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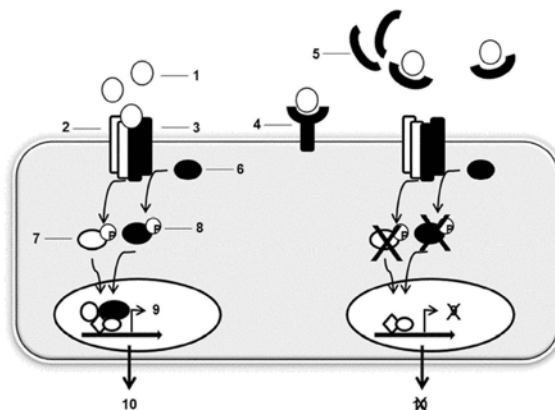
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(54) 发明名称

用于治疗骨疾病的转铁蛋白受体-2的拮抗剂和激动剂

(57) 摘要

本发明涉及一种用于在诊断和治疗原发性或继发性硬化性疾病中使用的蛋白、融合蛋白和核苷酸序列和载体,并且涉及一种用于在诊断和治疗原发性或继发性硬化性疾病中使用的药物组合物。本发明还涉及一种用于治疗骨疾病、铁代谢紊乱或造血功能障碍的转铁蛋白受体2抑制剂。



1. 一种用于在治疗或预防人或动物受试者中的骨疾病或病况的方法中使用的转铁蛋白受体2 (Tfr2) 拮抗剂或激动剂, 所述方法包括向所述受试者施用所述拮抗剂或激动剂以及拮抗所述受试者中的Tfr2。

2. 根据权利要求1所述的拮抗剂, 其中, 所述方法包括

(i) 通过拮抗细胞的Tfr2来抑制骨细胞中p38 MAP激酶途径信号转导;

(ii) 通过拮抗所述受试者中的Tfr2来上调骨细胞中的Wnt表达;

(iii) 通过拮抗细胞的Tfr2来抑制骨细胞中硬化蛋白、Dkk1和/或活化素A的活性或表达; 或

(iv) 通过拮抗细胞的Tfr2来抑制骨细胞中Phex、Dmp1、Dkk1和/或Sost的表达。

3. 根据任一前述权利要求所述的拮抗剂, 其中, 所述方法包括抑制所述受试者中Tfr2与BMP的结合。

4. 根据任一前述权利要求所述的拮抗剂, 其中

(i) 所述疾病或病况为骨质疏松症;

(ii) 所述方法用于引起以下中的一种或多种:—

(a) 骨体积增大;

(b) 骨密度增加;

(c) 骨小梁数量 (Tb.N) 增加;

(d) 骨小梁厚度 (Tb.Th) 增加;

(e) 骨小梁间隙 (Tb.Sp) 减小;

(f) 骨矿物质密度增加;

(g) 骨微矿化密度增加;

(h) 骨量增加; 和

(i) 骨强度增加;

(iii) 所述方法用于增加所述受试者中的骨形成;

(iv) 所述方法用于降低所述受试者中的骨吸收;

(v) 所述方法用于提高所述受试者中的成骨细胞 (或其骨形成活性);

(vi) 所述方法用于降低所述受试者中的破骨细胞 (或其骨吸收活性);

(vii) 所述方法用于提高所述受试者中的骨转换;

(viii) 所述方法用于提高所述受试者中的I型前胶原N末端肽 (P1NP);

(ix) 所述方法用于提高所述受试者中的I型胶原C末端端肽 (CTX); 或

(x) 所述方法用于增加所述受试者中的骨细胞。

5. 根据任一前述权利要求所述的拮抗剂, 其中, 所述方法包括向所述受试者施用硬化蛋白、Dkk1或活化素A拮抗剂。

6. 根据权利要求1所述的激动剂, 其中, 所述方法包括 (i) 通过激动细胞的Tfr2, 刺激骨细胞中p38 MAP激酶途径信号转导; (ii) 通过激动细胞的Tfr2, 下调骨细胞中的Wnt表达; 或 (iii) 通过激动细胞的Tfr2, 刺激骨细胞中硬化蛋白的活性或表达。

7. 根据1或6所述的激动剂, 其中, 所述方法包括促进Tfr2的BMP结合。

8. 根据权利要求7所述的激动剂, 其中, 所述BMP是BMP2、4、6和7中的一种或多种。

9. 根据权利要求1和6至8中任一项所述的激动剂, 其中, 所述方法包括向所述受试者施

用硬化蛋白、Dkk1或活化素A激动剂。

10. 一种结合骨形态发生蛋白 (BMP) 的试剂, 用于在治疗或预防人或动物受试者中的疾病或病况的方法中使用, 所述方法包括向所述受试者施用结合BMP的试剂, 其中, 所述试剂与可溶性Tfr2-ECD竞争对BMP的结合, 并且其中, 通过所述BMP介导所述疾病或病况。

11. 根据权利要求10所述的试剂, 其中, 所述试剂是BMP捕获剂。

12. 根据权利要求10或11所述的试剂, 其中, 所述BMP是BMP2、4、6或7。

13. 根据权利要求10至12中任一项所述的试剂, 其中, 所述试剂与BMP2、4、6和7中的一个、多个或全部的结合比全铁转铁蛋白和/或BMPR与所述BMP的结合更强烈。

14. 根据权利要求10至13中任一项所述的试剂, 其中, 所述试剂包括Tfr2胞外域 (Tfr2-ECD), 任选地其中, 包含第二部分的融合蛋白包括所述试剂。

15. 根据权利要求14所述的试剂, 其中, 所述第二部分是用于提高捕获剂在受试者中的半衰期的半衰期延长部分; 任选地其中, 所述第二部分选自抗体Fc区、聚乙二醇 (PEG) 部分、血清白蛋白和抗血清白蛋白结合部分。

16. 根据权利要求10至15中任一项所述的试剂, 其中, 所述疾病或病况是骨疾病或病况。

17. 根据任一前述权利要求所述的拮抗剂、激动剂或试剂, 其中, 所述疾病或病况为

(a) 硬化性疾病或病况;

(b) 包括病理性骨形成的疾病或病况; 或

(c) 骨化疾病或病况, 任选地是异型骨化 (HO) 疾病或病况, 或进行性骨化性纤维发育不良 (FOP) 疾病或病况。

18. 根据权利要求17所述的拮抗剂、激动剂或试剂, 其中, 所述疾病或病况选自肌肉HO、Van Buchem病和硬化性骨化病。

19. 根据权利要求1和10至18中任一项所述的激动剂或试剂, 其中, 所述方法包括与Tfr2激动剂或捕获剂同时或顺序地向所述受试者施用视黄酸受体 γ (RAR- γ) 激动剂 (任选帕罗伐汀)。

20. 根据权利要求1和10至19中任一项所述的激动剂或试剂, 其中, 所述方法包括与Tfr2激动剂或捕获剂同时或顺序地向所述受试者施用BMP信号转导拮抗剂。

21. 根据权利要求10至20中任一项所述的试剂, 其中, 所述方法抑制所述受试者中的软骨形成。

22. 根据权利要求10至21中任一项所述的试剂, 其中, 所述方法抑制所述受试者中的软骨细胞形成。

23. 根据权利要求10至22中任一项所述的试剂, 其中, 所述疾病或病况是BMP-2诱导的HO、BMP-4诱导的HO、BMP-6诱导的HO、或BMP-7诱导的HO。

24. 根据任一前述权利要求所述的拮抗剂、激动剂或试剂, 其中, 所述拮抗剂或所述激动剂为 (i) 特异性结合至Tfr2的抗Tfr2抗体或抗体片段; (ii) Tfr2-ECD单体; 或 (iii) Tfr2-ECD二聚体。

25. 根据权利要求24所述的拮抗剂、激动剂或试剂, 其中, 通过表面等离子共振 (SPR) 确定, 所述抗体或片段与选自以下的抗体竞争对Tfr2的结合: 1B1 (MyBioSource, MBS833691)、3C5 (Abnova, H00007036-M01)、CY-TFR (Abnova, MAB6780) 和B-6 (Santa Cruz

Biotechnology,sc-376278)、353816 (R&D Systems,MAB3120) 和9F8 1C11 (Santa Cruz Biotechnology,sc-32271)。

26. 根据权利要求24所述的拮抗剂、激动剂或试剂,其中,所述Tfr2-ECD单体是Tfr2-ECD-Fc单体;所述Tfr2-ECD二聚体为Tfr2-ECD-Fc二聚体;并且ECD和Fc是人Tfr2 ECD和人Fc。

27. 根据权利要求24或26所述的拮抗剂、激动剂或试剂,其中,Tfr2-ECD是Tfr2 α -ECD或Tfr2 β -ECD。

28. 一种药物组合物,包含任一前述权利要求所述的拮抗剂、激动剂或试剂和药学上可接受的稀释剂、赋形剂或载体。

29. 根据权利要求28所述的组合物,还包含抗硬化蛋白抗体(任选罗莫索珠单抗)、抗Dkk1抗体或抗活化素A抗体、或它们的片段。

30. 一种药物组合物,包含权利要求24至27任一项中所列举的抗体、片段、二聚体或单体和药学上可接受的稀释剂、赋形剂或载体。

31. 根据权利要求30所述的当从属于权利要求10时的组合物,还包含视黄酸受体 γ (RAR- γ) 激动剂(任选帕罗伐汀) 和/或BMP拮抗剂。

用于治疗骨疾病的转铁蛋白受体-2的拮抗剂和激动剂

技术领域

[0001] 本发明涉及硬化性疾病的诊断、治疗或预防。本发明还涉及用于在骨疾病、铁代谢紊乱和造血功能障碍的治疗中使用的转铁蛋白受体2抑制剂。

背景技术

[0002] 转铁蛋白受体2 (Tfr2) 主要在肝脏中表达。商业上可获得的抗-Tfr2抗体是可获得的。例如, 1B1 (MyBioSource, MBS833691)、3C5 (Abnova, H00007036-M01)、CY-TFR (Abnova, MAB6780) 和B-6 (Santa Cruz Biotechnology, sc376278)、353816 (R&D Systems, MAB3120) 和9F8 1C11 (Santa Cruz Biotechnology, sc32271)。

发明内容

[0003] 在第一构造中, 本发明涉及用于在诊断和/或治疗原发性或继发性硬化性疾病中使用的蛋白、融合蛋白和核苷酸序列和载体, 并且涉及用于在诊断和治疗原发性或继发性硬化性疾病中使用的药物组合物。

[0004] 在第二构造中, 本发明涉及用于在骨疾病、铁代谢紊乱和造血功能障碍的治疗中使用的转铁蛋白受体2抑制剂。

[0005] 因此, 本发明提供了:-

[0006] 具有与SEQ ID NO.1的序列具有至少70、75、80、85、90、95、96、97、98或99%的同一性的氨基酸序列的蛋白或其片段, 用于在诊断和治疗原发性或继发性硬化性疾病中使用。

[0007] 包含序列SEQ ID NO.1或SEQ ID NO.2的蛋白, 用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0008] 用于治疗骨疾病、铁代谢紊乱和/或造血功能障碍的转铁蛋白受体2抑制剂。

附图说明

[0009] 图1: BMP (1) 对骨形成的影响的示意性描绘 (左手边)。BMP结合BMP受体 (BMPR-I (2) 或BMPR-II (3)), 从而引发了信号转导级联 (Smad蛋白 (6) 和MAP激酶 (7) 的磷酸化 (8)), 这通过成骨细胞基因 (9) 的表达激活骨形成 (10)。BMP (1) 与Tfr2 α (4) 结合的示意性描绘 (中间)。根据本发明的蛋白 (5) 对骨形成 (10) 的影响的示意性描绘 (右手边)。根据本发明的蛋白 (5) 结合BMP (1), 由此与BMP受体 (BMPR-I (2) 或BMPR-II (3)) 的结合未发生并且未激活骨形成。

[0010] 图2显示了BMP与根据本发明的蛋白的结合的SPR测量。图2A显示了BMP-2、BMP-4、BMP-6和BMP-7与Tfr2-ECD的结合。图2B显示了与BMPR-II和BMPR-IA的结合水平相比, 基于BMP-2、BMP-4、BMP-6和BMP-7的摩尔质量, 对与Tfr2-ECD的结合水平的量化。

[0011] 图3示意地显示了BMP-2-竞争性ELISA (酶联免疫吸附测定): 由于BMP (1), 尤其是BMP-2与捕获抗体 (11) 的结合和检测抗体 (12) 与BMP-2的结合所产生的信号 (左手边)。由于根据本发明的蛋白 (5) 或BMPR-I (2) 与BMP-2的结合所造成的信号降低, 由此未发生捕获抗体 (11) 和检测抗体 (12) 的结合 (右手边)。图3B: BMP-2-竞争性ELISA: 根据本发明的蛋白或

BMP-1的浓度对BMP-2检测抗体的信号的影响,同时BMP-2浓度保持不变。

[0012] 图4显示了使用根据本发明的蛋白,尤其是Tfr2-ECD,通过BMP-2的结合,在小鼠(C57BL/6小鼠)中的H0抑制。图4A和4B显示了通过 μ CT(显微断层成像),通过确定骨体积的矿化。图4A显示了当施用BMP-2和当与Tfr2-ECD一起施用BMP-2时的骨形成的CT扫描。图4B显示了骨体积的量化。PBS用作阴性对照。当施用BMP-2时,两周后骨体积增加明显。与作为参考的BMP-2相比,与Tfr2-ECD一起施用BMP-2显示出骨形成显著减少(平均值 $\pm$ 标准偏差; $n=3-6$ 只每组;相对于PBS(对照),*** $p<0.001$ 。

[0013] 图5是不同的小梁骨体积的图。

[0014] 图6是不同皮质骨厚度的图。

[0015] 图7是不同骨质量的图。

[0016] 图8是不同骨形成的图。

[0017] 图9是不同骨吸收的图。

[0018] 图10:Tfr2缺陷导致了高骨量(bone mass,骨质)。(a-1)使用 μ CT、组织学和ELISA分析了十周大的雄性WT或Tfr2^{-/-}小鼠的骨和血清骨转换标志物。(a) WT和Tfr2^{-/-}小鼠的股骨远端和第四椎骨体的骨体积/总体积(BV/TV)的3D重构和定量。股骨, $n=5$ 只每组;椎骨体, $n=4$ 只每组。(b)中段股骨干处的皮质骨矿物密度(BMD)。 $n=4$ 只每组。(c-e)椎骨小梁数量(Tb.N)、小梁厚度(Tb.Th)和小梁间隙(Tb.Sp)的定量。 $n=4$ 只每组。(f)通过3-点-弯曲评价的股骨干处的最大力。(WT, $n=6$;Tfr2^{-/-}, $n=7$)。(g)来自WT和Tfr2^{-/-}小鼠的第三椎骨体的代表性组织切片,其显示了钙黄绿素复染。比例尺表示100 μ m。将这些实验重复四次,结果类似。(h)骨形成速率/骨表面(BFR/BS)的定量。(WT, $n=4$;Tfr2^{-/-}, $n=5$)。(i)作为骨形成标志物的血清P1NP的定量。(WT, $n=4$;Tfr2^{-/-}, $n=5$)。(j)来自WT和Tfr2^{-/-}小鼠的第四椎骨体的代表性组织学耐酒石酸酸性磷酸酯酶切片,其显示了以粉红色染色的破骨细胞。比例尺表示100 μ m。将这些检查进行四次,结果类似。(k)破骨细胞数/骨周长(N.Oc/B.Pm)的定量。(WT, $n=4$;Tfr2^{-/-}, $n=5$)。(l)作为骨吸收标志物的血清CTX的定量。(WT, $n=4$;Tfr2^{-/-}, $n=5$)。(a-f,h-i,k-l)将双尾t检验用于统计分析。(m)12周大的假手术(SHAM)或卵巢切除的(OVX)WT和Tfr2^{-/-}小鼠的股骨的 μ CT分析(WT假手术, $n=6-10$;WT OVX, $n=9$;Tfr2^{-/-}假手术, $n=5$;Tfr2^{-/-}OVX, $n=10$)。将通过邦费罗尼(Bonferroni)事后检验的双向方差分析用于统计分析。所有子面板中的数据表示为平均值 $\pm$ SD,并且显著性定义为* $p<0.05$,** $p<0.01$,*** $p<0.001$ 。

[0019] 图11:Tfr2^{-/-}小鼠中的高骨量不依赖于铁过载和Tfr2的肝功能。(a,c)从断奶开始,雄性WT和Tfr2^{-/-}小鼠接受无铁纯饲料(-Fe)直至10周大。对照小鼠接受具有0.2g铁/kg食物的标准饲料(+Fe)。(a)使用光度法,确定干燥组织的肝脏铁含量。(平均值 $\pm$ SD; $n=10$ 只每组)。(c)使用 μ CT评价骨体积/总体积(BV/TV)。(平均值 $\pm$ SD;WT+Fe $n=9$;WT-Fe, Tfr2^{-/-}+Fe和Tfr2^{-/-}-Fe, $n=8$ 只每组)。(b,d)十周大的雌性WT和Tfr2^{-/-}小鼠每天接受250mg/kg去铁胺(DF0)或PBS的i.p注射,共进行三周。在13周,将小鼠处死以测量(b)肝脏铁含量和(d)BV/TV。(n=3-5只每组)。(a-d)将通过邦费罗尼事后检验的双向方差分析用于统计分析。(e)缺少Tfr2 β 同种型的Tfr2敲入(KI)小鼠的示意图。10周大的雄性Tfr2 KI小鼠和对照小鼠的BV/TV和肝脏铁含量。(BV/TV,WT $n=11$,KI $n=15$;肝脏铁,WT $n=8$,KI $n=7$)。(f)在Tfr2 KI背景下,肝-特异性Tfr2 α 敲除(LCKO)小鼠的Tfr2结构的示意图。10周大的雄

性LCKO和WT小鼠的BV/TV和肝脏铁含量。(n=8只每组)。(e, f) 将双尾t检验用于统计分析。所有数据表示为平均值±SD。*p<0.05; **p<0.01; ***p<0.001。

[0020] 图12: 生骨细胞中的Tfr2缺陷提高了骨量。(a, d) 对WT小鼠椎骨进行Tfr2的免疫组织化学分析。显示了三幅图中的一幅代表性图。箭头表示多核破骨细胞和成骨细胞/骨细胞中的Tfr2表达(成骨细胞: 黑色箭头; 骨细胞: 橙色箭头)。比例尺: 20μm。(b, e) 在WT细胞(n=4)的破骨细胞(b)和成骨细胞(e)分化期间, Tfr2 mRNA的表达。(c, f) 成熟的破骨细胞(c)和未成熟的成骨细胞(f)中的Tfr2的免疫荧光染色。比例尺: 20μm。将这些染色重复两次, 结果类似。(g) 来自WT小鼠的第7天的成骨细胞蛋白裂解液的亚细胞分离。显示了三幅印迹中的一幅代表性印迹。CP: 细胞质; M: 膜; Nuc: 核部分。Cx-43: 连接蛋白-43。(h) 将来自12周大的雄性WT或Tfr2^{-/-}小鼠的骨髓移植到致死辐射的9周大的雄性WT和Tfr2^{-/-}受体(recip)小鼠中。16周后, 使用μCT测量骨体积/总体积(BV/TV)。(L4, WT-WT n=11, Tfr2^{-/-}-WT n=11, Tfr2^{-/-}-Tfr2^{-/-} n=7, WT-Tfr2^{-/-} n=9; 股骨, WT-WT n=12, Tfr2^{-/-}-WT n=10, Tfr2^{-/-}-Tfr2^{-/-} n=8, WT-Tfr2^{-/-} n=10)。将通过邦费罗尼事后检验的双向方差分析用于统计分析。(i) 10周大的雄性cre-阳性和cre-阴性Tfr2^{f/f}; Lysm-Cre和Tfr2^{f/f}; Ctsk-Cre小鼠的第四腰椎的BV/TV。(Tfr2^{f/f}; Lysm-cre, Cre-n=16, Cre+n=9; Tfr2^{f/f}; Ctsk-Cre, Cre-n=8, Cre+n=12)。(j-o) 10周大的雄性cre-阳性和cre-阴性同窝对照Tfr2^{f/f}; Osx-Cre小鼠的骨分析。(j) BV/TV (L4, Cre-n=18, Cre+n=12; 股骨, Cre-n=18, Cre+n=13)。(k) 骨小梁数量(Tb.N)和骨小梁间隙(Tb.Sp) (Tb.N., Cre-n=18, Cre+n=13; Tb.Sp., Cre-n=19, Cre+n=12)。(l) P1NP的血清水平。(n=6只每组)。(m) 在腰脊椎确定的单位骨表面的矿化表面(MS/BS)、矿化沉积率(MAR)和单位骨表面的骨形成速率(BFR/BS)。(MS/BS, Cre-n=11, Cre+n=10; MAR, Cre-n=9, Cre+n=6; BFR, Cre-n=10, Cre+n=6)。(n) 在腰脊椎分析的单位骨表面的破骨细胞表面(Oc.S/BS)。(Cre-n=7, Cre+n=6)。(o) 血清CTX水平(n=6只每组)。(i-o) 将双尾t检验用于统计分析。所有数据表示为平均值±SD。*p<0.05; **p<0.01; ***p<0.001。

[0021] 图13: Tfr2-缺陷中BMP信号转导和Wnt抑制剂的下调。(a) 如来自WT和Tfr2^{-/-}小鼠的第7天的成骨细胞使用下一代测序所鉴别的, 升高或降低最大的前25个基因(n=4每基因型)。(b) 来自Tfr2^{f/f}; Osx-Cre小鼠和同窝对照的第7天分化的成骨细胞中的Dkk1和Sost的基因表达。对β-肌动蛋白归一化。(n=4只每组)。(c) WT和Tfr2^{-/-}小鼠中Dickkopf-1和硬化蛋白的血清浓度。(硬化蛋白, WT n=13, Tfr2^{-/-} n=10; Dickkopf, WT n=15, Tfr2^{-/-} n=14)。(d) 对来自WT和Tfr2^{-/-}小鼠的股骨切片进行的β-连环蛋白和轴蛋白抑制蛋白-2(axin-2)的免疫组织化学分析。比例尺: 20μm。根据它们的染色强度(阴性(通过星号举例说明)、弱(井号)、强(分节号))定量细胞。(n=9只每组)。(e) 对WT成骨细胞归一化的来自Tfr2^{-/-}小鼠的离体分化的成骨细胞(第7天)中激活的Smad和MAPK信号转导状态分析。将磷酸化蛋白对它们的非磷酸化的对应物归一化。将β-连环蛋白的表达对β-肌动蛋白归一化。5次独立免疫印迹实验的光密度测定结果的定量。虚线代表WT水平。(Smad1/5/8 n=4; pERK、pp38和β-连环蛋白 n=3)。(f-g) 用50ng/ml BMP-2处理来自WT和Tfr2^{-/-}小鼠的离体分化的成骨细胞0-20-40min。在蛋白提取后, 使用免疫印迹分析信号转导蛋白的磷酸化(f)。(g) 图代表4次独立实验的定量。(n=4只每组)。(h) 用50ng/ml BMP-4或BMP-6刺激20min后, WT和Tfr2^{-/-}成骨细胞中Smad1/5、ERK和p38的诱导。虚线代表WT水平。(n=3只每组)。(b-e, g-h) 将双尾t检验用于统计分析。所有数据表示为平均值±SD(除(d)以外, 其显示为百分比)。*p<0.05; **p<

0.01;***p<0.001。

[0022] 图14:通过SOST的过表达或MAPK信号转导的再激活来挽回Tfr2-缺陷中的高骨量。

(a) 使WT或Tfr2^{-/-}成骨细胞分化7天并用50ng/ml BMP或TGF-β1刺激48h。使用qPCR确定Sost mRNA表达。(n=4)。将双尾t检验用于统计分析。(b) 用空pcDNA3.1载体(CO)或含有Tfr2基因的pcDNA3.1载体(Tfr2-OE)转染第7天的WT或Tfr2^{-/-}成骨细胞。用50ng/ml BMP-2或PBS处理细胞。48h后,使用qPCR确定Sost的mRNA表达。(n=3)。(c) 含有SOST转基因的一个(SOST^{+tg})或不含等位基因(SOST^{+/+})的10周大的雌性Tfr2^{-/-}或WT小鼠的骨体积/总体积(BV/TV)、WT/Sost^{+/+}n=6,WT Sost^{+tg} n=4,Tfr2^{-/-}Sost^{+/+}n=8,Tfr2^{-/-}Sost^{+tg} n=5和(d) 骨形成速率/骨表面(BFR/BS)。(WT/Sost^{+/+}n=5,WT/Sost^{+tg} n=3,Tfr2^{-/-}/Sost^{+/+}n=7,Tfr2^{-/-}/Sost^{+tg} n=6)。(b-d)将通过邦费罗尼事后检验的双向方差分析用于统计分析。(e) 在茴香霉素处理(100nM)24h后,来自WT或Tfr2^{-/-}小鼠的离体分化的成骨细胞中Sost mRNA的表达。(n=3只每组)。将单因素方差分析用于统计分析。(f-h) 用5mg/kg茴香霉素处理10周大的雄性WT和Tfr2^{-/-}小鼠3周。显示了(f) 硬化蛋白的血清水平(WT/PBS n=5,WT/茴香酶素(Aniso)n=4,Tfr2^{-/-}/PBS n=4,Tfr2^{-/-}/茴香酶素(Aniso)n=5)。(g) 成骨细胞数/骨周长(N.Ob/B.Pm) (n=6只每组)和(h) 第四腰椎的BV/TV。(n=5只每组)。(i-j) 在第7天的WT和Tfr2^{-/-}成骨细胞中ERK2(pCMV6-Mapk1)和p38α(pCMV6Mapk14)的过表达。在48h后分析Sost表达并对β-肌动蛋白归一化。(n=3)。(f-j)将通过邦费罗尼事后检验的双向方差分析用于统计分析。所有数据表示为平均值±SD。*p<0.05;**p<0.01;***p<0.001。(k) 成骨细胞中Tfr2作用的示意图:Tfr2结合BMP并直接激活BMP/MAPK信号转导(1.)或通过结合至BMPR激活它们(2.)以引起Sost和Dkk1的转录。分泌的硬化蛋白用作Wnt拮抗剂并抑制骨形成和降低骨量。

[0023] 图15:Tfr2结合BMP配体并阻断异位骨化(HO)。(a-b) 使用固定在传感器芯片上的Tfr2-ECD和1mg/ml全铁转铁蛋白(holo-transferrin,饱和铁转铁蛋白,含铁转铁蛋白)(全铁-Tf)、不同的BMP配体(50nM)或200nM BMP受体作为分析物的表面等离子共振(SPR)实验。所有实验独立进行三次。(a) 对分子量归一化的结合水平的定量。(BMP-2n=6,BMP-4、6、7、BMPR-II和BMPR-IA n=4每组,全铁-Tf n=3)。(b) 不同浓度的全铁-Tf(holo-Tf)和/或BMP-2的结合反应。(n=3;####p<0.001与单独的全铁-Tf;***p<0.001与单独的BMP-2)。(c) 实施竞争性BMP-2夹心ELISA以测试Tfr2-ECD(或作为阳性对照的BMPR-IA)对BMP-2的结合。将确定浓度的BMP-2(1,500pg/ml)与升高浓度的Tfr2-ECD和BMPR-IA一起使用。右侧示意图显示了测定原理。(n=4)。(d) SPR分析。单独或与升高浓度的BMPR-IA一起注射BMP-2。结合反应是相对于单独的BMP-2的。(n=4;####p<0.001与单独的BMPR-IA;***p<0.001与单独的BMP-2)。(b,d) 将单因素方差分析用于统计分析。(e) 通过μCT定量两周后12周大的雌性WT和Tfr2^{-/-}小鼠中的HO(无胫骨骨体积)。右侧显示了代表性图像。(WT PBS n=5,WT Tfr2-ECD n=3,Tfr2^{-/-}PBS n=4,Tfr2^{-/-}Tfr2-ECD n=4;*p<0.05;***p<0.001对各个PBS对照;####p<0.001与WT)将通过邦费罗尼事后检验的双向方差分析用于统计分析。(f) 通过μCT定量两周后12周大的雌性WT小鼠中的HO(无胫骨骨体积)。(PBS n=12,局部Tfr2-ECD n=6,全身Tfr2-ECD n=8,Pal n=11;*p<0.05与PBS对照)。(g) 12周大的雌性WT小鼠中创伤-引起的HO模型。三周后,使用μCT评价HO。(n=6只每组;*p<0.05,***p<0.001与PBS对照)。(f,g) 将单因素方差分析用于统计分析。所有数据表示为平均值±SD。(h) HO治疗中Tfr2-ECD的作用模式的示意图。左侧:通过过度活跃的BMP信号转导引起HO,从而导致成骨细胞基因的诱导

和骨形成。右侧:Tfr2-ECD中和BMP,从而防止它们激活BMP信号转导。因此,抑制了成骨细胞的骨形成。

[0024] 图16:Tfr2缺陷导致了铁过载。测量了雄性10周大的Tfr2^{-/-}和WT小鼠血清中的(a)转铁蛋白饱和度,n=4只每组、(b)铁和(c)铁蛋白。铁,n=4只每组;铁蛋白,n=5只每组。(d)使用光度法测量干燥组织中肝脏的铁含量。(n=4只每组)。(e)使用原子吸收光谱确定皮质骨中的铁含量。(n=6只每组)。平均值±SD;*p<0.05,**p<0.001。将双尾t检验用于统计分析。

[0025] 图17:铁过载模型中骨量减少。使用μCT,在雄性10周大的转基因和WT小鼠的第四椎骨体测量骨体积/总体积。(a) Hfe^{-/-}小鼠。(n=5只每组)。(b) Slc40a1^{C326S}小鼠,其具有功能失调的肝抗菌肽-结合域。(n=5只每组)和(c)饲喂高铁饲料8周的WT小鼠。(CO n=4,高铁饲料n=5)。(a-c)平均值±SD;*p<0.05,**p<0.01。将双尾t检验用于统计分析。

[0026] 图18:Tfr2缺陷在不同年龄以及在雄性和雌性中影响骨体积。(a)使用μCT,在10周大的雄性和雌性WT和Tfr2^{-/-}小鼠中评价骨体积/总体积(BV/TV)。(雌性,WT n=6,Tfr2^{-/-}=5;雄性,WT+Tfr2^{-/-}n=4只每组)。(b)分析10周、6个月和12个月大的雄性WT和Tfr2^{-/-}小鼠的BV/TV。(10周,n=4只每组;6个月,n=4只每组;12个月,WT n=6,Tfr2^{-/-}n=5)。(c)来自12周大的雄性WT和Tfr2^{-/-}小鼠的第四腰椎的伪彩色qBSE-SEM图像,其中将所关心的小梁骨区显示为白色正方形。如方法中所示,相对于卤化二甲基丙烯酸酯标准品,在0至256水平之间拉伸灰度像素分布。将灰度图像分成8个相等间隔,用不同颜色表示每个间隔以辅助数字图像的目视显示。在这些伪彩色图像中,低矿化密度为黄色,高密度为灰色。图片显示了微矿化密度的相对和累积频率,其中相对于8个相同大小的色坐标(color bin)中的每一个显示灰度像素分布。使用柯尔莫哥罗夫-斯米尔诺夫检验比较骨微矿化密度的累积频率分布。(平均值;WT n=4,Tfr2^{-/-}n=5;*p<0.05)。比例尺200μm。(d-e)不同年龄的雄性和雌性WT和Tfr2^{-/-}小鼠的血清P1NP和CTX水平。(P1NP雌性,WT n=10,Tfr2^{-/-}n=9;雄性10周,WT n=4,Tfr2^{-/-}n=5;雄性12个月,WT n=6,Tfr2^{-/-}n=5;)。(ab,d-e)平均值±SD;*p<0.05,**p<0.01。将双尾t检验用于统计分析。

[0027] 图19:骨组织中的Tfr2表达。(a)分离自WT小鼠的多种器官中的Tfr2a mRNA表达。(平均值±SD;n=3) (b) 12周大的Tfr2^{-/-}小鼠的骨中的Tfr2的免疫组织化学分析。显示了三幅图中的一幅代表性图。比例尺:100μm。(c)来源于12周大的Tfr2^{-/-}小鼠的成骨细胞中的Tfr2的免疫荧光。显示了四幅图中的一幅代表性图。比例尺:20μm。

[0028] 图20:骨细胞-特异的Tfr2-缺陷型小鼠中的骨体积和铁处理。(a)雄性10周大的Tfr2^{f/f};Lysm-cre和Tfr2^{f/f};Ctsk-cre小鼠以及它们的同窝对照的股骨体积/总体积(BV/TV)。(Tfr2^{f/f};Lysm-cre,Cre-n=17,Cre+n=9;Tfr2^{f/f};Ctsk-cre,Cre-n=8,Cre+n=12;)。(b-c)在10周大的雄性Tfr2^{f/f};Ctsk-cre (Cre-,n=7,Cre+n=6)和Tfr2^{f/f};Ox-cre小鼠以及它们相应的同窝对照(n=4只每组)的肝脏中测量铁含量。(a-c)平均值±SD;*p<0.05。将双尾t检验用于统计分析。

[0029] 图21:Tfr2缺陷中BMP信号转导和Wnt抑制剂的下调。(a)在来自WT和Tfr2^{-/-}小鼠骨髓的已分化7天的成骨细胞中进行下一代测序(n=4只每组)。Tfr2^{-/-}成骨细胞中的生物过程、分子功能和过少出现(下调,截止值:-1.5(log2))或过多出现(上调,截止值:+1.0(log2))细胞组分的基因本体分析。将在DESeq2中实施的沃尔德(Wald)检验用于统计分析。

(b) 使用Broad Institute GSEA软件进行基因集富集分析。对Wnt信号转导和成骨细胞分化显示了富集图($n=4$ 只每组)。(c) 使用qPCR,对分离自Tfr2^{-/-}小鼠且对WT小鼠归一化的不同的成骨细胞集进行调节基因的验证。将基因对 β -肌动蛋白和GAPDH归一化(平均值 $\pm$ SD; $n=4$ 只每组;* $p<0.05$;** $p<0.01$ *** $p<0.001$)。将双尾t检验用于统计分析。(d) 用50ng/ml BMP-4或BMP-6处理来自WT和Tfr2^{-/-}小鼠的离体分化的成骨细胞0-20-40min。在蛋白提取后,使用免疫印迹分析信号转导蛋白的磷酸化。显示了四次实验中的一次。

[0030] 图22:通过Tfr2和茴香霉素处理对Sost表达的调控。(a) 用空pcDNA3.1载体(C0)或含有Tfr2 α 基因的pcDNA3.1载体(Tfr2-0E)转染分化第7天的WT或Tfr2^{-/-}成骨细胞。48h后,使用qPCR确定Tfr2 α 的mRNA表达。 $(n=3)$ 。(b) 含有一个(SOST^{+tg})或不含转基因SOST等位基因(SOST^{+/+})的10周大的雌性WT和Tfr2^{-/-}小鼠的破骨细胞表面/骨表面(Oc.S/BS)。(WT Sost^{+/+} $n=5$,WT Sost^{+tg} $n=3$,Tfr2^{-/-}Sost^{+/+} $n=9$,Tfr2^{-/-}Sost^{+tg} $n=5$)。(c-f) 在分化第7天的WT和Tfr2^{-/-}成骨细胞中Smad1 (pCMV6-Smad1) 和Smad4 (pCMV6-Smad4) 的过表达。在48h后分析Sost、Mapk1和Mapk14的表达并对 β -肌动蛋白归一化。 $(n=3)$ 。(g) 从WT或Tfr2小鼠分离成骨细胞并用茴香霉素(100nM)刺激20min。将免疫印迹分析用于评价ERK (pERK) 和p38 (pp38) 信号转导的激活。显示了三次独立实验中一幅代表性印迹。(h) 用5mg/kg茴香霉素处理3周的雄性10周大的WT和Tfr2^{-/-}小鼠的破骨细胞表面/骨表面(Oc.S/BS)。 $(n=5$ 只每组)。(a-f,h) 平均值 $\pm$ SD;* $p<0.05$;** $p<0.01$ *** $p<0.001$ 。将通过邦费罗尼事后检验的双向方差分析用于统计分析。

[0031] 图23:Tfr2-ECD结合至BMP。(a) Tfr2-ECD洗脱液上的Tfr2的SDS-PAGE的考马斯亮蓝染色和免疫印迹。泳道1代表柱清洗,而泳道2-6代表来自柱的Tfr2-ECD的第一洗脱部分。(b) 浓度50nM的BMP与固定化的Tfr2-ECD的代表性传感图。(a+b) 将这些实验重复三次,结果类似。(c) 在运行缓冲液中的高盐浓度(500mM NaCl)下,Tfr2-ECD与固定化的BMP-2、4和6的结合。实验进行两次。(d-e) 使用固定在传感器芯片表面上的BMP-2或BMP-4和在所述芯片上流过的多种浓度的Tfr2,通过Tfr2-BMP-2和Tfr2-BMP-4结合的SPR确定静态亲和力。该实验进行两次。(f) 结合至Tfr2-ECD的全铁转铁蛋白(全铁-Tf)的传感图。在所述芯片上顺序流过升高浓度的全铁-Tf而无中间再生。该实验进行两次。(g-h) 顺序结合实验。首先注射BMP-2或全铁-Tf,然后是全铁-Tf或BMP-2。 $N=3$;平均值 $\pm$ SD。(i) BMPR-IA、BMPR-II和全铁-Tf与固定化的Tfr2-ECD的代表性传感图。(g-i) 将这些实验重复三次,结果类似。(j) BMPR-IA与HuH7肝癌细胞中过表达的Tfr2的免疫共沉淀(Co-IP)。将BMPR-IA和LDLR的Co-IP用作阴性对照。在使用或不使用BMP-2的情况下,实施Tfr2与BMPR-IA的Co-IP。显示了三次实验中的一次。

[0032] 图24:Tfr2-ECD阻断异位骨化。(a-b) 通过向WT和Tfr2^{-/-}小鼠的胫骨前肌肌肉注射2.5 μ g BMP-2来诱导异位骨化。在一些实验中,以与BMP-2相等的浓度另外注射Tfr2-ECD。两周后,使用(a) HE染色(通过箭头表示骨化)或(b) 冯库萨(von Kossa)/范吉森(van Gieson)染色(黑色区域表示骨化)评价肌肉中的骨化。每组显示了一幅代表性图像($n=3-6$ 只每组)。比例尺:200 μ m。(c-d) 通过向WT小鼠的胫骨前肌肌肉注射2.5 μ g BMP-2来诱导异位骨化。用PBS(每隔一天i.p.注射)、帕罗伐汀(前5天,口服100 μ g/小鼠;然后,对于剩余实验,50 μ g/小鼠)或者用Tfr2-ECD(前10天,10mg/kg BW i.p.;然后,对于剩余时间,5mg/kg BW)处理小鼠。8天后,使用番红O染色评价肌肉中软骨的产生。(c) 软骨细胞(通过箭头表示)

数目的定量和番红O-阳性区。(平均值 $\pm$ SD, PBS $n=5$, Tfr2-ECD $n=4$, Pal $n=6$; * $p<0.05$, *** $p<0.001$)。(d) 代表性图像。比例尺:100 μ m。(a-b,d) 将这些实验重复两次, 结果类似。

具体实施方式

[0033] 除非在本文中另外定义, 否则科学和技术术语应具有本领域那些技术人员通常所理解的含义。此外, 除非上下文另外要求, 否则单数术语应包括复数并且复数术语应包括单数。除非上下文另外明确指明, 否则单数术语“一种”、“一个”和“该”包括复数对象。类似地, 除非上下文中明确指出, 否则单词“或”旨在包括“和”。尽管可以在本发明公开的实践或测试中使用与本文所述的那些类似或等价的方法和材料, 但是以下描述了适合的方法和材料。缩写“例如”来源于拉丁语例如(exempli gratia)并且在本文中用于表示非限制性实例。因此, 缩写“例如(e.g.)”与术语“例如(for example)”同义。

[0034] 在说明书和权利要求中, 术语“约”用于修饰例如在描述本公开的实施方式中使用的组合物中成分的量、浓度、体积、处理温度、处理时间、得率、流速、压力以及类似的值及其范围。术语“约”是指可以例如通过用于制备化合物、组合物、浓缩物或使用制剂的典型测量和处理程序; 通过这些程序中的偶然误差; 通过用于实施所述方法的起始材料或成分的生产、来源或纯度的差异以及类似考虑发生的数值量的变化。术语“约”还涵盖了由于具有特定初始浓度或混合物的制剂的老化而不同的量和由于具有特定初始浓度或混合物的制剂的混合或加工而不同的量。当被术语“约”修饰时, 它所附的主张包括这些量的等价值。

[0035] 如本文所使用的, “施用(administer)”或“施用(administration)”是指将存在于体外的物质(例如, 本文所提供的抗-Tfr2抗体)注射或另外物理递送到患者中的操作, 如通过粘膜、皮内、静脉内、肌内递送和/或本文所述的或者本领域中已知的任何其它物理递送方法。当正在治疗疾病或其症状时, 所述物质的施用通常发生在所述疾病或其症状发病后。当正在预防疾病或其症状时, 所述物质的施用通常发生在所述疾病或其症状发病之前。

[0036] 术语“抗体”、“免疫球蛋白”或“Ig”在本文中可互换使用并且表示通过免疫球蛋白分子可变区内的至少一个抗原识别位点识别并特异性结合至靶标, 如蛋白、多肽、肽、碳水化合物、多核苷酸、脂质或上述组合的免疫球蛋白分子。如本文所使用的, 术语“抗体”涵盖了完整的多克隆抗体、完整的单克隆抗体、抗体片段(如Fab、Fab'、F(ab')₂和Fv片段)、单链Fv(scFv)突变体、多重特异性抗体, 如双特异性抗体(包括双结合抗体)、嵌合抗体、人源化抗体、人抗体、包含抗体的抗原决定部分的融合蛋白和包含抗原识别位点的任何其它修饰的免疫球蛋白分子, 只要所述抗体显示出所期望的生物活性。术语“抗体”还可以表示Y-形糖蛋白, 其分子量大致为150kDa, 由四条多肽链: 两条轻链(L)和两条重链(H)组成。存在五种类型的哺乳动物Ig重链同种型, 其通过希腊字母阿尔法(α)、德尔塔(δ)、艾普斯龙(ϵ)、伽马(γ)和穆(mu)(μ)表示。重链类型限定抗体类型, 即分别为IgA、IgD、IgE、IgG和IgM。基于恒定域序列和功能的差异, γ 和 α 类还进一步被分为亚类, 例如, IgG1、hIgG2、mIgG2A、mIgG2B、IgG3、IgG4、IgA1和IgA2。在哺乳动物中, 存在两类免疫球蛋白轻链, λ 和 κ 。抗体的“可变区”或“可变域”是指抗体重链或轻链的氨基末端域。重链和轻链的可变域可以分别被称为“V_H”和“V_L”。这些域通常是抗体最可变的部分(相对于同类其它抗体)并且含有抗原结合位点。抗体的实例是仅有重链(即H2)的抗体, 其包含重链(5'-VH-(任选的铰链)-

CH2-CH3-3')的二聚体并且缺少轻链。

[0037] 本文所述的抗体可以是寡克隆、多克隆、单克隆(包括全长单克隆抗体)、骆驼化、嵌合、CDR-移植、多重特异性、双特异性(包括双结合抗体)、催化、嵌合、人源化、完全人、抗独特型抗体,包括可以以可溶或结合形式标记的抗体及其片段、变体或衍生物,其是通过已知技术单独或与其它氨基酸序列组合提供的。抗体可以来自任何物种。本文所述的抗体可以是裸抗体或缀合至其它分子,如毒素、放射性同位素等。

[0038] 术语“抗原结合位点”、“抗原结合域”、“抗原结合区”、“抗原结合框”以及类似术语表示包含与抗原相互作用的氨基酸残基并且赋予结合剂对抗原的特异性和亲合力的抗体部分(例如,互补决定区(CDR))。抗原结合区可以来源于任何动物物种,如啮齿类(例如,兔、大鼠或仓鼠)和人。优选地,抗原结合区将是人来源的。

[0039] 本文所述的抗原结合片段可以包括单链Fv(scFv)、单链抗体、单域抗体、域抗体、Fv片段、Fab片段、F(ab')片段、F(ab')₂片段、显示出所期望的生物活性的抗体片段、二硫化物-稳定的可变区(dsFv)、二聚可变区(双链抗体(diabody,双价抗体,双体,双特异抗体,双功能抗体))、抗-独特型(antiId)抗体(包括,例如,抗抗体的抗-Id抗体)、胞内抗体、线性抗体、单链抗体分子以及由抗体片段和任何上述的表位-结合片段所形成的多重特异性抗体。具体地,本文所述的抗体和抗体片段可以包括免疫球蛋白分子和免疫球蛋白分子的免疫活性片段,即含有抗原结合位点的分子。通过酶木瓜蛋白酶对抗体的消化导致产生了两个相同的抗原结合片段,其也称为“Fab”片段和“Fc”片段,其不具有抗原-结合活性,但是具有结晶能力。当在本文中使用时,“Fab”是指包括重链和轻链中每一个的一个恒定域和一个可变域的抗体片段。在本文中术语“Fc区”用于定义免疫球蛋白重链的C末端区,其包括天然-序列Fc区和变体Fc区。“Fc片段”是指通过二硫化物保持在一起的两条H链的羧基末端部分。通过Fc区中的序列确定抗体的效应因子功能,该区还通过存在于特定类型细胞上的Fc受体(FcR)识别。通过酶胃蛋白酶对抗体的消化导致产生了F(ab')₂片段,其中抗体分子的两个臂保持连接并且包括两个抗原结合位点。F(ab')₂片段具有交联抗原的能力。

[0040] 当在本文中使用时,“Fv”是指保留了抗原识别和抗原结合位点两者的抗体的最小片段。这区包括处于紧密、非共价或共价结合的一条重链和一条轻链可变域的二聚体。在该构造中,每条可变域的三个CDR相互作用以定义V_H-V_L二聚体表面上的抗原结合位点。六个CDR共同赋予抗体抗原-结合特异性。然而,即使单个可变域(或仅含有对抗原特异的三个CDR的半个Fv)具有识别并结合抗原的能力,尽管以比完整结合位点低的亲合力。

[0041] 如本文所使用的术语“单克隆抗体”是指获得自基本均一的抗体群体的抗体,即包含各个抗体的群体除可能少量存在的可能天然存在的突变和/或翻译后修饰(例如,异构化、酰胺化)外是相同的。单克隆抗体是高度特异的并且抗单一抗原决定簇或表位。相反,多克隆抗体试剂通常包括抗不同抗原决定簇(或表位)的不同的抗体。如本文所使用的术语“单克隆抗体”涵盖了完整和全长单克隆抗体以及抗体片段(如Fab、Fab'、F(ab')₂、Fv)、单链(scFv)突变体、包含抗体部分的融合蛋白和包含抗原识别位点的任何其它修饰的免疫球蛋白分子。此外,“单克隆抗体”是指以多种方法制备的这些抗体,其包括但不限于杂交瘤、噬菌体选择、重组表达和转基因动物。

[0042] 在本文中,单克隆抗体可以包括“嵌合”抗体(免疫球蛋白),其中重链和/或轻链部分与来源于特定物种或属于特定抗体种类或亚类的抗体中的相应序列相同或同源,而所述

链的剩余部分与来源于另一物种或属于另一抗体种类或亚类的抗体中的相应序列以及显示出所期望的生物活性的这些抗体片段相同或同源。

[0043] 术语“人源化抗体”是指其中来自非人免疫球蛋白(供体抗体)的“高变区”替换了来自人免疫球蛋白(受体抗体)高变区的残基的嵌合抗体亚型。通常,人源化抗体将包括基本全部的至少一个并且通常两个可变域,其中全部或基本全部的高变环对应于非人免疫球蛋白序列的那些,并且全部或基本全部的框架区是人免疫球蛋白序列的那些,尽管框架区可以包括改善抗体性能,如结合亲和力、异构化、免疫原性等的一个或多个替换。

