC):30mM HEPES pH 7.5、200mM NaCl和3%甘油。

[0613] 复合物形成和纯化

[0614] 将纯化的TfR-AD和CH3C.18Fc与过量的顶端结构域混合,在室温下孵育1小时,并使用尺寸排阻色谱法,在Superdex200 26/60凝胶过滤柱上,使用先前提及的SEC缓冲液纯化所述复合物。尺寸排阻色谱得到所预期的两个主要峰:一个对应于所述复合物(保留体积=180ml)且另一个对应于过量的顶端结构域(保留体积=240ml)。通过考马斯(Coomassie)染色的SDS-PAGE凝胶分析峰部分(图29)。

[0615] 结晶

[0616] 利用沉滴气相扩散法,在15℃和室温(RT)下以8.5mg/mlL蛋白质浓度进行所述复合物的初始结晶筛选。在含有25%PEG 3350、0.1M Tris pH 8.5和0.2M $MgCl_2$的条件下观察到大量细针状晶体。在相同条件但在20%PEG 3350下,使用所述晶体接种以产生可安装尺寸的单一细针。

[0617] X射线数据收集

[0618] 使用补充有20%(v/v)乙二醇的结晶母液,通过直接浸入液氮中使晶体快速冷却。

使用Rayonix 300高速检测器,在先进光子源(Advanced Photon Source,APS)的SER-CAT射束线下收集X射线强度数据。晶体衍射至3.6 Å,并且属于六方晶系空间组$P6_4$且具有呈不对称单元的两个复合分子(表12)。使用程序HKL2000对数据编索引,积分并按比例缩放。将从两个晶体收集的数据合并以产生3.6 Å数据。

[0619] 表12.CH3C.18Fc-TfR-AD复合物结构的晶体数据

[0620]

名称/代码		CH3C.18 Fc-TfR-AD 复合物
晶胞尺寸	a (Å)	124.3
	b	124.3
	c	113.1
	α(°)	90.0
	β	90.0
	γ	120.0
空间组		$P6_4$
解析范围(Å)	整体	50–3.6
	最后一个壳	3.71-3.6
独特反射的次数		11,259
完整度(%)	(整体/最后一个壳)	95.9/74.1
$R_{合并}$[1]	(整体/最后一个壳)	20/93
精度统计	分辨率(Å)	50-3.6
	R因子[2]/R自由(%)	30/39

[0621] [1]$R_{合并}=\Sigma_j(|I_h-\langle I\rangle_h|)/\Sigma I_h$,其中$\langle I_h\rangle$施在对称等效物内的平均强度

[0622] [2]R因子$=\Sigma|F_{obs}-F_{calc}|/\Sigma|F_{obs}|$

[0623] 结构测定和精修

[0624] 通过利用PHASER的分子置换法,使用CH3C.18Fc二聚体和TFR-AD单体作为初始搜索模型来测定复合物的晶体结构。通过刚性体精修,随后使用REFMAC进行限制性精修,对模型进行精修。所有结晶学计算均利用CCP4程序包(www.ccp4.ac.uk/)进行。使用图形程序COOT构建所述复合物的电子密度模型。复合物分子的电子密度良好,尤其是在CH3C.18Fc-TfF-AD界面处(2Fo-Fc图谱等值线达到1.2δ水平)。在反复模型构建和精修之后,由于数据分辨率降低和CH2结构域失序,而观察到高R和自由R(R/自由R=0.30/0.39)。如在其他可用Fc结构中所见,CH2失序是因为CH2与CH3结构域之间存在柔性弯角。

[0625] 结合界面相互作用

[0626] CH3C.18Fc与TfR-AD之间的结合界面描绘于图30A-30B和图31A-31B中。如图32A-

32B中所示,在以下各残基之间观察到相互作用:

[0627] CH3C.18的Trp154与TfR-AD的Arg208;

[0628] CH3C.18的Glu155与TfR-AD的Arg208;

[0629] CH3C.18的Ser156与TfR-AD的Arg208和Leu212;

[0630] CH3C.18的Leu157与TfR-AD的Ser 199和Asn215;

[0631] CH3C.18的His159与TfR-AD的Lys188、Ser199和Arg208;

[0632] CH3C.18的Val160与TfR-AD的Gly207和Arg208;

[0633] CH3C.18的Trp161与TfR-AD的Arg208、Val210和Leu212;

[0634] CH3C.18的Ala162与TfR-AD的Arg208;

[0635] CH3C.18的Val163与TfR-AD的Leu209;

[0636] CH3C.18的Ser188与TfR-AD的Tyr211;

[0637] CH3C.18的Thr189与TfR-AD的Tyr211和Leu212;

[0638] CH3C.18的Gln192与TfR-AD的Lys158和Glu294;

[0639] CH3C.18的Trp194与TfR-AD的Leu212、Val213、Glu214和Asn215;以及

[0640] CH3C.18的Phe196与TfR-AD的Arg208。

[0641] 此外,如实施例2题为“互补位定位”的部分中所描述且如图32A-32B中所示,在CH3C定位区外的若干位置还参与结合至TfR。

[0642] 实施例7.CH3C.35Fc和转铁蛋白受体顶端结构域结晶

[0643] 此实施例描述CH3C.35与转铁蛋白受体顶端结构域(TfR-AD)之间的结合界面的结晶和分析。

[0644] 表达

[0645] 在初始细胞密度为2.5×10^{6}个细胞/mL的CHO细胞中表达人转铁蛋白受体顶端结构域(TfR-AD)和工程改造的人Fc(CH3C.35Fc)(分别为SEQ ID NO:104和181)。如果需要,以500mL或更高体积进行表达。转染后3至4天,当细胞活力明显降低时,收集表达培养物。

[0646] 纯化

[0647] 分别用蛋白质A(Genescript)和Ni-NTA(Sigma)树脂纯化表达的TfR-AD和CH3C.35Fc,随后在Superdex200 26/60凝胶过滤柱上进行尺寸排阻色谱。使用以下缓冲液:

[0648] 蛋白质A洗脱缓冲液:30mM甘氨酸pH 2.5(洗脱物收集于含有1M Tris pH 9.0的管中以立即中和洗脱物);

[0649] Ni-NTA洗脱缓冲液:30mM Tris pH 8.0、200mM NaCl和250mM咪唑;和

[0650] 尺寸排阻缓冲液(SEC):30mM HEPES pH 7.5、150mM NaCl、50mM KCl、3%甘油和0.01%叠氮化钠。

[0651] 复合物形成和纯化

[0652] 将纯化的TfR-AD和CH3C.35Fc与过量的顶端结构域混合,在室温下孵育1小时,并使用尺寸排阻色谱法,在Superdex200 26/60凝胶过滤柱上,使用先前提及的SEC缓冲液纯化所述复合物。

[0653] 结晶

[0654] 利用沉滴气相扩散法,在4℃、15℃和室温(RT)下进行所述复合物的初始结晶筛选。在含有25%PEG 3350、0.1M Bis-Tris pH 6.5和0.2M $LiSO_4$的条件下观察到大量细针

状晶体。在相同条件但使用20％PEG 3350下,使用所述晶体接种以产生单一细针且依序重复接种四次以产生可安装尺寸的晶体。

[0655] X射线数据收集

[0656] 使用补充有20％(v/v)乙二醇的结晶母液,通过直接浸入液氮中使晶体快速冷却。使用PILATUS检测器,在钻石光源(Diamond Light Source,DLS)的I04射束线下收集X射线强度数据。使用尺寸为5微米的聚焦微束进行数据收集。晶体衍射至3.38 Å,且属于六方晶系空间组$P6_4$且具有呈不对称单元的两个复合分子(表13)。使用CCP4软件包(Xia2-XDS和XSCALE)对数据编索引,积分并按比例缩放。

[0657] 表13.CH3C.35Fc-TfR-AD复合物结构的晶体数据

[0658]

名称/代码		CH3C.35 Fc-TfR-AD 复合物
晶胞尺寸	a (Å)	126.4
	b	126.4
	c	113.8
	α(°)	90.0
	β	90.0
	γ	120.0

[0659]

名称/代码		CH3C.35 Fc-TfR-AD 复合物
空间组		$P6_4$
解析范围(Å)	整体	50–3.38
	最后一个壳	3.44-3.38
独特反射的次数		14,541
完整度(%)	(整体/最后一个壳)	100/99.7
$R_{合并}$[1]	(整体/最后一个壳)	31/152
精度统计	分辨率(Å)	50-3.38
	R 因子[2]/R 自由(%)	27/35

[0660] [1]$R_{合并}=\Sigma_j(|I_h-\langle I\rangle_h|)/\Sigma I_h$,其中$\langle I_h\rangle$是在对称等效物内的平均强度

[0661] [2]R因子$=\Sigma|F_{obs}-F_{calc}|/\Sigma|F_{obs}|$

[0662] 结构测定和精修

[0663] 通过利用PHASER的分子置换法,使用CH3C.35Fc-AD TfR复合物作为搜索模型来测定复合物的晶体结构。通过刚性体精修,随后使用REFMAC进行限制性精修,对模型进行精修。所有结晶学计算均利用CCP4程序包进行。使用图形程序COOT构建所述复合物的电子密度模型。所述复合物分子的电子密度良好,尤其是在CH3C.35Fc-TfF-AD界面处。

[0664] 结合界面相互作用

[0665] CH3C.35Fc与TfR-AD之间的结合界面描绘于图34A-34C中。图34A示出CH3C.35Fc与

TfR-AD的复合物在3.4 Å处。图34B示出TfR-AD中的残基L209、L212和Y211使CH3C.35Fc中的残基W161稳定。图34C示出作为主要结合相互作用的CH3C.35Fc中的残基E160与TfR-AD中的残基R208之间的盐桥,其可部分引起Fc多肽与人TfR(在208位的Arg)和与食蟹猴TfR(在208位Gly)的结合亲和力的差异。图35A示出CH3C.35Fc/TfR-AD复合物与CH3C.18Fc/TfR-AD复合物(如实施例6中所述)之间的重叠结构,展示CH3C.35与CH3C.18之间不存在明显Fc主链构象变化。图35B示出图35A中的重叠结构的放大图。CH3C.35Fc/TfR-AD复合物的TfR-AD中的残基206-212呈现的构象不同于CH3C.18Fc/TfR-AD复合物的TfR-AD中的残基。TfR-AD中的残基R208看起来埋在CH3C.18Fc/TfR-AD复合物的表面下,而在CH3C.35Fc/TfR-AD复合物中看起来暴露于溶剂。另外,CH3C.35Fc/TfR-AD复合物的TfR-AD中的残基L209看起来旋转180°且结合至表面,而在CH3C.18Fc/TfR-AD复合物中看起来远离表面。

[0666] 如图36A和36B中所示,在以下残基之间观察到相互作用:

[0667] CH3C.35的Thr159与TfR-AD的Gly207、Arg208、Lys188和Leu209;

[0668] CH3C.35的Glu160与TfR-AD的Arg208和Leu209;

[0669] CH3C.35的Ser162与TfR-AD的Arg208和Leu209;

[0670] CH3C.35的Ser156与TfR-AD的Leu209;

[0671] CH3C.35的Trp161与TfR-AD的Leu209、Tyr211和Leu212;

[0672] CH3C.35的Glu189与TfR-AD的Tyr211和Leu212;

[0673] CH3C.35的Phe194与TfR-AD的Leu212、Asn215和Val213;

[0674] CH3C.35的Tyr157与TfR-AD的Leu212、Asn215和Ser199;

[0675] CH3C.35的Gln192与TfR-AD的Val213和Lys158;以及

[0676] CH3C.35的Phe196与TfR-AD的Val213和Leu212。

[0677] 此外,如实施例2题为“互补位定位”的部分中所描述且如图36A和36B中所示,在CH3C定位区外的若干位置也参与结合至TfR。

[0678] 实施例8.包含CH3C变体的Fc-Fab融合物多肽在食蟹猴中的药物动力学/药效学研究

[0679] 此实施例描述包含本发明的CH3C变体多肽的Fc-Fab融合物在食蟹猴中的药物动力学/药效学(PK/PD)特征。

[0680] 研究设计

[0681] 在29天疗程中,向2-4岁的雄性食蟹猴静脉内施用单次30mg/kg剂量的Ab122(作为对照IgG的抗RSV抗体)、Ab153(抗BACE1抗体)、Ab210(抗TfR/BACE1双特异性抗体)或包含与Ab153 Fab结构域融合的CH3C变体多肽的Fc-Fab融合多肽以评价血浆PK、血浆PD(Aβ40)和脑脊髓液(CSF)PD(Aβ40)(n=4只/组)。为了确定基线,在给药前7天,从每只动物取得给药前CSF和血液样品。给药后,在给药后12小时、24小时、48小时、72小时和96小时,以及对于PD分析在研究日第8天、第11天、第15天、第18天、第22天、第25天和第29天,经由IT-L导管收集CSF。在给药后0.25小时、1小时、6小时、12小时、24小时、72小时,以及在研究日第8天、第11天、第15天、第18天、第22天、第25天和第29天,收集血液样品进行血浆和血清PK研究。

[0682] 表14显示出研究设计的概述。“CH3C.35.21.16:Ab153”使包含与Ab153 Fab结构域融合的克隆CH3C.35.21.16的单价Fc-Fab融合多肽。“CH3C.35.21:Ab153”是包含与Ab153 Fab结构域融合的克隆CH3C.35.21的单价Fc-Fab融合多肽。“CH3C.35.9:Ab153”是包含与

Ab153 Fab结构域融合的克隆CH3C.35.21的二价Fc-Fab融合多肽。“CH3C.35.8:Ab153”是包含与Ab153 Fab结构域融合的克隆CH3C.35.20的二价Fc-Fab融合多肽。“LALAPG”指示抗体或Fc-Fab融合多肽在Fc序列中含有突变L7A、L8A和P102G(参照SEQ ID NO:1编号)。“LALAPG.YTE”指示Fc-Fab融合多肽在Fc序列中含有突变L7A、L8A、P102G、M25Y、S27T和T29E(参照SEQ ID NO:1编号)。

[0683] 表14

[0684]

处理	同种型	食蟹猴 TfR 全长亲和力 (nM)	食蟹猴 TfR 顶端结构域亲和力(nM)	剂量	N	材 料 (mg)
Ab122 (对照 IgG)	huIgG1.LALAPG	--		30	4	750
Ab153	huIgG1.LALAPG	--		30	4	750
Ab210	huIgG1.LALAPG	52	140	30	4	750
CH3C.35.21.16:Ab153 (单价)	huIgG1.LALAPG	1800	1900	30	4	750
CH3C.35.21.16:Ab153 (单价)	huIgG1.LALAPG.YTE	1800	1900	30	4	750
CH3C.35.21:Ab153 (单价)	huIgG1.LALAPG.YTE	2100	2200	30	4	750
CH3C.35.9:Ab153 (二价)	huIgG1.LALAPG.YTE	700		30	4	750
CH3C.35.8:Ab153 (二价)	huIgG1.LALAPG.YTE	1700		30	4	750

[0685] 方法

[0686] 人IgG PK测定

[0687] 使用人IgG特异性夹心ELISA定量食蟹猴血清中抗体或Fc-Fab融合多肽的浓度。用对人IgG Fc具有特异性的抗体包被384孔MaxiSorp板过夜。血清样品以1:100、1:1,000、1:10,000和1:100,000稀释且添加至封闭的板中。检测抗体是多克隆抗人IgG猴吸收的抗体。单独制备各抗体或Fc-Fab融合多肽的标准曲线(48-200,000pg/mL IgG)且测定在血清中的定量下限(LLOQ)是20ng/mL。

[0688] PD测定

[0689] 使用MesoScale Discovery(MSD)多重药盒(MSD#K15120E)测量食蟹猴CSF中的可溶性APPα/β水平。两种不同的抗体特异性捕获sAPPα或sAPPβ,且然后利用SULFO标签标记的抗APP小鼠单克隆抗体检测两种分析物。使用MSD超灵敏药盒(MSD#K151FTE)测量食蟹猴Aβ40水平。这种测定使用huAβ特异性6E10抗体作为捕获物且对所述肽的C末端具有特异性的抗Aβ40抗体作为检测分子。两项测定均根据制造商的说明书进行。简言之,用MSD封闭剂A封闭预包被板1分钟。CSF样品以1:5稀释且一式两份添加至封闭的板中,随后在4℃下孵育过夜。接下来,添加对应的检测抗体并在Sector S600仪器上读取板。使用四参数逻辑回归法

拟合标准曲线,对于huAβ40为0.92-3750pg/mL且对于sAPPα/β两者为0.1-100ng/mL。所述测定对于Aβ40的LLOQ为73pg/mL且对于sAPPα/β的LLOQ为0.5ng/mL。

[0690] 结果

[0691] 来自给药后前7天的中期血清PK显示,Ab210和CH3C.35.9:Ab153因其结合至周围中的TfR而具有预期的靶标介导的清除率(图37A)。Ab153和Ab210抗体以及CH3C.35.9:Ab153使血浆Aβ40相较于对照IgG有明显且持续的减少(图37B),从而证实全部三个分子均能够在体内以类似程度抑制BACE1活性。在CSF中,Ab210和CH3C.35.9:Ab153能够使CSF Aβ40和sAPPβ/sAPPα比率相较于对照IgG分别减少约70%和约75%(图38A和38B)。相较于对照IgG,Ab153(一种不结合TfR的抗BACE1抗体)对CSF Aβ40和sAPPβ/sAPPα比率显示极小影响。这些结果展示,以CH3C变体多肽(例如克隆CH3C.35.9)结合至TfR使包含与抗BACE1抗体Fab结构域融合的CH3C变体多肽的Fc-Fab融合物(例如CH3C.35.9:Ab153)的CNS渗透性增强,由此抑制CSF Aβ40和sAPPβ/sAPPα产生。

[0692] 在单次剂量后,还评价血清PK、血浆Aβ和CSF Aβ水平,持续四周。与在小鼠中观察到的情形类似,TfR结合Fc-Fab融合物(CH3C.35.21.16:Ab153 LALAPG、CH3C.35.21.16:Ab153 LALAPGYTE和CH3C.35.21:Ab153 LALAPGYTE)的周围血清PK因结合至周围组织上的TfR而展现比Ab122和Ab153快的清除率(图41A)。Ab153和CH3C:Ab153融合物使血浆Aβ水平相较于对照IgG_Ab122减少超过约50%(图41B)。Ab153与CH3C:Ab153融合物的最大Aβ类似,从而表明Fc修饰不影响抗BACE1 Fab在体内抑制APP裂解的能力(图41B)。血浆Aβ的持续时间与Ab153和CH3C:Ab153随时间的暴露量相关。在CSF中,全部三种Fc-Fab融合物能够使Aβ40和sAPPβ/sAPPα比率相较于对照IgG_Ab122明显减少至约70%,而在给与A b153的动物中未观察到显著减少(图41C和41D)。这些结果展示,以CH3C变体多肽(例如克隆CH3C.35.21.16和CH3C.35.21)结合至TfR使包含与抗BACE1抗体Fab结构域融合的CH3C变体多肽的Fc-Fab融合物(例如CH3C.35.21.16:Ab153和CH3C.35.21:Ab153)的CNS渗透性增强,由此抑制CSF Aβ40和sAPPβ/sAPPα产生。

[0693] 由于不成熟红细胞上TfR的表达水平较高,所以在整个研究过程中评价外周血临床病理学以评价网织红细胞数量、血清铁和红细胞计数。血清铁水平评估利用了使用TPTZ[2,4,6-三(2-吡啶基)-5-三嗪]作为色原体的方法的变化。在酸性介质中,转铁蛋白结合的铁解离成游离三价铁离子和载脂转铁蛋白。盐酸和抗坏血酸钠将三价铁离子还原成亚铁状态。亚铁离子然后与TPTZ反应形成蓝色复合物,所述复合物在600/800nm下以双色法测量。吸光度增加与存在的转铁蛋白结合的铁的量成正比。这在Beckman/Olympus AU640e化学分析仪上进行。利用Siemens Advia 120自动血液系统分析绝对网织红细胞和RBC形态。相较于给药前值,Fc-Fab融合物对网织红细胞数量无影响(图42A)。另外,血清铁以及红细胞数量也不受影响(图42B和42C)。总的说来,这些数据指示,经修饰的TfR结合Fc多肽-Fab融合物可安全且有效地增加非人灵长类动物中抗体的脑暴露量以产生稳健药效学反应(即,CSF Aβ减少)。

[0694] 实施例9.含有M201L和N207S突变的CH3C.35的药物动力学分析

[0695] 此实施例描述突变M201L和N207S与CH3C.35相容。

[0696] 为了评价增加血清稳定性的突变,如参照SEQ ID NO:1编号的M201L和N207S(根据EU编号的M428L/N434S;还称为"LS"突变)是否与TfR结合Fc修饰相容,向人FcRn基因敲入小

鼠给与10mg/kg的Ab153_LALAPG、Ab153_LALA.LS、CH3C.35.21:Ab153_LALA.LS或Ab153_LALAPG.YTE。14天内血浆PK评价显示,Ab153_LALA.LS、CH3C.35.21:Ab153_LALA.LS和Ab153_LALAPG.YTE相较于无任何血清稳定性突变的Ab153_LALAPG有类似约2倍改善(图43A和43B)。由此指示,用于TfR结合的另外Fc突变不影响LS突变改善体内huIgG1半衰期的能力。

[0697] 实施例10.CH3C.35.21的单一氨基酸取代

[0698] 此实施例描述CH3C.35.21单一氨基酸突变体的文库的构建。

[0699] 方法

[0700] 使用Kunkel诱变构建各自含有CH3C.35.21的单一氨基酸取代的CH3C.35.21突变体文库(Kunkel,Proc Natl Acad Sci U S A.82(2):488-92,1985)。对于CH3C.35.21的各位置,使用简并致突变寡核苷酸,使如根据SEQ ID NO:1编号的W153、Y157、T159、E160、W161、S162、S163、K165、T186、K187、E188、E189、F194、S197和S199(如根据EU编号方案所编号,W380、Y384、T386、E387、W388、S389、S390、K392、T413、K414、E415、E416、F421、S424和S426)单独地突变成密码子NNK。为避免在文库中获得原始CH3C.35.21克隆,使用单链DNA(ssDNA)Kunkel模板编码野生型IgG1 Fc。组合使用两个致突变寡核苷酸(其中一个具有NNK且另一个编码另一CH3C.35.21区),由此当并入两个寡核苷酸时,其产生CH3C.35.21氨基酸序列,但在所需文库位置处具有NNK密码子。由于模板是野生型Fc,所以单一寡核苷酸插入或无寡核苷酸插入将不结合TfR,因此这些构建体易于从任何分析中除去。类似地,来源于NNK位置的终止密码子被排除。将文库转染至EBY100酵母中。对来自各文库的八个集落进行测序以确保天然文库含有所需位置随机突变。

[0701] 在TfR浓度下收集通过酵母展示和流式细胞术测量的大约前10%的呈环形排列的TfR顶端结构域结合群体,由此提供用于区别亲和力的最佳范围。获得12个克隆各位置的序列。对于具有独特群体的文库,利用更好界定的高、中等、低门控进行类似实验。对每个收集的群体的36个克隆进行测序。另外,为了比较突变体与在相应氨基酸位置处具有野生型残基的相应突变体的结合,使用致突变寡核苷酸以类似方法,使所述位置处的氨基酸回复突变成野生型IgG1残基。

[0702] 表15显示CH3C.35.21突变体的文库。每一突变体含有CH3C.35.21的单一氨基酸取代。举例而言,一个突变体可含有W380E且其余位置的氨基酸与CH3C.35.21中的那些氨基酸相同。表15中显示的位置是根据EU编号方案编号。

[0703] 表15.CH3C.35.21单一氨基酸突变体

[0704]

位置	380	384	386	387	388	389	390	413	415	416	421	424	426
野生型 Fc	E	N	Q	P	E	N	N	D	S	R	N	S	S
CH3C.35.21	W	Y	T	E	W	S	S	T	E	E	F	S	S
发现具有在以下范围内的亲和力的残基:<190nM 至约 500 nM	ELSVWY	YFMPVW	TNV	EIPV	W	SAITV	SNRT	THS	SDGTPQR	ER	FHKY	STW	SCPMW

[0705] 实施例11.CH3C.18变体的构建

[0706] 此实施例描述CH3C.18变体的文库的构建。

[0707] 分离单一克隆,且使其在补充有0.2%葡萄糖的SG-CAA培养基中生长过夜以诱导CH3C.18变体的表面表达。对于每一克隆,在pH7.4的PBS+0.5%BSA中洗涤两百万个细胞三次。在4℃下,用生物素化靶、250nM人TfR、250nM食蟹猴TfR或250nM不相关的生物素化的蛋白质对细胞染色,在振荡下保持1小时,然后用相同缓冲液洗涤两次。在4℃下,用中性抗生物素蛋白-Alexafluor647(AF647)对细胞染色,保持30分钟,然后再洗涤两次。使用抗c-myc抗体和抗鸡-Alexfluor488(AF488)第二抗体测量表达水平。使细胞再悬浮,并在BD FACS CantoII上测量AF647和AF488的中值荧光强度(MFI)。计算每一群体的TfR结合群体的MFI并关于人TfR、食蟹猴TfR或对照结合作图(图44)。

[0708] 表16显示CH3C.18变体的文库。每一列表示在各位置处含有指定氨基酸取代的变体且其余位置的氨基酸与CH3C.18中的氨基酸相同。表16中显示的位置是根据EU编号方案编号。

[0709] 表16.CH3C.18变体

[0710]

位置	384	386	387	389	390	391	413	416	421
野生型 Fc	N	Q	P	N	N	Y	D	R	N
CH3C.4 (CH3C.18.1)	V	T	P	A	L	Y	L	E	W
CH3C.2 (CH3C.18.2)	Y	T	V	S	H	Y	S	E	Y
CH3C.3 (CH3C.18.3)	Y	T	E	S	Q	Y	E	D	H
CH3C.1 (CH3C.18.4)	L	L	V	V	G	Y	A	T	W
CH3C.18 (CH3C.18.1.18)	L	H	V	A	V	Y	P	T	W
CH3C.3.1-3 (CH3C.18.3.1-3)	L	H	V	V	A	T	P	T	W
CH3C.3.1-9 (CH3C.18.3.1-9)	L	P	V	V	H	T	P	T	W
CH3C.3.2-1 (CH3C.18.3.2-1)	L	H	V	V	N	F	P	T	W

[0711]

位置	384	386	387	389	390	391	413	416	421
CH3C.3.2-5 (CH3C.18.3.2-5)	L	H	V	V	D	Q	P	T	W
CH3C.3.2-19 (CH3C.18.3.2-19)	L	H	V	V	N	Q	P	T	W
CH3C.3.4-1 (CH3C.18.3.4-1)	W	F	V	S	T	T	P	N	F
CH3C.3.4-19 (CH3C.18.3.4-19)	W	H	V	S	T	T	P	N	Y
CH3C.3.2-3 (CH3C.18.3.2-3)	L	H	V	V	E	Q	P	T	W
CH3C.3.2-14 (CH3C.18.3.2-14)	L	H	V	V	G	V	P	T	W
CH3C.3.2-24 (CH3C.18.3.2-24)	L	H	V	V	H	T	P	T	W
CH3C.3.4-26 (CH3C.18.3.4-26)	W	T	V	G	T	Y	P	N	Y
CH3C.3.2-17 (CH3C.18.3.2-17)	L	H	V	V	G	T	P	T	W

[0712] 如果出现矛盾,表(例如表4)中描述的各克隆的氨基酸取代指示在所述克隆的定位区位置处的氨基酸取代,而非序列表中列出的序列中所见的氨基酸。

[0713] 应了解,本文所述的实施例和实施方案仅出于说明的目的,并且本领域的技术人

员将提出根据所述实施例和实施方案的各种修改或改变,并且所述修改和改变均包括在本申请的精神和范围以及随附权利要求的范围内。本文引用的序列登录号的序列特此以引用的方式并入。

[0714] 表1.CH3C定位区位置和突变

[0715]

序列名称	序列组	157	158	159	160	161	162	163	164	…	186	187	188	189	190	191	192	193	194
野生型	n/a	N	G	Q	P	E	N	N	Y	…	D	K	S	R	W	Q	Q	G	N
CH3C.1		L	G	L	V	W	V	G	Y	…	A	K	S	T	W	Q	Q	G	W
CH3C.2		Y	G	T	V	W	S	H	Y	…	S	K	S	E	W	Q	Q	G	Y
CH3C.3		Y	G	T	E	W	S	Q	Y	…	E	K	S	D	W	Q	Q	G	H
CH3C.4		V	G	T	P	W	A	L	Y	…	L	K	S	E	W	Q	Q	G	W
CH3C.17	2	Y	G	T	V	W	S	K	Y	…	S	K	S	E	W	Q	Q	G	F
CH3C.18	1	L	G	H	V	W	A	V	Y	…	P	K	S	T	W	Q	Q	G	W
CH3C.21	1	L	G	L	V	W	V	G	Y	…	P	K	S	T	W	Q	Q	G	W
CH3C.25	1	M	G	H	V	W	V	G	Y	…	D	K	S	T	W	Q	Q	G	W
CH3C.34	1	L	G	L	V	W	V	F	S	…	P	K	S	T	W	Q	Q	G	W
CH3C.35	2	Y	G	T	E	W	S	S	Y	…	T	K	S	E	W	Q	Q	G	F
CH3C.44	2	Y	G	T	E	W	S	N	Y	…	S	K	S	E	W	Q	Q	G	F
CH3C.51	1/2	L	G	H	V	W	V	G	Y	…	S	K	S	E	W	Q	Q	G	W
CH3C.3.1-3	1	L	G	H	V	W	V	A	T	…	P	K	S	T	W	Q	Q	G	W
CH3C.3.1-9	1	L	G	P	V	W	V	H	T	…	P	K	S	T	W	Q	Q	G	W
CH3C.3.2-5	1	L	G	H	V	W	V	D	Q	…	P	K	S	T	W	Q	Q	G	W
CH3C.3.2-19	1	L	G	H	V	W	V	N	Q	…	P	K	S	T	W	Q	Q	G	W
CH3C.3.2-1	1	L	G	H	V	W	V	N	F	…	P	K	S	T	W	Q	Q	G	W
CH3C.3.4-1		W	G	F	V	W	S	T	Y		P	K	S	N	W	Q	Q	G	F
CH3C.3.4-19		W	G	H	V	W	S	T	Y		P	K	S	N	W	Q	Q	G	Y
CH3C.3.2-3		L	G	H	V	W	V	E	Q		P	K	S	T	W	Q	Q	G	W
CH3C.3.2-14		L	G	H	V	W	V	G	V		P	K	S	T	W	Q	Q	G	W
CH3C.3.2-24		L	G	H	V	W	V	H	T		P	K	S	T	W	Q	Q	G	W
CH3C.3.4-26		W	G	T	V	W	G	T	Y		P	K	S	N	W	Q	Q	G	Y
CH3C.3.2-17		L	G	H	V	W	V	G	T		P	K	S	T	W	Q	Q	G	W

[0716]

[0717] 表4.有关CH3C.35.21的定位区和热点位置内可接受的多样性的研究

[0718]

	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165		184	185	186	187	188	189	190	191	192	193	194	195	196
野生型	A	V	E	W	E	S	N	G	Q	P	E	N	N	Y	K		T	V	D	K	S	R	W	Q	Q	G	N	V	F
CH3C.35.20.1	.	.	.	.	.	.	F	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.20.2	.	.	.	.	.	.	Y	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.20.3	.	.	.	.	.	.	Y	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.20.4	.	.	.	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	S	.	E	E	.	.	.	.	F	.	.
CH3C.35.20.5	.	.	.	.	.	.	F	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.20.6	.	.	.	.	.	.	F	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.1	.	.	W	.	.	.	F	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.2	.	.	W	.	.	.	Y	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.3	.	.	W	.	.	.	Y	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.4	.	.	W	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	S	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.5	.	.	W	.	.	.	F	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.a.6	.	.	W	.	.	.	F	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.1	.	.	.	.	.	.	F	.	T	E	W	S	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.2	.	.	.	.	.	.	Y	.	T	E	W	A	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.3	.	.	.	.	.	.	Y	.	T	E	W	V	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.4	.	.	.	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	S	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.5	.	.	.	.	.	.	F	.	T	E	W	A	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.23.6	.	.	.	.	.	.	F	.	T	E	W	V	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.1	.	.	W	.	.	.	F	.	T	E	W	S	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.2	.	.	W	.	.	.	Y	.	T	E	W	A	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.3	.	.	W	.	.	.	Y	.	T	E	W	V	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.4	.	.	W	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	S	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.5	.	.	W	.	.	.	F	.	T	E	W	A	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24.6	.	.	W	.	.	.	F	.	T	E	W	V	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.1	.	.	L	.	.	.	F	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.2	.	.	L	.	.	.	Y	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.3	.	.	L	.	.	.	Y	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.4	.	.	L	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	S	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.5	.	.	L	.	.	.	F	.	T	E	W	A	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17.6	.	.	L	.	.	.	F	.	T	E	W	V	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.20	.	.	.	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21	.	.	W	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.22	.	.	W	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	T	.	.	E	.	.	.	.	F	.	.
CH3C.35.23	.	.	.	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.24	.	.	W	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.21.17	.	.	L	.	.	.	Y	.	T	E	W	S	S	.	.		.	.	T	.	E	E	.	.	.	.	F	.	.
CH3C.35.N390	.	.	.	.	.	.	Y	.	T	E	W	S	.	.	.		.	.	T	.	.	E	.	.	.	.	F	.	.
CH3C.35.20.1.1							F		T	E	W	S	S						S		E	E					F		
CH3C.35.23.2.1							Y		T	E	W	A							S			E					F		
CH3C.35.23.1.1							F		T	E	W	S							S		E	E					F		
CH3C.35.S413							Y		T	E	W	S	S						S			E					F		
CH3C.35.23.3.1							Y		T	E	W	V							S		E	E					F		
CH3C.35.N390.1							Y		T	E	W	S							S			E					F		
CH3C.35.23.6.1							F		T	E	W	V							S		E	E					F		

[0719] 非正式序列表

[0720]

SEQ ID NO:	序列	描述
1	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK	野生型人 Fc 序列 氨基酸 1-3 (PCP)是来自铰链区

[0721]

SEQ ID NO:	序列	描述
2	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAK	CH2 结构域序列，包括在铰链区的 N 末端的三个氨基酸(PCP)
3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	CH3 结构域序列
4	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGLVWVGYKTTPPV LDSDGSFFLYSKLTVAKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.1 (克隆 CH3C.18.4)
5	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTVWSHYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGYVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.2 (克隆 CH3C.18.2)
6	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSQYKTTPPVL DSDGSFFLYSKLTVEKSDWQQGHVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.3 (克隆 CH3C.18.3)
7	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESVGTPWALYKTTPPVL DSDGSFFLYSKLTVLKSEWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.4 (克隆 CH3C.18.1)
8	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTVWSKYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.17
9	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWAVYKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18 (克隆 CH3C.18.1.18)

[0722]

SEQ ID NO:	序列	描述
10	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGLVWVGYKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.21
11	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESMGHVWVGYKTTPPV LDSDGSFFLYSKLTVDKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.25
12	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGLVWVFSKTTPPVL DSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.34
13	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35
14	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.44
15	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVGYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.51
16	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVATKTTPPVL DSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.3.1-3 (克隆 CH3C.18.3.1-3)

[0723]

SEQ ID NO:	序列	描述
17	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGPVWVHTKTTPPVL DSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.3.1-9 (克隆 CH3C.18.3.1-9)
18	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVDQKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.3.2-5 (克隆 CH3C.18.3.2-5)
19	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVNQKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.3.2-19 (克隆 CH3C.18.3.2-19)
20	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVNFKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.3.2-1 (克隆 CH3C.18.3.2-1)
21	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESLGHVWAVYKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.E153W (CH3C.35.13)
22	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWAVYQTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.K165Q (CH3C.35.14)
23	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESLGHVWAVYQTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.E153W. K165Q (CH3C.35.15)

[0724]

SEQ ID NO:	序列	描述
24	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.E153W (CH3C.35.19)
25	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.S188E (CH3C.35.20)
26	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.E153W. S188E (CH3C.35.21)
27	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.N163
28	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYQTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.K165Q
29	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYQTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.N163. K165Q
30	NSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGK LVHANFGTKKDFEDLYTPVNGSIVIVRAGKITFAE KVANAESLNAIGVLIYMDQTKFPIVNAELSFFGHA HLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTI SRAAAEKLFGNMEGDCPSDWKTDSTCRMVTSES KNVKLTVS	人 TfR 顶端结构域

[0725]

SEQ ID NO:	序列	描述
31	NSVIIVDKNGGLVYLVENPGGYVAYSKAATVTGK LVHANFGTKKDFEDLDSPVNGSIVIVRAGKITFAE KVANAESLNAIGVLIYMDQTKFPIVKADLSFFGH AHLGTGDPYTPGFPSFNHTQFPPSQSSGLPNIPVQ TISRAAAEKLFGNMEGDCPSDWKTDSTCKMVTS ENKSVKLTVS	食蟹猴 TfR 顶端结构域
32	SSGLPNIPVQTISRAAAEKLFGNMEGDCPSDWKT DSTCRMVTSESKNVKLTVSNDSAQNSVIIVDKNG RLVYLVENPGGYVAYSKAATVTGKLVHANFGTK KDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLN AIGVLIYMDQTKFPIVNAELSGP	展示于噬菌体上的环截短的人 TfR 顶端结构域
33	SSGLPNIPVQTISRAAAEKLFGNMEGDCPSDWKT DSTCKMVTSENKSVKLTVSNDSAQNSVIIVDKNG GLVYLVENPGGYVAYSKAATVTGKLVHANFGTK KDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLN AIGVLIYMDQTKFPIVKADLSGP	展示于噬菌体上的环截短的食蟹猴 TfR 顶端结构域
34	WESXGXXXXXYK	第一部分 CH3C 定位区
35	TVXKSXWQQGXV	第二部分 CH3C 定位区
36	YGTEW	CH3C 保守序列
37	EPKSCDKTHTCPPCP	人 IgG1 铰链氨基酸序列
38	MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDN SHVEMKLAVDEEENADNNTKANVTKPKRCSGSI CYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERL AGTESPVREEPGEDFPAARRLYWDDLKRKLSEKL DSTDFTGTIKLLNENSYVPREAGSQKDENLALYV ENQFREFKLSKVWRDQHFVKIQVKDSAQNSVIIV DKNGRLVYLVENPGGYVAYSKAATVTGKLVHAN FGTKKDFEDLYTPVNGSIVIVRAGKITFAEKVANA ESLNAIGVLIYMDQTKFPIVNAELSFFGHAHLGTG DPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAA EKLFGNMEGDCPSDWKTDSTCRMVTSESKNVKL TVSNVLKEIKILNIFGVIKGFVEPDHYVVVGAQRD AWGPGAAKSGVGTALLLKLAQMFSDMVLKDGF QPSRSIIFASWSAGDFGSVGATEWLEGYLSSLHLK AFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQN VKHPVTGQFLYQDSNWASKVEKLTLDNAAFPFLA YSGIPAVSFCFCEDTDYPYLGTTMDTYKELIERIPE LNKVARAAAEVAGQFVIKLTHDVELNLDYERYNS QLLSFVRDLNQYRADIKEMGLSLQWLYSARGDFF RATSRLTTDFGNAEKTDRFVMKKLNDRVMRVEY HFLSPYVSPKESPFRHVFWGSGSHTLPALLENLKL RKQNNGAFNETLFRNQLALATWTIQGAANALSG DVWDIDNEF	人转铁蛋白受体蛋白 1 (TFR1)

[0726]

SEQ ID NO:	序列	描述
39	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.19
40	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20
41	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21
42	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.22
43	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23
44	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24
45	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESLGHVWAVYKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	CH3C.18 变体

[0727]

SEQ ID NO:	序列	描述
46	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESLGHVWAVYKTTPPVL DSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	CH3C.18 变体
47	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVYWESLGHVWAVYKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	CH3C.18 变体
48	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWAVYQTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	CH3C.18 变体
49	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWAVYFTTPPVL DSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHEA LHNHYTQKSLSLSPGK	CH3C.18 变体
50	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWAVYHTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	CH3C.18 变体
51	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.1
52	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.2

[0728]

SEQ ID NO:	序列	描述
53	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.3
54	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTGEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.4
55	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFSCWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.5
56	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.6
57	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFTCWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.7
58	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFTCGVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.8
59	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFECWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.9

[0729]

SEQ ID NO:	序列	描述
60	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTREEWQQGFVFKCWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.10
61	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTPEEWQQGFVFKCWVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.11
62	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYRTTPPV LDSDGSFFLYSKLTVTREEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.12
63	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYRTTPPV LDSDGSFFLYSKLTVTGEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.13
64	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYRTTPPV LDSDGSFFLYSKLTVTREEWQQGFVFTCWVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.35.21.14
65	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYRTTPPV LDSDGSFFLYSKLTVTGEEWQQGFVFTCWVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.35.21.15
66	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYRTTPPV LDSDGSFFLYSKLTVTREEWQQGFVFTCGVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.16

[0730]

SEQ ID NO:	序列	描述
67	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17
68	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYRTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.18
69	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.1
70	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWASYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.2
71	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWVSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.3
72	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.4
73	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWASYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.5

[0731]

SEQ ID NO:	序列	描述
74	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWVSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.6
75	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C35.21.a.1
76	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.a.2
77	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWVSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.a.3
78	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.a.4
79	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.a.5
80	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWVSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.21.a.6

[0732]

SEQ ID NO:	序列	描述
81	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.1
82	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.23.2
83	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.23.3
84	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.4
85	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWANYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.5
86	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWVNYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.6
87	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.1

[0733]

SEQ ID NO:	序列	描述
88	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.2
89	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.3
90	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.4
91	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWANYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.5
92	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESFGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.24.6
93	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.1
94	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWASYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.2

[0734]

SEQ ID NO:	序列	描述
95	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWVSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.3
96	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.4
97	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESFGTEWASYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.5
98	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESFGTEWVSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.21.17.6
99	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVTKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.N390
100	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESLGHVWVNQKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.35.16
101	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVNQQTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.35.17

[0735]

SEQ ID NO:	序列	描述
102	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESLGHVWVNQQTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.35.18
103	MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDN SHVEMKLGVDEEENTDNNTKANGTKPKRCGGNI CYGTIAVIIFFLIGFMIGYLGYCKGVEPKTECERLA GTESPAREEPEEDFPAAPRLYWDDLKRKLSEKLD TTDFTSTIKLLNENLYVPREAGSQKDENLALYIEN QFREFKLSKVWRDQHFVKIQVKDSAQNSVIIVDK NGGLVYLVENPGGYVAYSKAATVTGKLVHANFG TKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAES LNAIGVLIYMDQTKFPIVKADLSFFGHAHLGTGD PYTPGFPSFNHTQFPPSQSSGLPNIPVQTISRAAAE KLFGNMEGDCPSDWKTDSTCKMVTSENKSVKLT VSNVLKETKILNIFGVIKGFVEPDHYVVVGAQRD AWGPGAAKSSVGTALLLKLAQMFSDMVLKDGF QPSRSIIFASWSAGDFGSVGATEWLEGYLSSLHLK AFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQD VKHPVTGRSLYQDSNWASKVEKLTLDNAAFPFLA YSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERIP ELNKVARAAAEVAGQFVIKLTHDTELNLDYERYN SQLLLFLRDLNQYRADVKEMGLSLQWLYSARGD FFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRV EYYFLSPYVSPKESPFRHVFWGSGSHTLSALLESL KLRRQNNSAFNETLFRNQLALATWTIQGAANALS GDVWDIDNEF	食蟹猴 TfR
104	MGWSCIILFLVATATGAYAGTSSGLPNIPVQTISRA AAEKLFGNMEGDCPSDWKTDSTCRMVTSESKNV KLTVSNDSAQNSVIIVDKNGRLVYLVENPGGYVA YSKAATVTGKLVHANFGTKKDFEDLYTPVNGSIV IVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPI VNAELSASHHHHHH	His 标记的全突变的 TfR 顶端结构域
105	METDTLLLWVLLLWVPGSTGDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESLGHVWAVYKTTPPVLDSDGSF FLYSKLTVPKSTWQQGWVFSCSVMHEALHNHYT QKSLSLSPGK	表达的 CH3C.18 Fc 序列
106	TVXKXXWQQGXV	第二部分 CH3C 定位区

[0736]

SEQ ID NO:	序列	描述
107	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.8 (具有 YTE 和 LALAPG 突变的克隆 CH3C.35.20)
108	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.9 (具有 YTE 和 LALAPG 突变的克隆 CH3C.35.21)
109	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.20.1
110	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.20.1
111	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALAPG 突变的克隆 CH3C.35.20.1
112	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有节和 YTE 突变的克隆 CH3C.35.20.1
113	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.20.1

[0737]

SEQ ID NO:	序列	描述
114	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.20.1
115	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.20.1
116	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHE ALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.20.1
117	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHE ALHNHYTQKSLSLSPGK	具有孔和 LALAPG 突变的克隆 CH3C.35.20.1
118	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔和 YTE 突变的克隆 CH3C.35.20.1
119	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALA 和 YTE 突变的克隆 CH3C.35.20.1
120	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALAPG 和 YTE 突变的克隆 CH3C.35.20.1

[0738]

SEQ ID NO:	序列	描述
121	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮突变的克隆CH3C.35.23.2
122	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.23.2
123	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮和LALAPG突变的克隆CH3C.35.23.2
124	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮和YTE突变的克隆 CH3C.35.23.2
125	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮、LALA和YTE突变的克隆CH3C.35.23.2
126	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮、LALAPG和YTE突变的克隆CH3C.35.23.2
127	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔突变的克隆CH3C.35.23.2

[0739]

SEQ ID NO:	序列	描述
128	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.23.2
129	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALAPG 突变的克隆 CH3C.35.23.2
130	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和 YTE 突变的克隆 CH3C.35.23.2
131	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA 和 YTE 突变的克隆 CH3C.35.23.2
132	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG 和 YTE 突变的克隆 CH3C.35.23.2
133	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.23.3
134	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWVNYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVM HEALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.23.3

[0740]

SEQ ID NO:	序列	描述
135	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWVNYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVM HEALHNHYTQKSLSLSPGK	具有钮和LALAPG突变的克隆CH3C.35.23.3
136	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和YTE突变的克隆CH3C.35.23.3
137	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA和YTE突变的克隆CH3C.35.23.3
138	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG和YTE突变的克隆CH3C.35.23.3
139	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔突变的克隆CH3C.35.23.3
140	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWVNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALA突变的克隆CH3C.35.23.3
141	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWVNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALAPG突变的克隆CH3C.35.23.3

[0741]

SEQ ID NO:	序列	描述
142	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和YTE突变的克隆CH3C.35.23.3
143	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA和YTE突变的克隆CH3C.35.23.3
144	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG和YTE突变的克隆CH3C.35.23.3
145	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆CH3C.35.23.4
146	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和LALA突变的克隆CH3C.35.23.4
147	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和LALAPG突变的克隆CH3C.35.23.4
148	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和YTE突变的克隆CH3C.35.23.4

[0742]

SEQ ID NO:	序列	描述
149	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.23.4
150	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.23.4
151	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.23.4
152	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.23.4
153	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALAPG 突变的克隆 CH3C.35.23.4
154	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和 YTE 突变的克隆 CH3C.35.23.4
155	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA 和 YTE 突变的克隆 CH3C.35.23.4

[0743]