[0044] 术语“双特异性抗体”表示包含对两种靶标分子的特异性的抗体,并且包括但不限于以下形式,如DVD-Ig(参见DiGiammarino等人,“Design and generation of DVD-IgTM molecules for dual-specific targeting”,Meth.Mo.Biol.,2012,889,145-156)、mAb²(参见W02008/003103,对mAb²形式的描述作为参考并入本文)、FIT-Ig(参见W02015/103072,将对FIT-Ig骨架的描述作为参考并入本文)、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、κλ-体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH3、双链抗体-CH3、三体(Triple body)、微型抗体、微抗体、TriBi微抗体、scFv-CH3 KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、Fab-scFv-Fc、四价HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DT-IgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig和zy体(zybody)。有关双特异性形式的综述,参见Spiess,C等人,Mol.Immunol.(2015)。在另一个实施方式中,双特异性分子包括融合至另一非-Ig形式的抗体,例如,T细胞受体结合域;免疫球蛋白超家族域;无颌纲动物可变淋巴细胞受体;纤连蛋白域(例如,AdnectinTM);抗体恒定域(例如,CH₃域,例如,FcabTM的CH₂和/或CH₃),其中恒定域不是功能性CH₁域;scFv;(scFv)₂;sc-双链抗体;scFab;琴都灵蛋白(centyrin)和来源于选自CTLA-4的骨架的表位结合域(EvibodyTM);脂质运载蛋白域;蛋白A,如蛋白A的Z域(例如,AffibodyTM或SpA);A-域(例如,AvimerTM或MaxibodyTM);热休克蛋白(如来源于GroEI和GroES的表位结合域);转铁蛋白域(例如,反体(trans-body));锚蛋白重复序列蛋白(例如,DARPinTM);肽适体;C-型凝集素域(例如,TetranectinTM);人γ-晶体蛋白或人泛素(affilin);PDZ域;蝎毒素;和人蛋白酶抑制剂的库尼兹(kunitz)型域。

[0045] 在一个实施方式中,双特异性抗体是mAb²。mAb²包括来自完整抗体,稠合至修饰的恒定区的V_H和V_L域,其已工程化以形成抗原结合位点,其被称为“Fcab”。在W02008/003103中更详细地描述了Fcab/mAb²形式背后的技术,并且将对mAb²形式的描述作为参考并入本文。

[0046] 在另一个实施方式中,双特异性抗体是“双结合抗体”。如本文所使用的,术语“双结合抗体”是双特异性抗体,其中通过V_H/V_L对形成了两个抗原-结合域,并且其包括FIT-Ig(参见W02015/103072,通过引证并入本文)、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、κλ-体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH3、双链抗体-CH3、三体(Triple body)、微型

抗体、微抗体、scFv-CH₃ KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、FabscFv-Fc、四价 HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DT-IgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv和scFv4-Ig。

[0047] 术语“高变区”、“CDR区”或“CDR”是指序列高变和/或形成结构上限定的环的抗体可变域的区域。一般地,抗体的抗原结合位点包括六个高变区:三个在V_H中(CDRH1、CDRH2、CDRH3)并且三个在V_L中(CDRL1、CDRL2、CDRL3)。抗体的重链和轻链的这些区域赋予抗体抗原-结合特异性。可以根据Kabat系统定义CDR(参见Kabat,E.A.等人,1991,“Sequences of Proteins of Immunological Interest”,第5版,NIH公开号91-3242,U.S.卫生与公众服务部(Department of Health and Human Services))。其它系统可以用于定义CDR,其作为Chothia等人(参见Chothia,C.&Lesk,A.M.,1987,“Canonical structures for the hypervariable regions of immunoglobulins”,J.Mol.Biol.,196,901-917)所设计的系统和IMGT系统(参见Lefranc,M.P.,1997,“Unique database numbering system for immunogenetic analysis”,Immunol.Today,18,50)。抗体通常含有3个重链CDR和3个轻链CDR。在本文中使用术语CDR或CDRs以表示这些区域中的一个或几个。本领域技术人员能够容易地比较不同命名系统并确定是否可以将具体序列定义为CDR。

[0048] 在本文中抑制剂可以例如是人抗体。“人抗体”是具有对应于通过人所产生的抗体的序列的氨基酸序列和/或已使用用于制备人抗体的任何技术制备并且具体地排除了包含非人抗原-结合残基的人源化抗体的抗体。术语“特异性结合至”是指可测量且可重复的相互作用,如靶标和抗体之间的结合,它是在存在包含生物分子的非均一分子群体的情况下对靶标的存在具有决定作用的。例如,特异性结合至靶标(其可以是表位)的抗体是以比它结合至其它靶标时更大的亲合力、总亲合力、更易于和/或更长持续时间地结合该靶标的抗体。在一个实施方式中,抗体与不相关的靶标的结合程度小于抗体与靶标的结合的约10%,例如通过放射免疫测定(RIA)所测量的。

[0049] 特异性结合至Tfr2抗原的抗体或其片段可以与相关抗原交叉反应。优选地,特异性结合至Tfr2抗原的抗体或其片段不与其它抗原交叉反应(但是可以任选地与不同物种,例如,恒河猴或鼠科的Tfr2交叉反应)。可以例如通过免疫测定、BIAcore™或本领域技术人员已知的其它技术鉴别特异性结合至Tfr2抗原的抗体或其片段。如使用实验技术,如放射免疫测定(RIA)和酶联免疫吸附测定(ELISA)所确定的,当以比结合至任何交叉反应抗原更高的亲合力结合至Tfr2抗原时,抗体或其片段特异性结合至Tfr2抗原。通常,特异性或选择性反应将是背景信号或噪音的至少两倍,并且更通常地是背景的大于10倍(如大于15倍、大于20倍、大于50倍或大于100倍)。有关抗体特异性的讨论,参见,例如,Paul,主编,1989, Fundamental Immunology 第二版, Raven Press, 纽约, 332-336页。

[0050] 如本文所使用的,“授权编号”或“上市授权编号”是指由管理机构所发布的编号,该机构决定特定医学产品和/或组合物可以在该机构管辖区域内上市和/或提供销售。如本文所使用的,“管理机构”是指负责评价例如医学产品和/或组合物的安全性和效力并且控制这些产品和/或组合物在给定区域内销售/上市的机构之一。美国的食物和药物管理局(FDA)和欧洲的欧洲药物管理局(EPA)是这些管理机构的两个实例。其它非限制性实例可以

包括SDA、MPA、MHPRA、IMA、ANMAT、香港卫生署-药物办公室、CDSCO、Medsafe和KFDA。

[0051] 如本文所使用的,“缓冲液”是指能够吸收一定量的酸或碱,而不会经历pH剧烈变化的化学试剂。

[0052] 本发明的组合物可以包括载体。如上下文中所使用的,术语“载体”是指稀释剂、佐剂(例如,弗氏佐剂(完全和不完全))、赋形剂或通过其施用治疗剂的媒介物。这些药物载体可以是无菌液体,如水和油,包括石油、动物、植物或合成来源的那些,如花生油、豆油、矿物油、芝麻油等。当静脉内施用药物组合物时,水是优选的载体。盐溶液以及葡萄糖和甘油水溶液也可以用作液体载体,具体地用于可注射溶液。

[0053] 如本文所使用的,术语“组合物”旨在涵盖含有任选地处于指定量的指定成分(例如,本发明的抗体)的产品,以及由任选地处于指定量的指定成分的组合直接或间接所产生的的任何产品。

[0054] 在实例中,本发明的抑制剂或蛋白包括具有效应因子功能的抗体恒定区。如本文所使用的术语“效应因子功能”(或“效应因子-使能的”)是指抗体依赖性细胞介导的细胞毒活性(ADCC)、补体依赖性细胞毒活性(CDC)介导的反应、Fc-介导的吞噬作用或抗体依赖性细胞吞噬作用(ADCP)和通过FcRn受体的抗体再循环中的一种或多种。

[0055] “有效量”是指以所需的剂量和持续时间,对于实现所期望的结果,包括治疗或预防结果有效的量。“治疗有效量”是指对于特定病症实现可测量的改善或预防所需的最小浓度。在本文中,治疗有效量可以根据以下因素而不同,如疾病状态、患者的年龄、性别和体重以及抗体在个体中引起所期望的反應的能力。治疗有效量还是其中治疗有益效果大于抗体的毒性或不利影响的量。“预防有效量”是指以所需的剂量和持续时间,对于实现所期望的预防结果有效的量。在一些实施方式中,本发明的抗体的有效量为约0.1mg/kg (mg抗体每kg受试者重量)至约100mg/kg。在某些实施方式中,其中所提供的抗体的有效量为约0.1mg/kg、约0.5mg/kg、约1mg/kg、3mg/kg、5mg/kg、约10mg/kg、约15mg/kg、约20mg/kg、约25mg/kg、约30mg/kg、约35mg/kg、约40mg/kg、约45mg/kg、约50mg/kg、约60mg/kg、约70mg/kg、约80mg/kg、约90mg/kg或约100mg/kg (或其中的范围)。在一些实施方式中,如本文所使用的“有效量”还是指实现所指明的结果(例如,细胞Tfr2生物活性的抑制)的本发明的抗体的量。

[0056] 如本文所使用的术语“表位”是指抗原,如Tfr2多肽或Tfr2多肽片段表面上的局部区域,其能够结合至抗体的一个或多个抗原结合区并且在动物,优选地哺乳动物并且最优选地人中具有能够引起免疫应答的抗原性或免疫原性活性。具有免疫原性活性的表位是在动物中引起抗体应答的多肽部分。具有抗原性活性的表位是如通过本领域中熟知的任何方法所确定的,例如,通过本文所述的免疫测定所确定的,抗体特异地结合的多肽部分。抗原性表位不必是免疫原性的。表位通常由化学活性表面分子组群(surface groupings of molecule),如氨基酸或糖侧链组成,并且具有特定的三维结构特征以及特定的电荷特征。有助于表位的多肽区可以是多肽的邻接氨基酸或者表位可以从多肽的两个或更多个非邻接区聚集而成。表位可以或可以不是抗原的三维表面特征。在某些实施方式中,Tfr2表位是Tfr2多肽的三维表面特征。在其它实施方式中,Tfr2表位是Tfr2多肽的线性特征。

[0057] 在实例中,在本文中,组合物包含赋形剂。如本文所使用的术语“赋形剂”是指惰性物质,其通常用作药物的稀释剂、媒介物、防腐剂、粘结剂或稳定剂并且包括但不限于蛋白(例如,血清白蛋白等)、氨基酸(例如,门冬氨酸、谷氨酸、赖氨酸、精氨酸、甘氨酸、组氨酸

等)、脂肪酸和磷脂(例如,烷基磺酸酯、辛酸酯等)、表面活性剂(例如,SDS、聚山梨醇酯、非离子表面活性剂等)、糖(例如,蔗糖、麦芽糖、海藻糖等)和多元醇(例如,甘露糖醇、山梨糖醇等)。还参见,Remington的Pharmaceutical Sciences(1990)Mack Publishing Co., Easton,Pa.,该文献以其全部内容作为参考并入本文。

[0058] 在本文中,抗体或片段可以包含如本段中所述的重链。当在提及抗体使用时,术语“重链”是指基于重链恒定域的氨基酸序列的五种不同的类型,其称为阿尔法(α)、德尔塔(δ)、艾普斯龙(ϵ)、伽马(γ)和穆(μ)。这些不同类型的重链是熟知的并且产生了五种抗体种类,分别为IgA、IgD、IgE、IgG和IgM,包括四种IgG亚类,即IgG1、IgG2、IgG3和IgG4。优选地,重链是人重链。在人群中,每个免疫球蛋白或免疫球蛋白亚类存在多个重链恒定区等位基因。这些等位变体的核苷酸和氨基酸序列是在公开可获得的数据库,如IMGT、ENSEMBL、Swiss-Prot和Uniprot中可访问的。还可以在多种基因组测序计划中鉴别等位变体。在一个实施方式中,本文所公开的抗体和抗体片段包括IgG1恒定区等位基因编码的重链,其包括但不限于人IGHG1*01、IGHG1*02、IGHG1*03、IGHG1*04和IGHG1*05。在一个实施方式中,本文所公开的抗体和抗体片段包括IgG2恒定区等位基因编码的蛋白,其包括但不限于人IGHG2*01、IGHG2*02、IGHG2*03、IGHG2*04、IGHG2*05和IGHG2*06。在一个实施方式中,本文所公开的抗体或抗体片段包括IgG3恒定区等位基因编码的蛋白,其包括但不限于人IGHG3*01、IGHG3*02、IGHG3*03、IGHG3*04、IGHG3*05、IGHG3*06、IGHG3*07、IGHG3*08、IGHG3*09、IGHG3*10、IGHG3*11、IGHG3*12、IGHG3*13、IGHG3*14、IGHG3*15、IGHG3*16、IGHG3*17、IGHG3*18和IGHG3*19。在一个实施方式中,本文所公开的抗体或抗体片段包括IgG4恒定区等位基因编码的蛋白,其包括但不限于人IGHG4*01、IGHG4*02、IGHG4*03和IGHG4*04。在另一个实例中,重链是失去功能的(disabled)IgG同种型,例如,失去功能的IgG4。在某些实施方式中,本发明的抗体包括人 γ 4恒定区。在另一个实施方式中,重链恒定区不结合Fc- γ 受体,并且例如包含Leu235Glu突变。在另一个实施方式中,重链恒定区包含Ser228Pro突变以提高稳定性。在另一个实施方式中,重链恒定区是IgG4-PE(参见,例如,本文中的序列列表)。在另一个实施方式中,本文所公开的抗体和抗体片段包括鼠科IgG1恒定区等位基因编码的重链恒定区,其包括但不限于小鼠IGHG1*01或IGHG1*02。在一个实施方式中,本文所公开的抗体和抗体片段包括鼠科IgG2恒定区等位基因编码的重链恒定区,其包括但不限于小鼠IGHG2A*01、IGHG2A*02、IGHG2B*01、IGHG2B*02、IGHG2C*01、IGHG2C*02或IGHG2C*03。在一个实施方式中,本文所公开的抗体或抗体片段包括鼠科IgG3恒定区等位基因编码的蛋白,其包括但不限于小鼠IGHG3*01。

[0059] 可以将本发明的蛋白、抑制剂或组合物与另一种疗法组合施用于受试者。在其它疗法的施用的背景中,术语“组合”是指多于一种疗法的使用。术语“组合”的使用不限制其中向患病受试者施用疗法的顺序。可以在向已患有、患有Tfr2-介导的疾病或者对所述疾病敏感的受试者施用第二疗法之前(例如,1分钟、45分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周或12周),同时或之后(例如,1分钟、45分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周、5周、6周、8周或12周)施用第一疗法。可以以任何顺序与其它额外的疗法一起使用任何额外的疗法。在某些实施方式中,可以与当前施用以预防、治疗、控制和/或改善Tfr2-介导的疾病的一种或多种疗法(例如,非本

发明的抗体的疗法组合施用本发明的抗体。可以与本发明的抗体组合施用的疗法的非限制性实例包括止痛剂、麻醉剂、抗生素或免疫调节剂或者美国药典和/或医师手册 (Physician's Desk Reference) 中所列的任何其它试剂。

[0060] 如本文所使用的,“注射装置”是指设计用于实施注射的装置,注射包括将注射装置与人的组织,通常皮下组织暂时流体偶联的步骤。注射还包括将一定量的液体药物施用到组织中并将注入装置与组织脱离或移除。在一些实施方式中,注射装置可以是静脉内装置或IV装置,它是当靶组织是循环系统内的血液,例如,静脉中的血液时所使用的一类注射装置。注射装置的常见但非限制性实例是针头和注射器。

[0061] 如本文所使用的,“说明书”是指制品的直接包装上的书写、印刷或图示材料的显示,例如,在含有药物活性剂的小瓶上显示书写材料,或者有关包含在含有所关心的组合物的试剂盒中的所关心的产品的组成和使用的详细信息。说明书显示了考虑进行施用或实施的治疗方法。

[0062] 术语“Kabat编号”等术语是本领域中承认的并且表示对比抗体的重链可变区或其抗原结合部分中的其它氨基酸残基更易变化(即高变)的氨基酸残基编号的系统(Kabat等人,(1971) Ann. NY Acad. Sci., 190:382-391和Kabat等人(1991) Sequences of Proteins of Immunological Interest, 第五版, U.S. 卫生与公众服务部, NIH公开号91-3242)。对于重链可变区,对于CDR1,高变区通常在氨基酸位置31至35的范围内,对于CDR2,在氨基酸位置50至65的范围内,对于CDR3,在氨基酸位置95至102的范围内。

[0063] 本发明的抗体、蛋白或抑制剂可以包括如本段中所述的轻链。当用于提及抗体时,术语“轻链”是指免疫球蛋白轻链,其中在哺乳动物中存在两种类型:拉姆达(λ)和卡帕(κ)。优选地,轻链是人轻链。优选地,轻链恒定区是人恒定区。在人群中,存在多个轻链恒定区等位基因。这些等位变体的核苷酸和氨基酸序列在公开可用的数据库,如IMGT、ENSEMBL、Swiss-Prot和Uniprot中是可访问的。在一个实施方式中,本文所公开的抗体或抗体片段包括人 κ 恒定区等位基因编码的蛋白,其包括但不限于IGKC*01(参见,例如,本文中的序列表)、IGKC*02(参见,例如,本文中的序列表)、IGKC*03(参见,例如,本文中的序列表)、IGKC*04(参见,例如,本文中的序列表)和IGKC*05(参见,例如,本文中的序列表)。在一个实施方式中,本文所公开的抗体或抗体片段包括人 λ 恒定区等位基因编码的蛋白,其包括但不限于IGLC1*01(参见,例如,本文中的序列表)、IGLC1*02(参见,例如,本文中的序列表)、IGLC2*01(参见,例如,本文中的序列表)、IGLC2*02(参见,例如,本文中的序列表)、IGLC2*03(参见,例如,本文中的序列表)、IGLC3*01(参见,例如,本文中的序列表)、IGLC3*02(参见,例如,本文中的序列表)、IGLC3*03(参见,例如,本文中的序列表)、IGLC3*04(参见,例如,本文中的序列表)、IGLC6*01(参见,例如,本文中的序列表)、IGLC7*01(参见,例如,本文中的序列表)、IGLC7*02(参见,例如,本文中的序列表)、IGLC7*03(参见,例如,本文中的序列表)。在另一个实施方式中,本文所公开的抗体和抗体片段包括小鼠 κ 恒定区等位基因编码的轻链恒定区,其包括但不限于IGKC*01、IGKC*03或IGKC*03。在另一个实施方式中,本文所公开的抗体和抗体片段包括小鼠 λ 恒定区等位基因编码的轻链恒定区,其包括但不限于IGLC1*01、IGLC2*01或IGLC3*01。

[0064] 受试者可以是任何动物,其包括但不限于哺乳动物。如本文所使用的,术语“哺乳动物”是指对它们的幼崽哺乳并且分泌活的幼崽(真哺乳亚纲或胎盘哺乳动物)或者产卵

(后哺乳下纲或非胎盘哺乳动物)的任何脊椎动物。哺乳动物物种的实例包括但不限于人及其它灵长类,其包括非人灵长类,如黑猩猩及其它猿类和猴物种;农畜,如牛、绵羊、猪、山羊和马;驯养哺乳动物,如狗和猫;实验动物,包括啮齿类,如小鼠、大鼠(包括棉鼠)和豚鼠;鸟类,包括驯养、野生和猎禽,如鸡、火鸡及其它鹑鸡类鸟、鸭、鹅等。

[0065] 如本文所使用的,“基本全部”是指至少约60%,至少约70%,至少约75%,至少约80%,至少约85%,至少约90%,至少约95%,至少约98%,至少约99%或约100%。

[0066] 术语“可变区”或“可变域”是指轻链和重链部分,通常在重链中约氨基-末端120至130个氨基酸,并且在轻链中约100至110个氨基酸,其在抗体之间序列大量变化并且在每种具体抗体对其具体抗原的结合和特异性中使用。序列中的可变性集中在称为互补决定区(CDR)的区域,而在可变域中更高度保守的区域被称为框架区(FR)。重链的CDR主要负责抗体与抗原的相互作用。本文所使用的氨基酸位置编号是根据EU指数进行的,如Kabat等人(1991)Sequences of proteins of immunological interest(U.S.卫生与公众服务部,Washington,D.C.)第5版(“Kabat等人”)。在优选的实施方式中,可变区是人可变区。

[0067] 细胞生物学和分子生物学中的常规术语的定义可见于“The Merck Manual of Diagnosis and Therapy”,第19版,Merck Research Laboratories出版,2006(ISBN 0-911910-19-0);Robert S.Porter等人(主编),The Encyclopedia of Molecular Biology,Blackwell Science Ltd.出版,1994(ISBN 0-632-02182-9);Benjamin Lewin,Genes X,Jones&Bartlett Publishing出版,2009(ISBN-10:0763766321);Kendrew等人(主编),Molecular Biology and Biotechnology:a Comprehensive Desk Reference,VCH Publishers,Inc.出版,1995(ISBN 1-56081-569-8)和Current Protocols in Protein Sciences 2009,Wiley Intersciences,Coligan等人主编。

[0068] 除非另作说明,否则使用标准程序实施本发明,如以下文献中所述的,例如,Sambrook等人,Molecular Cloning:A Laboratory Manual(第4版),Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y.,USA(2012);Davis等人,Basic Methods in Molecular Biology,Elsevier Science Publishing,Inc.,New York,USA(1995);或Methods in Enzymology:Guide to Molecular Cloning Techniques 152卷,S.L.Berger和A.R.Kimmel主编,Academic Press Inc.,San Diego,USA(1987);Current Protocols in Protein Science(CPPS)(John E.Coligan等人主编,John Wiley and Sons,Inc.),Current Protocols in Cell Biology(CPCB)(Juan S.Bonifacino等人主编,John Wiley and Sons,Inc.)和Culture of Animal Cells:A Manual of Basic Technique,R.Ian Freshney,出版商:Wiley-Liss;第5版(2005),Animal Cell Culture Methods(Methods in Cell Biology,57卷,Jennie P.Mather和David Barnes主编,Academic Press,第1版,1998),所有文献均以其全部内容作为参考并入本文。

[0069] 在本文中,在本发明的多个方面的描述内定义了其它术语。

[0070] 第一构造:转铁蛋白受体2胞外域用于诊断和治疗原发性或继发性硬化性疾病的用途

[0071] 在第一构造中,本发明涉及用于在诊断和/或治疗原发性或继发性硬化性疾病中使用的蛋白、融合蛋白和核苷酸序列和载体,并且涉及用于在诊断和治疗原发性或继发性硬化性疾病中使用的药物组合物。

[0072] 存在多种与不受控制的骨形成有关的硬化性疾病,包括进行性骨化性纤维发育不良 (FOP)。这种罕见的疾病的特征在于异位骨化 (HO),其导致在骨骼外部骨化,具体地,肌肉、腱和柔软部分骨化,并因此极大地损害了患者的移动性。FOP患者具有56岁的平均期望寿命并且死因通常为胸腔无法支持正常呼吸。FOP患者在ACVR1基因中具有突变,其编码ACVR1/ALK2受体。该受体是骨形态发生蛋白 (BMP) 信号通路中的一部分并且在软骨和骨发育调控中具有确定性的重要作用。这种突变导致ACVR1/ALK2受体活性升高,并因此导致过度的BMP信号转导,从而导致骨形成升高且不受控制 (Shore和Kaplan 2008)。

[0073] 除FOP之外,存在其它硬化性疾病并且其产生自不同机制。这些包括van Buchem病、硬化性骨化病、肢骨纹状肥大、骨膜增生性厚皮症、纤维性结构不良、骨软骨发育不良、粘多糖病、关节强硬性脊椎炎、创伤后HO,例如,在关节置换手术、爆发、截肢、截瘫后或在钙化防御后或在恶性疾病或退行性疾病,例如,前列腺癌、肾细胞癌、肿瘤样钙质沉着症、乳腺癌、关节或良性骨病变的情况下。这些硬化性疾病的特征在于骨骼内部和外部的不受控制的骨化。本发明可以用于治疗任何这些疾病。本发明可以用于诊断任何这些疾病。本发明可以用于预防或降低任何这些疾病的风险。

[0074] 用于治疗硬化性疾病的常规方法包括非特异性治疗、类固醇、非类固醇抗炎药物 (NSAID)、切除术或放射疗法 (Kölbl等人2003)。WO 2016/039796 A2描述了用于治疗硬化性疾病进行性骨化性纤维发育不良 (FOP) 的方法,其包括施用2A型活化素受体 (ACVR2A) 拮抗剂和/或2B型活化素受体 (ACVR2B) 拮抗剂或1型活化素受体 (ACVR1) 拮抗剂。

[0075] 然而,这些治疗的应用是有限的并且通常仅减轻症状,但是不可以防止疾病发展。例如,在切除术后,HO恢复的可能性达到80%。具体地,类固醇引起骨形成抑制,但是具有大量副作用,如肥胖症、糖尿病、皮肤干燥或肌肉萎缩。

[0076] WO 2015/107075 A1公开了人转铁蛋白受体2胞外域的氨基酸序列 (在本文中SEQ ID NO.1)。Baschant等人描述了使用转铁蛋白受体2对破骨细胞形成的铁-依赖性细胞内源负调控 (Baschant等人2017)。

[0077] 因此,本发明的目标在于提供用于治疗硬化性疾病的药物。

[0078] 本发明的目标还在于提供具有比已知治疗方法更少的副作用的药物。

[0079] 通过使用具有与SEQ ID NO.1的序列具有至少70、75、80、85、90、95、96、97、98或99%同一性的氨基酸序列或其片段的蛋白用于诊断和治疗原发性或继发性硬化性疾病来实现根据本发明的目标。

[0080] “同一性”将被理解为基于氨基酸总数的匹配的氨基酸的数目。

[0081] 相对于本发明的蛋白的“片段”将被理解为蛋白的氨基酸序列的一部分,优选地由PA域 (SEQ ID NO.5或者与之具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列) 组成的片段,由肽酶M28域 (SEQ ID NO.6或者与之具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列) 组成的片段或者由Tfr-样二聚化域 (SEQ ID NO.7或者与之具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列) 组成的片段。

[0082] “原发性或继发性硬化性疾病”将被理解为与组织骨化有关的疾病,它是作为疾病的原发性或继发性后果存在的硬化症。

[0083] 原发性或继发性硬化性疾病包括进行性骨化性纤维发育不良 (FOP)、van Buchem病、硬化性骨化病、肢骨纹状肥大、骨膜增生性厚皮症、纤维性结构不良、骨软骨发育不良、

粘多糖病、关节强硬性脊椎炎、创伤后H0,优选地,在关节置换手术、爆发、截肢、截瘫、钙化防御后的硬化症的情况下和在恶性疾病和退行性疾病的情况下,特别优选地,在前列腺癌、肾细胞癌、肿瘤样钙质沉着症、乳腺癌、关节和良性骨病变的情况下。

[0084] 在优选的实施方式中,用途是诊断和/或治疗异位骨化(H0)、van Buchem病、硬化性骨化病或进行性骨化性纤维发育不良(FOP)。

[0085] “H0”也称为骨化性肌炎,其将被理解为其中作为组织损伤的后果,在骨骼系统以外的柔软部分组织中发生骨化的疾病。

[0086] “进行性骨化性纤维发育不良(FOP)”也称为进行性多发性骨化性纤维发育不良、进行性骨化性肌炎或Munchmeyer病,其将被理解为其中人体的结缔组织和支持组织发生进行性骨化的遗传疾病。

[0087] “Van Buchem病”也称为van Buchem综合征、硬化性骨化病、常见全身性骨皮质增厚(Hyperostosis corticalis generalisata familiaris)、van Buchem-型骨内膜骨质增生,其将被理解为遗传性骨骼发育异常,包括长骨和颅盖骨增生,该疾病是常染色体隐性的。

[0088] “纤维性结构不良”将被理解为由GNAS基因中的突变引起并且导致产生骨赘生物的疾病。

[0089] “肢骨纹状肥大”将被理解为由LEMD3基因中的突变引起并且导致产生骨赘生物的疾病。该基因编码参与转化生长因子- β (TGF- β) 信号通路的蛋白。

[0090] “粘多糖病”将被理解为一组溶酶体贮积症,它是常染色体隐性的并且导致骨变化。

[0091] “关节强硬性脊椎炎”或贝希德莱氏病(Bechterew's disease)、马-施二氏病、强直性脊髓关节炎是优选地在脊柱和在骶髂关节中表现出症状的慢性炎性疾病。在这种情况下,关节强直和硬化通常发生在脊柱中。

[0092] 具有氨基酸序列SEQ ID NO.1的蛋白可以分离自人转铁蛋白受体(Tfr) 2 α 或者人转铁蛋白受体(Tfr) 2 β ,优选地人Tfr2 α 的胞外域。

[0093] 根据本发明的蛋白优选地结合转化生长因子- β (TGF- β) /骨形态发生蛋白BMP家族成员,优选BMP,特别优选地结合至BMP-2、BMP-4、BMP-6和BMP-7中的一种或多种,优选地结合至所有这些BMP。

[0094] “转化生长因子- β (TGF- β) /骨形态发生蛋白,BMP家族”将被理解为一组类似的信号转导蛋白,其结合TGF- β 受体家族成员。TGF- β /BMP家族包括TGF β 1、TGF β 2、TGF β 3、BMP、生长分化因子(GDF)、活化素和抑制素、肌生成抑制蛋白、抗苗勒管激素(AMH)和nodal。

[0095] “骨形态发生蛋白(BMP)”将被理解为一组结合BMP受体的旁分泌信号转导蛋白。在一个实施方式中,BMP选自BMP1、BMP2、BMP3、BMP4、BMP5、BMP6、BMP7、BMP8a、BMP8b、BMP-9、BMP10或BMP15,优选地BMP-2、BMP-4、BMP-6或BMP-7。

[0096] 有利地,当使用根据本发明的蛋白治疗原发性或继发性硬化性疾病时,具体地抑制了BMP信号通路和因此的骨形成和Wnt信号通路。

[0097] 在一个实施方式中,通过检测TGF- β /BMP家族成员,优选地BMP,特别优选地BMP-2、BMP-4、BMP-6和BMP-7中的一种或多种,优选地所有这些BMP,使用根据本发明的蛋白进行原发性或继发性硬化性疾病的诊断。

[0098] 在一个实施方式中,在血液中,在血浆中,在血清中或在组织中使用根据本发明的蛋白进行原发性或继发性硬化性疾病的诊断。在优选的实施方式中,组织是骨或软骨。“血浆”将被理解为血液的流体组分。“血清”将被理解为无凝血因子的血浆。

[0099] 在一个实施方式中,通过免疫测定使用根据本发明的蛋白进行原发性或继发性硬化性疾病的诊断。“免疫测定”将被理解为其中通过抗原-抗体结合,在流体相中检测分析物的检测程序。

[0100] 在一个实施方式中,免疫测定选自酶联免疫吸附测定(ELISA)或酶联免疫斑点测定(ELISPOT测定)。“ELISA”将被理解为基于酶促显色反应的基于抗体的检测过程。“ELISPOT测定”将被理解为检测在使用抗原刺激后通过免疫细胞分泌的并且固定化在膜上的抗体的检测程序。

[0101] 在一个实施方式中,实施原发性或继发性硬化性疾病的诊断以评价疾病的预后,以评价对治疗的反应和/或用于风险分层。“风险分层”将被理解为评价疾病发展或导致并发症或死亡的风险。

[0102] 在一个实施方式中,用于诊断和治疗原发性或继发性硬化性疾病的根据本发明的蛋白包括序列SEQ ID NO.1或SEQ ID NO.2。

[0103] 具有氨基酸序列SEQ ID NO.2的蛋白可以分离自鼠科转铁蛋白受体(Tfr) 2 α ,或者鼠科转铁蛋白受体(Tfr) 2 β ,优选地鼠科Tfr2 α 的胞外域。

[0104] 在一个实施方式中,根据本发明的蛋白包括232个氨基酸至801个氨基酸,优选地487个氨基酸至801个氨基酸,特别优选地600个氨基酸至750个氨基酸或者由其组成。

[0105] 在一个实施方式中,用于诊断和/或治疗原发性或继发性硬化性疾病的根据本发明的蛋白是人转铁蛋白受体(Tfr) 2 α (SEQ ID NO.3)、鼠科转铁蛋白受体(Tfr) 2 α (SEQ ID NO.4)、人转铁蛋白受体(Tfr) 2 β (SEQ ID NO.1)或人Tfr2 α 的胞外域(SEQ ID NO.1)、鼠科转铁蛋白受体(Tfr) 2 β (SEQ ID NO.2)或鼠科Tfr2 α 的胞外域(SEQ ID NO.2)。

[0106] 本发明还涉及用于诊断和/或治疗原发性或继发性硬化性疾病的包含根据本发明的至少一种蛋白的融合蛋白。

[0107] 在一个实施方式中,融合蛋白包含至少一种蛋白标签。在一个实施方式中,至少一种蛋白标签选自多组氨酸(His)标签、谷胱甘肽S-转移酶(GST)标签、麦芽糖结合蛋白(MBP)标签、Myc标签、抗生蛋白链菌素(Strep)标签或染料,优选地荧光染料,特别优选地绿色荧光蛋白(GFP)或黄色荧光蛋白(YFP)。

[0108] 在一个实施方式中,根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白包含至少一种修饰。

[0109] 在一个实施方式中,至少一种修饰选自含有D-氨基酸、伪肽键、氨基醇、非蛋白氨基酸、具有修饰的侧基的氨基酸的蛋白和/或环形蛋白。

[0110] 包含修饰的蛋白是更稳定的。

[0111] 在一个实施方式中,将根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白用于治疗与BMP受体激活升高有关的疾病。

[0112] 本发明还涉及包含编码用于诊断和/或治疗原发性或继发性硬化性疾病的根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白的序列的核苷酸序列。

[0113] 在一个实施方式中,核苷酸序列包括SEQ ID NO.8或SEQ ID NO.9。

[0114] 本发明的其它方面涉及用于诊断和/或治疗原发性或继发性硬化性疾病的载体，其包含含有编码根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白的序列的核苷酸序列。

[0115] 应理解“载体”是通过转染或转导将核酸转移至细胞中的核酸载体。在一个实施方式中，载体选自质粒、病毒载体或其它核酸载体，其通过遗传重组(重组体)含有包含编码根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白的序列的核苷酸序列。

[0116] 本发明还涉及用于治疗原发性或继发性硬化性疾病的药物组合物，其包含至少一种根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白。

[0117] 在一个实施方式中，药物组合物是溶液、片剂或胶囊。在一个实施方式中，将根据本发明的蛋白用作植入材料，优选地金属或塑料材料，和/或植入物，优选地假体、螺钉或钉的涂层。

[0118] 在一个实施方式中，在关节内或肌肉局部施用，或者全身或皮下或静脉内或口服施用药物组合物。在一个实施方式中，药物组合物处于适合于关节内、肌肉、皮下、静脉内或口服施用的形式。

[0119] 在一个实施方式中，药物组合物含有10 μ g/kg至100mg/kg体重/施用的剂量的根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白。

[0120] 在其它实施方式中，药物组合物还含有药学上可接受的稀释剂或碱。在一个实施方式中，药学上可接受的稀释剂或碱是水溶液，优选地缓冲水溶液、盐水溶液或甘氨酸水溶液。在一个实施方式中，缓冲水溶液选自pH从pH 5.0至pH 7.0的组氨酸-缓冲水溶液，或者琥珀酸钠-、柠檬酸钠-、磷酸钠-或磷酸钾-缓冲水溶液。在一个实施方式中，缓冲水溶液具有1mmol/l (mM) 至500mM，优选地1mM至50mM的浓度。在其它实施方式中，药学上可接受的稀释剂或碱包括氯化钠，优选地，其浓度在0mM至300mM之间，特别优选地浓度为150mM。

[0121] 在一个实施方式中，药物组合物还包含至少一种药学上可接受的赋形剂。应理解“赋形剂”是调节与pH和/或离子强度有关的生理条件，和/或提高药物组合物的稳定性的化合物。在一个实施方式中，至少一种药学上可接受的赋形剂选自乙酸钠、氯化钠、氯化钾、氯化钙或乳酸钠。

[0122] 在一个实施方式中，药物组合物是无菌的。通过已知方法对药物组合物灭菌。

[0123] 本发明的其它方面涉及药物组合物在原发性或继发性硬化性疾病的诊断和治疗中的用途。

[0124] 在一个实施方式中，药物组合物的使用是用于向受试者施用。应理解“受试者”是个体或患者。在一个实施方式中，受试者选自人或动物，例如，男人、女人、成年人或儿童。在一个实施方式中，选自啮齿类，优选地小鼠、大鼠、仓鼠或豚鼠；狗、兔、农畜，优选地山羊、绵羊、猪；和非人灵长类，优选地黑猩猩、猩猩或大猩猩。在实例中，人已接受了假体植入，例如，已接受了髋关节移植。

[0125] 在一个实施方式中，在TGF β /BMP家族成员的诊断和与BMP受体激活升高有关的疾病的治疗中使用药物组合物。

[0126] 本发明还涉及诊断和/或治疗原发性或继发性硬化性疾病的方法，其包括施用根据本发明的蛋白和/或药物组合物。

[0127] 在一个实施方式中，对人，例如，成年人实施原发性或继发性硬化性疾病的诊断

和/或治疗。

[0128] 对于诊断和/或治疗,将含有药理学活性剂量的一种或多种根据本发明的蛋白的无菌药物组合物施用于患者以诊断和/或治疗原发性或继发性硬化性疾病。

[0129] 在一个实施方式中,局部施用,优选地作为关节内或肌肉注射;或者全身施用,优选地作为皮下、肌内或静脉注射或输注或者通过口服或透皮施用。

[0130] 本发明的其它方面涉及根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白在诊断TGF- β /BMP家族成员或在诊断与BMP受体激活升高有关的疾病中的用途。

[0131] 应理解“BMP受体激活升高”是至少一种BMP受体的激活,其激活是由于BMP受体突变(Shore和Kaplan 2008),优选地组成型激活突变所造成的。应理解“组成型激活突变”是其中在不存在BMP的情况下,至少一种BMP受体激活的突变。

[0132] 本发明的其它方面涉及包含编码根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白的序列的核苷酸序列,和/或包含含有编码根据本发明的蛋白或包含至少一种根据本发明的蛋白的融合蛋白的序列的核苷酸序列的载体在诊断TGF β /BMP家族成员或在诊断与BMP受体激活升高有关的疾病中的用途。

[0133] 除在诊断和/或治疗原发性或继发性硬化性疾病中的用途之外,根据本发明的蛋白适合于生物学研究以及其中关注TGF- β /BMP家族成员的检测的其它应用。这类应用具体地为免疫印迹、细胞的免疫染色(例如,用于流式细胞术和显微镜观察)和ELISA,以及在成像技术,如CT(计算机断层扫描)、PET/CT(正电子发射断层成像)中用作示踪剂。

[0134] 第一构造概念

[0135] 1.具有与SEQ ID NO.1的序列具有至少70、75、80、85、90、95、96、97、98或99%同一性的氨基酸序列的蛋白或其片段用于在诊断和治疗原发性或继发性硬化性疾病中使用。

[0136] 2.包含序列SEQ ID NO.1或SEQ ID NO.2的蛋白,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0137] 3.根据概念1或概念2的蛋白,具有232个氨基酸至801个氨基酸的长度,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0138] 4.根据概念1至3中任一项的蛋白,其特征在于蛋白是转铁蛋白受体(Tfr) 2 α 、转铁蛋白受体(Tfr) 2 β 或Tfr2 α 的胞外域,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0139] 5.用于在诊断和治疗原发性或继发性硬化性疾病中使用的根据概念1至4中任一项的蛋白,其特征在于蛋白是人转铁蛋白受体(Tfr) 2 α (SEQ ID NO.3)、鼠科转铁蛋白受体(Tfr) 2 α (SEQ ID NO.4)、人转铁蛋白受体(Tfr) 2 β (SEQ ID NO.1)或人Tfr2 α 的胞外域(SEQ ID NO.1)、鼠科转铁蛋白受体(Tfr) 2 β (SEQ ID NO.2)或鼠科Tfr2 α 的胞外域(SEQ ID NO.2)。

[0140] 6.包含至少一种根据概念1至5中任一项的蛋白的融合蛋白,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0141] 7.用于在诊断和/或治疗原发性或继发性硬化性疾病中使用的根据概念1至5中任一项的蛋白或根据概念6的融合蛋白,其特征在于蛋白或融合蛋白包含至少一种修饰,其选自含有D-氨基酸、伪肽键、氨基醇、非蛋白氨基酸、具有修饰的侧基的氨基酸的蛋白和/或环形蛋白。

[0142] 8. 根据概念1至5或7中任一项的蛋白或根据概念6或概念7的融合蛋白,用于在诊断和/或治疗与BMP受体激活升高有关的疾病中使用。

[0143] 9. 包含编码根据概念1至5或7中任一项的蛋白或根据概念6或概念7的融合蛋白的序列的核苷酸序列,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0144] 10. 包含根据概念9的核苷酸序列的载体,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0145] 11. 包含至少一种根据概念1至5或7中任一项的蛋白或根据概念6或概念7的融合蛋白的药物组合物,用于在诊断和/或治疗原发性或继发性硬化性疾病中使用。

[0146] 12. 包含至少一种根据概念1至5或7中任一项的蛋白或根据概念6或概念7的融合蛋白的药物组合物,用于在诊断和/或治疗与BMP受体激活升高有关的疾病中使用。

[0147] 13. 根据概念1至5或7中任一项的蛋白或根据概念6或概念7的融合蛋白在诊断TGF- β /BMP家族成员或者在诊断与BMP受体激活升高有关的疾病中的用途。

[0148] 14. 根据概念9的核苷酸序列和/或根据概念10的载体在诊断TGF- β /BMP家族成员或在诊断与BMP受体激活升高有关的疾病中的用途。

[0149] 第二构造:用于在骨疾病、铁代谢紊乱和造血功能障碍的治疗中使用的转铁蛋白受体2抑制剂

[0150] 本发明的第二构造涉及用于在骨疾病、铁代谢紊乱和造血功能障碍的治疗中使用的转铁蛋白受体2抑制剂。

[0151] 骨质疏松症是最常见的骨疾病,其中骨密度和骨质量降低,这与骨折风险升高相关。骨流失可以具有多种原因,并且可以追溯至通过破骨细胞的骨吸收的升高和通过成骨细胞的骨形成的抑制。到目前为止,治疗形式,如二膦酸酯或单克隆抗体,如地诺单抗(抗-RANKL抗体)旨在抑制破骨细胞并因此抑制骨吸收。到目前为止,特异地促进骨合成的骨合成、骨质代谢疗法选择仅以特立帕肽的形式存在,而特立帕肽仅可以在骨质疏松症的严重情况下使用。

[0152] 贫血症的特征在于血液中携氧血红蛋白的量过低,并且它可以是遗传性的或者发展的。最常见的贫血症的形式为缺铁性贫血症,其通常是由于营养不良或出血所造成的。通常在病因学上治疗贫血症,并因此在缺铁性贫血症的情况下,作为药物施用铁。

[0153] 本发明涉及用于在骨疾病、铁代谢紊乱和造血功能障碍的治疗中使用的转铁蛋白受体2的调节或抑制。

[0154] 转铁蛋白受体2(Tfr2)主要在肝脏中表达,在此它调节铁代谢。在小鼠和人中,由于肝脏中肝抗菌肽表达下调以及随后所导致的铁再吸收的升高,Tfr2的丧失导致铁过载。另外,Tfr2是红细胞分化所必需的。

[0155] 本发明的实施方式涉及用于在治疗原发性和/或继发性骨质疏松症中使用的抑制剂。

[0156] 本发明的实施方式涉及用于治疗由肿瘤所造成的贫血症或在慢性疾病(炎症、透析、糖尿病等)的背景内的贫血症的抑制剂。在这种情况下,肝抗菌肽上调,从而通过膜铁转运蛋白的降解,导致铁在单核细胞和巨噬细胞中的保留。Tfr2的可溶性形式将起到(BMP的)配体陷阱(ligand trap,配体捕获)的作用,并因此抑制Tfr2信号转导级联,从而导致肝抗菌肽在肝脏中表达的下调,然后导致铁再吸收的升高和来自MPS的更好提供。

[0157] 本发明的实施方式涉及用于治疗脊髓发育不良综合征、 β 地中海贫血、肾机能不全和慢性病贫血(ACD)的抑制剂。

[0158] 在本发明的实施方式中,抑制剂与至少一种同种型选择形式Tfr2 α 或Tfr2 β 相互作用。

[0159] 在本发明的实施方式中,抑制剂选自抗体或其片段、肽、融合蛋白、适体或RNA干扰,例如,siRNA、shRNA、miRNA、Crispr/Cas、其它重组酶等。

[0160] 以下列举了抑制剂类型的实例(然而,本发明的抑制剂的不同之处在于它们抑制Tfr2,但不抑制这些实例的受试者的生物蛋白):

[0161] 适体:

[0162] 哌加他尼,聚乙二醇化的抗-VEGF(血管内皮生长因子)适体;Adamis AP,Altaweel M,Bressler NM,et al.Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals.Ophthalmology 2006;113(1):23-8。

[0163] 肿瘤治疗中的抗-PDGF(血小板源生长因子)适体:Pietras K,Rubin K,Sjoblom T.Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy.Cancer Res 2002;62:5476-84。

[0164] 肽:

[0165] STI-571:蛋白酪氨酸酶(c-Abl、Bcr-Abl、c-kit)的抑制剂:Biochem Biophys Res Commun.2003年10月3日;309(4):709-17.STI-571:抗癌蛋白-酪氨酸激酶抑制剂(an anticancer protein-tyrosine kinase inhibitor).Roskoski R Jr。

[0166] RNA干扰:

[0167] 用于治疗哮喘的抗-IL-13siRNA:Lively,TN,Kossen,K,Balhorn,A,Koya,T,Zinnen,S,Takeda,K et al.(2008).Effect of chemically modified IL-13 short interfering RNA on development of airway hyperresponsiveness in mice.J Allergy Clin Immunol 121:88-94。

[0168] 用于治疗耐药性前列腺癌的抗-Hsp27 siRNA:Liu,C,Liu,X,Rocchi,P,Qu,F,Iovanna,JL和Peng,L(2014).Arginine-terminated generation 4 PAMAM dendrimer as an effective nanovector for functional siRNA delivery in vitro and in vivo.Bioconjug Chem 25:521-532。

[0169] 重组酶:Karpinski J,Hauber I,Chemnitz J,**Schäfer** C,Paszkowski-Rogacz M,Chakraborty D,Beschorner N,Hofmann-Sieber H,Lange UC,Grundhoff A,Hackmann K,Schrock E,Abi-Ghanem J,Pisabarro MT,Surendranath V,Schambach A,Lindner C,van Lunzen J,Hauber J,Buchholz FDirected evolution of a recombinase that excises the provirus of most HIV-1 primary isolates with high specificity.Nat Biotechnol.2016年4月;34(4):401-9。

[0170] Crispr/Cas:Modzelewski AJ,Chen S,Willis BJ,Lloyd KCK,Wood JA,He L.Efficient mouse genome engineering by CRISPR-EZ technology.Nat Protoc.2018年6月;13(6):1253-1274。

[0171] 抗体:

[0172] 用于治疗自体免疫疾病的抗-细胞因子抗体,如TNF α 或IL-1 β :Susan J.Lee,MD,a,

b Javier Chinen, MD, PhD, c 和 Arthur Kavanaugh, M Immunomodulator therapy: Monoclonal antibodies, fusion proteins, cytokines, and immunoglobulins. J Allergy Clin Immunol. 2010, 125 (2)。

[0173] 嵌合抗原受体T细胞疗法: Cartellieri M, Feldmann A, Koristka S, Arndt C, Löff S, Ehninger A, von Bonin M, Bejestani EP, Ehninger G, Bachmann MP. Switching CAR T cells on and off: a novel modular platform for retargeting of T cells to AML blasts. Blood Cancer J. 2016年8月12日; 6 (8): e458。

[0174] 用于多种癌症类型的免疫疗法中的抗-PD-1抗体: Riley JL. Combination checkpoint blockade—taking melanoma immunotherapy to the next level. N Engl J Med. 2013年7月11日; 369 (2): 187–9. doi:10.1056/NEJMe1305484. Epub 2013年6月2日。

[0175] 在MDS中, 治疗贫血症的抗-TGFβ抗体: Platzbecker et al. Lancet Oncology 2017。

[0176] 在本发明的实施方式中, 抑制剂是抗体或其片段。在本发明的背景中, 应理解片段是包含至少一种Tfr2-结合序列的抗体片段。这种情况下, 举例来说, 片段可以是scFv、Fab或Fc片段。

[0177] 在本发明的实施方式中, 抑制剂是双特异性抗体。在这种情况下, 双特异性抗体对Tfr2具有第一亲合力, 并且对其它组织-特异性膜蛋白具有第二亲合力。在本发明的实施方式中, 组织-特异性膜蛋白是糖蛋白。膜蛋白CD (分化簇) 抗原是优选的。

[0178] 术语“分化簇”(简称CD) 表示细胞的免疫表型表面特征组, 其可以根据生物化学或功能标准分类。由于其组织-特异性表达, CD分子可以用于以组织-特异性方式靶向双特异性抗体。因此, 可以以组织-特异性方式抑制Tfr2。

[0179] 本发明还涉及包含至少一种根据本发明的转铁蛋白受体2抑制剂的药物组合物。

[0180] 在本发明的实施方式中, 药物组合物是溶液、片剂或胶囊。在本发明的实施方式中, 类似地将根据本发明的抑制剂用作植入材料, 优选地金属或塑料材料, 和/或植入物, 优选地假体、螺钉或钉眼的涂层。

[0181] 在一个实施方式中, 以关节内或肌内方式局部施用药物组合物, 或者以皮下或静脉内方式或通过口服施用来全身施用药物组合物。在一个实施方式中, 药物组合物处于适合于关节内、肌内、皮下、静脉内、吸入或口服施用的形式。

[0182] 在一个实施方式中, 药物组合物含有10μg/kg至100mg/kg体重/施用的剂量的根据本发明的抑制剂。

[0183] 在其它实施方式中, 药物组合物还包含药学上可接受的稀释剂或碱。在一个实施方式中, 药学上可接受的稀释剂或碱是水溶液, 优选地缓冲水溶液、盐水溶液或甘氨酸水溶液。在一个实施方式中, 缓冲水溶液选自pH从pH 5.0至pH 7.0的组氨酸-缓冲水溶液, 或者琥珀酸钠-、柠檬酸钠-、磷酸钠-或磷酸钾-缓冲水溶液。在一个实施方式中, 缓冲水溶液具有1mmol/l (mM) 至500mM, 优选地1mM至50mM的浓度。在其它实施方式中, 药学上可接受的稀释剂或碱包括氯化钠, 优选地, 其浓度在0mM至300mM之间, 特别优选地浓度为150mM。

[0184] 在本发明的一个实施方式中, 药物组合物还包含至少一种药学上可接受的赋形剂。应理解“赋形剂”是调节与pH和/或离子强度有关的生理条件, 和/或提高药物组合物的稳定性的化合物。在一个实施方式中, 至少一种药学上可接受的赋形剂选自乙酸钠、氯化

钠、氯化钾、氯化钙或乳酸钠。

[0185] 在本发明的实施方式中,药物组合物是无菌的。通过已知方法对药物组合物灭菌。

[0186] 本发明还涉及根据本发明的抑制剂或药物组合物用于治疗骨疾病、铁代谢紊乱和造血功能障碍的用途。

[0187] 本发明的实施方式涉及用于在治疗原发性和/或继发性骨质疏松症中使用的抑制剂。

[0188] 来自我们实验室的新的数据表明还在骨中表达Tfr2。Tfr2-缺陷型小鼠显示出骨量的两倍增加,骨形成和骨吸收两者均升高。所述数据表明阻断Tfr2可以对红细胞生成和骨代谢两者具有积极的作用。

[0189] 本发明的实施方式涉及用于治疗由肿瘤所造成的贫血症或者在慢性疾病(炎症、透析、糖尿病等)的背景中的贫血症的抑制剂。在这种情况下,肝抗菌肽上调,从而通过膜铁转运蛋白的降解,导致铁在单核细胞和巨噬细胞中的保留。Tfr2的可溶性形式将起到(针对BMP的)配体陷阱的作用,并因此准抑制Tfr2信号转导级联,从而导致肝抗菌肽在肝脏中表达的下调,然后导致铁再吸收的升高和来自MPS的更好提供。

[0190] 本发明的实施方式涉及用于治疗脊髓发育不良综合征、 β 地中海贫血、肾机能不全和慢性病贫血(ACD)的抑制剂。

[0191] 第二构造项

[0192] 1.一种用于治疗骨疾病、铁代谢紊乱和/或造血功能障碍的转铁蛋白受体2抑制剂。

[0193] 2.根据项1的抑制剂,用于治疗骨质疏松症。

[0194] 3.根据项1的抑制剂,用于治疗贫血症。

[0195] 4.根据项1的抑制剂,用于治疗脊髓发育不良综合征。

[0196] 5.根据以上项中任一项的抑制剂,其特征不在于抑制剂选自抗体或其片段、肽、融合蛋白、适体或RNA干扰。

[0197] 6.根据以上项中任一项的抑制剂,其特征不在于抑制剂是抗体或其片段。

[0198] 7.根据以上项中任一项的抑制剂,其特征不在于抑制剂是双特异性抗体。

[0199] 8.包含至少一种根据项1至7中任一项的抑制剂和药学上可接受的赋形剂的药物组合物。

[0200] 9.根据项8的药物组合物用于治疗骨疾病、铁代谢紊乱和造血功能障碍的用途。

[0201] 其它实施方式

[0202] 本发明的构造还提供了以下方面。

[0203] 例如,用于骨质疏松症的拮抗剂(抗体)

[0204] 1.一种治疗或预防或降低人或动物受试者中骨疾病或病况(condition,病症)的风险的方法,所述方法包括拮抗受试者中的转铁蛋白受体2(Tfr2)。

[0205] 2.根据方面1的方法,其中所述方法包括通过拮抗细胞的Tfr2抑制骨细胞(任选成骨细胞)中的p38 MAP激酶途径的信号转导。

[0206] 骨细胞的实例是成骨细胞、骨细胞和破骨细胞。

[0207] 3.根据方面1或2的方法,其中所述方法包括通过拮抗受试者中的Tfr2上调骨细胞(任选成骨细胞)中的Wnt的表达。

- [0208] 受试者中的Tfr2可以是细胞-结合的(如其中细胞是成骨细胞)或可溶性的Tfr2。
- [0209] 4.根据任何以上方面的方法,其中所述方法包括通过拮抗细胞的Tfr2来抑制骨细胞(任选成骨细胞)中硬化蛋白、Dkk1和/或活化素A的活性或表达。
- [0210] 我们的研究显示Dkk1(Wnt拮抗剂)严重下调。
- [0211] 5.根据任何以上方面的方法,其中所述方法包括通过拮抗细胞的Tfr2来抑制骨细胞(任选成骨细胞)中Phex、Dmp1、Dkk1和/或Sost的表达。
- [0212] 6.根据任何以上方面的方法,其中所述方法包括抑制受试者中Tfr2与BMP和/或转铁蛋白的结合。
- [0213] 7.根据方面6的方法,其中BMP是BMP2、4、6和7中的一种或多种。
- [0214] 8.根据方面7的方法,其中BMP是BMP2。
- [0215] 9.根据方面7的方法,其中BMP是BMP4。
- [0216] 10.根据方面7的方法,其中BMP是BMP6。
- [0217] 11.根据方面7的方法,其中BMP是BMP7。
- [0218] 12.根据任何以上方面的方法,其中疾病或病况是骨质疏松症。
- [0219] 例如,骨质疏松症是原发性骨质疏松症。例如,骨质疏松症是继发性骨质疏松症。例如,骨质疏松症是过早的骨质疏松症。例如,骨质疏松症是绝经后妇女中的骨质疏松症。
- [0220] 在实例中,受试者是绝经后妇女或雌性动物。
- [0221] 13.根据任何以上方面的方法,其中所述方法用于造成以下(任选股骨和/或椎骨和/或脊柱骨)中的一种或多种:
- [0222] (a) 骨体积升高;
- [0223] (b) 骨密度升高;
- [0224] (c) 骨小梁数量(Tb.N)升高;
- [0225] (d) 骨小梁厚度(Tb.Th)增加;
- [0226] (e) 骨小梁间隙(Tb.Sp)减小;
- [0227] (f) 骨矿物质密度升高;
- [0228] (g) 骨微矿化密度升高;
- [0229] (h) 骨量升高;和
- [0230] (i) 骨强度升高。
- [0231] 有关这些本领域承认的术语的解释,参见,例如,<http://microctworld.net/trabecular-thickness-tb-th-trabecular-spacing-tb-sp-trabeculardensity-tb-n/>。
- [0232] 任选地,骨是颅骨、下颌、锁骨、肋骨或长骨。
- [0233] 在实例中,本发明的方法用于:-
- [0234] 造成以下(任选股骨和/或椎骨和/或脊柱骨)中的一种或多种:-
- [0235] (a) 小梁骨体积升高;
- [0236] (b) 皮质骨密度升高;
- [0237] (c) 骨小梁数量(Tb.N)升高;
- [0238] (d) 骨小梁厚度(Tb.Th)增加;
- [0239] (e) 骨小梁间隙(Tb.Sp)减小;
- [0240] (f) 小梁骨微矿化密度升高;

[0241] (g) 骨量升高;和(h) 骨强度升高。

[0242] 14. 根据任何以上方面的方法,其中所述方法用于提高受试者中的骨形成和/或降低受试者中的骨吸收。

[0243] 15. 根据任何以上方面的方法,其中所述方法用于提高受试者中的成骨细胞(或其骨形成活性)和/或降低受试者中的破骨细胞(或其骨吸收活性)。

[0244] 在实例中,所述方法用于提高例如受试者中表达成骨相关转录因子(osterix)的成骨细胞或提高成骨相关转录因子(也称为转录因子Sp7)的表达。

[0245] 提高成骨细胞可以包括提高祖细胞向成骨细胞的分化和/或降低成骨细胞的转换。降低破骨细胞可以包括降低祖细胞向破骨细胞的分化和/或提高成骨细胞的转换。

[0246] 16. 根据任何以上方面的方法,其中所述方法用于提高受试者中的骨转换。

[0247] 17. 根据任何以上方面的方法,其中所述方法用于提高受试者中的I型前胶原(pro-collagen type I,I型前胶原蛋白)N末端肽(P1NP)和/或提高受试者中的I型胶原C末端肽(CTX)。

[0248] 任选地,所述方法用于提高受试者中的骨钙素、骨-特异性碱性磷酸酶或OB或NTX或DPD。

[0249] 18. 根据任何以上方面的方法,其中所述方法用于提高受试者中的骨细胞。

[0250] 19. 根据任何以上方面的方法,其中所述方法包括向受试者施用Tfr2拮抗剂,任选地其中拮抗剂是特异性结合至Tfr2的抗-Tfr2抗体或抗体片段。

[0251] 例如,拮抗剂是特异性结合至Tfr2-ECD(例如人Tfr2ECD)的抗体。

[0252] 在本发明的任何方面,在实例中,Tfr2是人Tfr2。

[0253] 20. 根据方面19的方法,其中抗体或片段与选自下列的抗体竞争:1B1(MyBioSource,MBS833691)、3C5(Abnova,H00007036-M01)、CY-TFR(Abnova,MAB6780)和B-6(Santa Cruz Biotechnology,sc-376278)、353816(R&D Systems,MAB3120)和9F8 1C11(Santa Cruz Biotechnology,sc-32271)对Tfr2的结合,如通过表面等离子共振(SPR)所确定的。

[0254] 在实例中,在以下条件进行SPR:-

[0255] • 流速:50μl/min

[0256] • 接触时间:220s

[0257] • 运行缓冲液:HBS-P

[0258] • 37°C

[0259] • 再生:1) 120s Gly-HCl (pH 1.5), 2) 120s 4M MgCl₂, 3) 60s 5M NaCl+50mM NaOH, 4) 60s 100mM NaOH

[0260] 在实例中,通过Biacore™,例如,使用Biacore T200进行SPR并使用评价软件3.1分析。

[0261] 21. 根据任何以上方面的方法,其中所述方法包括向受试者施用硬化蛋白、Dkk1或活化素A拮抗剂,任选地其中拮抗剂是特异性结合至硬化蛋白、Dkk1或活化素A的抗-硬化蛋白抗体或抗体片段。

[0262] 22. 根据方面21的方法,其中向受试者施用多重特异性抗体或片段,其中抗体或片段特异性结合至Tfr2(例如,人Tfr2)和硬化蛋白、Dkk1或活化素A。

- [0263] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和硬化蛋白(例如,人硬化蛋白)。
- [0264] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和Dkk1(例如,人Dkk1)。
- [0265] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和活化素A(例如,人活化素A)。
- [0266] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和CD63(例如,人CD63)。
- [0267] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和粘结蛋白聚糖-3(例如,人粘结蛋白聚糖-3)。
- [0268] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和FGFR1(例如,人FGFR1)。
- [0269] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和LIFR(例如,人LIFR)。
- [0270] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和CD47(例如,人CD47)。
- [0271] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和CX3CR1(例如,人CX3CR1)。
- [0272] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和CD68(例如,人CD68)。
- [0273] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和骨钙素(例如,人骨钙素)。
- [0274] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和DMP-1(例如,人DMP-1)。
- [0275] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和骨黏附蛋白聚糖(例如,人骨黏附蛋白聚糖)。
- [0276] 在实例中,抗体特异性结合至Tfr2(例如,人Tfr2)和碱性磷酸酶(例如,人碱性磷酸酶)。
- [0277] HO、FOP等的激动剂
- [0278] 23.一种治疗或预防人或动物受试者中骨疾病或病况的方法,所述方法包括激动受试者中的转铁蛋白受体2(Tfr2)。
- [0279] 因此,所述方法可以降低受试者中的疾病或病况的风险。
- [0280] 24.根据方面23的方法,其中所述方法包括通过激动细胞的Tfr2刺激骨细胞(任选成骨细胞)中的p38 MAP激酶途径的信号转导。
- [0281] 25.根据方面23或24的方法,其中所述方法包括通过激动细胞的Tfr2下调骨细胞(任选成骨细胞)中的Wnt表达。
- [0282] 26.根据方面23至25中任一项的方法,其中所述方法包括通过激动细胞的Tfr2来刺激骨细胞(任选成骨细胞)中硬化蛋白的活性或表达。
- [0283] 27.根据方面23至26中任一项的方法,其中所述方法包括促进Tfr2的BMP结合。
- [0284] 28.根据方面27的方法,其中BMP是BMP2、4、6和7中的一种或多种。
- [0285] 29.根据方面28的方法,其中BMP是BMP2。
- [0286] 30.根据方面28的方法,其中BMP是BMP4。
- [0287] 31.根据方面28的方法,其中BMP是BMP6。
- [0288] 32.根据方面28的方法,其中BMP是BMP7。
- [0289] 33.根据方面23至32中任一项的方法,其中所述方法包括向受试者施用Tfr2激动剂,任选地其中激动剂是特异性结合至Tfr2(例如,人Tfr2)的抗-Tfr2抗体或抗体片段。
- [0290] 34.根据方面23至33中任一项的方法,其中所述方法包括向受试者施用硬化蛋白、Dkk1或活化素A激动剂,任选地其中激动剂是特异性结合至硬化蛋白、Dkk1或活化素A的抗硬化蛋白、Dkk1或活化素A抗体或抗体片段。

[0291] 在实例中,激动剂抗体是罗莫索珠单抗(romosozumab)或包含其硬化蛋白结合位点。

[0292] 35.根据方面34的方法,其中向受试者施用多重特异性抗体或片段,其中抗体或片段特异性结合至Tfr2和硬化蛋白、Dkk1或活化素A。

[0293] H0、F0P等的BMP捕获剂(trap,陷阱剂,抑制物,阻止物)

[0294] 36.一种治疗或预防人或动物受试者中的疾病或病况的方法,所述方法包括向受试者施用结合BMP的试剂(BMP-binding agent,BMP结合剂),其中试剂与可溶性Tfr2-ECD竞争对BMP的结合,并且其中通过所述BMP介导疾病或病况。

[0295] 因此,所述方法可以降低受试者中的疾病或病况的风险。

[0296] 在实例中,试剂是蛋白试剂,例如,包括一种或多种多肽,如Fc融合多肽。在实例中,试剂是BMP捕获剂,如包含融合至延长半衰期的部分(例如,PEG、血清白蛋白、抗体Fc或域或者抗-血清白蛋白结合部分)的BMP的结合位点的捕获剂。

[0297] 在本文中,对于“Tfr2-ECD-Fc”,Tfr2可以位于Fc的N-或C-末端。例如,在N-至C-方向,Tfr2-ECD-Fc包含Fc和ECD。

[0298] 37.根据方面36的方法,其中试剂是BMP捕获剂。

[0299] 38.根据方面36或37的方法,其中BMP是BMP2。

[0300] 39.根据方面36或37的方法,其中BMP是BMP4。

[0301] 40.根据方面36或37的方法,其中BMP是BMP6。

[0302] 41.根据方面36或37的方法,其中BMP是BMP7。

[0303] 42.根据方面36至41中任一项的方法,其中融合蛋白包含可溶性Tfr2-ECD,其中ECD融合(任选地通过接头,如IEGR接头)至抗体Fc区。

[0304] 任选地,融合蛋白包含可溶性Tfr2-ECD,其中ECD融合(任选地通过接头)至人抗体IgG Fc区。

[0305] 在实例中,在本文中,Fc是人Fc。在实例中,在本文中,Fc是人 γ Fc(例如, γ -1、 γ -2、 γ -3或 γ -4)。在实例中,在本文中,Fc是人 α Fc。在实例中,在本文中,Fc是人 δ Fc。在实例中,在本文中,Fc是人 ϵ Fc。在实例中,在本文中,Fc是人 μ Fc。

[0306] 43.根据方面42的方法,其中融合蛋白包含Tfr2-ECD-Fc二聚体。

[0307] 44.根据方面36至43中任一项的方法,其中试剂对BMP2、4、6和7中的一个、多个或全部的结合比全铁-转铁蛋白和/或BMPR与所述BMP的结合更强烈。

[0308] 45.根据方面36至44中任一项的方法,其中试剂与BMP2的结合比全铁-转铁蛋白和/或BMPRIA与所述BMP的结合更强烈。

[0309] 结合强度可以是KD,例如,如通过SPR所确定的。

[0310] 46.根据方面36至45中任一项的方法,其中试剂与BMP4的结合比全铁-转铁蛋白与所述BMP的结合更强烈。

[0311] 47.根据方面36至46中任一项的方法,其中试剂与BMP6的结合比全铁-转铁蛋白与所述BMP的结合更强烈。

[0312] 48.根据方面36至47中任一项的方法,其中试剂与BMP7的结合比全铁-转铁蛋白与所述BMP的结合更强烈。

[0313] 49.根据方面36至48中任一项的方法,其中试剂包含融合蛋白所包含的Tfr2-ECD,

其中ECD融合(任选地通过接头,如IEGR接头)至抗体Fc区。

[0314] 任选地,融合蛋白包含可溶性Tfr2-ECD,其中ECD融合(任选地通过接头)至人抗体IgG Fc区。

[0315] 在实例中,在本文中,Fc是人Fc。在实例中,在本文中,Fc是人 γ Fc(例如, γ -1、 γ -2、 γ -3或 γ -4)。在实例中,在本文中,Fc是人 α Fc。在实例中,在本文中,Fc是人 δ Fc。在实例中,在本文中,Fc是人 ϵ Fc。在实例中,在本文中,Fc是人 μ Fc。

[0316] 50.根据方面49的方法,其中融合蛋白包含Tfr2-ECD-Fc二聚体。

[0317] 51.根据方面36至50中任一项的方法,其中试剂包含Tfr2胞外域(Tfr2-ECD),任选地其中包含第二部分的融合蛋白包含试剂。

[0318] 52.根据方面51的方法,其中第二部分是用于提高捕获剂在受试者中的半衰期的半衰期延长部分。

[0319] 53.根据方面51或52的方法,其中第二部分选自抗体域(例如,Fc区)、聚乙二醇(PEG)部分、血清白蛋白或抗血清白蛋白结合部分(任选地,抗体片段或域、如scFv、Fab或域抗体(或Nanobody™))。

[0320] 54.根据方面36至53中任一项的方法,其中疾病或病况是骨疾病或病况。

[0321] 具体适应症

[0322] 55.根据任何以上方面的方法,其中疾病或病况是硬化性疾病或病况。

[0323] 任选地,硬化性疾病是骨骼的硬化性疾病。任选地,硬化性疾病是骨骼以外的硬化性疾病。

[0324] 任选地,受试者已接受或正经历类固醇治疗、NSAID治疗、切除术或辐射治疗。任选地,(与Tfr2激动同时或顺序)向受试者施用类固醇治疗、NSAID治疗、切除术或辐射治疗。

[0325] 56.根据任何以上方面的方法,其中疾病或病况是包含病理性骨形成的疾病或病况。

[0326] 57.根据方面55或56的方法,其中疾病或病况是骨化疾病或病况,任选地,异型骨化(HO)疾病或病况或者进行性骨化性纤维发育不良(FOP)疾病或病况。

[0327] 58.根据方面55或56的方法,其中疾病或病况选自异型骨化(HO)(任选地,肌肉HO)、Van Buchem病、硬化性骨化病和进行性骨化性纤维发育不良(FOP)。

[0328] FOP也称为进行性多发性骨化性纤维发育不良、进行性骨化性肌炎或Münchmeyer综合征。

[0329] 任选地,在本文中,H0是创伤-增强的H0,例如,其中创伤是爆发性损伤或髋关节手术或膝盖手术。

[0330] 在实例中,所述方法治疗或预防颅骨、下颌、锁骨、肋骨或长骨的骨疾病。

[0331] 59.根据方面36至58中任一项的方法,其中所述方法包括与Tfr2激动剂或捕获剂同时或顺序向受试者施用视黄酸受体 γ (RAR- γ)激动剂(任选帕罗伐汀)。

[0332] 任选地,向受试者静脉内、皮下或肌肉施用拮抗剂、激动剂、试剂、捕获剂、抗体或片段。

[0333] 60.根据方面36至59中任一项的方法,其中所述方法包括与Tfr2激动剂或捕获剂同时或顺序向受试者施用BMP信号转导拮抗剂。

[0334] 61.根据方面36至60中任一项的方法,其中所述方法抑制受试者中的软骨形成。

[0335] 62. 根据方面36至61中任一项的方法, 其中所述方法抑制受试者中的软骨细胞形成。

[0336] 抗体

[0337] 63. 一种特异地结合Tfr2的抗-Tfr2抗体或片段, 用于在根据任何以上方面的方法中使用或者用于治疗或预防人中骨疾病或病况。

[0338] 64. 根据方面63的抗体或片段, 其中抗体或片段是人抗体或片段。

[0339] 在实例中, 抗体或片段包含一个或多个Tfr2结合位点, 其中每个结合位点包含人VH域(其任选地与人VL域配对)。在实例中, 抗体或片段包含一个或多个Tfr2结合位点, 其中每个结合位点包含人VL域(其任选地与人VH域配对)。

[0340] 例如, 通过核苷酸序列编码每个VH域, 核苷酸序列是人VH、DH和JH基因节段的重组体。例如, VH选自表7中公开的VH基因节段。另外或者作为另外一种选择, 例如, DH选自表7中公开的D基因节段。另外或者作为另外一种选择, 例如, JH选自表7中公开的J基因节段。例如, VH、DH和JH选自表7中公开的基因节段。在实例中, VH是任选地与JH1、JH2、JH3、JH4、JH5或JH6组合的VH1家族的VH基因节段; 例如, 与JH4组合的VH1或者与JH6组合的VH1。在实例中, VH是任选地与JH1、JH2、JH3、JH4、JH5或JH6组合的VH2家族的VH基因节段; 例如, 与JH4组合的VH2或者与JH6组合的VH2。在实例中, VH是任选地与JH1、JH2、JH3、JH4、JH5或JH6组合的VH3家族的VH基因节段; 例如, 与JH4组合的VH3或者与JH6组合的VH3。

[0341] 例如, 通过核苷酸序列编码每个VL域, 核苷酸序列是人VL和JL基因节段的重组体。例如, VL选自表8中公开的VL基因节段。另外或者作为另外一种选择, 例如, JL选自表8中公开的J基因节段。例如, VL和JL选自表8中公开的基因节段。在实例中, VL是任选地与J κ 1、J κ 2、J κ 3、J κ 4或J κ 5组合的V κ 1家族的基因节段; 例如, 与J κ 1组合的V κ 1或者与J κ 4组合的V κ 1。

[0342] 另外或者作为另外一种选择, 抑制剂, Trf2-ECD-Fc, 抗体或片段包含表4中公开的重链恒定区。另外或者作为另外一种选择, 抑制剂, Trf2-ECD-Fc, 抗体或片段包含表4中公开的 λ 轻链恒定区; 作为另外一种选择, 抑制剂, Trf2-ECD-Fc, 抗体或片段包含表4中公开的 κ 轻链恒定区。在实例中, VL是融合至 λ 恒定区的 λ VL。在另一个实例中, VL是融合至 κ 恒定区的 κ VL。在另一个实例中, VL是融合至 λ 恒定区的 κ VL。

[0343] 另外或者作为另外一种选择, 抑制剂, Trf2-ECD-Fc, 抗体或片段包含哺乳动物型糖基化作用, 例如, 仓鼠、小鼠或人糖基化作用。例如, 抑制剂, Trf2-ECD-Fc, 抗体或片段是HEK293细胞的表达产物。例如, 抑制剂, Trf2-ECD-Fc, 抗体或片段是CHO细胞的表达产物。例如, 抑制剂, Trf2-ECD-Fc, 抗体或片段是Cos细胞的表达产物。例如, 抑制剂, Trf2-ECD-Fc, 抗体或片段是毕赤酵母(Picchia)细胞的表达产物。例如, 抑制剂, Trf2-ECD-Fc, 抗体或片段是大肠杆菌(E coli)细胞的表达产物。

[0344] 65. 根据方面63或64的抗体或片段, 其中抗体或片段与参考抗体竞争对人Tfr2(任选人Tfr2-ECD)的结合, 如通过SPR所确定的, 其中参考抗体选自1B1(MyBioSource, MBS833691)、3C5(Abnova, H00007036-M01)、CY-TFR(Abnova, MAB6780)和B-6(Santa Cruz Biotechnology, sc-376278)、353816(R&D Systems, MAB3120)和9F8 1C11(Santa Cruz Biotechnology, sc-32271)。

[0345] 66. 一种包含根据方面63至65中任一项的抗体、片段、二聚体或单体和药学上可接受的稀释剂、赋形剂或载体的药物组合物。

[0346] 67. 根据方面66的组合物, 还包含抗-硬化蛋白抗体(任选罗莫索珠单抗)、抗-Dkk1抗体或抗-活化素A抗体(例如, REGN-2477)或其片段。

[0347] 在实例中, 抗体是抗-硬化蛋白抗体。在实例中, 抗体是罗莫索珠单抗。在实例中, 抗体是抗-Dkk1抗体。在实例中, 抗体是抗-活化素A抗体。在这些实施例中, 疾病或病况可以是FOP。

[0348] Fc融合

[0349] 68. 一种Tfr2-ECD-Fc二聚体, 其任选地用于根据任何以上方面的方法或用于治疗或预防人中的骨疾病或病况。

[0350] 在一个实施方式中, 二聚体包含多肽链的第一和第二拷贝, 其中每条多肽链包含(以N-至C-末端方向)Fc和ECD。在另一个实施方式中, 二聚体包含多肽链的第一和第二拷贝, 其中每条多肽链包含(以N-至C-末端方向)ECD和Fc。

[0351] 本发明还提供了Tfr2-ECD-Fc单体。在实例中, 单体包含多肽链, 其中链包含(以N-至C-末端方向)Fc和ECD。在实例中, 单体包含多肽链, 其中链包含(以N-至C-末端方向)ECD和Fc。

[0352] 在实例中, 本发明的单体、二聚体、蛋白或抑制剂的每条多肽链包含SEQ ID NO:10或与SEQ ID NO:10具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列或者由所述序列组成。

[0353] 在实例中, 本发明的单体、二聚体、蛋白或抑制剂的每条多肽链包含SEQ ID NO:11或与SEQ ID NO:11具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列或者由所述序列组成。

[0354] 在实例中, 本发明的单体、二聚体、蛋白或抑制剂的每条多肽链包含SEQ ID NO:12或与SEQ ID NO:12具有至少70、75、80、85、90、95、96、97、98或99%的同一性的序列或者由所述序列组成。

[0355] 任选地, 二聚体或单体是分离自哺乳动物、CHO、HEK293或Cos细胞的表达产物。

[0356] 69. 一种Tfr2-ECD单体, 其任选地用于根据任何以上方面的方法, 或者用于治疗或预防人中的骨疾病或病况。

[0357] 70. 根据方面68的二聚体或根据方面69的单体, 在本文中ECD和Fc是人的。

[0358] 71. 根据方面68至70中任一项的二聚体或单体, 其中Fc是人 γ Fc。

[0359] 72. 根据方面68至71的抗体或片段, 其中Tfr2-ECD是Tfr2 α -ECD。

[0360] 73. 根据方面68至71的抗体或片段, 其中Tfr2-ECD是Tfr2 β -ECD。

[0361] 74. 根据方面68至73中任一项的二聚体或单体, 其中疾病或病况是病理性骨形成。

[0362] 75. 根据方面68至74中任一项的二聚体或单体, 其中疾病或病况选自骨化疾病或病况, 任选地异型骨化(HO)疾病或病况和进行性骨化性纤维发育不良(FOP)疾病或病况。

76. 根据方面75的二聚体或单体, 其中疾病或病况是BMP-2引起的HO。

[0363] 77. 根据方面75的二聚体或单体, 其中疾病或病况是BMP-4引起的HO。

[0364] 78. 根据方面75的二聚体或单体, 其中疾病或病况是BMP-6引起的HO。

[0365] 79. 根据方面75的二聚体或单体, 其中疾病或病况是BMP-7引起的HO。

[0366] 80. 一种药物组合物, 包含根据方面63至79中任一项的抗体、片段、二聚体或单体和药学上可接受的稀释剂、赋形剂或载体。

- [0367] 81. 根据方面80的组合物, 还包含视黄酸受体 γ (RAR- γ) 激动剂 (任选帕罗伐汀)。
- [0368] 82. 根据方面80或81的组合物, 还包含BMP拮抗剂, 任选地抗BMP抗体或片段。
- [0369] 83. 根据方面82的组合物, 其中BMP是BMP2、4、6或7。
- [0370] 在W02016098079、US20160176956A1和W02017191437中公开了适合的抗-BMP6抗体和片段的实例。
- [0371] 84. 根据任何以上方面的方法、抗体、片段、二聚体、单体或组合物, 其中Tfr2是Tfr2 α 。
- [0372] 85. 根据方面1至83中任一项的方法、抗体、片段、二聚体、单体或组合物, 其中Tfr2是Tfr2 β 。
- [0373] 86. 根据任何以上方面的方法、抗体、片段、二聚体、单体或组合物, 其用于
- [0374] (a) 导致 (任选地股骨和/或椎骨和/或脊柱骨小梁骨体积升高;
- [0375] (b) 导致 (任选地股骨和/或椎骨和/或脊柱骨皮质骨密度升高;
- [0376] (c) 导致 (任选地股骨和/或椎骨和/或脊柱骨骨小梁数量 (Tb.N) 升高;
- [0377] (d) 导致 (任选地股骨和/或椎骨和/或脊柱骨骨小梁厚度 (Tb.Th) 增加;
- [0378] (e) 导致 (任选地股骨和/或椎骨和/或脊柱骨间隙 (Tb.Sp) ;
- [0379] (f) 导致 (任选地股骨和/或椎骨和/或脊柱骨小梁骨微矿化密度升高;
- [0380] (g) 导致 (任选地股骨和/或椎骨和/或脊柱骨骨强度升高;
- [0381] (h) 提高受试者中的骨形成和/或降低受试者中的骨吸收;
- [0382] (i) 提高受试者中的成骨细胞 (或其骨形成活性) 和/或提高受试者中的破骨细胞 (或其骨吸收活性);
- [0383] (j) 提高受试者中的骨转换;
- [0384] (k) 提高受试者中的I型前胶原N末端肽 (P1NP) 和/或提高受试者中的I型胶原C末端肽 (CTX) ;
- [0385] (l) 提高受试者中的骨细胞;
- [0386] (m) 治疗或预防受试者中的硬化性疾病或病况, 任选地骨化疾病或病况, 任选地异型骨化 (HO) 疾病或病况或者进行性骨化性纤维发育不良 (FOP) 疾病或病况;
- [0387] (n) 治疗或预防受试者中的病理性骨形成; 或者
- [0388] (o) 治疗或预防受试者中的异型骨化 (HO) (任选地, 肌肉HO或创伤增强的HO, 例如, 其中创伤是爆发性损伤或髋关节手术或膝盖手术)、Van Buchem病、硬化性骨化病和进行性骨化性纤维发育不良 (FOP)。
- [0389] 在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高受试者中的骨转换。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高受试者中的骨形成 (BFR/BS)。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高受试者中的骨吸收 (Oc.S/BS)。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高或维持受试者中的骨体积, 例如, 如通过微型计算机断层成像所确定的。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高或维持受试者中的小梁骨体积 (BV/TV), 例如, 如通过微型计算机断层成像所确定的。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高或维持受试者中的骨硬度, 例如, 如通过三点弯曲测试所确定的。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高或维持受试者中的骨抗断裂性能, 例如, 如通过三点弯曲测试所确定的。在实例中, Tfr2抑制剂 (例如, 抗体) 用于提高或维持受试者中的骨强度, 例如, 如通过三点弯曲测试所确定的。任

选地,弯曲测试包括对骨施加力。在实例中,在替代非人动物模型,例如,非人灵长类、猪、啮齿类、大鼠或小鼠中进行任何这些确定。

[0390] 在本文的任何构造中,任选地本发明的蛋白或抑制剂包含含有抗体CH2域和CH3域的抗体Fc区。例如,Fc区是 γ -1、 γ -2、 γ -3、 γ -4Fc、 μ 、 δ 、 ϵ 或 α Fc区。优选地,Fc区是 γ -1Fc区。优选地,Fc区是人Fc区。

[0391] 在本文的任何构造中,任选地,医疗装置或容器(例如,封闭且含有无菌内容物的无菌容器或容器)包含本发明的组合物、蛋白或抑制剂。任选地,组合物、蛋白、抑制剂、装置或容器与标签或使用说明书组合以用于治疗 and/or 预防人中的硬化性疾病、骨疾病、铁代谢紊乱或造血功能障碍;任选地其中标签或说明书包括上市授权编号(任选地,FDA或EMA授权编号);任选地其中装置是或包含含有蛋白或抑制剂,例如,抗体或片段的IV或注射装置。

[0392] 任选地,任何蛋白、抑制剂、试剂、抗体或片段包含双特异性形式,其选自DVD-Ig、mAb²、FIT-Ig、mAb-dAb、对接和锁定(dock and lock)、链交换工程域体(SEEDbody)、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、微抗体、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对,具体地mAb²、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼和FIT-Ig,例如,mAb²和FIT-Ig。

[0393] 在一个实施方式中,双特异性形式选自DVD-Ig、mAb²、FIT-Ig、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、 $\kappa\lambda$ -体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、三体(Triple body)、微型抗体、微抗体、TriBi微抗体、scFv-CH₃ KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、Fab-scFv-Fc、四价HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DT-IgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig和zy体(zybody)。

[0394] 在一个实施方式中,双特异性形式选自DVD-Ig、FIT-Ig、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、 $\kappa\lambda$ -体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、三体(Triple body)、微型抗体、微抗体、TriBi微抗体、scFv-CH₃ KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、Fab-scFv-Fc、四价HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DT-IgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig和zy体(zybody),例如,DVD-Ig、FIT-Ig、mAb-dAb、对接和锁定(dock and lock)、链交换工程域体(SEEDbody)、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、微抗体、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对,具体地杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼和FIT-Ig,例如,FIT-Ig。

[0395] 在一个实施方式中,双特异性形式选自DVD-Ig、mAb²、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、κλ-体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、三体(Triple body)、微型抗体、微抗体、TriBi微抗体、scFv-CH₃ KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、Fab-scFv-Fc、四价HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DT-IgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig和zy体(zybody),例如,DVD-Ig、mAb²、mAb-dAb、对接和锁定(dock and lock)、链交换工程域体(SEEDbody)、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、微抗体、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对,具体地mAb²,杵臼、具有通用轻链和电荷对的杵臼和具有通用轻链的杵臼,例如,mAb²。

[0396] 在一个实施方式中,双特异性形式选自DVD-Ig、mAb-dAb、对接和锁定(dock and lock)、Fab-臂交换、链交换工程域体(SEEDbody)、三功能抗体(Triomab)、LUZ-Y、Fcab、κλ-体、正交Fab、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、三体(Triple body)、微型抗体、微抗体、TriBi微抗体、scFv-CH₃ KIH、scFv-CH-CL-scFv、F(ab')₂-scFv、scFv-KIH、Fab-scFv-Fc、四价HCab、ImmTAC、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对、DTIgG、DutaMab、IgG(H)-scFv、scFv-(H) IgG、IgG(L)-scFv、scFv-(L) IgG、IgG(L,H)-Fv、IgG(H)-V、V(H)-IgG、IgG(L)-V、V(L)-IgG、KIH IgG-scFab、2scFv-IgG、IgG-2scFv、scFv4-Ig和zy体(zybody),例如,DVD-Ig、mAb-dAb、对接和锁定(dock and lock)、链交换工程域体(SEEDbody)、sc双链抗体-Fc、双链抗体-Fc、串联scFv-Fc、Fab-scFv-Fc、Fab-scFv、胞内抗体、BiTE、双链抗体、DART、TandAb、sc双链抗体、sc双链抗体-CH₃、双链抗体-CH₃、微抗体、杵臼、具有通用轻链的杵臼、具有通用轻链和电荷对的杵臼、电荷对、具有通用轻链的电荷对,具体地,杵臼、具有通用轻链和电荷对的杵臼和具有通用轻链的杵臼。

[0397] 在实例中,受试者是人。在替代选择中,受试者是非人动物。在实例中,受试者是成年人。在实例中,受试者是儿科患者。

[0398] 例如,同一性%为至少85%。例如,同一性为至少90%。例如,同一性为至少95%。

[0399] 在实例中,本发明的抗体或片段的重链是人γ1、γ-2、γ-3、γ-4、μ、δ、ε或α同种型,优选地γ同种型(例如,IgG4同种型)。在实例中,本发明的抗体或片段的轻链包含人κ恒定区。作为另外一种选择,在实例中,本发明的抗体或片段的轻链包含人λ恒定区。任选地,本发明的抗体包含人IgG4恒定区。任选地,本发明的抗体包含人IgG1恒定区。

[0400] 任选地,抗体是包含与轻链二聚体结合的重链二聚体的4-链抗体。

[0401] 在一个实施方式中,抗体或片段是人抗体或片段。在一个实施方式中,抗体或片段是完全人抗体或片段。在一个实施方式中,抗体或片段是完全人单克隆抗体或片段。

[0402] 在一个实施方式中,抗体或片段是人源化抗体或片段。在一个实施方式中,抗体或

片段是人源化单克隆抗体或片段。

[0403] 在实例中,本发明的抗体或片段以例如 $5 \times 10^6 \text{M}^{-1} \times \text{s}^{-1}$;或者约 $5 \times 10^6 \text{M}^{-1} \times \text{s}^{-1}$ 的 K_a 结合至人Tfr2(或硬化蛋白、活化素A或其它列举的抗原)。在实例中,本发明的抗体或片段以例如 4 或 5s^{-1} ;或者约 4 或 5s^{-1} 的 K_d 结合。在实例中,本发明的抗体或片段以例如 0.07 或 0.14nM ;或者约 0.07 或 0.14nM 的 KD 结合。在一个实施方式中,片段是Fab片段。在一个实施方式中,片段是scFv。

[0404] 优选地,特异性结合至Tfr2(例如,人Tfr2)的抗体或其片段不与其它抗原交叉反应(但是可以任选地与不同Tfr2物种,例如,恒河猴或鼠科交叉反应;和/或可以任选地与不同的Tfr2交叉反应)。可以例如通过免疫测定、BIAcore™或本领域技术人员已知的其它技术鉴别特异性结合至Tfr2抗原的抗体或其片段。如使用实验技术,如放射免疫测定(RIA)和酶联免疫吸附测定(ELISA)所确定的,当以比结合至任何交叉反应抗原更高的亲和力结合至hBMP6抗原时,抗体或其片段特异性结合至Tfr2抗原。通常,特异性或选择性反应将是背景信号或噪音的至少两倍并且更通常地,是背景的大于10倍。有关抗体特异性的讨论,参见,例如,Paul主编,1989,Fundamental Immunology第二版,Raven Press,New York,332-336页。

[0405] 在一个实施方式中,如果抗体识别线性Tfr2表位,则可以产生基于抗原序列的短肽并且可以使用标准技术评价抗体与这些肽的结合。

[0406] 在一个实施方式中,限制性蛋白水解消化和质谱分析可以用于鉴别结合表位。

[0407] 在一个实施方式中,通过X-射线晶体学鉴别表位的接触残基。在一个实施方式中,通过冷冻-电子显微镜鉴别表位的接触残基。在一个实施方式中,通过限制性蛋白水解消化和质谱的组合鉴别表位的接触残基。

[0408] 本文所公开的一种构造、实例、实施方式或方面的任何特征在细节上作必要的修改的情况下与本文中的任何其它构造、实例、实施方式或方面是可组合的。

[0409] 为了实施本发明,还有利地将上述实施方式与权利要求的特征组合。本发明提供了本文所述的用途以及相应方法,如在受试者中的诊断、治疗或预防方法。

[0410] 实施例

[0411] 实施例1:第一构造实施方式

[0412] 以下将参考一些实施方式和附图1至4更详细地解释本发明。在这种情况下,实施方式旨在描述本发明,但不具有限制效果。

[0413] Tfr2胞外域(Tfr2-ECD)的制备

[0414] 通过Genscript(德国)实施整个Tfr2的鼠科胞外域(ECD, aa 103-798)的核酸序列,包括6x His标签。使用杆状病毒表达系统(pOCC211-Tfr2-ECD),在Sf9昆虫细胞中表达重组His-Tfr2-ECD。收集细胞培养上清液并使用HisTrap柱纯化。在使用磷酸盐缓冲盐水溶液(PBS)的清洗步骤之后,通过PBS用咪唑洗脱His-Tfr2ECD-蛋白。

[0415] 表面等离子共振测量(SPR)

[0416] 使用Biacore™ T100(GE Healthcare)分析Tfr2-ECD和BMP(R&D Systems的BMP-2、-4、-6、-7)和BMP受体(R&D Systems的BMPRII、BMPRII)之间的相互作用。

[0417] 为此目的,通过 25°C 下氨基的偶联,将Tfr2-ECD固定在系列S传感器芯片C1(GE Healthcare)上。使用 196mM 1-乙基-3-(3-二甲基氨丙基)碳二亚胺-盐酸盐和 50mM n-羟基

琥珀酰亚胺的混合物,以10 μ l/min的流速,对芯片表面上的羧基激活7分钟。随后,以5 μ l/min的流速注入用乙酸钠缓冲液(pH 4.5)稀释的5 μ g/ml Tfr2-ECD,直至200RU的相对占用(relative occupancy)。通过以10 μ l/min的流速注入1M乙醇胺-HCl(pH 8.5)7分钟使未反应的基团失活。为了制备参考表面,在不注入Tfr2-ECD的情况下进行相同程序。

[0418] 在37 $^{\circ}$ C,以30 μ l/min的流速进行结合测定。通过运行缓冲液(HBS-P, pH 7.4,以及50nM的FeCl₃)稀释每种分析物。以50nM的浓度使用BMP并且以200nM的浓度使用BMP受体。通过在Tfr2-ECD表面上注入分析物300s,随后解离1000s来进行结合测定。在注入结束前10s,相对于基线,读出结合水平值并相对于摩尔质量进行修正。解离1000s后,通过HBS-P以及5M NaCl和50mM NaOH再生芯片表面60s并稳定1000s。使用Biacore™ T100评价软件2.03确定结合参数。

[0419] 图2显示了根据本发明的蛋白与多种BMP配体(BMP2、BMP-4、BMP-6、BMP-7)的结合。

[0420] BMP-2-竞争性ELISA(酶联免疫吸附测定)

[0421] 为了进行BMP-2-竞争性ELISA,使用了R&D Systems的Duo Set BMP-2ELISA试剂盒。在用BMP-2捕获抗体涂板过夜后,将1.5ng/ml BMP-2以及逐渐升高浓度的Tfr2-ECD或BMPR-1A(阳性对照,R&D Systems)加入至测定。在室温下培育1小时并彻底清洗后,根据生产商的说明书加入检测抗体并定量结合至捕获和检测抗体的未结合至Tfr2-ECD或BMPR-1A的BMP-2的量。

[0422] 图3显示了根据本发明的蛋白与BMP,具体地BMP-2的结合。随着根据本发明的蛋白的浓度升高,BMP-2检测抗体的信号降低,尽管BMP-2的浓度保持不变。进展与BMP-2和BMP受体I(BMPR-I)的结合相当。

[0423] 小鼠异位骨化(HO)模型

[0424] 将雄性和雌性C57BL/6小鼠用于HO模型。通过将BMP-2注射到肌肉中引发HO(Woszczyzna等人2012)。

[0425] 对所有小鼠饲喂标准饲料和饮水无限制,并且以每笼五只小鼠一组饲养。将小鼠暴露于12-小时明/暗循环并将空气冷却至23 $^{\circ}$ C(无特殊的无病原体的房间)。以纸板房和垫底材料形式提供装饰(Enrichment)。将小鼠随机分成不同的处理组并随后作为盲法实验进行测定。

[0426] 在0 $^{\circ}$ C,通过使用2.5 μ l 1mg/ml重组BMP-2溶液(Thermo Fisher Scientific)或与47.5 μ l Matrigel(BD Bioscience)混合的2.5 μ l 1mg/ml Tfr2-ECD的处理来检查HO。对于组合治疗,将2.5的1mg/ml重组BMP-2溶液与2.5 μ l 1mg/ml Tfr2-ECD和45 μ l Matrigel混合。将Matrigel混合物注射到10周大的雌性野生型小鼠的胫骨前肌中。两周后,检查腿部。

[0427] μ CT(显微断层成像)和骨微矿化密度

[0428] 使用vivaCT40(Scanco Medical,瑞士)分析骨微结构。使用70kVp,114mA的X射线,以10.5 μ m的分辨率并且以200s的积分时间测量整个小腿骨。将来自Scanco的预定脚本用于分析骨(#1)。

[0429] 小鼠HO模型出现BMP-2-诱导的肌肉组织骨化。图4显示了通过Tfr2-ECD,通过BMP-2的结合,在小鼠(C57BL/6小鼠)中对骨化或HO的抑制。

[0430] 统计分析

[0431] 数据表示为平均值 $\pm$ 标准偏差(SD)。使用Graphpad Prism 6.0-软件产生图和统

计结果。通过柯尔莫哥罗夫-斯米尔诺夫检验确定数据的正态性。就正态分布来说,使用学生T检验双样本检验,通过双-样本比较进行统计学评价。将单因素方差分析(ANOVA)用于具有大于两组的实验。将包括邦费尼罗事后检验的双向方差分析用于分析处理效果。如果数据不对应于正态分布,则将曼-惠特尼U检验和威氏符号秩次检验用于数据分析。

[0432] 实施例2:第二构造实施方式

[0433] 在一个实施方式中,通过微型计算机断层成像所采集的Tfr2-缺陷型小鼠的骨测量显示Tfr2损失在小鼠中导致较高的小梁骨体积(骨体积/总体积,BV/TV)(图5)和较厚的皮质骨(图6)。另外,在不存在Tfr2的情况下,骨质量(硬度参数)(图7)优于野生型小鼠(WT)。通过其中施加作用力以造成骨折的三点弯曲测试确定了骨的机械性质,如抗断裂性能。

[0434] 在图8和图9中,Tfr2-缺陷型小鼠的研究进一步显示Tfr2的缺失导致了更高的骨转换,即更高的骨形成速率(单位骨表面的骨形成速率(BFR/BS)(图8)和更高的骨吸收速率(单位骨表面的破骨细胞表面(Oc.S/BS)(图9)。

[0435] 实施例3:转铁蛋白受体2通过BMP和Wnt信号转导控制骨量和病理性骨形成

[0436] 概要

[0437] 转铁蛋白受体2(Tfr2)主要在肝脏中表达并控制铁平衡。在本文中,我们将Tfr2鉴别为抑制骨形成的骨平衡的调节剂。缺乏Tfr2的小鼠显示出独立于铁平衡和肝Tfr2的骨量和矿化的升高。骨髓移植实验和细胞-特异性Tfr2敲除小鼠的研究证明Tfr2损害BMP-p38MAPK信号转导并且降低了成骨细胞中特异的Wnt抑制剂硬化蛋白的表达。MAPK的再激活或硬化蛋白的过表达挽回了Tfr2敲除小鼠中的骨骼异常。我们还显示Tfr2的胞外域结合BMP并且通过作为诱骗受体起作用来抑制BMP-2-诱导的异位骨化。这些数据表明Tfr2通过调节BMP信号转导来限制骨形成,这可能是通过作为受体或者作为与其它BMP受体复合的共受体与BMP的直接相互作用。最终,Tfr2胞外域可以在与病理性骨形成有关的病况的治疗中是有效的。