SEQ ID NO:	序列	描述
156	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG 和 YTE 突变的克隆 CH3C.35.23.4
157	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVLWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.21.17.2
158	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.21.17.2
159	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALAPG 突变的克隆 CH3C.35.21.17.2
160	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVLWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和 YTE 突变的克隆 CH3C.35.21.17.2
161	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVLWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.21.17.2
162	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVLWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.21.17.2

[0744]

SEQ ID NO:	序列	描述
163	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔突变的克隆CH3C.35.21.17.2
164	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔和LALA突变的克隆CH3C.35.21.17.2
165	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔和LALAPG突变的克隆CH3C.35.21.17.2
166	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔和YTE突变的克隆CH3C.35.21.17.2
167	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔、LALA和YTE突变的克隆CH3C.35.21.17.2
168	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有孔、LALAPG和YTE突变的克隆CH3C.35.21.17.2
169	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK	具有钮突变的克隆CH3C.35.23

[0745]

SEQ ID NO:	序列	描述
170	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.23
171	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALAPG 突变的克隆 CH3C.35.23
172	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和 YTE 突变的克隆 CH3C.35.23
173	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.23
174	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.23
175	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.23
176	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.23

[0746]

SEQ ID NO:	序列	描述
177	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALAPG突变的克隆CH3C.35.23
178	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和YTE突变的克隆CH3C.35.23
179	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA和YTE突变的克隆CH3C.35.23
180	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG和YTE突变的克隆CH3C.35.23
181	METDTLLLWVLLLWVPGSTGDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESYGTEWSSYKTTPPVLDSDGSFF LYSKLTVTKSEWQQGFVFSCSVMHEALHNHYTQ KSLSLSPGK	表达的CH3C.35 Fc序列
182	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESWGFVWSTYKTTPPV LDSDGSFFLYSKLTVPKSNWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆CH3C.18.3.4-1 (CH3C.3.4-1)
183	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESWGHVWSTYKTTPPV LDSDGSFFLYSKLTVPKSNWQQGYVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆CH3C.18.3.4-19 (CH3C.3.4-19)

[0747]

SEQ ID NO:	序列	描述
184	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVEQKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.3.2-3 (CH3C.3.2-3)
185	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVGVKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.3.2-14 (CH3C.3.2-14)
186	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVHTKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.3.2-24 (CH3C.3.2-24)
187	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESWGTVWGTYKTTPPV LDSDGSFFLYSKLTVPKSNWQQGYVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.18.3.4-26 (CH3C.3.4-26)
188	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESLGHVWVGTKTTPPV LDSDGSFFLYSKLTVPKSTWQQGWVFSCSVMHE ALHNHYTQKSLSLSPGK	克隆 CH3C.18.3.2-17 (CH3C.3.2-17)
189	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.20.1.1
190	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.23.2.1

[0748]

SEQ ID NO:	序列	描述
191	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.1.1
192	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.S413
193	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	克隆 CH3C.35.23.3.1
194	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.N390.1
195	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWVNYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	克隆 CH3C.35.23.6.1
196	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.21
197	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVWWESYGTEWSSYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVM HEALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.21

[0749]

SEQ ID NO:	序列	描述
198	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVWWESYGTEWSSYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVM HEALHNHYTQKSLSLSPGK	具有钮和LALAPG突变的克隆CH3C.35.21
199	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和YTE突变的克隆CH3C.35.21
200	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA和YTE突变的克隆CH3C.35.21
201	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG和YTE突变的克隆CH3C.35.21
202	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔突变的克隆CH3C.35.21
203	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVWWESYGTEWSSYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALA突变的克隆CH3C.35.21
204	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVWWESYGTEWSSYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALAPG突变的克隆CH3C.35.21

[0750]

SEQ ID NO:	序列	描述
205	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和YTE突变的克隆 CH3C.35.21
206	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA和YTE突变的克隆 CH3C.35.21
207	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG和YTE突变的克隆 CH3C.35.21
208	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.20.1.1
209	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和LALA突变的克隆 CH3C.35.20.1.1
210	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和LALAPG突变的克隆 CH3C.35.20.1.1
211	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮和YTE突变的克隆 CH3C.35.20.1.1

[0751]

SEQ ID NO:	序列	描述
212	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.20.1.1
213	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.20.1.1
214	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.20.1.1
215	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHE ALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.20.1.1
216	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHE ALHNHYTQKSLSLSPGK	具有孔和 LALAPG 突变的克隆 CH3C.35.20.1.1
217	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔和 YTE 突变的克隆 CH3C.35.20.1.1
218	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALA 和 YTE 突变的克隆 CH3C.35.20.1.1

[0752]

SEQ ID NO:	序列	描述
219	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALAPG 和 YTE 突变的克隆 CH3C.35.20.1.1
220	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.23.2.1
221	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.23.2.1
222	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALAPG 突变的克隆 CH3C.35.23.2.1
223	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和 YTE 突变的克隆 CH3C.35.23.2.1
224	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.23.2.1
225	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.23.2.1

[0753]

SEQ ID NO:	序列	描述
226	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.23.2.1
227	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.23.2.1
228	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALAPG 突变的克隆 CH3C.35.23.2.1
229	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔和 YTE 突变的克隆 CH3C.35.23.2.1
230	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALA 和 YTE 突变的克隆 CH3C.35.23.2.1
231	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVSKSEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有孔、LALAPG 和 YTE 突变的克隆 CH3C.35.23.2.1
232	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮突变的克隆 CH3C.35.23.1.1

[0754]

SEQ ID NO:	序列	描述
233	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALA 突变的克隆 CH3C.35.23.1.1
234	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有钮和 LALAPG 突变的克隆 CH3C.35.23.1.1
235	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮和 YTE 突变的克隆 CH3C.35.23.1.1
236	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALA 和 YTE 突变的克隆 CH3C.35.23.1.1
237	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVMHEA LHNHYTQKSLSLSPGK	具有钮、LALAPG 和 YTE 突变的克隆 CH3C.35.23.1.1
238	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔突变的克隆 CH3C.35.23.1.1
239	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和 LALA 突变的克隆 CH3C.35.23.1.1

[0755]

SEQ ID NO:	序列	描述
240	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVMH EALHNHYTQKSLSLSPGK	具有孔和LALAPG突变的克隆CH3C.35.23.1.1
241	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔和YTE突变的克隆CH3C.35.23.1.1
242	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALA和YTE突变的克隆CH3C.35.23.1.1
243	PCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL GAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVMHEAL HNHYTQKSLSLSPGK	具有孔、LALAPG和YTE突变的克隆CH3C.35.23.1.1
244	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	M201L和N207S突变的克隆CH3C.35.20.1
245	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有钮和M201L和N207S突变的克隆CH3C.35.20.1
246	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA和M201L和N207S突变的克隆CH3C.35.20.1

[0756]

SEQ ID NO:	序列	描述
247	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 和 N207S 突变的克隆 CH3C.35.20.1
248	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有孔和 M201L 和 N207S 突变的克隆 CH3C.35.20.1
249	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 和 N207S 突变的克隆 CH3C.35.20.1
250	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 和 N207S 突变的克隆 CH3C.35.20.1
251	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23.2
252	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 和 N207S 突变的克隆 CH3C.35.23.2
253	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 和 N207S 突变的克隆 CH3C.35.23.2

[0757]

SEQ ID NO:	序列	描述
254	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 和 N207S 突变的克隆 CH3C.35.23.2
255	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 和 N207S 突变的克隆 CH3C.35.23.2
256	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 和 N207S 突变的克隆 CH3C.35.23.2
257	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 和 N207S 突变的克隆 CH3C.35.23.2
258	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23.3
259	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 和 N207S 突变的克隆 CH3C.35.23.3
260	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWVNYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 和 N207S 突变的克隆 CH3C.35.23.3

[0758]

SEQ ID NO:	序列	描述
261	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWVNYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 和 N207S 突变的克隆 CH3C.35.23.3
262	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWVNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 和 N207S 突变的克隆 CH3C.35.23.3
263	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWVNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 和 N207S 突变的克隆 CH3C.35.23.3
264	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWVNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.3
265	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23.4
266	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.23.4
267	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及的 N207S 突变克隆 CH3C.35.23.4

[0759]

SEQ ID NO:	序列	描述
268	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.4
269	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.23.4
270	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.4
271	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.4
272	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVLWESYGTEWASYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.21.17.2
273	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVLWESYGTEWASYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2
274	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2

[0760]

SEQ ID NO:	序列	描述
275	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2
276	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVLWESYGTEWASYKTTPPVL DSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2
277	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2
278	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVLWESYGTEWASYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.21.17.2
279	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWSNYKTTPPVL DSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23
280	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.23
281	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23

[0761]

SEQ ID NO:	序列	描述
282	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23
283	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWSNYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.23
284	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23
285	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWSNYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23
286	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.21
287	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.21
288	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVWWESYGTEWSSYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.21

[0762]

SEQ ID NO:	序列	描述
289	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVWWESYGTEWSSYKTT PPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.21
290	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVWWESYGTEWSSYKTTPPV LDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.21
291	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVWWESYGTEWSSYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.21
292	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVWWESYGTEWSSYKTTP PVLDSDGSFFLVSKLTVTKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.21
293	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.20.1.1
294	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1
295	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1

[0763]

SEQ ID NO:	序列	描述
296	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSSYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1
297	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1
298	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1
299	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSSYKTTPP VLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.20.1.1
300	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23.2.1
301	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLYSKLTVSKSEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1
302	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVSKSEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1

[0764]

SEQ ID NO:	序列	描述
303	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLYSKLTVSKSEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1
304	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESYGTEWANYKTTPPV LDSDGSFFLVSKLTVSKSEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1
305	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVSKSEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1
306	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESYGTEWANYKTTP PVLDSDGSFFLVSKLTVSKSEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.2.1
307	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有 M201L 和 N207S 突变的克隆 CH3C.35.23.1.1
308	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESFGTEWSNYKTTPPV LDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHEA LHSHYTQKSLSLSPGK	具有钮和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1
309	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1

[0765]

SEQ ID NO:	序列	描述
310	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLYSKLTVSKEEWQQGFVFSCSVLHE ALHSHYTQKSLSLSPGK	具有钮、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1
311	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLSCAVKGFYPSDIAVEWESFGTEWSNYKTTPPVL DSDGSFFLVSKLTVSKEEWQQGFVFSCSVLHEAL HSHYTQKSLSLSPGK	具有孔和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1
312	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALA 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1
313	PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESFGTEWSNYKTTP PVLDSDGSFFLVSKLTVSKEEWQQGFVFSCSVLH EALHSHYTQKSLSLSPGK	具有孔、LALAPG 和 M201L 以及 N207S 突变的克隆 CH3C.35.23.1.1
314	X_1WESX_2GX_3X_4WX_5X_6 X_1 是 E、L、S、V、W 或 Y；X_2 是芳香族氨基酸(例如，Y、F 或 W)、M、P 或 V；X_3 是 T、N 或 V；X_4 是 E、I、P 或 V；X_5 是脂肪族氨基酸(例如，A、I 或 V)、S 或 T；并且 X_6 是 S、N、R 或 T	CH3C.35_共有序列_1
315	X_1KX_2X_3WQQGX_4V FX_5CX_6 X_1 是 T、H 或 S；X_2 是 E、S、D、G、T、P、Q 或 R；X_3 是 E 或 R；X_4 是 F、H、K、Y 或 W；X_5 是 S、T 或 W；并且 X_6 是 S、C、P、M 或 W	CH3C.35_共有序列_2

[0766]

SEQ ID NO:	序列	描述
316	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVX$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$YKTTPPVLDSDGSFFLYSKLTVX$_7$KX$_8$X$_9$WQQGX$_{10}$VFX$_{11}$CX$_{12}$VMHEALHNHYTQKSLSLSPGK X$_1$是E、L、S、V、W或Y；X$_2$是芳香族氨基酸(例如，Y、F或W)、M、P或V；X$_3$是T、N或V；X$_4$是E、I、P或V；X$_5$是脂肪族氨基酸(例如，A、I或V)、S或T；X$_6$是S、N、R或T；X$_7$是T、H或S；X$_8$是E、S、D、G、T、P、Q或R；X$_9$是E或R；X$_{10}$是F、H、K、Y或W；X$_{11}$是S、T或W；并且X$_{12}$是S、C、P、M或W	CH3C.35_共有序列_3
317	X$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$ X$_1$是E、L或W；X$_2$是芳香族氨基酸(例如，Y或F)；X$_3$是T；X$_4$是E；X$_5$是脂肪族氨基酸(例如，A或V)或S；并且X$_6$是S或N	CH3C.35_共有序列_4
318	X$_1$KX$_2$X$_3$WQQGX$_4$VFX$_5$CX$_6$ X$_1$是T或S；X$_2$是E或S；X$_3$是E；X$_4$是F、H、Y或W；X$_5$是S；并且X$_6$是S	CH3C.35_共有序列_5
319	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVX$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$YKTTPPVLDSDGSFFLYSKLTVX$_7$KX$_8$X$_9$WQQGX$_{10}$VFX$_{11}$CX$_{12}$VMHEALHNHYTQKSLSLSPGK X$_1$是E、L或W；X$_2$是芳香族氨基酸(例如，Y或F)；X$_3$是T；X$_4$是E；X$_5$是脂肪族氨基酸(例如，A或V)或S；X$_6$是S或N；X$_7$是T或S；X$_8$是E或S；X$_9$是E；X$_{10}$是F、H、Y或W；X$_{11}$是S；并且X$_{12}$是S	CH3C.35_共有序列_6
320	X$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$ X$_1$是E、L或W；X$_2$是Y或F；X$_3$是T；X$_4$是E；X$_5$是S、A或V；并且X$_6$是S或N	CH3C.35_共有序列_7
321	X$_1$KX$_2$X$_3$WQQGX$_4$VFX$_5$CX$_6$ X$_1$是T或S；X$_2$是E或S；X$_3$是E；X$_4$是F；X$_5$是S；并且X$_6$是S	CH3C.35_共有序列_8
322	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVX$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$YKTTPPVLDSDGSFFLYSKLTVX$_7$KX$_8$X$_9$WQQGX$_{10}$VFX$_{11}$CX$_{12}$VMHEALHNHYTQKSLSLSPGK X$_1$是E、L或W；X$_2$是Y或F；X$_3$是T；X$_4$是E；X$_5$是S、A或V；X$_6$是S或N；X$_7$是T或S；X$_8$是E或S；X$_9$是E；X$_{10}$是F；X$_{11}$是S；并且X$_{12}$是S	CH3C.35_共有序列_9

[0767]

SEQ ID NO:	序列	描述
323	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVXWESYGTEWSSYKTTPPVLDSDGSFFLYSKL TVTKEEWQQGFVFSCSVMHEALHNHYTQKSLSL SPGK X是E、L、S、V、W或Y	CH3C.35_共有序列_10
324	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESXGTEWSSYKTTPPVLDSDGSFFLYSK LTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是Y、F、M、P、V或W	CH3C.35_共有序列_11
325	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGXEWSSYKTTPPVLDSDGSFFLYSK LTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是T、N或V	CH3C.35_共有序列_12
326	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGTXWSSYKTTPPVLDSDGSFFLYSK LTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是E、I、P或V	CH3C.35_共有序列_13
327	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGTEWXSYKTTPPVLDSDGSFFLYSK LTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是S、A、I、T或V	CH3C.35_共有序列_14
328	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGTEWSXYKTTPPVLDSDGSFFLYSK LTVTKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是S、N、R或T	CH3C.35_共有序列_15
329	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSK LTVXKEEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是T、H或S	CH3C.35_共有序列_16
330	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSK LTVTKXEWQQGFVFSCSVMHEALHNHYTQKSLS LSPGK X是E、S、D、G、T、P、Q或R	CH3C.35_共有序列_17

[0768]

SEQ ID NO:	序列	描述
331	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSKLTVTKEXWQQGFVFSCSVMHEALHNHYTQKSLSLSPGK X 是 E 或 R	CH3C.35_共有序列_18
332	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGXVFSCSVMHEALHNHYTQKSLSLSPGK X 是 F、H、K 或 Y	CH3C.35_共有序列_19
333	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFXCSVMHEALHNHYTQKSLSLSPGK X 是 S、T 或 W	CH3C.35_共有序列_20
334	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVWWESYGTEWSSYKTTPPVLDSDGSFFLYSKLTVTKEEWQQGFVFSCXVMHEALHNHYTQKSLSLSPGK X 是 S、C、P、M 或 W	CH3C.35_共有序列_21
335	X_1WESX_2GX_3X_4W$X_5X_6X_7$ X_1 是 E 或 W；X_2 是 V、W、L 或 Y；X_3 是 L、P、F、T 或 H；X_4 是 P、V 或 E；X_5 是 A、S、V 或 G；X_6 是 L、H、Q、G、V、A N、D、T 或 E；并且 X_7 是 T、F、Q、V 或 Y	CH3C.18_共有序列_1
336	X_1KSX_2WQQGX_3 X_1 是 L、S、E、A 或 P；X_2 是 E、D、T 或 N；并且 X_2 是 W、Y、H 或 F	CH3C.18_共有序列_2
337	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVX_1WESX_2GX_3X_4W$X_5X_6X_7$KTTPPVLDSDGSFFLYSKLTVX_8KSX_9WQQGX_{10}VFSCSVMHEALHNHYTQKSLSLSPGK X_1 是 E 或 W；X_2 是 V、W、L 或 Y；X_3 是 L、P、F、T 或 H；X_4 是 P、V 或 E；X_5 是 A、S、V 或 G；X_6 是 L、H、Q、G、V、A N、D、T 或 E；X_7 是 T、F、Q、V 或 Y；X_8 是 L、S、E、A 或 P；X_9 是 E、D、T 或 N；并且 X_{10} 是 W、Y、H 或 F	CH3C.18_共有序列_3
338	X_1WESX_2GX_3X_4W$X_5X_6X_7$ X_1 是 E 或 W；X_2 是 W、L 或 Y；X_3 是 T 或 H；X_4 是 V；X_5 是 A、S 或 V；X_6 是 V、T 或 N；并且 X_7 是 Y 或 Q	CH3C.18_共有序列_4

[0769]

SEQ ID NO:	序列	描述
339	$X_1KSX_2WQQGX_3$ X_1是P；X_2是T或N；并且X_3是W、Y、H或F	CH3C.18_共有序列_5
340	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVX$_1$WESX$_2$GX$_3$X$_4$WX$_5$X$_6$X$_7$KTTPPVLDSDGSFF LYSKLTVX$_8$KSX$_9$WQQGX$_{10}$VFSCSVMHEALHNHY TQKSLSLSPGK X_1是E或W；X_2是W、L或Y；X_3是T或H；X_4是V；X_5是A、S或V；X_6是V、T或N；X_7是Y或Q；X_8是P；X_9是T或N；并且X_{10}是W、Y、H或F	CH3C.18_共有序列_6
341	TXWSX	克隆基序
342	NSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGK LVHANFGTKKDFEDLDSPVNGSIVIVRAGKITFAE KVANAESLNAIGVLIYMDQTKFPIVNAXLSFFGH AHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQ TISRAAAEKLFGNMEGDCPSDWKTDSTCRMVTS ENKNVKLTVS X是D或E	人与食蟹猴TfR之间的共有序列
343	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK	IGHG1_P01857
344	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCC VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK	IGHG2_P01859

[0770]

SEQ ID NO:	序列	描述
345	ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK	IGHG3_P01860
346	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	IGHG4_P01861
347	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESX$_1$GTEWX$_2$NYKTTPPVLDSDGSFFLYSKLTVX$_3$KEEWQQGFVFSCSVX$_4$HEALHX$_5$HYTQKSLSLSPGK，其中 X$_1$ 是 F 或 Y；X$_2$ 是 S、A 或 V；X$_3$ 是 S 或 T；X$_4$ 是 M 或 L；并且 X$_5$ 是 N 或 S	具有钮、LALA 以及任选的 M428L 和 N434S 突变(EU 编号)的克隆 CH3C.35.23.1.1、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.23 和 CH3C.35.23.2 的共有序列
348	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESX$_1$GTEWX$_2$NYKTTPPVLDSDGSFFLVSKLTVX$_3$KEEWQQGFVFSCSVX$_4$HEALHX$_5$HYTQKSLSLSPGK，其中 X$_1$ 是 F 或 Y；X$_2$ 是 S、A 或 V；X$_3$ 是 S 或 T；X$_4$ 是 M 或 L；并且 X$_5$ 是 N 或 S	具有孔、LALA 以及任选的 M428L 和 N434S 突变(EU 编号)的克隆 CH3C.35.23.1.1、CH3C.35.23.3、CH3C.35.23.4、CH3C.35.23 和 CH3C.35.23.2 的共有序列
349	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVX$_1$HEALHX$_2$HYTQKSLSLSPGK，其中 X$_1$ 是 M 或 L；并且 X$_2$ 是 N 或 S	具有钮、LALA 以及任选的 M428L 和 N434S 突变(EU 编号)的 Fc 序列

[0771]

SEQ ID NO:	序列	描述
350	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLVSKLTVDKSRWQQGNVFSCSVX$_1$HEALH X$_2$HYTQKSLSLSPGK，其中 X$_1$ 是 M 或 L；并且 X$_2$ 是 N 或 S	具有孔、LALA 以及任选的 M428L 和 N434S 突变(EU 编号)的 Fc 序列
351	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	具有钮突变的Fc序列
352	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	具有钮和 LALA 突变的 Fc 序列
353	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHS HYTQKSLSLSPGK	具有钮、LALA 和 M428L 以及 N434S 突变(EU 编号)的 Fc 序列
354	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	具有孔突变的Fc序列
355	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	具有孔和 LALA 突变的 Fc 序列
356	APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLVSKLTVDKSRWQQGNVFSCSVLHEALHS HYTQKSLSLSPGK	具有孔、LALA 和 M428L 以及 N434S 突变(EU 编号)的 Fc 序列

[0001] 序列表

[0002] <110> 德纳利治疗公司(Denali Therapeutics Inc.)

[0003] <120> 工程改造的转铁蛋白受体结合多肽

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[0578] 210 215 220

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[0628] 50 55 60

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[0633] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

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[0637] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[0638] 130 135 140

[0639] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Leu Gly His Val

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[0644] 180 185 190

[0645] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[0646] 195 200 205

[0647] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[0648] 210 215 220

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[0659] 20 25 30

[0660] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[0661] 35 40 45

[0662] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[0663] 50 55 60

[0664] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[0665] 65 70 75 80

[0666] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[0667] 85 90 95

[0668] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[0669] 100 105 110

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[0671] 115 120 125

[0672] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

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[0678] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln

[0679] 180 185 190

[0680] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[0681] 195 200 205

[0682] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

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[0703] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

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[0713] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln

[0714] 180 185 190

[0715] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[0716] 195 200 205

[0717] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[0718] 210 215 220

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[0731] 35 40 45

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[0733] 50 55 60

[0734] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[0735] 65 70 75 80

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[0737] 85 90 95

[0738] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

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[0748] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln

[0749] 180 185 190

[0750] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[0752] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

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[0773] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

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[0784] 180 185 190
[0785] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[0786] 195 200 205
[0787] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[0788] 210 215 220
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[0801] 35 40 45
[0802] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[0803] 50 55 60
[0804] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[0805] 65 70 75 80
[0806] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[0807] 85 90 95
[0808] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[0810] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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[0814] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu
[0815] 145 150 155 160
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[0817] 165 170 175
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[0819] 180 185 190

[0820] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[0842] 85 90 95

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[0853] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[0854] 180 185 190

[0855] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[0857] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

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[0923] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Ser Glu Trp Gln Gln

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[0925] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[1014] Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro Ile Val Asn Ala
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[1016] Glu Leu Ser Phe Phe Gly His Ala His Leu Gly Thr Gly Asp Pro Tyr
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[1018] Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe Pro Pro Ser Arg
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[1025] 165 170 175
[1026] Lys Leu Thr Val Ser
[1027] 180
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[1043] Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro Ile Val Lys Ala
[1044] 85 90 95
[1045] Asp Leu Ser Phe Phe Gly His Ala His Leu Gly Thr Gly Asp Pro Tyr
[1046] 100 105 110
[1047] Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe Pro Pro Ser Gln
[1048] 115 120 125
[1049] Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile Ser Arg Ala Ala
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[1051] Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys Pro Ser Asp Trp
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[1053] Lys Thr Asp Ser Thr Cys Lys Met Val Thr Ser Glu Asn Lys Ser Val
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[1055] Lys Leu Thr Val Ser
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[1069] 35 40 45
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[1072] Asp Lys Asn Gly Arg Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr
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[1082] Asp Gln Thr Lys Phe Pro Ile Val Asn Ala Glu Leu Ser Gly Pro
[1083] 145 150 155
[1084] <210> 33
[1085] <211> 159
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[1096] 35 40 45
[1097] Lys Leu Thr Val Ser Asn Asp Ser Ala Gln Asn Ser Val Ile Ile Val
[1098] 50 55 60
[1099] Asp Lys Asn Gly Gly Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr
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[1102] 85 90 95
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[1104] 100 105 110
[1105] Gly Ser Ile Val Ile Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys
[1106] 115 120 125
[1107] Val Ala Asn Ala Glu Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met
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[1157] 1 5
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[1164] 1 5 10 15
[1165] <210> 38
[1166] <211> 760
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[1168] <213> 智人(Homo sapiens)
[1169] <400> 38

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[1175] 35 40 45
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[1179] 65 70 75 80
[1180] Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
[1181] 85 90 95
[1182] Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro
[1183] 100 105 110
[1184] Gly Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys
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[1186] Arg Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile
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[1194] Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg
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[1202] Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
[1203] 260 265 270
[1204] Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
[1205] 275 280 285
[1206] Pro Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly
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[1208] Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln

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[1212] Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
[1213] 340 345 350
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[1226] Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
[1227] 450 455 460
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[1230] Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
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[1235] 515 520 525
[1236] Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
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[1238] Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
[1239] 545 550 555 560
[1240] Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu
[1241] 565 570 575
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[1244] Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn
[1245] 595 600 605
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[1253] 660 665 670
[1254] Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro
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[1256] Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
[1257] 690 695 700
[1258] Gly Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys
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[1260] Gln Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
[1261] 725 730 735
[1262] Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
[1263] 740 745 750
[1264] Val Trp Asp Ile Asp Asn Glu Phe
[1265] 755 760
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[1275] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
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[1277] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[1278] 35 40 45
[1279] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1280] 50 55 60
[1281] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1282] 65 70 75 80
[1283] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1284] 85 90 95
[1285] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[1287] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[1288] 115 120 125
[1289] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1290] 130 135 140
[1291] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu
[1292] 145 150 155 160
[1293] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1294] 165 170 175
[1295] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Ser Glu Trp Gln Gln
[1296] 180 185 190
[1297] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[1299] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[1313] 35 40 45
[1314] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1315] 50 55 60
[1316] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[1318] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1319] 85 90 95
[1320] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[1323] 115 120 125
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[1326] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[1327] 145 150 155 160
[1328] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1329] 165 170 175
[1330] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[1331] 180 185 190
[1332] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[1334] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1335] 210 215 220
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[1348] 35 40 45
[1349] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1350] 50 55 60
[1351] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1352] 65 70 75 80
[1353] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1354] 85 90 95
[1355] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[1356] 100 105 110
[1357] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[1358] 115 120 125
[1359] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1360] 130 135 140
[1361] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu
[1362] 145 150 155 160
[1363] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1364] 165 170 175

[1365] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[1366] 180 185 190
[1367] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1368] 195 200 205
[1369] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1370] 210 215 220
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[1381] 20 25 30
[1382] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[1383] 35 40 45
[1384] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1385] 50 55 60
[1386] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1387] 65 70 75 80
[1388] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1389] 85 90 95
[1390] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[1394] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1395] 130 135 140
[1396] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu
[1397] 145 150 155 160
[1398] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1399] 165 170 175
[1400] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Ser Glu Trp Gln Gln
[1401] 180 185 190
[1402] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[1404] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1405] 210 215 220
[1406] <210> 43
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[1410] <220>
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[1418] 35 40 45
[1419] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1420] 50 55 60
[1421] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[1423] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1424] 85 90 95
[1425] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[1427] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[1428] 115 120 125
[1429] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1430] 130 135 140
[1431] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[1432] 145 150 155 160
[1433] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1434] 165 170 175
[1435] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[1436] 180 185 190
[1437] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1438] 195 200 205
[1439] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1440] 210 215 220
[1441] <210> 44
[1442] <211> 220

[1443] <212> PRT

[1444] <213> 人工序列(Artificial Sequence)

[1445] <220>

[1446] <223> 合成构建体

[1447] <400> 44

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[1449] 1 5 10 15

[1450] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

[1451] 20 25 30

[1452] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[1453] 35 40 45

[1454] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[1455] 50 55 60

[1456] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[1457] 65 70 75 80

[1458] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[1459] 85 90 95

[1460] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[1461] 100 105 110

[1462] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[1463] 115 120 125

[1464] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[1465] 130 135 140

[1466] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu

[1467] 145 150 155 160

[1468] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[1469] 165 170 175

[1470] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[1471] 180 185 190

[1472] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[1473] 195 200 205

[1474] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[1475] 210 215 220

[1476] <210> 45

[1477] <211> 220

[1478] <212> PRT

[1479] <213> 人工序列(Artificial Sequence)

[1480] <220>

[1481] <223> 合成构建体

[1482] <400> 45

[1483] Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe

[1484] 1 5 10 15

[1485] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

[1486] 20 25 30

[1487] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[1488] 35 40 45

[1489] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[1490] 50 55 60

[1491] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[1492] 65 70 75 80

[1493] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[1494] 85 90 95

[1495] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[1496] 100 105 110

[1497] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[1498] 115 120 125

[1499] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[1500] 130 135 140

[1501] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Leu Gly His Val

[1502] 145 150 155 160

[1503] Trp Ala Val Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[1504] 165 170 175

[1505] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln

[1506] 180 185 190

[1507] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[1508] 195 200 205

[1509] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[1510] 210 215 220

[1511] <210> 46

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[1645] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln
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[1647] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1648] 195 200 205
[1649] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[1682] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[1684] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[1719] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1720] 210 215 220
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[1733] 35 40 45
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[1751] 180 185 190
[1752] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1753] 195 200 205
[1754] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[1755] 210 215 220

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[1768] 35 40 45

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[1770] 50 55 60

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[1774] 85 90 95

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[1786] 180 185 190

[1787] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[1788] 195 200 205

[1789] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[1790] 210 215 220

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[1803] 35 40 45

[1804] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[1805] 50 55 60

[1806] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[1807] 65 70 75 80

[1808] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[1809] 85 90 95

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[1820] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Gly Glu Glu Trp Gln Gln

[1821] 180 185 190

[1822] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[1947] 65 70 75 80
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[1986] 100 105 110
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[1988] 115 120 125

[1989] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1990] 130 135 140
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[1992] 145 150 155 160
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[1994] 165 170 175
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[2519] 165 170 175

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[2836] 180 185 190

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[2840] 210 215 220

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[2977] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[3003] 115 120 125
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[3033] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
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[3035] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3036] 100 105 110
[3037] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3038] 115 120 125
[3039] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
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[3041] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu

[3042] 145 150 155 160
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[3045] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
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[3047] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3048] 195 200 205
[3049] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3050] 210 215 220
[3051] <210> 90
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[3060] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3061] 20 25 30
[3062] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3063] 35 40 45
[3064] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3065] 50 55 60
[3066] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3067] 65 70 75 80
[3068] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3069] 85 90 95
[3070] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3071] 100 105 110
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[3076] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu
[3077] 145 150 155 160
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[3079] 165 170 175
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[3081] 180 185 190

[3082] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[3085] 210 215 220

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[3087] <211> 220

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[3091] <223> 合成构建体

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[3095] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

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[3097] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[3098] 35 40 45

[3099] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[3100] 50 55 60

[3101] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[3102] 65 70 75 80

[3103] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[3104] 85 90 95

[3105] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[3106] 100 105 110

[3107] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[3108] 115 120 125

[3109] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[3110] 130 135 140

[3111] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Phe Gly Thr Glu

[3112] 145 150 155 160

[3113] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

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[3115] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[3116] 180 185 190

[3117] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[3118] 195 200 205

[3119] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[3120] 210 215 220

[3121] <210> 92

[3122] <211> 220

[3123] <212> PRT

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[3125] <220>

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[3130] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

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[3133] 35 40 45

[3134] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[3135] 50 55 60

[3136] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[3137] 65 70 75 80

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[3139] 85 90 95

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[3141] 100 105 110

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[3143] 115 120 125

[3144] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[3145] 130 135 140

[3146] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Phe Gly Thr Glu

[3147] 145 150 155 160

[3148] Trp Val Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[3149] 165 170 175

[3150] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[3151] 180 185 190

[3152] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[3153] 195 200 205

[3154] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[3155] 210 215 220

[3156] <210> 93

[3157] <211> 220

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[3160] <220>

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[3165] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

[3166] 20 25 30

[3167] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[3168] 35 40 45

[3169] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[3170] 50 55 60

[3171] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[3172] 65 70 75 80

[3173] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[3174] 85 90 95

[3175] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[3176] 100 105 110

[3177] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[3178] 115 120 125

[3179] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly

[3180] 130 135 140

[3181] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Phe Gly Thr Glu

[3182] 145 150 155 160

[3183] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

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[3185] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[3186] 180 185 190

[3187] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[3188] 195 200 205

[3189] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[3190] 210 215 220

[3191] <210> 94

[3192] <211> 220

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[3194] <213> 人工序列(Artificial Sequence)

[3195] <220>

[3196] <223> 合成构建体

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[3201] 20 25 30
[3202] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3203] 35 40 45
[3204] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3205] 50 55 60
[3206] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3207] 65 70 75 80
[3208] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
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[3210] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[3212] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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[3214] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
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[3216] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Tyr Gly Thr Glu
[3217] 145 150 155 160
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[3220] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3221] 180 185 190
[3222] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3223] 195 200 205
[3224] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3225] 210 215 220
[3226] <210> 95
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[3235] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3236] 20 25 30

[3237] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3238] 35 40 45
[3239] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3240] 50 55 60
[3241] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3242] 65 70 75 80
[3243] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3244] 85 90 95
[3245] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3246] 100 105 110
[3247] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3248] 115 120 125
[3249] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
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[3251] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Tyr Gly Thr Glu
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[3255] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3256] 180 185 190
[3257] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3258] 195 200 205
[3259] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3260] 210 215 220
[3261] <210> 96
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[3271] 20 25 30
[3272] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3273] 35 40 45
[3274] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3275] 50 55 60

[3276] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3277] 65 70 75 80
[3278] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3279] 85 90 95
[3280] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3281] 100 105 110
[3282] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3283] 115 120 125
[3284] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3285] 130 135 140
[3286] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Tyr Gly Thr Glu
[3287] 145 150 155 160
[3288] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3289] 165 170 175
[3290] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[3291] 180 185 190
[3292] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3293] 195 200 205
[3294] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3295] 210 215 220
[3296] <210> 97
[3297] <211> 220
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[3305] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3306] 20 25 30
[3307] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3308] 35 40 45
[3309] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3310] 50 55 60
[3311] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3312] 65 70 75 80
[3313] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3314] 85 90 95

[3315] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3316] 100 105 110
[3317] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3318] 115 120 125
[3319] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3320] 130 135 140
[3321] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Phe Gly Thr Glu
[3322] 145 150 155 160
[3323] Trp Ala Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3324] 165 170 175
[3325] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3326] 180 185 190
[3327] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[3329] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3330] 210 215 220
[3331] <210> 98
[3332] <211> 220
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[3340] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3341] 20 25 30
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[3343] 35 40 45
[3344] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3345] 50 55 60
[3346] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3347] 65 70 75 80
[3348] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3349] 85 90 95
[3350] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3351] 100 105 110
[3352] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3353] 115 120 125

[3354] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3355] 130 135 140
[3356] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Phe Gly Thr Glu
[3357] 145 150 155 160
[3358] Trp Val Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3359] 165 170 175
[3360] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3361] 180 185 190
[3362] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3363] 195 200 205
[3364] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3365] 210 215 220
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[3376] 20 25 30
[3377] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3378] 35 40 45
[3379] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3380] 50 55 60
[3381] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3382] 65 70 75 80
[3383] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3384] 85 90 95
[3385] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3386] 100 105 110
[3387] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3388] 115 120 125
[3389] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3390] 130 135 140
[3391] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[3392] 145 150 155 160

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[3395] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Ser Glu Trp Gln Gln
[3396] 180 185 190
[3397] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[3399] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3400] 210 215 220
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[3414] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[3416] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[3418] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
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[3420] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[3422] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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[3424] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3425] 130 135 140
[3426] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Leu Gly His Val
[3427] 145 150 155 160
[3428] Trp Val Asn Gln Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3429] 165 170 175
[3430] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln
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[3432] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3433] 195 200 205
[3434] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3435] 210 215 220
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[3446] 20 25 30
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[3449] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3450] 50 55 60
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[3453] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3454] 85 90 95
[3455] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3456] 100 105 110
[3457] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3458] 115 120 125
[3459] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
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[3461] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Leu Gly His Val
[3462] 145 150 155 160
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[3465] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln
[3466] 180 185 190
[3467] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3468] 195 200 205
[3469] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3470] 210 215 220

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[3483] 35 40 45
[3484] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[3486] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[3488] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3489] 85 90 95
[3490] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3491] 100 105 110
[3492] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3493] 115 120 125
[3494] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3495] 130 135 140
[3496] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Leu Gly His Val
[3497] 145 150 155 160
[3498] Trp Val Asn Gln Gln Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3499] 165 170 175
[3500] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln
[3501] 180 185 190
[3502] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3503] 195 200 205
[3504] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3505] 210 215 220
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[3507] <211> 760
[3508] <212> PRT
[3509] <213> 食蟹猴(Macaca fascicularis)

[3510] <400> 103

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[3513] Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
[3514] 20 25 30

[3515] Asn Ser His Val Glu Met Lys Leu Gly Val Asp Glu Glu Glu Asn Thr
[3516] 35 40 45

[3517] Asp Asn Asn Thr Lys Ala Asn Gly Thr Lys Pro Lys Arg Cys Gly Gly
[3518] 50 55 60

[3519] Asn Ile Cys Tyr Gly Thr Ile Ala Val Ile Ile Phe Phe Leu Ile Gly
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[3527] Arg Lys Leu Ser Glu Lys Leu Asp Thr Thr Asp Phe Thr Ser Thr Ile
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[3535] Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Gly
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[3538] 210 215 220

[3539] Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys
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[3541] Lys Asp Phe Glu Asp Leu Asp Ser Pro Val Asn Gly Ser Ile Val Ile
[3542] 245 250 255

[3543] Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
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[3545] Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
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[3549] Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
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[3560] 385 390 395 400
[3561] His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
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[3568] 450 455 460
[3569] Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
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[3571] Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
[3572] 485 490 495
[3573] Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asp
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[3575] Val Lys His Pro Val Thr Gly Arg Ser Leu Tyr Gln Asp Ser Asn Trp
[3576] 515 520 525
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[3579] Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
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[3588] 610 615 620
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[3591] Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
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[3593] Thr Thr Asp Phe Arg Asn Ala Glu Lys Arg Asp Lys Phe Val Met Lys
[3594] 660 665 670
[3595] Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr Tyr Phe Leu Ser Pro
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[3597] Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
[3598] 690 695 700
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[3601] Gln Asn Asn Ser Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
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[3603] Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
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[3618] Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
[3619] 35 40 45
[3620] Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser
[3621] 50 55 60
[3622] Glu Ser Lys Asn Val Lys Leu Thr Val Ser Asn Asp Ser Ala Gln Asn
[3623] 65 70 75 80
[3624] Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu Val Tyr Leu Val Glu
[3625] 85 90 95
[3626] Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala Ala Thr Val Thr Gly

[3627] 100 105 110
[3628] Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys Asp Phe Glu Asp Leu
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[3630] Tyr Thr Pro Val Asn Gly Ser Ile Val Ile Val Arg Ala Gly Lys Ile
[3631] 130 135 140
[3632] Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser Leu Asn Ala Ile Gly
[3633] 145 150 155 160
[3634] Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro Ile Val Asn Ala Glu
[3635] 165 170 175
[3636] Leu Ser Ala Ser His His His His His His
[3637] 180 185
[3638] <210> 105
[3639] <211> 247
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[3647] Gly Ser Thr Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
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[3649] Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[3650] 35 40 45
[3651] Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val
[3652] 50 55 60
[3653] Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
[3654] 65 70 75 80
[3655] Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
[3656] 85 90 95
[3657] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
[3658] 100 105 110
[3659] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
[3660] 115 120 125
[3661] Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[3662] 130 135 140
[3663] Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
[3664] 145 150 155 160
[3665] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

[3666] 165 170 175

[3667] Ile Ala Val Glu Trp Glu Ser Leu Gly His Val Trp Ala Val Tyr Lys

[3668] 180 185 190

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[3670] 195 200 205

[3671] Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln Gly Trp Val Phe Ser

[3672] 210 215 220

[3673] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

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[3676] 245

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[3678] <211> 12

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[3694] <223> Xaa可以是任何天然存在的氨基酸

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[3699] <211> 220

[3700] <212> PRT

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[3702] <220>

[3703] <223> 合成构建体

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[3707] Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val
[3708] 20 25 30
[3709] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3710] 35 40 45
[3711] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3712] 50 55 60
[3713] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3714] 65 70 75 80
[3715] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3716] 85 90 95
[3717] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3718] 100 105 110
[3719] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3720] 115 120 125
[3721] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3722] 130 135 140
[3723] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[3724] 145 150 155 160
[3725] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3726] 165 170 175
[3727] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3728] 180 185 190
[3729] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3730] 195 200 205
[3731] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3732] 210 215 220
[3733] <210> 108
[3734] <211> 220
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[3743] 20 25 30

[3744] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3745] 35 40 45
[3746] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3747] 50 55 60
[3748] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3749] 65 70 75 80
[3750] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3751] 85 90 95
[3752] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3753] 100 105 110
[3754] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3755] 115 120 125
[3756] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[3757] 130 135 140
[3758] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3759] 145 150 155 160
[3760] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3761] 165 170 175
[3762] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3763] 180 185 190
[3764] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3765] 195 200 205
[3766] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3767] 210 215 220
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[3777] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3778] 20 25 30
[3779] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3780] 35 40 45
[3781] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3782] 50 55 60

[3783] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3784] 65 70 75 80
[3785] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3786] 85 90 95
[3787] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3788] 100 105 110
[3789] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3790] 115 120 125
[3791] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3792] 130 135 140
[3793] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3794] 145 150 155 160
[3795] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3796] 165 170 175
[3797] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3798] 180 185 190
[3799] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3800] 195 200 205
[3801] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3802] 210 215 220
[3803] <210> 110
[3804] <211> 220
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[3807] <220>
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[3811] 1 5 10 15
[3812] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3813] 20 25 30
[3814] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3815] 35 40 45
[3816] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3817] 50 55 60
[3818] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3819] 65 70 75 80
[3820] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3821] 85 90 95

[3822] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3823] 100 105 110
[3824] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3825] 115 120 125
[3826] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3827] 130 135 140
[3828] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3829] 145 150 155 160
[3830] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3831] 165 170 175
[3832] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3833] 180 185 190
[3834] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3835] 195 200 205
[3836] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3837] 210 215 220
[3838] <210> 111
[3839] <211> 220
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[3846] 1 5 10 15
[3847] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3848] 20 25 30
[3849] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[3850] 35 40 45
[3851] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3852] 50 55 60
[3853] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3854] 65 70 75 80
[3855] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3856] 85 90 95
[3857] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3858] 100 105 110
[3859] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3860] 115 120 125

[3861] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3862] 130 135 140
[3863] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3864] 145 150 155 160
[3865] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3866] 165 170 175
[3867] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3868] 180 185 190
[3869] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3870] 195 200 205
[3871] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3872] 210 215 220
[3873] <210> 112
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[3883] 20 25 30
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[3885] 35 40 45
[3886] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[3887] 50 55 60
[3888] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3889] 65 70 75 80
[3890] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3891] 85 90 95
[3892] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3893] 100 105 110
[3894] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3895] 115 120 125
[3896] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3897] 130 135 140
[3898] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3899] 145 150 155 160

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[3901] 165 170 175
[3902] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3903] 180 185 190
[3904] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3905] 195 200 205
[3906] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3907] 210 215 220
[3908] <210> 113
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[3920] 35 40 45
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[3922] 50 55 60
[3923] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[3925] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3926] 85 90 95
[3927] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3928] 100 105 110
[3929] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[3930] 115 120 125
[3931] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3932] 130 135 140
[3933] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[3934] 145 150 155 160
[3935] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[3936] 165 170 175
[3937] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3938] 180 185 190

[3939] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[3940] 195 200 205
[3941] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3942] 210 215 220
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[3955] 35 40 45
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[3957] 50 55 60
[3958] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3959] 65 70 75 80
[3960] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3961] 85 90 95
[3962] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[3966] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[3967] 130 135 140
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[3971] 165 170 175
[3972] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[3973] 180 185 190
[3974] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[3977] 210 215 220

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[3987] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[3988] 20 25 30
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[3990] 35 40 45
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[3992] 50 55 60
[3993] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[3994] 65 70 75 80
[3995] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[3996] 85 90 95
[3997] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[3998] 100 105 110
[3999] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[4000] 115 120 125
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[4002] 130 135 140
[4003] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[4004] 145 150 155 160
[4005] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[4006] 165 170 175
[4007] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4008] 180 185 190
[4009] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[4010] 195 200 205
[4011] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4012] 210 215 220
[4013] <210> 116
[4014] <211> 220
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[4017] <220>

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[4025] 35 40 45

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[4027] 50 55 60

[4028] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[4029] 65 70 75 80

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[4035] 115 120 125

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[4039] 145 150 155 160

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[4043] 180 185 190

[4044] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[4046] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[4047] 210 215 220

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[4059] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[4060] 35 40 45
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[4062] 50 55 60
[4063] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[4064] 65 70 75 80
[4065] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[4066] 85 90 95
[4067] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[4078] 180 185 190
[4079] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[4081] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4082] 210 215 220
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[4095] 35 40 45
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[4108] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
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[4111] 165 170 175
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[4113] 180 185 190
[4114] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[4115] 195 200 205
[4116] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4117] 210 215 220
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[4130] 35 40 45
[4131] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[4133] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[4134] 65 70 75 80
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[4137] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[4143] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
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[4146] 165 170 175
[4147] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4148] 180 185 190
[4149] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[4150] 195 200 205
[4151] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4152] 210 215 220
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[4165] 35 40 45
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[4167] 50 55 60
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[4170] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[4171] 85 90 95
[4172] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[4173] 100 105 110
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[4177] 130 135 140
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[4179] 145 150 155 160
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[4181] 165 170 175
[4182] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4183] 180 185 190
[4184] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[4185] 195 200 205
[4186] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4187] 210 215 220
[4188] <210> 121
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[4198] 20 25 30
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[4202] 50 55 60
[4203] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[4204] 65 70 75 80
[4205] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
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[4208] 100 105 110
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[4217] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4218] 180 185 190
[4219] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[4221] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4222] 210 215 220
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[4236] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[4237] 50 55 60
[4238] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[4239] 65 70 75 80
[4240] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
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[4242] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[4249] 145 150 155 160
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[4251] 165 170 175
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[4254] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[4256] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4257] 210 215 220
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[4273] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[4290] 195 200 205

[4291] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[4292] 210 215 220

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[4297] <220>

[4298] <223> 合成构建体

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[4304] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[4305] 35 40 45