[0438] 铁对红细胞的产生、细菌防御和细胞呼吸是不可缺少的¹,然而,铁过量是细胞毒的。因此,全身铁水平维持在较窄的范围内以避免缺铁和贫血,或者导致多器官损伤的铁过载。在其它器官中,骨对铁平衡的变化高度敏感。骨矿物质密度与全身铁浓度²负相关并且患有遗传性色素沉着症(以铁过载为特征的病症)的患者出现过早的骨质疏松症³。除了这些观察结果外,铁平衡和骨转换之间的关系在很大程度上仍是未研究的。

[0439] 通过膳食铁吸收和来自网状内皮系统的铁再循环的平衡来维持全身铁浓度¹。肝抗菌肽是肝脏肽类激素并且是铁平衡的重要调节剂⁴。通过结合至膜铁转运蛋白(铁转运蛋白),肝抗菌肽导致膜铁转运蛋白的内化和降解,借此限制铁向循环系统的排出。这种机制的调控异常导致铁过载。因此,编码肝抗菌肽的基因或肝抗菌肽-调控基因中的突变导致了遗传性色素沉着症⁵。

[0440] 转铁蛋白受体2(Tfr2)是肝抗菌肽的重要调节剂。与人类类似,具有全局或肝-特异性Tfr2缺失的小鼠在肝脏中积累铁⁶⁻⁹。已提出Tfr2通过调控肝抗菌肽表达来控制铁平衡并且它具有两种同种型:Tfr2 α ,其代表全长蛋白并且调控肝脏中的铁平衡,和Tfr2 β ,其缺少胞内和跨膜域并且在脾中的铁流出中起重要作用⁸。到目前为止,其中Tfr2感知并调控全身铁浓度的机制仍未完全理解。然而,全铁转铁蛋白可以结合Tfr2并延长其半衰期¹⁰。因此,已

假定Tfr2感知循环铁并对转铁蛋白饱和度升高起反应而激活肝抗菌肽。

[0441] Tfr2-缺陷型肝细胞具有降低的骨形态发生蛋白(BMP)和p38MAPK/ERK信号转导¹¹⁻¹³,从而使这些途径参与其信号转导。尽管BMP信号转导主要以其在骨发育和出生后的骨平衡中的重要作用而闻名¹⁴,但是它还用作铁平衡的重要调节剂。BMP途径的几种组分(Bmpr1a、Bmpr2、Acvr1、Acvr2a、Smad4、Bmp2、Bmp6)的缺陷或它们的药理学抑制导致铁过载¹⁵⁻²⁰。此外,作为另一种肝抗菌肽表达的调节剂,铁调素调节蛋白已鉴别为肝BMP共受体¹⁶,从而进一步将BMP信号转导与铁平衡相联系。重要地,激活控制铁平衡的BMP受体之一(ACVR1)中的突变导致了罕见的人病症,进行性肌肉骨化症(FOP),其特征在于过量的异位骨化²¹。因此,BMP信号转导的平衡是将骨和铁平衡维持在生理学范围内所必需的。

[0442] 最近的证据表明Tfr2不局限于肝脏,而是也在红系祖细胞中表达以确保它们正确分化^{8,22,23}。由于BMP信号转导在骨骼中具有重要作用^{14,24},因此我们假设Tfr2可以具有另外的肝外功能并调节骨平衡。在本文中,我们证明Tfr2是骨转换的新型负调节剂。通过结合BMP配体,Tfr2激活成骨细胞中的p38MAPK信号转导以诱导Wnt抑制剂硬化蛋白的表达并限制骨形成。最终,通过利用Tfr2胞外域的BMP-结合性质,我们显示在两个临床前模型中该蛋白片段有效抑制异位骨化,从而表明它还可以对治疗病理性骨形成病症有效。

[0443] 结果

[0444] Tfr2-缺陷导致高骨量

[0445] 为了研究铁-感知受体Tfr2是否调控骨平衡,我们研究了铁过载的Tfr2^{-/-}小鼠。与先前报道^{8,25}一致,与野生型(WT)小鼠相比,在Tfr2^{-/-}小鼠中,转铁蛋白饱和度、血清铁和铁蛋白浓度以及肝脏中的铁含量升高(补充图10a-d)。另外,原子吸收测定显示Tfr2^{-/-}小鼠的皮质骨中铁含量较高(补充图10e)。由于铁过载与骨流失有关³,因此我们预期Tfr2^{-/-}小鼠中骨体积降低。然而,与饲料-诱导的铁过载小鼠的低骨量表型相反并且在不同的小鼠色素沉着症模型中,包括Hfe^{-/-}小鼠²⁶和Fpn^{C326S}突变体小鼠²⁷(补充图11a-c),与WT对照相比,Tfr2^{-/-}小鼠显示在股骨和椎骨中小梁骨体积高1.5-3-倍并且皮质骨密度高1.5-倍(图10a-b)。高骨量不依赖于性别且随年龄而降低(补充图12a-b)。在结构水平上,Tfr2^{-/-}椎骨具有升高的骨小梁数量(Tb.N)和厚度(Tb.Th)和降低的间隙(Tb.Sp)(图10c-e)。此外,Tfr2^{-/-}小鼠具有升高的小梁骨微矿化密度(补充图12c),其与升高的骨体积一起提高骨强度(图10f)。

[0446] 我们实施了动态和静态组织形态测定以确定高骨量表型是否是骨形成升高或骨吸收降低的结果。Tfr2缺陷导致成骨细胞和破骨细胞参数升高。在Tfr2^{-/-}小鼠中,骨形成速率和骨形成标志物I型前胶原N末端肽(PINP)的血清浓度升高超过两倍,并且破骨细胞数目和骨吸收标志物I型胶原C末端端肽(CTX)的血清浓度类似地升高(图10g-1)。在所研究的所有年龄中,雄性和雌性两者中均出现高骨转换(补充图12d-e)。有趣地,Tfr2^{-/-}小鼠未受到保护以抵抗卵巢切除-引起的骨流失,而是比WT小鼠的骨流失更多(图10m)。总的来说,这些数据表明Tfr2不仅控制铁平衡,而且还控制骨转换。

[0447] Tfr2-缺陷型小鼠中的高骨量不依赖于肝脏铁状态或肝脏中的Tfr2表达

[0448] 由于Tfr2^{-/-}小鼠具有铁过载和高骨量,而铁过载通常与骨量降低有关^{3,28},因此我们研究了异常铁代谢是否有助于Tfr2^{-/-}小鼠中的骨骼表型。因此,Tfr2^{-/-}小鼠从断奶起接受无铁饲料8周或者从10周大起,用铁-螯合剂去铁胺处理三周。尽管通过两种方案使铁成

功排除,但是在Tfr2^{-/-}小鼠中骨量仍然升高(图11a-d),表明Tfr2^{-/-}小鼠中的高骨量表型不依赖于肝脏铁状态。

[0449] 为了证实这些发现,我们研究了两种不同的Tfr2突变体小鼠模型,其全局缺少Tfr2 β ,但具有导致不同的铁平衡异常的差异Tfr2 α 表达⁸:Tfr2敲入小鼠(KI)全局缺少Tfr2 β ,但具有正常的Tfr2 α 并因此具有正常的铁参数。相反,肝细胞-特异性Tfr2敲除(LCKO)小鼠全局缺乏Tfr2 β ,并且具有局限于肝脏的Tfr2 α 缺陷,但是严重铁-过载。与对照相比,两种模型具有相当的骨体积分数(图11e-f),表明Tfr2 β 和肝脏Tfr2 α 在骨平衡的控制中均不起作用。

[0450] 成骨细胞中的Tfr2-缺陷驱动高骨量表型

[0451] 为了研究Tfr2是否直接通过其在骨细胞中的表达调控骨量,我们确定了多种小鼠组织中的Tfr2 α 和Tfr2 β 的表达。如所期望的,Tfr2 α 主要在肝脏中表达,其次在股骨皮质骨中的表达最高(补充图13a)。还在股骨皮质骨中检测了Tfr2 β mRNA表达,尽管以低得多的水平(脾脏(阳性对照)C_T值:26,骨C_T值:32)。使用结合至Tfr2胞外域并因此检测Tfr2 α 和Tfr2 β 同种型两者的抗体,我们确认了Tfr2在椎骨切片中的表达,从而显示出Tfr2-阳性破骨细胞、成骨细胞和骨细胞(图12a,d)。来自Tfr2^{-/-}小鼠的骨切片的染色显示Tfr2抗体无非特异性结合(补充图12b)。从WT小鼠骨髓分化的破骨细胞和成骨细胞两者均离体表达Tfr2 α 和Tfr2 β mRNA转录本,但是在每种细胞类型中Tfr2 β 的表达极低(Tfr2 β 的数据未显示)。Tfr2 α 在破骨细胞和成骨细胞中是容易可检测的,在成熟破骨细胞(7/7天)和未成熟的成骨细胞(7/21天)中具有峰值表达水平(图12b,e)。免疫细胞化学确认了Tfr2在离体分化的破骨细胞和表达成骨相关转录因子的成骨细胞中的表达(图12c,f)。成骨细胞的亚细胞分离将大部分Tfr2进一步定位至膜部分(图12g)。在细胞质中也检测到了低信号。

[0452] 为了确定Tfr2是否在破骨细胞或在成骨细胞中调控骨转换,我们实施了交互骨髓移植。在WT和Tfr2^{-/-}小鼠中,不论供体基因型如何,骨髓移植对椎骨或股骨体积无影响(图12h),表明造血区室(hematopoietic compartment)中的Tfr2缺陷不负责Tfr2^{-/-}小鼠中的高骨量表型。与这些发现一致,髓系(Lysm-cre)和成熟破骨细胞(Ctsk-cre)中特异的Tfr2缺失不影响脊柱的骨体积(图12i)。然而,Tfr2^{f/f};Lysm-cre小鼠中股骨体积减少,但Tfr2^{f/f};Ctsk-cre小鼠中不减少(补充图20a)。相反,其中Tfr2表达最高的成骨细胞祖细胞中的Tfr2的缺失提高了股骨和脊柱的骨量(图12j),提高了骨小梁数量并且降低了骨小梁间隙(图12k)。Tfr2^{f/f};Ox-cre中骨形成增加,如通过较高的血清PINP水平(图12l)和较高的骨形成速率(图12m)所反映的。最终,成骨细胞中的Tfr2缺失不改变破骨细胞数目,但是往往提高CTX的血清水平(图12n-o)。与发表的Tfr2^{f/f};Lysm-cre小鼠²⁹一致,Tfr2^{f/f};Ctsk-cre和Tfr2^{f/f};Ox-cre小鼠还显示出正常的肝脏铁含量(补充图20b-c)。总体来说,这些数据表明Tfr2在成骨细胞中主要调控骨形成,但是无助于全身铁平衡。

[0453] 成骨细胞中的Tfr2-缺陷减弱了BMP-MAPK信号转导并且导致Wnt抑制剂表达降低

[0454] 由于数据表明了Tfr2在成骨细胞中的直接作用,我们使用来自WT和Tfr2^{-/-}小鼠的原代成骨细胞实施基因组-范围的RNA测序分析以鉴别受Tfr2缺失影响的信号通路。鉴别出总计5,841个差异表达的基因(DEG)。我们实施了基因本体分析以确定受Tfr2缺陷影响的生物过程。Tfr2^{-/-}成骨细胞中上调的基因属于蛋白分泌和肌肉系统的负调控生物过程。相反,在Tfr2^{-/-}成骨细胞中参与骨化、胞外基质组织、Wnt信号转导的负调控和Smad磷酸化的基因

下调(补充图21a)。这些数据与分子功能和细胞组分分析一致,其显示出参与糖胺聚糖和肝素结合,和BMP受体结合以及蛋白质胞外基质和胶原蛋白形成的基因的产生不足(补充图21a)。基因集富集分析进一步表明参与晚期成骨细胞分化和Wnt信号转导的基因的产生不足,后者与Wnt抑制剂Dickkopf-1(Dkk1)的显著抑制有关(补充图21b-c)。在补充表2中提供了显著富集的基因集的完整列表。

[0455] Dkk1和Sost(编码Wnt抑制剂硬化蛋白)在离体Tfr2^{-/-}成骨细胞中下调程度最大的25个基因中(图13a)。通过qPCR验证了两种Wnt抑制剂的表达降低,并且这与Wnt靶标基因(Axin2、Lef1、Cd44)的表达升高一致(补充图21c)。在得自Tfr2^{f/f};Osx-cre小鼠的成骨细胞中,Dkk1和Sost mRNA水平也下调(图13b)。此外,骨细胞-相关基因Phex和Dmp1的表达降低(补充图21c)。重要地,骨细胞标志物的表达受损不是由于Tfr2^{-/-}骨中骨细胞数目的降低(WT:8.73±2.74相对于Tfr2^{-/-}:9.77±0.85个骨细胞/骨体积分数)所造成的。还在Tfr2^{-/-}小鼠血清中检测到了低浓度的硬化蛋白和Dkk1(图13c),以及更大比例的具有高β-连环蛋白和轴蛋白抑制蛋白-2表达的成骨细胞/骨细胞(图13d)。最终,使用β-连环蛋白的免疫印迹分析,在分化7天的Tfr2^{-/-}成骨细胞中证实了Wnt信号转导的升高(图13e)。

[0456] 深度测序分析还表明Tfr2^{-/-}成骨细胞中BMP信号转导降低,并且最近的研究显示Sost和Dkk1是BMP信号转导的下游靶标^{30,31}。因此,我们分析了Tfr2^{-/-}和WT成骨细胞中的BMP靶标基因以及基础典型(Smad)和非典型(MAPK)BMP信号通路。在Tfr2^{-/-}成骨细胞中Smad6和Id1显著下调,而Id2不同(补充图21c)。与WT成骨细胞相比,Smad 1/5/8磷酸化以及ERK和p38激活两者在Tfr2^{-/-}中降低(图13e)。此外,BMP-2处理后,BMP信号转导的激活显示在Tfr2^{-/-}成骨细胞中Smad激活延迟,而p38MAPK和ERK的激活持续受损(图13f-g)。Tfr2^{-/-}成骨细胞中的非典型BMP信号转导的激活的降低不局限于BMP-2,而是在BMP-4后也能观察到,并且对于BMP-6刺激来说,降低程度较低(图13h,补充图21d)。总体上,成骨细胞中的Tfr2缺陷导致BMP信号转导受损并且Wnt途径的激活升高。

[0457] MAPK信号转导的再激活或硬化蛋白的过表达挽回了Tfr2-缺陷中的高骨量

[0458] 我们接下来研究了Tfr2-介导的Sost表达控制的潜在机制,因为这可能是对骨的Tfr2-依赖性作用的主要驱动因素。体外使用Tfr2^{-/-}成骨细胞,我们确认了用BMP-2、BMP-4和BMP-7刺激后,Sost表达诱导的缺少(图14a)。相反,WT和Tfr2^{-/-}成骨细胞中Tfr2的过表达显著提高了Sost,特别是在用BMP-2刺激后(图14b,补充图22a)。为了测试硬化蛋白在Tfr2^{-/-}小鼠中对产生高骨量的影响,我们将Tfr2^{-/-}小鼠与在晚期成骨细胞/骨细胞中过表达人SOST(受Dmp1-8kb-启动子控制)的小鼠杂交。SOST的过表达显著降低了Tfr2^{-/-}小鼠中的脊椎小梁骨体积(图14c)并且归一化了骨形成速率(图14d)。与具有正常Sost表达的小鼠相比,在Tfr2^{-/-}和在成骨细胞/骨细胞中过表达SOST的WT小鼠中破骨细胞-覆盖的骨表面更大(补充图22b)。

[0459] 先前的研究表明BMP通过BMP-Smad和BMPMAPK途径刺激Sost表达^{30,31}。由于在Tfr2^{-/-}成骨细胞中pERK和pp38最显著降低,并且Tfr2^{-/-}成骨细胞中Smad1和Smad4过表达均不能恢复Sost mRNA水平(补充图22c-f),因此我们使用茴香霉素再激活MAPK途径以挽回Sost表达。使用茴香霉素处理引起ERK和p38磷酸化(补充图22g)并且以100nM茴香霉素,提高了Tfr2^{-/-}和WT成骨细胞中的Sost mRNA表达:Tfr2^{-/-}成骨细胞中提高19倍,WT成骨细胞中提高14倍。类似地,用茴香霉素处理Tfr2^{-/-}小鼠3周使得硬化蛋白的血清水平升高(图14f),

成骨细胞数目降低(图14g)并且骨体积降低回到WT水平(图14h)。茴香霉素处理未改变破骨细胞数目(补充图22h)。最终,我们研究了哪些特异性MAPK途径,ERK还是p38调控Sost表达。仅Mapk14(编码p38 α)的过表达,而不是Mapk1(编码ERK2)恢复了Tfr2^{-/-}成骨细胞中降低的Sost水平(图20i-j)。因此,Tfr2经由p38MAPK信号通路通过诱导Sost表达控制骨量。

[0460] Tfr2是BMP的新型相互作用伴侣

[0461] 最后,我们思考Tfr2如何可以导致成骨细胞中BMP-MAPK信号转导受损,并因此研究Tfr2是否可以起BMP受体的作用。我们产生了含有Tfr2胞外域(Tfr2-ECD)的蛋白片段,使用SDS-PAGE和免疫印迹确认其存在(补充图23a)并且实施了表面等离子共振(SPR)分析。固定在传感器芯片上的Tfr2-ECD比全铁转铁蛋白(Tf),唯一已知的Tfr2配体¹⁰更强烈地结合BMP-2、4、6和7(图21a,补充图23b)。BMP-2、4和6还在高盐浓度下结合至Tfr2-ECD,其用于降低非特异性结合,尽管水平较低(补充图23c)。还使用Tfr2-ECD作为分析物以及固定在传感器芯片上的BMP-2或BMP-4,使用相反方法验证了Tfr2-BMP的结合(补充图23d-e)。使用这种方法,我们通过稳态分析确定了Tfr2/BMP-2 (488.0 ± 37.0 nM)和Tfr2/BMP-4 (409.1 ± 39.0 nM)结合的K_d值。全铁-Tf以微摩尔级浓度结合至Tfr2,表明K_d值在微摩尔范围内(补充图23f)。全铁-Tf和BMP-2不竞争对Tfr2的结合,因为BMP2然后全铁-Tf或者全铁-Tf然后BMP-2的连续注射不会改变初始结合反应(补充图23g-h)。有趣地,BMP-2和全铁-Tf的同时注射导致了比任一种单独的分析物要强得多的对Tfr2的结合反应(图15b)。由于BMP通常通过由I型和II型BMP受体组成的受体复合物进行信号转导,我们测试BMPR是否结合至Tfr2-ECD。BMPR-IA和BMPR-II两者具有弱于BMP的结合反应(图15a,补充图23i)。使用其中它们两者均过表达的细胞系统进一步研究了Tfr2和BMPR-IA的物理相互作用。通过免疫共沉淀确认了它们的相互作用并且这种相互作用不受BMP-2的存在的影响(补充图23j)。以BMPR-IA作为对照,使用竞争性夹心ELISA进一步验证了BMP-2与Tfr2-ECD的结合(图15c)。其它SPR实验显示BMPR-IA与Tfr2竞争对BMP-2的结合,因为添加逐渐升高的浓度的BMPR-IA降低了BMP-2与Tfr2-ECD的结合(图15d)。值得注意地,对于与Tfr2/BMP-2的竞争,需要高纳摩尔浓度的BMPR-IA。

[0462] 我们使用异位骨化模型验证了Tfr2-ECD的体内BMP配体结合性质。在该模型中,将BMP-2注射到小鼠的胫骨前肌肌肉中,这导致肌肉骨化³²。尽管单独的BMP-2导致WT小鼠中肌肉的异位骨化,但是Tfr2-ECD的添加完全终止了这种作用(图15e,补充图24a-b),表明Tfr2结合BMP-2并且防止它结合至其同源BMPR。Tfr2^{-/-}小鼠中的类似实验表明与WT小鼠相比,在BMP-2注射后,异位骨化升高,其通过Tfr2-ECD的共施用而被显著抑制(图15e,补充图25a-b)。因此,除了确认Tfr2-ECD的体内功能性BMP-结合活性外,这些数据强调了Tfr2作为BMP-依赖性背景中骨化的负调节剂的作用。

[0463] Tfr2-ECD在两种不同的临床前模型中有效抑制异位骨化。由于Tfr2-ECD降低BMP-2-诱导的异位骨化的稳健作用,我们将Tfr2-ECD与帕罗伐汀相比较,帕罗伐汀是间接抑制BMP信号转导的选择性视黄酸受体- γ 激动剂³³,并且目前处于用于FOP治疗的临床研究。Tfr2ECD用作对肌肉的单一局部治疗或者用作全身治疗(每隔一天i.p.注射)。两种方案在两周后以与每日帕罗伐汀施用类似的效力降低了WT小鼠中BMP-2-诱导的异位骨化(图15f)。在WT小鼠中,在第8天的异位骨化的软骨形成期的研究显示全身Tfr2-ECD和帕罗伐汀处理两者均抑制软骨细胞数目和软骨的产生(补充图24c-d)。对于血细胞计数、铁参数、骨

平衡或内脏的一般形态来说,未观察到全身Tfr2-ECD治疗的副作用。最后,我们在创伤-加强的异位骨化(创伤、爆发性损伤或髋关节置换手术后的常见并发症)模型中测试了两种化合物。单一剂量的Tfr2-ECD以与帕罗伐汀相当的效果抑制肌肉中的新的骨形成(图15g)。每天用布洛芬治疗(髋关节手术后常见的异位骨化治疗³⁴)不会预防创伤-引起的异位骨化(图15g)。这些数据表明Tfr2-ECD是异位骨化的有效抑制剂并且代表了用于治疗过量骨形成病症的潜在新型治疗策略。

[0464] 讨论

[0465] 使用一系列基因修饰小鼠和体外分析,这些研究鉴别了Tfr2作为成骨细胞中BMP和Wnt信号转导的调节剂的新作用。Tfr2与BMP配体和受体相互作用,激活p38MAPK信号转导,并且诱导Wnt抑制剂Sost表达。这反过来阻断了典型的Wnt信号转导,借此限制骨形成和骨量增加(图14k)。此外,作为预防异位骨化的新型治疗策略,对处于诱骗受体形式的Tfr2-ECD的BMP-结合性质的利用是有希望的(图15h),由于目前对于先天性或创伤-引起的异位骨化尚无特效治疗,因此它受到了特别关注。

[0466] 除其在全身铁水平调控中的熟知功能外⁶⁻⁹,Tfr2确保了正确的红血球生成^{8,22,23}。我们的研究目前已鉴别了Tfr2的新型肝外作用,通过成骨细胞中的直接作用控制骨量,尽管不可以排除在骨髓细胞,包括早期破骨细胞中较小的影响。在铁-调控蛋白中,这似乎是Tfr2的独特性质,因为所有其它所研究的小鼠血色素沉着症模型显示出低骨量。因此,其它已在Hfe-依赖性血色素沉着症患者³以及在Hfe-和肝抗菌肽-缺陷型小鼠^{35,36}中显示出低骨量。在两种情况下,提出骨形成的抑制是低骨量的主要潜在机制^{35,37}。然而,由于Hfe-和肝抗菌肽-缺陷型小鼠两者是铁-过载的,因此不清楚低骨量是否是铁过载的负面作用的间接结果,或者Hfe和肝抗菌肽是否在骨细胞中发挥直接作用。重要地,Tfr2-缺陷型小鼠中的高骨量不依赖于铁的状态和Tfr2的肝脏功能,这表明Tfr2在成骨细胞(即基质产生的控制)和肝细胞(即肝抗菌肽表达和全身铁平衡的调控)中具有不同的作用。

[0467] 尽管Tfr2作为铁平衡的调节剂已有超过15年的历史,但是其作用机制仍是难懂的。Tfr2-缺陷型肝细胞中Smad1/5/8和MAPK/ERK信号转导的水平降低表明可能涉及BMP信号转导^{11,13,38},但是仍不清楚Tfr2如何激活BMP信号转导。先前在肝细胞中的研究表明Tfr2与Hfe和铁调素调节蛋白形成三元复合物以激活肝抗菌肽表达¹²。然而,我们的数据提供了体外和体内证据,这表明Tfr2可以直接结合BMP并激活下游信号转导。BMP-2与Tfr2的结合比全铁-Tf(唯一已知的Tfr2配体¹⁰)高超过10倍。与BMP-BMPR相互作用相比^{39,40},BMP-Tfr2结合显著较低,表明Tfr2可以起作用以微调BMP信号转导。由于我们的研究还显示Tfr2与BMPR直接相互作用,因此还需要研究Tfr2是否结合单独的或处于与BMPR和/或其它BMP共受体的多受体复合物内的BMP。除作为BMP(共)-受体的这些Tfr2的第一指示外,将需要其它实验来限定解释化学计量的准确结合亲和力,受体二聚化或寡聚的可能性和Tfr2-ECD的纯度。有趣地,全铁-Tf和BMP-2的组合对Tfr2的结合比任一种单独的全铁-Tf或BMP-2更加强烈,表明全铁-Tf仅可以在存在BMP的情况下显示出显著的Tfr2结合。由于已将肝内皮细胞鉴别为在肝细胞上局部起作用以控制肝抗菌肽表达和铁平衡的BMP-2和BMP-6的主要生产者,因此这可能是特别重要的^{41,42}。尽管已认识到铁调素调节蛋白传输BMP-6信号来调节肝抗菌肽表达,但BMP-6仍可以诱导铁调素调节蛋白敲除小鼠中的肝抗菌肽表达⁴³,表明必需包括了其它受体。因此,新鉴别的Tfr2的BMP-结合性质可以代表通过BMP的肝抗菌肽的调控

中缺少的一环。

[0468] 我们的研究进一步显示Tfr2^{-/-}成骨细胞中BMP下游信号转导,具体地BMP-p38MAPK途径受损,从而导致典型的Wnt抑制剂Dkk1和Sost的表达降低,这两种抑制剂均为骨形成的有效的负调节剂⁴⁴⁻⁴⁶。近期工作已显示BMP-2通过激活BMP依赖性Smad信号转导刺激Dkk1和Sost的表达,并且就Dkk1来说,还通过经由ERK和p38的MAPK信号转导^{30,47}。最近的研究,包括我们自己的研究显示还通过成骨细胞中p38MAPK信号转导诱导Sost的表达^{30,48}。因此,激活全部三种MAPK的茴香霉素处理⁴⁹挽回了Tfr2^{-/-}小鼠中的Sost表达并恢复了骨量。与Tfr2^{-/-}小鼠的表型类似并且与BMP信号转导对成骨细胞骨形成的支持作用的直观理解相反,成骨细胞中Bmpr1a或Acvr1的靶向破坏损害了Sost的表达并导致了高骨量^{47,50}。另外,用重组硬化蛋白离体处理Bmpr1a缺陷型颅顶恢复了正常的骨形态⁴⁷,类似地Tfr2^{-/-}小鼠中SOST的过表达将骨体积降低回到WT水平。然而,Tfr2缺陷型小鼠不能完全表型模拟Bmpr1a-或Sost-缺陷型小鼠的骨骼表型。考虑成骨细胞/骨细胞-特异性敲除株,全部三个基因的缺失导致了高骨量。然而,尽管Bmpr1a-条件性敲除小鼠具有低骨转换^{30,47,51},但是Tfr2-条件性敲除小鼠具有高骨形成速率和正常的破骨细胞参数,并且Sost-条件性敲除小鼠具有高骨形成速率⁵²。尚未在Sost-条件性敲除小鼠中报道破骨细胞参数,但是这些参数在Sost^{-/-}小鼠中是正常的⁴⁴。尽管骨形成的增加似乎是Tfr2-和Sost-条件性敲除小鼠中高骨量的主要机制,但是Bmpr1a-条件性敲除小鼠中的高骨量的主要驱动因素似乎是由于成骨细胞中低RANKL与OPG比所造成的降低的破骨细胞发生^{30,47}。据报道这种机制不依赖于Wnt信号转导,因为Sost的过表达不能挽回Bmpr1a条件性敲除小鼠中的破骨细胞表型⁴⁷。相反,Tfr2^{-/-}小鼠的破骨细胞数目升高且RANKL与OPG比升高(WT:0.225±0.046,Tfr2^{-/-}:0.696±0.120,n=4,p=0.0003),但是与Bmpr1a-条件性敲除小鼠类似,不能通过Sost过表达挽回这种表型。有趣地,成骨细胞中的Bmpr2缺陷导致高骨量,以及相伴的高骨形成速率和正常的骨吸收⁵³,从而表明Tfr2与Bmpr2具有比与Bmpr1a更多的相似性。最终,Bmpr1a-条件性敲除小鼠具有无组织的骨基质,从而导致骨强度降低^{54,55}。这与Tfr2^{-/-}和Sost^{-/-}小鼠相反,两者具有正常的骨基质组织和骨强度升高⁴⁴。总体来说,尽管具有相似性,表明Tfr2以与BMPR类似的方式或甚至结合BMPR起作用,但是其它途径似乎独立于BMP信号转导来介导其对骨的作用。总之,Tfr2明显是成骨细胞中Sost表达的重要调节剂并且在BMP和Wnt信号转导之间提供了另一种联系。

[0469] 最后,我们显示Tfr2-ECD结合BMP并用作诱骗受体的能力降低了两种不同的临床前模型中的异位骨化。异位骨化是在爆发性损伤之后,如在士兵和平民、烧伤受害者和全髋关节假体置换受体中所发现的严重且常见的医学并发症。多达30%经历髋关节置换术的患者和50%的重伤士兵出现异位骨化^{56,57}。广泛的异位骨化也是FOP的标志,这是通过激活BMP I型受体ACVR1中的突变所引起的罕见人类疾病²¹。由于这种突变的鉴别,BMP信号转导已涉及异位骨化的病理发生。迄今为止,用于FOP和创伤-引起的异位骨化的治疗选择是有限的。辐射和非类固醇抗-风湿药物经常用于抑制手术-引起的异位骨化,其具有不同程度的成功³⁴。在我们的研究中,布洛芬不能显著降低异位骨化。在FOP中,糖皮质激素用于降低急性发作期间的炎症。然而,它们不能阻断进行性骨化。最近,抗-活化素抗体雷帕霉素和帕罗伐汀已显示通过不同机制降低FOP临床前模型中的异位骨化^{33,58-60}。帕罗伐汀间接干扰BMP途径,并且是目前唯一处于临床研究的药物。通过Tfr2ECD的局部和全身治疗两者均以与帕罗

伐汀类似的程度抑制异位骨化。在2周治疗期内,用Tfr2-ECD全身治疗未对铁或骨代谢显示出副作用,这与缺少Tfr2 β 的小鼠具有相关性,这与Tfr2-ECD具有类似的结构,在脾脏中不具有升高的铁含量⁸,并因此可以预期铁代谢的差异。未来需要更长期且更广泛的药理学研究来确定地解决Tfr2-ECD的安全性谱。

[0470] 总的来说,我们已揭示Tfr2通过调节BMP-p38MAPK-Wnt信号传导轴成为骨量的新型调节剂,并且将Tfr2-ECD鉴别为治疗异位骨化和过量骨形成病症的有希望的治疗选择。

[0471] 方法

[0472] 小鼠

[0473] 先前描述了Tfr2 $^{-/-}$ 小鼠和仅缺少Tfr2 β 同种型的Tfr2敲入(Tfr2-KI)小鼠的产生⁸。在Tfr2-KI小鼠(129X1/svJ)的背景中产生了条件性Tfr2敲除小鼠,借此产生了还全局缺少Tfr2 β 的细胞类型特异的Tfr2 α 敲除小鼠。使用白蛋白cre(albuminre)(sv129背景)产生了肝脏-特异性Tfr2-敲除小鼠(LCKO)。为了使成骨细胞前体中的Tfr2缺失,使用了多西环素-可抑制性成骨相关转录因子-cre(Osx-cre)⁶¹。对繁殖配对和小于5周的小鼠施用多西环素(0.5g/l)。对于成熟破骨细胞中Tfr2 α 的缺失,使用组织蛋白酶K cre(Ctskcre)⁶²。将溶菌酶M(Lysm-cre)用于早期破骨细胞中的Tfr2缺失⁶³。将Tfr2 $^{f/f}$;Osx-cre、Tfr2 $^{f/f}$;Lysm-cre和Tfr2 $^{f/f}$;Ctsk-cre小鼠处于混合sv129/C57BL/6背景中。将同窝小鼠用作对照。

[0474] 为了获得人硬化蛋白过量产生的Tfr2-缺陷型小鼠,将Tfr2 $^{-/-}$ 小鼠与Dmp1-SOST转基因小鼠杂交以获得Tfr2 $^{-/-}$;Dmp1-SOST $^{+/tg}$ 小鼠⁶⁴。先前描述了具有点突变(C326S)的膜铁转运蛋白敲入小鼠和Hfe敲除小鼠的产生^{26,27}。通常使用标准PCR规程对所有小鼠基因分型。

[0475] 体内实验

[0476] 所有动物程序经实验动物关怀委员会和Landesdirektion Sachsen的批准。所有小鼠饲喂标准饮食且饮水无限制,并将小鼠以每笼5只动物一组饲养。将小鼠暴露于12h明/暗循环和23℃的空调房间(无特殊的无病原体的房间)。以纸板房和垫底材料形式提供装饰。将小鼠随机分配至处理组并以盲法方式进行后续分析。

[0477] 骨表型分型:使用10-12周大的雄性和雌性Tfr2 $^{-/-}$ 和野生型小鼠。对于Tfr2 $^{-/-}$ 小鼠的鉴别,还使用了更大的小鼠(6和12个月)。在10-12周,将雄性Tfr2 $^{f/f}$;Osx-cre和Tfr2 $^{f/f}$;Ctsk-cre以及相应的cre-阴性同窝对照处死以用于骨表型分析。

[0478] 卵巢切除术:将雌性11-14-周大的WT或Tfr2 $^{-/-}$ 小鼠双侧卵巢切除或进行假手术。四周后,将小鼠处死以用于进一步分析。每组由510只小鼠组成。

[0479] 高铁饲料:WT动物从断奶(14天大)起接受2%的高铁标准饲料直至处死(处理8周)。每组四-五只小鼠。

[0480] 无铁饲料:雄性Tfr2 $^{-/-}$ 和WT小鼠从断奶起接受无铁饲料(Envigo,Italy)直至10周大。对照小鼠接受含有0.2g铁/kg食物的标准饲料(GLOBAL DIET 2018,Envigo,Italy)。每组九只小鼠。

[0481] 铁螯合:十周大的雄性Tfr2 $^{-/-}$ 和WT小鼠每天接受腹膜内注射250mg/kg DFO(Sigma,德国,溶于PBS)或PBS,实施三周。使用3-5只小鼠,将该实验独立进行两次。

[0482] 完全骨髓移植:从12周大的雄性Tfr2 $^{-/-}$ 小鼠或WT对照分离骨髓细胞。通过眶后静脉丛注射,将两百万个细胞植入到致死辐射(8Gy)的雄性WT或Tfr2 $^{-/-}$ 小鼠中。使用流式细胞术,每四周监测移植效率。16周后,将小鼠处死以用于骨分析。以每组7-12只小鼠,将该实验

分别进行两次。

[0483] 茴香霉素处理:用5mg/kg茴香霉素(i.p.) 3x/周处理雌性11-周大的WT和Tfr2^{-/-}小鼠,实施三周。以每组5只小鼠,将该实验分别进行两次。

[0484] 异位骨化(HO):根据Wosczyzna等人³²,实施HO模型。简要地,将2.5μl 1mg/ml的重组BMP-2(Thermo Fisher)或2.5μl 1mg/ml的Tfr2-ECD与47.5μl基质胶(matrigel)(BD Bioscience)在冰上混合。对于局部组合治疗,将2.5μl BMP-2与2.5μl Tfr2-ECD和45μl基质胶混合。将基质胶混合物注射到10周大的雌性WT和Tfr2-缺陷型小鼠的胫骨前肌肌肉的中部。使用先前发表的规程⁵⁸,通过口服灌胃用帕罗伐汀每天处理一些小鼠。将帕罗伐汀(Hycultec)溶于DMSO并用玉米油1:4稀释。小鼠前五天接受100μg/小鼠的剂量的帕罗伐汀,并且在其余实验中接受50μg/小鼠(6-14天)。BMP-2注射后两周,收获腿部用于分析。以每组3-11只小鼠,将该实验进行三次。为了分析HO的软骨形成期,我们如上所述实施了在第8天终止的实验。以每组4-6只小鼠,实施该实验一次。

[0485] 对于全身Tfr2-ECD处理,每隔一天用Tfr2-ECD腹膜内处理WT小鼠两周。在对肌肉注射BMP-2/基质胶后,小鼠前10天每次注射接受250μg Tfr2-ECD(10mg/kg BW),并且剩余时间接受每次注射125μg(5mg/kg BW)。以每组8-10只小鼠,将该实验进行一次。落重HO:根据Liu等人,以少量修改⁶⁵实施该实验。将雌性10-12周大的WT小鼠麻醉并置于塑料容器的脊上,在其上使右腿弯曲,从而使股骨水平放置。小鼠接受在50μl基质胶中混合的1μg BMP-2的注射。然后,将16g的不锈钢珠(16mm直径)从80cm高的距离处下落到四头肌肌肉上。小鼠接受单一剂量的1μg Tfr2-ECD,其与BMP-2/基质胶混合物共注射,或者帕罗伐汀(Hycultec),其通过口服灌胃每天施用。将帕罗伐汀溶于DMSO并用玉米油1:4稀释。小鼠前五天接受100μg/小鼠的剂量的帕罗伐汀,并且在其余实验中接受50μg/小鼠(621天)。一组小鼠通过饮水接受100mg/ml剂量的布洛芬,水每隔一天更换一次⁶⁶。在整个实验持续期间,小鼠接受甲硫咪唑(200mg/kg)以减少疼痛。以每组6只小鼠,将该实验进行两次。

[0486] 微-CT、骨微矿化密度和生物力学测试

[0487] 使用vivaCT40(Scanco Medical,瑞士)分析骨微结构。使用70kVp,114mA的X射线能,以10.5μm的分辨率并且以200ms的积分时间,对股骨和第四腰椎成像。使用150个切片,在生长板以下的干骺端的20个切片中评价股骨中的小梁骨。在脊椎骨中,测量两个生长板之间的150个切片。在股骨中干中确定皮质骨(150个切片)。将来自Scanco的预定脚本用于评价。

[0488] 通过定量背向散射电子扫描电子显微镜(qBSE-SEM)确定骨微矿化密度。将来自12周大的雄性小鼠的中性缓冲的福尔马林固定的第四腰椎(L4)包埋在甲基丙烯酸酯中。通过样品切下纵向块体面(block face),然后将其抛光并使用高分辨率溅射仪(Agar Scientific Stanstead UK)用25nm的碳涂覆。使用配备有Deben 24mm 4-象限背向散射检测器(Deben,Bury St.Edmunds,UK)的Tescan VEGA3 XMU(Tescan,Brno,Czech Republic),使用20kV,0.4nA的背向散射电子和17mm的工作距离对样品成像。通过与卤化二甲基丙烯酸酯标准品比较来确定骨矿化密度,并且将八间隔伪彩色图像用于表示微矿化刻度,如前所述⁶⁷。

[0489] 引入股骨的三点弯曲以评价骨强度。将股骨保存在70%的乙醇中并在测试前在PBS中复水。使用来自德国Zwick的zwicki-Line进行机械测试。对股骨干前侧施加负荷以测

量最大断裂负荷 (F最大 (Fmax), N)。

[0490] 骨组织形态测定

[0491] 在处死前五天和两天,对小鼠注射20mg/kg钙黄绿素 (Sigma)。如上所述⁶⁸,进行动态骨组织形态测定。简要地,将第三腰椎和胫骨固定在4%PBS-缓冲的多聚甲醛中并在逐渐升高的乙醇系列中脱水。随后,将骨包埋在甲基丙烯酸酯中并切成7 μ m切片以评价荧光钙黄绿素标记。使用荧光显微术分析未染色的切片以确定矿化表面/骨表面 (MS/BS)、矿化沉积率 (MAR) 和骨形成速率/骨表面 (BFR/BS) 以及骨体积/总体积 (BV/TV)、骨小梁数量 (Tb.N)、骨小梁间隙 (Tb.Sp) 和骨小梁厚度 (Tb.Th)。

[0492] 为了确定破骨细胞数目,使用Osteosoft (Merck) 对股骨和第四腰椎脱钙一周,脱水并包埋在石蜡中。将耐酒石酸酸性磷酸酯酶 (TRAP) 染色用于评价单位骨表面的破骨细胞表面 (Oc.S/BS)。按照国际标准,使用Osteomeasure软件 (Osteometrics, USA) 分析骨切片。

[0493] 为了评价使用苏木精/曙红染色的H0,使小腿 (H0) 和大腿 (落重) 脱钙、脱水并包埋在石蜡中。将四肢切成2 μ m切片并用苏木精/曙红染色。对于冯库萨 (von Kossa) /范吉森 (van Gieson) 和番红O染色,使腿部不脱钙,包埋到甲基丙烯酸酯中并切成4 μ m厚的切片。

[0494] 免疫组织化学

[0495] 对于免疫组织化学分析,将来自WT和Tfr2^{-/-}骨的石蜡切片脱蜡、复水和抗原热修复。在室温下,使用0.3% H₂O₂/PBS阻断内源过氧化物酶活性10min,并且在室温下,使用VECTASTAIN Elite ABC试剂盒 (VECTOR Laboratories) 的封闭缓冲液封闭非特异性结合位点45min。然后,将切片与抗-Tfr2抗体 (H-140, Santa Cruz)、 β -连环蛋白抗体 (BD Bioscience) 或轴蛋白抑制蛋白-2抗体 (#ab107613, Abcam) 一起在4°C温育过夜。随后,用缀合至生物素的抗-小鼠第二抗体处理载玻片,然后以二氨基联苯胺作为底物 (DAKO),使用抗生物素蛋白-缀合的HRP显色。使用Zeiss Axio Imager M.1显微镜检查载玻片。对每个载玻片的两百个细胞计数并根据未染色 (0)、弱染色 (1) 和强染色 (2) 分级。

[0496] 肝脏和骨中的铁含量的测量

[0497] 如先前所报道的,使用20mg干燥肝脏组织确定肝脏中的铁浓度⁸。如先前所报道的,使用原子吸收光谱 (PerkinElmer Analyst 800) 确定干燥骨组织 (骨髓-冲洗的股骨和胫骨) 的骨中铁浓度⁶⁹。

[0498] 血清分析

[0499] 使用ELISA (IDS, 德国) 测量血清中的骨转换标志物C末端端肽 (CTX) 和I型前胶原N末端肽 (P1NP)。使用来自R&D Systems (德国) 的ELISA测量血清dickkopf-1和BMP-2。使用来自Alpco (USA) 的ELISA测量小鼠硬化蛋白。使用用于临床分析的常规方法,在Roche Modular PPE分析仪上测量血清铁蛋白和铁。使用来自Randox的总铁结合能力试剂盒确定转铁蛋白饱和度。

[0500] 原代破骨细胞培养

[0501] 从WT小鼠骨髓产生破骨细胞并以1 $\times 10^6$ 个细胞/cm²的密度接种。将具有10% FCS、1% 青霉素/链霉素和25ng/ml M-CSF (均来自Life Technologies) 的 α -MEM (Biochrom, 德国) 用于分化的前两天。然后,对于培养的剩余阶段 (5-7天),对培养基补充30ng/ml RANKL (Life Technologies)。在多个时间点分离RNA,并将成熟破骨细胞用于免疫荧光分析。

[0502] 原代成骨细胞培养

[0503] 使用标准成骨培养基,在具有10%FCS、1%青霉素/链霉素(Life Technologies, 德国)的DMEM中,从骨髓分化原代鼠科成骨细胞。在多个时间点分离RNA,并将第7天的成骨细胞用于Tfr2的免疫荧光分析和用于深度测序分析。

[0504] 信号转导研究:用50ng/ml BMP-2、BMP-4或BMP-6处理第7天分化的细胞0、20和40min并在蛋白裂解缓冲液中裂解(至少两个独立实验,每个实验为3n)。将茴香霉素用于激活第7天分化的成骨细胞的MAPK信号转导。用100nM茴香霉素处理细胞20min以用于后续蛋白质分析。对于RNA分离和基因表达检测,用不同剂量的茴香霉素处理细胞24h(两个独立实验,每个实验为3n)。

[0505] 过表达:使用Fugene HD (Roche)⁸,将1μg含有鼠科Tfr2基因的pcDNA3.1载体转染到70-80%汇合的细胞中。将空pcDNA3.1载体用作对照。另外,过表达载体pCMV6-MAPK1 (ERK2)、pCMV6-MAPK14 (p38α)、pCMV6-Smad1和pCMV6-Smad4购自Origene以过表达各个信号转导蛋白。将pCMV6-入门载体用作对照。使用来自4只不同小鼠的细胞,对每个实验进行一次。

[0506] RNA分离、RT和实时PCR

[0507] 通过高纯度RNA分离试剂盒 (Roche) 从细胞培养物分离RNA,并且通过在液氮中挤压冲洗的骨(股骨和胫骨)并在Trifast (Peglab, 德国) 中收集骨粉,从小鼠的骨中分离RNA。使用ultraturrax (IKA, 德国),将其它器官直接在Trifast中匀质化。使用Superscript II (Invitrogen, 德国) 反转录500ng RNA,并随后使用标准规程 (Life Technologies),用于SYBR绿-基实时PCR。使用ΔΔCT法计算结果并表示为相对于β-肌动蛋白(或当指明时, GAPDH) mRNA水平的x-倍升高。

[0508] 蛋白质分离和免疫印迹

[0509] 将细胞在含有20mM Tris/HCl pH 7.4、1%SDS和蛋白酶抑制剂(complete mini, Roche, 德国)的缓冲液中裂解。为了从组织中分离蛋白,使用Trifast程序的蛋白部分并根据生产商的规程将其进一步处理。使用BCA法(Pierce, 德国) 确定蛋白浓度。将20μg热变性蛋白上样至10%凝胶,分离并转移至0.2μm硝化纤维素膜(Whatman, 德国)。在用5%脱脂奶粉或2%BSA在具有1%吐温-20的Tris-缓冲盐水(TBS-T) 中的溶液封闭1h后,将膜与信号转导蛋白的第一抗体(Cell Signaling) 培育过夜并用TBS-T清洗三次。对于Tfr2的检测,使用来自Santa Cruz (德国) 的H-140抗体,其检测对应于氨基酸531-670的表位。所使用的其它抗体为:核纤层蛋白A/C(#sc-20681, Santa Cruz)、连接蛋白-43(#3512, Cell Signaling)、微管蛋白(#2146, Cell Signaling)、GAPDH(#5G4, Hytest)。此后,将膜与适当的HRP缀合的第二抗体一起在RT培育1h。最后,用TBS-T清洗膜并与ECL底物(Thermo Fisher Scientific) 培育。使用MF-ChemiBIS 3.2生物成像系统(Biostep, 德国) 使蛋白显像。

[0510] 亚细胞蛋白分离

[0511] 对于成骨细胞的细胞质、膜和核蛋白提取物的分离,从三只WT小鼠的骨髓中分化原代鼠科成骨细胞。在第7天,收获细胞并根据生产商的建议,使用亚细胞蛋白分离试剂盒(Thermo Fisher Scientific) 分离亚细胞蛋白部分。

[0512] 免疫荧光染色

[0513] 对于免疫荧光染色,使细胞在载玻片上生长。在所期望的时间点,用100%甲醇固定细胞15min,用0.5%Triton X-100透性化10min并在清洗三次后,用1%BSA在PBS中的溶

液封闭30min。然后,将细胞与抗-小鼠Tfr2抗体(H-140,Santa Cruz)一起在4℃培育过夜。清洗后,用抗-小鼠成骨相关转录因子抗体(sc-393325,Santa Cruz)或鬼笔环肽在RT下染色1h。随后,清洗细胞并与Alexa Fluor 488或Alexa Fluor 594-标记的第二抗体(Life Technologies)一起培育1h,清洗并用DAPI染色5min。再次清洗后,将载玻片包埋在封固剂(Dako)小液滴中。使用Zeiss LSM 510共聚焦显微镜(Zeiss EC PlanNeofluar 40x/1.30i1)检查载玻片,并采集照片并用Zen 2009软件处理。