[4306] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[4307] 50 55 60

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[4309] 65 70 75 80

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[4311] 85 90 95

[4312] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[4313] 100 105 110

[4314] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[4315] 115 120 125

[4316] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly

[4317] 130 135 140

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[4319] 145 150 155 160

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[4322] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[4323] 180 185 190

[4324] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[4325] 195 200 205

[4326] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[4327] 210 215 220

[4328] <210> 125

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[4347] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[4348] 100 105 110
[4349] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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[4353] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[4354] 145 150 155 160
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[4356] 165 170 175
[4357] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4358] 180 185 190
[4359] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[4361] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4362] 210 215 220
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[4374] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[4375] 35 40 45

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[4381] 85 90 95

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[4383] 100 105 110

[4384] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[4385] 115 120 125

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[4393] 180 185 190

[4394] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[4396] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[4397] 210 215 220

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[4410] 35 40 45
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[4417] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[4419] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[4420] 115 120 125
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[4443] 20 25 30
[4444] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[4445] 35 40 45

[4446] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[4447] 50 55 60
[4448] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[4451] 85 90 95
[4452] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[4453] 100 105 110
[4454] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[4455] 115 120 125
[4456] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
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[4466] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4467] 210 215 220
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[4479] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[4480] 35 40 45
[4481] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[4482] 50 55 60
[4483] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[4484] 65 70 75 80

[4485] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[4486] 85 90 95
[4487] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[4489] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[4490] 115 120 125
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[4496] 165 170 175
[4497] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[4498] 180 185 190
[4499] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[4500] 195 200 205
[4501] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[4502] 210 215 220
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[4513] 20 25 30
[4514] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[4515] 35 40 45
[4516] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[4517] 50 55 60
[4518] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[4519] 65 70 75 80
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[4747] 210 215 220

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[4849] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[4976] 85 90 95

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[4980] 115 120 125

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[4988] 180 185 190

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[5012] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

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[5014] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[5015] 115 120 125

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[5017] 130 135 140

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[5019] 145 150 155 160

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[5024] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[5164] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5166] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[5167] 210 215 220
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[5199] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5201] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[5202] 210 215 220
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[5221] 85 90 95
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[5304] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5358] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[5374] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5408] 180 185 190

[5409] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[5411] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[5412] 210 215 220

[5413] <210> 156

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[5415] <212> PRT

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[5418] <223> 合成构建体

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[5424] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[5425] 35 40 45
[5426] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[5427] 50 55 60
[5428] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[5429] 65 70 75 80
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[5444] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5459] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[5460] 35 40 45
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[5467] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[5469] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[5470] 115 120 125
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[5472] 130 135 140
[5473] Phe Tyr Pro Ser Asp Ile Ala Val Leu Trp Glu Ser Tyr Gly Thr Glu
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[5477] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
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[5479] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5481] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[5482] 210 215 220
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[5494] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[5495] 35 40 45
[5496] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[5507] 130 135 140
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[5512] Phe Phe Leu Tyr Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln
[5513] 180 185 190
[5514] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[5516] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[5517] 210 215 220
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[6090] 35 40 45

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[6108] 180 185 190

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[6112] 210 215 220

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[6177] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

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[6179] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[6182] 210 215 220

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[6214] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[6306] 85 90 95
[6307] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
[6308] 100 105 110
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[6314] 145 150 155 160
[6315] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[6316] 165 170 175
[6317] Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu Trp Ser Ser Tyr Lys

[6318] 180 185 190

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[6320] 195 200 205

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[6328] <211> 220

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[6339] 35 40 45

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[6345] 85 90 95

[6346] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[6347] 100 105 110

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[6353] 145 150 155 160

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[6396] 210 215 220

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[6415] 85 90 95

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[6417] 100 105 110

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[6423] 145 150 155 160

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[6426] Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Thr Trp Gln Gln

[6427] 180 185 190

[6428] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[6431] 210 215 220

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[6460] 165 170 175

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[6462] 180 185 190

[6463] Gly Trp Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

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[6466] 210 215 220

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[7061] 210 215 220

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[7074] 35 40 45

[7075] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[7076] 50 55 60

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[7078] 65 70 75 80

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[7080] 85 90 95

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[7084] 115 120 125

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[7090] 165 170 175

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[7094] 195 200 205

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[7144] 35 40 45

[7145] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

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[7148] 65 70 75 80

[7149] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[7150] 85 90 95

[7151] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[7152] 100 105 110

[7153] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[7154] 115 120 125

[7155] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly

[7156] 130 135 140

[7157] Phe Tyr Pro Ser Asp Ile Ala Val Trp Trp Glu Ser Tyr Gly Thr Glu

[7158] 145 150 155 160

[7159] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[7160] 165 170 175

[7161] Phe Phe Leu Val Ser Lys Leu Thr Val Thr Lys Glu Glu Trp Gln Gln

[7162] 180 185 190

[7163] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[7164] 195 200 205

[7165] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[7166] 210 215 220

[7167] <210> 206

[7168] <211> 220

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[7171] <220>

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[7179] 35 40 45
[7180] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7181] 50 55 60
[7182] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[7183] 65 70 75 80
[7184] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[7185] 85 90 95
[7186] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[7198] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7199] 195 200 205
[7200] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7201] 210 215 220
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[7214] 35 40 45

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[7233] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7234] 195 200 205
[7235] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7236] 210 215 220
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[7248] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[7249] 35 40 45
[7250] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7251] 50 55 60
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[7268] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7269] 195 200 205
[7270] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7271] 210 215 220
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[7284] 35 40 45
[7285] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7286] 50 55 60
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[7290] 85 90 95
[7291] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[7303] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7304] 195 200 205
[7305] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7306] 210 215 220
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[7319] 35 40 45
[7320] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[7325] 85 90 95
[7326] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[7329] 115 120 125
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[7331] 130 135 140

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[7337] 180 185 190
[7338] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[7341] 210 215 220
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[7356] 50 55 60
[7357] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[7358] 65 70 75 80
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[7360] 85 90 95
[7361] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
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[7367] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
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[7370] 165 170 175

[7371] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[7372] 180 185 190
[7373] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7374] 195 200 205
[7375] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7376] 210 215 220
[7377] <210> 212
[7378] <211> 220
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[7387] 20 25 30
[7388] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[7389] 35 40 45
[7390] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7391] 50 55 60
[7392] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[7393] 65 70 75 80
[7394] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[7395] 85 90 95
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[7407] 180 185 190
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[7422] 20 25 30
[7423] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[7424] 35 40 45
[7425] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7426] 50 55 60
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[7443] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[7457] 20 25 30
[7458] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[7459] 35 40 45
[7460] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7461] 50 55 60
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[7465] 85 90 95
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[7467] 100 105 110
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[7469] 115 120 125
[7470] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[7471] 130 135 140
[7472] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[7473] 145 150 155 160
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[7475] 165 170 175
[7476] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[7477] 180 185 190
[7478] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[7479] 195 200 205
[7480] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[7481] 210 215 220
[7482] <210> 215
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[7484] <212> PRT
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[7488] <400> 215

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[7491] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

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[7493] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

[7494] 35 40 45

[7495] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

[7496] 50 55 60

[7497] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

[7498] 65 70 75 80

[7499] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[7500] 85 90 95

[7501] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

[7502] 100 105 110

[7503] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[7504] 115 120 125

[7505] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly

[7506] 130 135 140

[7507] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu

[7508] 145 150 155 160

[7509] Trp Ser Ser Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[7510] 165 170 175

[7511] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln

[7512] 180 185 190

[7513] Gly Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

[7514] 195 200 205

[7515] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[7516] 210 215 220

[7517] <210> 216

[7518] <211> 220

[7519] <212> PRT

[7520] <213> 人工序列(Artificial Sequence)

[7521] <220>

[7522] <223> 合成构建体

[7523] <400> 216

[7524] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe

[7525] 1 5 10 15

[7526] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

[7527] 20 25 30
[7528] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[7529] 35 40 45
[7530] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[7531] 50 55 60
[7532] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[7533] 65 70 75 80
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[8527] 180 185 190

[8528] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His

[8529] 195 200 205

[8530] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[8531] 210 215 220

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[10548] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

[10549] 115 120 125

[10550] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly

[10551] 130 135 140

[10552] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu

[10553] 145 150 155 160

[10554] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

[10555] 165 170 175

[10556] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Ser Glu Trp Gln Gln

[10557] 180 185 190

[10558] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His

[10559] 195 200 205

[10560] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[10561] 210 215 220

[10562] <210> 303

[10563] <211> 220

[10564] <212> PRT

[10565] <213> 人工序列(Artificial Sequence)

[10566] <220>

[10567] <223> 合成构建体

[10568] <400> 303

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[10571] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10572] 20 25 30
[10573] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10574] 35 40 45
[10575] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10576] 50 55 60
[10577] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10578] 65 70 75 80
[10579] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10580] 85 90 95
[10581] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10582] 100 105 110
[10583] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10584] 115 120 125
[10585] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[10586] 130 135 140
[10587] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[10588] 145 150 155 160
[10589] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10590] 165 170 175
[10591] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Ser Glu Trp Gln Gln
[10592] 180 185 190
[10593] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10594] 195 200 205
[10595] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10596] 210 215 220
[10597] <210> 304
[10598] <211> 220
[10599] <212> PRT
[10600] <213> 人工序列(Artificial Sequence)
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[10605] 1 5 10 15
[10606] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10607] 20 25 30

[10608] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10609] 35 40 45
[10610] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10611] 50 55 60
[10612] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10613] 65 70 75 80
[10614] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10615] 85 90 95
[10616] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10617] 100 105 110
[10618] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10619] 115 120 125
[10620] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10621] 130 135 140
[10622] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[10623] 145 150 155 160
[10624] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10625] 165 170 175
[10626] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Ser Glu Trp Gln Gln
[10627] 180 185 190
[10628] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10629] 195 200 205
[10630] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10631] 210 215 220
[10632] <210> 305
[10633] <211> 220
[10634] <212> PRT
[10635] <213> 人工序列(Artificial Sequence)
[10636] <220>
[10637] <223> 合成构建体
[10638] <400> 305
[10639] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
[10640] 1 5 10 15
[10641] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10642] 20 25 30
[10643] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10644] 35 40 45
[10645] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10646] 50 55 60

[10647] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10648] 65 70 75 80
[10649] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10650] 85 90 95
[10651] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10652] 100 105 110
[10653] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10654] 115 120 125
[10655] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10656] 130 135 140
[10657] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[10658] 145 150 155 160
[10659] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10660] 165 170 175
[10661] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Ser Glu Trp Gln Gln
[10662] 180 185 190
[10663] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10664] 195 200 205
[10665] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10666] 210 215 220
[10667] <210> 306
[10668] <211> 220
[10669] <212> PRT
[10670] <213> 人工序列(Artificial Sequence)
[10671] <220>
[10672] <223> 合成构建体
[10673] <400> 306
[10674] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
[10675] 1 5 10 15
[10676] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10677] 20 25 30
[10678] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10679] 35 40 45
[10680] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10681] 50 55 60
[10682] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10683] 65 70 75 80
[10684] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10685] 85 90 95

[10686] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10687] 100 105 110
[10688] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10689] 115 120 125
[10690] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10691] 130 135 140
[10692] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Tyr Gly Thr Glu
[10693] 145 150 155 160
[10694] Trp Ala Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10695] 165 170 175
[10696] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Ser Glu Trp Gln Gln
[10697] 180 185 190
[10698] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10699] 195 200 205
[10700] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10701] 210 215 220
[10702] <210> 307
[10703] <211> 220
[10704] <212> PRT
[10705] <213> 人工序列(Artificial Sequence)
[10706] <220>
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[10708] <400> 307
[10709] Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
[10710] 1 5 10 15
[10711] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10712] 20 25 30
[10713] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10714] 35 40 45
[10715] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10716] 50 55 60
[10717] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10718] 65 70 75 80
[10719] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10720] 85 90 95
[10721] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10722] 100 105 110
[10723] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10724] 115 120 125

[10725] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[10726] 130 135 140
[10727] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10728] 145 150 155 160
[10729] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10730] 165 170 175
[10731] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10732] 180 185 190
[10733] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10734] 195 200 205
[10735] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10736] 210 215 220
[10737] <210> 308
[10738] <211> 220
[10739] <212> PRT
[10740] <213> 人工序列(Artificial Sequence)
[10741] <220>
[10742] <223> 合成构建体
[10743] <400> 308
[10744] Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
[10745] 1 5 10 15
[10746] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10747] 20 25 30
[10748] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10749] 35 40 45
[10750] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10751] 50 55 60
[10752] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10753] 65 70 75 80
[10754] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10755] 85 90 95
[10756] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10757] 100 105 110
[10758] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10759] 115 120 125
[10760] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[10761] 130 135 140
[10762] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10763] 145 150 155 160

[10764] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10765] 165 170 175
[10766] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10767] 180 185 190
[10768] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10769] 195 200 205
[10770] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10771] 210 215 220
[10772] <210> 309
[10773] <211> 220
[10774] <212> PRT
[10775] <213> 人工序列(Artificial Sequence)
[10776] <220>
[10777] <223> 合成构建体
[10778] <400> 309
[10779] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
[10780] 1 5 10 15
[10781] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10782] 20 25 30
[10783] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10784] 35 40 45
[10785] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10786] 50 55 60
[10787] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10788] 65 70 75 80
[10789] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10790] 85 90 95
[10791] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10792] 100 105 110
[10793] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10794] 115 120 125
[10795] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[10796] 130 135 140
[10797] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10798] 145 150 155 160
[10799] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10800] 165 170 175
[10801] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10802] 180 185 190

[10803] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10804] 195 200 205
[10805] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10806] 210 215 220
[10807] <210> 310
[10808] <211> 220
[10809] <212> PRT
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[10815] 1 5 10 15
[10816] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10817] 20 25 30
[10818] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10819] 35 40 45
[10820] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10821] 50 55 60
[10822] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10823] 65 70 75 80
[10824] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10825] 85 90 95
[10826] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10827] 100 105 110
[10828] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10829] 115 120 125
[10830] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
[10831] 130 135 140
[10832] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10833] 145 150 155 160
[10834] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10835] 165 170 175
[10836] Phe Phe Leu Tyr Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10837] 180 185 190
[10838] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10839] 195 200 205
[10840] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10841] 210 215 220

[10842] <210> 311
[10843] <211> 220
[10844] <212> PRT
[10845] <213> 人工序列(Artificial Sequence)
[10846] <220>
[10847] <223> 合成构建体
[10848] <400> 311
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[10851] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10852] 20 25 30
[10853] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10854] 35 40 45
[10855] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10856] 50 55 60
[10857] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10858] 65 70 75 80
[10859] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10860] 85 90 95
[10861] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10862] 100 105 110
[10863] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10864] 115 120 125
[10865] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10866] 130 135 140
[10867] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10868] 145 150 155 160
[10869] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10870] 165 170 175
[10871] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10872] 180 185 190
[10873] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10874] 195 200 205
[10875] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10876] 210 215 220
[10877] <210> 312
[10878] <211> 220
[10879] <212> PRT
[10880] <213> 人工序列(Artificial Sequence)

[10881] <220>
[10882] <223> 合成构建体
[10883] <400> 312
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[10885] 1 5 10 15
[10886] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10887] 20 25 30
[10888] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10889] 35 40 45
[10890] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10891] 50 55 60
[10892] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10893] 65 70 75 80
[10894] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10895] 85 90 95
[10896] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10897] 100 105 110
[10898] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10899] 115 120 125
[10900] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10901] 130 135 140
[10902] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10903] 145 150 155 160
[10904] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10905] 165 170 175
[10906] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10907] 180 185 190
[10908] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10909] 195 200 205
[10910] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10911] 210 215 220
[10912] <210> 313
[10913] <211> 220
[10914] <212> PRT
[10915] <213> 人工序列(Artificial Sequence)
[10916] <220>
[10917] <223> 合成构建体
[10918] <400> 313
[10919] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe

[10920] 1 5 10 15
[10921] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[10922] 20 25 30
[10923] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[10924] 35 40 45
[10925] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[10926] 50 55 60
[10927] Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[10928] 65 70 75 80
[10929] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[10930] 85 90 95
[10931] Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[10932] 100 105 110
[10933] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[10934] 115 120 125
[10935] Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
[10936] 130 135 140
[10937] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Phe Gly Thr Glu
[10938] 145 150 155 160
[10939] Trp Ser Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[10940] 165 170 175
[10941] Phe Phe Leu Val Ser Lys Leu Thr Val Ser Lys Glu Glu Trp Gln Gln
[10942] 180 185 190
[10943] Gly Phe Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His
[10944] 195 200 205
[10945] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[10946] 210 215 220
[10947] <210> 314
[10948] <211> 11
[10949] <212> PRT
[10950] <213> 人工序列(Artificial Sequence)
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[10952] <223> 合成构建体
[10953] <220>
[10954] <221> MISC_FEATURE
[10955] <222> (1)..(1)
[10956] <223> Xaa = Glu、Leu、Ser、Val、Trp或Tyr
[10957] <220>
[10958] <221> MISC_FEATURE

[10959] <222> (5)..(5)
[10960] <223> Xaa = 芳香族氨基酸(例如,Tyr、Phe或Trp)、Met、Pro
[10961] 或Val
[10962] <220>
[10963] <221> MISC_FEATURE
[10964] <222> (7)..(7)
[10965] <223> Xaa = Thr、Asn或Val
[10966] <220>
[10967] <221> MISC_FEATURE
[10968] <222> (8)..(8)
[10969] <223> Xaa = Glu、Ile、Pro或Val
[10970] <220>
[10971] <221> MISC_FEATURE
[10972] <222> (10)..(10)
[10973] <223> Xaa = 脂肪族氨基酸(例如,Ala、Ile或Val)、Ser或
[10974] Thr
[10975] <220>
[10976] <221> MISC_FEATURE
[10977] <222> (11)..(11)
[10978] <223> Xaa = Ser、Asn、Arg或Thr
[10979] <400> 314
[10980] Xaa Trp Glu Ser Xaa Gly Xaa Xaa Trp Xaa Xaa
[10981] 1 5 10
[10982] <210> 315
[10983] <211> 14
[10984] <212> PRT
[10985] <213> 人工序列(Artificial Sequence)
[10986] <220>
[10987] <223> 合成构建体
[10988] <220>
[10989] <221> MISC_FEATURE
[10990] <222> (1)..(1)
[10991] <223> Xaa = Thr、His或Ser
[10992] <220>
[10993] <221> MISC_FEATURE
[10994] <222> (3)..(3)
[10995] <223> Xaa = Glu、Ser、Asp、Gly、Thr、Pro、Gln或Arg
[10996] <220>
[10997] <221> MISC_FEATURE

[10998] <222> (4)..(4)
[10999] <223> Xaa = Glu或Arg
[11000] <220>
[11001] <221> MISC_FEATURE
[11002] <222> (9)..(9)
[11003] <223> Xaa = Phe、His、Lys、Tyr或Trp
[11004] <220>
[11005] <221> MISC_FEATURE
[11006] <222> (12)..(12)
[11007] <223> Xaa = Ser、Thr或Trp
[11008] <220>
[11009] <221> MISC_FEATURE
[11010] <222> (14)..(14)
[11011] <223> Xaa = Ser、Cys、Pro、Met或Trp
[11012] <400> 315
[11013] Xaa Lys Xaa Xaa Trp Gln Gln Gly Xaa Val Phe Xaa Cys Xaa
[11014] 1 5 10
[11015] <210> 316
[11016] <211> 107
[11017] <212> PRT
[11018] <213> 人工序列(Artificial Sequence)
[11019] <220>
[11020] <223> 合成构建体
[11021] <220>
[11022] <221> MISC_FEATURE
[11023] <222> (40)..(40)
[11024] <223> Xaa = Glu、Leu、Ser、Val、Trp或Tyr
[11025] <220>
[11026] <221> MISC_FEATURE
[11027] <222> (44)..(44)
[11028] <223> Xaa = 芳香族氨基酸(例如,Tyr、Phe或Trp)、Met、Pro、
[11029] 或Val
[11030] <220>
[11031] <221> MISC_FEATURE
[11032] <222> (46)..(46)
[11033] <223> Xaa = Thr、Asn或Val
[11034] <220>
[11035] <221> MISC_FEATURE
[11036] <222> (47)..(47)

[11037] <223> Xaa = Glu、Ile、Pro或Val
[11038] <220>
[11039] <221> MISC_FEATURE
[11040] <222> (49)..(49)
[11041] <223> Xaa = 脂肪族氨基酸(例如,Ala、Ile或Val)、Ser或
[11042] Thr
[11043] <220>
[11044] <221> MISC_FEATURE
[11045] <222> (50)..(50)
[11046] <223> Xaa = Ser、Asn、Arg或Thr
[11047] <220>
[11048] <221> MISC_FEATURE
[11049] <222> (73)..(73)
[11050] <223> Xaa = Thr、His或Ser
[11051] <220>
[11052] <221> MISC_FEATURE
[11053] <222> (75)..(75)
[11054] <223> Xaa = Glu、Ser、Asp、Gly、Thr、Pro、Gln或Arg
[11055] <220>
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[11080] Phe Leu Tyr Ser Lys Leu Thr Val Xaa Lys Xaa Xaa Trp Gln Gln Gly
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[11172] 35 40 45
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[11176] 65 70 75 80
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[11263] 65 70 75 80
[11264] Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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[11313] 65 70 75 80
[11314] Phe Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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[11509] 35 40 45
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[11597] <223> Xaa = Leu、His、Gln、Gly、Val、Ala、Asn、Asp、Thr或Glu
[11598] <220>
[11599] <221> MISC_FEATURE
[11600] <222> (12)..(12)
[11601] <223> Xaa = Thr、Phe、Gln、Val或Tyr
[11602] <400> 335
[11603] Xaa Trp Glu Ser Xaa Gly Xaa Xaa Trp Xaa Xaa Xaa
[11604] 1 5 10
[11605] <210> 336
[11606] <211> 9
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[11610] <223> 合成构建体
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[11612] <221> MISC_FEATURE
[11613] <222> (1)..(1)
[11614] <223> Xaa = Leu、Ser、Glu、Ala或Pro
[11615] <220>
[11616] <221> MISC_FEATURE
[11617] <222> (4)..(4)
[11618] <223> Xaa = Glu、Asp、Thr或Asn
[11619] <220>
[11620] <221> MISC_FEATURE
[11621] <222> (9)..(9)

[11622] <223> Xaa = Trp、Tyr、His或Phe
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[11624] Xaa Lys Ser Xaa Trp Gln Gln Gly Xaa
[11625] 1 5
[11626] <210> 337
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[11634] <222> (40)..(40)
[11635] <223> Xaa = Glu或Trp
[11636] <220>
[11637] <221> MISC_FEATURE
[11638] <222> (44)..(44)
[11639] <223> Xaa = Val、Trp、Leu或Tyr
[11640] <220>
[11641] <221> MISC_FEATURE
[11642] <222> (46)..(46)
[11643] <223> Xaa = Leu、Pro、Phe、Thr或His
[11644] <220>
[11645] <221> MISC_FEATURE
[11646] <222> (47)..(47)
[11647] <223> Xaa = Pro、Val或Glu
[11648] <220>
[11649] <221> MISC_FEATURE
[11650] <222> (49)..(49)
[11651] <223> Xaa = Ala、Ser、Val或Gly
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[11654] <222> (50)..(50)
[11655] <223> Xaa = Leu、His、Gln、Gly、Val、Ala、Asn、Asp、Thr或Glu
[11656] <220>
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[11659] <223> Xaa = Thr、Phe、Gln、Val或Tyr
[11660] <220>

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[11663] <223> Xaa = Leu、Ser、Glu、Ala或Pro
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[11666] <222> (76)..(76)
[11667] <223> Xaa = Glu、Asp、Thr或Asn
[11668] <220>
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[11670] <222> (81)..(81)
[11671] <223> Xaa = Trp、Tyr、His或Phe
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[11674] 1 5 10 15
[11675] Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[11676] 20 25 30
[11677] Tyr Pro Ser Asp Ile Ala Val Xaa Trp Glu Ser Xaa Gly Xaa Xaa Trp
[11678] 35 40 45
[11679] Xaa Xaa Xaa Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[11680] 50 55 60
[11681] Phe Leu Tyr Ser Lys Leu Thr Val Xaa Lys Ser Xaa Trp Gln Gln Gly
[11682] 65 70 75 80
[11683] Xaa Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[11684] 85 90 95
[11685] Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[11686] 100 105
[11687] <210> 338
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[11689] <212> PRT
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[11696] <223> Xaa = Glu或Trp
[11697] <220>
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[11699] <222> (5)..(5)

[11700] <223> Xaa = Trp、Leu或Tyr
[11701] <220>
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[11703] <222> (7)..(7)
[11704] <223> Xaa = Thr或His
[11705] <220>
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[11707] <222> (10)..(10)
[11708] <223> Xaa = Ala、Ser或Val
[11709] <220>
[11710] <221> MISC_FEATURE
[11711] <222> (11)..(11)
[11712] <223> Xaa = Val、Thr或Asn
[11713] <220>
[11714] <221> MISC_FEATURE
[11715] <222> (12)..(12)
[11716] <223> Xaa = Tyr或Gln
[11717] <400> 338
[11718] Xaa Trp Glu Ser Xaa Gly Xaa Val Trp Xaa Xaa Xaa
[11719] 1 5 10
[11720] <210> 339
[11721] <211> 9
[11722] <212> PRT
[11723] <213> 人工序列(Artificial Sequence)
[11724] <220>
[11725] <223> 合成构建体
[11726] <220>
[11727] <221> MISC_FEATURE
[11728] <222> (4)..(4)
[11729] <223> Xaa = Thr或Asn
[11730] <220>
[11731] <221> MISC_FEATURE
[11732] <222> (9)..(9)
[11733] <223> Xaa = Trp、Tyr、His或Phe
[11734] <400> 339
[11735] Pro Lys Ser Xaa Trp Gln Gln Gly Xaa
[11736] 1 5
[11737] <210> 340
[11738] <211> 107

[11739] <212> PRT
[11740] <213> 人工序列(Artificial Sequence)
[11741] <220>
[11742] <223> 合成构建体
[11743] <220>
[11744] <221> MISC_FEATURE
[11745] <222> (40)..(40)
[11746] <223> Xaa = Glu或Trp
[11747] <220>
[11748] <221> MISC_FEATURE
[11749] <222> (44)..(44)
[11750] <223> Xaa = Trp、Leu或Tyr
[11751] <220>
[11752] <221> MISC_FEATURE
[11753] <222> (46)..(46)
[11754] <223> Xaa = Thr或His
[11755] <220>
[11756] <221> MISC_FEATURE
[11757] <222> (49)..(49)
[11758] <223> Xaa = Ala、Ser或Val
[11759] <220>
[11760] <221> MISC_FEATURE
[11761] <222> (50)..(50)
[11762] <223> Xaa = Val、Thr或Asn
[11763] <220>
[11764] <221> MISC_FEATURE
[11765] <222> (51)..(51)
[11766] <223> Xaa = Tyr或Gln
[11767] <220>
[11768] <221> MISC_FEATURE
[11769] <222> (76)..(76)
[11770] <223> Xaa = Thr或Asn
[11771] <220>
[11772] <221> MISC_FEATURE
[11773] <222> (81)..(81)
[11774] <223> Xaa = Trp、Tyr、His或Phe
[11775] <400> 340
[11776] Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
[11777] 1 5 10 15

[11778] Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[11779] 20 25 30
[11780] Tyr Pro Ser Asp Ile Ala Val Xaa Trp Glu Ser Xaa Gly Xaa Val Trp
[11781] 35 40 45
[11782] Xaa Xaa Xaa Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[11783] 50 55 60
[11784] Phe Leu Tyr Ser Lys Leu Thr Val Pro Lys Ser Xaa Trp Gln Gln Gly
[11785] 65 70 75 80
[11786] Xaa Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[11787] 85 90 95
[11788] Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[11789] 100 105
[11790] <210> 341
[11791] <211> 5
[11792] <212> PRT
[11793] <213> 人工序列(Artificial Sequence)
[11794] <220>
[11795] <223> 合成构建体
[11796] <220>
[11797] <221> misc_feature
[11798] <222> (2)..(2)
[11799] <223> Xaa可以是任何天然存在的氨基酸
[11800] <220>
[11801] <221> misc_feature
[11802] <222> (5)..(5)
[11803] <223> Xaa可以是任何天然存在的氨基酸
[11804] <400> 341
[11805] Thr Xaa Trp Ser Xaa
[11806] 1 5
[11807] <210> 342
[11808] <211> 181
[11809] <212> PRT
[11810] <213> 人工序列(Artificial Sequence)
[11811] <220>
[11812] <223> 合成构建体
[11813] <220>
[11814] <221> MISC_FEATURE
[11815] <222> (97)..(97)
[11816] <223> Xaa = Asp或Glu

[11817] <400> 342

[11818] Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu Val Tyr Leu Val
[11819] 1 5 10 15

[11820] Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala Ala Thr Val Thr
[11821] 20 25 30

[11822] Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys Asp Phe Glu Asp
[11823] 35 40 45

[11824] Leu Asp Ser Pro Val Asn Gly Ser Ile Val Ile Val Arg Ala Gly Lys
[11825] 50 55 60

[11826] Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser Leu Asn Ala Ile
[11827] 65 70 75 80

[11828] Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro Ile Val Asn Ala
[11829] 85 90 95

[11830] Xaa Leu Ser Phe Phe Gly His Ala His Leu Gly Thr Gly Asp Pro Tyr
[11831] 100 105 110

[11832] Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe Pro Pro Ser Arg
[11833] 115 120 125

[11834] Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile Ser Arg Ala Ala
[11835] 130 135 140

[11836] Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys Pro Ser Asp Trp
[11837] 145 150 155 160

[11838] Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser Glu Asn Lys Asn Val
[11839] 165 170 175

[11840] Lys Leu Thr Val Ser
[11841] 180

[11842] <210> 343

[11843] <211> 330

[11844] <212> PRT

[11845] <213> 智人(Homo sapiens)

[11846] <400> 343

[11847] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
[11848] 1 5 10 15

[11849] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[11850] 20 25 30

[11851] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[11852] 35 40 45

[11853] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[11854] 50 55 60

[11855] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr

[11856] 65 70 75 80
[11857] Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[11858] 85 90 95
[11859] Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
[11860] 100 105 110
[11861] Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[11862] 115 120 125
[11863] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[11864] 130 135 140
[11865] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[11866] 145 150 155 160
[11867] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[11868] 165 170 175
[11869] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[11870] 180 185 190
[11871] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[11872] 195 200 205
[11873] Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[11874] 210 215 220
[11875] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
[11876] 225 230 235 240
[11877] Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[11878] 245 250 255
[11879] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[11880] 260 265 270
[11881] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[11882] 275 280 285
[11883] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[11884] 290 295 300
[11885] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[11886] 305 310 315 320
[11887] Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[11888] 325 330
[11889] <210> 344
[11890] <211> 326
[11891] <212> PRT
[11892] <213> 智人(Homo sapiens)
[11893] <400> 344
[11894] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg

[11895] 1 5 10 15
[11896] Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[11897] 20 25 30
[11898] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[11899] 35 40 45
[11900] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[11901] 50 55 60
[11902] Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
[11903] 65 70 75 80
[11904] Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
[11905] 85 90 95
[11906] Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
[11907] 100 105 110
[11908] Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
[11909] 115 120 125
[11910] Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
[11911] 130 135 140
[11912] Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
[11913] 145 150 155 160
[11914] Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
[11915] 165 170 175
[11916] Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
[11917] 180 185 190
[11918] Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
[11919] 195 200 205
[11920] Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
[11921] 210 215 220
[11922] Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
[11923] 225 230 235 240
[11924] Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
[11925] 245 250 255
[11926] Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
[11927] 260 265 270
[11928] Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
[11929] 275 280 285
[11930] Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
[11931] 290 295 300
[11932] Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
[11933] 305 310 315 320

[11934] Ser Leu Ser Pro Gly Lys
[11935] 325
[11936] <210> 345
[11937] <211> 377
[11938] <212> PRT
[11939] <213> 智人(Homo sapiens)
[11940] <400> 345
[11941] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
[11942] 1 5 10 15
[11943] Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[11944] 20 25 30
[11945] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[11946] 35 40 45
[11947] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[11948] 50 55 60
[11949] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
[11950] 65 70 75 80
[11951] Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
[11952] 85 90 95
[11953] Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
[11954] 100 105 110
[11955] Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
[11956] 115 120 125
[11957] Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
[11958] 130 135 140
[11959] Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
[11960] 145 150 155 160
[11961] Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[11962] 165 170 175
[11963] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[11964] 180 185 190
[11965] Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
[11966] 195 200 205
[11967] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[11968] 210 215 220
[11969] Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
[11970] 225 230 235 240
[11971] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[11972] 245 250 255

[11973] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
[11974] 260 265 270
[11975] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
[11976] 275 280 285
[11977] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
[11978] 290 295 300
[11979] Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
[11980] 305 310 315 320
[11981] Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
[11982] 325 330 335
[11983] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
[11984] 340 345 350
[11985] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
[11986] 355 360 365
[11987] Lys Ser Leu Ser Leu Ser Pro Gly Lys
[11988] 370 375
[11989] <210> 346
[11990] <211> 327
[11991] <212> PRT
[11992] <213> 智人(Homo sapiens)
[11993] <400> 346
[11994] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
[11995] 1 5 10 15
[11996] Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[11997] 20 25 30
[11998] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[11999] 35 40 45
[12000] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[12001] 50 55 60
[12002] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
[12003] 65 70 75 80
[12004] Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
[12005] 85 90 95
[12006] Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
[12007] 100 105 110
[12008] Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[12009] 115 120 125
[12010] Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[12011] 130 135 140

[12012] Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
[12013] 145 150 155 160
[12014] Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
[12015] 165 170 175
[12016] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
[12017] 180 185 190
[12018] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
[12019] 195 200 205
[12020] Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[12021] 210 215 220
[12022] Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
[12023] 225 230 235 240
[12024] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[12025] 245 250 255
[12026] Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
[12027] 260 265 270
[12028] Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[12029] 275 280 285
[12030] Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
[12031] 290 295 300
[12032] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
[12033] 305 310 315 320
[12034] Leu Ser Leu Ser Leu Gly Lys
[12035] 325
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[12038] <212> PRT
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[12044] <222> (154)..(154)
[12045] <223> Xaa = Phe或Tyr
[12046] <220>
[12047] <221> MISC_FEATURE
[12048] <222> (159)..(159)
[12049] <223> Xaa = Ser、Ala或Val
[12050] <220>

[12051] <221> MISC_FEATURE
[12052] <222> (183)..(183)
[12053] <223> Xaa = Ser或Thr
[12054] <220>
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[12056] <222> (198)..(198)
[12057] <223> Xaa = Met或Leu
[12058] <220>
[12059] <221> MISC_FEATURE
[12060] <222> (204)..(204)
[12061] <223> Xaa = Asn或Ser
[12062] <400> 347
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[12065] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[12066] 20 25 30
[12067] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[12068] 35 40 45
[12069] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[12070] 50 55 60
[12071] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[12072] 65 70 75 80
[12073] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[12074] 85 90 95
[12075] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[12076] 100 105 110
[12077] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
[12078] 115 120 125
[12079] Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
[12080] 130 135 140
[12081] Ser Asp Ile Ala Val Glu Trp Glu Ser Xaa Gly Thr Glu Trp Xaa Asn
[12082] 145 150 155 160
[12083] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[12084] 165 170 175
[12085] Tyr Ser Lys Leu Thr Val Xaa Lys Glu Glu Trp Gln Gln Gly Phe Val
[12086] 180 185 190
[12087] Phe Ser Cys Ser Val Xaa His Glu Ala Leu His Xaa His Tyr Thr Gln
[12088] 195 200 205
[12089] Lys Ser Leu Ser Leu Ser Pro Gly Lys

[12090] 210 215

[12091] <210> 348

[12092] <211> 217

[12093] <212> PRT

[12094] <213> 人工序列(Artificial Sequence)

[12095] <220>

[12096] <223> 合成构建体

[12097] <220>

[12098] <221> MISC_FEATURE

[12099] <222> (154)..(154)

[12100] <223> Xaa = Phe或Tyr

[12101] <220>

[12102] <221> MISC_FEATURE

[12103] <222> (159)..(159)

[12104] <223> Xaa = Ser、Ala或Val

[12105] <220>

[12106] <221> MISC_FEATURE

[12107] <222> (183)..(183)

[12108] <223> Xaa = Ser或Thr

[12109] <220>

[12110] <221> MISC_FEATURE

[12111] <222> (198)..(198)

[12112] <223> Xaa = Met或Leu

[12113] <220>

[12114] <221> MISC_FEATURE

[12115] <222> (204)..(204)

[12116] <223> Xaa = Asn或Ser

[12117] <400> 348

[12118] Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys

[12119] 1 5 10 15

[12120] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

[12121] 20 25 30

[12122] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

[12123] 35 40 45

[12124] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

[12125] 50 55 60

[12126] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

[12127] 65 70 75 80

[12128] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

[12129] 85 90 95
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[12131] 100 105 110
[12132] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
[12133] 115 120 125
[12134] Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
[12135] 130 135 140
[12136] Ser Asp Ile Ala Val Glu Trp Glu Ser Xaa Gly Thr Glu Trp Xaa Asn
[12137] 145 150 155 160
[12138] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[12139] 165 170 175
[12140] Val Ser Lys Leu Thr Val Xaa Lys Glu Glu Trp Gln Gln Gly Phe Val
[12141] 180 185 190
[12142] Phe Ser Cys Ser Val Xaa His Glu Ala Leu His Xaa His Tyr Thr Gln
[12143] 195 200 205
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[12168] 50 55 60

[12169] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

[12170] 65 70 75 80

[12171] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

[12172] 85 90 95

[12173] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

[12174] 100 105 110

[12175] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu

[12176] 115 120 125

[12177] Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro

[12178] 130 135 140

[12179] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

[12180] 145 150 155 160

[12181] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

[12182] 165 170 175

[12183] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

[12184] 180 185 190

[12185] Phe Ser Cys Ser Val Xaa His Glu Ala Leu His Xaa His Tyr Thr Gln

[12186] 195 200 205

[12187] Lys Ser Leu Ser Leu Ser Pro Gly Lys

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[12209] 35 40 45
[12210] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[12211] 50 55 60
[12212] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[12213] 65 70 75 80
[12214] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[12215] 85 90 95
[12216] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[12217] 100 105 110
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[12225] 165 170 175
[12226] Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[12227] 180 185 190
[12228] Phe Ser Cys Ser Val Xaa His Glu Ala Leu His Xaa His Tyr Thr Gln
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[12244] 35 40 45
[12245] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

[12246] 50 55 60

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[12252] 100 105 110

[12253] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu

[12254] 115 120 125

[12255] Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro

[12256] 130 135 140

[12257] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

[12258] 145 150 155 160

[12259] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

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[12261] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

[12262] 180 185 190

[12263] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

[12264] 195 200 205

[12265] Lys Ser Leu Ser Leu Ser Pro Gly Lys

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[12278] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

[12279] 35 40 45

[12280] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

[12281] 50 55 60

[12282] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

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[12294] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
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[12296] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[12297] 180 185 190
[12298] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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[12319] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
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[12324] 115 120 125
[12325] Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
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[12327] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
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[12329] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
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[12332] 180 185 190
[12333] Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His Tyr Thr Gln
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[12335] Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[12348] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[12349] 35 40 45
[12350] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[12351] 50 55 60
[12352] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
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[12363] 145 150 155 160
[12364] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[12365] 165 170 175
[12366] Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[12367] 180 185 190
[12368] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
[12369] 195 200 205
[12370] Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[12384] 35 40 45
[12385] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[12386] 50 55 60
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[12389] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
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[12394] 115 120 125
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[12399] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[12400] 165 170 175
[12401] Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

[12402] 180 185 190
[12403] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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[12405] Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[12419] 35 40 45
[12420] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[12421] 50 55 60
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[12423] 65 70 75 80
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[12426] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[12427] 100 105 110
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[12429] 115 120 125
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[12436] Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[12437] 180 185 190
[12438] Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ser His Tyr Thr Gln
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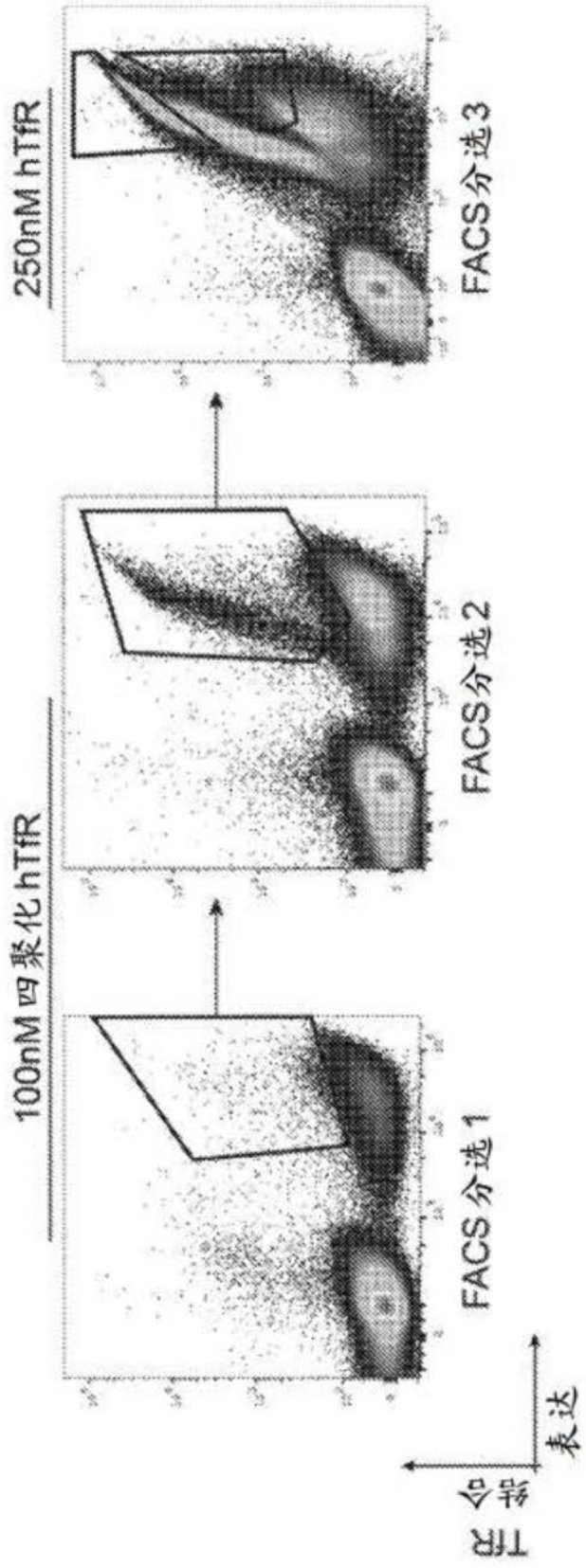


图1

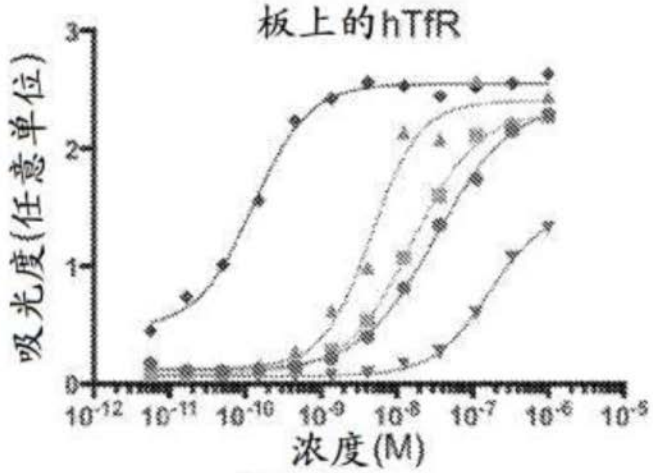

板上的hTfR
吸光度(任意单位)
浓度(M)

图 2A

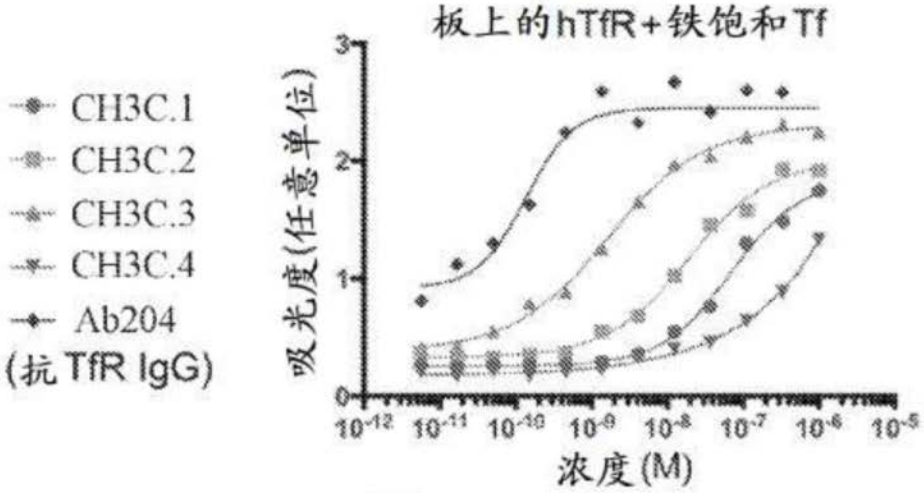

板上的hTfR+铁饱和Tf
CH3C.1
CH3C.2
CH3C.3
CH3C.4
Ab204
(抗TfR IgG)
吸光度(任意单位)
浓度(M)

图 2B

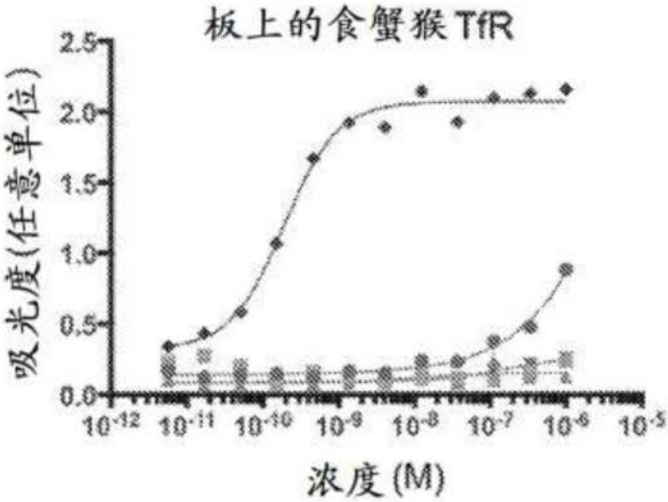

板上的食蟹猴TfR
吸光度(任意单位)
浓度(M)