[0514] 免疫共沉淀

[0515] 按照生产商的规程,使用**TransIT®-LT1**转染试剂(Mirus Bio LLC),用7.5μg pCMV-3XFLAG-BMP-1A和7.5μg pcDNA3-TFR2-HA或pcDNA3-LDLR-HA转染人肝癌细胞(HuH7)。转染后48小时,当指明时,用50ng/ml BMP-2(Peprotech)处理细胞1.5h。将细胞裂解液与预平衡的抗-FLAG M2亲和凝胶(Sigma Aldrich)一起在4℃培育2h。然后,用50μl含有300μg/ml 3X FLAG肽(Sigma Aldrich)的裂解缓冲液洗脱样品。将总裂解液的10%用作输入(In)。使用αFLAG和αHA抗体(1:1,000,Sigma Aldrich)使免疫识别显像。

[0516] 下一代测序和数据分析

[0517] 使用Trifast,从Tfr2^{-/-}和WT小鼠的第7天分化细胞分离总RNA。使用Agilent生物分析仪评价RNA质量,并使用完整指数≥9的总RNA。根据生产商的说明,使用NEBNext多聚(A)mRNA磁性分离模块(Magnetic Isolation Module)从1μg总RNA分离mRNA。化学断裂后,对样品进行链-特异的RNA-Seq文库制备(Ultra Directional RNA Library Prep,NEB)。在接头连接后(寡核苷酸1:5'-ACA CTC TTT CCC TAC ACG ACG CTC TTC CGA TCT-3',寡核苷酸2:5'-P-GAT CGG AAG AGC ACA CGT CTG AAC TCC AGT CAC-3'),通过珠纯化(XP, Beckman Coulter)除去残余寡核苷酸。在后续PCR富集(15个循环)期间,对文库建立索引(引物1:Oligo_Seq AAT GAT ACG GCG ACC ACC GAG ATC TAC ACT CTT TCC CTA CAC GAC GCT CTT CCG ATC T,引物2:GTG ACT GGA GTT CAG ACG TGT GCT CTT CCG ATC T,引物3:CAA GCA GAA GAC GGC ATA CGA GAT NNNNN GTG ACT GGA GTT)。在最终纯化(XP珠)后,定量文库(Qubit dsDNA HS测定试剂盒,Invitrogen),等摩尔混合并在多个泳道上分布以用于在Illumina HiSeq 2500和Illumina NextSeq 500上的75bp单一读序测序。

[0518] 测序后,将FastQC(<http://www.bioinformatics.babraham.ac.uk/>)用于基础质量控制。然后,使用GSNAP(2014-12-17版)以及已知的剪接位点(Ensembl v75)作为支持,将读序绘制成小鼠基因组图谱(mm10)。通过研究定位读序中的冗余度,评价文库的多样性。使用Ensembl v75基因注释,通过对唯一定位的读序运行featureCounts(v1.4.6)获得了具有每个基因的计数的表。基于文库大小和对KO和WT之间差异表达的测试,通过R软件包DESeq2(v1.6.3)进行原始读序计数的归一化。调整(Benjamini-Hochberg)p-值小于0.05的基因被认为是差异表达的。

[0519] 通过Cytoscape 3.2.1和ClueGO插件进行基因本体分析。仅将显著(p<0.05)上调或下调的基因进行分析。使用Broad Institute GSEA软件“GseaPreRanked”工具(nperm=1000,set_min=5,set_max=500,得分(scoring)_方案(scheme)=加权(weighted))进行基因集富集分析(GSEA)以分析通过它们在Tfr2^{-/-}和WT条件之间的表达的log2倍数变化排序的18,106个非冗余基因符号的列表。在用于分析的总计58个基因集,包括50个标志基因集中,三个成骨细胞特异性基因集来自Park等人和Zaidi等人,并且五个其它基因集来自

Sanjuan-Pla等人⁷⁰⁻⁷²。

[0520] Tfr2胞外域的表达

[0521] 通过Genscript (德国) 合成了鼠科Tfr2的全长胞外域 (ECD, aa 103-798) 的编码序列。使用杆状病毒表达系统 (pOCC211-Tfr2-ECD), 在Sf9昆虫细胞中表达重组His-MBP-c3-Tfr2-ECD。收获培养上清液 (5升), 过滤并加载到HisTrap柱上, 在用PBS彻底清洗后, 使用具有250mM咪唑的PBS洗脱Tfr2-ECD蛋白。第一次蛋白质生产中的得率为40mg, 第二次为46mg Tfr2-ECD。使用还原条件的SDS-PAGE的考马斯亮蓝染色和免疫印迹分析Tfr2的存在。

[0522] 通过来自Cusabio的商品化生产的Tfr2-ECD重复实验。该片段也含有完整的ECD (aa 103-798) 并且仅溶于PBS。

[0523] 表面等离子共振结合和动力学分析

[0524] 使用Biacore T100仪 (GE Healthcare) 分析了Tfr2-ECD与全铁-Tf、BMP配体 (BMP-2、-4、-6、-7, R&D Systems) 以及BMP受体 (BMPR-IA、BMPR-II, R&D Systems) 的相互作用。将Tfr2-ECD、BMP-2和BMP-4在25℃通过其胺基固定在Series S传感器芯片C1 (GE Healthcare) 上。以10μl/min的流速, 用含有196mM 1-乙基-3-(3-二甲基氨基丙基) 碳二亚胺盐酸盐和50mM N-羟基琥珀酰亚胺的混合物对芯片表面上的羧基激活7min。随后, 以5μl/min的流速注入用乙酸钠缓冲液 (pH 4.5) 稀释的5μg/ml Tfr2-ECD或者2μg/ml BMP2或BMP-4, 直至实现约200RU (在Tfr2-ECD的情况下) 或者100RU (在BMP-2和BMP-4的情况下) 的固定化水平。通过注入1M乙醇胺-HCl, pH 8.5 (7min, 10μL/min) 使未反应的基团失活。根据相同规程, 但是省略Tfr2注射, 产生了参考表面。

[0525] 在37℃, 以30μl/min的流速进行结合分析。通过运行缓冲液 (HBS-P (pH 7.4), 150mM NaCl, 补充有50nM FeCl₃) 稀释每种分析物。在一些实验中, 将500mM NaCl用于降低潜在的非特异性结合。以指定浓度 (0-50nM) 使用BMP配体; 以2-200nM的浓度使用BMP受体, 以2.5-100μM使用全铁-Tf并且以10⁻⁵, 000nM使用Tfr2-ECD。在一些实验中, 同时注入BMP-2/BMPR-IA和BMP-2/全铁-Tf。实施全铁-Tf的浓度-依赖性结合, 且无中间体再生。

[0526] 对于结合分析, 在Tfr2-ECD表面上注射分析物240s或300s, 随后进行1000s解离。在注入结束前10s, 相对于基线响应, 从参考信号记录结合水平值。然后, 将它们对各自分子量进行修正。解离1000s后, 用5M NaCl, 50mM NaOH在HBS-P中的溶液使芯片表面再生60s, 随后是1000s的稳定时间。

[0527] 通过灵敏度增强的Biacore T200 (GE Healthcare) 进行5次连续分析物注入的单循环动力学以确定全铁-Tf/Tfr2的K_d值范围以及对于结合至BMP-2和BMP-4表面的Tfr2的解离速率k_{off} (复合物稳定性)。通过使用1:1朗格缪尔结合模型的全局拟合进行动力学拟合 (A+B=AB)。引入稳态分析以确定亲和力 (K_d)。因此, 通过将平衡时所测量的结合反应对浓度的拟合, 认为Tfr2与BMP-2或BMP-4是1:1相互作用。为了对图实现稳健的拟合和典型的曲线, 分析了更宽范围的Tfr2浓度 (10-5000nM)。通过Biacore™ T200评价软件3.1评价结合和动力学参数。

[0528] BMP-2竞争性ELISA

[0529] 使用来自R&D Systems的Duo Set BMP-2 ELISA试剂盒。在用BMP2捕获抗体涂板过夜后, 将1.5ng/ml BMP-2与逐渐升高浓度的Tfr2-ECD或BMPR-IA (阳性对照, R&D Systems) 一起加入。在RT下培育1小时并彻底清洗后, 根据生产商的规程加入检测抗体并定量BMP-2

的量。将该实验独立进行至少3次。

[0530] 统计分析

[0531] 数据表示为平均值±标准偏差(SD)。使用Graphpad Prism 6.0软件产生图和统计结果。通过柯尔莫哥罗夫-斯米尔诺夫检验确定数据的正态性。在数据正态分布的情况下,使用双侧学生t检验,进行两组比较的统计学评价。将单因素方差分析(ANOVA)用于具有大于两组的实验。将具有邦费罗尼事后检验的双向方差分析用于分析基因型和处理效果。如果数据不是正态分布,则将曼-惠特尼检验和威氏符号秩次检验用于分析数据。使用柯尔莫哥罗夫-斯米尔诺夫检验比较来自qBSE-SEM灰度图像的微矿化密度的频率分布⁶⁷。

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[0609] 表1: 参考符号列表

[0610] 1 BMP

[0611] 2 BMP-I

[0612] 3 BMP-II

- [0613] 4 Tfr2 α
 [0614] 5 蛋白
 [0615] 6 Smad蛋白
 [0616] 7 MAP激酶
 [0617] 8 磷酸化
 [0618] 9 成骨细胞基因
 [0619] 10 骨形成
 [0620] 11 捕获抗体
 [0621] 12 检测抗体
 [0622] 表2:序列

[0623]

SEQ ID NO:	
1	人 Tfr2-ECD 氨基酸序列
2	小鼠 Tfr2-ECD 氨基酸序列
3	人 Tfr2 α 氨基酸序列
4	小鼠 Tfr2 α 氨基酸序列
5	人 Tfr2 蛋白酶相关 (PA) 域氨基酸序列
6	人肽酶 M28 域氨基酸序列
7	人 Tfr-样二聚化域氨基酸序列
8	人 Tfr2 核苷酸序列
9	小鼠 Tfr2 核苷酸序列
10	人 Tfr2-his 氨基酸序列
11	人 Tfr2-Fc (N-末端融合, 即 Fc 在 Tfr2 ECD 的 N-末端侧融合) 氨基酸序列
12	人 Tfr2 (C-末端融合) 氨基酸序列

[0624] 蛋白-序列

[0625] 人Tfr2a (SEQ ID NO:3)

[0626]

MERLWGLFQRAQQLSPRSSQTVYQVRVEGPRKGHLEEEEDGEEGAETLAHFCEMELRGPEP
 LGSRRPQPNLIPWAAAGRRAAPYLVL TALLIFTGAFL LGYVAFRGSCQACGDSVLVSEDVNYE
 PDLDFHQGRLYWSDLQAMFLQLGEGRLED TIRQTSLRERVAGSAGMAALTQDIRAALS RQKL
 DHVWTDTHYVGLQFPDPAHPNTLHWVDEAGKVGEQLPLEDPDVYCPYSAIGNVTGELVYAHY
 GRPEDLQDLRARGVDPVGRLLLVRVGVISFAQKV TNAQDFGAQGVLIYPEPADFSQDPPKPSL
 SSQQAVYGHVHLGTGDPYTPGFPSFNQTQFP PVASSGLPSIPAQPISADIASRLLRKLKGPVAP
 QEWQGSLLGSPYHLGPGPRLRLVNNHRTSTPINNIFGCIEGRSEPDHYVVIGAQRDAWGPGA
 AKSAVGTAILELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSGSTEWLEGYLSVLHLKAVVY
 VSLDNAVLGDDKFHAKTSPLTSLIESVLKQVDSPNHSGQTLYEQVVFTNPSWDAEVIRPLPMD
 SSAYSFTA FVGVPAVEFSFMEDDQAYPFLHTKEDTYENLHKVLQGRLPAVAQAVAQLAGQLLI
 RLSHDRLLPLDFGRYGDVLRHIGNLNEFSGDLKARGLTLQWVYSARGDYIRAAEKL RQEIYSS
 EERDERLTRMYNVRIMRVEFYFLSQYVSPADSPFRHIFMGRGDHTLGALLDHLRLLRNSSGT
 PGATSSTGFQESRFRRQLALLTWTLQGAANALSGDWWNIDNNF

[0627] 人Tfr2b=Tfr2-ECD (SEQ ID NO:1)

- [0628] RGSCQACGDSVLVSEDEVNYEPDLDFHQGRLYWSDLQAMFLQLGEGRLDITRQTSLRERV
AGSAGMAALTQDIRAALSRLKLDHWVTDTHYVGLQFPDPAHPNTLHWVDEAGKVGEQLPLED
PDVYCPYSAIGNVTGELVYAHYGRPEDLQDLRARGVDPVGRLLLVRVGVISFAQKVNAQDFG
AQGVLIYPEPADFSQDPPKPSLSSQQAVYGHVHLGTGDPYTPGFPSFNQTQFPPVASSGLPSI
PAQPISADIASRLRLKGPVAPQEWQGSLLGSPYHLGPGPRLRLVNNHRTSTPINNIFGCIEG
RSEPDHYVWIGAQRDAWGPGAASAVGTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFG
SVGSTEWLEGYLSVLHLKAVVYVSLDNAVLGDDKFHAKTSPLLSLIESVLKQVDSPNHSGQTL
YEQVFTNPSSWDAEVIRPLPMDSSAYSFTAFVGVPAVEFSFMEDDQAYPFLHTKEDTYENLHK
VLQGRLPAAVAQAQLAGQLLIRLSDRLPLDFGRYGDVLRHIGNLNEFSGDLKARGTLQ
WVYSARGDYIRAAEKLKQEIYSSEERDERLTRMYNVRIMRVEFYFLSQYVSPADSPFRHIFMG
RGDHTLGALLDHLRLRLSNSSGTPGATSSTGFQESRFRRLALLTWTLQGAANALSGDVWNID
NNF
- [0629] 小鼠Tfr2a (SEQ ID NO:4)
MEQRWGLLRVQWSPRPSQTIYRRVEGPQLEHLEEDREEGAELPAQFCPMELKGPEHLG
SCPGRSIPWAAAGRKAAPYLVLTLLIFTGAFLLGYVAFRGSCQACGDSVLVDEDEVNPEDSG
RTTLYWSDLQAMFLRFLGEGRMEDTIRLTSLRERVAGSARMATLVQDILDKLSRQKLDHWVTD
THYVGLQFPDPAHANTLHWVDADGSVQEQLPLEDPEVYCPYSATGNATGKLVYAHYGRSED
QDLKAGVELAGSLLLVRVGITSFAQKVAVAQDFGAQGVLIYPDPSDFSQDPHPGLSSHQAV
YGHVHLGTGDPYTPGFPSFNQTQFPPVESSGLPSIPAQPISADIADQLLRKLTGPVAPQEWKG
[0630] HLSGSPYRLGPGDLRLVNNHRVSTPISNIFACIEGFAEPDHYVWIGAQRDAWGPGAASAV
GTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSGATEWLEGYLSVLHLKAVVYVSLDN
SVLGDGKFHAKTSPLLSLIENILKQVDSPNHSGQTLYEQVALTHPSWDAEVIQPLPMDSSAYS
FTAFAGVPAVEFSFMEDDRVYPFLHTKEDTYENLHKMLRGRLPVVQAVAQLAGQLLIRLSD
HLLPLDFGRYGDVLRHIGNLNEFSGDLKERGLTLQWVYSARGDYIRAAEKLKQEIYSSEERND
RLMRMYNVRIMRVEFYFLSQYVSPADSPFRHIFLGQGDHTLGALVDHLRMLRADGSGAASSRL
TAGLGFQESRFRRLALLTWTLQGAANALSGDVWNIDNNF
- [0631] 小鼠Tfr2-ECD (SEQ ID NO:2)
RGSCQACGDSVLVDEDEVNPEDSGRTTLYWSDLQAMFLRFLGEGRMEDTIRLTSLRERVAGS
ARMATLVQDILDKLSRQKLDHWVTDTHYVGLQFPDPAHANTLHWVDADGSVQEQLPLEDPEV
YCPYSATGNATGKLVYAHYGRSEDQDLKAGVELAGSLLLVRVGITSFAQKVAVAQDFGAQGV
LIYPDPSDFSQDPHPGLSSHQAVYGHVHLGTGDPYTPGFPSFNQTQFPPVESSGLPSIPAQ
PISADIADQLLRKLTGPVAPQEWKGHLSGSPYRLGPGDLRLVNNHRVSTPISNIFACIEGFAE
[0632] PDHYVWIGAQRDAWGPGAASAVGTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSG
ATEWLEGYLSVLHLKAVVYVSLDNSVLGDGKFHAKTSPLLSLIENILKQVDSPNHSGQTLYEQ
VALTHPSWDAEVIQPLPMDSSAYSFTAFAGVPAVEFSFMEDDRVYPFLHTKEDTYENLHKMLR
GRLPVVQAVAQLAGQLLIRLSDHLLPLDFGRYGDVLRHIGNLNEFSGDLKERGLTLQWVY
SARGDYIRAAEKLKQEIYSSEERNDERLMRMYNVRIMRVEFYFLSQYVSPADSPFRHIFLGQGDH
TLGALVDHLRMLRADGSGAASSRLTAGLGFQESRFRRLALLTWTLQGAANALSGDVWNIDN
NF
- [0633] 人Tfr2蛋白酶相关 (PA) 域氨基酸序列 (SEQ ID NO:5)

Tyr Cys Pro Tyr Ser Ala Ile Gly Asn Val Thr Gly Glu Leu Val Tyr
Ala His Tyr Gly Arg Pro Glu Asp Leu Gln Asp Leu Arg Ala Arg Gly
Val Asp Pro Val Gly Arg Leu Leu Leu Val Arg Val Gly Val Ile Ser
[0634] Phe Ala Gln Lys Val Thr Asn Ala Gln Asp Phe Gly Ala Gln Gly Val
Leu Ile Tyr Pro Glu Pro Ala Asp Phe Ser Gln Asp Pro Pro Lys Pro
Ser Leu Ser Ser Gln Gln Ala Val Tyr Gly His Val His Leu

[0635] 人肽酶M28域氨基酸序列 (SEQ ID NO:6)

Gly Arg Ser Glu Pro Asp His Tyr Val Val Ile Gly Ala Gln Arg Asp
Ala Trp Gly Pro Gly Ala Ala Lys Ser Ala Val Gly Thr Ala Ile Leu
Leu Glu Leu Val Arg Thr Phe Ser Ser Met Val Ser Asn Gly Phe Arg
Pro Arg Arg Ser Leu Leu Phe Ile Ser Trp Asp Gly Gly Asp Phe Gly
Ser Val Gly Ser Thr Glu Trp Leu Glu Gly Tyr Leu Ser Val Leu His
[0636] Leu Lys Ala Val Val Tyr Val Ser Leu Asp Asn Ala Val Leu Gly Asp
Asp Lys Phe His Ala Lys Thr Ser Pro Leu Leu Thr Ser Leu Ile Glu
Ser Val Leu Lys Gln Val Asp Ser Pro Asn His Ser Gly Gln Thr Leu
Tyr Glu Gln Val Val Phe Thr Asn Pro Ser Trp Asp Ala Glu Val Ile
Arg Pro Leu Pro Met Asp Ser Ser Ala Tyr Ser Phe Thr Ala Phe Val
Gly Val Pro Ala Val Glu Phe Ser Phe Met Glu Asp Asp Gln Ala Tyr
Pro Phe Leu His Thr Lys Glu Asp Thr Tyr

[0637] 人Tfr-样二聚化域氨基酸序列 (SEQ ID NO:7)

Leu Lys Ala Arg Gly Leu Thr Leu Gln Trp Val Tyr Ser Ala Arg Gly
Asp Tyr Ile Arg Ala Ala Glu Lys Leu Arg Gln Glu Ile Tyr Ser Ser
Glu Glu Arg Asp Glu Arg Leu Thr Arg Met Tyr Asn Val Arg Ile Met
Arg Val Glu Phe Tyr Phe Leu Ser Gln Tyr Val Ser Pro Ala Asp Ser
[0638] Pro Phe Arg His Ile Phe Met Gly Arg Gly Asp His Thr Leu Gly Ala
Leu Leu Asp His Leu Arg Leu Leu Arg Ser Asn Ser Ser Gly Thr Pro
Gly Ala Thr Ser Ser Thr Gly Phe Gln Glu Ser Arg Phe Arg Arg Gln
Leu Ala Leu Leu Thr Trp Thr Leu Gln Gly Ala Ala Asn Ala

[0639] 核苷酸序列人Tfr2 (SEQ ID NO:8)

GTTCGTTGCAACAAATTGATGAGCAATGCTTTTTATAATGCCAACTTTGTACAAAAAGTTGGCACCAT
GGAGCGGCTTTGGGGTCTATTCCAGAGAGCGCAACAACGTGTCCCAAGATCCTCTCAGACCGTCTACCA
CGTGTGGAAGGCCCCGGAAAGGGCACCTGGAGGAGGAAGAGGAAGACGGGGAGGAGGGGGCGGAGACATTG
GCCCATTCTGCCCCATGGAGCTGAGGGGCCCTGAGCCCCTGGGCTCTAGACCCAGGCAGCCAAACCT
CATTCCTGGGCGGCAGCAGGACGGAGGGCTGCCCCCTACCTGGTCCTGACGGCCCTGCTGATCTTCACT
GGGGCCTTCTACTGGGCTACGTCGCCTTCGAGGGTCTGCCAGGCGTGCGGAGACTCTGTGTTGGTGG
TCAGTGAGGATGTCAACTATGAGCCTGACCTGGATTTCACCAGGGCAGACTCTACTGGAGCGACCTCCA
GGCCATGTTCTGCACTTCTGGGGGAGGGGCGCCTGGAGGACACCATCAGGCAAACCAGCCTTCGGGAA
CGGGTGGCAGGCTCGGCCGGGATGGCCGCTGACTCAGGACATTCGCGCGGCGCTCTCCCGCCAGAAGC
TGGACCACGTGTGGACCGACACGCACTACGTGGGGCTGCAATCCCGGATCCGGCTCACCCCAACACCT
GCACTGGGTGCGATGAGGCCGGGAAGGTGCGAGAGCAGCTGCCGCTGGAGGACCCTGACGTCTACTGCCCC
TACAGCGCCATCGGCAACGTACGGGAGAGCTGGTGACGCCACTACGGGCGGCCCCGAAGACCTGCAGG
ACCTGCGGGCCAGGGGCGTGGATCCAGTGGGCCGCTGCTGCTGGTGCGCGTGGGGGTGATCAGTTTCG
[0640] CCAGAAGGTGACCAATGCTCAGGACTTCGGGGCTCAAGGAGTGCTCATATACCAGAGCCAGCGGACTTC
TCCAGGACCCACCAAGCCAAGCCTGTCCAGCCAGCAGGCAGTGATGGACATGTGCACCTGGGAACTG
GAGACCCCTACACACCTGGCTTCCCTTCTTCAATCAAACCCAGTTCCCTCCAGTTGCATCATAGGCCT
TCCAGCATCCCAGCCCAGCCATCAGTGACAGACATTGCCTCCGCGCTGCTGAGGAAGCTCAAAGGCCCT
GTGGCCCCCAAGAATGGCAGGGGAGCCTCTAGGCTCCCTTATCACCTGGGCCCCGGGCCACGACTTC
GGCTAGTGGTCAACAATCACAGGACCTCCACCCCATCAACAACATCTTCGGCTGCATCGAAGGCCGCTC
AGAGCCAGATCACTACGTTGTCATCGGGGCCAGAGGGATGCATGGGGCCCAGGAGCAGCTAAATCCGCT
GTGGGGACGGCTATACTCCTGGAGCTGGTGCGGACCTTTTCTCCATGGTGAGCAACGGCTTCCGGCCCC
GCAGAAGTCTCCTTTCATCAGCTGGGACGGTGGTGACTTTGGAAGCGTGGGCTCCACGGAGTGGCTAGA
GGGCTACCTCAGCGTGCTGCACCTCAAAGCCGTAGTGACGTGAGCCTGGACAACGCAGTGCTGGGGGAT
GACAAGTTTCATGCCAAGACCAGCCCCCTTCTGACAAGTCTCATTGAGAGTGCTCTGAAGCAGGTGGATT
CTCCAACACAGTGGGCAGACTCTCTATGAACAGGTGGTGTTACCAATCCCAGCTGGGATGCTGAGGT
GATCCGGCCCCCTACCCATGGACAGCAGTGCCTATTCTTCACGGCCTTGTGGGAGTCCCTGCCGTGAG
TTCTCCTTATGGAGGACGACCAGGCCTACCCATTCTGCACACAAAGGAGGACACTTATGAGAACCTGC
ATAAGGTGCTGCAAGGCCGCTGCCCGCGTGGCCAGGCCGTGGCCAGCTCGCAGGGCAGCTCCTCAT
CCGGCTCAGCCACGATCGCTGCTGCCCTCGACTTCGGCCGCTACGGGGACGTCGTCCTCAGGCACATC
GGGAACCTCAACGAGTTCTCTGGGGACCTCAAGGCCCGGGGCTGACCTGCAGTGGGTGTA CTGGCGC
GGGGGGACTACATCCGGGCGGCGGAAAAGCTGCGGCCGGAGATCTACAGCTCGGAGGAGAGACGAGCG
[0641] ACTGACACGCATGTACAACGTGCGCATAATGCGGGTGGAGTTCTACTTCTTTCCAGTACGTGTCGCCA
GCCGACTCCCCGTTCCGCCACATCTTCATGGGCCGTGGAGACCACACGCTGGGCGCCCTGCTGGACCACC
TGCGGCTGCTGCGCTCCAACAGCTCCGGGACCCCCGGGGCCACCTCTCCACTGGCTTCCAGGAGAGCCG
TTTCCGGCGTCAGCTAGCCCTGCTCACCTGGACGCTGCAAGGGGCAGCCAATGCGCTTAGCGGGGATGTC
TGGAACATTGATAACAACCTTCTGCCAACTTCTTGTACAAAGTTGGCATTATAAGAAAGCATTGCTTAT
CAATTTGTTGCAACGAAC

[0642] 小鼠Tfr2 (SEQ ID NO:9)

[0643]

GAGTCTCCTGGGAGCATGGTCCAAGAAACCCAGAGACCTGTTGCTGAGCTGAACTTGGCTGCTGTGTCTT
CCCCTCAGGACTCGGCTTTGACAGGCACGAGGCAGGGACTGGGGTACTGGTGAGCCCCCTACCTCTCAGA
TCTTTCTGGACCTGGCTGCAGGTCCTGGTGTCTTCGTCGCGGCTTGGATTCAAACCTGGAGGAGTTCAGG
AGGGGGCACAAGCATGGAGCAACGTTGGGGTCTACTTCGGAGAGTGCAACAGTGGTCCCCAAGACCCCTCT
CAGACCATCTACAGACGCGTGGAAGGCCCTCAGCTGGAGCACCTGGAGGAGGAAGACAGGGAGGAAGGGG
CGGAGCTTCCTGCCAGTTCTGCCCCATGGAACCTCAAAGGCCCTGAGCACTTAGGCTCCTGTCCCGGGAG
GTCAATTCCCATACCCTGGGCTGCAGCAGGTCGAAAGGCTGCCCCCTATCTGGTCTGATCACCTGCTA
ATCTTCACTGGGGCCTTCCTCCTAGGCTACGTGGCCTTTCGAGGGTCTGCCAGGCGTGTGGGGACTCCG
TGTTGGTGGTCGATGAAGATGTCAACCCTGAGGACTCCGGCCGGACCACGTTGTACTGGAGCGACCTCCA
GGCCATGTTTCTCCGGTTCCTTGGGGAGGGGCGCATGGAAGACACCATCAGGCTGACCAGCCTCCGGGAA
CGCGTGGCTGGCTCAGCCAGAATGGCCACCCTGGTCCAAGATATCCTCGATAAGCTCTCGCGCCAGAAGC
TGGACCACGTGTGGACTGACACGCACTACGTGGGACTTCAGTTCAGATCCGGCTCACGCTAACACCCT
GCACTGGGTGGATGCAGACGGGAGCGTCCAGGAGCAGCTACCGCTGGAGGATCCGGAAGTCTACTGTCCC
TACAGCGCCACCGGCAACGCCACGGGCAAGCTGGTGTACGCCACTACGGGCGGTCCGAGGACCTACAGG
ACCTAAAAGCCAAGGGCGTGGAGCTGGCCGGCAGCCTCTGCTAGTGCGAGTTGGAATTACTAGCTTCGC
CCAGAAGGTAGCCGTTGCCAGGACTTTGGGGCTCAAGGAGTGCTGATATACCCTGACCCATCAGACTTC
TCCCAGGATCCCCACAAGCCAGGCCTGTCTAGCCACCAGGCTGTGTACGGACATGTGCACCTGGGAACTG
GAGACCCCTACACACCTGGCTTCCCGTCTTCAATCAAACCCAGTTCCTCCAGTAGAATCATCAGGCCT
TCCCAGCATCCCCGCCAGCCCATCAGTGCTGACATTGCTGATCAATTGCTCAGGAACTCACAGGCCCC
GTGGCTCCCCAGGAGTGGAAGGTCACCTCTCAGGCTCTCCTTATCGGCTGGGACCTGGGCCCCGACTTAC

[0644]

GCCTTGTGGTCAACAACCACAGAGTCTCTACCCCCATCAGTAACATCTTTGCGTGCATCGAGGGCTTTGC
AGAGCCAGATCACTATGTTGTCATTGGGGCCCAGAGGGATGCATGGGGCCCAGGAGCAGCCAAGTCTGCA
GTGGGGACTGCCATCCTGCTGGAGCTGGTTCGGACCTTCTCTCCATGGTCAGCAATGGGTTGAGACCTC
GAAGAAGTCTTTTGTTCATCAGCTGGGACGGAGGTGACTTTGGCAGCGTGGGAGCCACAGAGTGGTTGGA
GGGCTACCTCAGCGTGCTACACCTCAAAGCTGTTGTGTACGTGAGCCTGGACAACCTCCGTGTTGGGAGAT
GGCAAATTCCATGCTAAGACCAGCCCCCTTCTCGTCAGCCTCATTGAGAATATCTTGAAGCAGGTGGACT
CCCCTAACCATAGTGGACAGACCCTCTATGAACAAGTGGCACTCACCCACCCCAGCTGGGATGCTGAAGT
GATTGAGCCCCGCCCATGGACAGCAGTGCATATTCCTTACAGCCTTTGCGGGGGTCCCAGCTGTGGAG
TTCTCCTTCATGGAGGATGATCGGGTGTACCCATTCTGCACACGAAGGAGGACACATATGAGAATCTGC
ACAAGATGCTGCGAGGTGCGCTGCCCCGCGTGGTCCAGGCAGTGGCTCAGCTCGCGGGCCAGCTCCTCAT
CCGACTGAGCCACGATCACCTACTGCCGCTAGACTTCGGCCGCTATGGAGACGTGGTTCTCAGGCACATC
GGCAACCTCAATGAGTTCTCTGGGGACCTCAAGGAGCGCGGGCTGACCCTGCAGTGGGTGTACTCTGCAA
GGGGGGACTACATCCGTGCGGCGGAAAAGCTGCGGAAGGAGATTTACAGCTCGGAGCGGAACGATGAGCG
TCTGATGCGCATGTACAACGTGCGCATCATGAGGGTGGAGTTCTACTTCTGTCCCAGTATGTGTGCCA
GCCGACTCCCCATTCCGCCACATTTTCTAGGCCAAGGCGACCACACTTTGGGTGCCCTGGTAGACCACC
TGCGGATGCTGCGCGCCGATGGCTCAGGAGCCGCTCTTCCCGTTGACAGCAGGTCTGGGCTTCCAGGA
GAGTCGTTCCGGCGCCAGCTGGCGTGCTCACCTGGACACTGCAGGGGGCAGCCAACGCTCTCAGTGGC
GACGTTTGAACATTGACAATAACTTTTGAAGCCAAAAGCCCTCCATGGGCCCCACGTGATTCTCCTTTC
TCCCTCTTTGAGTGGTGCAGGCAAAGGAGGTGCCTGAGATTGTAACCTATTCTTAACACCCTTGGTCTCG
CAATGCTGGTGCGCCATATTTTCTCAGTGTGGTTGTCATGCCGTTGCTTACCCAGAAAGCGGTTTTCTTC
CCATCACAGGCCCTTCTGTCTCAGGAGCAAAGTTCCTCATATCTAGAGACTATCTAGATGCTGGGATCT
GATCAGCTCTCTTAGAGAGTGAGATGGACAGCGTCATTATTTTATGACACATGAGCTACGGTATGTGAGC
AGCCCAAGGGGATTAGATGTCAATAAACCAATTGTAACCCCTGTTGTCCATACGCAATTTAGCTTCCTCT
TCATGCCGTACCCACTCCTCATATCCGCCTTGAGACTAGGGAAGAAGGCACAGAAGGCACCTGACAGCAT
GCTTGCAAGATGCTATCCACATGGGAAAAATAACTGTTCTGATGTCTAAGAAAACCTGCCTAAAGATAATG
GATAGGAGGTGGGGCAGTGGGGATAACTCATCAGGAATGGGTGATTGCGGCCAAGCCTGATGACCTGAGT
TTAATCCCCAGGACCAACATGGCAAAGGAGAGAACTAGTTCCCAAGTTTTCTATATCCTCCAAATG
TATGCCATAAAAGCACAAATAGATAAATGTTTTGCTTTTGTTTTTTAAAGTGGCTTTGTGGTTAAGAG
CACTGGATGCCATTCTAGAAGACACCGTTTCGATTCCCAGCACCCACATGGCCGCTTACAACTGTCTGTA
ACTCCAGTTGCTGGGGATCAGATGCCCTCTTCTGGTATGGTGTACGACTGCATGCATGTAGTATACATAC
AAGCAGGCAAAATACCCATACATGTAAATTTTTAAAAATAGTTTAAATTATAAATTAATTTAAAGAAC
AAATAAAAGATTAATGCCTTTAATCCC

[0645] 人TfR2-his (SEQ ID NO:10)

[0646]

AFRGSCQACGDSVLVSEDEVNYEPDLDFHQGRLYWSDLQAMFLQFLGEGRLEDTIRQTSRERVAGSAGMAALTQDI
RAALSRLQKLDHVWTDTHYVGLQFPDPAHPNTLHWVDEAGKVGEQLPLEDPDVYCPYSAIGNVTGELVYAHYGRPEDL
QDLRARGVDPVGRLLLRVGVISFAQKVTNAQDFGAQGVLIYEPADFSQDPPKPSLSSQAVYGHVHLGTGDPYTPG
FPSFNQTQFPPVASSGLPSIPAQPISADIASRLRLKLGVPAPQEWQGSLLGSPYHLGPGPRLRLVNNHRTSTPINNIFG
CIEGRSEPDHYVVIGAQRDAWGPGAASAVGTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSGVSTEWLEGYL
SVLHLKAVVYVSLDNAVLGDDKFHAKTSPLTSLIESVLKQVDSPNHSGQTLYEQVVFTNPSWDAEVIRPLPMDSSAYSF
TAFVGVPAVEFSFMEDDQAYPFLHTKEDTYENLHKVLQGRLPAAVAQAQLAGQLLIRLSHDRLLPLDFGRYGDVVLRL
HIGNLNEFSGLKARGLTLQWVYSARGDYIRAAEKLQEIYSSEERDERLTRMYNVRIMRVEFYFLSQYVSPADSPFRHIF
MGRGDHTLGALLDHLRLRLSNSSGTPGATSSTGFQESRFRRLALLTWTLQGAANALSGDVWNIDGGGGSHHHHHH

[0647]

人TfR2-Fc (N-末端融合) (SEQ ID NO:11)

EPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKIEGRR
GSCQACGDSVLVSEDEVNYEPDLDFHQGRLYWSDLQAMFLQFLGEGRLEDTIRQTSRERVAGSAGMAALTQDIRAA
LSRQKLDHVWTDTHYVGLQFPDPAHPNTLHWVDEAGKVGEQLPLEDPDVYCPYSAIGNVTGELVYAHYGRPEDLQDL
RARGVDPVGRLLLRVGVISFAQKVTNAQDFGAQGVLIYEPADFSQDPPKPSLSSQAVYGHVHLGTGDPYTPGFPS
FNQTQFPPVASSGLPSIPAQPISADIASRLRLKLGVPAPQEWQGSLLGSPYHLGPGPRLRLVNNHRTSTPINNIFG
GRSEPDHYVVIGAQRDAWGPGAASAVGTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSGVSTEWLEGYLSV
LHLKAVVYVSLDNAVLGDDKFHAKTSPLTSLIESVLKQVDSPNHSGQTLYEQVVFTNPSWDAEVIRPLPMDSSAYSFTA
FVGVPAVEFSFMEDDQAYPFLHTKEDTYENLHKVLQGRLPAAVAQAQLAGQLLIRLSHDRLLPLDFGRYGDVVLRLHIG
NLNEFSGLKARGLTLQWVYSARGDYIRAAEKLQEIYSSEERDERLTRMYNVRIMRVEFYFLSQYVSPADSPFRHIFMG
RGDHTLGALLDHLRLRLSNSSGTPGATSSTGFQESRFRRLALLTWTLQGAANALSGDVWNIDNNF

[0649]

人TfR2 (C-末端融合) (SEQ ID NO:12)

RGSCQACGDSVLVSEDEVNYEPDLDFHQGRLYWSDLQAMFLQFLGEGRLEDTIRQTSRERVAGSAGMAALTQDIRA
ALSRLQKLDHVWTDTHYVGLQFPDPAHPNTLHWVDEAGKVGEQLPLEDPDVYCPYSAIGNVTGELVYAHYGRPEDLQD
LRARGVDPVGRLLLRVGVISFAQKVTNAQDFGAQGVLIYEPADFSQDPPKPSLSSQAVYGHVHLGTGDPYTPGF
SFNQTQFPPVASSGLPSIPAQPISADIASRLRLKLGVPAPQEWQGSLLGSPYHLGPGPRLRLVNNHRTSTPINNIFGCI
EGRSEPDHYVVIGAQRDAWGPGAASAVGTAILLELVRTFSSMVSNGFRPRRSLLFISWDGGDFGSGVSTEWLEGYLS
VLHLKAVVYVSLDNAVLGDDKFHAKTSPLTSLIESVLKQVDSPNHSGQTLYEQVVFTNPSWDAEVIRPLPMDSSAYSFT
AFVGVPAVEFSFMEDDQAYPFLHTKEDTYENLHKVLQGRLPAAVAQAQLAGQLLIRLSHDRLLPLDFGRYGDVVLRLHI
GNLNEFSGLKARGLTLQWVYSARGDYIRAAEKLQEIYSSEERDERLTRMYNVRIMRVEFYFLSQYVSPADSPFRHIFM
GRGDHTLGALLDHLRLRLSNSSGTPGATSSTGFQESRFRRLALLTWTLQGAANALSGDVWNIDNNFIEGREPKSCDKT
HTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[0651]

表3: 引物序列 (实施例3)

[0652]

SEQ ID NO.	基因	引物序列
SEQ ID NO. 13	β -肌动蛋白	s: ATCTGGCACCACACCTTCT
SEQ ID NO. 14		as: GGGGTGTTGAAGGTCTCAAA
SEQ ID NO. 15	轴蛋白抑制 蛋白 2	s: GCAGTGATGGAGGAAAATGC
SEQ ID NO. 16		as: ATTCAAGGTGGGGAGGTAGC
SEQ ID NO. 17	Bmp2	s: CGCTCCACAAACGAGAAAAG
SEQ ID NO. 18		as: CAGTCATTCCACCCCACATC
SEQ ID NO. 19	Bmp4	s: CTCAAGGGAGTGAGATTGG
SEQ ID NO. 20		as: CTTCTGCGGGTCAAGGTATG
SEQ ID NO. 21	Bmp6	s: TAGCAATCTGTGGGTGGTGA
SEQ ID NO. 22		as: GAAGGGCTGCTTGTCTGTAAG
SEQ ID NO. 23	Cd44	s: TCCTTCGATGGACCGTTACC
SEQ ID NO. 24		as: GTGGAGCCGCTGCTGACATC
SEQ ID NO. 25	Dkk1	s: GAGGGGAAATTGAGGAAAGC
SEQ ID NO. 26		as: AGCCTTCTTGTCTTTGGTG
SEQ ID NO. 27	Dmp1	s: TGTCATTCTCCTTGTGTTCTTTG
SEQ ID NO. 28		as: AGAGCTTTCAGATTAGTATTGTCGTAT
SEQ ID NO. 29	Id1	s: CCCACTGGACCGATCCGCCA
SEQ ID NO. 30		as: TGCTCTCGGTTCCCCAGGGG
SEQ ID NO. 31	Id2	s: TCTGGGGGATGCTGGGCACC
SEQ ID NO. 32		as: GCTTGGGCATCTCCCGGAGC
SEQ ID NO. 33	Lef1	s: CAAATAAAGTGCCCGTGGTG
SEQ ID NO. 34		as: TCGTCGCTGTAGGTGATGAG
SEQ ID NO. 35	Phex	s: GGAAGAAAACCATTGCCAATTATT
SEQ ID NO. 36		as: CGCCTGCTGAGGTTTGGA
SEQ ID NO. 37	Sfrp	s: AAGTCAGGGTGATTGGGGGAATCC
SEQ ID NO. 38		as: AAACCATCTCCTCGGATAGGGCAC
SEQ ID NO. 39	Smad6	s: ATTCTCGGCTGTCTCCTCCT
SEQ ID NO. 40		as: CCCTGAGGTAGGTCGTAGAA
SEQ ID NO. 41	Sost	s: CGTGCCTCATCTGCCTACTT
SEQ ID NO. 42		as: TGACCTCTGTGGCATCATTC
SEQ ID NO. 43	Tcf7	s: GGACATCAGCCAGAAGCAAG
SEQ ID NO. 44		as: GGACAGGGGGTAGAGAGGAG
SEQ ID NO. 45	α -Tfr2	s: GCCATGTTTCTCCCGGTTCTT
SEQ ID NO. 46		as: TGGCGCGAGAGCTTATCG
SEQ ID NO. 47	β -Tfr2	s: CCTGGCCCCTAGTGTGATTTC
SEQ ID NO. 48		as: TGGCGCGAGAGCTTATCG
SEQ ID NO. 49	Tgf- β	s: GACCTCCATAGAAGACACC
SEQ ID NO. 50		as: AACCCGTTGATGTCCACTTGC

[0653] 表4: 本发明的抗体恒定区、片段、抑制剂和蛋白

[0654]

SEQ ID NO. 51	人 IgG1 恒定区	IGHG1*01	人重链恒定 区 (IGH G1*01) 核 苷酸序列	gectccaccaaggcccacggtcttccccctggcaccctctccaagagcacctctgggggcacagcggccct gggctgctggtcaaggactacttccccgaaccggtgacgggtgtgtggaactcaggcgccctgaccagcggc gtgcacaccttcccggctgtctacagctctcaggactctactccctcagcagcgtgtgtgaccgtgcccctcagc agcttgggacccagacactacatctgcaacgtgaatcacaagcccagcaacaccaaaggtggacaagaagtt gagcccaaatctgtgacaaaactcacatgcccaccgtgcccagcacctgaactcttgggggggacgtcag tcttctcttcccccaaaacccaaggacacctcatgatctcccggacccctgaggtcacatgcgtgtgtgtg acgtgagccacgaagacctgaggtcaagttcaactgtgtacgtggacggcgtggagggtgcataatgccaaga caaagccgcccgggagggagcagtaacaacagcacgtaccgggtgtgacgcgtctcaccgtctctgaccaggact ggctgaatggcaaggagtacaaggtgcaaggtctccaacaaagccctccagcccccatcgagaaaacatct ccaaagccaaaggggcagccccgagaaccacaggtgtacacctgcccccatccccgggatgagctgaccaaga accaggtcagcctgacctgctgtgcaaaaggcttctatccagcgacatcgccgtggagtgggagagcaatgg gcagccggagaaactacaagaccacgctcccgtgctggactccgacggctcttctctctacagcaagc tcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctcgtgatgcatgaggtctgcacaa ccactacacgcagaagagcctctcctctcctccgggtaaa
SEQ ID NO. 52			人重链恒定 区 (IGHG1*0 1) 蛋白序列 (P01857)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGP SVFLPPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREQYN STYRVVSVLTVLIHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPRPEQVYITLPPSRDE LTKNQVSLTCLVKGFPYSDIAVEWESNGQPENNYKTITPPVLDSDGSFFLYSKLTVDKSRW QQGNVFCFSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 53	人 IgG1 恒定区	IGHG1*02 或 IGHG1*05	人重链恒定 区 (IGHG1*0 2 或 IGHG1*05) 核苷酸序列	gectccaccaaggcccacggtcttccccctggcaccctctccaagagcacctctgggggcacagcggccct gggctgctggtcaaggactacttccccgaaccggtgacgggtgtgtggaactcaggcgccctgaccagcggc gtgcacaccttcccggctgtctacagctctcaggactctactccctcagcagcgtgtgtgaccgtgcccctcagc agcttgggacccagacactacatctgcaacgtgaatcacaagcccagcaacaccaaaggtggacaagaagtt gagcccaaatctgtgacaaaactcacatgcccaccgtgcccagcacctgaactcttgggggggacgtcag tcttctcttcccccaaaacccaaggacacctcatgatctcccggacccctgaggtcacatgcgtgtgtgtg acgtgagccacgaagacctgaggtcaagttcaactgtgtacgtggacggcgtggagggtgcataatgccaaga caaagccgcccgggagggagcagtaacaacagcacgtaccgggtgtgacgcgtctcaccgtctctgaccaggactg gctgaatggcaaggagtacaaggtgcaaggtctccaacaaagccctccagcccccatcgagaaaacatctcc aaagccaaaggggcagccccgagaaccacaggtgtacacctgcccccatccccgggatgagctgaccaaga ccaggtcagcctgacctgctgtgcaaaaggcttctatccagcgacatcgccgtggagtgggagagcaatggg cagccggagaaactacaagaccacgctcccgtgctggactccgacggctcttctctctacagcaagct caccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctcgtgatgcatgaggtctgcacaa cactacacgcagaagagcctctcctctcctccgggtaaa
SEQ ID NO. 54			人重链恒定 区 (IGHG1*0 2) 蛋白序列	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGA LTSVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTL MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE QYNSTYRVVSVLTVLIHQDWLNGKEYKCKVSNKALPAPIEKTI AKGQPRPEQVYITLPPSRDELTKNQVSLTCLVKGFPYSDIAVEW ESNGQPENNYKTITPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFS VMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 55	人 IgG1 恒定区	IGHG1*03	人重链恒定 区 (IGHG1*0 3) 核苷酸序 列 (Y14737)	gectccaccaaggcccacggtcttccccctggcaccctctccaagagcacctctgggggcacagcggccct gggctgctggtcaaggactacttccccgaaccggtgacgggtgtgtggaactcaggcgccctgaccagcggc gtgcacaccttcccggctgtctacagctctcaggactctactccctcagcagcgtgtgtgaccgtgcccctcagc agcttgggacccagacactacatctgcaacgtgaatcacaagcccagcaacaccaaaggtggacaagaagtt gagcccaaatctgtgacaaaactcacatgcccaccgtgcccagcacctgaactcttgggggggacgtcag tcttctcttcccccaaaacccaaggacacctcatgatctcccggacccctgaggtcacatgcgtgtgtgtg acgtgagccacgaagacctgaggtcaagttcaactgtgtacgtggacggcgtggagggtgcataatgccaaga caaagccgcccgggagggagcagtaacaacagcacgtaccgggtgtgacgcgtctcaccgtctctgaccaggactg gctgaatggcaaggagtacaaggtgcaaggtctccaacaaagccctccagcccccatcgagaaaacatctcc aaagccaaaggggcagccccgagaaccacaggtgtacacctgcccccatccccgggagggatgaccaagaa ccaggtcagcctgacctgctgtgcaaaaggcttctatccagcgacatcgccgtggagtgggagagcaatggg cagccggagaaactacaagaccacgctcccgtgctggactccgacggctcttctctctatagcaagct caccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctcgtgatgcatgaggtctgcacaa cactacacgcagaagagcctctcctctcctccgggtaaa

[0655]