图 2C

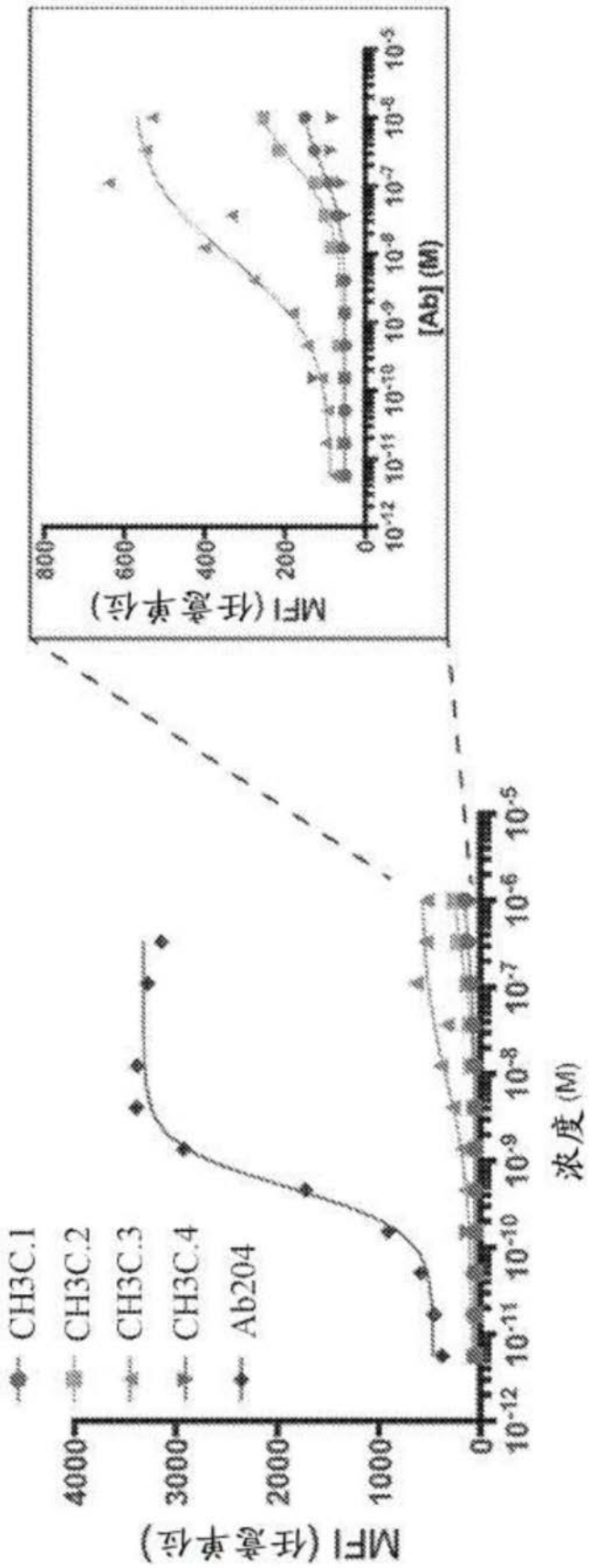


图3

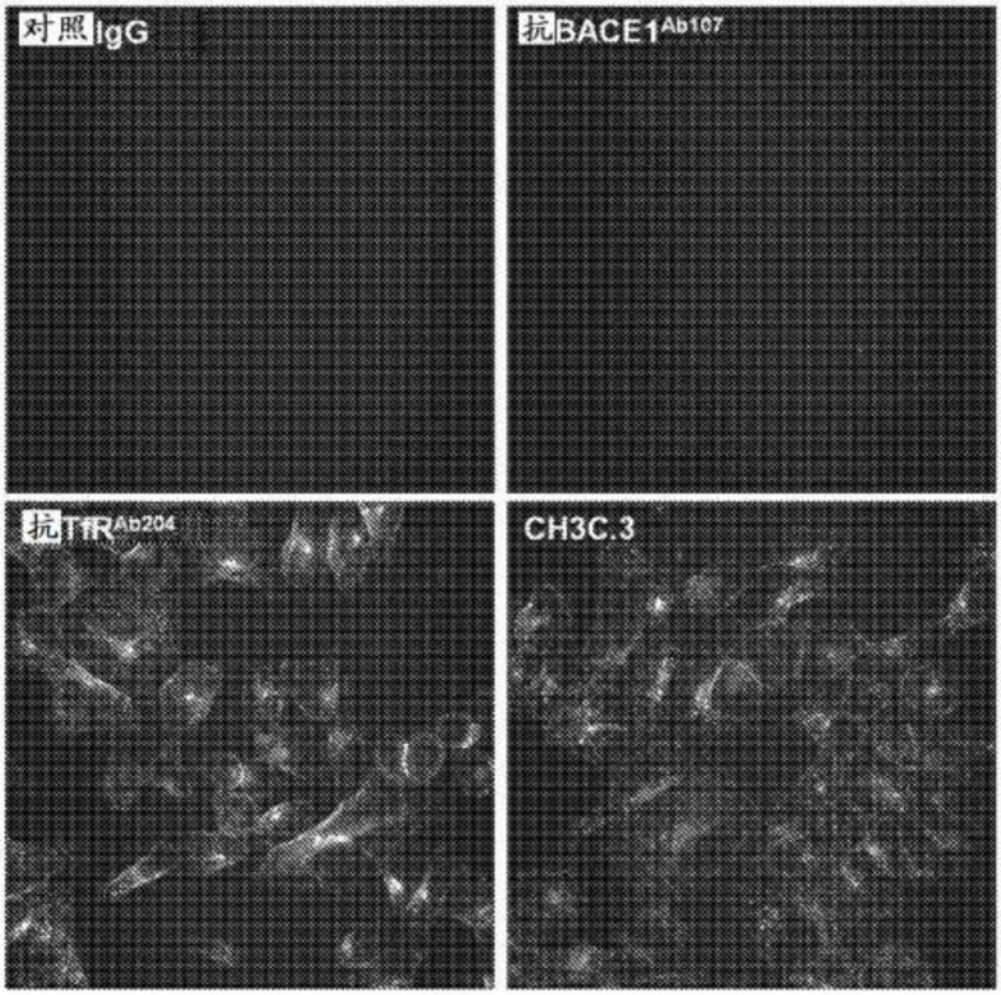


图4A

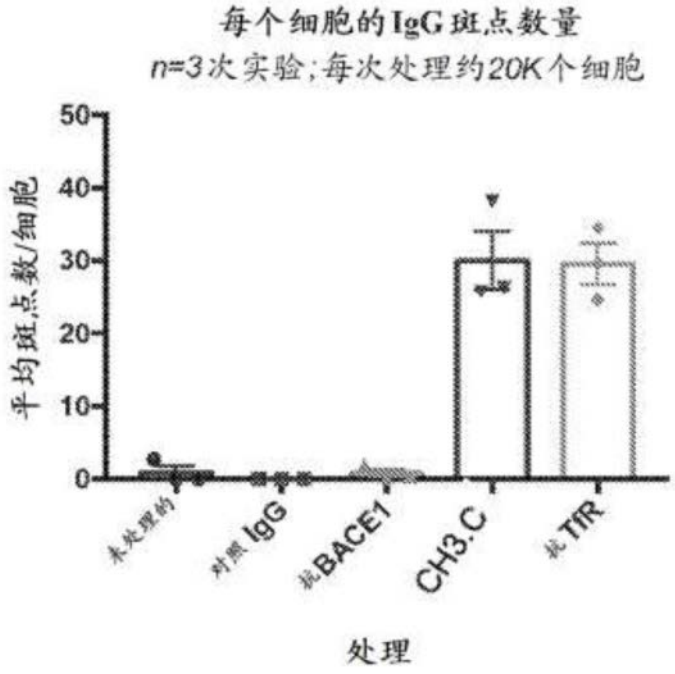

每个细胞的IgG斑点数量
n=3次实验;每次处理约20K个细胞
平均斑点数/细胞
50
40
30
20
10
0
未处理的
对照 IgG
抗BACE1
CH3.C
抗TfR
处理

图4B

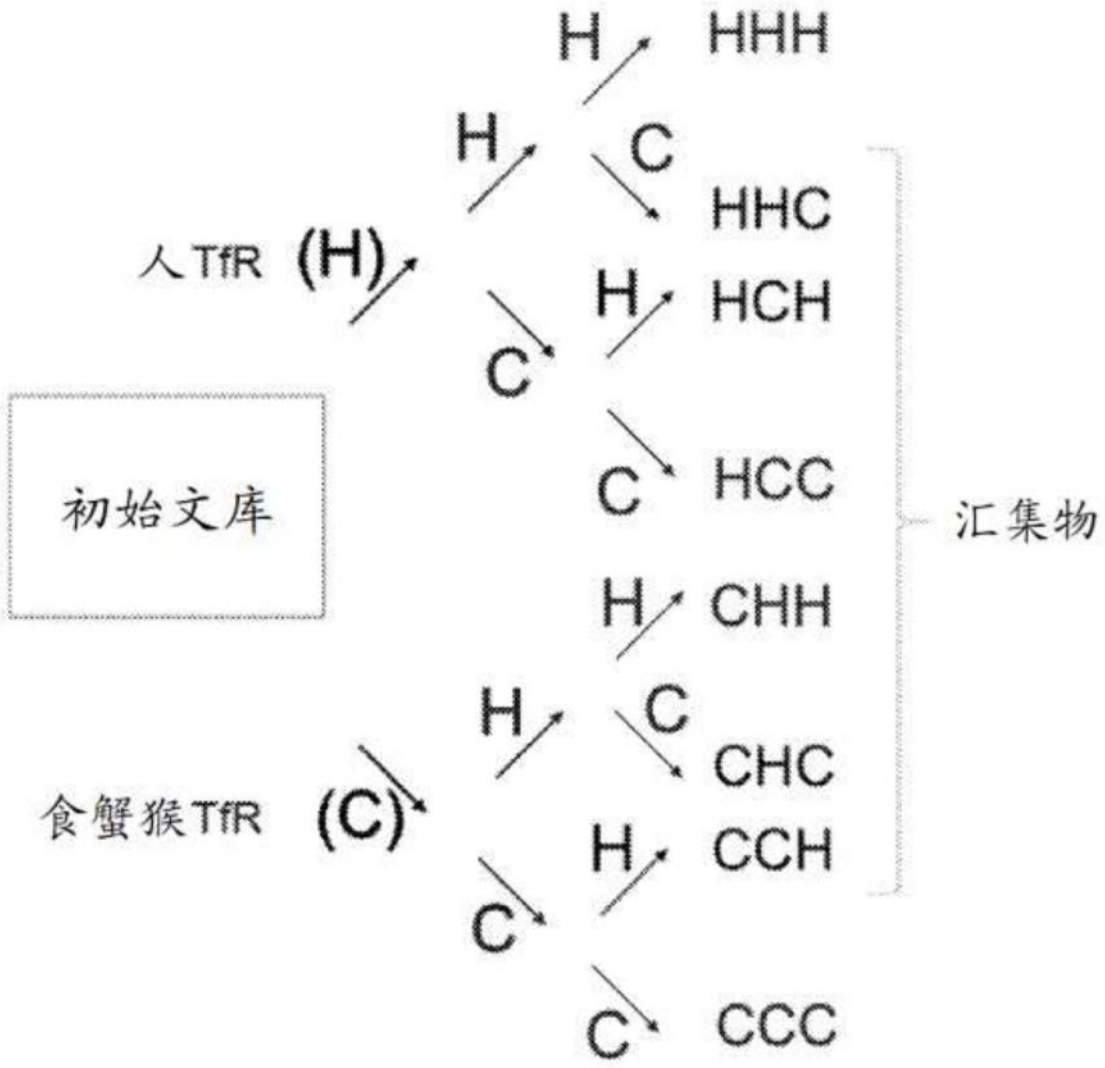

H
HHH
H
C
HHC
人TfR (H)
H
HCH
C
初始文库
C
HCC
汇集物
H
CHH
H
C
CHC
食蟹猴TfR (C)
H
CCH
C
C
CCC

图5

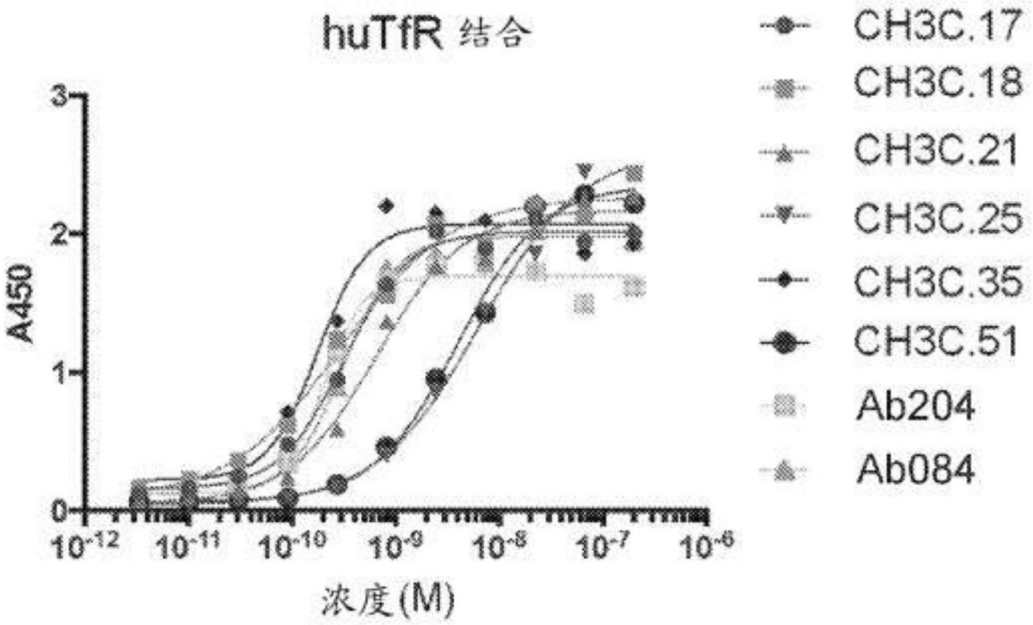

huTfR 结合
A450
浓度(M)
CH3C.17
CH3C.18
CH3C.21
CH3C.25
CH3C.35
CH3C.51
Ab204
Ab084

图6A

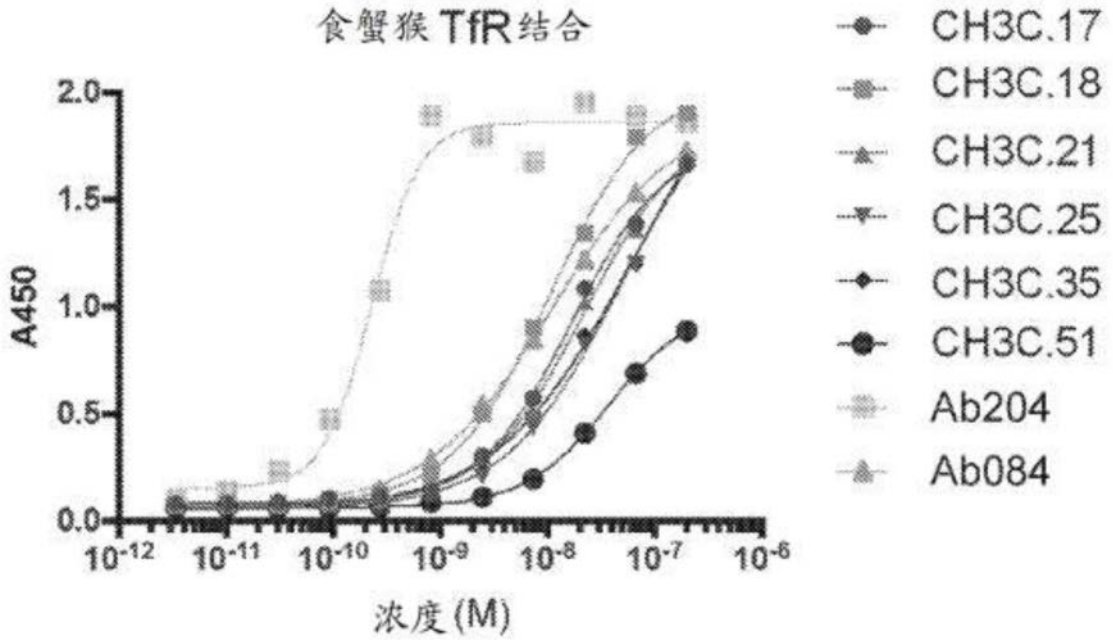

食蟹猴 TfR结合
A450
浓度(M)
CH3C.17
CH3C.18
CH3C.21
CH3C.25
CH3C.35
CH3C.51
Ab204
Ab084

图6B

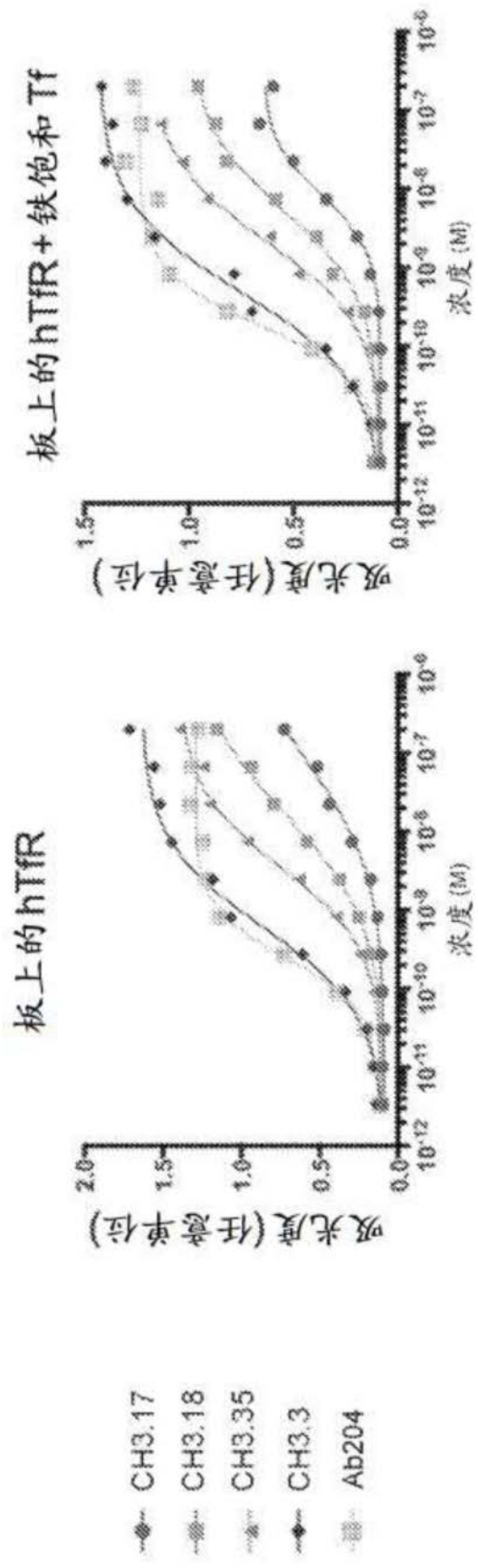

板上的hTfR
吸光度(任意单位)
浓度(M)
CH3.17
CH3.18
CH3.35
CH3.3
Ab204

图 7A

板上的hTfR+铁饱和Tf
吸光度(任意单位)
浓度(M)

图 7B

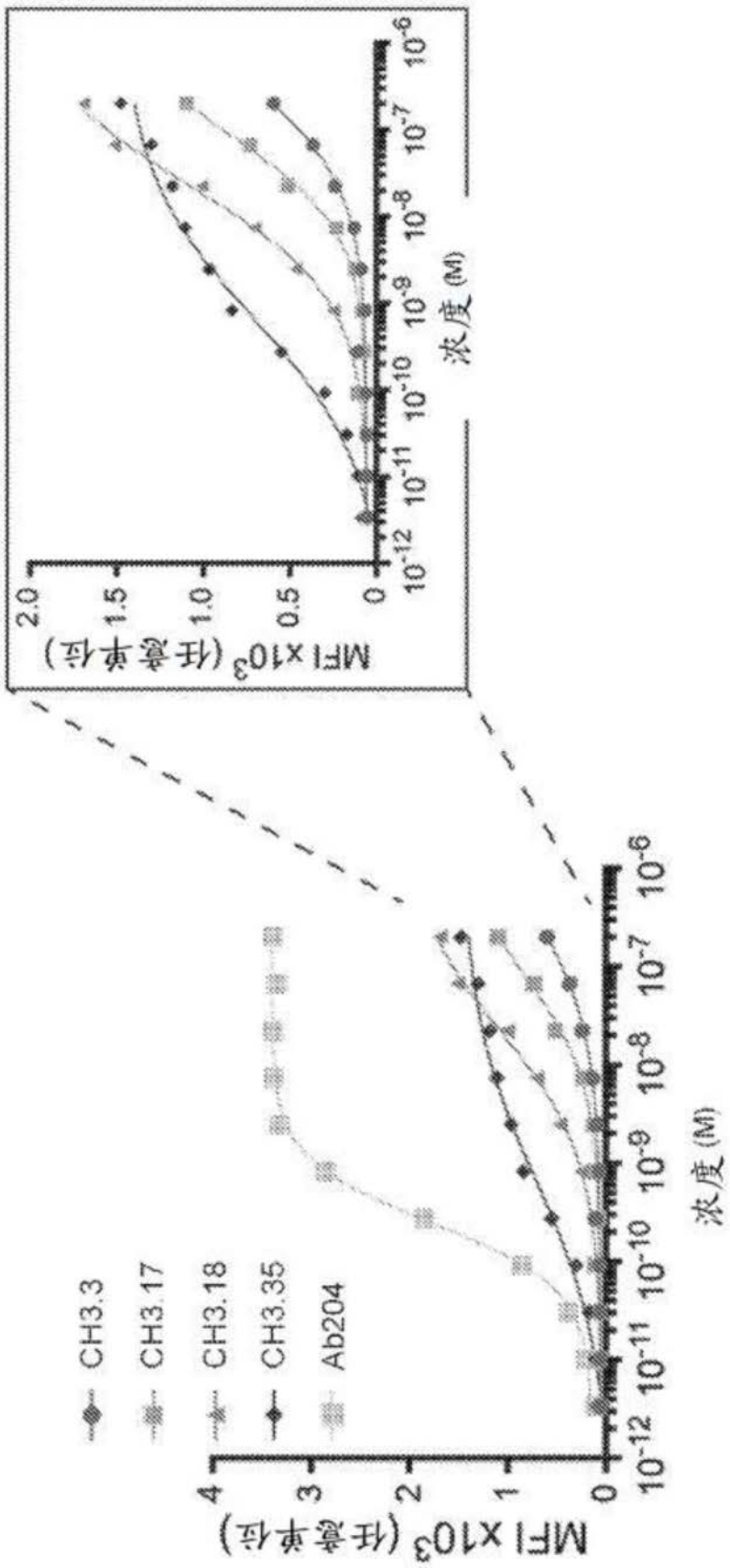


图8

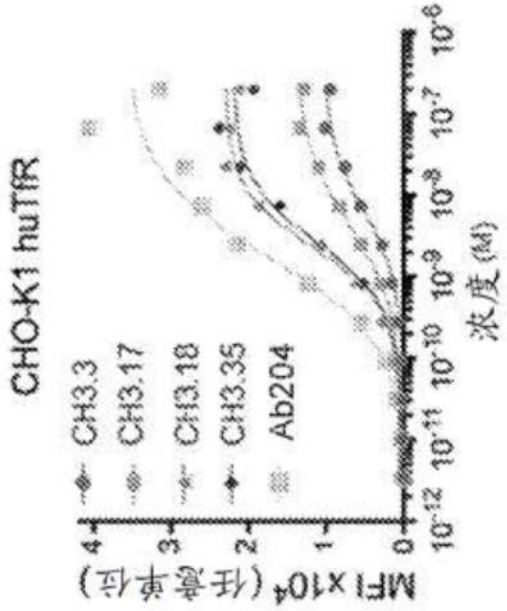


图9A

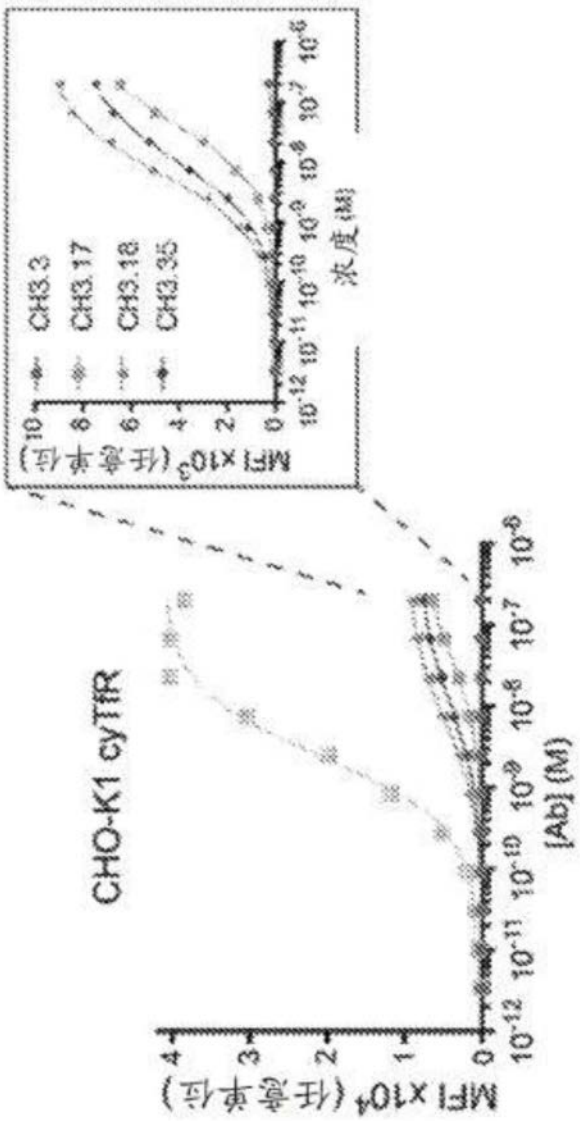

CHO-K1 cyTfR
MFI x10⁴ (任意单位)
[Ab] (M)
10⁻¹²
10⁻¹¹
10⁻¹⁰
10⁻⁹
10⁻⁸
10⁻⁷
10⁻⁶
0
1
2
3
4
MFI x10³ (任意单位)
浓度(M)
CH3.3
CH3.17
CH3.18
CH3.35
0
2
4
6
8
10

图9B

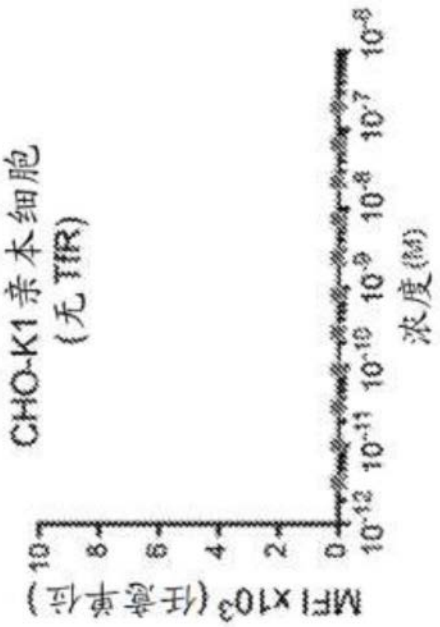

CHO-K1亲本细胞
(无TIR)
MFI x10³ (任意单位)
浓度(M)
0
2
4
6
8
10
10⁻¹²
10⁻¹¹
10⁻¹⁰
10⁻⁹
10⁻⁸
10⁻⁷
10⁻⁶

图9C

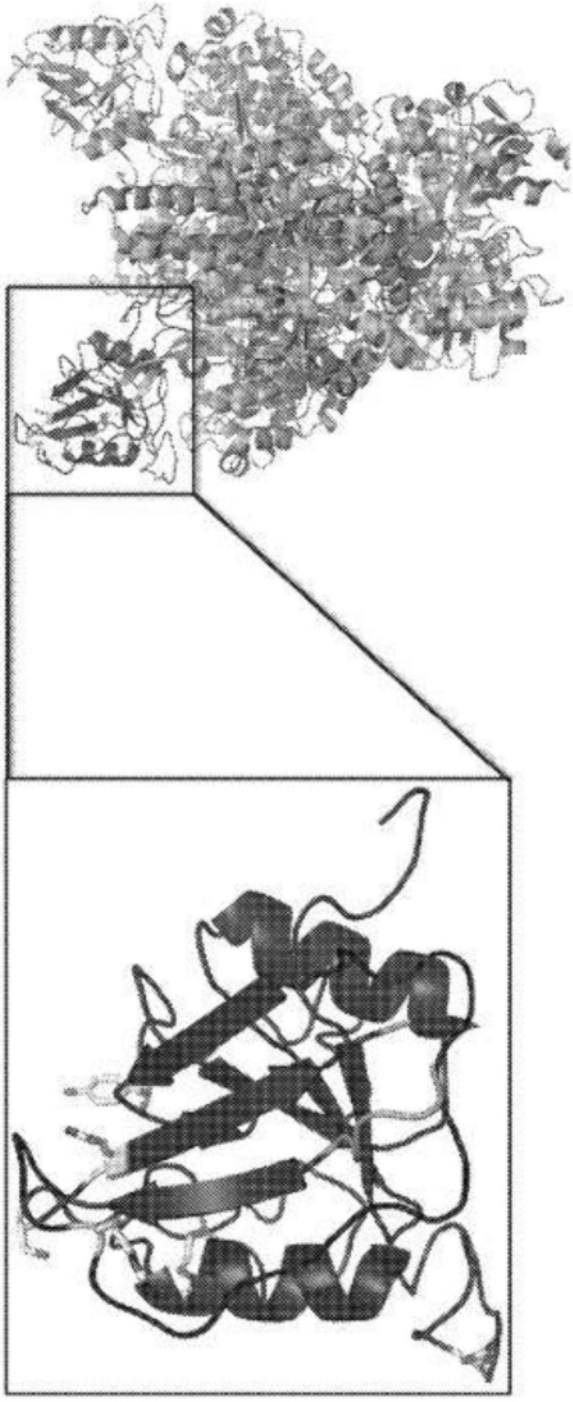


图10A

图10B

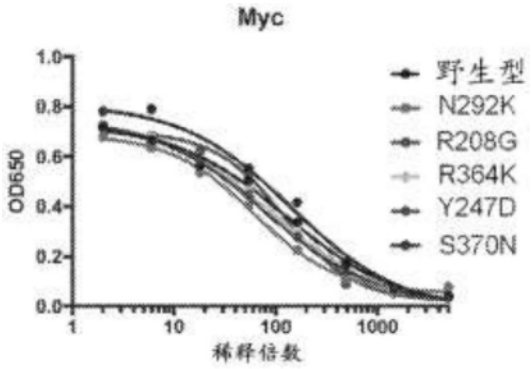


图11A

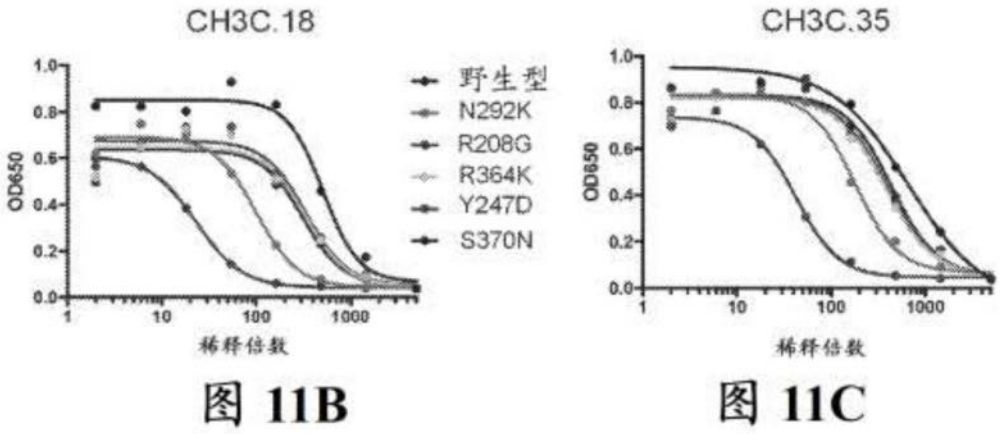


图 11B 图 11C

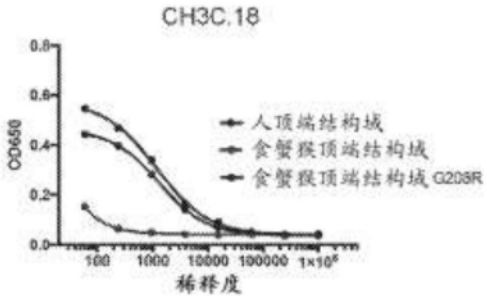


图11D

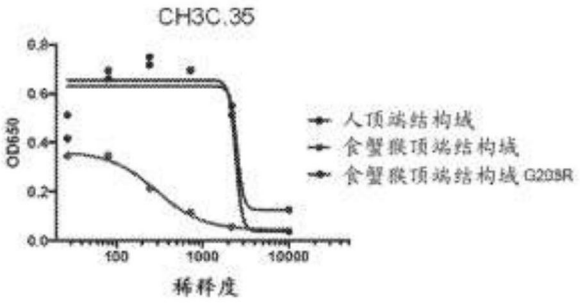

CH3C.35
OD650
0.8
0.6
0.4
0.2
0.0
100
1000
10000
稀释度
人顶端结构域
食蟹猴顶端结构域
食蟹猴顶端结构域 G209R

图11E

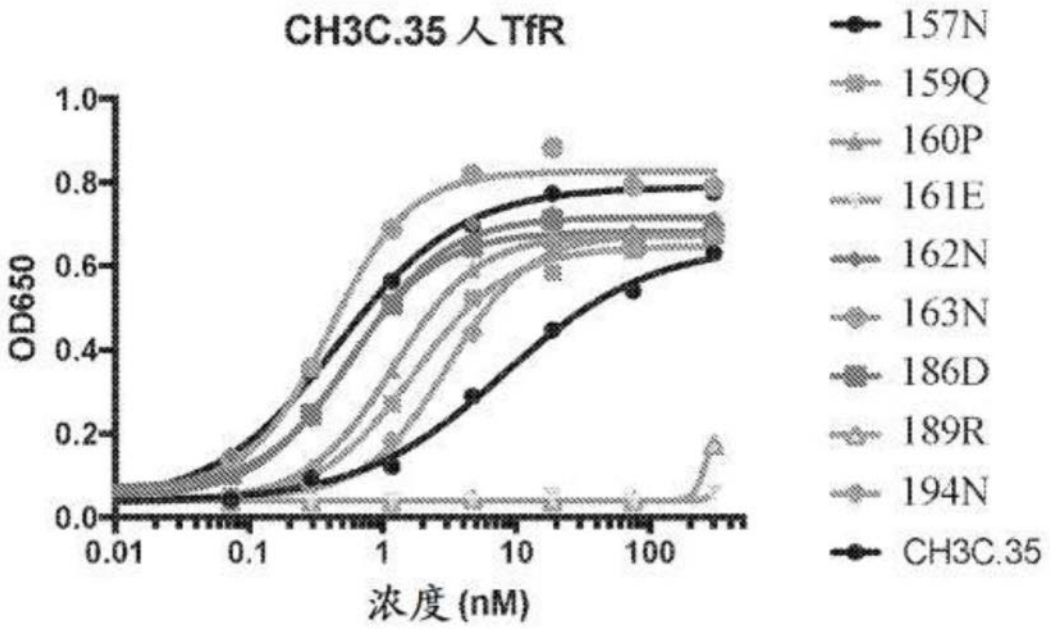

CH3C.35 人TfR
OD650
1.0
0.8
0.6
0.4
0.2
0.0
0.01
0.1
1
10
100
浓度(nM)
157N
159Q
160P
161E
162N
163N
186D
189R
194N
CH3C.35

图12A

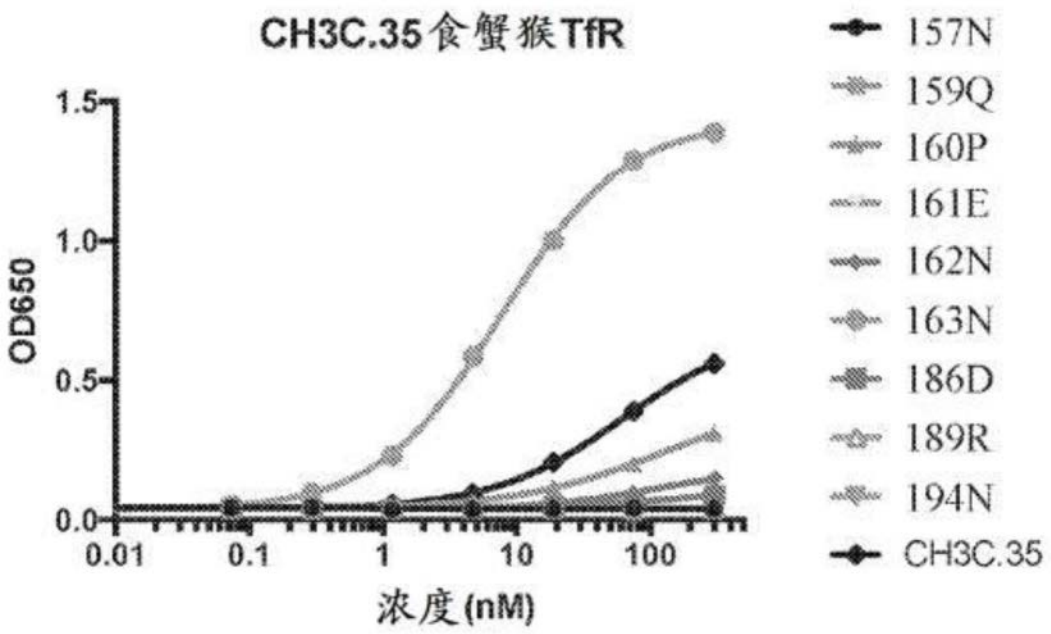

CH3C.35食蟹猴TfR
OD650
1.5
1.0
0.5
0.0
0.01
0.1
1
10
100
浓度(nM)
157N
159Q
160P
161E
162N
163N
186D
189R
194N
CH3C.35

图12B

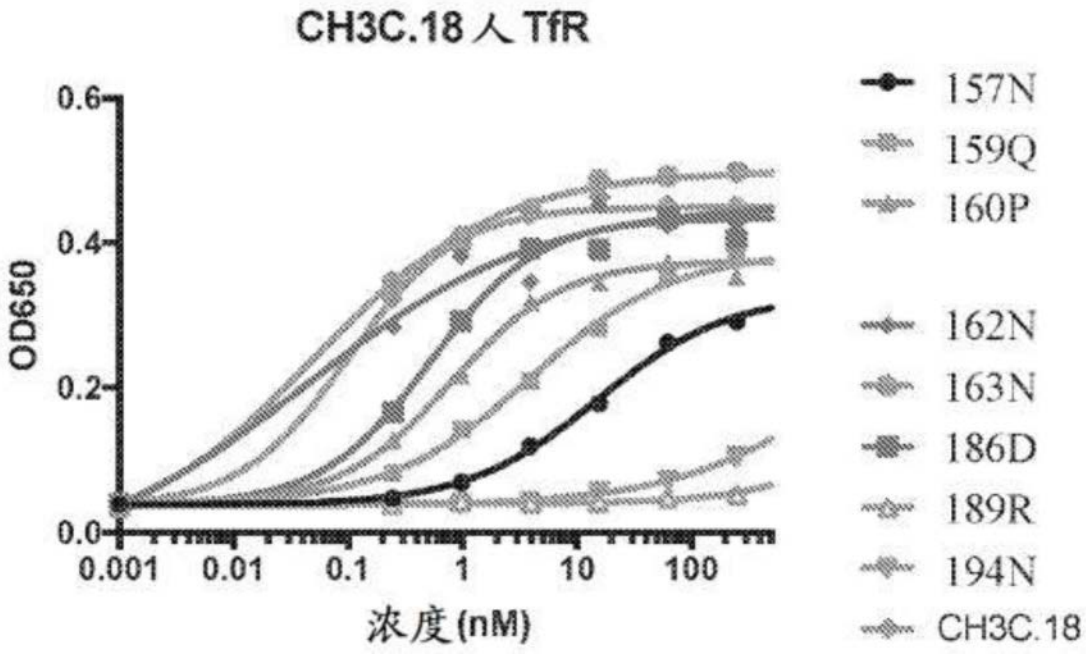

CH3C.18人TfR
OD650
0.6
0.4
0.2
0.0
0.001
0.01
0.1
1
10
100
浓度(nM)
157N
159Q
160P
162N
163N
186D
189R
194N
CH3C.18

图12C

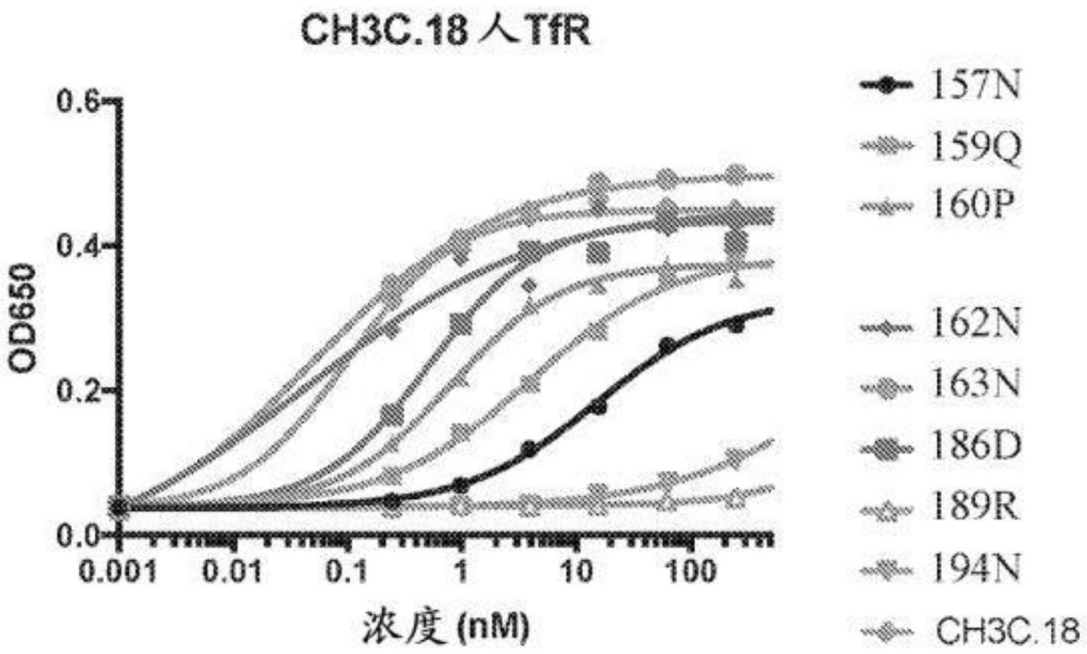


图12D

共有序列1-35

野生型	E	W	E	S	N	G	Q	P	E	N	N	Y	K	V	D	K	S	R	W	Q	Q	G	N
克隆3					Y		T	E	W	S	Q				E			D					H
1-35					Y		T	E	W	S	S				T			E					F
1-44					Y		T	E	W	S	N				S			E					F
文库3.1					Y		T	E	W	S	X	X			X			X					X

图13A

共有序列1-18

野生型	E	W	E	S	N	G	Q	P	E	N	N	Y	K	V	D	K	S	R	W	Q	Q	G	N
克隆4					L		L	V	W	V	G	Y			A			T					W
1-21					L		L	V	W	V	G				P			T					W
1-18					L		H	V	W	A	V				P			T					W
1-25					M		H	V	W	V	G				D			T					W
1-34					L		L	V	G	V	F	S			P			T					W
1-51					L		H	V	W	V	G				S			E					W
文库3.2					L		L	V	W	V	X	X			P:50			X					W:50
					M		H		G	A					X:50								F:25
																							H:25
																							Y:25
																							(L):25

图13B

空位

野生型	E	W	E	S	N	G	Q	P	E	N	N	Y	K	V	D	K	S	R	W	Q	Q	G	N
野生型	x	W	x		N	G	Q	P	E	N	N	x			D		x	R			x		N
1-18空位	x		x		L		H	V	W	A	V	x			P		x	T			x		W
1-34空位	x		x		L		L	V	G	V	F	x			P		x	T			x		W
1-35空位	x		x		Y		T	E	W	S	S	x			T		x	E			x		F

图13C

芳香族氨基酸

野生型	E	W	E	S	N	G	Q	P	E	N	N	Y	K	V	D	K	S	R	W	Q	Q	G	N
1-18					L		H	V	W	A	V				P			T					W
文库3.4					X		X	V	W	X	X				P			X					W:50 F:25 H:25 Y:25 (L):25