SEQ ID NO. 56			人重链恒定区 (IGHG1*03) 蛋白序列	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 57	人 IgG1 恒定区	IGHG1*04	人重链恒定区 (IGHG1*04) 核苷酸序列	gcctccaccaaggcccatcggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccct gggctgcctggtaaggactacttccccgaaccgggtgacgggtgtcgtggaactcaggcgccctgaccagcggc gtgcacaccttccgggtgtctctacagtcctcaggactctactccctcagcagcgtgggtgaccgtgacctccagc agcttgggcacccagactacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaagt gagcccaaatctgtgacaaaactcacatgccaccgtgccagcactgaactctggggggaccgtcag tcttcttccccccaaaacccaaggacacctcatgatctccggaccctgagggtcacatgcgtgtgtgtgtg acgtgagccacgaagacctgaggtcaaggtcaactgtacgtggacggcgtggaggtgcataatgccaa caagccgcgggaggagcagtacaacagcagctaccgtgtgtgacgtcctcaccgtctctgaccaggactg gctgaatggcaaggagtacaaggtgcaaggtctccaacaaagccctccagcccccagcagaaaacacatcc aaagccaaagggcagccccgagaaccacaggtgtacacctgccccatccccggatgagctgaccaagaa ccaggtcagcctgacctgctgcaaaaggcttctatccagcgacatcgccgtggagtgaggagagcaatggg cagccggagaacaaactacaagaccacgctcccgtgctgactccgacgctcttctctctacagcaagct caccgtggacaagagcaggtggcagcaggggaacatcttctcatgctcgtgatgatgaggctctgcacaac cactacacgcagaagagcctctcctgtctcgggtgtaa
SEQ ID NO. 58			人重链恒定区 (IGHG1*04) 蛋白序列	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 59	失去功能的人 IgG1 重链恒定区	失去功能的人 IGHG1*01	失去功能的人 IGHG1*01 重链恒定区核苷酸序列	Gcctccaccaaggcccatcggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccct gggctgcctggtaaggactacttccccgaaccgggtgacgggtgtcgtggaactcaggcgccctgaccagcggc gtgcacaccttccgggtgtctctacagtcctcaggactctactccctcagcagcgtgggtgaccgtgacctccagc agcttgggcacccagactacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaagt gagcccaaatctgtgacaaaactcacatgccaccgtgccagcactgaactcgcggggggaccgtcag tcttcttccccccaaaacccaaggacacctcatgatctccggaccctgaggtcacatgcgtgtgtgtgtg acgtgagccacgaagacctgaggtcaaggtcaactgtacgtggacggcgtggaggtgcataatgccaa caagccgcgggaggagcagtacaacagcagctaccgtgtgtgacgtcctcaccgtctgaccaggactg gctgaatggcaaggagtacaaggtgcaaggtctccaacaaagccctccagcccccagcagaaaacacatcc aaagccaaagggcagccccgagaaccacaggtgtacacctgccccatccccggatgagctgaccaagaa ccaggtcagcctgacctgctgcaaaaggcttctatccagcgacatcgccgtggagtgaggagagcaatggg cagccggagaacaaactacaagaccacgctcccgtgctgactccgacgctcttctctctacagcaagct caccgtggacaagagcaggtggcagcaggggaacgttctctcatgctcgtgatgatgaggctctgcacaac cactacacgcagaagagcctctcctgtctcgggtgtaa
SEQ ID NO. 60			失去功能的人 IGHG1*01 重链恒定区氨基酸序列。 加粗 显示与野生型序列不同的两个残基。	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELAGA PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0656]

SEQ ID NO. 61	人 IgG2 恒定区	IGHG2*01 或 IGHG2*04 或 IGHG2*05	人重链恒定 区 (IGHG2*0 1 或 IGHG2*03 或 IGHG2*05) 核苷酸序列	gctctccaccaagggcccatcggtcttccccctggcgccctgtccaggagcacctccgagagcacagccgccct gggctgcctgggtcaaggactacttccccgaaccgggtgacgggtgtcgtggaactcaggcgctctgaccagcggc gtgcacaccttccagctgtctacagctctcaggaacttactcctcagcagcgtgtgtgacctgtccctccagc aacttcggcaccagacactacacgtgcaacgtatgacacagccagcaacaccaaggtggacaagacaggt gagcgcgaatgtgtgtcgtgagtgccacacgtgcccagcaccactgtggcaggaccgtcagcttctcttcccc ccaaaacccaaggacacctcatgatctccggaccctgagggtacgtgcgtgggtggagcgtgagccacg aagaccccgaggtccagttcaactgggtacgtggacggcggtggaggtgcataatgccaagacaagccacggg aggagcagttcaacagcacgttccgtgtgtgcagcgtctcaccgtgtgtcaccaggactggctgaacggcaa ggagtacaagtgcaaggtctccaaacaggcctccagcccccatcgagaaaacctctccaaaccaaagg gcagccccgagaaccacaggtgtacacctgccccatccccggaggagatgaccaagaacacaggtcagcct gacctgcctgtgcaaggcttctacccagcgacatcgccgtggaggtggagagcaatggcgagccggagaa caactacaagaccacacctccatgctgactccgacggctctcttctctacagcaagctcaccgtggaca agagcaggtggcagcaggggaacgtcttctcatgctccgtgatgatgaggtctgcacaacctacacgca gaagagcctctccctgtctccgggtaaa
SEQ ID NO. 62			人重链恒定 区 (IGHG2*0 1) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVTPSSNFGTQTYTCNVDHKPSNTKVDKTVVERKCCVECP APPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNST FRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSK LTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 63	人 IgG2 恒定区	IGHG2*02	人重链恒定 区 (IGHG2*0 2) 核苷酸序 列	GCCTCCACCAAGGGCCCATCGGTCTTCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTGCTGGAACTCAGGCGCTCTGACCAGCGCGGTGCACACCTTCCCGGTGTCTCT ACAGTCTCTCAGGACTTACTTCCCTCAGCAGCGTGGTGACCGTGAACCTCAGCAACT CGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCAGCAACACCAAGGTGG ACAAGACAGTTGAGCGCAAATGTTGTGTGAGTGCCCAACCGTGCCAGCACCACCT GTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCCTCATGATCT CCCGGACCCCTGAGGTGACGTGCGTGGTGGTGGAGCGTGAGCCAGCAAGACCCCGA GGTCCAGTTCAACTGGTACGTGGACGGCATGGAGGTGCATAATGCCAAGACCAAGC CACGGGAGGAGCAGTTCAACAGCACGTTCCTGTGGTACGCTCTCACCCTGCTG CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGAAGGTCTCCAACAAGGCCT CCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCGGAGAACAC AGGTGTACACCTTGCCCCATCCGGGAGGAGATGACCAAGAACCAGGTGACGCTG ACCTGCTGGTCAAGGCTTCTACCCAGCGACATCGCGTGGAGTGGGAGAGCA TGGGAGCCCGGAGAACAACTACAAGACCACCTCCCATGCTGACTCCGACGGCT CCTTCTCTCTACAGCAAGCTCACCCTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGATGAGGCTCTGCACAACCATACACAGAAAGAGC CTCTCCCTGCTCTCCGGGTAAA
SEQ ID NO. 64			人重链恒定 区 (IGHG2*0 2) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVTSSNFGTQTYTCNVDHKPSNTKVDKTVVERKCCVECP APPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGMEVHNAKT KPREEQFNST FRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSK LTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 65	人 IgG2 恒定区	IGHG2*04	人重链恒定 区 (IGHG2*0 4) 核苷酸序 列	gctctccaccaagggcccatcggtcttccccctggcgccctgtccaggagcacctccgagagcacagcgccct gggctgcctgggtcaaggactacttccccgaaccgggtgacgggtgtcgtggaactcaggcgctctgaccagcggc gtgcacaccttccagctgtctacagctctcaggaacttactcctcagcagcgtgtgtgacctgtccctccagc agcttggcaccagacactacacgtgcaacgtatgacacagccagcaacaccaaggtggacaagacaggt gagcgcgaatgtgtgtcgtgagtgccacacgtgcccagcaccactgtggcaggaccgtcagcttctcttcccc ccaaaacccaaggacacctcatgatctccggaccctgagggtacgtgcgtgggtggagcgtgagccacg aagaccccgaggtccagttcaactgggtacgtggacggcggtggaggtgcataatgccaagacaagccacggg aggagcagttcaacagcacgttccgtgtgtgcagcgtctcaccgtgtgtcaccaggactggctgaacggcaa ggagtacaagtgcaaggtctccaaacaggcctccagcccccatcgagaaaacctctccaaaccaaagg gcagccccgagaaccacaggtgtacacctgccccatccccggaggagatgaccaagaacacaggtcagcct gacctgcctgtgcaaggcttctacccagcgacatcgccgtggaggtggagagcaatggcgagccggagaa caactacaagaccacacctccatgctgactccgacggctctcttctctacagcaagctcaccgtggaca agagcaggtggcagcaggggaacgtcttctcatgctccgtgatgatgaggtctgcacaacctacacgca gaagagcctctccctgtctccgggtaaa

[0657]

SEQ ID NO. 66			人重链恒定区 (IGHG2*04) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKTVERKCCVECP APPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAIEKTIKTKGQPREPQV YTLPPSREMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSGDSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 67	人 IgG2 恒定区	IGHG2*06	人重链恒定区 (IGHG2*06) 核苷酸序列	GCCTCCACCAAGGGCCCATCGGTCTTCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCCTGGAC GGTGTCTGGAAGCTCAGGCGCTCTGACAGCGCGCTGCACACCTTCCCGGCTGTCT ACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTT CGGCACCCAGAGCTACACCTGCAACGTAGATCAACAAGCCAGCAACACCAAGCGGTG ACAAGACAGTTGAGCGCAATGTTGTGTGAGTGCCACCGTGCCAGCACCACCT GTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCTCATGATCT CCCGGACCCCTGAGGTACAGTGCCTGGTGGTGACGTGAGCCACGAAGACCCGA GGTCCAGTTCAACTGGTACGTGGACGCGCTGGAGGTGCATAATGCCAAGACAAAGC CACGGGAGGAGCAGTTCAACAGCAGCTTCCGTGTGTCAGCGTCTCACCCTCGGTG CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGAAGGTCTCAACAAGAGCCCT CCCGACCCCATCGAGAAACCATCTCCAAAACCAAGGGCAGCCCGAGAGAACAC AGGTGTACACCTGCCCATCCCGGAGGAGATGACCAAGAACCAGGTACAGCTG ACCTGCTGGTCAAAGGCTTCTACCCAGCGACATCTCCGTGGAGTGGGAGAGCAA TGGGACCGCGAGAACAACTACAAGACACACCTCCATGCTGGAGTCCAGCGGTG CCTTCTCTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTATGCTCCGTGATGATGAGGCTCTGCAACAACCTACACAGAGAGC CTCTCCCTGTCTCCGGTAAA
SEQ ID NO. 68			人重链恒定区 (IGHG2*06) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECP APPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAIEKTIKTKGQPREPQV YTLPPSREMT KNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTTPMLDSGDSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO. 69	人 IgG4 恒定区	IGHG4*01 或 IGHG4*04	人重链恒定区 (IGHG4*01 或 IGHG4*04) 核苷酸序列	gcttcaccaaggcccatcgtctccctggcgccctgctccaggagcacctccgagagcacagccgct gggctgctgtgtaagactacttccccgaaccggtagcgtgtcgtggaactcaggcgcctgaccagcggc gtgcacacttccggctgtctctacagtctcaggactctactccctcagcagcgtggtgagcgtccctcagc agcttgggcagcaagactacacgtgcaacgtagatcacaaagccagcaacacaaaggtggacaagaggt gagtcacaaatgtgcccccatgcccacatgcccagcacctgagttcctgggggacacatgcttctctgttc cccccaaaaccaaagacactctcatgctcccgaccctgaggtcagctgctggtggtgagcgtgagcc aggaaagccccgaggtccagttcaactgtgacgtggtgaggtgcataatgccaagacaaagccgc gggaggagcagttcaacagcagctaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggtgacagc caaggagtaacaagtgaaggtctcaacaagcctccgctccatcgagaaacacatctccaagccaa agggcagccccgagagccacaggtgtacacctgccccatccagaggagatgaccaagaaccagggtca gcctgacctgctggtcaaaagcttctacccagcagacatgccgtggagtgaggagagcaatggcgagccgga gaacaactacaagaccacgctccctgctgactccgagcgtctcttctctacagaggttaacgtgg acaagagcaggtggcaggggaatgtcttctcatgctccgtgatgaggtctgcacaacactacac acagaagagcctcctctgtctctgggtaaa
SEQ ID NO. 70			人重链恒定区 (IGHG4*01) 蛋白序列 (P01861)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPCCPSCP APEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTK PREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

[0658]

SEQ ID NO. 71	人 IgG4 恒定区	IGHG4*02	人重链恒定 区 (IGHG4*0 2) 核苷酸序 列	ggtccaccaaggcccacccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgccct gggtgctcgtgtaaggactacttccccgaaccgggtgacgggtgctggtgaactcaggcgccctgaccagcggc gtgcacacctcccggctgctctacagctctcaggactctactcctcagcagcgtggtgaccgtgcccctccagc agcttgggcacgaagactacacctgcaacgtagatcacaagccagcaacaccaaggtggacaagagagtt gagtcacaatatgttccccctggtcccatcatgccagcacctgagttctggggggaccatcagttctctgttc ccccaaaaaccaggacactctcatgctcctccggaccctgaggtcacgtgcgtggtggagcgtgagcc aggaagaccccagggtccagttcaactgtacgtggtgacgtggtgaggtgcataatgccaagacaaagccgc gggaggagcagttcaacagcacgtaccgtgtgtgacgtcgtcctaccgtcgtgcaccaggtggtgaacgg caaggagtacaagtgcagggtctcacaagaaggcctcccgtcctccatcgagaaaaccatctccaaagccaa aggcgagccccgagagccacaggtgtacacctgcccccatccaggaggagatgaccaagaaccaggtca gcctgacctgctggtcgaaggcttctacccagcgacatcgccgtggaggtggagagcaatggcgagccgga gaacaactacaagaccacgctcccgtgctggaactccgacggctcttctctctacagcaggttaaccgtgg acaagagcaggtggcaggagggaatgtcttctcatgctcgtgatgcatgaggctctgcacaaccactacac gcagaagagcctcctcctgtctctgggtaaa
SEQ ID NO. 72			人重链恒定 区 (IGHG4*0 2) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTKVKRVEISKYGPCCPSCP APEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNST YRVVSVLTIVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYS RLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLSLGK
SEQ ID NO. 73	人 IgG4 恒定区	IGHG4*03	人重链恒定 区 (IGHG4*0 3) 核苷酸序 列	ggtccaccaaggcccacccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgccct gggtgctcgtgtaaggactacttccccgaaccgggtgacgggtgctggtgaactcaggcgccctgaccagcggc gtgcacacctcccggctgctctacagctctcaggactctactcctcagcagcgtggtgaccgtgcccctccagc agcttgggcacgaagactacacctgcaacgtagatcacaagccagcaacaccaaggtggacaagagagtt gagtcacaatatgttccccctggtcccatcatgctcctccggaccctgaggtcacgtgcgtggtggagcgtgagcc ccccaaaaaccaggacactctcatgctcctccggaccctgaggtcacgtgcgtggtggagcgtgagcc aggaagaccccagggtccagttcaactgtgacgtggtgacgtggtgaggtgcataatgccaagacaaagccgc gggaggagcagttcaacagcacgtaccgtgtgtgacgtcgtcctaccgtcctgcaccaggtggtgaacgg caaggagtacaagtgcagggtctcacaagaaggcctcccgtcctccatcgagaaaaccatctccaaagccaa aggcgagccccgagagccacaggtgtacacctgcccccatccaggaggagatgaccaagaaccaggtca gcctgacctgctggtcgaaggcttctacccagcgacatcgccgtggaggtggagagcaatggcgagccgga gaacaactacaagaccacgctcccgtgctggaactccgacggctcttctctctacagcaggtacacgtgg acaagagcaggtggcaggagggaacgtcttctcatgctcgtgatgcatgaggctctgcacaaccactacac gcagaagagcctcctcctgtctctgggtaaa
SEQ ID NO. 74			人重链恒定 区 (IGHG4*0 3) 蛋白序列	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSS GLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTKVKRVEISKYGPCCPSCP APEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNST YRVVSVLTIVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQ EGNVFSCSVMEALHNHYTQKSLSLSLGK
SEQ ID NO. 75	人 IgG4PE 恒定区	IGHG4-PE	人重链恒定 区 (IGHG4-P E) 核苷酸序 列形式 A	ggtccaccaaggcccacccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgccct gggtgctcgtgtaaggactacttccccgaaccaggtgacgggtgctggtgaactcaggcgccctgaccagcggc gtgcacacctcccggctgctctacagctctcaggactctactcctcagcagcgtggtgaccgtgcccctccagc agcttgggcacgaagactacacctgcaacgtagatcacaagccagcaacaccaaggtggacaagagagtt gagtcacaatatgttccccctggtcccatcatgccagcgccgtgaattggagggggaccatcagttctctgttc ccccaaaaaccaggacactctcatgctcctccggaccctgaggtcacgtgcgtggtggagcgtgagcc aggaagaccccagggtccagttcaactgtacgtggtgacgtggtgaggtgcataatgccaagacaaagccgc gggaggagcagttcaacagcacgtaccgtgtgtgacgtcgtcctaccgtcgtgcaccaggtggtgaacgg caaggagtacaagtgcagggtctcacaagaaggcctcccgtcctccatcgagaaaaccatctccaaagccaa aggcgagccccgagagccacaggtgtacacctgcccccatccaggaggagatgaccaagaaccaggtca gcctgacctgctggtcgaaggcttctacccagcgacatcgccgtggaggtggagagcaatggcgagccgga gaacaactacaagaccacgctcccgtgctggaactccgacggatcttctctctacagcaggttaaccgtgg acaagagcaggtggcaggagggaatgtcttctcatgctcgtgatgcatgaggctctgcacaaccactacac acagaagagcctcctcctgtctctgggtaaa

[0659]

[illegible]

[0660]

SEQ ID NO. 81	人 Cκ 恒定区	IGKC*01	人 Cκ 轻链恒定区 (IGKC*01) 核苷酸序列	cgtacgtgtggcctccctccgtgttcatcttccacctccgacgagcagctgaagtcggcaccgtctgtgtgtgctgtgaacaacttctacccccgcgagggccaaggtgcagtggaaggtggacaacgccctgcagtcggcaactcccaggaaatcctgtacgagcaggactccaaggacagcacctactcctgtctccacctgacctgtccaagggcgtactacgagaacacaaggtgtacgctgcggaagtgaccaccagggtctgtagctcccggtgacaaagtcttcaacggggagagtggt
SEQ ID NO. 82			Cκ 轻链恒定区 (IGKC*01) 氨基酸序列	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO. 83	人 Cκ 恒定区	IGKC*02	Cκ 轻链恒定区 (IGKC*02) 核苷酸序列	cgaactgtggctgcaccatctgttctcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgtgtgtgctgtgaataacttctatcccagagaggccaaggtacagtggaaggtggataacgccctccaatcgggttaactcccaggagagtggtcacagagcaggagagcaaggacagcacctacagcctcagcagcacctgacctgagcacaagcagactacgagaacacaaggtctacgctgcggaagtcacccatcagggtcgtgagctgcgccgtcacaaagagcttcaacaggggagagtggt
SEQ ID NO. 84			Cκ 轻链恒定区 (IGKC*02) 氨基酸序列	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ ESKDSTYLSLSSTLTLSKADYEKHKVYAGEVTHQGLSSPVTKSFNRGEC
SEQ ID NO. 85	人 Cκ 恒定区	IGKC*03	Cκ 轻链恒定区 (IGKC*03) 核苷酸序列	cgaactgtggctgcaccatctgttctcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgtgtgtgctgtgaataacttctatcccagagaggccaaggtacagtcggaaggtggataacgccctccaatcgggttaactcccaggagagtggtcacagagcaggagagcaaggacagcacctacagcctcagcagcacctgacctgagcacaagcagactacgagaacacaaggtctacgctgcggaagtcacccatcagggtcgtgagctgcgccgtcacaaagagcttcaacaggggagagtggt
SEQ ID NO. 86			Cκ 轻链恒定区 (IGKC*03) 氨基酸序列	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ ESKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO. 87	人 Cκ 恒定区	IGKC*04	Cκ 轻链恒定区 (IGKC*04) 核苷酸序列	cgaactgtggctgcaccatctgttctcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgtgtgtgctgtgaataacttctatcccagagaggccaaggtacagtggaaggtggataacgccctccaatcgggttaactcccaggagagtggtcacagagcaggacagcaaggacagcacctacagcctcagcagcacctgacctgagcacaagcagactacgagaacacaactctacgctgcggaagtcacccatcagggtcgtgagctgcgccgtcacaaagagcttcaacaggggagagtggt
SEQ ID NO. 88			Cκ 轻链恒定区 (IGKC*04) 氨基酸序列	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSLSSTLTLSKADYEKHKLYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO. 89	人 Cκ 恒定区	IGKC*05	Cκ 轻链恒定区 (IGKC*05) 核苷酸序列	cgaactgtggctgcaccatctgttctcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgtgtgtgctgtgaataacttctatcccagagaggccaaggtacagtggaaggtggataacgccctccaatcgggttaactcccaggagagtggtcacagagcaggacagcaaggacagcacctacagcctcagcaacacctgacctgagcacaagcagactacgagaacacaaggtctacgctgcggaagtcacccatcagggtcgtgagctgcgccgtcacaaagagcttcaacaggggagagtggt
SEQ ID NO. 90			Cκ 轻链恒定区 (IGKC*05) 氨基酸序列	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYLSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0661]

SEQ ID NO. 91	人 Cλ 恒 定区	IGLC1*01	Cλ 轻链恒 定区 (IGLC1*0 1)核苷酸序 列 (ENST0000 0390321.2)	cccaaggccaacccacggtaactctgttcccgccctctctgaggagctccaagccaacaaggccactagt gtgtctgatcagtgacttctaccggagctgtgacagtggttggaaggcagatggcagccccgtcaaggcg ggagtggaagacgaccaaacctccaacagagcaacaacaagtacgcggccagcagctacctgagcctgac gcccgaagcagtggaagtcacagaagctacagctgccaggctacgcatgaaggagcaccgtggagaaga cagtgcccctacagaatgttca
SEQ ID NO. 92			Cλ 轻链恒 定区 (IGLC1*0 1)氨基酸 序 列 (A0A075B 6K8)	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAG VETTKPSKQS NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 93	人 Cλ 恒 定区	IGLC1*02	Cλ 轻链恒 定区 (IGLC1*0 2)核苷酸序 列形式 A	ggtcagcccaaggccaacccactgtcactctgttcccgccctctctgaggagctccaagccaacaaggccac actagtgtgtctgatcagtgacttctaccgggagctgtgacagtgccctggaaggcagatggcagccccgtca aggcgggagtggaagaccaccaaacctccaacagagcaacaacaagtacgcggccagcagctacctgagc ctgacggccgagcagtggaagtcacagaagctacagctgccaggctcacgcatgaaggagcaccgtggag aagacagtgggccctacagaatgttca
SEQ ID NO. 94			Cλ 轻链恒 定区 (IGLC1*0 2)核苷酸序 列形式 B	ggtcagcccaaggccaacccactgtcactctgttcccgccctctctgaggagctccaagccaacaaggccac actagtgtgtctgatcagtgacttctaccgggagctgtgacagtgccctggaaggcagatggcagccccgtca aggcgggagtggaagaccaccaaacctccaacagagcaacaacaagtacgcggccagcagctacctgagc ctgacggccgagcagtggaagtcacagaagctacagctgccaggctcacgcatgaaggagcaccgtggag aagacagtgggccctacagaatgttca
SEQ ID NO. 95			Cλ 轻链恒 定区 (IGLC1*0 2)氨基酸序 列	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVK AGVETTKPS KQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 96	人 Cλ 恒 定区	IGLC2*01	Cλ 轻链恒 定区 (IGLC2*0 1)核苷酸序 列形式 A	ggccagcctaaggcgctcctctgtgacctgttcccccatctctcagggaactgcaggctaaacaaggccac cctctgtgtgctgatcagcagcttctaccctggcgccgtgacctggcctggaaggctgatagctctctgtgaa ggccggcgtggaaccaccacccctccaagcagtcacaacaatacggcgccctcctctacctgtctctga ccccgtgacagtggaagtcaccgggtctacagctgccaagtgaccacagagggtccaccgtggaaaaaga cgtggctctctaccagtgctcc
SEQ ID NO. 97			Cλ 轻链恒 定区 (IGLC2*0 1)核苷酸序 列形式 B	ggccagcctaaggcgctccccagcgtaccctgttctcctcctcagcgaggagctccaggccaacaaggcca ccctctgtgtgctgatctcagcttctaccggcgctgtgacctgtgcttggaaagccgaactcagccctgtca aagccggcgtggagaccacacccctccaagcagtcacaacaagaagtcacggcctcagctatctctcct gacccctgagcagtggaagtcaccgggtctactctgtcaggtgaccacagagggtccaccgtggaaaaag accgtgccccaccagtgctcc
SEQ ID NO. 98			Cλ 轻链恒 定区 (IGLC1*0 2)氨基酸序 列	GQPKAAPSVTLPSPSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSK QSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 99	人 Cλ 恒 定区	IGLC2*02 或 IGLC2*03	Cλ 轻链恒 定区 (IGLC2*0 2 或 IGLC2*03) 核苷酸序列	ggtcagcccaaggctccccctcggtactctgttcccgccctctctgaggagcttcaagccaacaaggccac actgtgtgtctcataagtgtacttctaccgggagcgtgacagtgccctggaaggcagatagcagccccgtca aggcgggagtggaagaccacacccctccaacaaagcaacaagaagtcacggccagcagctatctgagc ctgacgctgagcagtggaagtcacagaagctacagctgccaggctcacgcatgaaggagcaccgtggag aagacagtgggccctacagaatgttca
SEQ ID NO. 100			Cλ 轻链恒 定区 (IGLC2*0 2)氨基酸序 列	GQPKAAPSVTLPSPSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSK QSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

[0662]

SEQ ID NO. 101	人 Cλ 恒定区	IGLC3*01	Cλ 轻链恒定区 (IGLC3*01) 1) 核苷酸序列	cccaaggctgccccctcggtcactctgttccaccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgacagtgccctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacacctccaaacaagaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacaaagctacagctgccaggtcacgcatgaaggagcaccgtggagaagacagtgccccctacggaatgttca
SEQ ID NO. 102			Cλ 轻链恒定区 (IGLC3*01) 1) 氨基酸序列	PKAAPSVTLPFPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSKQS NNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 103	人 Cλ 恒定区	IGLC3*02	Cλ 轻链恒定区 (IGLC3*02) 2) 核苷酸序列	ggtcagcccaaggctgccccctcggtcactctgttccaccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgacagtgccctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacacctccaaacaagaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacaaagctacagctgccaggtcacgcatgaaggagcaccgtggagaagacagtgccccctacggaatgttca
SEQ ID NO. 104	SEQ ID NO. 102		Cλ 轻链恒定区 (IGLC1*02) 2) 氨基酸序列	GQPKAAPSVTLPFPSSEELQANKATLVCLISDFYPGPVTVAWKADSSPVKAGVETTPSK QSNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 105	人 Cλ 恒定区	IGLC3*03	Cλ 轻链恒定区 (IGLC3*03) 3) 核苷酸序列	ggtcagcccaaggctgccccctcggtcactctgttccaccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgacagtgccctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacacctccaaacaagaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacaaagctacagctgccaggtcacgcatgaaggagcaccgtggagaagacagtgccccctacagaatgttca
SEQ ID NO. 106			Cλ 轻链恒定区 (IGLC3*03) 3) 氨基酸序列	GQPKAAPSVTLPFPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSK QSNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 107	人 Cλ 恒定区	IGLC3*04	Cλ 轻链恒定区 (IGLC3*04) 4) 核苷酸序列	ggtcagcccaaggctgccccctcggtcactctgttccgcccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgacagtgccctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacacctccaaacaagaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacagaagctacagctgccaggtcacgcatgaaggagcaccgtggagaagacagtgccccctacagaatgttca
SEQ ID NO. 108			Cλ 轻链恒定区 (IGLC3*04) 4) 氨基酸序列	GQPKAAPSVTLPFPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSK QSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
SEQ ID NO. 109	人 Cλ 恒定区	IGLC6*01	Cλ 轻链恒定区 (IGLC6*01) 1) 核苷酸序列	ggtcagcccaaggctgccccctcggtcactctgttccgcccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgaaagtgccctggaaggcagatggcagccccgtcaaacggggagtgagaccaccacacctccaaacagagcaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacagaagctacagctgccaggtcacgcatgaaggagcaccgtggagaagacagtgccccctgcagaatgttca
SEQ ID NO. 110			Cλ 轻链恒定区 (IGLC6*01) 1) 氨基酸序列	GQPKAAPSVTLPFPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTPSK QSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
SEQ ID NO. 111	人 Cλ 恒定区	IGLC7*01 或 IGLC7*02	Cλ 轻链恒定区 (IGLC7*01 或 IGLC7*02) 核苷酸序列	ggtcagcccaaggctgccccctcggtcactctgttccaccctctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctaccgggagccgtgacagtgccctggaaggcagatggcagccccgtcaagggtgggagtgagaccaccacacctccaaacaagaacaacaagtaacgcggccagcagctactgagcctgacgctgagcagtggaagtcacacagaagctacagctgccgggtcacgcatgaaggagcaccgtggagaagacagtgccccctgcagaatgtct

[0663]

SEQ ID NO. 112			Cλ 轻链恒定区 (IGLC7*01)氨基酸序列	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGA VTVAWKADGSPVK VGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
SEQ ID NO. 113	人 Cλ 恒定区	IGLC7*03	Cλ 轻链恒定区 (IGLC7*03)核苷酸序列	GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCACCCCTCCTCT GAGGAGCTTC AAGCCAACAAGGCCACACTGGTGTGTCTCGTAAGTGACTTCAACCCG GGAGCCGTG ACAGTGGCCTGGAAGGCAGATGGCAGCCCCGTCAAGGTGGGAGTGGA GACCACCA AACCTCCAAACAAGCAACAACAAGTATGCGGCCAGCAGCTACCTG AGCCTGACG CCCGAGCAGTGGAAGTCCACAGAAGCTACAGCTGCCGGGTACGCA TGAAGGGA GCACGTGGAGAAGACAGTGGCCCCTGCAGAATGCTCT
SEQ ID NO. 114			Cλ 轻链恒定区 (IGLC7*03)氨基酸序列	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFNPGA VTVAWKADGSPVK VGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS

[0664] 表5:获得自基因集富集分析的结果汇总(实施例3)

[0665]

标志途径	数目	NES	P 值	FDR q 值
下调				
肌细胞生成	192	-1.499	0.0036	0.0891
未折叠蛋白反应	105	-1.610	0.0040	0.1081
上皮向间充质转变	189	-1.374	0.0245	0.1675
成骨细胞分化*	12	-1.573	0.0296	0.0822
成骨细胞转录因子**	14	-1.525	0.0450	0.0909
MTORC1 信号转导	182	-1.328	0.0450	0.2176
糖酵解	188	-1.299	0.0489	0.2437
WNT β 连环蛋白信号转导	39	-1.458	0.0492	0.1018
上调				
G2M 检查点	189	2.185	0.0000	0.0000
E2F 靶标	189	2.171	0.0000	0.0000
干扰素 α 反应	87	2.164	0.0000	0.0000
有丝分裂纺锤体	194	2.112	0.0000	0.0000
干扰素 γ 反应	183	1.959	0.0000	0.0000
炎症反应	190	1.860	0.0000	0.0035
通过 NFκB 的 TNFA 信号转导	193	1.624	0.0000	0.0192
同种异体移植物排斥	175	1.576	0.0000	0.0265
补体	178	1.370	0.0056	0.1166
细胞凋亡	156	1.373	0.0207	0.1266

[0666] P值:用邦费尼罗事后检验修正。NES:归一化富集得分;FDR:错误发现率;*数据集来自Park等人;**数据集来自Zaidi等人。

[0667] 表6:通过Tfr2-ECD全身处理的野生型小鼠的铁、血液和骨参数

	PBS (n=9)	Tfr2-ECD (n=8)	P 值
铁状态			
血浆铁[μmol/L]	31.1±4.5	30.1±3.3	0.608
肝脏铁[μg/g 干组织]	600.4±333	578.3±273	0.889
脾脏铁[μg/g 干组织]	692.0±157	620.2±113	0.301
肾脏铁[μg/g 干组织]	112.2±14.4	112.6±15.0	0.961
心脏铁[μg/g 干组织]	189.8±54.3	207.8±54.1	0.727
血液计数			
RBC[10 ¹² /L]	9.18±1.39	10.1±0.40	0.129
血红蛋白[mmol/L]	8.91±1.25	9.77±0.41	0.105
HCT	0.47±0.07	0.51±0.02	0.189
血小板[10 ⁹ /L]	414±99.5	385±69.5	0.525
网织红细胞[10 ⁹ /L]	191±69.6	197±24.2	0.840
WBC [10 ⁹ /L]	9.23±4.11	11.0±3.09	0.369
分化计数, 绝度值%			
嗜中性粒细胞	9.52±2.23	7.33±2.82	0.104
淋巴细胞	88.6±3.37	90.1±4.35	0.428
单核细胞	1.63±1.47	2.17±2.55	0.603
μCT			
BV/TV [%]股骨	9.40±2.62	10.7±3.09	0.346
BV/TV [%]椎骨	25.1±4.52	24.1±3.36	0.612

[0669] 数据为平均值±SD,通过学生t检验分析

[0670] RBC,红细胞;HCT,红细胞比容;WBC:白细胞;BV/TV,骨体积/总体积。

[0671] 表7:抗体重链可变区基因节段

基因节段	实施例等位基因	基因节段	实施例等位基因	基因节段	实施例等位基因	基因节段	实施例等位基因
JH6	02	D1-14	01	VH2-5	10	VH3-43	01
JH5	02	D6-13	01	VH3-7	01	VH1-45	02
JH4	02	D5-12	01	VH1-8	01	VH1-46	01
JH3	02	D4-11	01	VH3-9	01	VH3-48	01
JH2	01	D3-10	01	VH3-11	01	VH3-49	05
JH1	01	D3-9	01	VH3-13	01	VH5-51	01
D7-27	02	D2-8	01	VH3-15	01	VH3-53	01
D1-26	01	D1-7	01	VH1-18	01	VH1-58	01
D6-25	01	D6-6	01	VH3-20	01	VH4-59	01
D5-24	01	D5-5	01	VH3-21	03	VH4-61	01
D4-23	01	D4-4	01	VH3-23	04	VH3-64	02
D3-22	01	D3-3	01	VH1-24	01	VH3-66	03
D2-21	02	D2-2	02	VH2-26	01	VH1-69	12
D1-20	01	D1-1	01	VH4-28	05	VH2-70	04
D6-19	01	VH6-1	01	VH3-30	18	VH3-72	01
D5-18	01	VH1-2	02	VH4-31	03	VH3-73	02
D4-17	01	VH1-3	01	VH3-33	01	VH3-74	01
D3-16	02	VH4-4	02	VH4-34	01		
D2-15	01	VH7-4	01	VH4-39	01		

[0673] 表8:抗体轻链可变区基因节段

[0674]

基因 节段	实施例等位基因	基因 节段	实施例等位基因	基因 节段	实施例等位基因
Jκ5		Vκ3-15	01	Vκ1-8	01
Jκ4		Vκ1-16	02	Vκ1-43	01
Jκ3		Vκ1-17	01	Vκ3-11	01
Jκ2		Vκ3-20	01	Vκ1-12	02
Jκ1		Vκ6-21	01	Vκ1-13	01
Vκ4-1		Vκ2-24	01	Vκ3-15	01
Vκ5-2		Vκ1-27	01	Vκ1-16	01
Vκ1-5		Vκ2-28	01	Vκ1-17	01
Vκ1-6	01	Vκ2-29	01	Vκ3-20	01
Vκ1-8	01	Vκ2-30	01	Vκ2-26	02
Vκ1-9	01	Vκ1-33	01	Vκ2-28	01
Vκ3-11	01	Vκ1-39	01	Vκ2-29	01
Vκ1-12	01	Vκ2-40	01	Vκ2-30	01
Vκ1-13	01	Vκ3-7	01	Vκ1-33	01

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Leu Glu Asp Thr Ile Arg Gln Thr Ser Leu Arg Glu Arg Val Ala Gly
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Arg Gln Lys Leu Asp His Val Trp Thr Asp Thr His Tyr Val Gly Leu
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Gln Phe Pro Asp Pro Ala His Pro Asn Thr Leu His Trp Val Asp Glu
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Glu Val Tyr Cys Pro Tyr Ser Ala Thr Gly Asn Ala Thr Gly Lys Leu		
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Lys Pro Gly Leu Ser Ser His Gln Ala Val Tyr Gly His Val His Leu		
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Gln Phe Pro Pro Val Glu Ser Ser Gly Leu Pro Ser Ile Pro Ala Gln		
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Arg	Leu	Gly	Pro	Gly	Pro	Asp	Leu	Arg	Leu	Val	Val	Asn	Asn	His	Arg	385	390	395
Val	Ser	Thr	Pro	Ile	Ser	Asn	Ile	Phe	Ala	Cys	Ile	Glu	Gly	Phe	Ala	405	410	415
Glu	Pro	Asp	His	Tyr	Val	Val	Ile	Gly	Ala	Gln	Arg	Asp	Ala	Trp	Gly	420	425	430
Pro	Gly	Ala	Ala	Lys	Ser	Ala	Val	Gly	Thr	Ala	Ile	Leu	Leu	Glu	Leu	435	440	445
Val	Arg	Thr	Phe	Ser	Ser	Met	Val	Ser	Asn	Gly	Phe	Arg	Pro	Arg	Arg	450	455	460
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Ala	Thr	Glu	Trp	Leu	Glu	Gly	Tyr	Leu	Ser	Val	Leu	His	Leu	Lys	Ala	485	490	495
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His	Ala	Lys	Thr	Ser	Pro	Leu	Leu	Val	Ser	Leu	Ile	Glu	Asn	Ile	Leu	515	520	525
Lys	Gln	Val	Asp	Ser	Pro	Asn	His	Ser	Gly	Gln	Thr	Leu	Tyr	Glu	Gln	530	535	540
Val	Ala	Leu	Thr	His	Pro	Ser	Trp	Asp	Ala	Glu	Val	Ile	Gln	Pro	Leu	545	550	555
Pro	Met	Asp	Ser	Ser	Ala	Tyr	Ser	Phe	Thr	Ala	Phe	Ala	Gly	Val	Pro	565	570	575
Ala	Val	Glu	Phe	Ser	Phe	Met	Glu	Asp	Asp	Arg	Val	Tyr	Pro	Phe	Leu	580	585	590
His	Thr	Lys	Glu	Asp	Thr	Tyr	Glu	Asn	Leu	His	Lys	Met	Leu	Arg	Gly	595	600	605
Arg	Leu	Pro	Ala	Val	Val	Gln	Ala	Val	Ala	Gln	Leu	Ala	Gly	Gln	Leu	610	615	620
Leu	Ile	Arg	Leu	Ser	His	Asp	His	Leu	Leu	Pro	Leu	Asp	Phe	Gly	Arg	625	630	635
Tyr	Gly	Asp	Val	Val	Leu	Arg	His	Ile	Gly	Asn	Leu	Asn	Glu	Phe	Ser	645	650	655
Gly	Asp	Leu	Lys	Glu	Arg	Gly	Leu	Thr	Leu	Gln	Trp	Val	Tyr	Ser	Ala			

660	665	670
Arg Gly Asp Tyr Ile Arg Ala Ala Glu Lys Leu Arg Lys Glu Ile Tyr		
675	680	685
Ser Ser Glu Arg Asn Asp Glu Arg Leu Met Arg Met Tyr Asn Val Arg		
690	695	700
Ile Met Arg Val Glu Phe Tyr Phe Leu Ser Gln Tyr Val Ser Pro Ala		
705	710	715
Asp Ser Pro Phe Arg His Ile Phe Leu Gly Gln Gly Asp His Thr Leu		
725	730	735
Gly Ala Leu Val Asp His Leu Arg Met Leu Arg Ala Asp Gly Ser Gly		
740	745	750
Ala Ala Ser Ser Arg Leu Thr Ala Gly Leu Gly Phe Gln Glu Ser Arg		
755	760	765
Phe Arg Arg Gln Leu Ala Leu Leu Thr Trp Thr Leu Gln Gly Ala Ala		
770	775	780
Asn Ala Leu Ser Gly Asp Val Trp Asn Ile Asp Asn Asn Phe		
785	790	795

<210> 5

<211> 94

<212> PRT

<213> 智人

<400> 5

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

<210> 6

<211> 186

<212> PRT

<213> 智人

<400> 6

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

<210> 7

<211> 126

<212> PRT

<213> 智人

<400> 7

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

Leu	Leu	Asp	His	Leu	Arg	Leu	Leu	Arg	Ser	Asn	Ser	Ser	Gly	Thr	Pro
				85					90					95	
Gly	Ala	Thr	Ser	Ser	Thr	Gly	Phe	Gln	Glu	Ser	Arg	Phe	Arg	Arg	Gln
				100				105					110		
Leu	Ala	Leu	Leu	Thr	Trp	Thr	Leu	Gln	Gly	Ala	Ala	Asn	Ala		
				115				120					125		
<210> 8															
<211> 2538															
<212> PRT															
<213> 智人															
<400> 8															
Gly	Thr	Thr	Cys	Gly	Thr	Thr	Gly	Cys	Ala	Ala	Cys	Ala	Ala	Ala	Thr
1				5					10					15	
Thr	Gly	Ala	Thr	Gly	Ala	Gly	Cys	Ala	Ala	Thr	Gly	Cys	Thr	Thr	Thr
				20				25					30		
Thr	Thr	Thr	Ala	Thr	Ala	Ala	Thr	Gly	Cys	Cys	Ala	Ala	Cys	Thr	Thr
				35				40					45		
Thr	Gly	Thr	Ala	Cys	Ala	Ala	Ala	Ala	Ala	Ala	Gly	Thr	Thr	Gly	Gly
				50				55				60			
Cys	Ala	Cys	Cys	Ala	Thr	Gly	Gly	Ala	Gly	Cys	Gly	Gly	Cys	Thr	Thr
65					70				75					80	
Thr	Gly	Gly	Gly	Gly	Thr	Cys	Thr	Ala	Thr	Thr	Cys	Cys	Ala	Gly	Ala
				85					90					95	
Gly	Ala	Gly	Cys	Gly	Cys	Ala	Ala	Cys	Ala	Ala	Cys	Thr	Gly	Thr	Cys
				100				105					110		
Cys	Cys	Cys	Ala	Ala	Gly	Ala	Thr	Cys	Cys	Thr	Cys	Thr	Cys	Ala	Gly
				115				120					125		
Ala	Cys	Cys	Gly	Thr	Cys	Thr	Ala	Cys	Cys	Ala	Gly	Cys	Gly	Thr	Gly
				130				135				140			
Thr	Gly	Gly	Ala	Ala	Gly	Gly	Cys	Cys	Cys	Cys	Cys	Gly	Gly	Ala	Ala
145					150				155					160	
Ala	Gly	Gly	Gly	Cys	Ala	Cys	Cys	Thr	Gly	Gly	Ala	Gly	Gly	Ala	Gly
				165					170					175	
Gly	Ala	Ala	Gly	Ala	Gly	Gly	Ala	Ala	Gly	Ala	Cys	Gly	Gly	Gly	Gly
				180				185					190		
Ala	Gly	Gly	Ala	Gly	Gly	Gly	Gly	Gly	Cys	Gly	Gly	Ala	Gly	Ala	Cys
				195				200				205			
Ala	Thr	Thr	Gly	Gly	Cys	Cys	Cys	Ala	Cys	Thr	Thr	Cys	Thr	Gly	Cys
				210				215				220			

Cys Cys Cys Ala Thr Gly Gly Ala Gly Cys Thr Gly Ala Gly Gly Gly			
225	230	235	240
Gly Cys Cys Cys Thr Gly Ala Gly Cys Cys Cys Thr Gly Gly Gly			
	245	250	255
Cys Thr Cys Thr Ala Gly Ala Cys Cys Cys Ala Gly Gly Cys Ala Gly			
	260	265	270
Cys Cys Ala Ala Ala Cys Cys Thr Cys Ala Thr Thr Cys Cys Cys Thr			
	275	280	285
Gly Gly Gly Cys Gly Gly Cys Ala Gly Cys Ala Gly Gly Ala Cys Gly			
	290	295	300
Gly Ala Gly Gly Gly Cys Thr Gly Cys Cys Cys Cys Cys Thr Ala Cys			
305	310	315	320
Cys Thr Gly Gly Thr Cys Cys Thr Gly Ala Cys Gly Gly Cys Cys Cys			
	325	330	335
Thr Gly Cys Thr Gly Ala Thr Cys Thr Thr Cys Ala Cys Thr Gly Gly			
	340	345	350
Gly Gly Cys Cys Thr Thr Cys Cys Thr Ala Cys Thr Gly Gly Gly Cys			
	355	360	365
Thr Ala Cys Gly Thr Cys Gly Cys Cys Thr Thr Cys Cys Gly Ala Gly			
	370	375	380
Gly Gly Thr Cys Cys Thr Gly Cys Cys Ala Gly Gly Cys Gly Thr Gly			
385	390	395	400
Cys Gly Gly Ala Gly Ala Cys Thr Cys Thr Gly Thr Gly Thr Thr Gly			
	405	410	415
Gly Thr Gly Gly Thr Cys Ala Gly Thr Gly Ala Gly Gly Ala Thr Gly			
	420	425	430
Thr Cys Ala Ala Cys Thr Ala Thr Gly Ala Gly Cys Cys Thr Gly Ala			
	435	440	445
Cys Cys Thr Gly Gly Ala Thr Thr Thr Cys Cys Ala Cys Cys Ala Gly			
	450	455	460
Gly Gly Cys Ala Gly Ala Cys Thr Cys Thr Ala Cys Thr Gly Gly Ala			
465	470	475	480
Gly Cys Gly Ala Cys Cys Thr Cys Cys Ala Gly Gly Cys Cys Ala Thr			
	485	490	495
Gly Thr Thr Cys Cys Thr Gly Cys Ala Gly Thr Thr Cys Cys Thr Gly			
	500	505	510
Gly Gly Gly Gly Ala Gly Gly Gly Cys Gly Cys Cys Thr Gly Gly			
	515	520	525
Ala Gly Gly Ala Cys Ala Cys Cys Ala Thr Cys Ala Gly Gly Cys Ala			

530	535	540
Ala Ala Cys Cys Ala Gly Cys Cys Thr Thr Cys Gly Gly Gly Ala Ala		
545	550	555
Cys Gly Gly Gly Thr Gly Gly Cys Ala Gly Gly Cys Thr Cys Gly Gly		560
	565	570
Cys Cys Gly Gly Gly Ala Thr Gly Gly Cys Cys Gly Cys Thr Cys Thr		575
	580	585
Gly Ala Cys Thr Cys Ala Gly Gly Ala Cys Ala Thr Thr Cys Gly Cys		590
	595	600
Gly Cys Gly Gly Cys Gly Cys Thr Cys Thr Cys Cys Cys Gly Cys Cys		605
610	615	620
Ala Gly Ala Ala Gly Cys Thr Gly Gly Ala Cys Cys Ala Cys Gly Thr		
625	630	635
Gly Thr Gly Gly Ala Cys Cys Gly Ala Cys Ala Cys Gly Cys Ala Cys		640
	645	650
Thr Ala Cys Gly Thr Gly Gly Gly Gly Cys Thr Gly Cys Ala Ala Thr		655
	660	665
Thr Cys Cys Cys Gly Gly Ala Thr Cys Cys Gly Gly Cys Thr Cys Ala		670
675	680	685
Cys Cys Cys Cys Ala Ala Cys Ala Cys Cys Cys Thr Gly Cys Ala Cys		
690	695	700
Thr Gly Gly Gly Thr Cys Gly Ala Thr Gly Ala Gly Gly Cys Cys Gly		
705	710	715
Gly Gly Ala Ala Gly Gly Thr Cys Gly Gly Ala Gly Ala Gly Cys Ala		720
	725	730
Gly Cys Thr Gly Cys Cys Gly Cys Thr Gly Gly Ala Gly Gly Ala Cys		735
	740	745
Cys Cys Thr Gly Ala Cys Gly Thr Cys Thr Ala Cys Thr Gly Cys Cys		750
755	760	765
Cys Cys Thr Ala Cys Ala Gly Cys Gly Cys Cys Ala Thr Cys Gly Gly		
770	775	780
Cys Ala Ala Cys Gly Thr Cys Ala Cys Gly Gly Gly Ala Gly Ala Gly		
785	790	795
Cys Thr Gly Gly Thr Gly Thr Ala Cys Gly Cys Cys Cys Ala Cys Thr		800
	805	810
Ala Cys Gly Gly Gly Cys Gly Gly Cys Cys Cys Gly Ala Ala Gly Ala		815
	820	825
Cys Cys Thr Gly Cys Ala Gly Gly Ala Cys Cys Thr Gly Cys Gly Gly		830
835	840	845