图13D

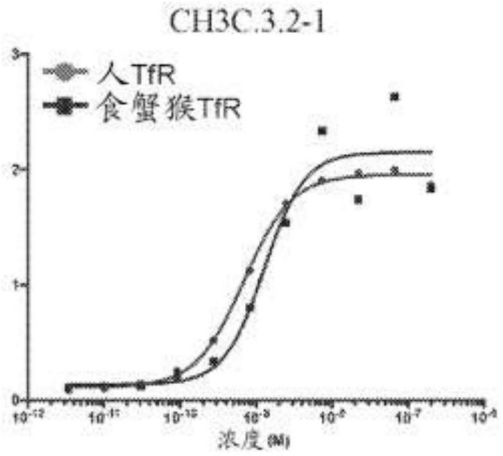


图14A

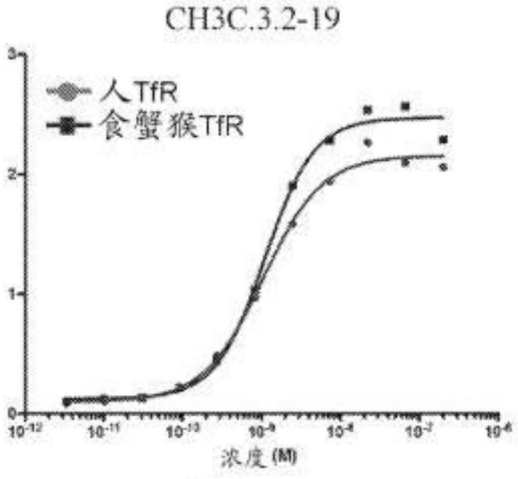


图14B

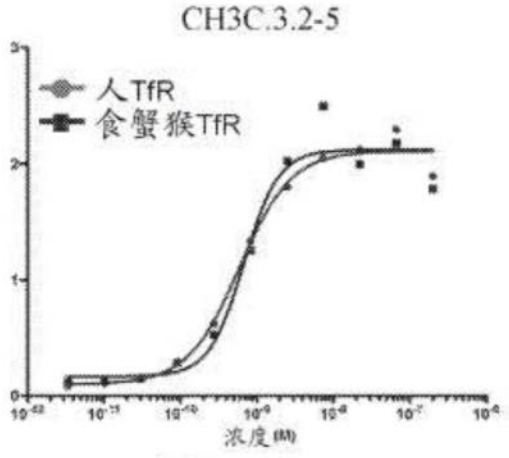


图14C

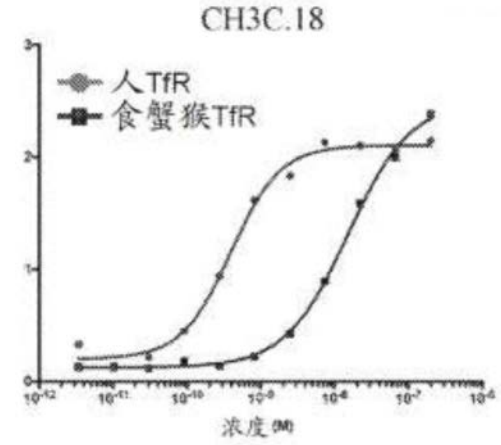


图14D

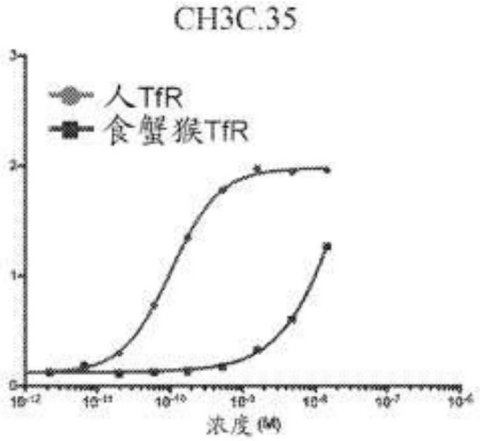


图14E

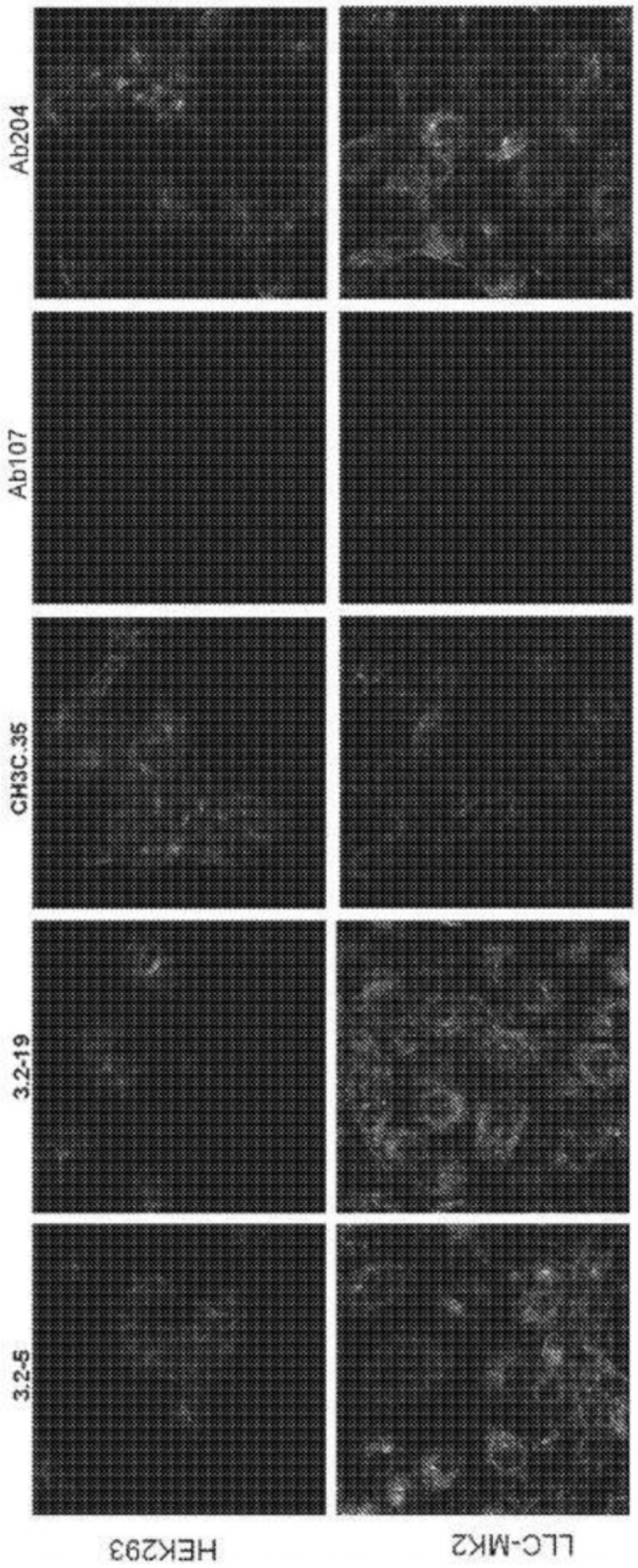


图15

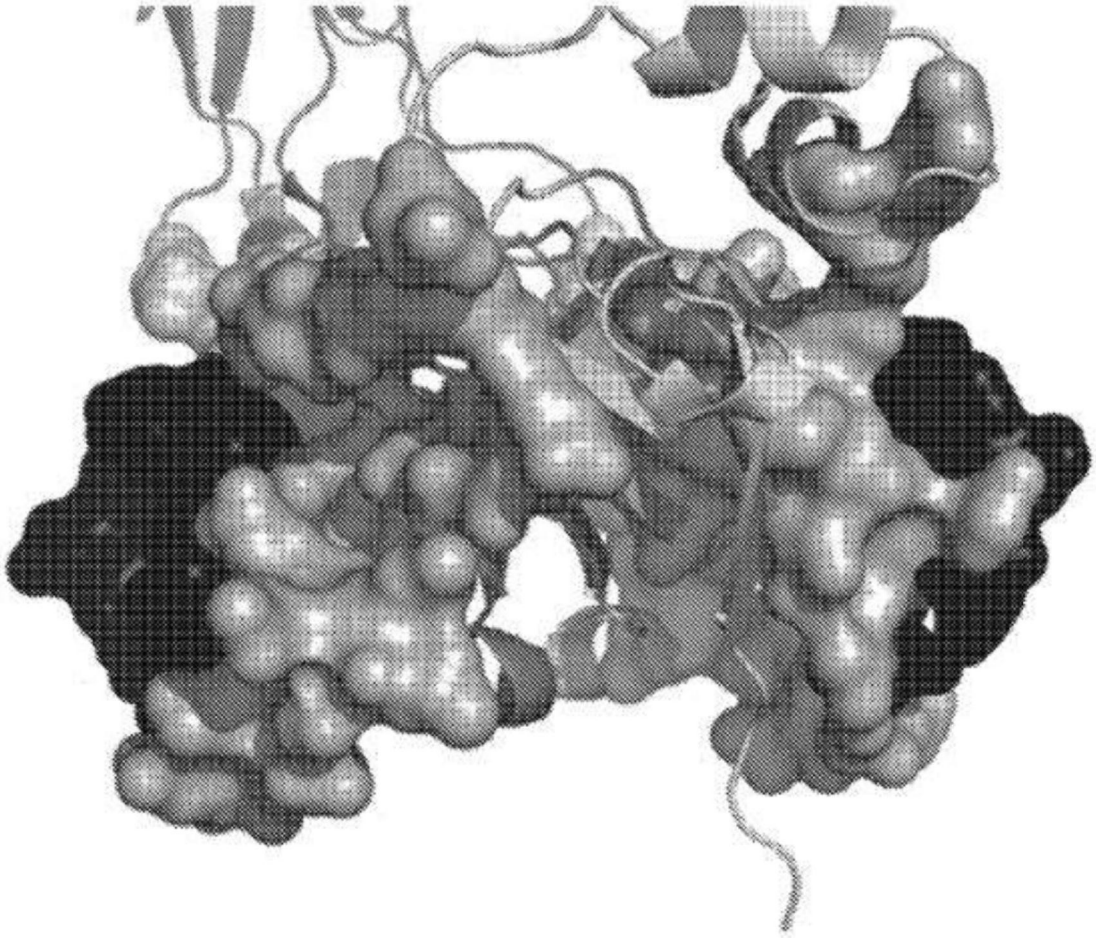


图16

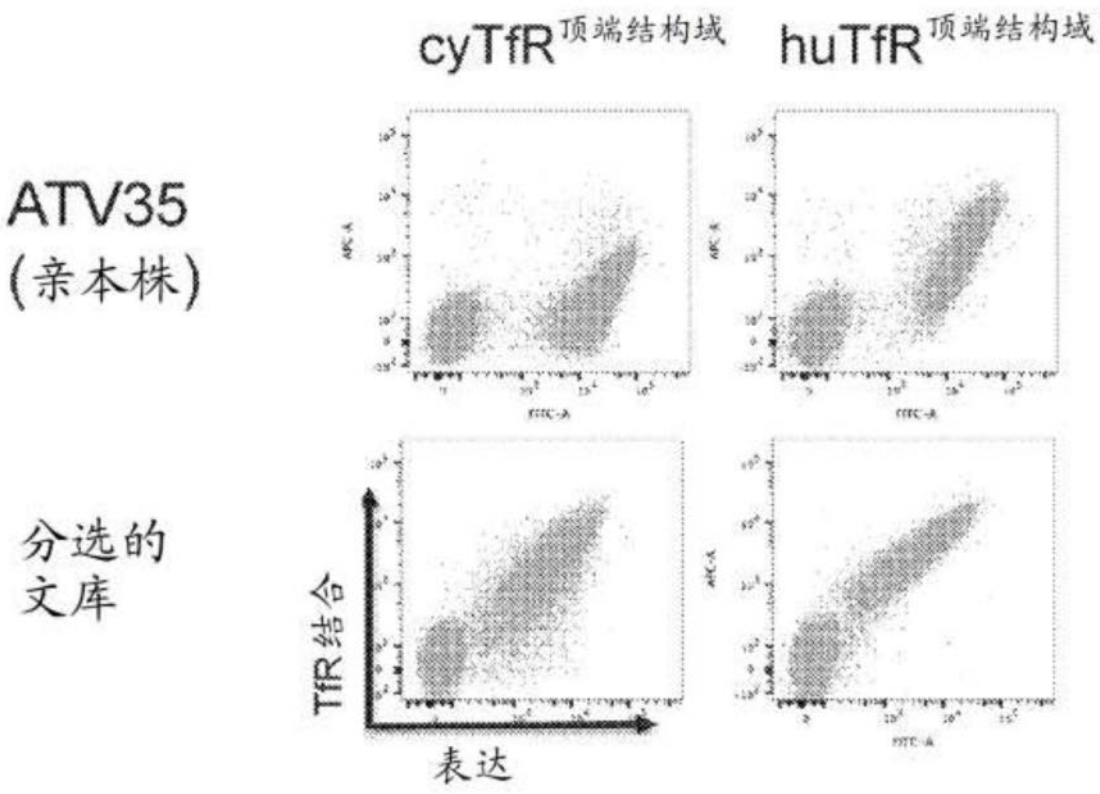


图17

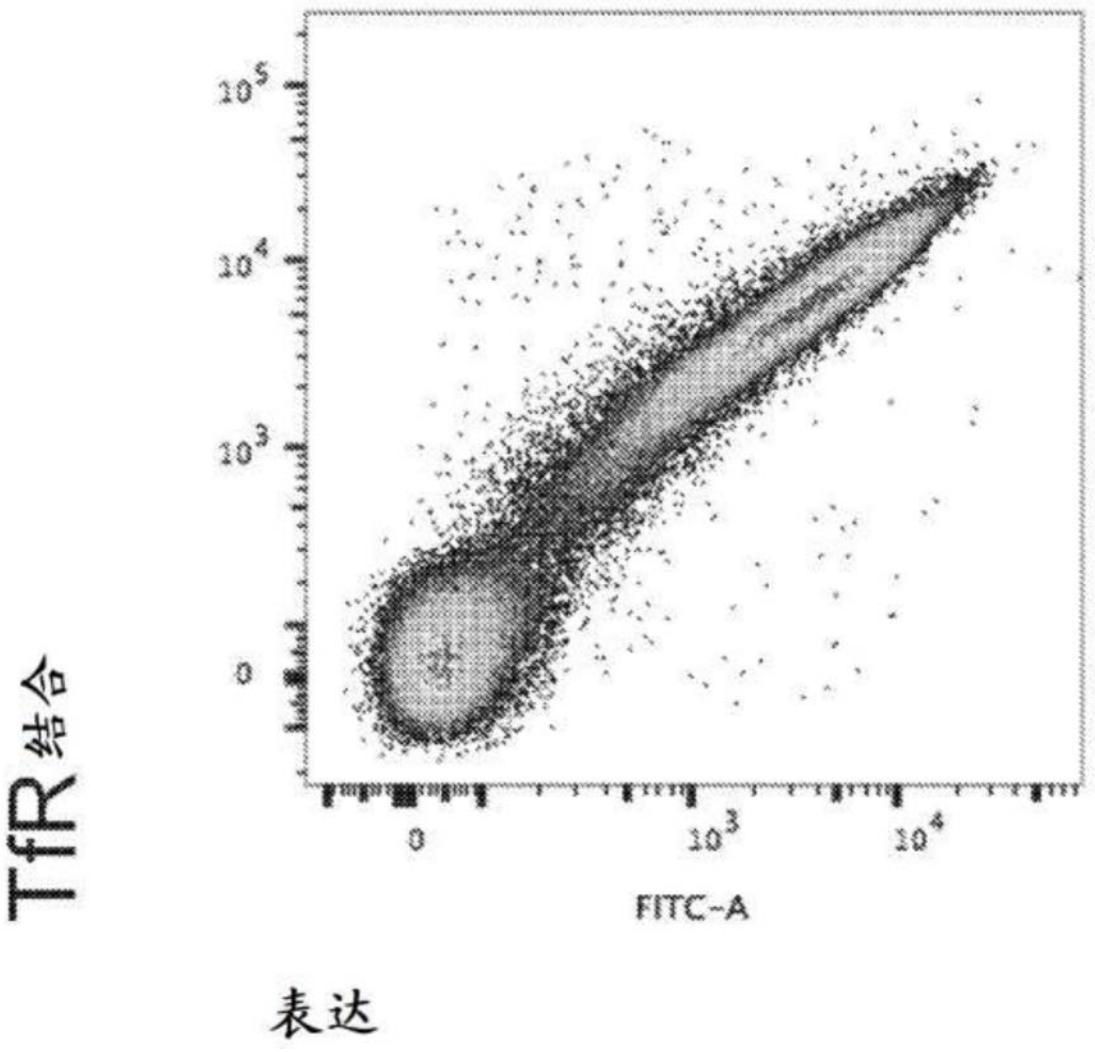


图18A

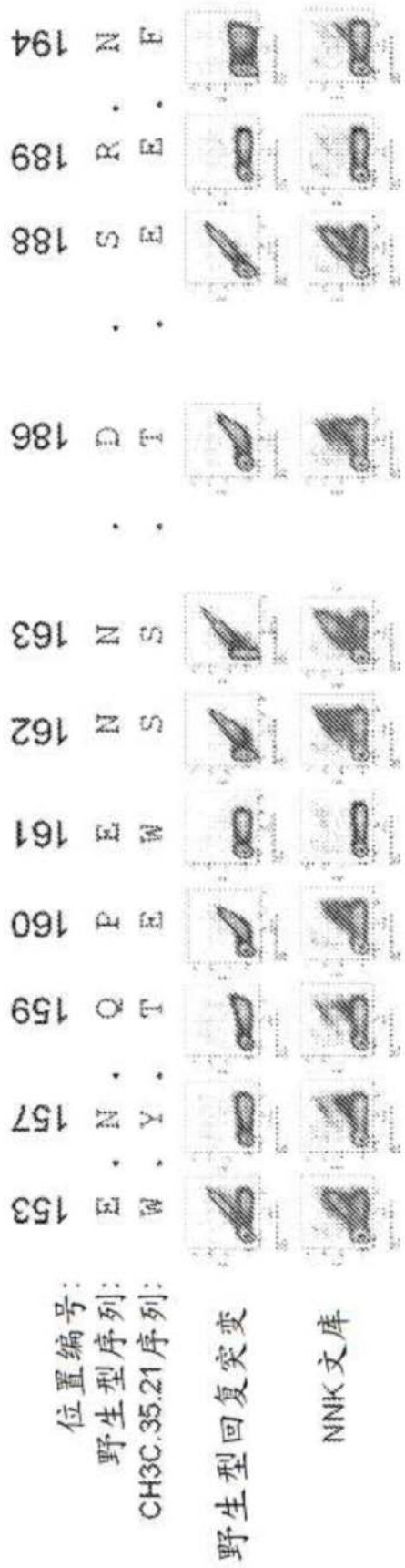

位置编号:
野生型序列:
CH3C.35.21序列:
153
157
159
160
161
162
163
186
188
189
194
野生型回复突变
NNK文库

图18B

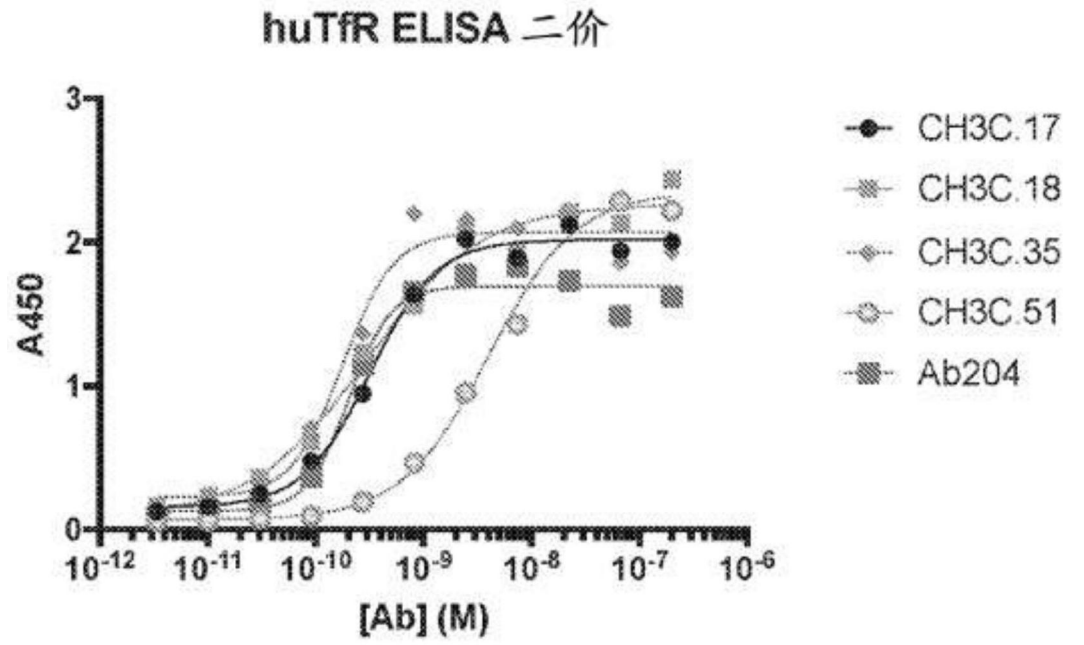

huTfR ELISA 二价
A450
[Ab] (M)
CH3C.17
CH3C.18
CH3C.35
CH3C.51
Ab204

图19A

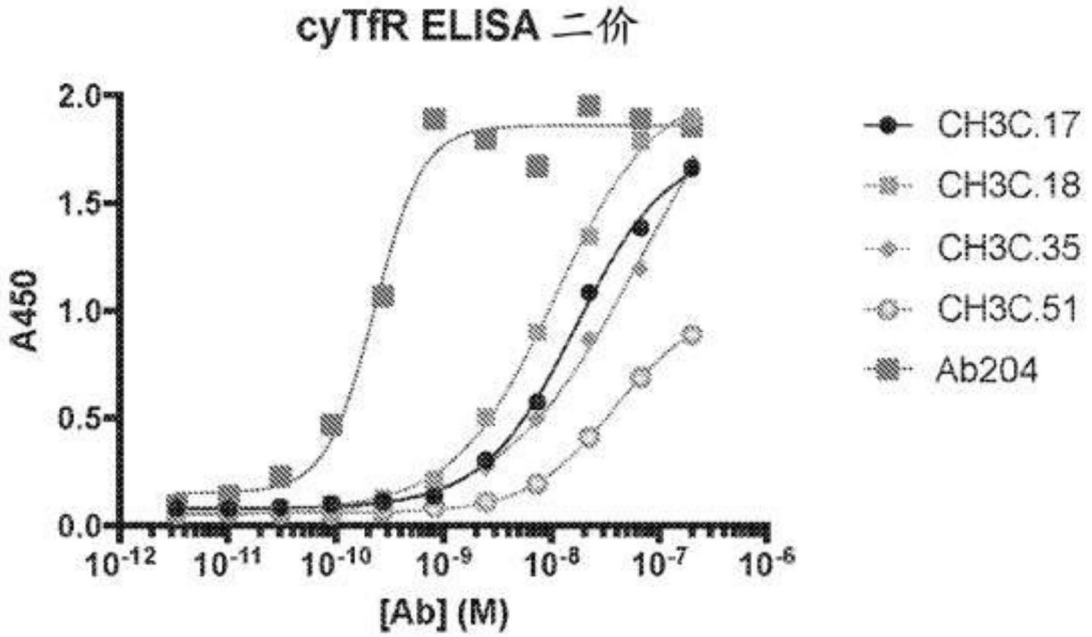

cyTfR ELISA 二价
A450
[Ab] (M)
CH3C.17
CH3C.18
CH3C.35
CH3C.51
Ab204

图19B

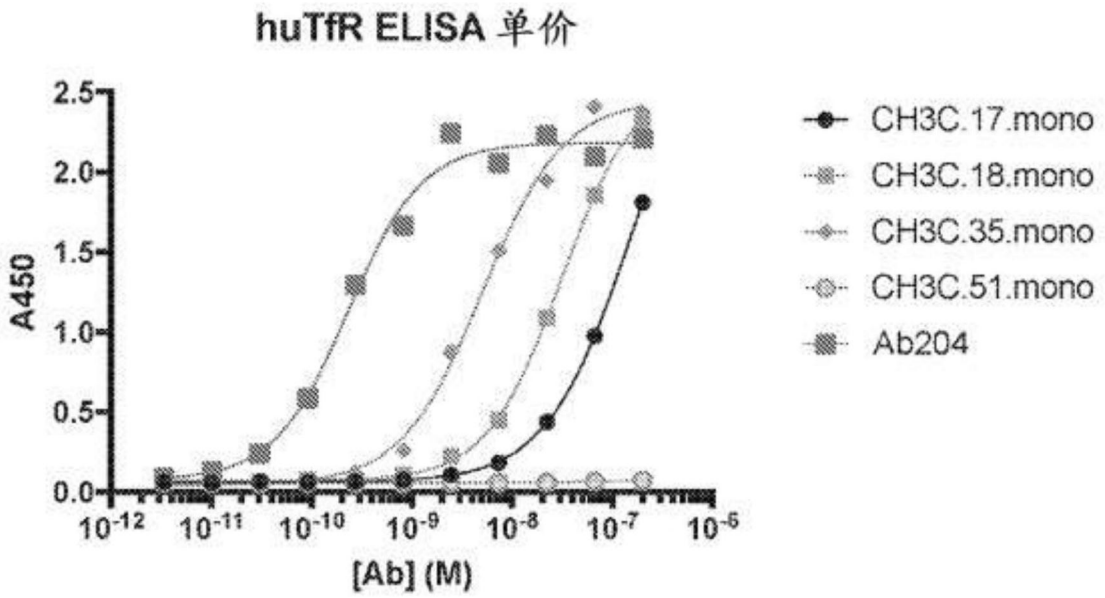

huTfR ELISA 单价
A450
2.5
2.0
1.5
1.0
0.5
0.0
10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7} 10^{-6}
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图19C

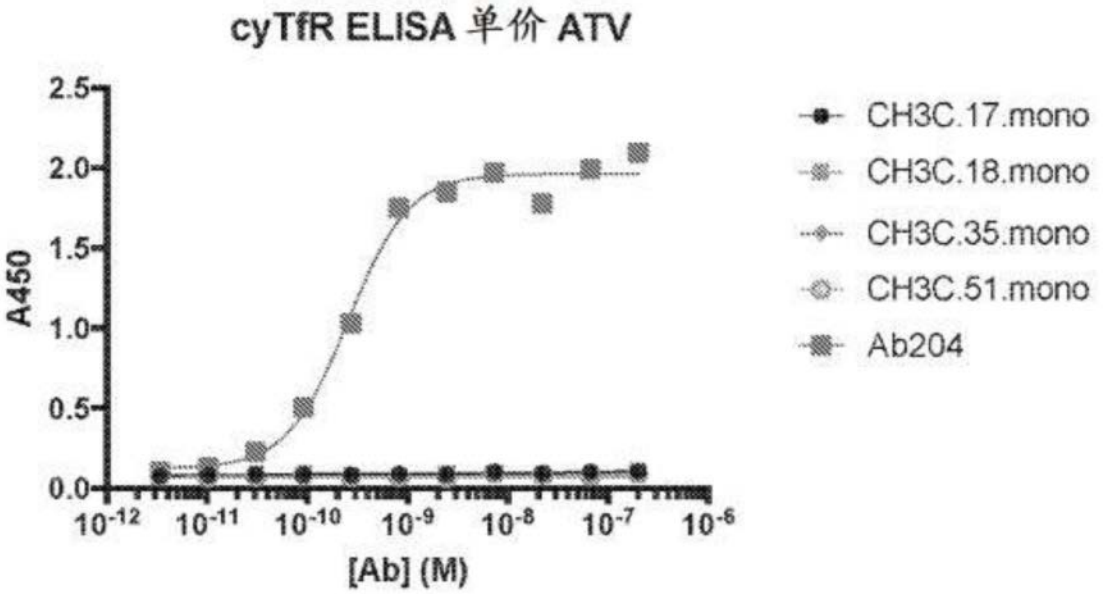

cyTfR ELISA 单价 ATV
A450
2.5
2.0
1.5
1.0
0.5
0.0
10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7} 10^{-6}
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图19D

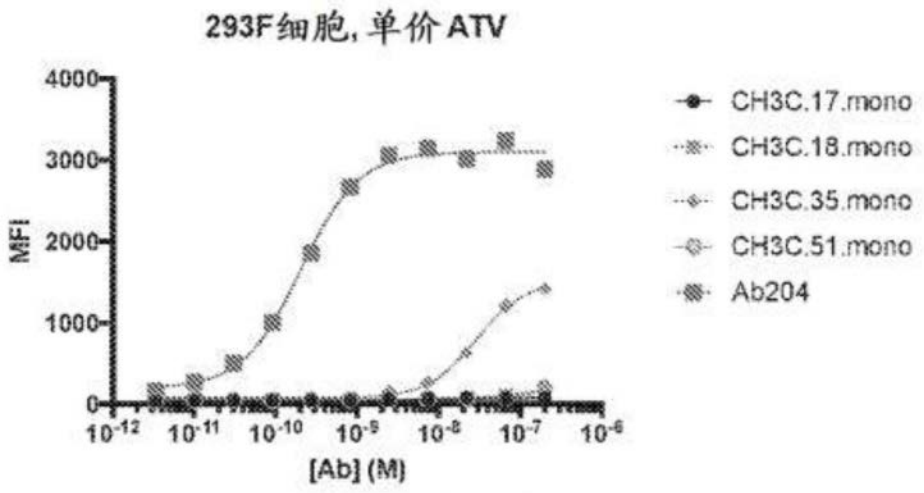

293F细胞,单价ATV
MFI
4000
3000
2000
1000
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图20A

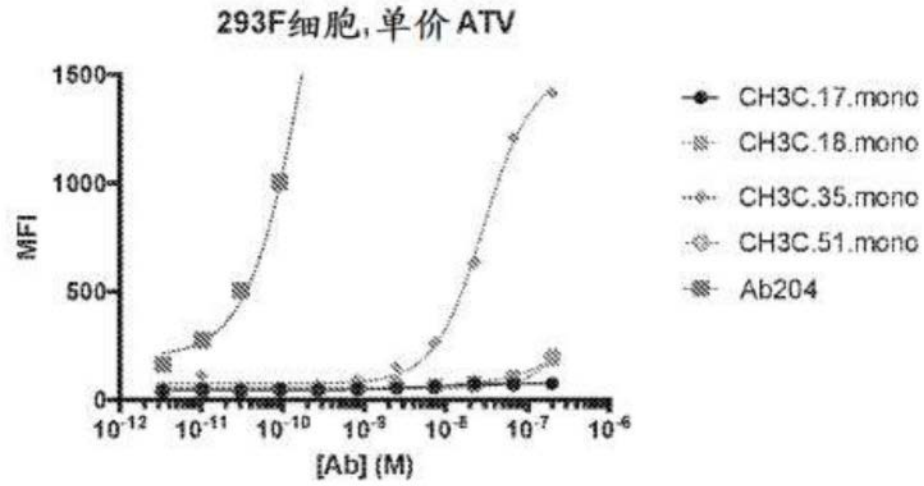

293F细胞,单价ATV
MFI
1500
1000
500
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图20B

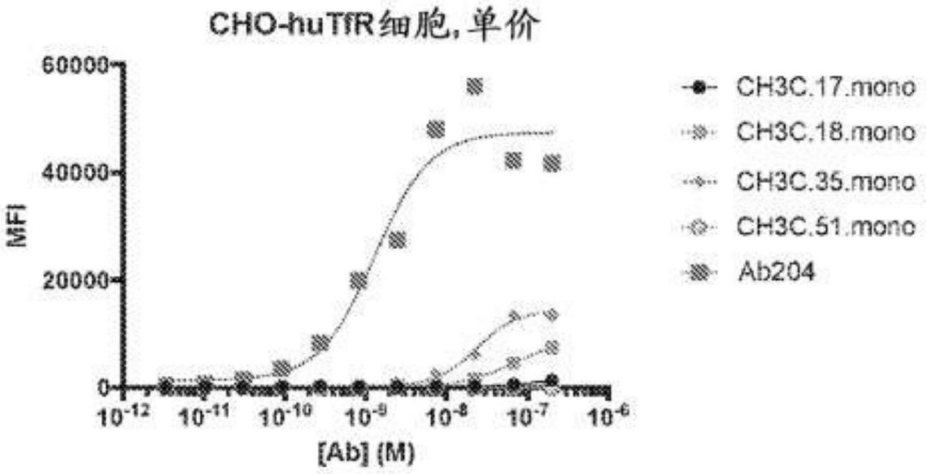

CHO-huTfR细胞,单价
60000
40000
20000
0
MFI
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图20C

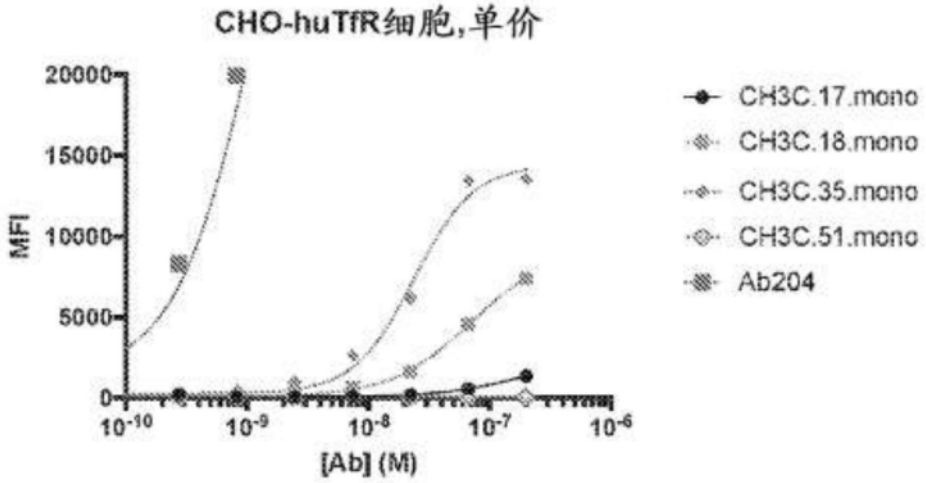

CHO-huTfR细胞,单价
20000
15000
10000
5000
0
MFI
10-10
10-9
10-8
10-7
10-6
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图20D

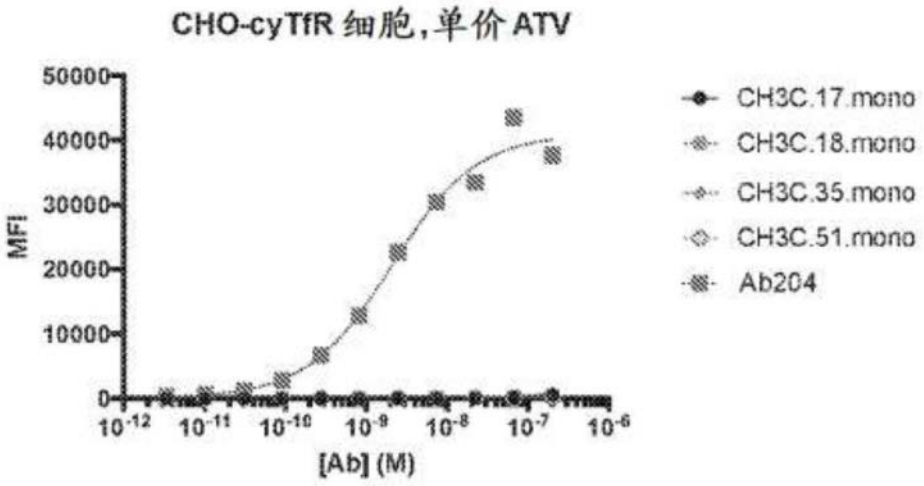

CHO-cyTfR 细胞,单价 ATV
MFI
50000
40000
30000
20000
10000
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[Ab] (M)
CH3C.17.mono
CH3C.18.mono
CH3C.35.mono
CH3C.51.mono
Ab204

图20E

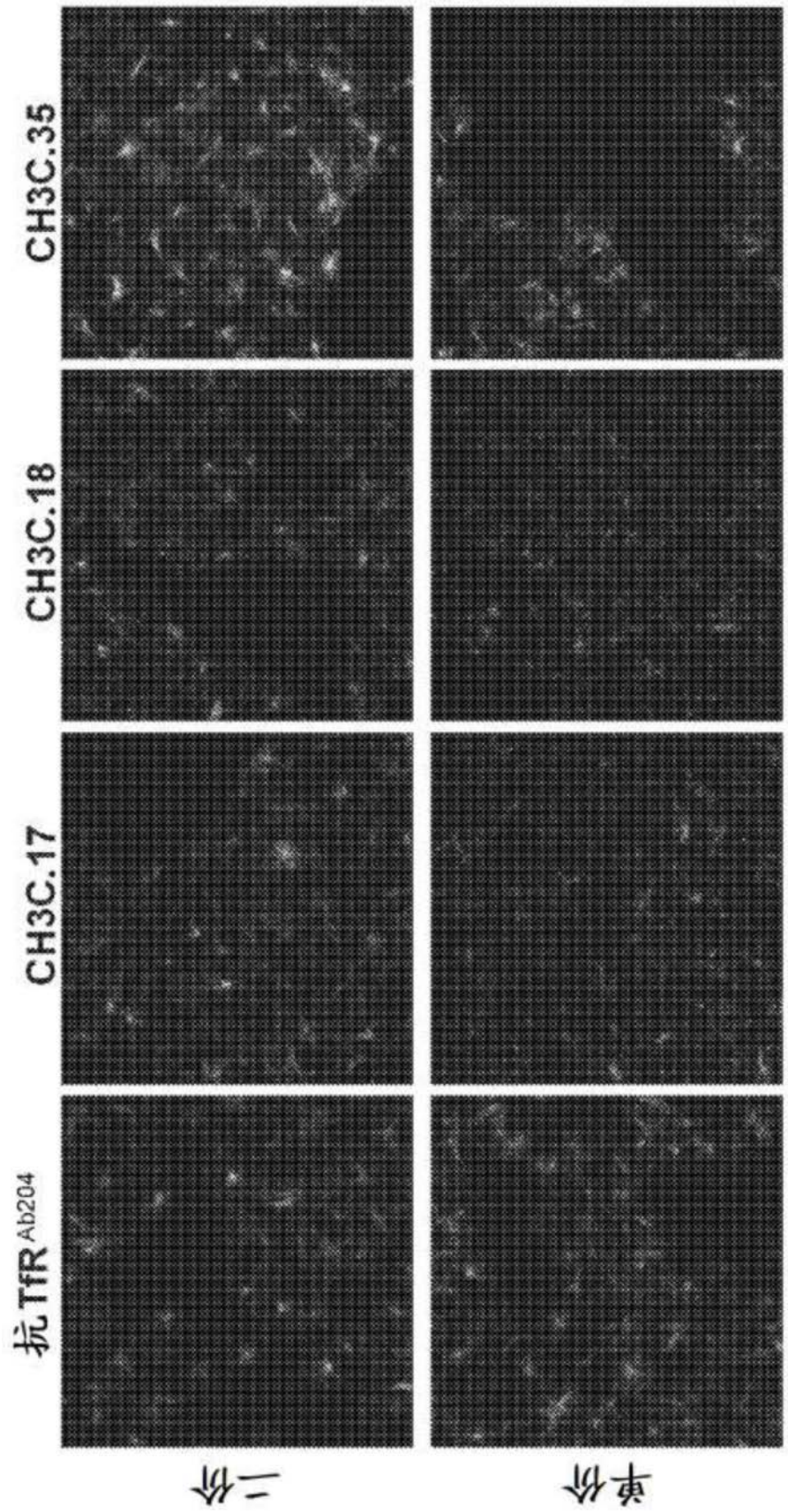


图21

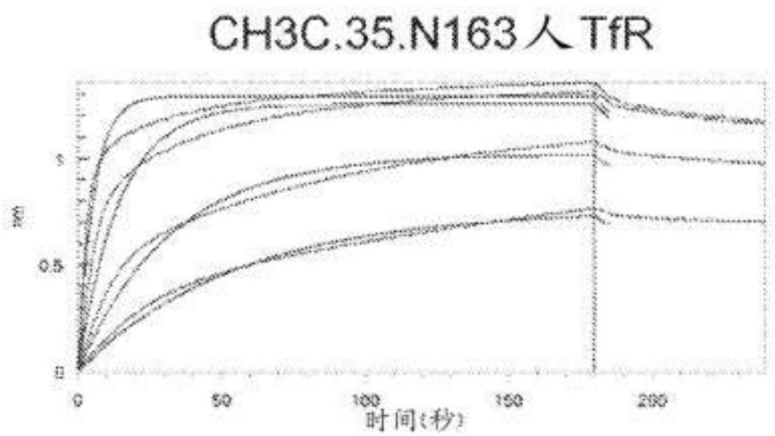


图22A

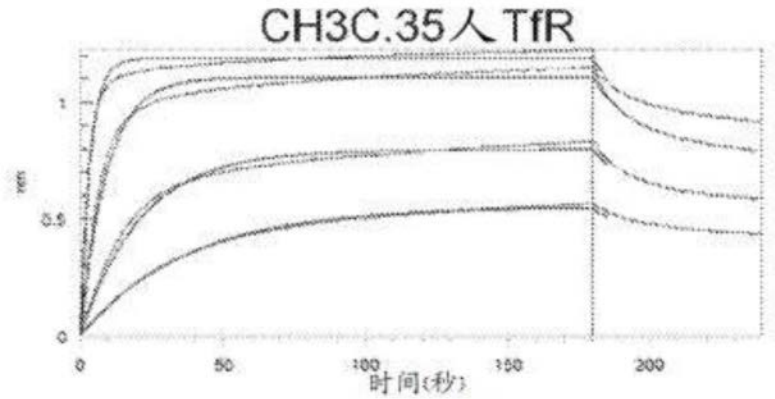


图22B

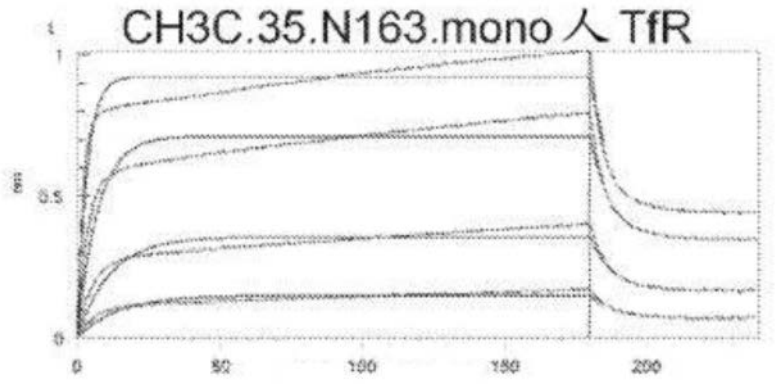


图22C

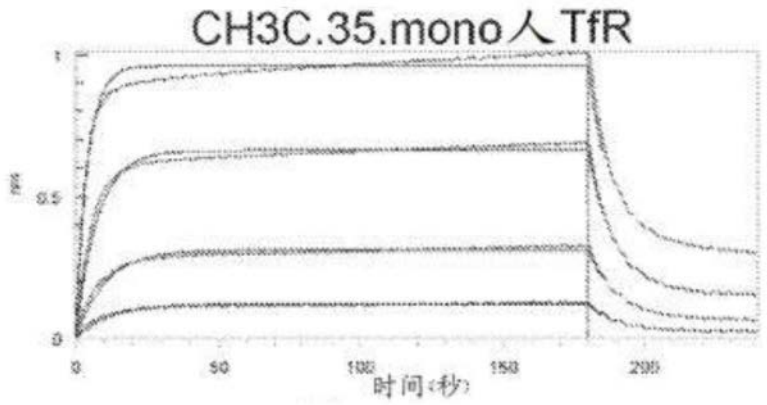


图22D

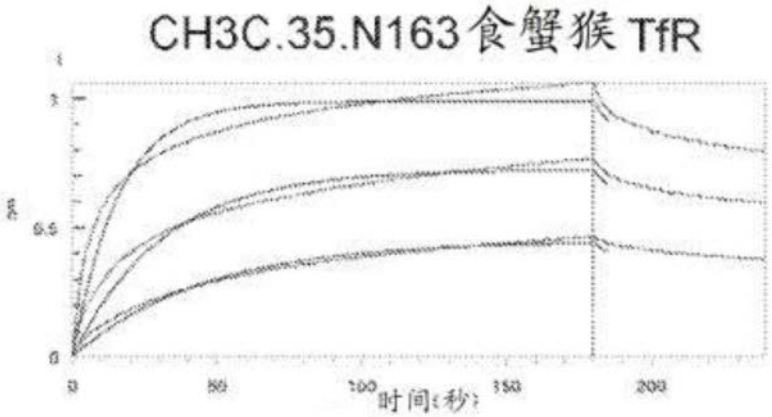


图22E

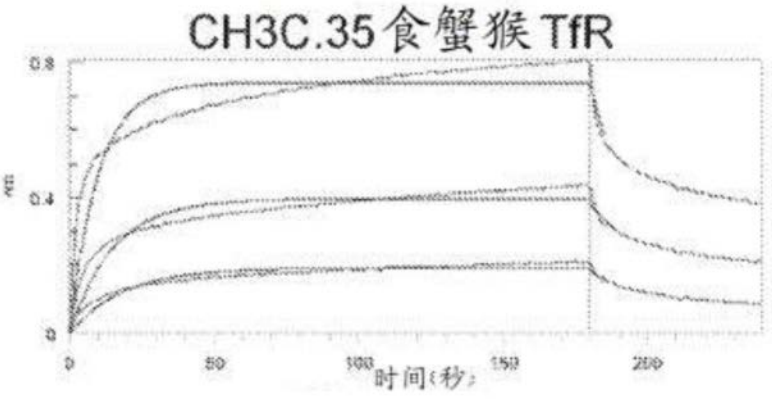


图22F

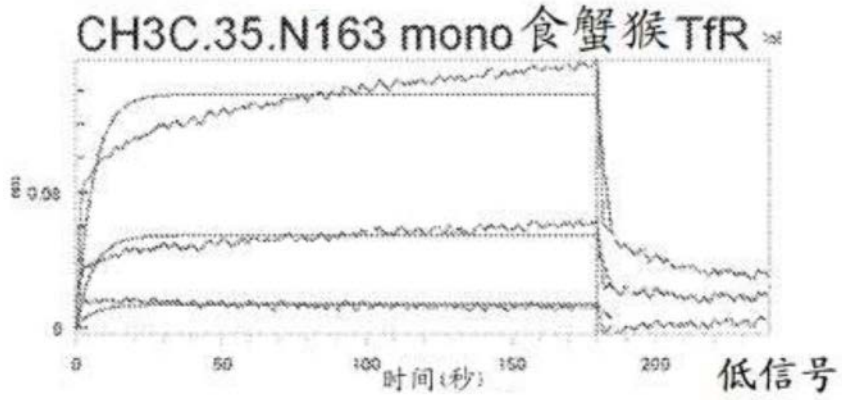


图22G

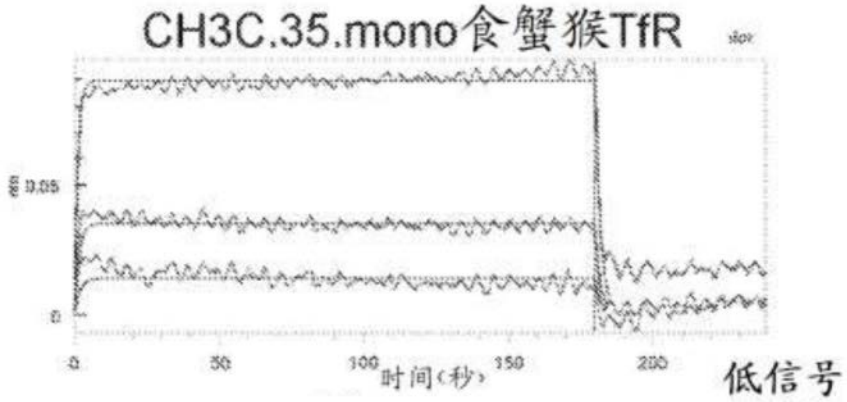


图22H

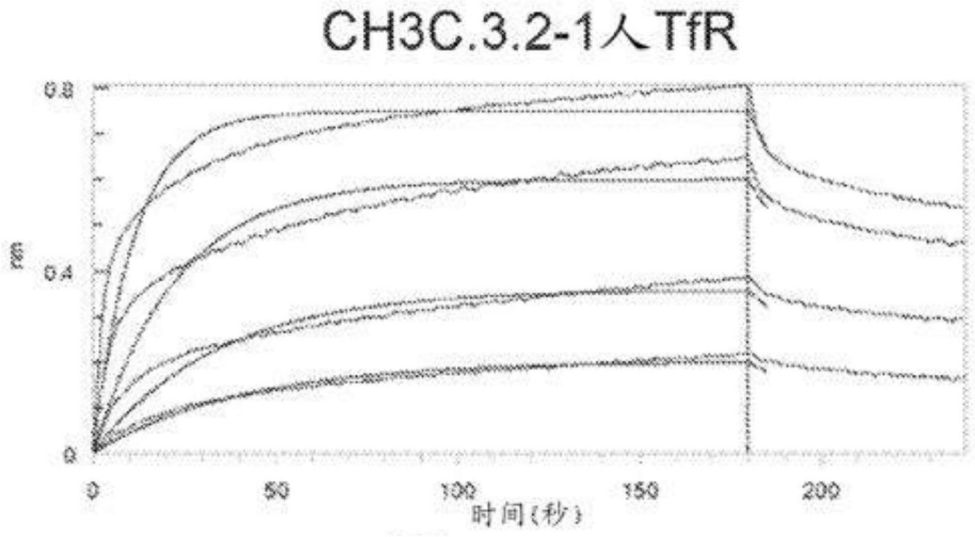


图23A

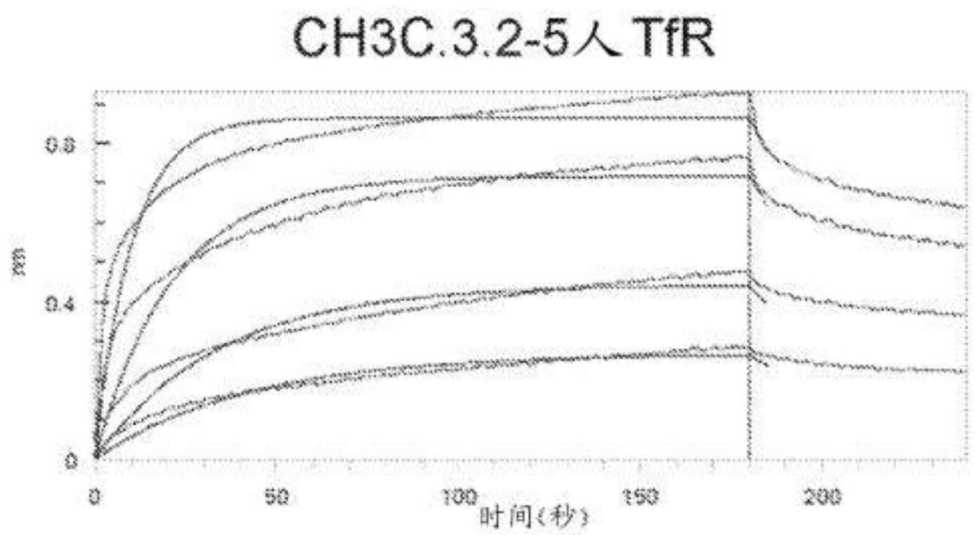

CH3C.3.2-5人TfR
0.8
0.4
0
0
50
100
150
200
时间(秒)

图23B

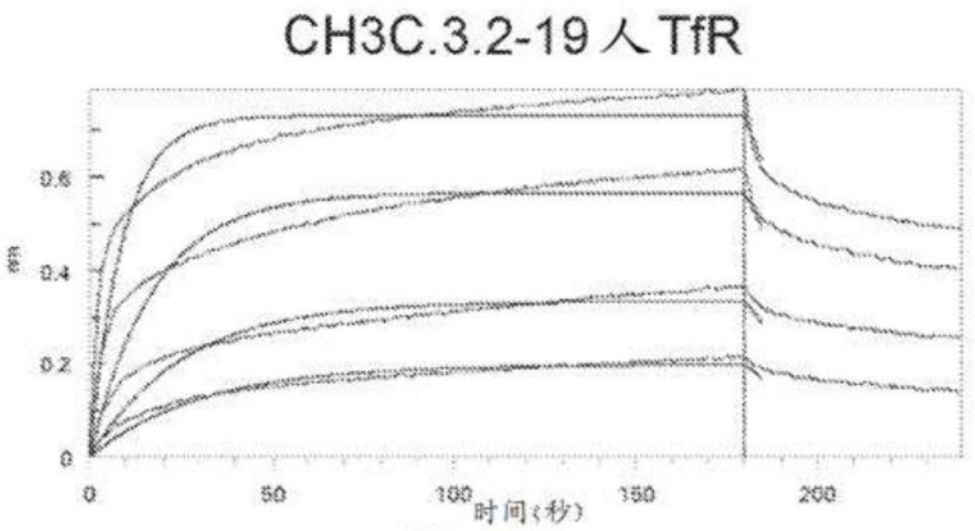

CH3C.3.2-19人TfR
0.6
0.4
0.2
0
0
50
100
150
200
时间(秒)

图23C

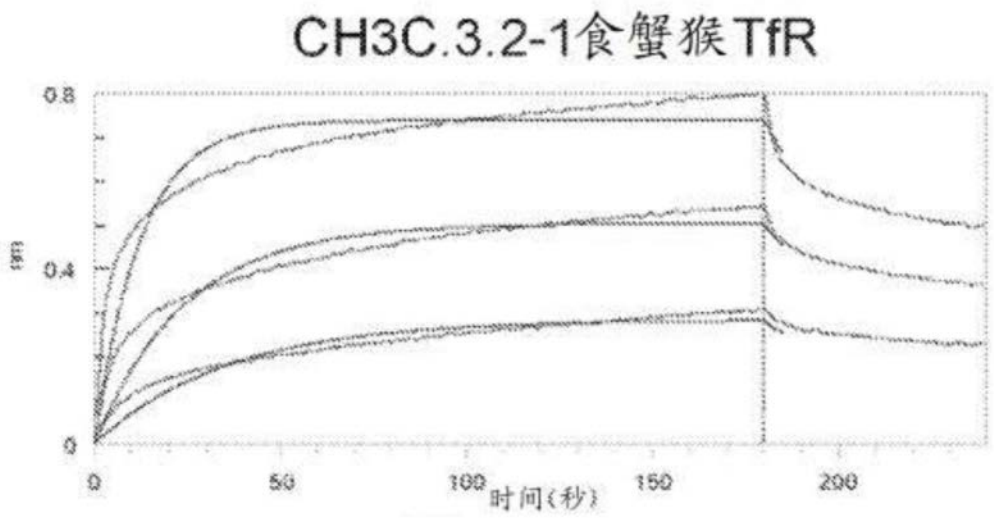

CH3C.3.2-1食蟹猴TfR
nm
0.8
0.4
0
0
50
100
150
200
时间(秒)

图23D

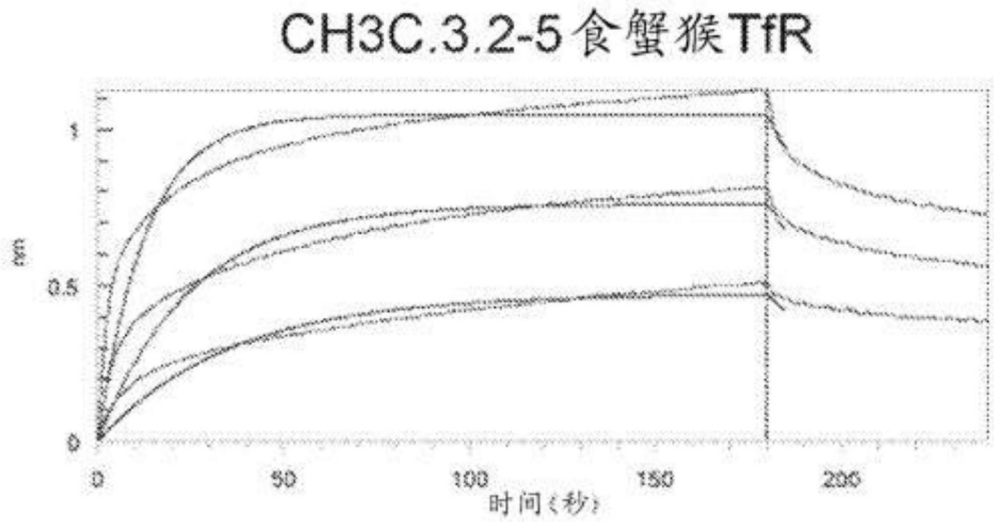

CH3C.3.2-5食蟹猴TfR
nm
1
0.5
0
0
50
100
150
200
时间(秒)

图23E

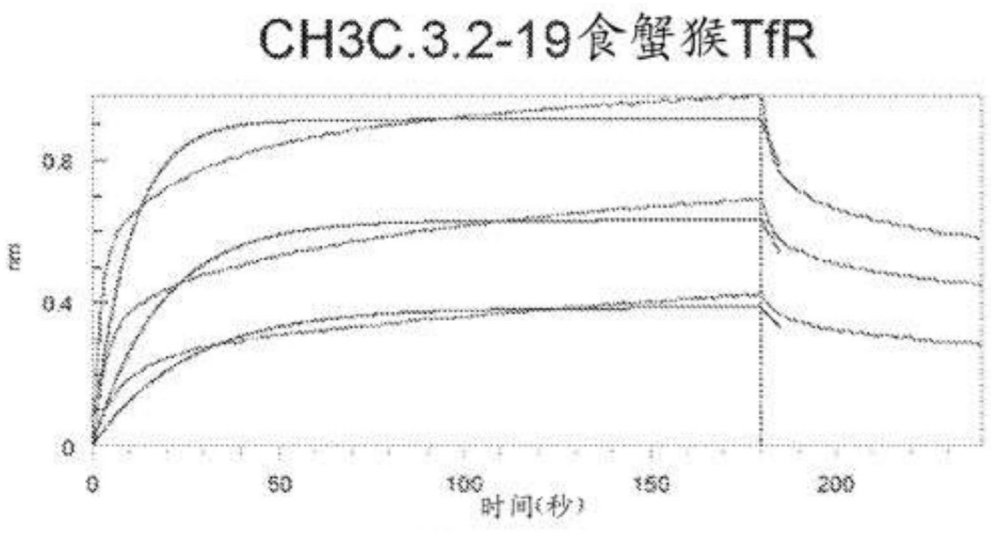
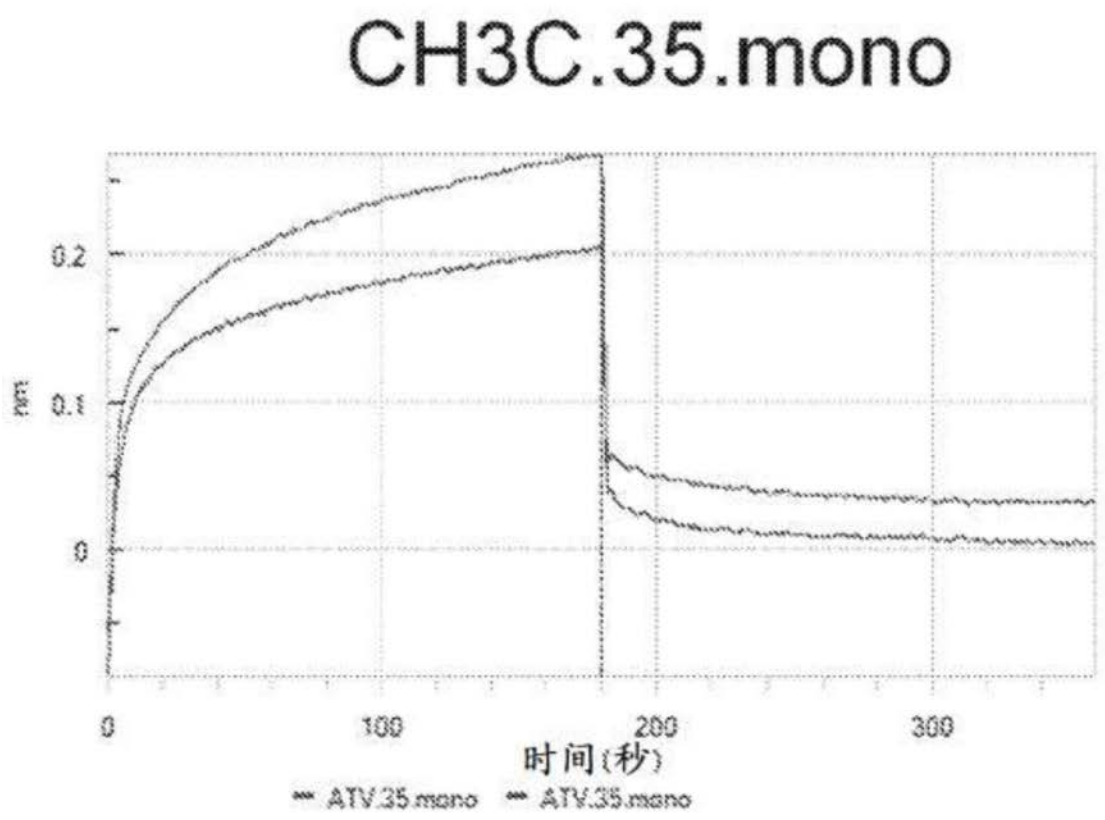


图23F


CH3C.35.mono
0.2
0.1
0
0
100
200
300
时间(秒)
ATV.35.mono
ATV.35.mono

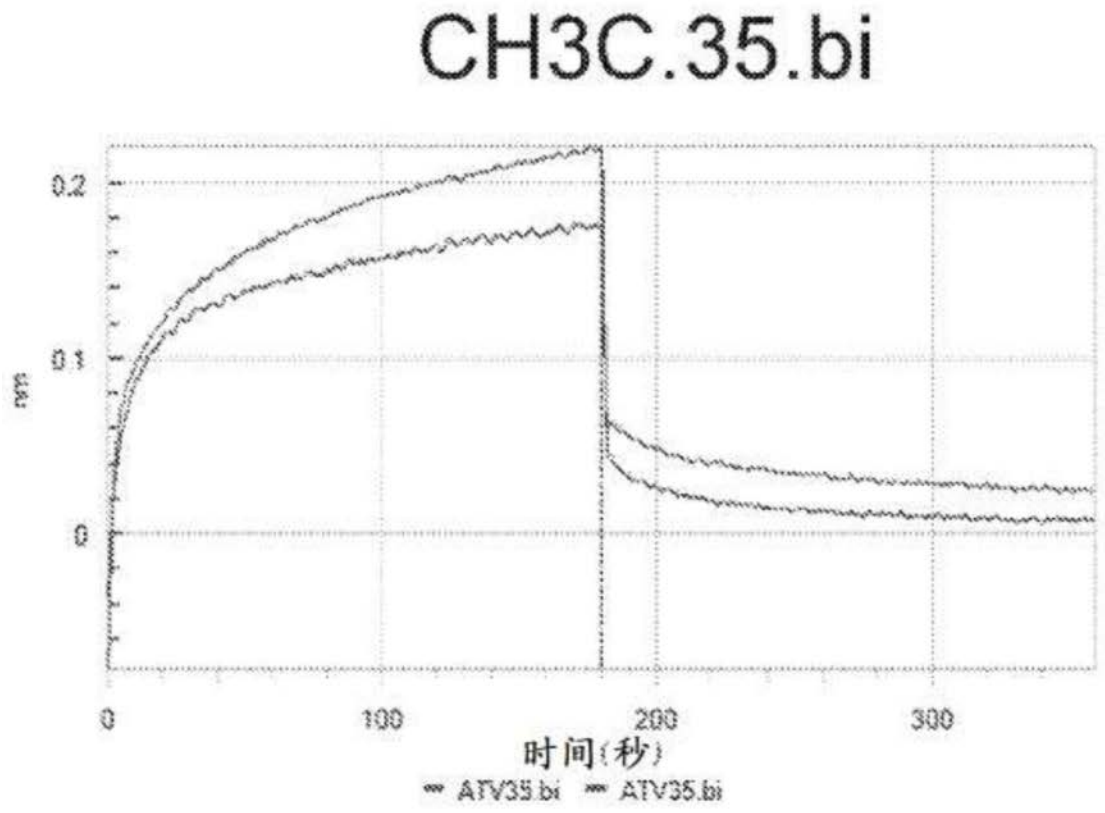
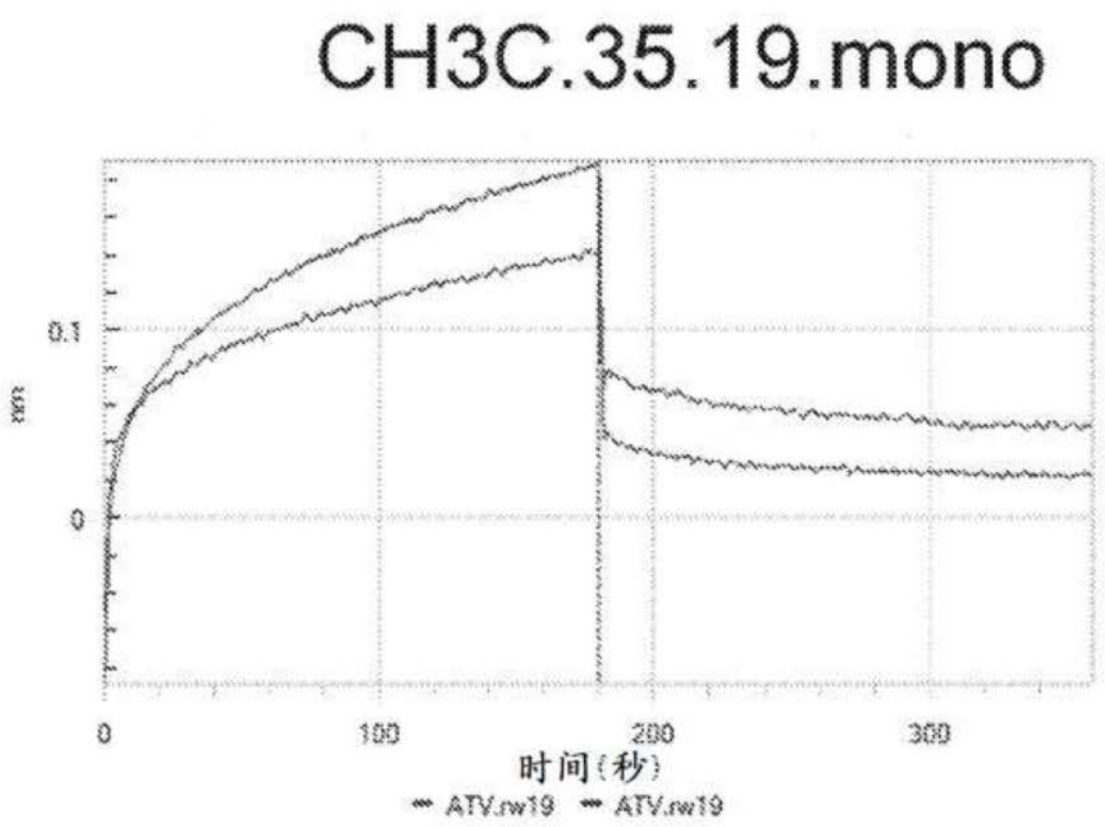

CH3C.35.bi
0.2
0.1
0
0
100
200
300
时间(秒)
ATV35.bi
ATV35.bi

图24A


CH3C.35.19.mono
0.1
0
0
100
200
300
时间(秒)
ATV.rw19
ATV.rw19

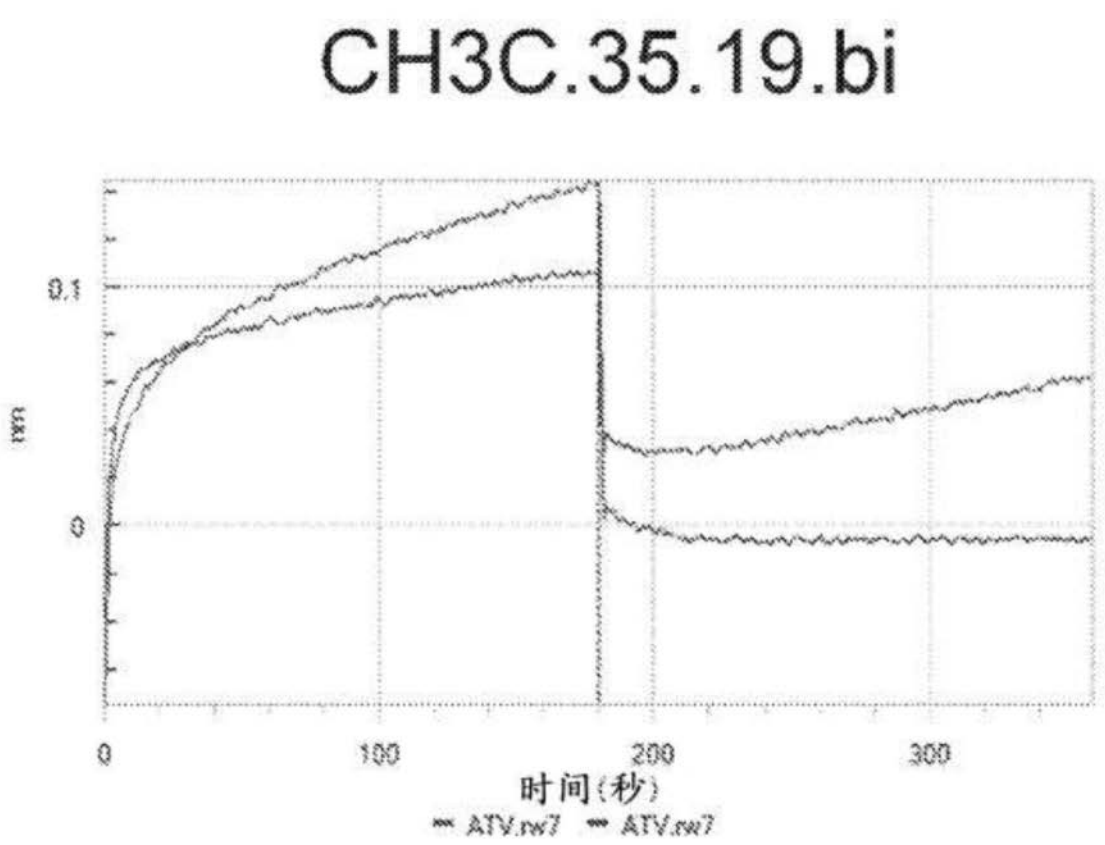
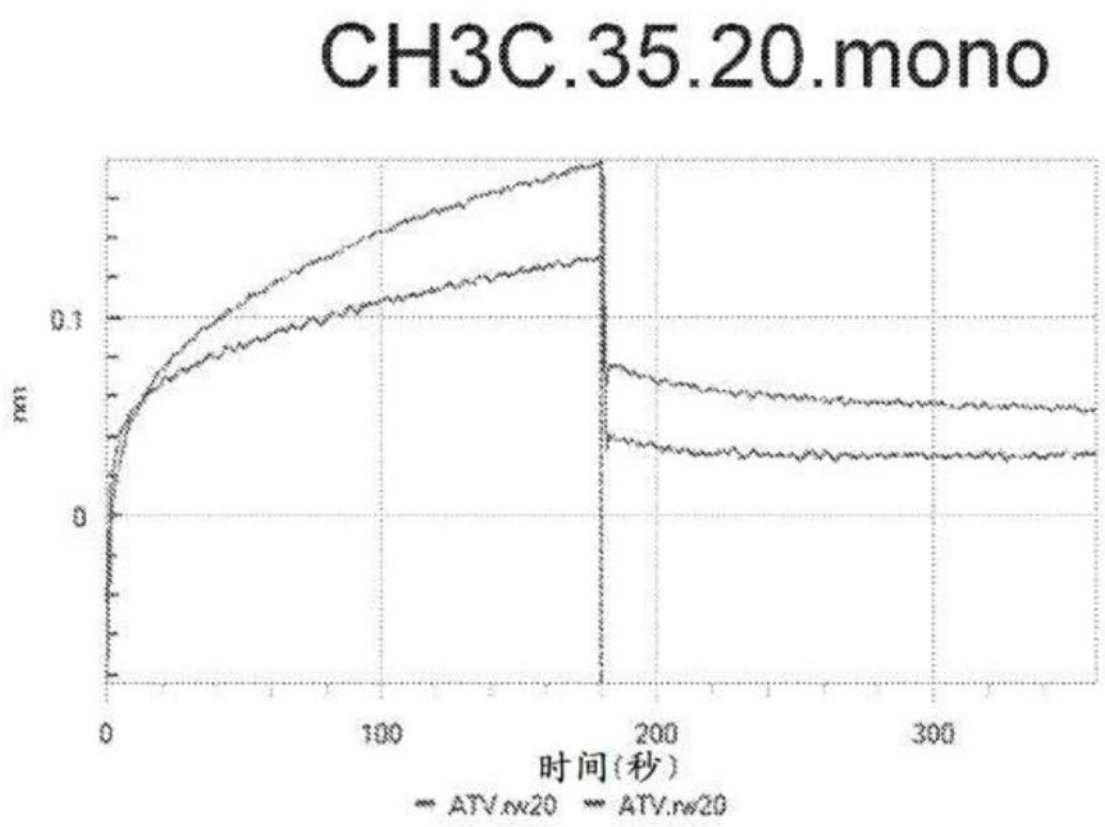

CH3C.35.19.bi
0.1
0
0
100
200
300
时间(秒)
ATV.rw7
ATV.rw7

图24B


CH3C.35.20.mono
0.1
0
0
100
200
300
时间(秒)
ATV.rw20
ATV.rw20

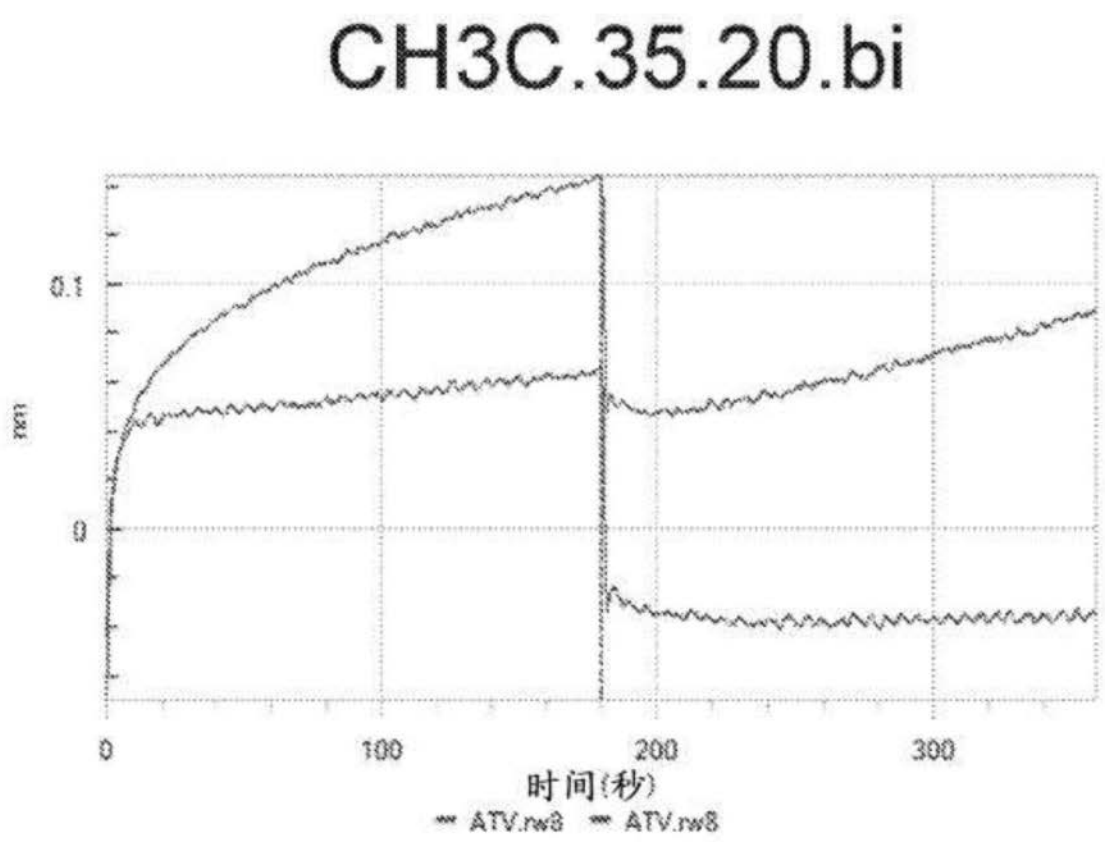

CH3C.35.20.bi
0.1
0
0
100
200
300
时间(秒)
ATV.rw8
ATV.rw8

图24C

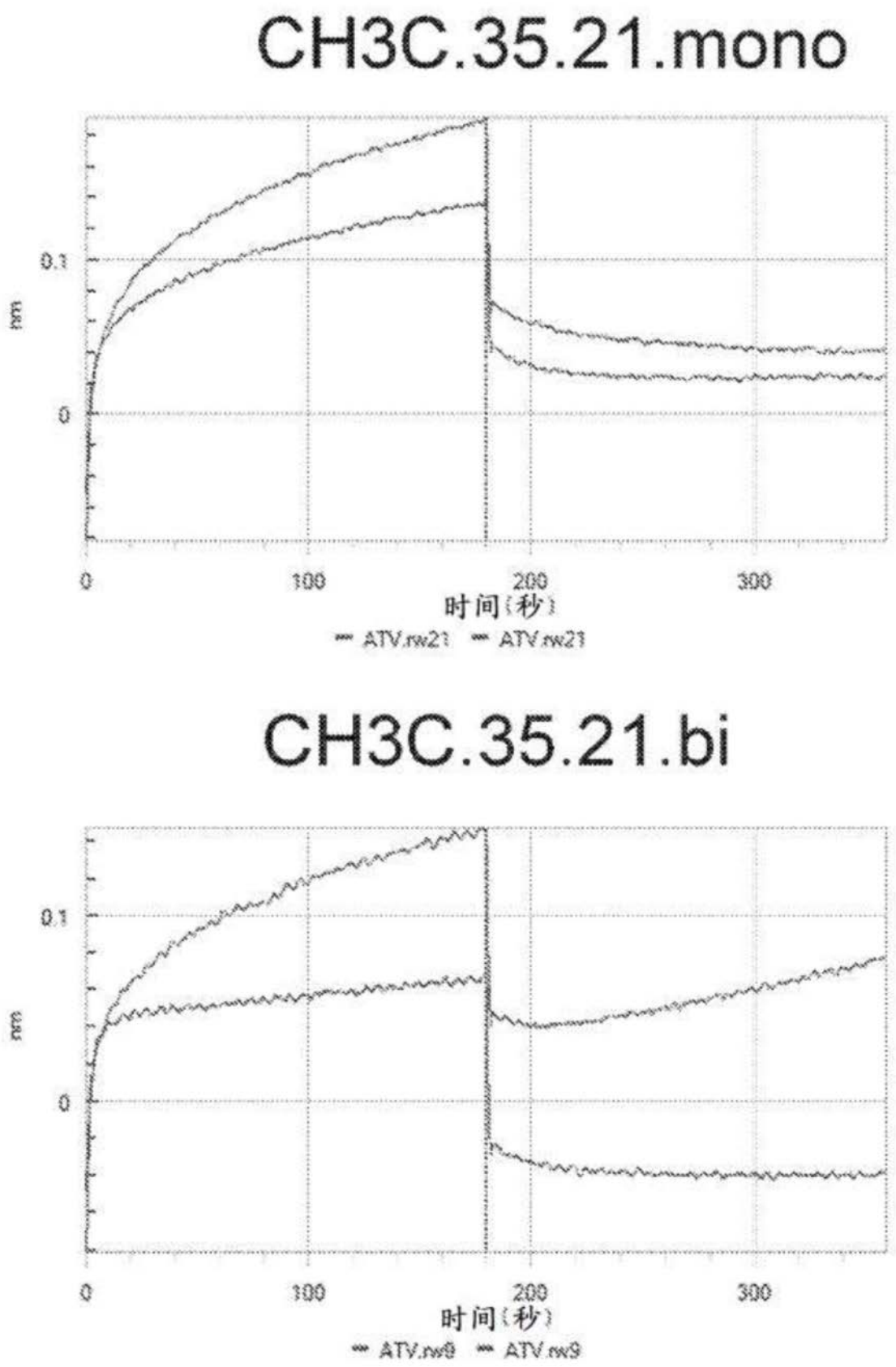
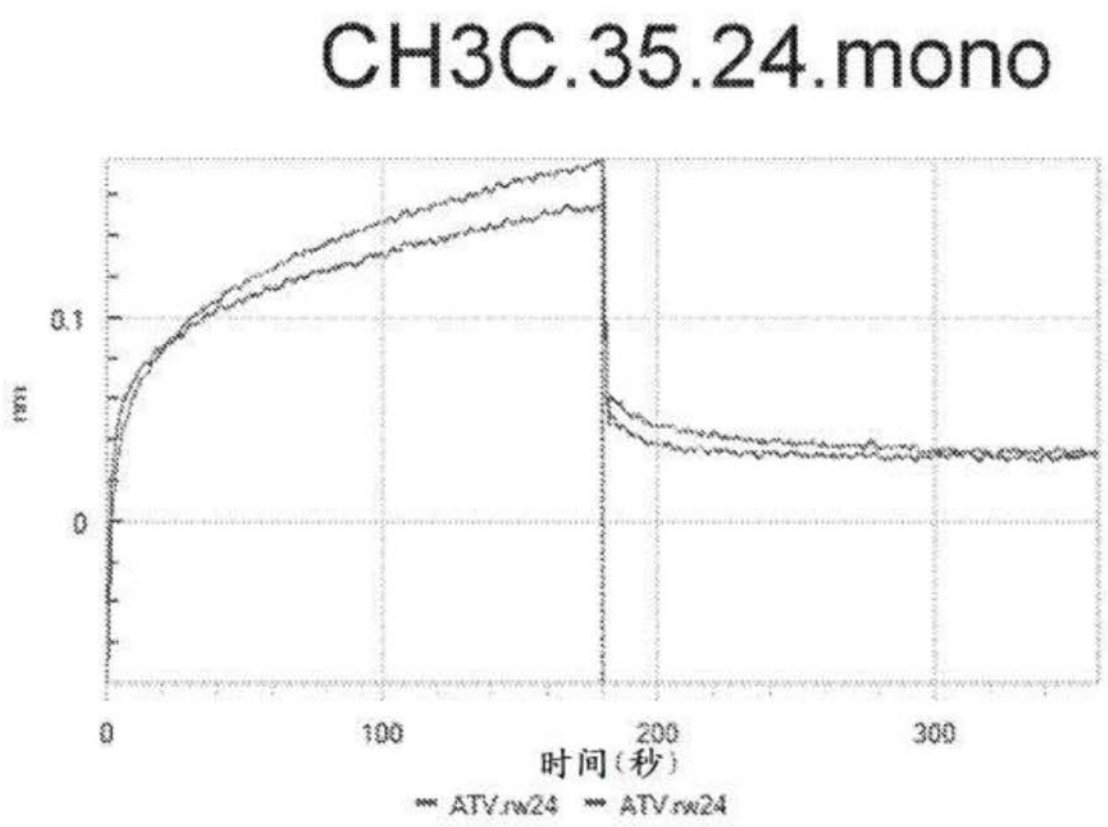

CH3C.35.21.mono
0.1
0
0
100
200
300
时间(秒)
ATV.rw21
ATV.rw21
CH3C.35.21.bi
0.1
0
0
100
200
300
时间(秒)
ATV.rw9
ATV.rw9

图24D


CH3C.35.24.mono
0.1
0
0
100
200
300
时间(秒)
ATV.rw24
ATV.rw24

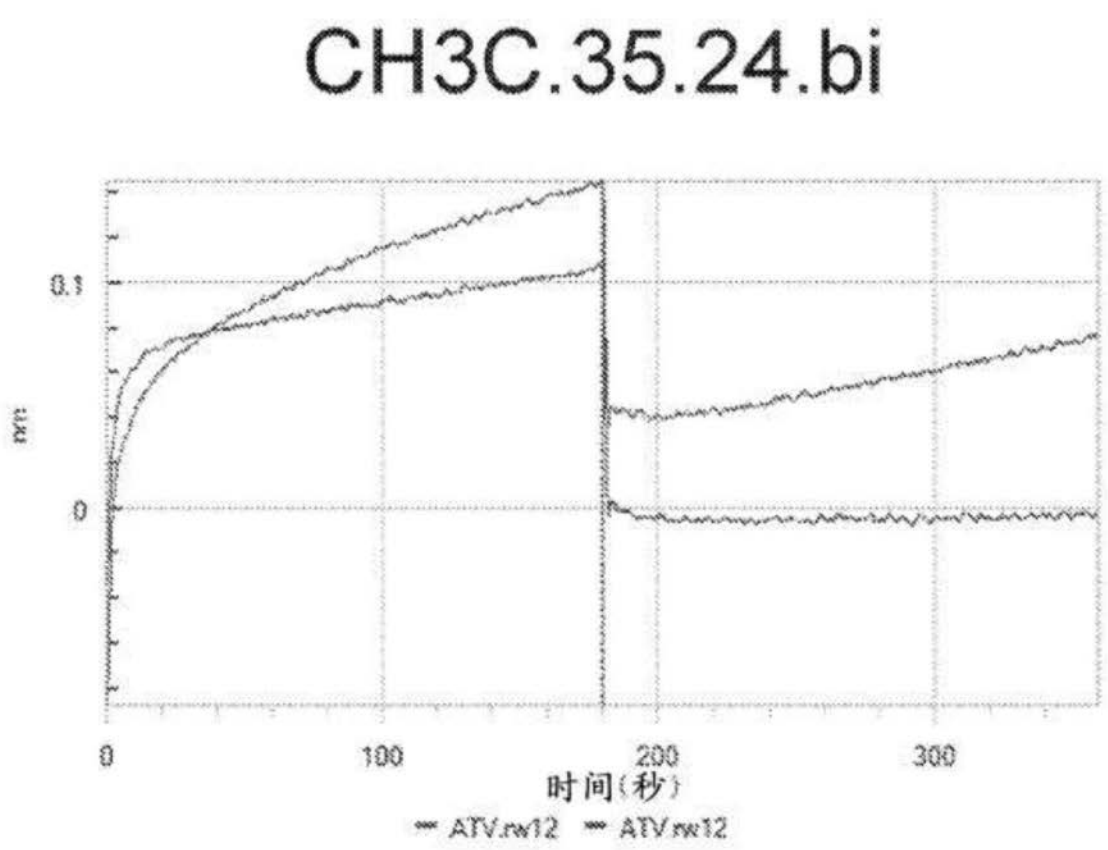

CH3C.35.24.bi
0.1
0
0
100
200
300
时间(秒)
ATV.rw12
ATV.rw12

图24E

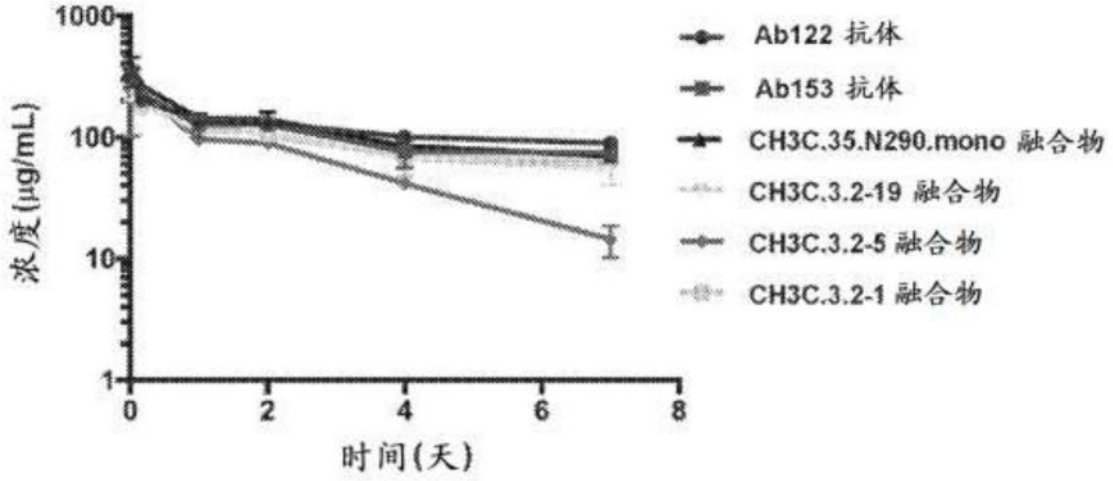

1000
100
10
1
浓度(μg/mL)
0
2
4
6
8
时间(天)
Ab122 抗体
Ab153 抗体
CH3C.35.N290.mono 融合物
CH3C.3.2-19 融合物
CH3C.3.2-5 融合物
CH3C.3.2-1 融合物

图25

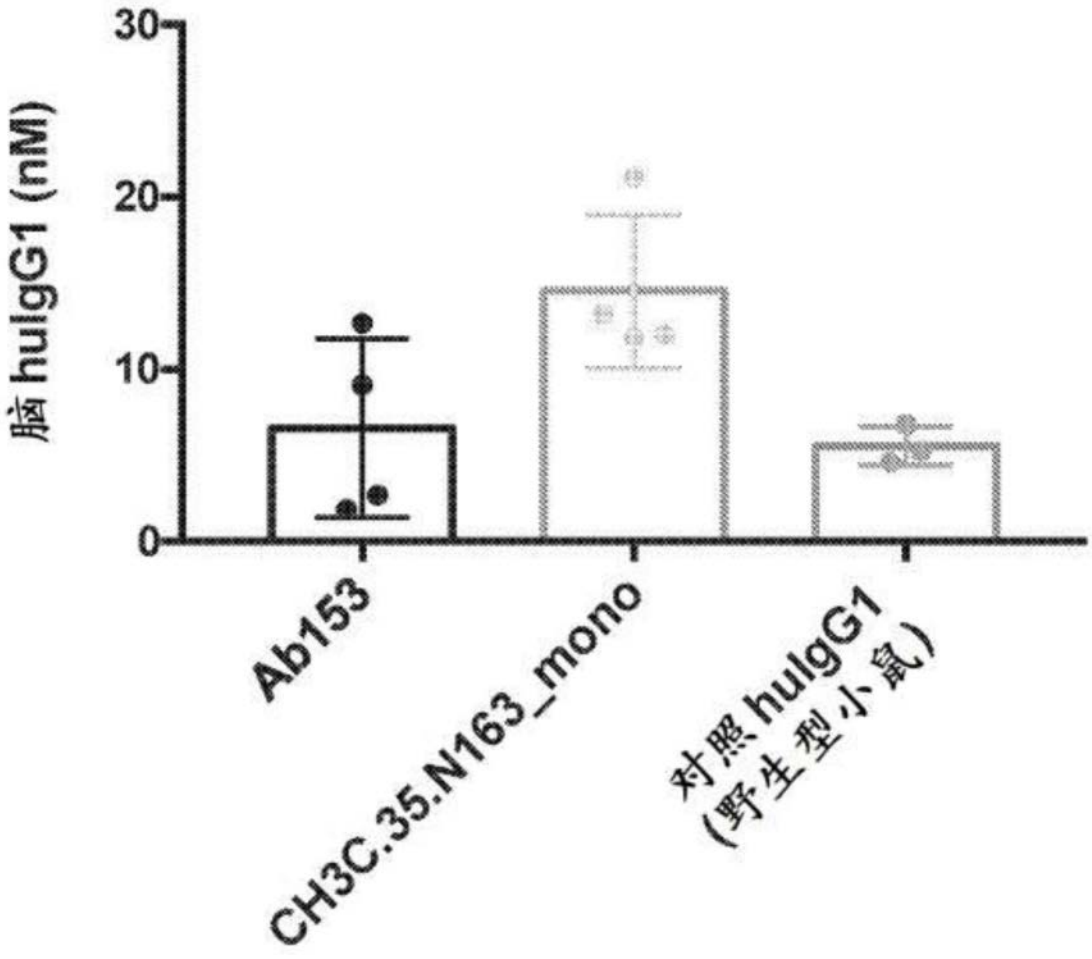

30
20
10
0
脑 hulgG1 (nM)
Ab153
CH3C.35.N163_mono
对照 hulgG1
(野生型小鼠)

图26

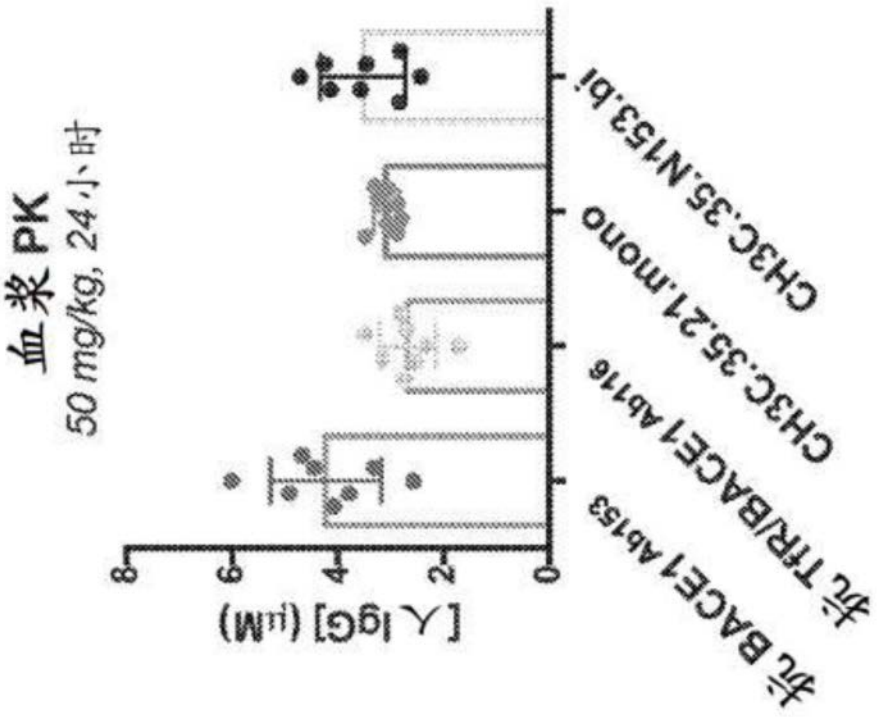

血浆 PK
50 mg/kg, 24 小时
[Aβ1-40] (μM)
0
2
4
6
8
抗 BACE1 Ab153
抗 TfR/BACE1 Ab116
CH3C.35.21.mono
CH3C.35.N153.bi

图27A

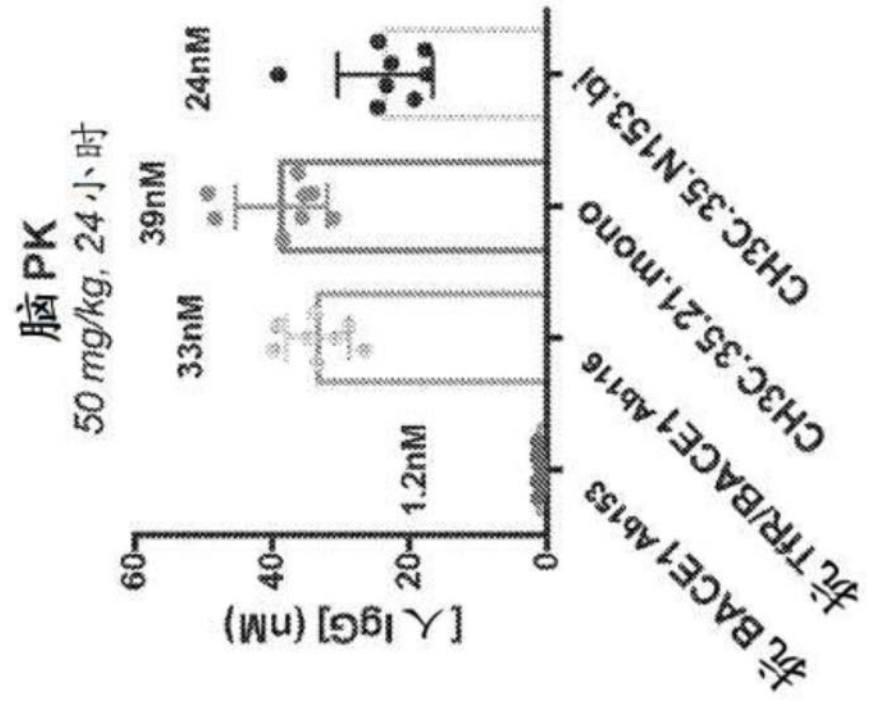

脑 PK
50 mg/kg, 24 小时
[Aβ1-40] (nM)
0
20
40
60
1.2nM
33nM
39nM
24nM
抗 BACE1 Ab153
抗 TfR/BACE1 Ab116
CH3C.35.21.mono
CH3C.35.N153.bi