Gly Cys Cys Ala Gly Gly Gly Gly Cys Gly Thr Gly Gly Ala Thr Cys		
850	855	860
Cys Ala Gly Thr Gly Gly Gly Cys Cys Gly Cys Thr Gly Cys Thr		
865	870	875
Gly Cys Thr Gly Gly Thr Gly Cys Gly Cys Gly Thr Gly Gly Gly Gly		
885	890	895
Gly Thr Gly Ala Thr Cys Ala Gly Cys Thr Thr Cys Gly Cys Cys Cys		
900	905	910
Ala Gly Ala Ala Gly Gly Thr Gly Ala Cys Cys Ala Ala Thr Gly Cys		
915	920	925
Thr Cys Ala Gly Gly Ala Cys Thr Thr Cys Gly Gly Gly Gly Cys Thr		
930	935	940
Cys Ala Ala Gly Gly Ala Gly Thr Gly Cys Thr Cys Ala Thr Ala Thr		
945	950	955
Ala Cys Cys Cys Ala Gly Ala Gly Cys Cys Ala Gly Cys Gly Gly Ala		
965	970	975
Cys Thr Thr Cys Thr Cys Cys Cys Ala Gly Gly Ala Cys Cys Cys Ala		
980	985	990
Cys Cys Cys Ala Ala Gly Cys Cys Ala Ala Gly Cys Cys Thr Gly Thr		
995	1000	1005
Cys Cys Ala Gly Cys Cys Ala Gly Cys Ala Gly Gly Cys Ala Gly		
1010	1015	1020
Thr Gly Thr Ala Thr Gly Gly Ala Cys Ala Thr Gly Thr Gly Cys		
1025	1030	1035
Ala Cys Cys Thr Gly Gly Gly Ala Ala Cys Thr Gly Gly Ala Gly		
1040	1045	1050
Ala Cys Cys Cys Cys Thr Ala Cys Ala Cys Ala Cys Cys Thr Gly		
1055	1060	1065
Gly Cys Thr Thr Cys Cys Cys Thr Thr Cys Cys Thr Thr Cys Ala		
1070	1075	1080
Ala Thr Cys Ala Ala Ala Cys Cys Cys Ala Gly Thr Thr Cys Cys		
1085	1090	1095
Cys Thr Cys Cys Ala Gly Thr Thr Gly Cys Ala Thr Cys Ala Thr		
1100	1105	1110
Cys Ala Gly Gly Cys Cys Thr Thr Cys Cys Cys Ala Gly Cys Ala		
1115	1120	1125
Thr Cys Cys Cys Ala Gly Cys Cys Cys Ala Gly Cys Cys Cys Ala		
1130	1135	1140
Thr Cys Ala Gly Thr Gly Cys Ala Gly Ala Cys Ala Thr Thr Gly		

1145	1150	1155
Cys Cys Thr Cys Cys Cys Gly Cys Cys Thr Gly Cys Thr Gly Ala		
1160	1165	1170
Gly Gly Ala Ala Gly Cys Thr Cys Ala Ala Ala Gly Gly Cys Cys		
1175	1180	1185
Cys Thr Gly Thr Gly Gly Cys Cys Cys Cys Cys Cys Ala Ala Gly		
1190	1195	1200
Ala Ala Thr Gly Gly Cys Ala Gly Gly Gly Gly Ala Gly Cys Cys		
1205	1210	1215
Thr Cys Cys Thr Ala Gly Gly Cys Thr Cys Cys Cys Cys Thr Thr		
1220	1225	1230
Ala Thr Cys Ala Cys Cys Thr Gly Gly Gly Cys Cys Cys Cys Gly		
1235	1240	1245
Gly Gly Cys Cys Ala Cys Gly Ala Cys Thr Thr Cys Gly Gly Cys		
1250	1255	1260
Thr Ala Gly Thr Gly Gly Thr Cys Ala Ala Cys Ala Ala Thr Cys		
1265	1270	1275
Ala Cys Ala Gly Gly Ala Cys Cys Thr Cys Cys Ala Cys Cys Cys		
1280	1285	1290
Cys Cys Ala Thr Cys Ala Ala Cys Ala Ala Cys Ala Thr Cys Thr		
1295	1300	1305
Thr Cys Gly Gly Cys Thr Gly Cys Ala Thr Cys Gly Ala Ala Gly		
1310	1315	1320
Gly Cys Cys Gly Cys Thr Cys Ala Gly Ala Gly Cys Cys Ala Gly		
1325	1330	1335
Ala Thr Cys Ala Cys Thr Ala Cys Gly Thr Thr Gly Thr Cys Ala		
1340	1345	1350
Thr Cys Gly Gly Gly Gly Cys Cys Cys Ala Gly Ala Gly Gly Gly		
1355	1360	1365
Ala Thr Gly Cys Ala Thr Gly Gly Gly Gly Cys Cys Cys Ala Gly		
1370	1375	1380
Gly Ala Gly Cys Ala Gly Cys Thr Ala Ala Ala Thr Cys Cys Gly		
1385	1390	1395
Cys Thr Gly Thr Gly Gly Gly Gly Ala Cys Gly Gly Cys Thr Ala		
1400	1405	1410
Thr Ala Cys Thr Cys Cys Thr Gly Gly Ala Gly Cys Thr Gly Gly		
1415	1420	1425
Thr Gly Cys Gly Gly Ala Cys Cys Thr Thr Thr Thr Cys Cys Thr		
1430	1435	1440

Cys Cys Ala Thr Gly Gly Thr Gly Ala Gly Cys Ala Ala Cys Gly		
1445	1450	1455
Gly Cys Thr Thr Cys Cys Gly Gly Cys Cys Cys Cys Gly Cys Ala		
1460	1465	1470
Gly Ala Ala Gly Thr Cys Thr Cys Cys Thr Cys Thr Thr Cys Ala		
1475	1480	1485
Thr Cys Ala Gly Cys Thr Gly Gly Gly Ala Cys Gly Gly Thr Gly		
1490	1495	1500
Gly Thr Gly Ala Cys Thr Thr Thr Gly Gly Ala Ala Gly Cys Gly		
1505	1510	1515
Thr Gly Gly Gly Cys Thr Cys Cys Ala Cys Gly Gly Ala Gly Thr		
1520	1525	1530
Gly Gly Cys Thr Ala Gly Ala Gly Gly Gly Cys Thr Ala Cys Cys		
1535	1540	1545
Thr Cys Ala Gly Cys Gly Thr Gly Cys Thr Gly Cys Ala Cys Cys		
1550	1555	1560
Thr Cys Ala Ala Ala Gly Cys Cys Gly Thr Ala Gly Thr Gly Thr		
1565	1570	1575
Ala Cys Gly Thr Gly Ala Gly Cys Cys Thr Gly Gly Ala Cys Ala		
1580	1585	1590
Ala Cys Gly Cys Ala Gly Thr Gly Cys Thr Gly Gly Gly Gly Gly		
1595	1600	1605
Ala Thr Gly Ala Cys Ala Ala Gly Thr Thr Thr Cys Ala Thr Gly		
1610	1615	1620
Cys Cys Ala Ala Gly Ala Cys Cys Ala Gly Cys Cys Cys Cys Cys		
1625	1630	1635
Thr Thr Cys Thr Gly Ala Cys Ala Ala Gly Thr Cys Thr Cys Ala		
1640	1645	1650
Thr Thr Gly Ala Gly Ala Gly Thr Gly Thr Cys Cys Thr Gly Ala		
1655	1660	1665
Ala Gly Cys Ala Gly Gly Thr Gly Gly Ala Thr Thr Cys Thr Cys		
1670	1675	1680
Cys Cys Ala Ala Cys Cys Ala Cys Ala Gly Thr Gly Gly Gly Cys		
1685	1690	1695
Ala Gly Ala Cys Thr Cys Thr Cys Thr Ala Thr Gly Ala Ala Cys		
1700	1705	1710
Ala Gly Gly Thr Gly Gly Thr Gly Thr Thr Cys Ala Cys Cys Ala		
1715	1720	1725
Ala Thr Cys Cys Cys Ala Gly Cys Thr Gly Gly Gly Ala Thr Gly		

1730	1735	1740
Cys Thr Gly Ala Gly Gly Thr Gly Ala Thr Cys	Cys Gly Gly Cys	
1745	1750	1755
Cys Cys Cys Thr Ala Cys Cys Cys Ala Thr Gly	Gly Ala Cys Ala	
1760	1765	1770
Gly Cys Ala Gly Thr Gly Cys Cys Thr Ala Thr	Thr Cys Cys Thr	
1775	1780	1785
Thr Cys Ala Cys Gly Gly Cys Cys Thr Thr Thr	Gly Thr Gly Gly	
1790	1795	1800
Gly Ala Gly Thr Cys Cys Cys Thr Gly Cys Cys	Gly Thr Cys Gly	
1805	1810	1815
Ala Gly Thr Thr Cys Thr Cys Cys Thr Thr Thr	Ala Thr Gly Gly	
1820	1825	1830
Ala Gly Gly Ala Cys Gly Ala Cys Cys Ala Gly	Gly Cys Cys Thr	
1835	1840	1845
Ala Cys Cys Cys Ala Thr Thr Cys Cys Thr Gly	Cys Ala Cys Ala	
1850	1855	1860
Cys Ala Ala Ala Gly Gly Ala Gly Gly Ala Cys	Ala Cys Thr Thr	
1865	1870	1875
Ala Thr Gly Ala Gly Ala Ala Cys Cys Thr Gly	Cys Ala Thr Ala	
1880	1885	1890
Ala Gly Gly Thr Gly Cys Thr Gly Cys Ala Ala	Gly Gly Cys Cys	
1895	1900	1905
Gly Cys Cys Thr Gly Cys Cys Cys Gly Cys Cys	Gly Thr Gly Gly	
1910	1915	1920
Cys Cys Cys Ala Gly Gly Cys Cys Gly Thr Gly	Gly Cys Cys Cys	
1925	1930	1935
Ala Gly Cys Thr Cys Gly Cys Ala Gly Gly Gly	Cys Ala Gly Cys	
1940	1945	1950
Thr Cys Cys Thr Cys Ala Thr Cys Cys Gly Gly	Cys Thr Cys Ala	
1955	1960	1965
Gly Cys Cys Ala Cys Gly Ala Thr Cys Gly Cys	Cys Thr Gly Cys	
1970	1975	1980
Thr Gly Cys Cys Cys Cys Thr Cys Gly Ala Cys	Thr Thr Cys Gly	
1985	1990	1995
Gly Cys Cys Gly Cys Thr Ala Cys Gly Gly Gly	Gly Ala Cys Gly	
2000	2005	2010
Thr Cys Gly Thr Cys Cys Thr Cys Ala Gly Gly	Cys Ala Cys Ala	
2015	2020	2025

Thr Cys Gly Gly Gly Ala Ala Cys Cys Thr Cys Ala Ala Cys Gly		
2030	2035	2040
Ala Gly Thr Thr Cys Thr Cys Thr Gly Gly Gly Gly Ala Cys Cys		
2045	2050	2055
Thr Cys Ala Ala Gly Gly Cys Cys Cys Gly Cys Gly Gly Gly Cys		
2060	2065	2070
Thr Gly Ala Cys Cys Cys Thr Gly Cys Ala Gly Thr Gly Gly Gly		
2075	2080	2085
Thr Gly Thr Ala Cys Thr Cys Gly Gly Cys Gly Cys Gly Gly Gly		
2090	2095	2100
Gly Gly Gly Ala Cys Thr Ala Cys Ala Thr Cys Cys Gly Gly Gly		
2105	2110	2115
Cys Gly Gly Cys Gly Gly Ala Ala Ala Ala Gly Cys Thr Gly Cys		
2120	2125	2130
Gly Gly Cys Cys Gly Gly Ala Gly Ala Thr Cys Thr Ala Cys Ala		
2135	2140	2145
Gly Cys Thr Cys Gly Gly Ala Gly Gly Ala Gly Ala Gly Ala Gly		
2150	2155	2160
Ala Cys Gly Ala Gly Cys Gly Ala Cys Thr Gly Ala Cys Ala Cys		
2165	2170	2175
Gly Cys Ala Thr Gly Thr Ala Cys Ala Ala Cys Gly Thr Gly Cys		
2180	2185	2190
Gly Cys Ala Thr Ala Ala Thr Gly Cys Gly Gly Gly Thr Gly Gly		
2195	2200	2205
Ala Gly Thr Thr Cys Thr Ala Cys Thr Thr Cys Cys Thr Thr Thr		
2210	2215	2220
Cys Cys Cys Ala Gly Thr Ala Cys Gly Thr Gly Thr Cys Gly Cys		
2225	2230	2235
Cys Ala Gly Cys Cys Gly Ala Cys Thr Cys Cys Cys Cys Gly Thr		
2240	2245	2250
Thr Cys Cys Gly Cys Cys Ala Cys Ala Thr Cys Thr Thr Cys Ala		
2255	2260	2265
Thr Gly Gly Gly Cys Cys Gly Thr Gly Gly Ala Gly Ala Cys Cys		
2270	2275	2280
Ala Cys Ala Cys Gly Cys Thr Gly Gly Gly Cys Gly Cys Cys Cys		
2285	2290	2295
Thr Gly Cys Thr Gly Gly Ala Cys Cys Ala Cys Cys Thr Gly Cys		
2300	2305	2310
Gly Gly Cys Thr Gly Cys Thr Gly Cys Gly Cys Thr Cys Cys Ala		

2315	2320	2325
Ala Cys Ala Gly Cys Thr	Cys Cys Gly Gly Gly	Ala Cys Cys Cys
2330	2335	2340
Cys Cys Gly Gly Gly Gly	Cys Cys Ala Cys Cys	Thr Cys Cys Thr
2345	2350	2355
Cys Cys Ala Cys Thr Gly	Gly Cys Thr Thr Cys	Cys Ala Gly Gly
2360	2365	2370
Ala Gly Ala Gly Cys Cys	Gly Thr Thr Thr Cys	Cys Gly Gly Cys
2375	2380	2385
Gly Thr Cys Ala Gly Cys	Thr Ala Gly Cys Cys	Cys Thr Gly Cys
2390	2395	2400
Thr Cys Ala Cys Cys Thr	Gly Gly Ala Cys Gly	Cys Thr Gly Cys
2405	2410	2415
Ala Ala Gly Gly Gly Gly	Cys Ala Gly Cys Cys	Ala Ala Thr Gly
2420	2425	2430
Cys Gly Cys Thr Thr Ala	Gly Cys Gly Gly Gly	Gly Ala Thr Gly
2435	2440	2445
Thr Cys Thr Gly Gly Ala	Ala Cys Ala Thr Thr	Gly Ala Thr Ala
2450	2455	2460
Ala Cys Ala Ala Cys Thr	Thr Cys Thr Thr Gly	Cys Cys Ala Ala
2465	2470	2475
Cys Thr Thr Thr Cys Thr	Thr Gly Thr Ala Cys	Ala Ala Ala Gly
2480	2485	2490
Thr Thr Gly Gly Cys Ala	Thr Thr Ala Thr Ala	Ala Gly Ala Ala
2495	2500	2505
Ala Gly Cys Ala Thr Thr	Gly Cys Thr Thr Ala	Thr Cys Ala Ala
2510	2515	2520
Thr Thr Thr Gly Thr Thr	Gly Cys Ala Ala Cys	Gly Ala Ala Cys
2525	2530	2535
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<211> 3596		
<212> PRT		
<213> 小家鼠		
<400> 9		
Gly Ala Gly Thr Cys Thr	Cys Cys Thr Gly Gly Gly	Ala Gly Cys Ala
1	5	10
Thr Gly Gly Thr Cys Cys	Ala Ala Gly Ala Ala	Ala Cys Cys Cys Ala
20	25	30
Gly Ala Gly Ala Cys Cys	Thr Gly Thr Thr Gly	Cys Thr Gly Ala Gly

35	40	45
Cys Thr Gly Ala Ala Cys Thr Thr Gly Gly Cys Thr Gly Cys Thr Gly		
50	55	60
Thr Gly Thr Cys Thr Thr Cys Cys Cys Ala Cys Thr Cys Ala Gly Gly		
65	70	75
Ala Cys Thr Cys Gly Gly Cys Thr Thr Thr Gly Ala Cys Ala Gly Gly		80
85	90	95
Cys Ala Cys Gly Ala Gly Gly Cys Ala Gly Gly Gly Ala Cys Thr Gly		
100	105	110
Gly Gly Gly Thr Ala Cys Thr Gly Gly Thr Gly Ala Gly Cys Cys Cys		
115	120	125
Cys Thr Ala Cys Cys Thr Cys Thr Cys Ala Gly Ala Thr Cys Thr Thr		
130	135	140
Thr Cys Thr Gly Gly Ala Cys Cys Thr Gly Gly Cys Thr Gly Cys Ala		
145	150	155
Gly Gly Thr Cys Cys Thr Gly Gly Thr Gly Thr Cys Thr Thr Cys Gly		
165	170	175
Thr Cys Gly Cys Gly Gly Cys Thr Thr Gly Gly Ala Thr Thr Thr Cys		
180	185	190
Ala Ala Ala Cys Thr Gly Gly Ala Gly Gly Ala Gly Thr Thr Cys Ala		
195	200	205
Gly Gly Ala Gly Gly Gly Gly Cys Ala Cys Ala Ala Gly Cys Ala		
210	215	220
Thr Gly Gly Ala Gly Cys Ala Ala Cys Gly Thr Thr Gly Gly Gly Gly		
225	230	235
Thr Cys Thr Ala Cys Thr Thr Cys Gly Gly Ala Gly Ala Gly Thr Gly		
245	250	255
Cys Ala Ala Cys Ala Gly Thr Gly Gly Thr Cys Cys Cys Cys Ala Ala		
260	265	270
Gly Ala Cys Cys Cys Thr Cys Thr Cys Ala Gly Ala Cys Cys Ala Thr		
275	280	285
Cys Thr Ala Cys Ala Gly Ala Cys Gly Cys Gly Thr Gly Gly Ala Ala		
290	295	300
Gly Gly Cys Cys Cys Thr Cys Ala Gly Cys Thr Gly Gly Ala Gly Cys		
305	310	315
Ala Cys Cys Thr Gly Gly Ala Gly Gly Ala Gly Gly Ala Ala Gly Ala		
325	330	335
Cys Ala Gly Gly Gly Ala Gly Gly Ala Ala Gly Gly Gly Gly Cys Gly		
340	345	350

Gly Ala Gly Cys Thr Thr Cys Cys Thr Gly Cys Cys Cys Ala Gly Thr		
355	360	365
Thr Cys Thr Gly Cys Cys Cys Cys Ala Thr Gly Gly Ala Ala Cys Thr		
370	375	380
Cys Ala Ala Ala Gly Gly Cys Cys Cys Thr Gly Ala Gly Cys Ala Cys		
385	390	395
Thr Thr Ala Gly Gly Cys Thr Cys Cys Thr Gly Thr Cys Cys Cys Gly		
405	410	415
Gly Gly Ala Gly Thr Cys Ala Ala Thr Thr Cys Cys Cys Ala Thr Ala		
420	425	430
Cys Cys Cys Thr Gly Gly Gly Cys Thr Gly Cys Ala Gly Cys Ala Gly		
435	440	445
Gly Thr Cys Gly Ala Ala Ala Gly Gly Cys Thr Gly Cys Cys Cys Cys		
450	455	460
Cys Thr Ala Thr Cys Thr Gly Gly Thr Cys Cys Thr Gly Ala Thr Cys		
465	470	475
Ala Cys Cys Cys Thr Gly Cys Thr Ala Ala Thr Cys Thr Thr Cys Ala		
485	490	495
Cys Thr Gly Gly Gly Gly Cys Cys Thr Thr Cys Cys Thr Cys Cys Thr		
500	505	510
Ala Gly Gly Cys Thr Ala Cys Gly Thr Gly Gly Cys Cys Thr Thr Thr		
515	520	525
Cys Gly Ala Gly Gly Gly Thr Cys Cys Thr Gly Cys Cys Ala Gly Gly		
530	535	540
Cys Gly Thr Gly Thr Gly Gly Gly Gly Ala Cys Thr Cys Cys Gly Thr		
545	550	555
Gly Thr Thr Gly Gly Thr Gly Gly Thr Cys Gly Ala Thr Gly Ala Ala		
565	570	575
Gly Ala Thr Gly Thr Cys Ala Ala Cys Cys Cys Thr Gly Ala Gly Gly		
580	585	590
Ala Cys Thr Cys Cys Gly Gly Cys Cys Gly Gly Ala Cys Cys Ala Cys		
595	600	605
Gly Thr Thr Gly Thr Ala Cys Thr Gly Gly Ala Gly Cys Gly Ala Cys		
610	615	620
Cys Thr Cys Cys Ala Gly Gly Cys Cys Ala Thr Gly Thr Thr Thr Cys		
625	630	635
Thr Cys Cys Gly Gly Thr Thr Cys Cys Thr Thr Gly Gly Gly Gly Ala		
645	650	655
Gly Gly Gly Gly Cys Gly Cys Ala Thr Gly Gly Ala Ala Gly Ala Cys		

660	665	670
Ala Cys Cys Ala Thr Cys Ala Gly	Gly Cys Thr Gly Ala Cys Cys Ala	
675	680	685
Gly Cys Cys Thr Cys Cys Gly Gly Gly	Ala Ala Cys Gly Cys Gly Thr	
690	695	700
Gly Gly Cys Thr Gly Gly Cys Thr Cys	Ala Gly Cys Cys Ala Gly Ala	
705	710	715
Ala Thr Gly Gly Cys Cys Ala Cys Cys	Cys Thr Gly Gly Thr Cys Cys	
725	730	735
Ala Ala Gly Ala Thr Ala Thr Cys Cys	Thr Cys Gly Ala Thr Ala Ala	
740	745	750
Gly Cys Thr Cys Thr Cys Gly Cys Gly	Cys Cys Ala Gly Ala Ala Gly	
755	760	765
Cys Thr Gly Gly Ala Cys Cys Ala Cys	Gly Thr Gly Thr Gly Gly Ala	
770	775	780
Cys Thr Gly Ala Cys Ala Cys Gly Cys	Ala Cys Thr Ala Cys Gly Thr	
785	790	795
Gly Gly Gly Ala Cys Thr Thr Cys Ala	Gly Thr Thr Cys Cys Cys Ala	
805	810	815
Gly Ala Thr Cys Cys Gly Gly Cys Thr	Cys Ala Cys Gly Cys Thr Ala	
820	825	830
Ala Cys Ala Cys Cys Cys Thr Gly Cys	Ala Cys Thr Gly Gly Gly Thr	
835	840	845
Gly Gly Ala Thr Gly Cys Ala Gly Ala	Cys Gly Gly Gly Ala Gly Cys	
850	855	860
Gly Thr Cys Cys Ala Gly Gly Ala Gly	Cys Ala Gly Cys Thr Ala Cys	
865	870	875
Cys Gly Cys Thr Gly Gly Ala Gly Gly	Ala Thr Cys Cys Gly Gly Ala	
885	890	895
Ala Gly Thr Cys Thr Ala Cys Thr Gly	Thr Cys Cys Cys Thr Ala Cys	
900	905	910
Ala Gly Cys Gly Cys Cys Ala Cys Cys	Gly Gly Cys Ala Ala Cys Gly	
915	920	925
Cys Cys Ala Cys Gly Gly Gly Cys Ala	Ala Gly Cys Thr Gly Gly Thr	
930	935	940
Gly Thr Ala Cys Gly Cys Cys Cys Ala	Cys Thr Ala Cys Gly Gly Gly	
945	950	955
Cys Gly Gly Thr Cys Gly Gly Ala Gly	Gly Ala Cys Cys Thr Ala Cys	
965	970	975

Ala Gly Gly Ala Cys Cys Thr Ala Ala Ala Ala Gly Cys Cys Ala Ala		
980	985	990
Gly Gly Gly Cys Gly Thr Gly Gly Ala Gly Cys Thr Gly Gly Cys Cys		
995	1000	1005
Gly Gly Cys Ala Gly Cys Cys Thr Cys Cys Thr Gly Cys Thr Ala		
1010	1015	1020
Gly Thr Gly Cys Gly Ala Gly Thr Thr Gly Gly Ala Ala Thr Thr		
1025	1030	1035
Ala Cys Thr Ala Gly Cys Thr Thr Cys Gly Cys Cys Cys Ala Gly		
1040	1045	1050
Ala Ala Gly Gly Thr Ala Gly Cys Cys Gly Thr Thr Gly Cys Cys		
1055	1060	1065
Cys Ala Gly Gly Ala Cys Thr Thr Thr Gly Gly Gly Gly Cys Thr		
1070	1075	1080
Cys Ala Ala Gly Gly Ala Gly Thr Gly Cys Thr Gly Ala Thr Ala		
1085	1090	1095
Thr Ala Cys Cys Cys Thr Gly Ala Cys Cys Cys Ala Thr Cys Ala		
1100	1105	1110
Gly Ala Cys Thr Thr Cys Thr Cys Cys Cys Ala Gly Gly Ala Thr		
1115	1120	1125
Cys Cys Cys Cys Ala Cys Ala Ala Gly Cys Cys Ala Gly Gly Cys		
1130	1135	1140
Cys Thr Gly Thr Cys Thr Ala Gly Cys Cys Ala Cys Cys Ala Gly		
1145	1150	1155
Gly Cys Thr Gly Thr Gly Thr Ala Cys Gly Gly Ala Cys Ala Thr		
1160	1165	1170
Gly Thr Gly Cys Ala Cys Cys Thr Gly Gly Gly Ala Ala Cys Thr		
1175	1180	1185
Gly Gly Ala Gly Ala Cys Cys Cys Thr Thr Ala Cys Ala Cys Ala		
1190	1195	1200
Cys Cys Thr Gly Gly Cys Thr Thr Cys Cys Cys Gly Thr Cys Cys		
1205	1210	1215
Thr Thr Cys Ala Ala Thr Cys Ala Ala Ala Cys Cys Cys Ala Gly		
1220	1225	1230
Thr Thr Cys Cys Cys Thr Cys Cys Ala Gly Thr Ala Gly Ala Ala		
1235	1240	1245
Thr Cys Ala Thr Cys Ala Gly Gly Cys Cys Thr Thr Cys Cys Cys		
1250	1255	1260
Ala Gly Cys Ala Thr Cys Cys Cys Cys Gly Cys Cys Cys Ala Gly		

1265	1270	1275
Cys Cys Cys Ala Thr Cys	Ala Gly Thr Gly Cys	Thr Gly Ala Cys
1280	1285	1290
Ala Thr Thr Gly Cys Thr	Gly Ala Thr Cys Ala	Ala Thr Thr Gly
1295	1300	1305
Cys Thr Cys Ala Gly Gly	Ala Ala Ala Cys Thr	Cys Ala Cys Ala
1310	1315	1320
Gly Gly Cys Cys Cys Cys	Gly Thr Gly Gly Cys	Thr Cys Cys Cys
1325	1330	1335
Cys Ala Gly Gly Ala Gly	Thr Gly Gly Ala Ala	Ala Gly Gly Thr
1340	1345	1350
Cys Ala Cys Cys Thr Cys	Thr Cys Ala Gly Gly	Cys Thr Cys Thr
1355	1360	1365
Cys Cys Thr Thr Ala Thr	Cys Gly Gly Cys Thr	Gly Gly Gly Ala
1370	1375	1380
Cys Cys Thr Gly Gly Gly	Cys Cys Cys Gly Ala	Cys Thr Thr Ala
1385	1390	1395
Cys Gly Cys Cys Thr Thr	Gly Thr Gly Gly Thr	Cys Ala Ala Cys
1400	1405	1410
Ala Ala Cys Cys Ala Cys	Ala Gly Ala Gly Thr	Cys Thr Cys Thr
1415	1420	1425
Ala Cys Cys Cys Cys Cys	Ala Thr Cys Ala Gly	Thr Ala Ala Cys
1430	1435	1440
Ala Thr Cys Thr Thr Thr	Gly Cys Gly Thr Gly	Cys Ala Thr Cys
1445	1450	1455
Gly Ala Gly Gly Gly Cys	Thr Thr Thr Gly Cys	Ala Gly Ala Gly
1460	1465	1470
Cys Cys Ala Gly Ala Thr	Cys Ala Cys Thr Ala	Thr Gly Thr Thr
1475	1480	1485
Gly Thr Cys Ala Thr Thr	Gly Gly Gly Gly Cys	Cys Cys Ala Gly
1490	1495	1500
Ala Gly Gly Gly Ala Thr	Gly Cys Ala Thr Gly	Gly Gly Gly Cys
1505	1510	1515
Cys Cys Ala Gly Gly Ala	Gly Cys Ala Gly Cys	Cys Ala Ala Gly
1520	1525	1530
Thr Cys Thr Gly Cys Ala	Gly Thr Gly Gly Gly	Gly Ala Cys Thr
1535	1540	1545
Gly Cys Cys Ala Thr Cys	Cys Thr Gly Cys Thr	Gly Gly Ala Gly
1550	1555	1560

Cys Thr Gly Gly Thr Thr	Cys Gly Gly Ala Cys Cys Thr Thr Cys
1565	1570 1575
Thr Cys Thr Thr Cys Cys	Ala Thr Gly Gly Thr Cys Ala Gly Cys
1580	1585 1590
Ala Ala Thr Gly Gly Gly	Thr Thr Cys Ala Gly Ala Cys Cys Thr
1595	1600 1605
Cys Gly Ala Ala Gly Ala	Ala Gly Thr Cys Thr Thr Thr Thr Gly
1610	1615 1620
Thr Thr Cys Ala Thr Cys	Ala Gly Cys Thr Gly Gly Gly Ala Cys
1625	1630 1635
Gly Gly Ala Gly Gly Thr	Gly Ala Cys Thr Thr Thr Gly Gly Cys
1640	1645 1650
Ala Gly Cys Gly Thr Gly	Gly Gly Ala Gly Cys Cys Ala Cys Ala
1655	1660 1665
Gly Ala Gly Thr Gly Gly	Thr Thr Gly Gly Ala Gly Gly Gly Cys
1670	1675 1680
Thr Ala Cys Cys Thr Cys	Ala Gly Cys Gly Thr Gly Cys Thr Ala
1685	1690 1695
Cys Ala Cys Cys Thr Cys	Ala Ala Ala Gly Cys Thr Gly Thr Thr
1700	1705 1710
Gly Thr Gly Thr Ala Cys	Gly Thr Gly Ala Gly Cys Cys Thr Gly
1715	1720 1725
Gly Ala Cys Ala Ala Cys	Thr Cys Cys Gly Thr Gly Thr Thr Gly
1730	1735 1740
Gly Gly Ala Gly Ala Thr	Gly Gly Cys Ala Ala Ala Thr Thr Cys
1745	1750 1755
Cys Ala Thr Gly Cys Thr	Ala Ala Gly Ala Cys Cys Ala Gly Cys
1760	1765 1770
Cys Cys Cys Cys Thr Thr	Cys Thr Cys Gly Thr Cys Ala Gly Cys
1775	1780 1785
Cys Thr Cys Ala Thr Thr	Gly Ala Gly Ala Ala Thr Ala Thr Cys
1790	1795 1800
Thr Thr Gly Ala Ala Gly	Cys Ala Gly Gly Thr Gly Gly Ala Cys
1805	1810 1815
Thr Cys Cys Cys Cys Thr	Ala Ala Cys Cys Ala Thr Ala Gly Thr
1820	1825 1830
Gly Gly Ala Cys Ala Gly	Ala Cys Cys Cys Thr Cys Thr Ala Thr
1835	1840 1845
Gly Ala Ala Cys Ala Ala	Gly Thr Gly Gly Cys Ala Cys Thr Cys

1850	1855	1860
Ala Cys Cys Cys Ala Cys Cys Cys Cys Ala Gly Cys Thr Gly Gly		
1865	1870	1875
Gly Ala Thr Gly Cys Thr Gly Ala Ala Gly Thr Gly Ala Thr Thr		
1880	1885	1890
Cys Ala Gly Cys Cys Cys Cys Thr Gly Cys Cys Cys Ala Thr Gly		
1895	1900	1905
Gly Ala Cys Ala Gly Cys Ala Gly Thr Gly Cys Ala Thr Ala Thr		
1910	1915	1920
Thr Cys Cys Thr Thr Cys Ala Cys Ala Gly Cys Cys Thr Thr Thr		
1925	1930	1935
Gly Cys Gly Gly Gly Gly Gly Thr Cys Cys Cys Ala Gly Cys Thr		
1940	1945	1950
Gly Thr Gly Gly Ala Gly Thr Thr Cys Thr Cys Cys Thr Thr Cys		
1955	1960	1965
Ala Thr Gly Gly Ala Gly Gly Ala Thr Gly Ala Thr Cys Gly Gly		
1970	1975	1980
Gly Thr Gly Thr Ala Cys Cys Cys Ala Thr Thr Cys Cys Thr Gly		
1985	1990	1995
Cys Ala Cys Ala Cys Gly Ala Ala Gly Gly Ala Gly Gly Ala Cys		
2000	2005	2010
Ala Cys Ala Thr Ala Thr Gly Ala Gly Ala Ala Thr Cys Thr Gly		
2015	2020	2025
Cys Ala Cys Ala Ala Gly Ala Thr Gly Cys Thr Gly Cys Gly Ala		
2030	2035	2040
Gly Gly Thr Cys Gly Cys Cys Thr Gly Cys Cys Cys Gly Cys Cys		
2045	2050	2055
Gly Thr Gly Gly Thr Cys Cys Ala Gly Gly Cys Ala Gly Thr Gly		
2060	2065	2070
Gly Cys Thr Cys Ala Gly Cys Thr Cys Gly Cys Gly Gly Gly Cys		
2075	2080	2085
Cys Ala Gly Cys Thr Cys Cys Thr Cys Ala Thr Cys Cys Gly Ala		
2090	2095	2100
Cys Thr Gly Ala Gly Cys Cys Ala Cys Gly Ala Thr Cys Ala Cys		
2105	2110	2115
Cys Thr Ala Cys Thr Gly Cys Cys Gly Cys Thr Ala Gly Ala Cys		
2120	2125	2130
Thr Thr Cys Gly Gly Cys Cys Gly Cys Thr Ala Thr Gly Gly Ala		
2135	2140	2145

Gly Ala Cys Gly Thr Gly Gly Thr Thr Cys Thr Cys Ala Gly Gly		
2150	2155	2160
Cys Ala Cys Ala Thr Cys Gly Gly Cys Ala Ala Cys Cys Thr Cys		
2165	2170	2175
Ala Ala Thr Gly Ala Gly Thr Thr Cys Thr Cys Thr Gly Gly Gly		
2180	2185	2190
Gly Ala Cys Cys Thr Cys Ala Ala Gly Gly Ala Gly Cys Gly Cys		
2195	2200	2205
Gly Gly Gly Cys Thr Gly Ala Cys Cys Cys Thr Gly Cys Ala Gly		
2210	2215	2220
Thr Gly Gly Gly Thr Gly Thr Ala Cys Thr Cys Thr Gly Cys Ala		
2225	2230	2235
Ala Gly Gly Gly Gly Gly Gly Ala Cys Thr Ala Cys Ala Thr Cys		
2240	2245	2250
Cys Gly Thr Gly Cys Gly Gly Cys Gly Gly Ala Ala Ala Ala Gly		
2255	2260	2265
Cys Thr Gly Cys Gly Gly Ala Ala Gly Gly Ala Gly Ala Thr Thr		
2270	2275	2280
Thr Ala Cys Ala Gly Cys Thr Cys Gly Gly Ala Gly Cys Gly Gly		
2285	2290	2295
Ala Ala Cys Gly Ala Thr Gly Ala Gly Cys Gly Thr Cys Thr Gly		
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Ala Thr Gly Cys Gly Cys Ala Thr Gly Thr Ala Cys Ala Ala Cys		
2315	2320	2325
Gly Thr Gly Cys Gly Cys Ala Thr Cys Ala Thr Gly Ala Gly Gly		
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Gly Thr Gly Gly Ala Gly Thr Thr Cys Thr Ala Cys Thr Thr Cys		
2345	2350	2355
Cys Thr Gly Thr Cys Cys Cys Ala Gly Thr Ala Thr Gly Thr Gly		
2360	2365	2370
Thr Cys Gly Cys Cys Ala Gly Cys Cys Gly Ala Cys Thr Cys Cys		
2375	2380	2385
Cys Cys Ala Thr Thr Cys Cys Gly Cys Cys Ala Cys Ala Thr Thr		
2390	2395	2400
Thr Thr Cys Cys Thr Ala Gly Gly Cys Cys Ala Ala Gly Gly Cys		
2405	2410	2415
Gly Ala Cys Cys Ala Cys Ala Cys Thr Thr Thr Gly Gly Gly Thr		
2420	2425	2430
Gly Cys Cys Cys Thr Gly Gly Thr Ala Gly Ala Cys Cys Ala Cys		

2435	2440	2445
Cys Thr Gly Cys Gly Gly	Ala Thr Gly Cys Thr	Gly Cys Gly Cys
2450	2455	2460
Gly Cys Cys Gly Ala Thr	Gly Gly Cys Thr Cys	Ala Gly Gly Ala
2465	2470	2475
Gly Cys Cys Gly Cys Cys	Thr Cys Thr Thr Cys	Cys Cys Gly Gly
2480	2485	2490
Thr Thr Gly Ala Cys Ala	Gly Cys Ala Gly Gly	Thr Cys Thr Gly
2495	2500	2505
Gly Gly Cys Thr Thr Cys	Cys Ala Gly Gly Ala	Gly Ala Gly Thr
2510	2515	2520
Cys Gly Cys Thr Thr Cys	Cys Gly Gly Cys Gly	Cys Cys Ala Gly
2525	2530	2535
Cys Thr Gly Gly Cys Gly	Cys Thr Gly Cys Thr	Cys Ala Cys Cys
2540	2545	2550
Thr Gly Gly Ala Cys Ala	Cys Thr Gly Cys Ala	Gly Gly Gly Gly
2555	2560	2565
Gly Cys Ala Gly Cys Cys	Ala Ala Cys Gly Cys	Thr Cys Thr Cys
2570	2575	2580
Ala Gly Thr Gly Gly Cys	Gly Ala Cys Gly Thr	Thr Thr Gly Gly
2585	2590	2595
Ala Ala Cys Ala Thr Thr	Gly Ala Cys Ala Ala	Thr Ala Ala Cys
2600	2605	2610
Thr Thr Thr Thr Gly Ala	Ala Gly Cys Cys Ala	Ala Ala Ala Gly
2615	2620	2625
Cys Cys Cys Thr Cys Cys	Ala Thr Gly Gly Gly	Cys Cys Cys Cys
2630	2635	2640
Ala Cys Gly Thr Gly Ala	Thr Thr Cys Thr Cys	Cys Thr Thr Thr
2645	2650	2655
Cys Thr Cys Cys Cys Thr	Cys Thr Thr Thr Gly	Ala Gly Thr Gly
2660	2665	2670
Gly Thr Gly Cys Ala Gly	Gly Cys Ala Ala Ala	Gly Gly Ala Gly
2675	2680	2685
Gly Thr Gly Cys Cys Thr	Gly Ala Gly Ala Thr	Thr Gly Thr Ala
2690	2695	2700
Ala Cys Cys Thr Ala Thr	Thr Cys Thr Thr Ala	Ala Cys Ala Cys
2705	2710	2715
Cys Cys Thr Thr Gly Gly	Thr Cys Cys Thr Gly	Cys Ala Ala Thr
2720	2725	2730

Gly Cys Thr Gly Gly Thr	Gly Cys Gly Cys Cys	Ala Thr Ala Thr
2735	2740	2745
Thr Thr Thr Cys Thr Cys	Ala Gly Thr Gly Thr	Gly Gly Thr Thr
2750	2755	2760
Gly Thr Cys Ala Thr Gly	Cys Cys Gly Thr Thr	Gly Cys Thr Thr
2765	2770	2775
Ala Cys Cys Cys Ala Gly	Ala Ala Ala Gly Cys	Gly Gly Thr Thr
2780	2785	2790
Thr Thr Cys Thr Thr Cys	Cys Cys Ala Thr Cys	Ala Cys Ala Gly
2795	2800	2805
Gly Cys Cys Cys Thr Thr	Cys Thr Gly Thr Cys	Thr Thr Cys Ala
2810	2815	2820
Gly Gly Ala Gly Cys Ala	Ala Ala Gly Thr Thr	Cys Cys Cys Cys
2825	2830	2835
Ala Thr Ala Thr Cys Thr	Ala Gly Ala Gly Ala	Cys Thr Ala Thr
2840	2845	2850
Cys Thr Ala Gly Ala Thr	Gly Cys Thr Gly Gly	Gly Ala Thr Cys
2855	2860	2865
Thr Gly Ala Thr Cys Ala	Gly Cys Thr Cys Thr	Cys Thr Thr Ala
2870	2875	2880
Gly Ala Gly Ala Gly Thr	Gly Ala Gly Ala Thr	Gly Gly Ala Cys
2885	2890	2895
Ala Gly Cys Gly Thr Cys	Ala Thr Thr Ala Thr	Thr Thr Thr Ala
2900	2905	2910
Thr Gly Ala Cys Ala Cys	Ala Thr Gly Ala Gly	Cys Thr Ala Cys
2915	2920	2925
Gly Gly Thr Ala Thr Gly	Thr Gly Ala Gly Cys	Ala Gly Cys Cys
2930	2935	2940
Cys Ala Ala Gly Gly Gly	Gly Ala Thr Thr Ala	Gly Ala Thr Gly
2945	2950	2955
Thr Cys Ala Ala Thr Ala	Ala Ala Cys Cys Ala	Ala Thr Thr Gly
2960	2965	2970
Thr Ala Ala Cys Cys Cys	Cys Thr Gly Thr Thr	Gly Thr Cys Cys
2975	2980	2985
Ala Thr Ala Cys Gly Cys	Ala Ala Thr Thr Thr	Ala Gly Cys Thr
2990	2995	3000
Thr Cys Cys Thr Cys Thr	Thr Cys Ala Thr Gly	Cys Cys Gly Thr
3005	3010	3015
Ala Cys Cys Cys Ala Cys	Thr Cys Cys Thr Cys	Ala Thr Ala Thr

3020	3025	3030
Cys Cys Gly Cys Cys Thr	Thr Gly Ala Gly Ala	Cys Thr Ala Gly
3035	3040	3045
Gly Gly Ala Ala Gly Ala	Ala Gly Gly Cys Ala	Cys Ala Gly Ala
3050	3055	3060
Ala Gly Gly Cys Ala Cys	Cys Thr Gly Ala Cys	Ala Gly Cys Ala
3065	3070	3075
Thr Gly Cys Thr Thr Gly	Cys Ala Ala Gly Ala	Thr Gly Cys Thr
3080	3085	3090
Ala Thr Cys Cys Ala Cys	Ala Thr Gly Gly Gly	Ala Ala Ala Ala
3095	3100	3105
Ala Thr Ala Ala Cys Thr	Gly Thr Thr Cys Thr	Gly Ala Thr Gly
3110	3115	3120
Thr Cys Thr Ala Ala Gly	Ala Ala Ala Ala Cys	Thr Gly Cys Cys
3125	3130	3135
Thr Ala Ala Ala Gly Ala	Thr Ala Ala Thr Gly	Gly Ala Thr Ala
3140	3145	3150
Gly Gly Ala Gly Gly Thr	Gly Gly Gly Gly Cys	Ala Gly Thr Gly
3155	3160	3165
Gly Gly Gly Ala Thr Ala	Ala Cys Thr Cys Ala	Thr Cys Ala Gly
3170	3175	3180
Gly Ala Ala Thr Gly Gly	Gly Thr Gly Ala Thr	Thr Gly Cys Gly
3185	3190	3195
Gly Cys Cys Ala Ala Gly	Cys Cys Thr Gly Ala	Thr Gly Ala Cys
3200	3205	3210
Cys Thr Gly Ala Gly Thr	Thr Thr Ala Ala Thr	Cys Cys Cys Cys
3215	3220	3225
Ala Gly Gly Ala Cys Cys	Ala Ala Cys Ala Thr	Gly Gly Cys Ala
3230	3235	3240
Ala Ala Ala Gly Gly Ala	Gly Ala Gly Ala Ala	Cys Thr Ala Gly
3245	3250	3255
Thr Thr Cys Cys Cys Ala	Cys Ala Ala Gly Thr	Thr Thr Thr Cys
3260	3265	3270
Cys Thr Ala Thr Ala Thr	Cys Cys Thr Cys Cys	Ala Ala Ala Thr
3275	3280	3285
Gly Thr Ala Thr Gly Cys	Cys Cys Ala Thr Ala	Ala Ala Ala Gly
3290	3295	3300
Cys Ala Cys Ala Ala Ala	Thr Ala Gly Ala Thr	Ala Ala Ala Thr
3305	3310	3315

Gly Thr Thr Thr Thr Thr Gly Cys Thr Thr Thr Thr Gly Thr Thr		
3320	3325	3330
Thr Thr Thr Thr Ala Ala Ala Gly Thr Gly Gly Cys Thr Thr Thr		
3335	3340	3345
Gly Thr Gly Gly Thr Thr Ala Ala Gly Ala Gly Cys Ala Cys Thr		
3350	3355	3360
Gly Gly Ala Thr Gly Cys Cys Ala Thr Thr Cys Thr Ala Gly Ala		
3365	3370	3375
Ala Gly Ala Cys Ala Cys Cys Gly Gly Thr Thr Cys Gly Ala Thr		
3380	3385	3390
Thr Cys Cys Cys Ala Gly Cys Ala Cys Cys Cys Ala Cys Ala Thr		
3395	3400	3405
Gly Gly Cys Cys Gly Cys Thr Thr Ala Cys Ala Ala Cys Thr Gly		
3410	3415	3420
Thr Cys Thr Gly Thr Ala Ala Cys Thr Cys Cys Ala Gly Thr Thr		
3425	3430	3435
Gly Cys Thr Gly Gly Gly Gly Ala Thr Cys Ala Gly Ala Thr Gly		
3440	3445	3450
Cys Cys Cys Thr Cys Thr Thr Cys Thr Gly Gly Thr Ala Thr Gly		
3455	3460	3465
Gly Thr Gly Thr Ala Cys Gly Ala Cys Thr Gly Cys Ala Thr Gly		
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Cys Ala Thr Gly Thr Ala Gly Thr Ala Thr Ala Cys Ala Thr Ala		
3485	3490	3495
Cys Ala Ala Gly Cys Ala Gly Gly Cys Ala Ala Ala Ala Thr Ala		
3500	3505	3510
Cys Cys Cys Ala Thr Ala Cys Ala Thr Gly Thr Ala Ala Ala Ala		
3515	3520	3525
Thr Thr Thr Thr Thr Ala Ala Ala Ala Ala Ala Thr Ala Gly Thr		
3530	3535	3540
Thr Thr Ala Ala Ala Thr Thr Ala Thr Ala Ala Ala Thr Thr Ala		
3545	3550	3555
Ala Thr Thr Thr Ala Ala Ala Gly Ala Ala Cys Ala Ala Ala Thr		
3560	3565	3570
Ala Ala Ala Ala Gly Ala Thr Thr Ala Ala Thr Gly Cys Cys Thr		
3575	3580	3585
Thr Thr Ala Ala Thr Cys Cys Cys		
3590	3595	

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<212> PRT

<213> 智人

<400> 10

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

275	280	285
Leu Gly Pro Gly Pro Arg	Leu Arg Leu Val Val	Asn Asn His Arg Thr
290	295	300
Ser Thr Pro Ile Asn Asn	Ile Phe Gly Cys Ile	Glu Gly Arg Ser Glu
305	310	315
Pro Asp His Tyr Val Val	Ile Gly Ala Gln Arg	Asp Ala Trp Gly Pro
325	330	335
Gly Ala Ala Lys Ser Ala	Val Gly Thr Ala Ile	Leu Leu Glu Leu Val
340	345	350
Arg Thr Phe Ser Ser Met	Val Ser Asn Gly Phe	Arg Pro Arg Arg Ser
355	360	365
Leu Leu Phe Ile Ser Trp	Asp Gly Gly Asp Phe	Gly Ser Val Gly Ser
370	375	380
Thr Glu Trp Leu Glu Gly	Tyr Leu Ser Val Leu	His Leu Lys Ala Val
385	390	395
Val Tyr Val Ser Leu Asp	Asn Ala Val Leu Gly	Asp Asp Lys Phe His
405	410	415
Ala Lys Thr Ser Pro Leu	Leu Thr Ser Leu Ile	Glu Ser Val Leu Lys
420	425	430
Gln Val Asp Ser Pro Asn	His Ser Gly Gln Thr	Leu Tyr Glu Gln Val
435	440	445
Val Phe Thr Asn Pro Ser	Trp Asp Ala Glu Val	Ile Arg Pro Leu Pro
450	455	460
Met Asp Ser Ser Ala Tyr	Ser Phe Thr Ala Phe	Val Gly Val Pro Ala
465	470	475
Val Glu Phe Ser Phe Met	Glu Asp Asp Gln Ala	Tyr Pro Phe Leu His
485	490	495
Thr Lys Glu Asp Thr Tyr	Glu Asn Leu His Lys	Val Leu Gln Gly Arg
500	505	510
Leu Pro Ala Val Ala Gln	Ala Val Ala Gln Leu	Ala Gly Gln Leu Leu
515	520	525
Ile Arg Leu Ser His Asp	Arg Leu Leu Pro Leu	Asp Phe Gly Arg Tyr
530	535	540
Gly Asp Val Val Leu Arg	His Ile Gly Asn Leu	Asn Glu Phe Ser Gly
545	550	555
Asp Leu Lys Ala Arg Gly	Leu Thr Leu Gln Trp	Val Tyr Ser Ala Arg
565	570	575
Gly Asp Tyr Ile Arg Ala	Ala Glu Lys Leu Arg	Gln Glu Ile Tyr Ser
580	585	590