图27B

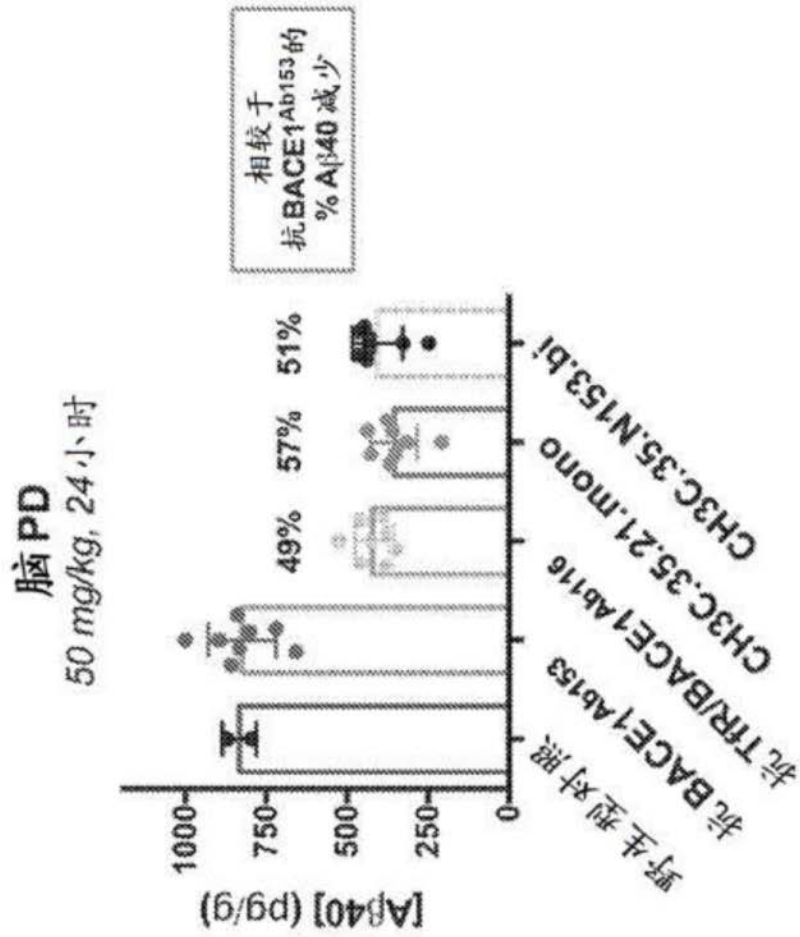

脑 PD
50 mg/kg, 24 小时
[Aβ40] (pg/g)
1000
750
500
250
0
49%
57%
51%
相较于
抗BACE1Ab153的
% Aβ40 减少
野生型对照
抗 BACE1Ab153
抗 TfR/BACE1Ab116
CH3C.35.21.mono
CH3C.35.N153.bi

图 28B

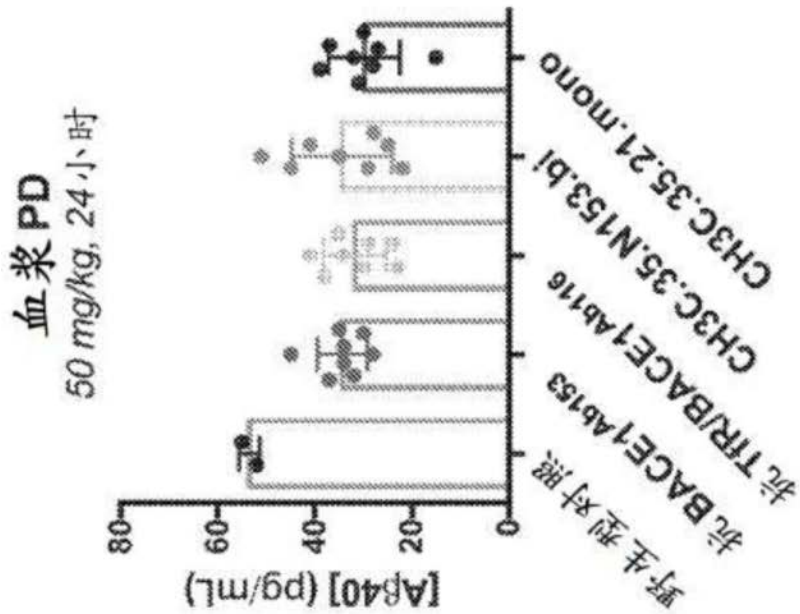

血浆 PD
50 mg/kg, 24 小时
[Aβ40] (pg/mL)
80
60
40
20
0
野生型对照
抗 BACE1Ab153
抗 TfR/BACE1Ab116
CH3C.35.N153.bi
CH3C.35.21.mono

图 28A

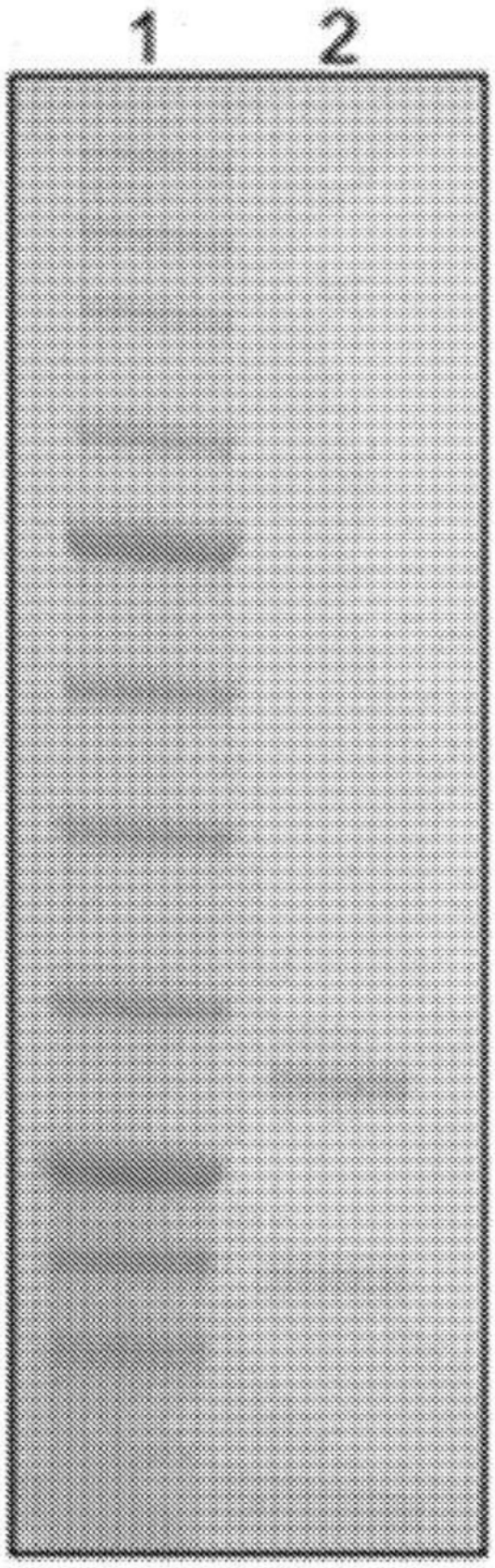


图29

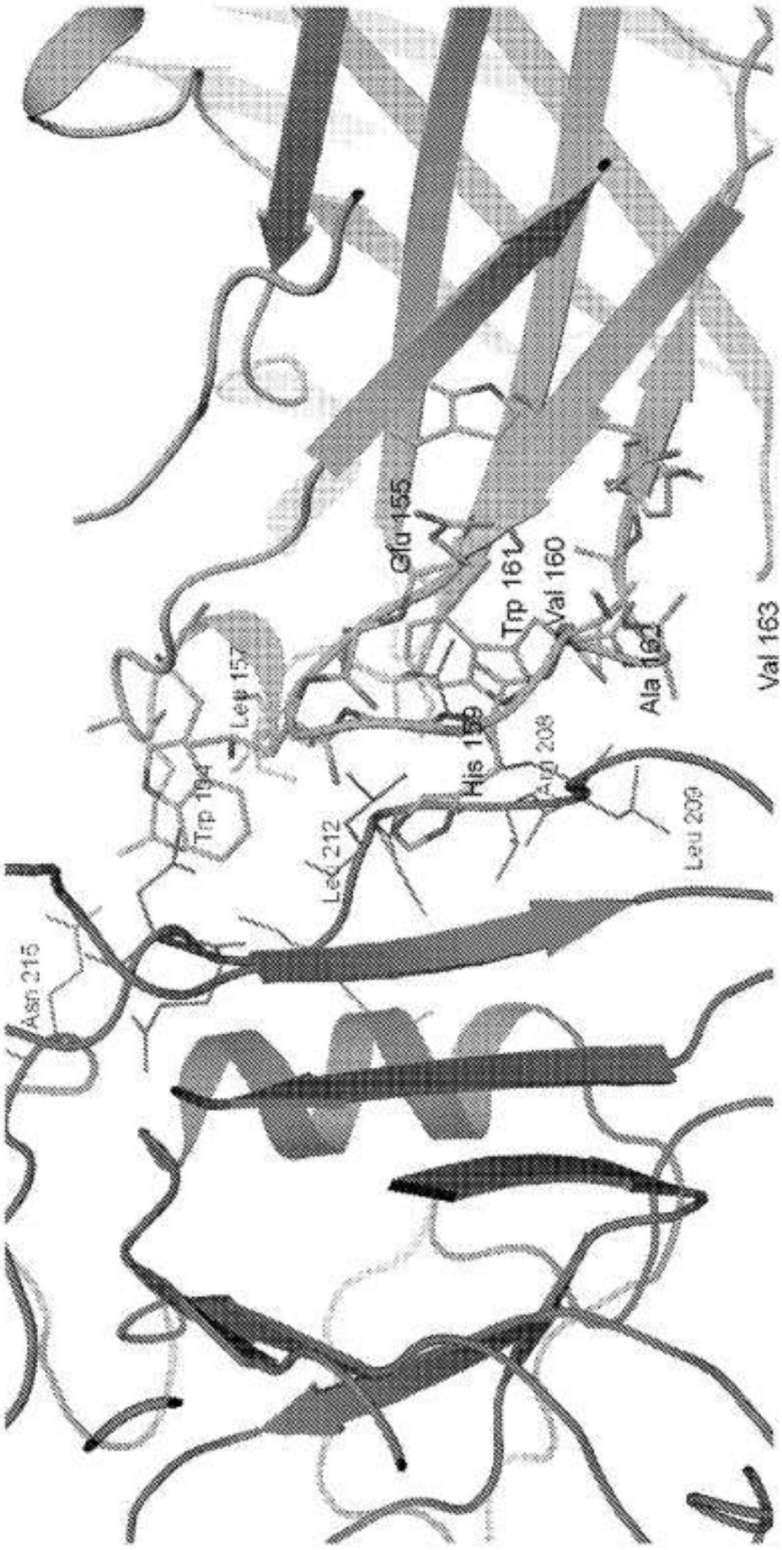

Glu 155
Trp 161
Val 160
Ala 162
Val 163
Leu 157
Trp 194
His 159
Asp 208
Leu 209
Leu 212
Asn 215

图30A

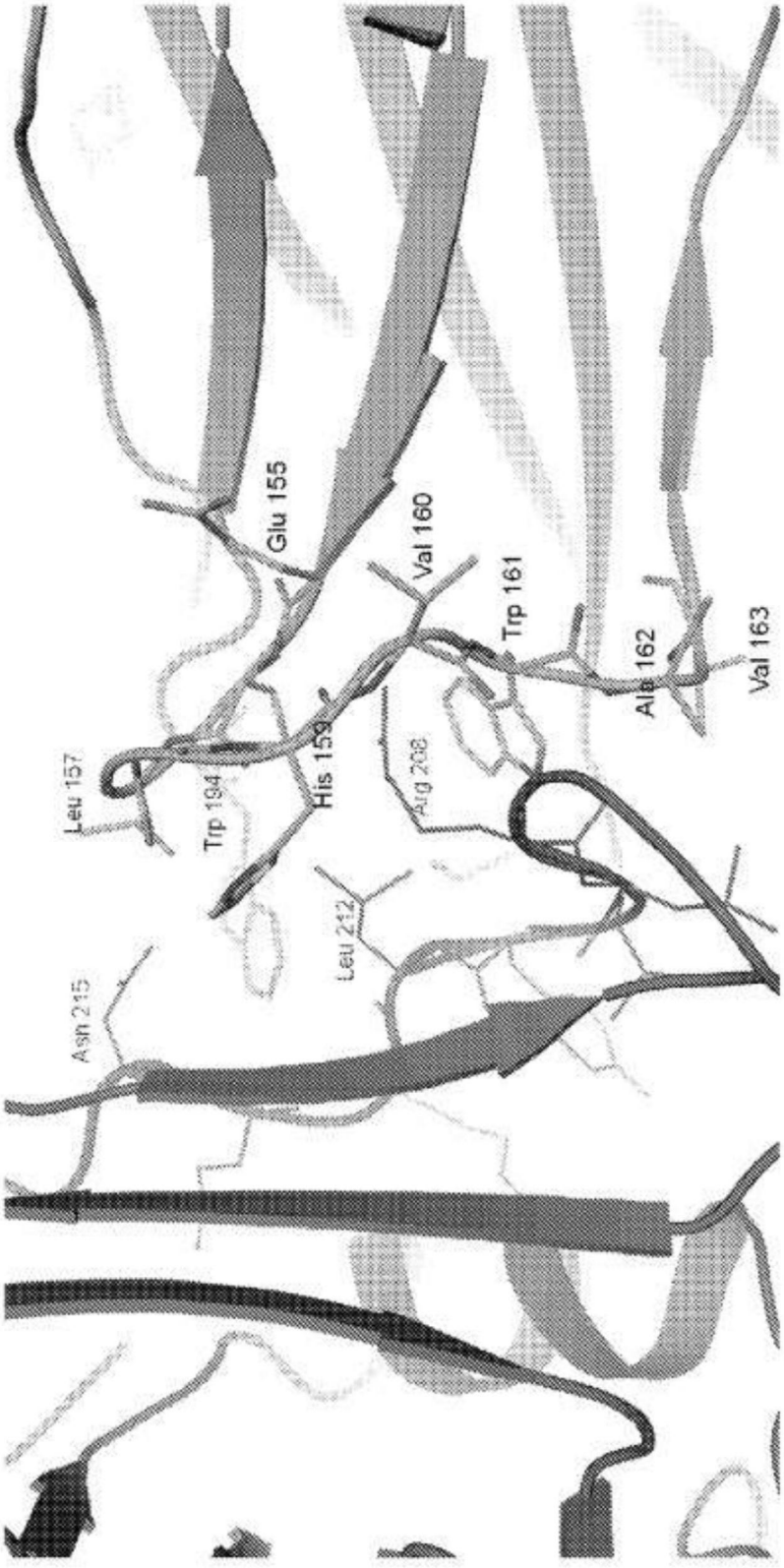

Glu 155
Val 160
Trp 161
Ala 162
Val 163
Leu 157
Trp 194
His 159
Arg 208
Leu 212
Asn 215

图30B

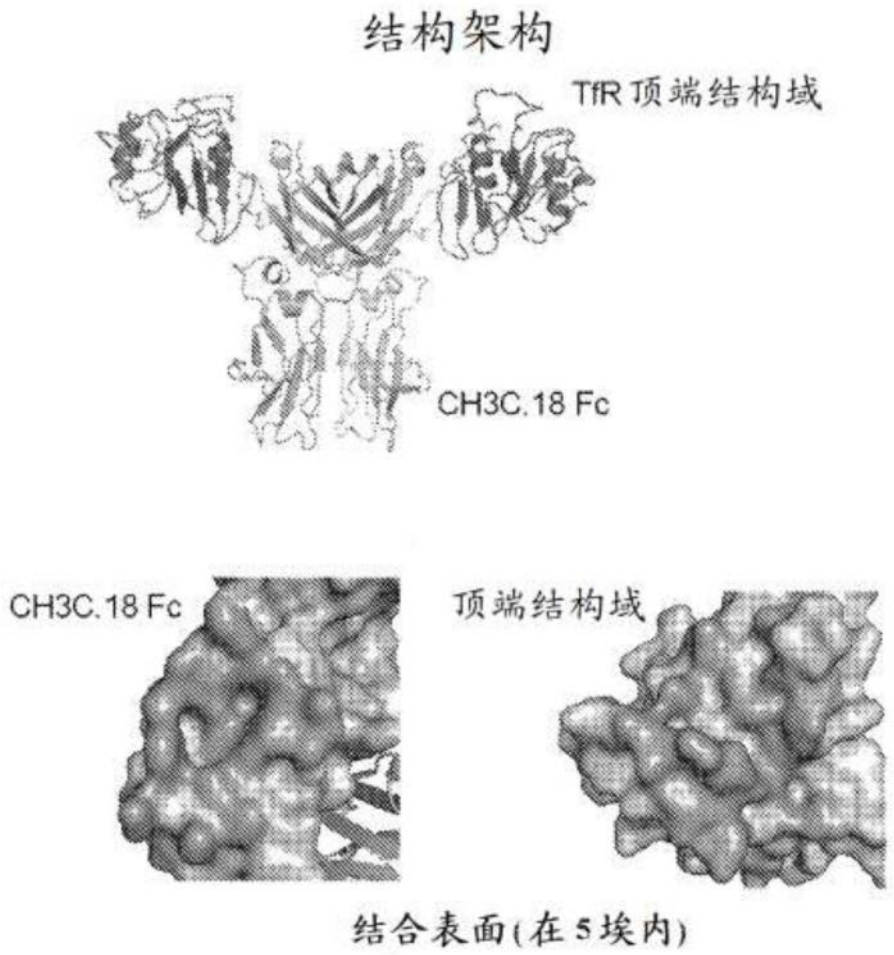


图31A

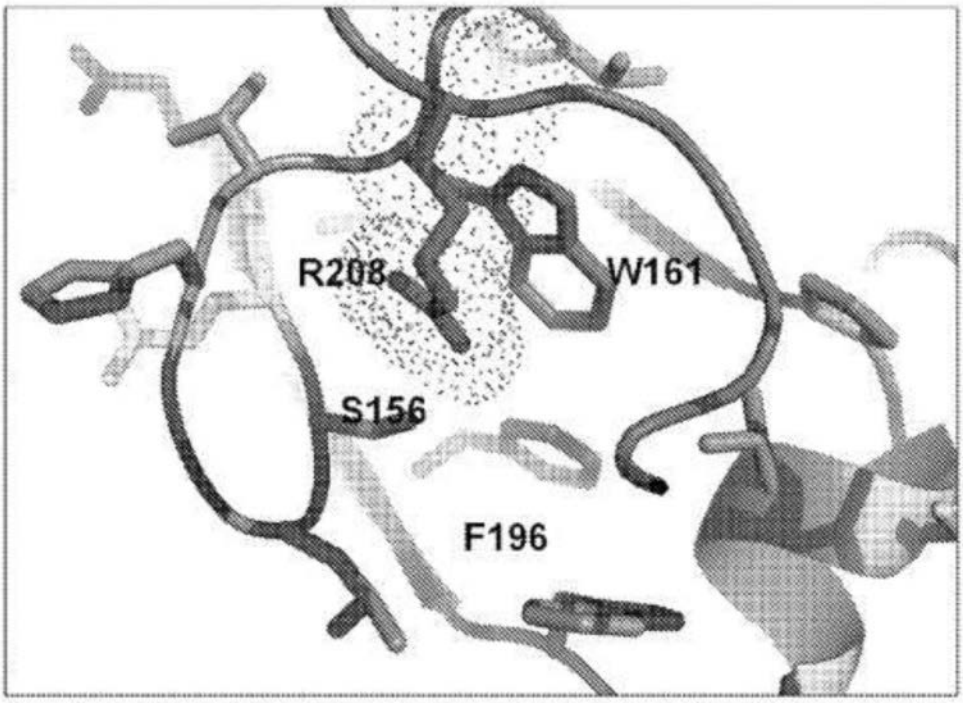


图31B

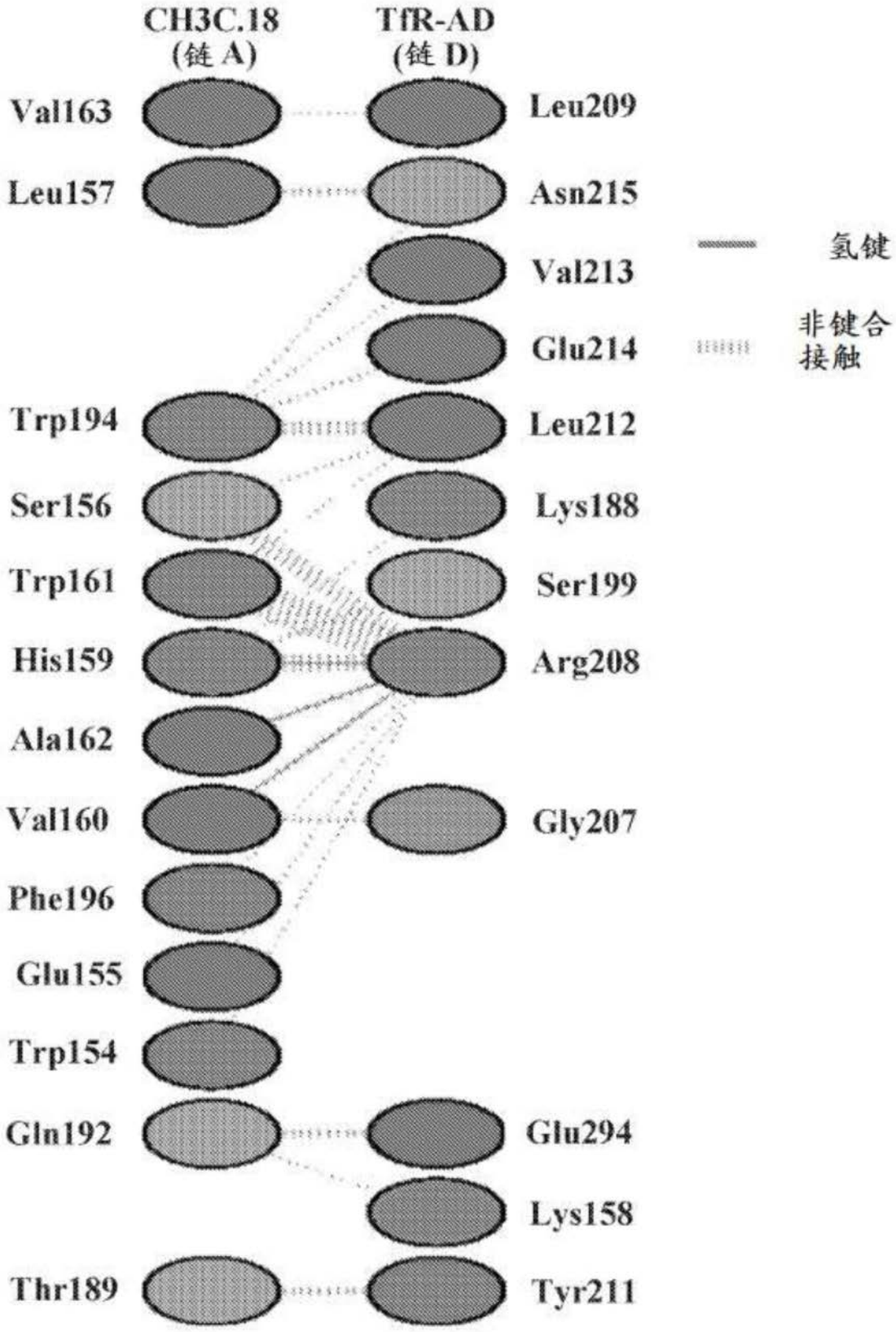

CH3C.18
(链 A)
TfR-AD
(链 D)
Val163
Leu157
Trp194
Ser156
Trp161
His159
Ala162
Val160
Phe196
Glu155
Trp154
Gln192
Thr189
Leu209
Asn215
Val213
Glu214
Leu212
Lys188
Ser199
Arg208
Gly207
Glu294
Lys158
Tyr211
氢键
非键合
接触

图32A

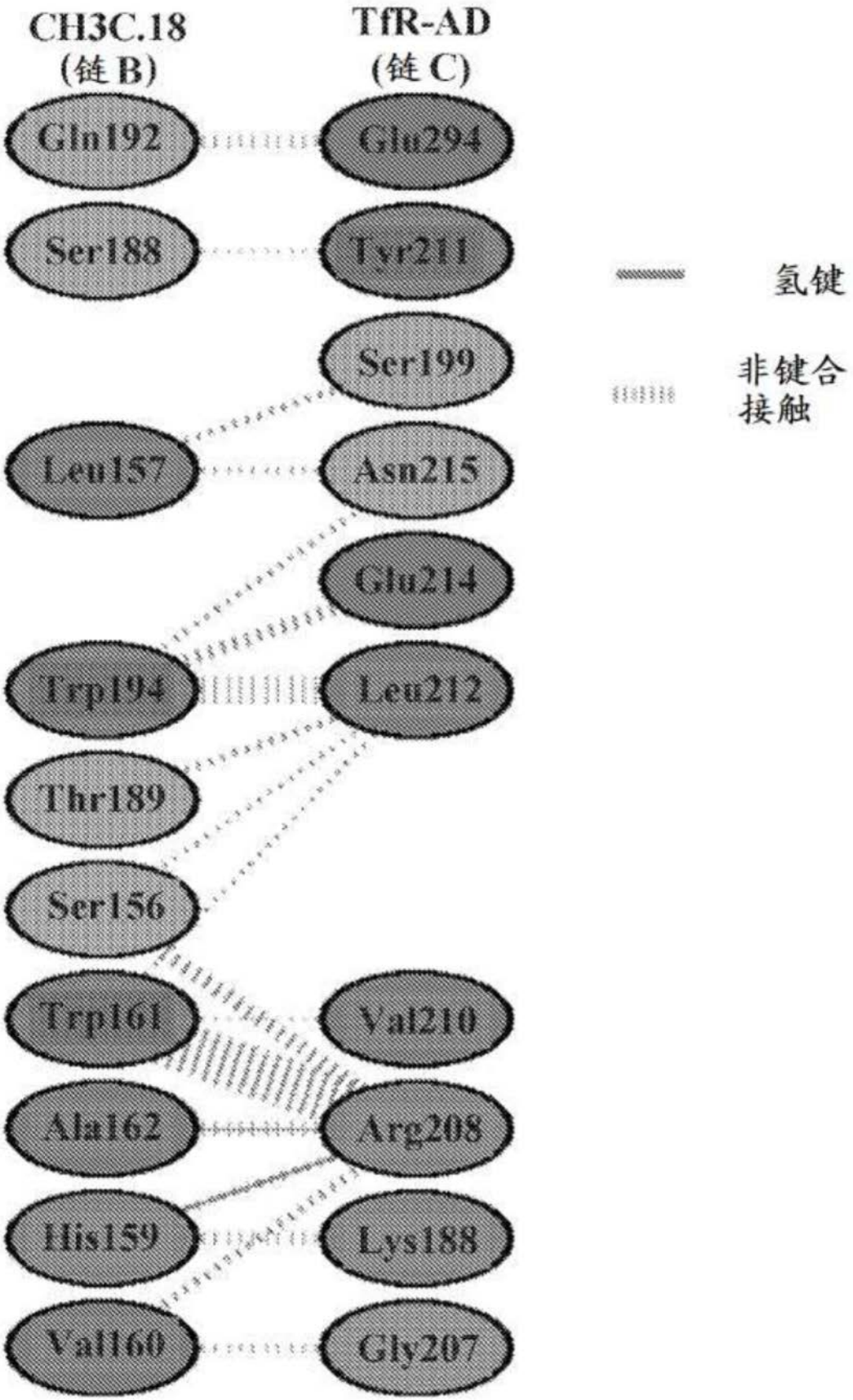

CH3C.18
(链B)
TfR-AD
(链C)
Gln192
Glu294
Ser188
Tyr211
Ser199
Leu157
Asn215
Glu214
Trp194
Leu212
Thr189
Ser156
Trp161
Val210
Ala162
Arg208
His159
Lys188
Val160
Gly207
氢键
非键合
接触

图32B

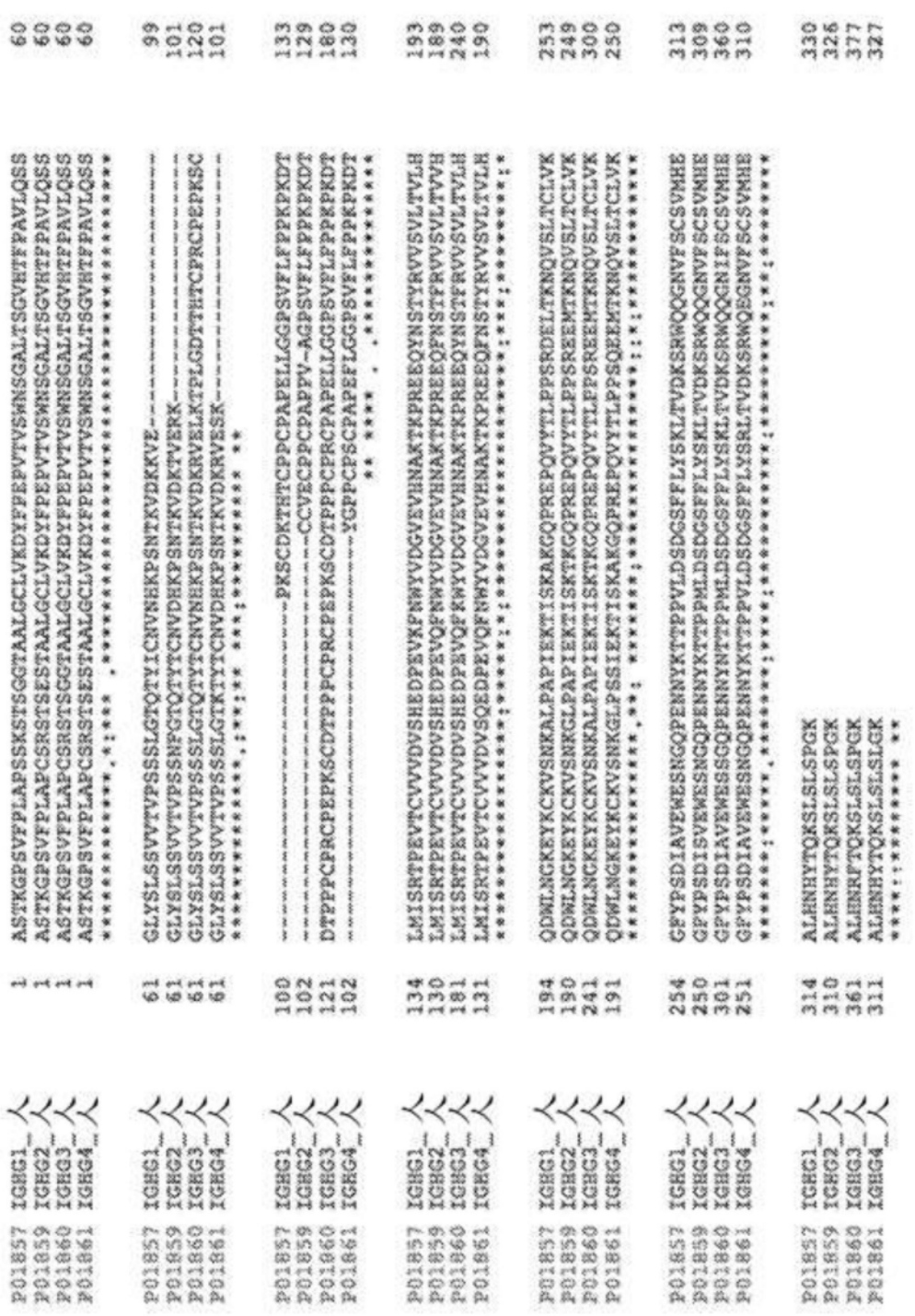


图33

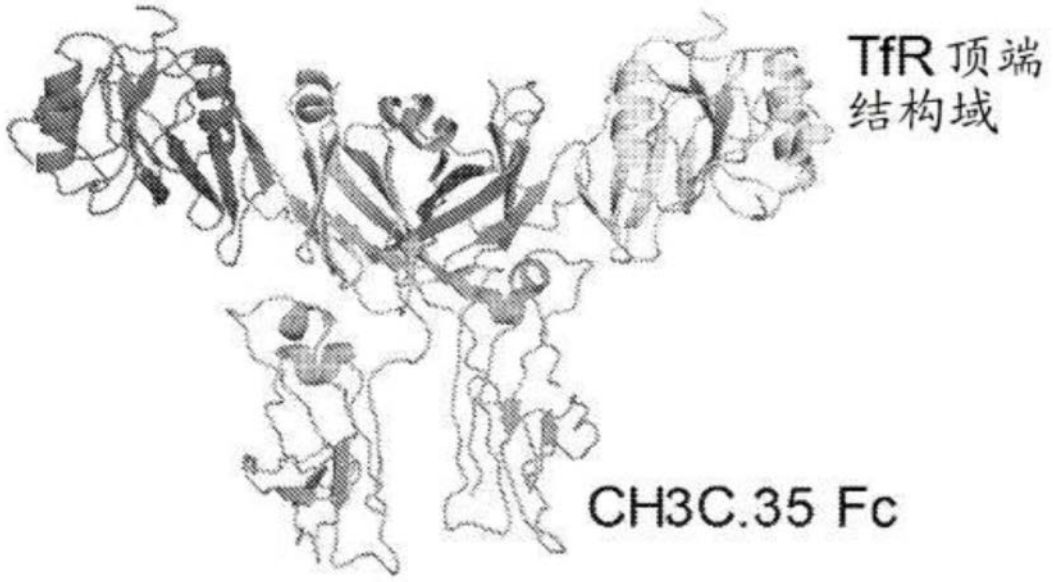

TfR 顶端
结构域
CH3C.35 Fc

图34A

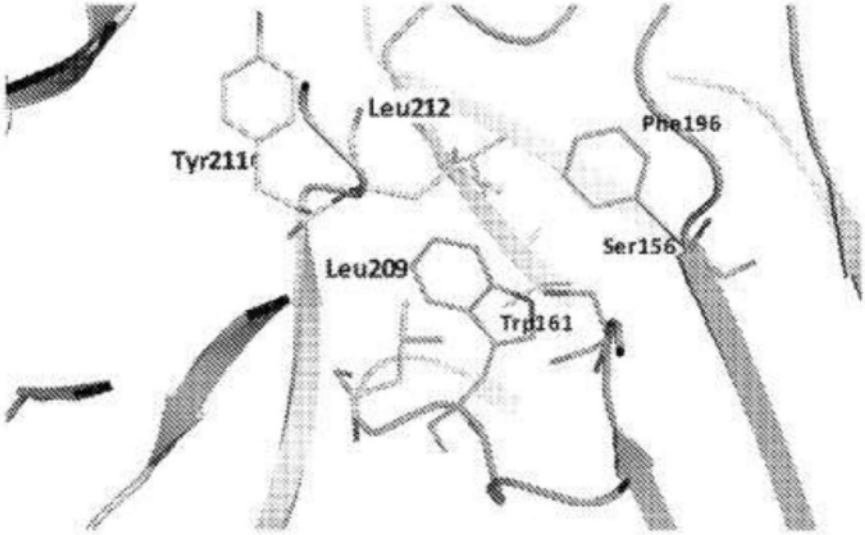

Leu212
Phe196
Tyr211
Ser156
Leu209
Trp161

图34B

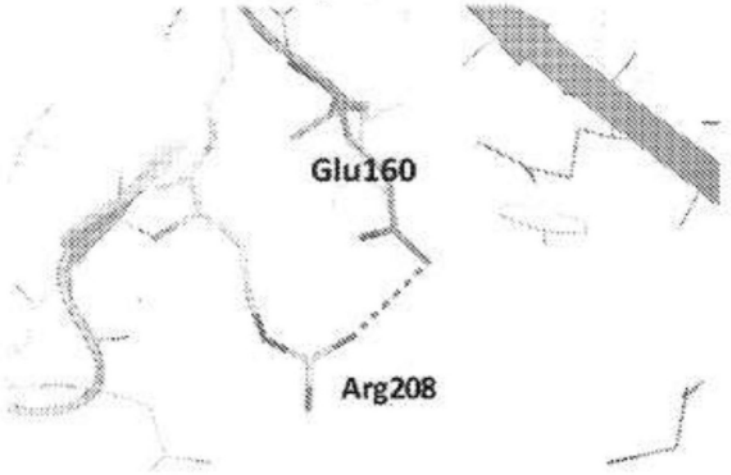


图34C

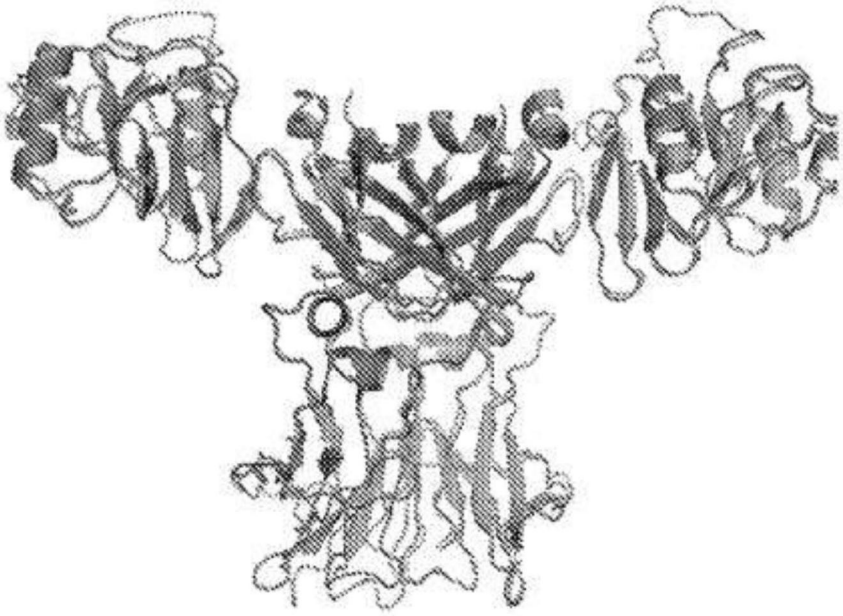


图35A

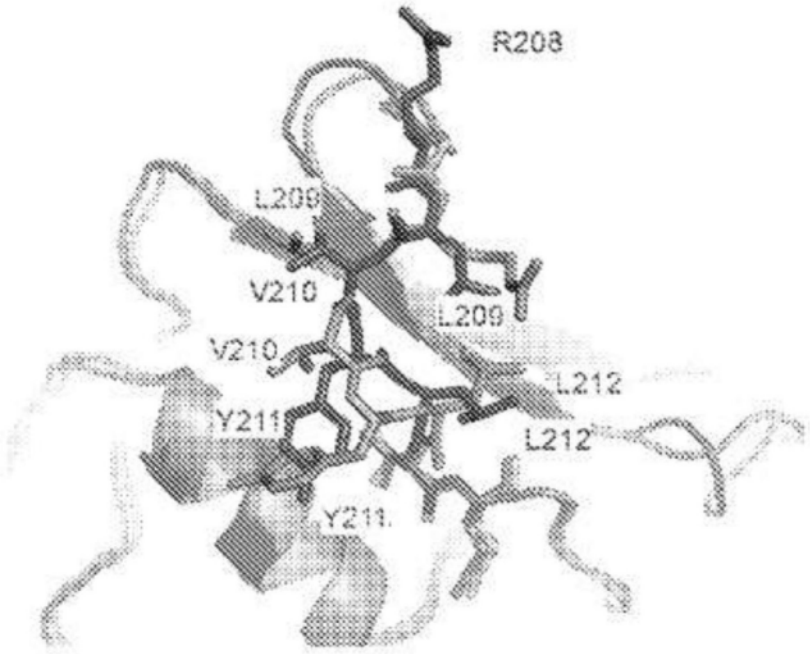


图35B

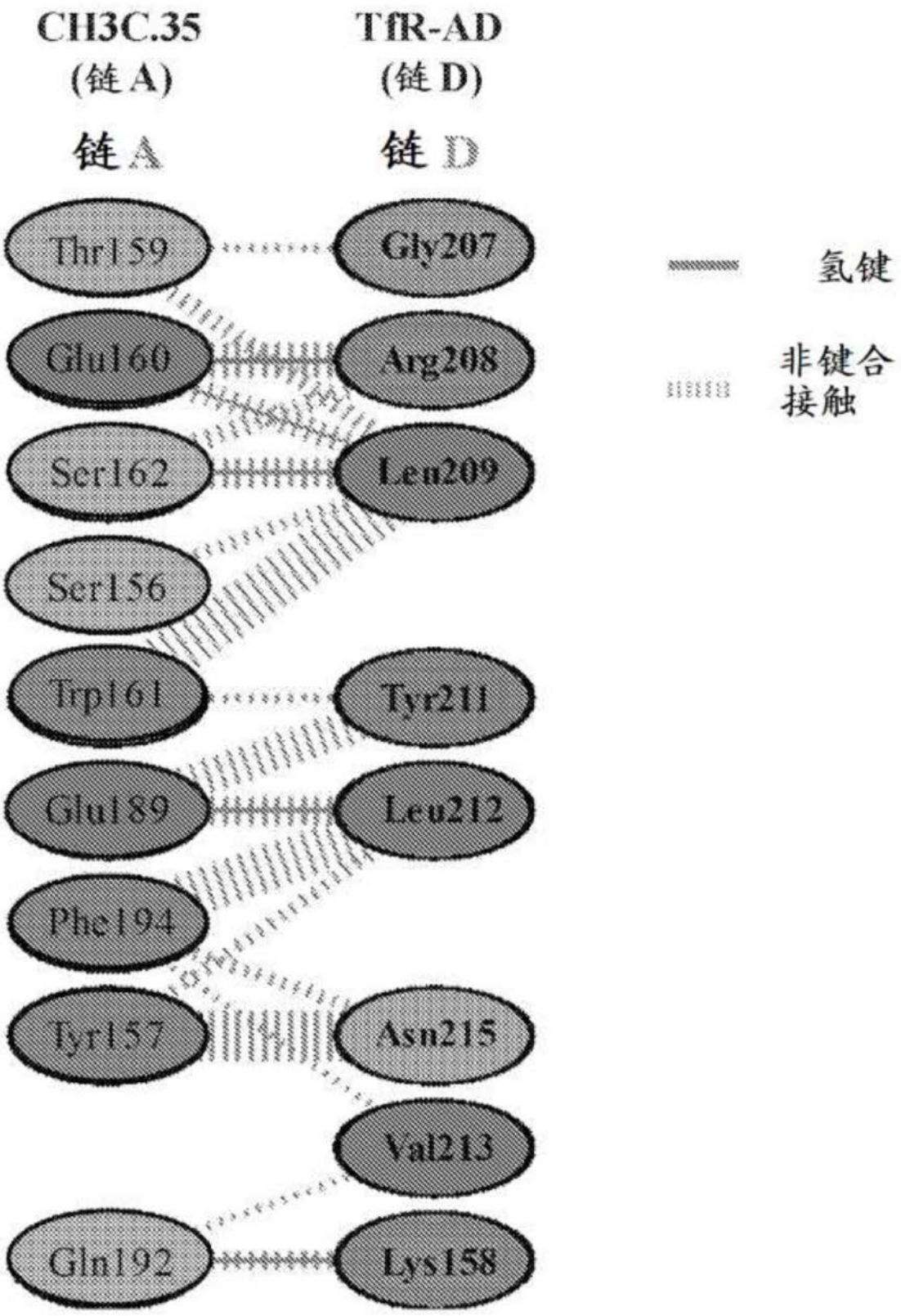

CH3C.35
(链A)
TfR-AD
(链D)
链A
链D
Thr159
Gly207
Glu160
Arg208
Ser162
Leu209
Ser156
Trp161
Tyr211
Glu189
Leu212
Phe194
Tyr157
Asn215
Val213
Gln192
Lys158
氢键
非键合
接触

图36A

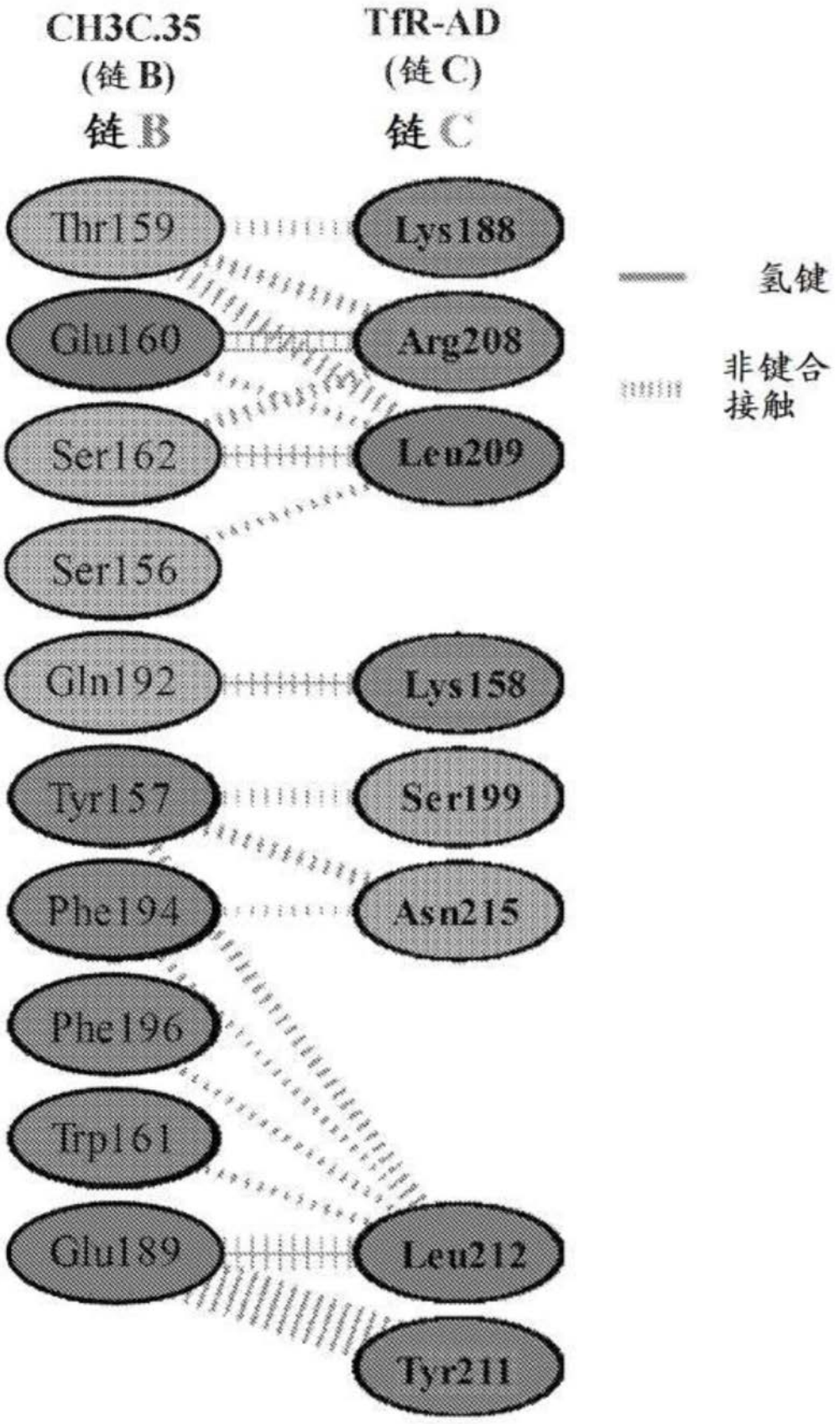

CH3C.35
(链B)
链B
TfR-AD
(链C)
链C
Thr159
Lys188
Glu160
Arg208
Ser162
Leu209
Ser156
Gln192
Lys158
Tyr157
Ser199
Phe194
Asn215
Phe196
Trp161
Glu189
Leu212
Tyr211
氢键
非键合
接触

图36B

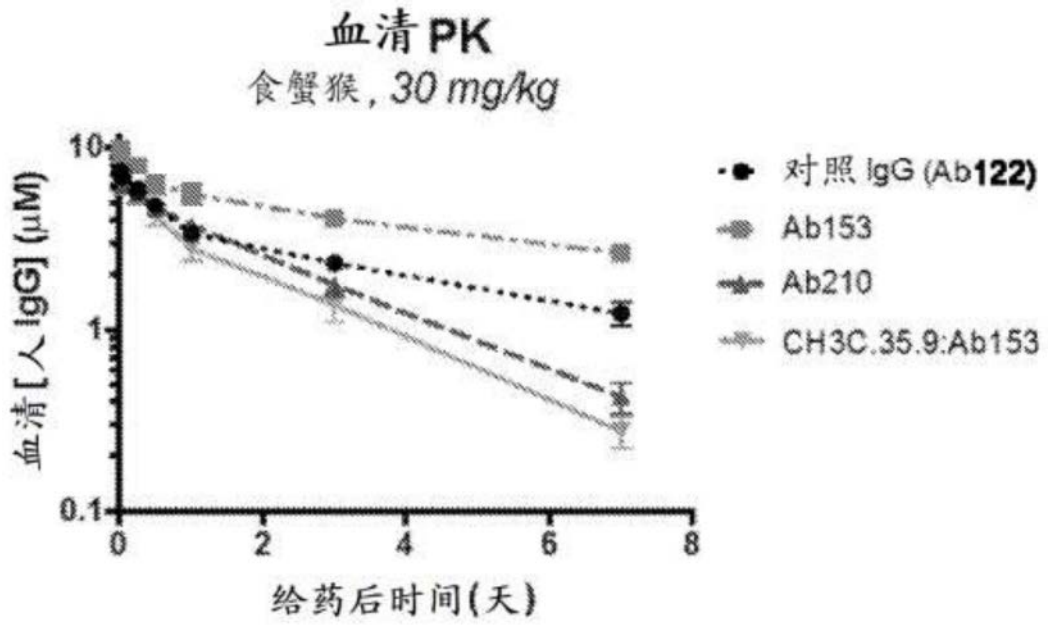

血清PK
食蟹猴，30 mg/kg
血清[人IgG] (μM)
10
1
0.1
0
2
4
6
8
给药后时间(天)
对照 IgG (Ab122)
Ab153
Ab210
CH3C.35.9:Ab153

图37A

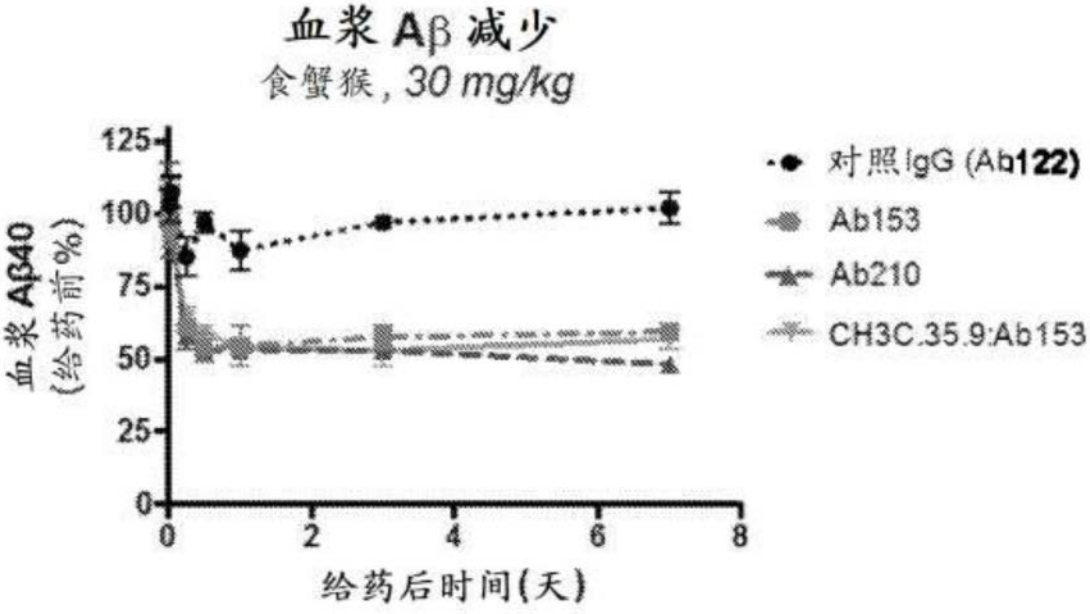

血浆Aβ减少
食蟹猴，30 mg/kg
血浆Aβ40
(给药前%)
125
100
75
50
25
0
0
2
4
6
8
给药后时间(天)
对照IgG (Ab122)
Ab153
Ab210
CH3C.35.9:Ab153

图37B

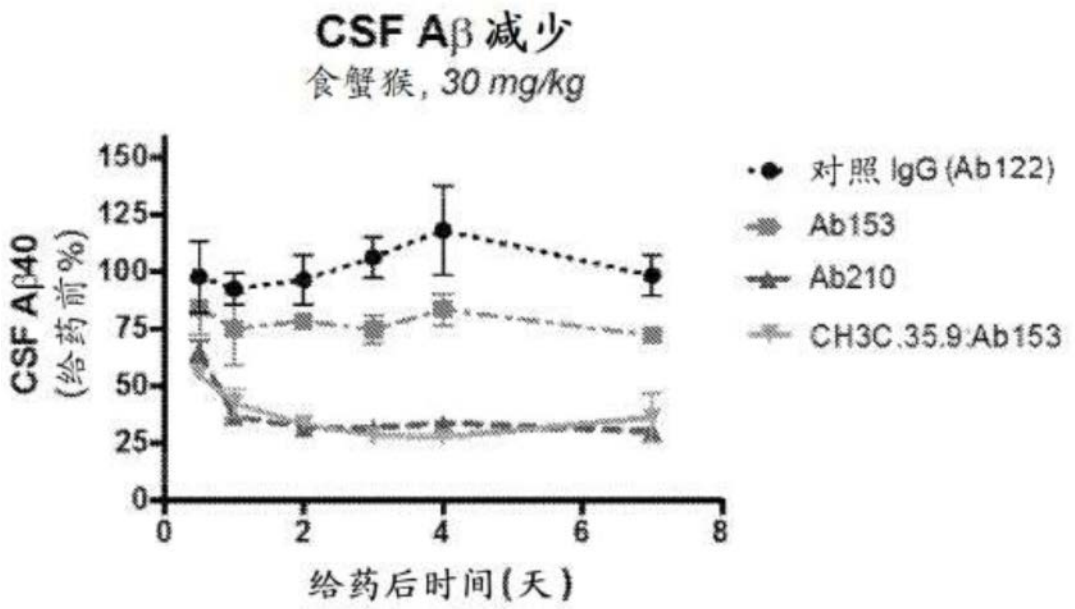

CSF Aβ 减少
食蟹猴，30 mg/kg
CSF Aβ40 (给药前%)
150
125
100
75
50
25
0
0
2
4
6
8
给药后时间(天)
对照 IgG (Ab122)
Ab153
Ab210
CH3C.35.9:Ab153

图38A

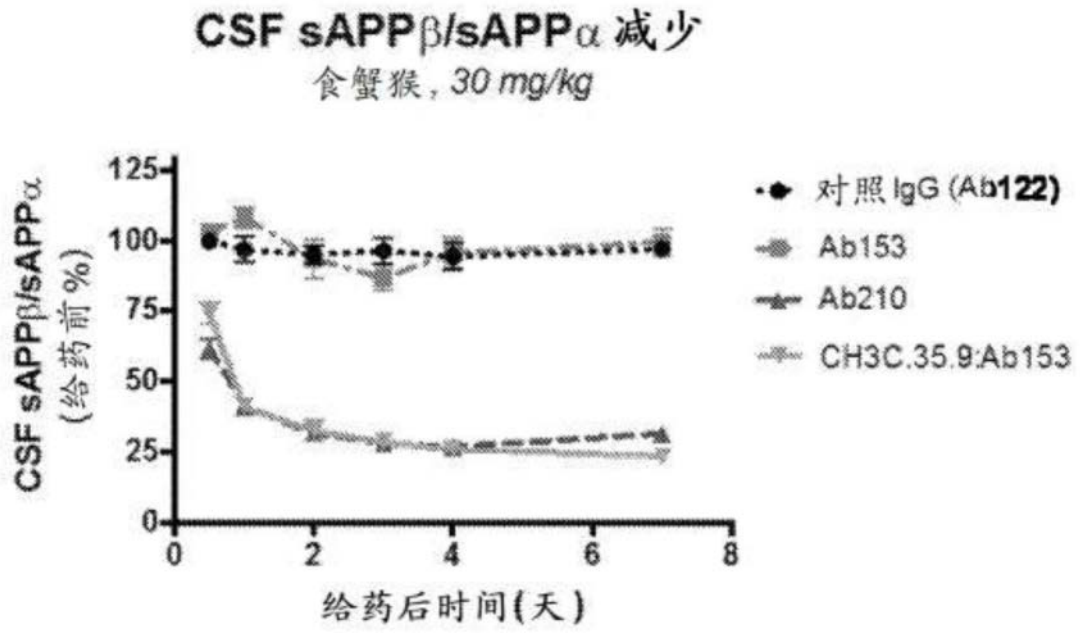

CSF sAPPβ/sAPPα 减少
食蟹猴，30 mg/kg
CSF sAPPβ/sAPPα (给药前%)
125
100
75
50
25
0
0
2
4
6
8
给药后时间(天)
对照 IgG (Ab122)
Ab153
Ab210
CH3C.35.9:Ab153

图38B

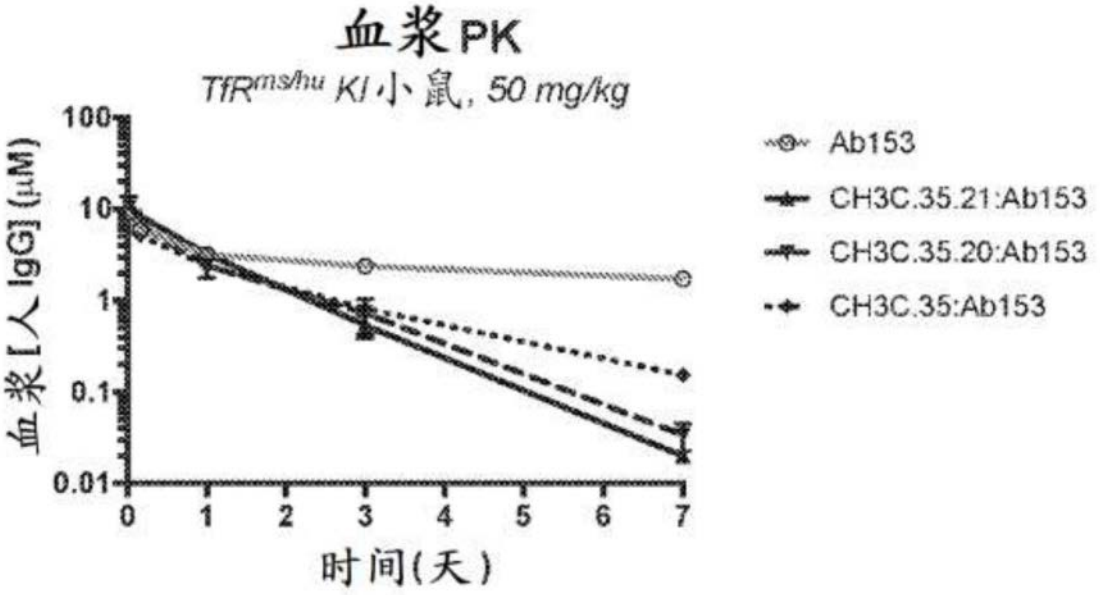

血浆PK
TfRms/hu KI小鼠, 50 mg/kg
血浆[人IgG] (μM)
100
10
1
0.1
0.01
0
1
2
3
4
5
6
7
时间(天)
Ab153
CH3C.35.21:Ab153
CH3C.35.20:Ab153
CH3C.35:Ab153

图39A

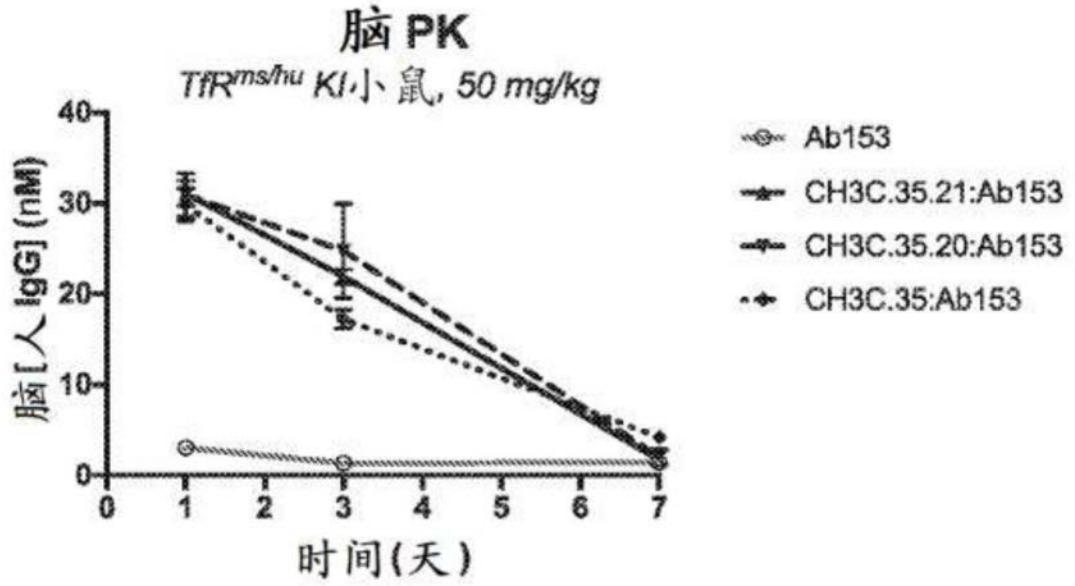

脑PK
TfRms/hu KI小鼠, 50 mg/kg
脑[人IgG] (nM)
40
30
20
10
0
0
1
2
3
4
5
6
7
时间(天)
Ab153
CH3C.35.21:Ab153
CH3C.35.20:Ab153
CH3C.35:Ab153

图39B

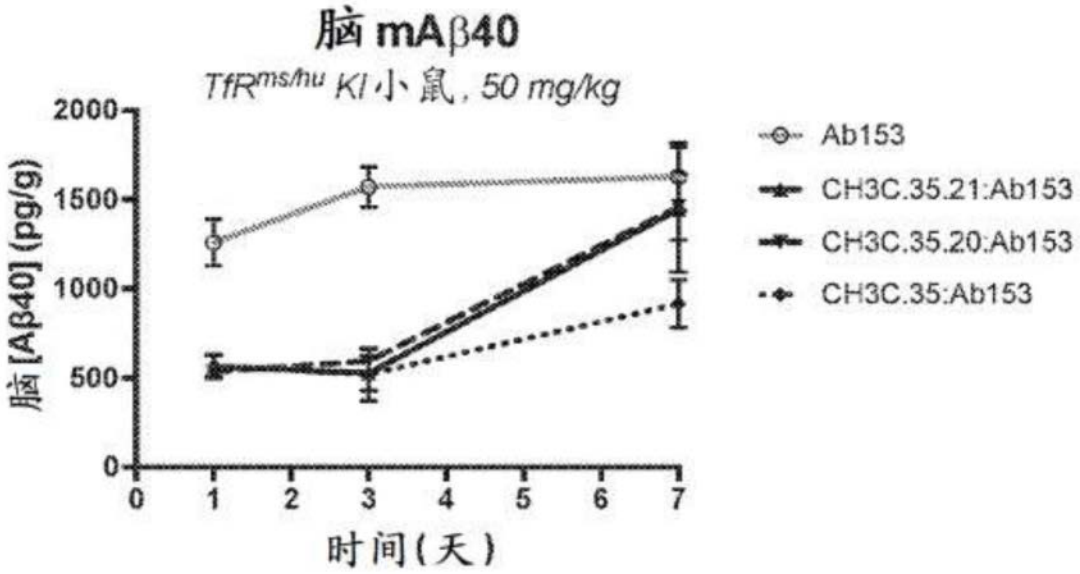

脑 mAβ40
TfRms/hu KI 小鼠，50 mg/kg
脑 [Aβ40] (pg/g)
2000
1500
1000
500
0
0 1 2 3 4 5 6 7
时间(天)
Ab153
CH3C.35.21:Ab153
CH3C.35.20:Ab153
CH3C.35:Ab153

图39C

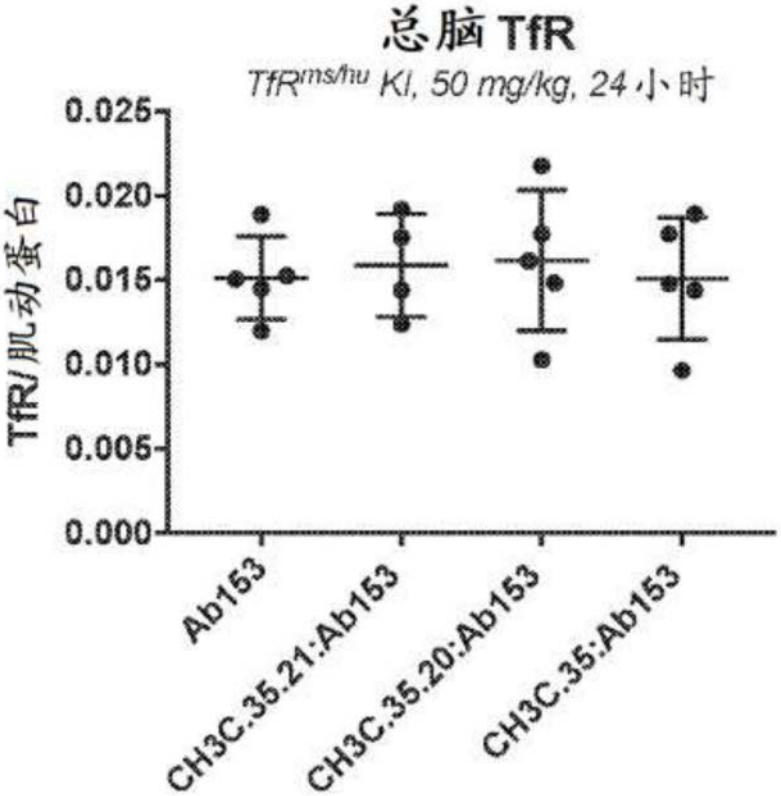

总脑 TfR
TfRms/hu KI, 50 mg/kg, 24 小时
TfR/ 肌动蛋白
0.025
0.020
0.015
0.010
0.005
0.000
Ab153
CH3C.35.21:Ab153
CH3C.35.20:Ab153
CH3C.35:Ab153

图39D

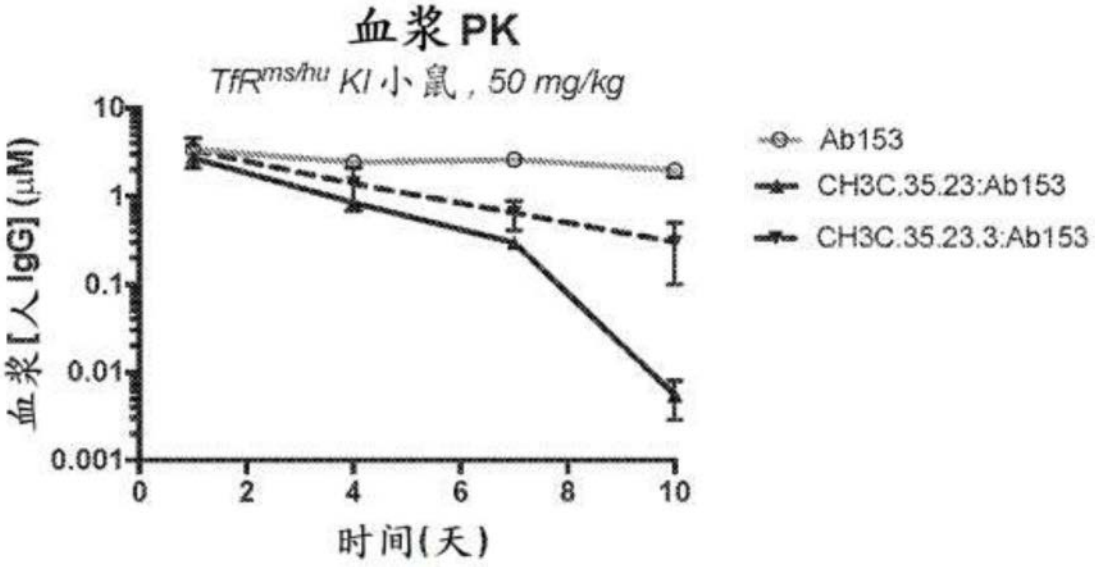

血浆PK
TfRms/hu KI小鼠，50 mg/kg
血浆[人IgG] (μM)
10
1
0.1
0.01
0.001
0
2
4
6
8
10
时间(天)
Ab153
CH3C.35.23:Ab153
CH3C.35.23.3:Ab153

图40A

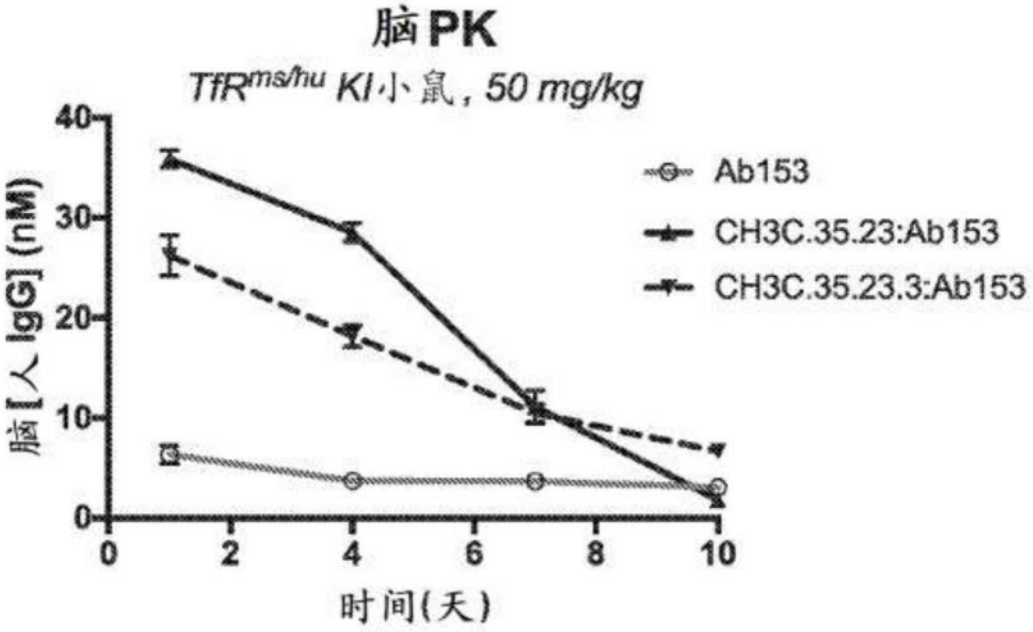

脑PK
TfRms/hu KI小鼠，50 mg/kg
脑[人IgG] (nM)
40
30
20
10
0
0
2
4
6
8
10
时间(天)
Ab153
CH3C.35.23:Ab153
CH3C.35.23.3:Ab153

图40B

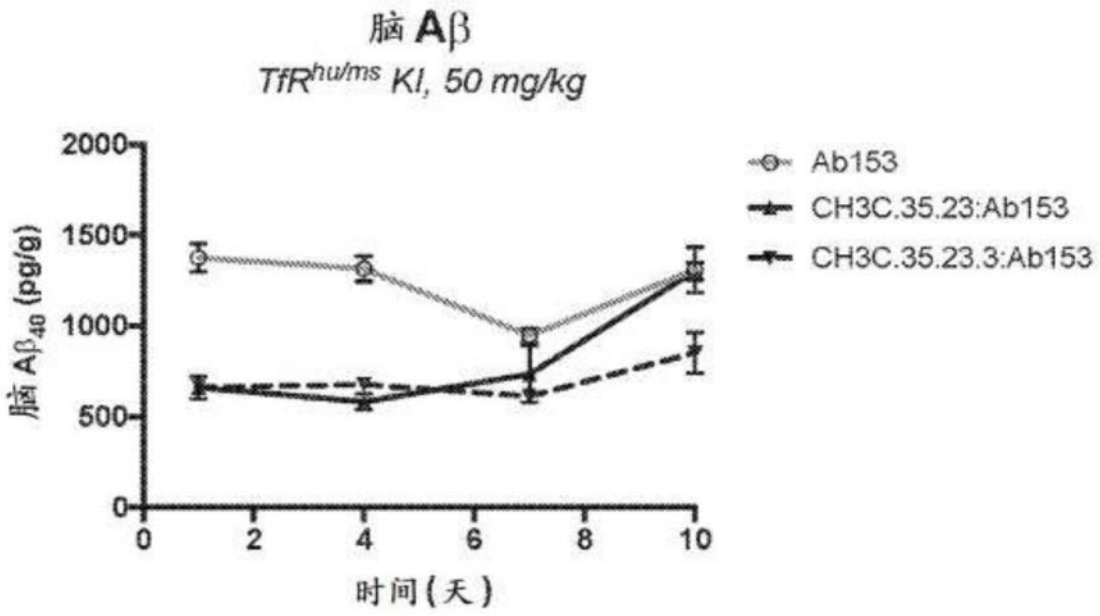

脑 Aβ
TfR^hu/ms KI, 50 mg/kg
脑 Aβ40 (pg/g)
2000
1500
1000
500
0
0
2
4
6
8
10
时间(天)
Ab153
CH3C.35.23:Ab153
CH3C.35.23.3:Ab153

图40C

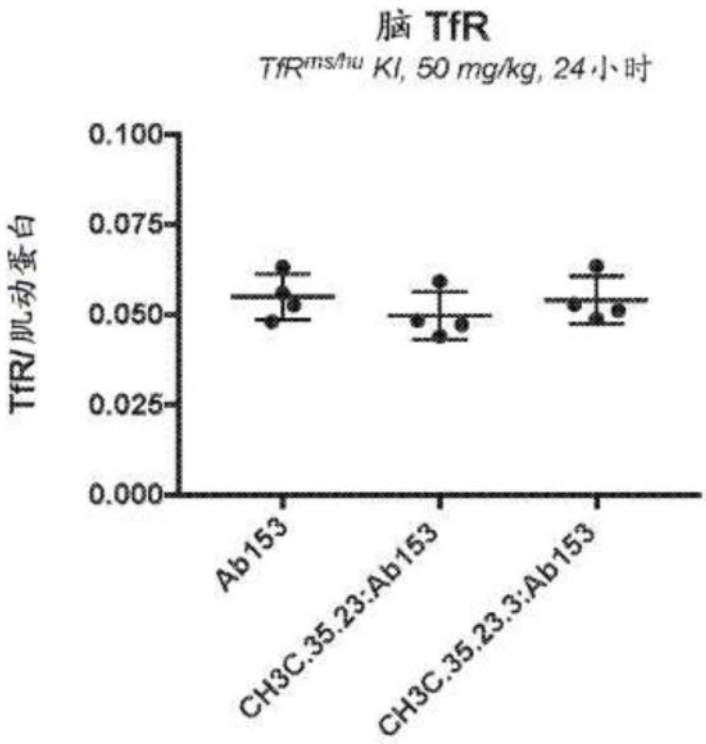

脑 TfR
TfR^ms/hu KI, 50 mg/kg, 24小时
TfR/肌动蛋白
0.100
0.075
0.050
0.025
0.000
Ab153
CH3C.35.23:Ab153
CH3C.35.23.3:Ab153

图40D

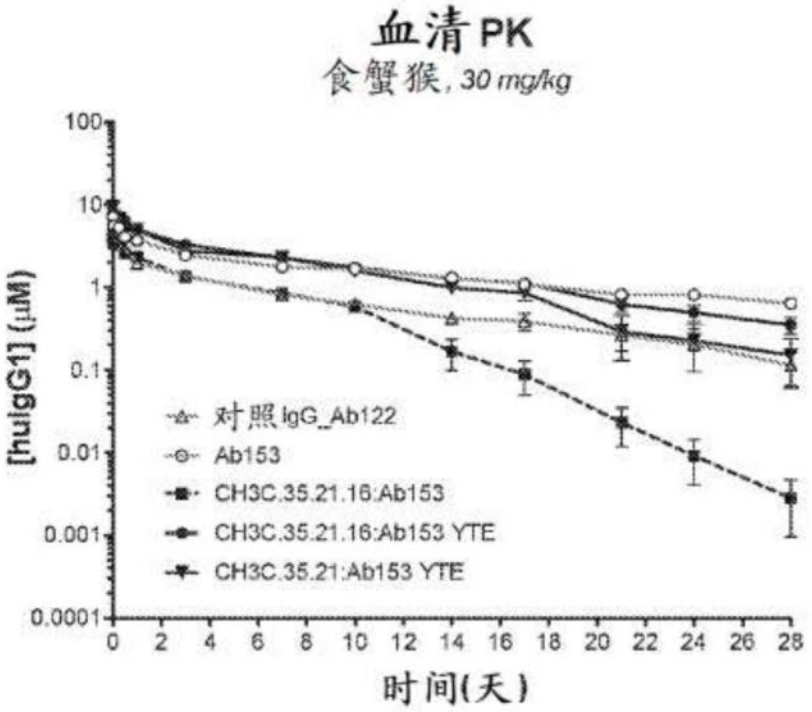

血清PK
食蟹猴, 30 mg/kg
[huIgG1] (μM)
100
10
1
0.1
0.01
0.001
0.0001
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
时间(天)
对照IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21:Ab153 YTE

图41A

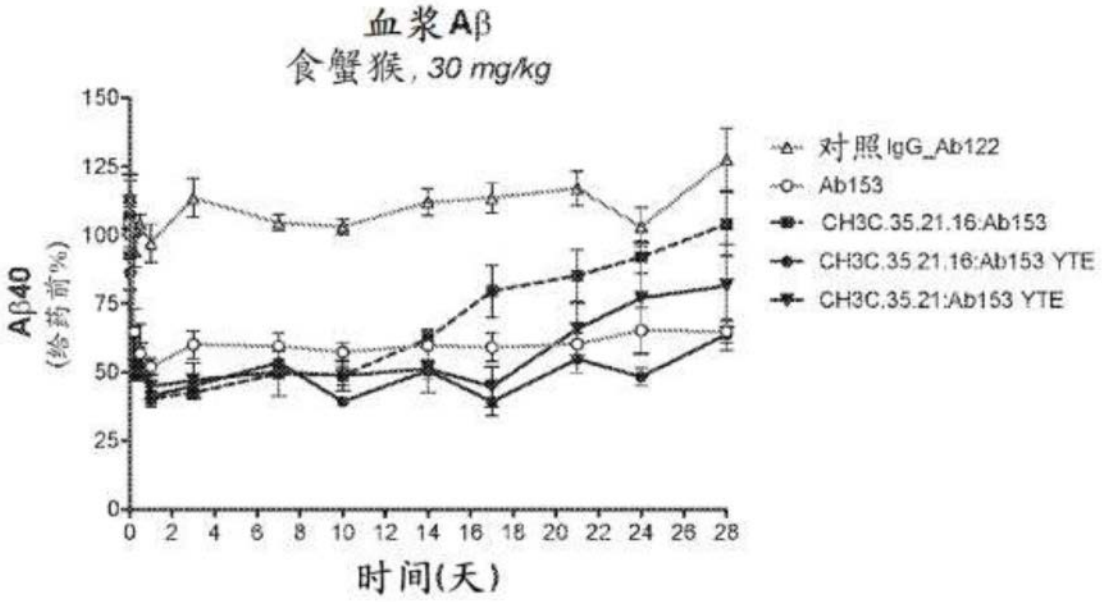

血浆Aβ
食蟹猴, 30 mg/kg
Aβ40
(给药前%)
150
125
100
75
50
25
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
时间(天)
对照IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21:Ab153 YTE

图41B

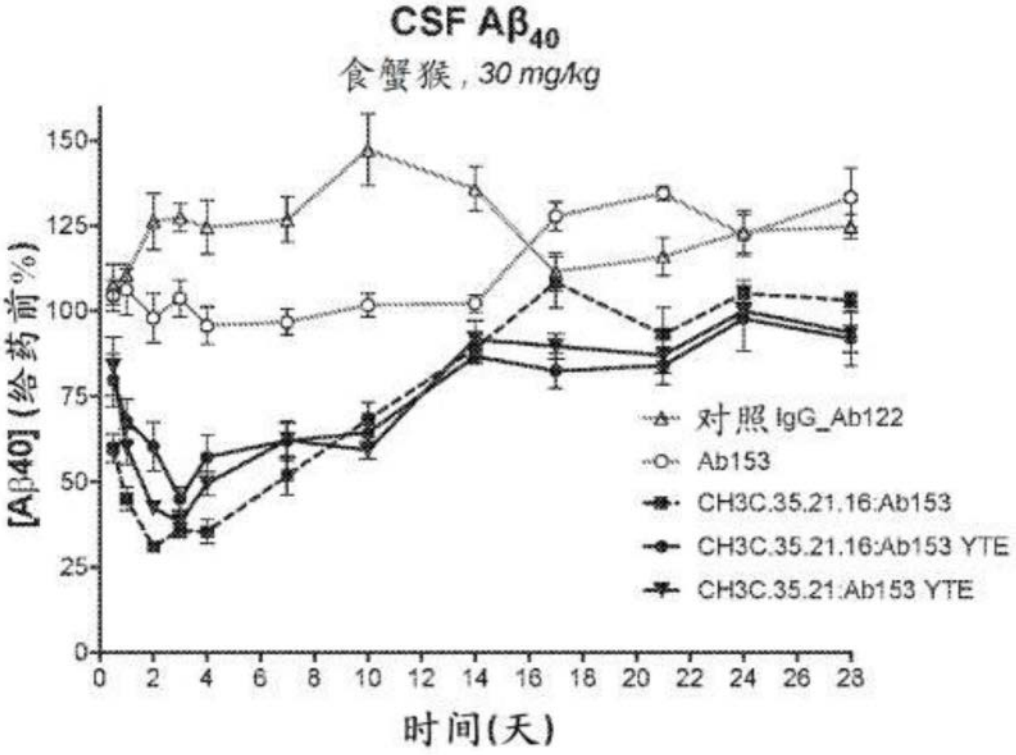

CSF Aβ40
食蟹猴，30 mg/kg
[Aβ40] (给药前%)
时间(天)
对照 IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21:Ab153 YTE

图41C

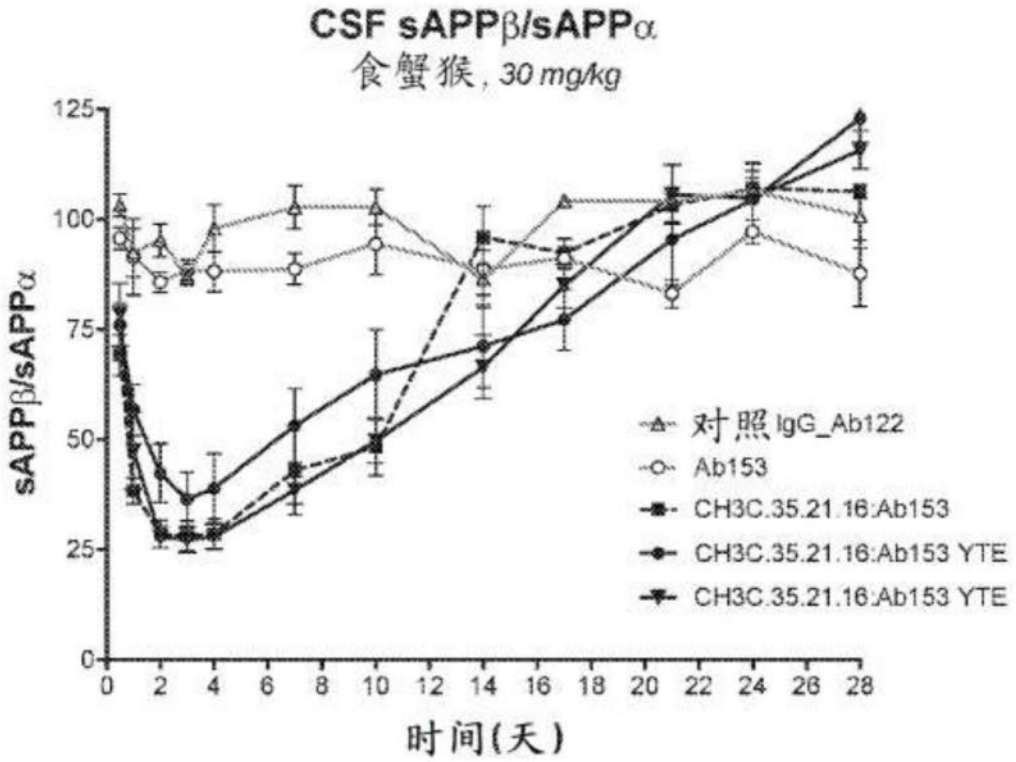

CSF sAPPβ/sAPPα
食蟹猴，30 mg/kg
sAPPβ/sAPPα
时间(天)
对照 IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21.16:Ab153 YTE

图41D

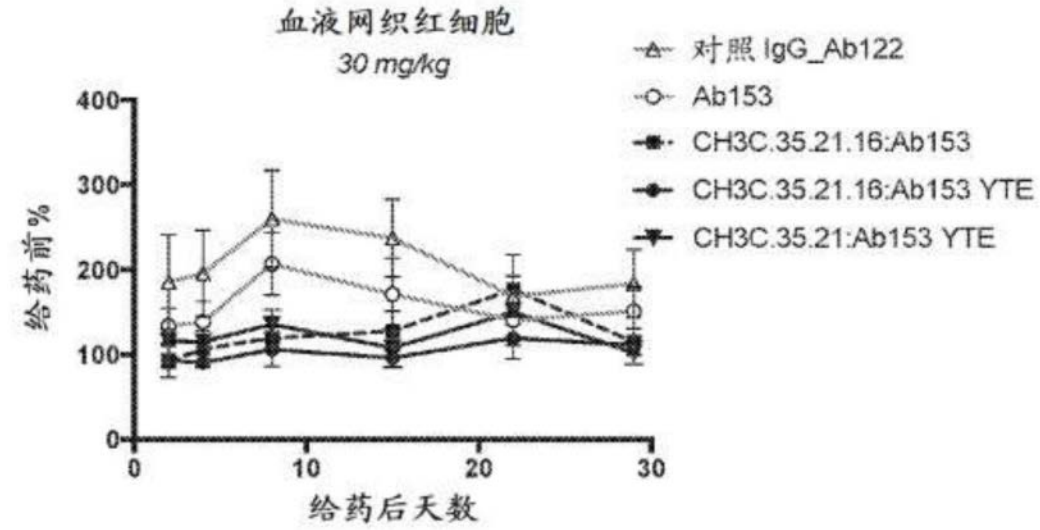

血液网织红细胞
30 mg/kg
对照 IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21:Ab153 YTE
给药前%
400
300
200
100
0
0
10
20
30
给药后天数

图42A

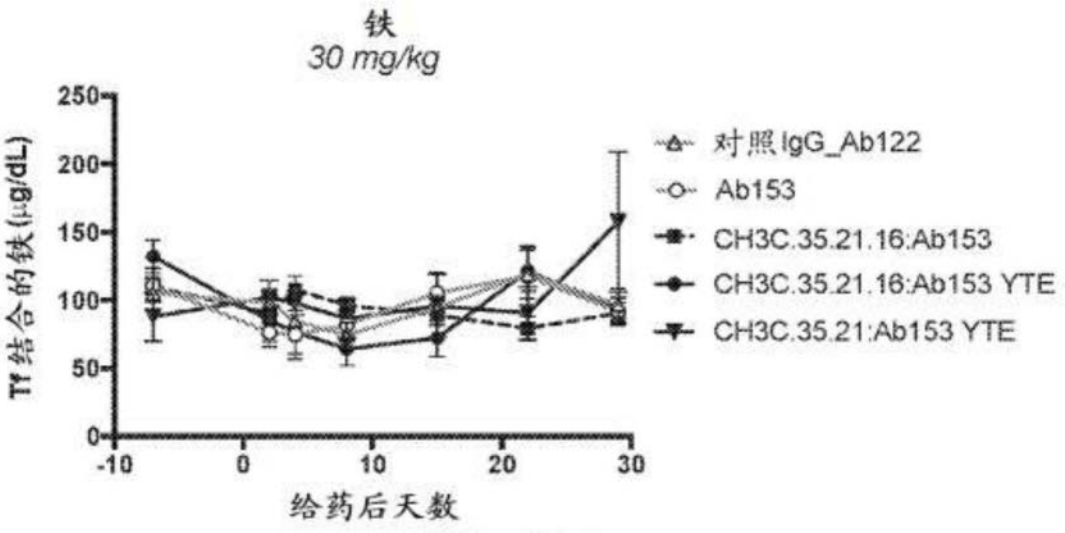

铁
30 mg/kg
对照 IgG_Ab122
Ab153
CH3C.35.21.16:Ab153
CH3C.35.21.16:Ab153 YTE
CH3C.35.21:Ab153 YTE
Tf 结合的铁(μg/dL)
250
200
150
100
50
0
-10
0
10
20
30
给药后天数

图42B

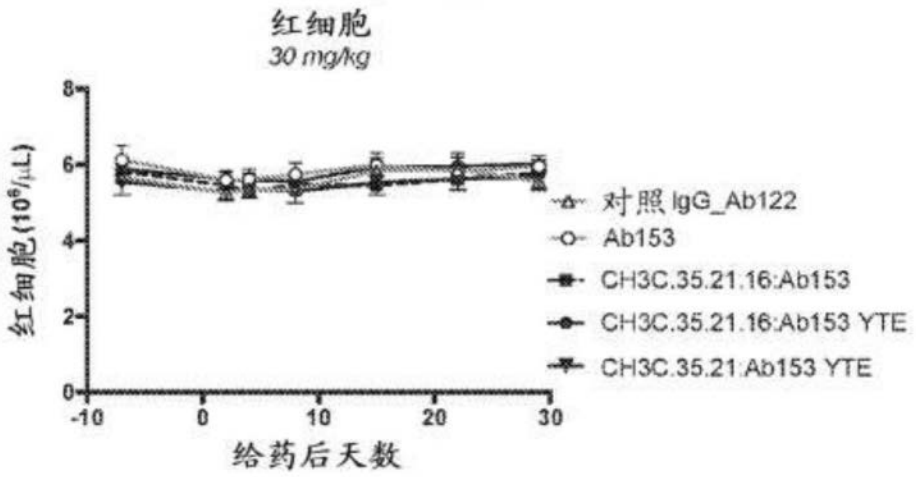


图42C

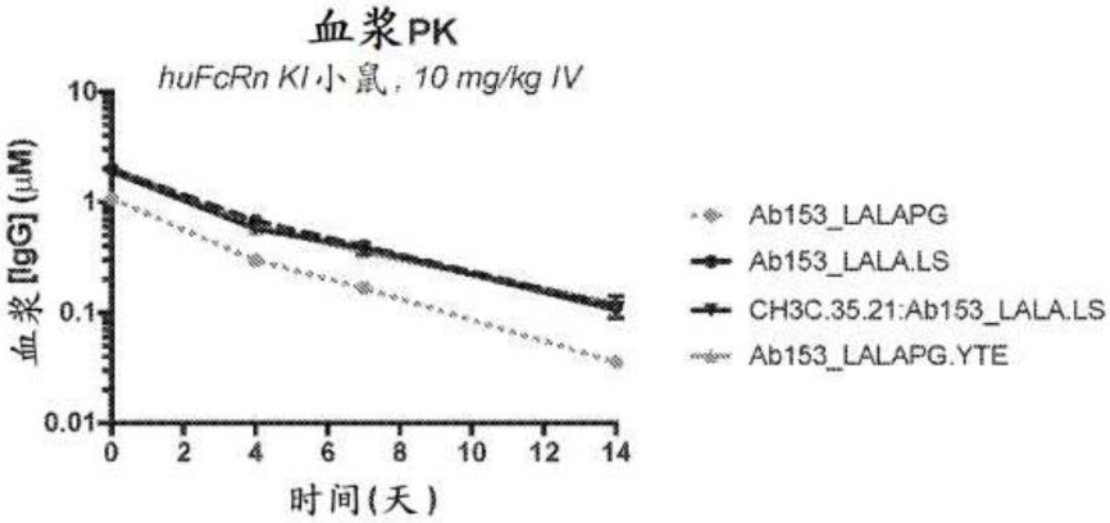


图43A

克隆	清除率 (mL/kg/天)
Ab153_LALAPG	17.9
Ab153_LALA.LS	8.1
CH3C.35.21:Ab153_LALA.LS	9.0
Ab153_LALAPG.YTE	8.4

图43B

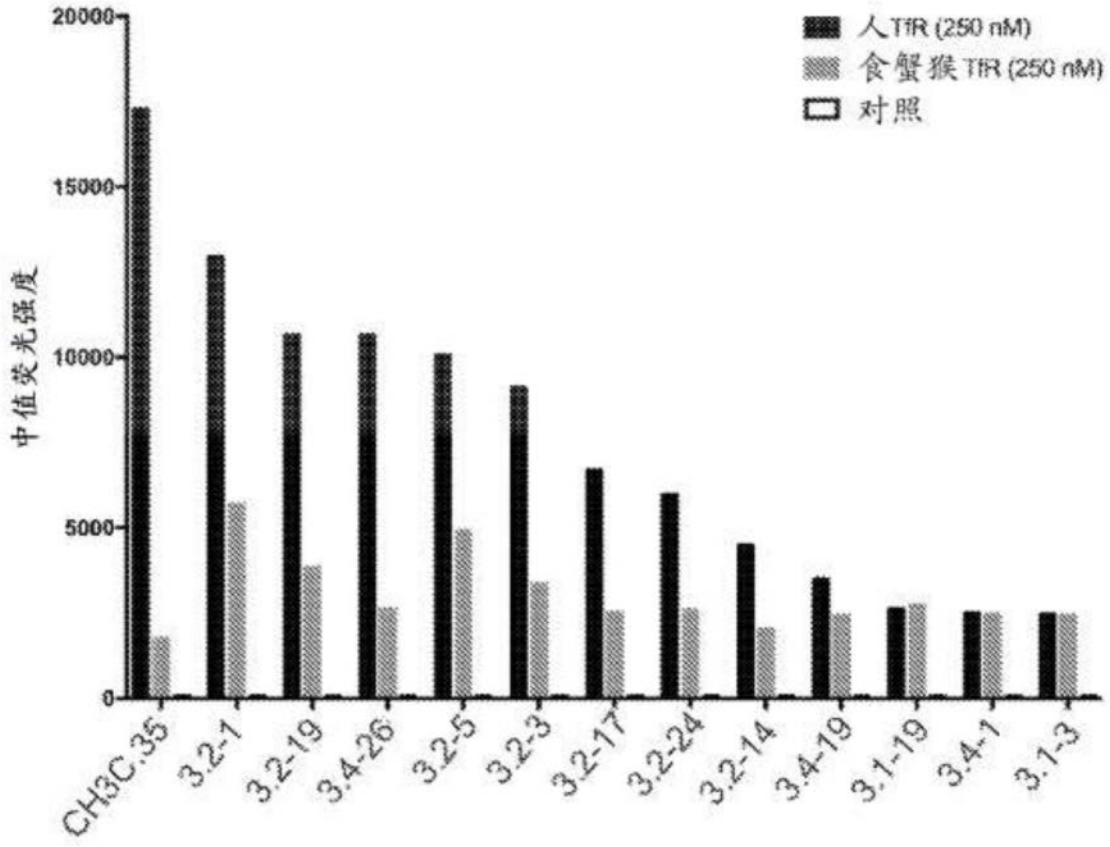

人TfR (250 nM)
食蟹猴TfR (250 nM)
对照
中值荧光强度
20000
15000
10000
5000
0
CH3C.35
3.2-1
3.2-19
3.4-26
3.2-5
3.2-3
3.2-17
3.2-24
3.2-14
3.4-19
3.1-19
3.4-1
3.1-3

图44