Ser Glu Glu Arg Asp Glu Arg Leu Thr Arg Met Tyr Asn Val Arg Ile
 595 600 605
 Met Arg Val Glu Phe Tyr Phe Leu Ser Gln Tyr Val Ser Pro Ala Asp
 610 615 620
 Ser Pro Phe Arg His Ile Phe Met Gly Arg Gly Asp His Thr Leu Gly
 625 630 635 640
 Ala Leu Leu Asp His Leu Arg Leu Leu Arg Ser Asn Ser Ser Gly Thr
 645 650 655
 Pro Gly Ala Thr Ser Ser Thr Gly Phe Gln Glu Ser Arg Phe Arg Arg
 660 665 670
 Gln Leu Ala Leu Leu Thr Trp Thr Leu Gln Gly Ala Ala Asn Ala Leu
 675 680 685
 Ser Gly Asp Val Trp Asn Ile Asp Gly Gly Gly Gly Ser His His His
 690 695 700
 His His His
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 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
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 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 65 70 75 80
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 130 135 140

Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
145						150				155					160
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
				165						170					175
Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
			180							185				190	
Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
		195						200					205		
Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
		210					215					220			
Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Ile	Glu	Gly	Arg	Arg	Gly	Ser	Cys
225						230				235					240
Gln	Ala	Cys	Gly	Asp	Ser	Val	Leu	Val	Val	Ser	Glu	Asp	Val	Asn	Tyr
				245						250					255
Glu	Pro	Asp	Leu	Asp	Phe	His	Gln	Gly	Arg	Leu	Tyr	Trp	Ser	Asp	Leu
			260						265					270	
Gln	Ala	Met	Phe	Leu	Gln	Phe	Leu	Gly	Glu	Gly	Arg	Leu	Glu	Asp	Thr
		275						280						285	
Ile	Arg	Gln	Thr	Ser	Leu	Arg	Glu	Arg	Val	Ala	Gly	Ser	Ala	Gly	Met
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Asp	His	Val	Trp	Thr	Asp	Thr	His	Tyr	Val	Gly	Leu	Gln	Phe	Pro	Asp
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Pro	Ala	His	Pro	Asn	Thr	Leu	His	Trp	Val	Asp	Glu	Ala	Gly	Lys	Val
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Gly	Glu	Gln	Leu	Pro	Leu	Glu	Asp	Pro	Asp	Val	Tyr	Cys	Pro	Tyr	Ser
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Ala	Ile	Gly	Asn	Val	Thr	Gly	Glu	Leu	Val	Tyr	Ala	His	Tyr	Gly	Arg
		370					375				380				
Pro	Glu	Asp	Leu	Gln	Asp	Leu	Arg	Ala	Arg	Gly	Val	Asp	Pro	Val	Gly
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Arg	Leu	Leu	Leu	Val	Arg	Val	Gly	Val	Ile	Ser	Phe	Ala	Gln	Lys	Val
				405						410				415	
Thr	Asn	Ala	Gln	Asp	Phe	Gly	Ala	Gln	Gly	Val	Leu	Ile	Tyr	Pro	Glu
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Pro	Ala	Asp	Phe	Ser	Gln	Asp	Pro	Pro	Lys	Pro	Ser	Leu	Ser	Ser	Gln
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Gln	Ala	Val	Tyr	Gly	His	Val	His	Leu	Gly	Thr	Gly	Asp	Pro	Tyr	Thr

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Pro Gly Phe Pro Ser Phe Asn Gln Thr Gln Phe Pro Pro Val Ala Ser		
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Ser Gly Leu Pro Ser Ile Pro Ala Gln Pro Ile Ser Ala Asp Ile Ala		480
	485	490
Ser Arg Leu Leu Arg Lys Leu Lys Gly Pro Val Ala Pro Gln Glu Trp		495
	500	505
Gln Gly Ser Leu Leu Gly Ser Pro Tyr His Leu Gly Pro Gly Pro Arg		510
	515	520
Leu Arg Leu Val Val Asn Asn His Arg Thr Ser Thr Pro Ile Asn Asn		525
	530	535
Ile Phe Gly Cys Ile Glu Gly Arg Ser Glu Pro Asp His Tyr Val Val		540
545	550	555
Ile Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala Ala Lys Ser Ala		560
	565	570
Val Gly Thr Ala Ile Leu Leu Glu Leu Val Arg Thr Phe Ser Ser Met		575
	580	585
Val Ser Asn Gly Phe Arg Pro Arg Arg Ser Leu Leu Phe Ile Ser Trp		590
	595	600
Asp Gly Gly Asp Phe Gly Ser Val Gly Ser Thr Glu Trp Leu Glu Gly		605
	610	615
Tyr Leu Ser Val Leu His Leu Lys Ala Val Val Tyr Val Ser Leu Asp		620
625	630	635
Asn Ala Val Leu Gly Asp Asp Lys Phe His Ala Lys Thr Ser Pro Leu		640
	645	650
Leu Thr Ser Leu Ile Glu Ser Val Leu Lys Gln Val Asp Ser Pro Asn		655
	660	665
His Ser Gly Gln Thr Leu Tyr Glu Gln Val Val Phe Thr Asn Pro Ser		670
	675	680
Trp Asp Ala Glu Val Ile Arg Pro Leu Pro Met Asp Ser Ser Ala Tyr		685
	690	695
Ser Phe Thr Ala Phe Val Gly Val Pro Ala Val Glu Phe Ser Phe Met		700
705	710	715
Glu Asp Asp Gln Ala Tyr Pro Phe Leu His Thr Lys Glu Asp Thr Tyr		720
	725	730
Glu Asn Leu His Lys Val Leu Gln Gly Arg Leu Pro Ala Val Ala Gln		735
	740	745
Ala Val Ala Gln Leu Ala Gly Gln Leu Leu Ile Arg Leu Ser His Asp		750
	755	760
		765

Arg Leu Leu Pro Leu Asp Phe Gly Arg Tyr Gly Asp Val Val Leu Arg		
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His Ile Gly Asn Leu Asn Glu Phe Ser Gly Asp Leu Lys Ala Arg Gly		
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Leu Thr Leu Gln Trp Val Tyr Ser Ala Arg Gly Asp Tyr Ile Arg Ala		
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Arg Leu Thr Arg Met Tyr Asn Val Arg Ile Met Arg Val Glu Phe Tyr		
	835	840 845
Phe Leu Ser Gln Tyr Val Ser Pro Ala Asp Ser Pro Phe Arg His Ile		
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Phe Met Gly Arg Gly Asp His Thr Leu Gly Ala Leu Leu Asp His Leu		
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Thr Gly Phe Gln Glu Ser Arg Phe Arg Arg Gln Leu Ala Leu Leu Thr		
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Leu Glu Asp Thr Ile Arg Gln Thr Ser Leu Arg Glu Arg Val Ala Gly		
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Ser Ala Gly Met Ala Ala Leu Thr Gln Asp Ile Arg Ala Ala Leu Ser		
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Arg Gln Lys Leu Asp His Val Trp Thr Asp Thr His Tyr Val Gly Leu		
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Gln Phe Pro Asp Pro Ala His Pro Asn Thr Leu His Trp Val Asp Glu		
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Ala Gly Lys Val Gly Glu Gln Leu Pro Leu Glu Asp Pro Asp Val Tyr		
115	120	125
Cys Pro Tyr Ser Ala Ile Gly Asn Val Thr Gly Glu Leu Val Tyr Ala		
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His Tyr Gly Arg Pro Glu Asp Leu Gln Asp Leu Arg Ala Arg Gly Val		
145	150	155
Asp Pro Val Gly Arg Leu Leu Leu Val Arg Val Gly Val Ile Ser Phe		
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Ala Gln Lys Val Thr Asn Ala Gln Asp Phe Gly Ala Gln Gly Val Leu		
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Ile Tyr Pro Glu Pro Ala Asp Phe Ser Gln Asp Pro Pro Lys Pro Ser		
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Leu Ser Ser Gln Gln Ala Val Tyr Gly His Val His Leu Gly Thr Gly		
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Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn Gln Thr Gln Phe Pro		
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Pro Val Ala Ser Ser Gly Leu Pro Ser Ile Pro Ala Gln Pro Ile Ser		
245	250	255
Ala Asp Ile Ala Ser Arg Leu Leu Arg Lys Leu Lys Gly Pro Val Ala		
260	265	270
Pro Gln Glu Trp Gln Gly Ser Leu Leu Gly Ser Pro Tyr His Leu Gly		
275	280	285
Pro Gly Pro Arg Leu Arg Leu Val Val Asn Asn His Arg Thr Ser Thr		
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Pro Ile Asn Asn Ile Phe Gly Cys Ile Glu Gly Arg Ser Glu Pro Asp		
305	310	315
His Tyr Val Val Ile Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala		
325	330	335
Ala Lys Ser Ala Val Gly Thr Ala Ile Leu Leu Glu Leu Val Arg Thr		
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Phe Ser Ser Met Val Ser Asn Gly Phe Arg Pro Arg Arg Ser Leu Leu		
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Phe Ile Ser Trp Asp Gly Gly Asp Phe Gly Ser Val Gly Ser Thr Glu		
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Trp Leu Glu Gly Tyr Leu Ser Val Leu His Leu Lys Ala Val Val Tyr		
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Val Ser Leu Asp Asn Ala Val Leu Gly Asp Asp Lys Phe His Ala Lys		

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Thr	Ser	Pro	Leu	Leu	Thr	Ser	Leu	Ile	Glu	Ser	Val	Leu	Lys	Gln	Val		
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Ser	Ser	Ala	Tyr	Ser	Phe	Thr	Ala	Phe	Val	Gly	Val	Pro	Ala	Val	Glu		
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Phe	Ser	Phe	Met	Glu	Asp	Asp	Gln	Ala	Tyr	Pro	Phe	Leu	His	Thr	Lys		
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Glu	Asp	Thr	Tyr	Glu	Asn	Leu	His	Lys	Val	Leu	Gln	Gly	Arg	Leu	Pro		
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				515					520					525			
Leu	Ser	His	Asp	Arg	Leu	Leu	Pro	Leu	Asp	Phe	Gly	Arg	Tyr	Gly	Asp		
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Val	Val	Leu	Arg	His	Ile	Gly	Asn	Leu	Asn	Glu	Phe	Ser	Gly	Asp	Leu		
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Lys	Ala	Arg	Gly	Leu	Thr	Leu	Gln	Trp	Val	Tyr	Ser	Ala	Arg	Gly	Asp		
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Leu	Asp	His	Leu	Arg	Leu	Leu	Arg	Ser	Asn	Ser	Ser	Gly	Thr	Pro	Gly		
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Ala	Thr	Ser	Ser	Thr	Gly	Phe	Gln	Glu	Ser	Arg	Phe	Arg	Arg	Gln	Leu		
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 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 740 745 750
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 755 760 765
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 770 775 780
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 820 825 830
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 865 870 875 880
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
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 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
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Cys Ala Gly Cys Gly Gly Cys Cys Cys Thr Gly Gly Gly Cys Thr Gly

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Thr Thr Cys Cys Cys Cys Gly Ala Ala Cys Cys Gly Gly Thr Gly Ala

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Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
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Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
225				230				235				240			
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
245				250				255							
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
260				265				270							
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
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Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
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565	570	575

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Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala Thr Gly Ala Gly		
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Cys Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala Cys Cys Ala Gly Gly		
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Cys Thr Cys Cys Cys Gly Thr Gly Cys Thr Gly Gly Ala Cys Thr Cys		
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Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys		
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Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly		

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

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Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu					
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His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn					
	195		200		205
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly					
	210		215		220
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu					
225		230		235	240
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr					
	245		250		255
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn					
	260		265		270
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe					
	275		280		285
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn					
	290		295		300
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Cys Cys Thr Gly Gly Thr Cys Ala Ala Gly Gly Ala Cys Thr Ala Cys															
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Cys Gly Gly Cys Thr Gly Thr	Cys Cys Thr Ala Cys Ala Gly Thr Cys	
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Cys Thr Cys Ala Gly Gly Ala	Cys Thr Cys Thr Ala Cys Thr Cys Cys	
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Cys Thr Cys Ala Gly Cys Ala	Gly Cys Gly Thr Gly Gly Thr Gly Ala	
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Cys Cys Gly Thr Gly Cys Cys	Cys Cys Thr Cys Cys Ala Gly Cys Ala Gly	
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Cys Ala Cys Cys Ala Ala Gly	Gly Thr Gly Gly Ala Cys Ala Ala Gly	
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Cys Thr Thr Gly Thr Gly Ala	Cys Ala Ala Ala Ala Cys Thr Cys Ala	
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Cys Cys Ala Gly Cys Ala Cys	Cys Cys Thr Gly Ala Ala Cys Thr Cys Cys	
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Cys Thr Thr Cys Cys Thr Cys	Thr Thr Cys Cys Cys Cys Cys Cys Ala	
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Ala Ala Ala Cys Cys Cys Ala	Ala Gly Gly Ala Cys Ala Cys Cys Cys	
385	390	395
Thr Cys Ala Thr Gly Ala Thr	Cys Thr Cys Cys Cys Gly Gly Ala Cys	
405	410	415

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420	425	430	
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Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys Cys Thr Gly Ala			
450	455	460	
Gly Gly Thr Cys Ala Ala Gly Thr Thr Cys Ala Ala Cys Thr Gly Gly			
465	470	475	480
Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly Cys Gly Thr Gly Gly			
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Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala Thr Gly Cys Cys Ala Ala			
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Cys Gly Thr Ala Cys Cys Gly Thr Gly Thr Gly Gly Thr Cys Ala Gly			
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Cys Gly Thr Cys Cys Thr Cys Ala Cys Cys Gly Thr Cys Cys Thr Gly			
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Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly Cys Thr Gly Ala			
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Ala Thr Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala			
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Gly Thr Gly Cys Ala Ala Gly Gly Thr Cys Thr Cys Cys Ala Ala Cys			
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Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Cys Cys Ala Thr			
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Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly Gly			
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Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala Cys Cys Ala Cys			
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Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys Thr Gly Cys Cys			
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Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala Gly Gly Ala Gly			
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Ala Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala Cys Cys Ala Gly Gly			

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

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Cys	Cys	Ala	Thr	Cys	Gly	Ala	Gly	Ala	Ala	Ala	Ala	Cys	Cys	Ala	Thr		
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Ala	Gly	Gly	Thr	Gly	Thr	Ala	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Cys	Cys		
				690					695					700			
Cys	Cys	Cys	Ala	Thr	Cys	Cys	Cys	Gly	Gly	Gly	Ala	Thr	Gly	Ala	Gly		
705																	
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Cys	Thr	Gly	Ala	Cys	Cys	Ala	Ala	Gly	Ala	Ala	Cys	Cys	Ala	Gly	Gly		
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Ala	Ala	Cys	Thr	Ala	Cys	Ala	Ala	Gly	Ala	Cys	Cys	Ala	Cys	Gly	Cys		
				820					825					830			
Cys	Thr	Cys	Cys	Cys	Gly	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Cys	Thr	Cys		
				835					840					845			
Cys	Gly	Ala	Cys	Gly	Gly	Cys	Thr	Cys	Cys	Thr	Thr	Cys	Thr	Thr	Cys		
				850					855					860			
Cys	Thr	Cys	Thr	Ala	Cys	Ala	Gly	Cys	Ala	Ala	Gly	Cys	Thr	Cys	Ala		
865																	
				870					875					880			

Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly		
	885	890 895
Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly Gly Ala Ala Cys		
	900	905 910
Ala Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys Thr Cys Cys Gly		
	915	920 925
Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly Cys Thr Cys Thr		
	930	935 940
Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala Cys Ala Cys Gly		
945	950	955 960
Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr Cys Thr Cys Cys Cys		
	965	970 975
Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala Ala Ala		
	980	985 990

<210> 58

<211> 330

<212> PRT

<213> 智人

<400> 58

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

Gly	Cys	Cys	Thr	Cys	Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Gly	Cys	Cys
1				5					10					15	
Cys	Ala	Thr	Cys	Gly	Gly	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Thr
			20					25					30		
Gly	Gly	Cys	Ala	Cys	Cys	Cys	Thr	Cys	Cys	Thr	Cys	Cys	Ala	Ala	Gly
		35					40					45			
Ala	Gly	Cys	Ala	Cys	Cys	Thr	Cys	Thr	Gly	Gly	Gly	Gly	Gly	Cys	Ala
	50					55				60					
Cys	Ala	Gly	Cys	Gly	Gly	Cys	Cys	Cys	Thr	Gly	Gly	Gly	Cys	Thr	Gly
65				70						75				80	

Cys	Cys	Thr	Gly	Gly	Thr	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Thr	Ala	Cys		
85						90					95						
Thr	Thr	Cys	Cys	Cys	Cys	Gly	Ala	Ala	Cys	Cys	Gly	Gly	Thr	Gly	Ala		
100						105					110						
Cys	Gly	Gly	Thr	Gly	Thr	Cys	Gly	Thr	Gly	Gly	Ala	Ala	Cys	Thr	Cys		
115						120					125						
Ala	Gly	Gly	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Ala	Cys	Cys	Ala	Gly	Cys		
130						135					140						
Gly	Gly	Cys	Gly	Thr	Gly	Cys	Ala	Cys	Ala	Cys	Cys	Thr	Thr	Cys	Cys		
145						150					155					160	
Cys	Gly	Gly	Cys	Thr	Gly	Thr	Cys	Cys	Thr	Ala	Cys	Ala	Gly	Thr	Cys		
165						170					175						
Cys	Thr	Cys	Ala	Gly	Gly	Ala	Cys	Thr	Cys	Thr	Ala	Cys	Thr	Cys	Cys		
180						185					190						
Cys	Thr	Cys	Ala	Gly	Cys	Ala	Gly	Cys	Gly	Thr	Gly	Gly	Thr	Gly	Ala		
195						200					205						
Cys	Cys	Gly	Thr	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Ala	Gly	Cys	Ala	Gly		
210						215					220						
Cys	Thr	Thr	Gly	Gly	Gly	Cys	Ala	Cys	Cys	Cys	Ala	Gly	Ala	Cys	Cys		
225						230					235					240	
Thr	Ala	Cys	Ala	Thr	Cys	Thr	Gly	Cys	Ala	Ala	Cys	Gly	Thr	Gly	Ala		
245						250					255						
Ala	Thr	Cys	Ala	Cys	Ala	Ala	Gly	Cys	Cys	Cys	Ala	Gly	Cys	Ala	Ala		
260						265					270						
Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Thr	Gly	Gly	Ala	Cys	Ala	Ala	Gly		
275						280					285						
Ala	Ala	Ala	Gly	Thr	Gly	Gly	Ala	Gly	Cys	Cys	Cys	Ala	Ala	Ala	Thr		
290						295					300						
Cys	Thr	Thr	Gly	Thr	Gly	Ala	Cys	Ala	Ala	Ala	Ala	Cys	Thr	Cys	Ala		
305						310					315					320	
Cys	Ala	Cys	Ala	Thr	Gly	Cys	Cys	Cys	Ala	Cys	Cys	Gly	Thr	Gly	Cys		
325						330					335						
Cys	Cys	Ala	Gly	Cys	Ala	Cys	Cys	Thr	Gly	Ala	Ala	Cys	Thr	Cys	Gly		
340						345					350						
Cys	Gly	Gly	Gly	Gly	Gly	Cys	Ala	Cys	Cys	Gly	Thr	Cys	Ala	Gly	Thr		
355						360					365						
Cys	Thr	Thr	Cys	Cys	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Cys	Ala		
370						375					380						
Ala	Ala	Ala	Cys	Cys	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Ala	Cys	Cys	Cys		

385	390	395	400
Thr Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys Gly Gly Ala Cys			
	405	410	415
Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys Ala Thr Gly Cys			
	420	425	430
Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys Gly Thr Gly Ala			
	435	440	445
Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys Cys Thr Gly Ala			
	450	455	460
Gly Gly Thr Cys Ala Ala Gly Thr Thr Cys Ala Ala Cys Thr Gly Gly			
465	470	475	480
Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly Cys Gly Thr Gly Gly			
	485	490	495
Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala Thr Gly Cys Cys Ala Ala			
	500	505	510
Gly Ala Cys Ala Ala Ala Gly Cys Cys Gly Cys Gly Gly Ala Gly			
	515	520	525
Gly Ala Gly Cys Ala Gly Thr Ala Cys Ala Ala Cys Ala Gly Cys Ala			
	530	535	540
Cys Gly Thr Ala Cys Cys Gly Thr Gly Thr Gly Thr Cys Ala Gly			
545	550	555	560
Cys Gly Thr Cys Cys Thr Cys Ala Cys Cys Gly Thr Cys Cys Thr Gly			
	565	570	575
Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly Cys Thr Gly Ala			
	580	585	590
Ala Thr Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala			
	595	600	605
Gly Thr Gly Cys Ala Ala Gly Gly Thr Cys Thr Cys Cys Ala Ala Cys			
	610	615	620
Ala Ala Ala Gly Cys Cys Cys Thr Cys Cys Cys Ala Gly Cys Cys Cys			
625	630	635	640
Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala Cys Cys Ala Thr			
	645	650	655
Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly Gly			
	660	665	670
Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala Cys Cys Ala Cys			
	675	680	685
Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys Thr Gly Cys Cys			
	690	695	700

Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala Thr Gly Ala Gly			
705	710	715	720
Cys Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala Cys Cys Ala Gly Gly			
	725	730	735
Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys Cys Thr Gly Cys Cys Thr			
	740	745	750
Gly Gly Thr Cys Ala Ala Ala Gly Gly Cys Thr Thr Cys Thr Ala Thr			
	755	760	765
Cys Cys Cys Ala Gly Cys Gly Ala Cys Ala Thr Cys Gly Cys Cys Gly			
	770	775	780
Thr Gly Gly Ala Gly Thr Gly Gly Gly Ala Gly Ala Gly Cys Ala Ala			
785	790	795	800
Thr Gly Gly Gly Cys Ala Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys			
	805	810	815
Ala Ala Cys Thr Ala Cys Ala Ala Gly Ala Cys Cys Ala Cys Gly Cys			
	820	825	830
Cys Thr Cys Cys Cys Gly Thr Gly Cys Thr Gly Gly Ala Cys Thr Cys			
	835	840	845
Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys			
	850	855	860
Cys Thr Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly Cys Thr Cys Ala			
865	870	875	880
Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly			
	885	890	895
Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly Gly Ala Ala Cys			
	900	905	910
Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys Thr Cys Cys Gly			
	915	920	925
Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly Cys Thr Cys Thr			
	930	935	940
Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala Cys Ala Cys Gly			
945	950	955	960
Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr Cys Thr Cys Cys Cys			
	965	970	975
Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala Ala Ala			
	980	985	990

<210> 60

<211> 330

<212> PRT

<213> 智人

<400> 60

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

290	295	300
Val Phe Ser Cys Ser	Val Met His Glu Ala	Leu His Asn His Tyr Thr
305	310	315
Gln Lys Ser Leu Ser	Leu Ser Pro Gly Lys	
	325	330
<210> 61		
<211> 978		
<212> PRT		
<213> 智人		
<400> 61		
Gly Cys Cys Thr Cys Cys	Ala Cys Cys Ala Ala	Gly Gly Gly Cys Cys
1	5	10
Cys Ala Thr Cys Gly Gly	Thr Cys Thr Thr Cys Cys	Cys Cys Cys Cys Thr
	20	25
Gly Gly Cys Gly Cys Cys	Cys Thr Gly Cys Thr Cys	Cys Cys Ala Gly Gly
	35	40
Ala Gly Cys Ala Cys Cys	Thr Cys Cys Gly Ala	Gly Ala Gly Cys Ala
	50	55
Cys Ala Gly Cys Cys Gly	Cys Cys Cys Thr Gly	Gly Gly Gly Cys Thr Gly
65	70	75
Cys Cys Thr Gly Gly Thr	Cys Ala Ala Gly Gly	Ala Cys Thr Ala Cys
	85	90
Thr Thr Cys Cys Cys Cys	Gly Ala Ala Cys Cys	Gly Gly Thr Gly Ala
	100	105
Cys Gly Gly Thr Gly Thr	Cys Gly Thr Gly Gly	Ala Ala Cys Thr Cys
	115	120
Ala Gly Gly Cys Gly Cys	Thr Cys Thr Gly Ala	Cys Cys Ala Gly Cys
	130	135
Gly Gly Cys Gly Thr Gly	Cys Ala Cys Ala Cys	Cys Thr Thr Cys Cys
145	150	155
Cys Ala Gly Cys Thr Gly	Thr Cys Cys Thr Ala	Cys Ala Gly Thr Cys
	165	170
Cys Thr Cys Ala Gly Gly	Ala Cys Thr Cys Thr	Ala Cys Thr Cys Cys
	180	185
Cys Thr Cys Ala Gly Cys	Ala Gly Cys Gly Thr	Gly Gly Thr Gly Ala
	195	200
Cys Cys Gly Thr Gly Cys	Cys Cys Cys Thr Cys	Cys Ala Gly Cys Ala Ala
	210	220
Cys Thr Thr Cys Gly Gly	Cys Ala Cys Cys Cys	Ala Gly Ala Cys Cys

225	230	235	240
Thr Ala Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Ala Gly			
	245	250	255
Ala Thr Cys Ala Cys Ala Ala Gly Cys Cys Cys Ala Gly Cys Ala Ala			
	260	265	270
Cys Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Gly			
	275	280	285
Ala Cys Ala Gly Thr Thr Gly Ala Gly Cys Gly Cys Ala Ala Ala Thr			
	290	295	300
Gly Thr Thr Gly Thr Gly Thr Cys Gly Ala Gly Thr Gly Cys Cys Cys			
305	310	315	320
Ala Cys Cys Gly Thr Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Ala			
	325	330	335
Cys Cys Thr Gly Thr Gly Gly Cys Ala Gly Gly Ala Cys Cys Gly Thr			
	340	345	350
Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Cys Thr Thr Cys Cys Cys			
	355	360	365
Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys			
	370	375	380
Ala Cys Cys Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys			
385	390	395	400
Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys			
	405	410	415
Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys			
	420	425	430
Gly Thr Gly Ala Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys			
	435	440	445
Cys Cys Gly Ala Gly Gly Thr Cys Cys Ala Gly Thr Thr Cys Ala Ala			
	450	455	460
Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly Cys			
465	470	475	480
Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala Thr Gly			
	485	490	495
Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys Ala Cys Gly			
	500	505	510
Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys Ala Ala Cys			
	515	520	525
Ala Gly Cys Ala Cys Gly Thr Thr Cys Cys Gly Thr Gly Thr Gly Gly			
	530	535	540

Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys Cys Gly Thr			
545	550	555	560
Thr Gly Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly			
	565	570	575
Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr			
	580	585	590
Ala Cys Ala Ala Gly Thr Gly Cys Ala Ala Gly Gly Thr Cys Thr Cys			
	595	600	605
Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys Cys Cys Ala			
	610	615	620
Gly Cys Cys Cys Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala			
625	630	635	640
Cys Cys Ala Thr Cys Thr Cys Cys Ala Ala Ala Ala Cys Cys Ala Ala			
	645	650	655
Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala			
	660	665	670
Cys Cys Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys			
	675	680	685
Thr Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala			
	690	695	700
Gly Gly Ala Gly Ala Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala Cys			
705	710	715	720
Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys Cys Thr			
	725	730	735
Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly Cys Thr Thr			
	740	745	750
Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys Ala Thr Cys			
	755	760	765
Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly Ala Gly Ala			
	770	775	780
Gly Cys Ala Ala Thr Gly Gly Gly Cys Ala Gly Cys Cys Gly Gly Ala			
785	790	795	800
Gly Ala Ala Cys Ala Ala Cys Thr Ala Cys Ala Ala Gly Ala Cys Cys			
	805	810	815
Ala Cys Ala Cys Cys Thr Cys Cys Cys Ala Thr Gly Cys Thr Gly Gly			
	820	825	830
Ala Cys Thr Cys Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Thr			
	835	840	845
Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly			

850	855	860
Cys Thr Cys Ala Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala		
865	870	875
Gly Cys Ala Gly Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly		880
885	890	895
Gly Ala Ala Cys Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys		
900	905	910
Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly		
915	920	925
Cys Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala		
930	935	940
Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr Cys		
945	950	955
Thr Cys Cys Cys Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala		960
965	970	975
Ala Ala		
<210> 62		
<211> 326		
<212> PRT		
<213> 智人		
<400> 62		
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg		
1	5	10
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		15
20	25	30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser		
35	40	45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
50	55	60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr		
65	70	75
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		80
85	90	95
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro		
100	105	110
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp		
115	120	125
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp		
130	135	140

Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
145					150					155					160
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
				165					170					175	
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp
			180					185					190		
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
		195					200					205			
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu
		210				215					220				
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn
225					230					235					240
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
				245					250					255	
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
			260					265					270		
Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
			275					280					285		
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
		290					295				300				
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
305					310					315					320
Ser	Leu	Ser	Pro	Gly	Lys										
				325											

<210> 63

<211> 978

<212> PRT

<213> 智人

<400> 63

Gly	Cys	Cys	Thr	Cys	Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Gly	Cys	Cys
1				5					10					15	
Cys	Ala	Thr	Cys	Gly	Gly	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Thr
			20					25					30		
Gly	Gly	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Cys	Thr	Cys	Cys	Ala	Gly	Gly
		35					40					45			
Ala	Gly	Cys	Ala	Cys	Cys	Thr	Cys	Cys	Gly	Ala	Gly	Ala	Gly	Cys	Ala
		50					55				60				
Cys	Ala	Gly	Cys	Gly	Gly	Cys	Cys	Cys	Thr	Gly	Gly	Gly	Cys	Thr	Gly
65						70				75					80

Cys Cys Thr Gly Gly Thr Cys Ala Ala Gly Gly Ala Cys Thr Ala Cys			
	85	90	95
Thr Thr Cys Cys Cys Cys Gly Ala Ala Cys Cys Gly Gly Thr Gly Ala			
	100	105	110
Cys Gly Gly Thr Gly Thr Cys Gly Thr Gly Gly Ala Ala Cys Thr Cys			
	115	120	125
Ala Gly Gly Cys Gly Cys Thr Cys Thr Gly Ala Cys Cys Ala Gly Cys			
	130	135	140
Gly Gly Cys Gly Thr Gly Cys Ala Cys Ala Cys Cys Thr Thr Cys Cys			
145	150	155	160
Cys Gly Gly Cys Thr Gly Thr Cys Cys Thr Ala Cys Ala Gly Thr Cys			
	165	170	175
Cys Thr Cys Ala Gly Gly Ala Cys Thr Cys Thr Ala Cys Thr Cys Cys			
	180	185	190
Cys Thr Cys Ala Gly Cys Ala Gly Cys Gly Thr Gly Gly Thr Gly Ala			
	195	200	205
Cys Cys Gly Thr Gly Ala Cys Cys Thr Cys Cys Ala Gly Cys Ala Ala			
210	215	220	
Cys Thr Thr Cys Gly Gly Cys Ala Cys Cys Cys Ala Gly Ala Cys Cys			
225	230	235	240
Thr Ala Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Ala Gly			
	245	250	255
Ala Thr Cys Ala Cys Ala Ala Gly Cys Cys Cys Ala Gly Cys Ala Ala			
	260	265	270
Cys Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Gly			
	275	280	285
Ala Cys Ala Gly Thr Thr Gly Ala Gly Cys Gly Cys Ala Ala Ala Thr			
290	295	300	
Gly Thr Thr Gly Thr Gly Thr Cys Gly Ala Gly Thr Gly Cys Cys Cys			
305	310	315	320
Ala Cys Cys Gly Thr Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Ala			
	325	330	335
Cys Cys Thr Gly Thr Gly Gly Cys Ala Gly Gly Ala Cys Cys Gly Thr			
	340	345	350
Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Cys Thr Thr Cys Cys Cys			
	355	360	365
Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys			
370	375	380	
Ala Cys Cys Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys			

385	390	395	400
Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys			
	405	410	415
Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys			
	420	425	430
Gly Thr Gly Ala Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys			
	435	440	445
Cys Cys Gly Ala Gly Gly Thr Cys Cys Ala Gly Thr Thr Cys Ala Ala			
	450	455	460
Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly Cys			
465	470	475	480
Ala Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala Thr Gly			
	485	490	495
Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys Ala Cys Gly			
	500	505	510
Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys Ala Ala Cys			
	515	520	525
Ala Gly Cys Ala Cys Gly Thr Thr Cys Cys Gly Thr Gly Thr Gly Gly			
	530	535	540
Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys Cys Gly Thr			
545	550	555	560
Cys Gly Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly			
	565	570	575
Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr			
	580	585	590
Ala Cys Ala Ala Gly Thr Gly Cys Ala Ala Gly Gly Thr Cys Thr Cys			
	595	600	605
Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys Cys Cys Ala			
	610	615	620
Gly Cys Cys Cys Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala			
625	630	635	640
Cys Cys Ala Thr Cys Thr Cys Cys Ala Ala Ala Ala Cys Cys Ala Ala			
	645	650	655
Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala			
	660	665	670
Cys Cys Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys			
	675	680	685
Thr Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala			
	690	695	700

Gly Gly Ala Gly Ala Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala Cys			
705	710	715	720
Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys Cys Thr			
	725	730	735
Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly Cys Thr Thr			
	740	745	750
Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys Ala Thr Cys			
	755	760	765
Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly Ala Gly Ala			
	770	775	780
Gly Cys Ala Ala Thr Gly Gly Gly Cys Ala Gly Cys Cys Gly Gly Ala			
785	790	795	800
Gly Ala Ala Cys Ala Ala Cys Thr Ala Cys Ala Ala Gly Ala Cys Cys			
	805	810	815
Ala Cys Ala Cys Cys Thr Cys Cys Cys Ala Thr Gly Cys Thr Gly Gly			
	820	825	830
Ala Cys Thr Cys Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Thr			
	835	840	845
Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly			
	850	855	860
Cys Thr Cys Ala Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala			
865	870	875	880
Gly Cys Ala Gly Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly			
	885	890	895
Gly Ala Ala Cys Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys			
	900	905	910
Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly			
	915	920	925
Cys Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala			
	930	935	940
Cys Ala Cys Ala Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr Cys			
945	950	955	960
Thr Cys Cys Cys Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala			
	965	970	975

Ala Ala

<210> 64

<211> 326

<212> PRT

<213> 智人

<400> 64

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

Thr	Ala	Cys	Ala	Cys	Cys	Thr	Gly	Cys	Ala	Ala	Cys	Gly	Thr	Ala	Gly	
Ala	Thr	Cys	Ala	Cys	Ala	Ala	Gly	Cys	Cys	Cys	Ala	Gly	Cys	Ala	Ala	
Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Thr	Gly	Gly	Ala	Cys	Ala	Ala	Gly	
Ala	Cys	Ala	Gly	Thr	Thr	Gly	Ala	Gly	Cys	Gly	Cys	Ala	Ala	Ala	Thr	
Gly	Thr	Thr	Gly	Thr	Gly	Thr	Cys	Gly	Ala	Gly	Thr	Gly	Cys	Cys	Cys	
Ala	Cys	Cys	Gly	Thr	Gly	Cys	Cys	Cys	Ala	Gly	Cys	Ala	Cys	Cys	Ala	
Cys	Cys	Thr	Gly	Thr	Gly	Gly	Cys	Ala	Gly	Gly	Ala	Cys	Cys	Gly	Thr	
Cys	Ala	Gly	Thr	Cys	Thr	Thr	Cys	Cys	Thr	Cys	Thr	Thr	Cys	Cys	Cys	
Cys	Cys	Cys	Ala	Ala	Ala	Ala	Cys	Cys	Cys	Ala	Ala	Gly	Gly	Ala	Cys	
Ala	Cys	Cys	Cys	Thr	Cys	Ala	Thr	Gly	Ala	Thr	Cys	Thr	Cys	Cys	Cys	
Gly	Gly	Ala	Cys	Cys	Cys	Cys	Thr	Gly	Ala	Gly	Gly	Thr	Cys	Ala	Cys	
Gly	Thr	Gly	Cys	Gly	Thr	Gly	Gly	Thr	Gly	Gly	Thr	Gly	Gly	Ala	Cys	
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Cys	Cys	Gly	Ala	Gly	Gly	Thr	Cys	Cys	Ala	Gly	Thr	Thr	Cys	Ala	Ala	
Cys	Thr	Gly	Gly	Thr	Ala	Cys	Gly	Thr	Gly	Gly	Ala	Cys	Gly	Gly	Cys	
Gly	Thr	Gly	Gly	Ala	Gly	Gly	Thr	Gly	Cys	Ala	Thr	Ala	Ala	Thr	Gly	
Cys	Cys	Ala	Ala	Gly	Ala	Cys	Ala	Ala	Ala	Gly	Cys	Cys	Ala	Cys	Gly	
Gly	Gly	Ala	Gly	Gly	Ala	Gly	Cys	Ala	Gly	Thr	Thr	Cys	Ala	Ala	Cys	
Ala	Gly	Cys	Ala	Cys	Gly	Thr	Thr	Cys	Cys	Gly	Thr	Gly	Thr	Gly	Gly	
Thr	Cys	Ala	Gly	Cys	Gly	Thr	Cys	Cys	Thr	Cys	Ala	Cys	Cys	Gly	Thr	

545	550	555	560
Thr Gly Thr Gly Cys	Ala Cys Cys Ala Gly	Gly Gly Ala Cys Thr Gly	Gly
565	570	575	
Cys Thr Gly Ala Ala Cys	Gly Gly Cys Ala Ala Gly	Gly Ala Gly Thr	
580	585	590	
Ala Cys Ala Ala Gly Thr	Gly Cys Ala Ala Gly Gly	Thr Cys Thr Cys	
595	600	605	
Cys Ala Ala Cys Ala Ala	Ala Gly Gly Cys Cys Thr	Cys Cys Cys Ala	
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Gly Cys Cys Cys Cys Cys	Ala Thr Cys Gly Ala Gly	Ala Ala Ala Ala	
625	630	635	640
Cys Cys Ala Thr Cys Thr	Cys Cys Ala Ala Ala Ala	Cys Cys Ala Ala	
645	650	655	
Ala Gly Gly Gly Cys Ala	Gly Cys Cys Cys Cys Gly	Ala Gly Ala Ala	
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Cys Cys Ala Cys Ala Gly	Gly Thr Gly Thr Ala Cys	Ala Cys Cys Cys	
675	680	685	
Thr Gly Cys Cys Cys Cys	Cys Ala Thr Cys Cys Cys	Gly Gly Gly Ala	
690	695	700	
Gly Gly Ala Gly Ala Thr	Gly Ala Cys Cys Ala Ala	Gly Ala Ala Cys	
705	710	715	720
Cys Ala Gly Gly Thr Cys	Ala Gly Cys Cys Thr Gly	Ala Cys Cys Thr	
725	730	735	
Gly Cys Cys Thr Gly Gly	Thr Cys Ala Ala Ala Gly	Gly Cys Thr Thr	
740	745	750	
Cys Thr Ala Cys Cys Cys	Cys Ala Gly Cys Gly Ala	Cys Ala Thr Cys	
755	760	765	
Gly Cys Cys Gly Thr Gly	Gly Ala Gly Thr Gly Gly	Gly Ala Gly Ala	
770	775	780	
Gly Cys Ala Ala Thr Gly	Gly Gly Cys Ala Gly Cys	Cys Gly Gly Ala	
785	790	795	800
Gly Ala Ala Cys Ala Ala	Cys Thr Ala Cys Ala Ala	Gly Ala Cys Cys	
805	810	815	
Ala Cys Ala Cys Cys Thr	Cys Cys Cys Ala Thr Gly	Cys Thr Gly Gly	
820	825	830	
Ala Cys Thr Cys Cys Gly	Ala Cys Gly Gly Cys Thr	Cys Cys Thr Thr	
835	840	845	
Cys Thr Thr Cys Cys Thr	Cys Thr Ala Cys Ala Gly	Cys Ala Ala Gly	
850	855	860	

Cys Thr Cys Ala Cys Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala
 865 870 875 880
 Gly Cys Ala Gly Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly
 885 890 895
 Gly Ala Ala Cys Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys
 900 905 910
 Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly
 915 920 925
 Cys Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala
 930 935 940
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 965 970 975
 Ala Ala
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 <213> 智人
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 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 100 105 110
 Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 115 120 125
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 130 135 140
 Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly

145	150							155							160		
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn		
				165				170				175					
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp		
				180				185				190					
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro		
				195				200				205					
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu		
				210				215				220					
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn		
225				230				235				240					
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile		
				245				250				255					
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr		
				260				265				270					
Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys		
				275				280				285					
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys		
				290				295				300					
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu		
305				310				315				320					
Ser	Leu	Ser	Pro	Gly	Lys												
				325													

67

922 $\langle 211 \rangle$

<212> PRT

〈213〉 智人

<400> 67

Gly	Cys	Cys	Thr	Cys	Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Gly	Cys	Cys
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Cys	Ala	Thr	Cys	Gly	Gly	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Thr
			20					25					30		
Gly	Gly	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Cys	Thr	Cys	Cys	Ala	Gly	Gly
		35					40					45			
Ala	Gly	Cys	Ala	Cys	Cys	Thr	Cys	Cys	Gly	Ala	Gly	Ala	Gly	Cys	Ala
	50					55					60				
Cys	Ala	Gly	Cys	Gly	Gly	Cys	Cys	Cys	Thr	Gly	Gly	Gly	Cys	Thr	Gly
65				70					75					80	
Cys	Cys	Thr	Gly	Gly	Thr	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Thr	Ala	Cys

85							90							95		
Thr	Thr	Cys	Cys	Cys	Cys	Gly	Ala	Ala	Cys	Cys	Gly	Gly	Thr	Gly	Ala	
100							105							110		
Cys	Gly	Gly	Thr	Gly	Thr	Cys	Gly	Thr	Gly	Gly	Ala	Ala	Cys	Thr	Cys	
115							120							125		
Ala	Gly	Gly	Cys	Gly	Cys	Thr	Cys	Thr	Gly	Ala	Cys	Cys	Ala	Gly	Cys	
130							135							140		
Gly	Gly	Cys	Gly	Thr	Gly	Cys	Ala	Cys	Ala	Cys	Cys	Thr	Thr	Cys	Cys	
145							150							160		
Cys	Gly	Gly	Cys	Thr	Gly	Thr	Cys	Cys	Thr	Ala	Cys	Ala	Gly	Thr	Cys	
165							170							175		
Cys	Thr	Cys	Ala	Gly	Gly	Ala	Cys	Thr	Cys	Thr	Ala	Cys	Thr	Cys	Cys	
180							185							190		
Cys	Thr	Cys	Ala	Gly	Cys	Ala	Gly	Cys	Gly	Thr	Gly	Gly	Thr	Gly	Ala	
195							200							205		
Cys	Cys	Gly	Thr	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Ala	Gly	Cys	Ala	Ala	
210							215							220		
Cys	Thr	Thr	Cys	Gly	Gly	Cys	Ala	Cys	Cys	Cys	Ala	Gly	Ala	Cys	Cys	
225							230							240		
Thr	Ala	Cys	Ala	Cys	Cys	Thr	Gly	Cys	Ala	Ala	Cys	Gly	Thr	Ala	Gly	
245							250							255		
Ala	Thr	Cys	Ala	Cys	Ala	Ala	Gly	Cys	Cys	Cys	Ala	Gly	Cys	Ala	Ala	
260							265							270		
Cys	Ala	Cys	Cys	Ala	Ala	Gly	Gly	Thr	Gly	Gly	Gly	Thr	Gly	Gly	Cys	
275							280							285		
Ala	Gly	Gly	Ala	Cys	Cys	Gly	Thr	Cys	Ala	Gly	Thr	Cys	Thr	Thr	Cys	
290							295							300		
Cys	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Cys	Ala	Ala	Ala	Ala	Cys	
305							310							320		
Cys	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Ala	Cys	Cys	Cys	Thr	Cys	Ala	Thr	
325							330							335		
Gly	Ala	Thr	Cys	Thr	Cys	Cys	Cys	Gly	Gly	Ala	Cys	Cys	Cys	Cys	Thr	
340							345							350		
Gly	Ala	Gly	Gly	Thr	Cys	Ala	Cys	Gly	Thr	Gly	Cys	Gly	Thr	Gly	Gly	
355							360							365		
Thr	Gly	Gly	Thr	Gly	Gly	Ala	Cys	Gly	Thr	Gly	Ala	Gly	Cys	Cys	Ala	
370							375							380		
Cys	Gly	Ala	Ala	Gly	Ala	Cys	Cys	Cys	Cys	Gly	Ala	Gly	Gly	Thr	Cys	
385							390							400		

Cys	Ala	Gly	Thr	Thr	Cys	Ala	Ala	Cys	Thr	Gly	Gly	Thr	Ala	Cys	Gly	
				405					410						415	
Thr	Gly	Gly	Ala	Cys	Gly	Gly	Cys	Gly	Thr	Gly	Gly	Ala	Gly	Gly	Thr	
			420					425						430		
Gly	Cys	Ala	Thr	Ala	Ala	Thr	Gly	Cys	Cys	Ala	Ala	Gly	Ala	Cys	Ala	
			435				440							445		
Ala	Ala	Gly	Cys	Cys	Ala	Cys	Gly	Gly	Gly	Ala	Gly	Gly	Ala	Gly	Cys	
			450				455						460			
Ala	Gly	Thr	Thr	Cys	Ala	Ala	Cys	Ala	Gly	Cys	Ala	Cys	Gly	Thr	Thr	
465				470					475						480	
Cys	Cys	Gly	Thr	Gly	Thr	Gly	Gly	Thr	Cys	Ala	Gly	Cys	Gly	Thr	Cys	
			485					490						495		
Cys	Thr	Cys	Ala	Cys	Cys	Gly	Thr	Cys	Gly	Thr	Gly	Cys	Ala	Cys	Cys	
			500					505						510		
Ala	Gly	Gly	Ala	Cys	Thr	Gly	Gly	Cys	Thr	Gly	Ala	Ala	Cys	Gly	Gly	
			515				520							525		
Cys	Ala	Ala	Gly	Gly	Ala	Gly	Thr	Ala	Cys	Ala	Ala	Gly	Thr	Gly	Cys	
			530				535					540				
Ala	Ala	Gly	Gly	Thr	Cys	Thr	Cys	Cys	Ala	Ala	Cys	Ala	Ala	Ala	Gly	
545				550					555						560	
Gly	Cys	Cys	Thr	Cys	Cys	Cys	Ala	Gly	Cys	Cys	Cys	Cys	Cys	Ala	Thr	
			565					570						575		
Cys	Gly	Ala	Gly	Ala	Ala	Ala	Ala	Cys	Cys	Ala	Thr	Cys	Thr	Cys	Cys	
			580					585						590		
Ala	Ala	Ala	Ala	Cys	Cys	Ala	Ala	Ala	Gly	Gly	Gly	Cys	Ala	Gly	Cys	
			595				600							605		
Cys	Cys	Cys	Gly	Ala	Gly	Ala	Ala	Cys	Cys	Ala	Cys	Ala	Gly	Gly	Thr	
			610				615							620		
Gly	Thr	Ala	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Cys	Cys	Cys	Cys	Cys	Ala	
625				630					635						640	
Thr	Cys	Cys	Cys	Gly	Gly	Gly	Ala	Gly	Gly	Ala	Gly	Ala	Thr	Gly	Ala	
			645					650						655		
Cys	Cys	Ala	Ala	Gly	Ala	Ala	Cys	Cys	Ala	Gly	Gly	Thr	Cys	Ala	Gly	
			660				665							670		
Cys	Cys	Thr	Gly	Ala	Cys	Cys	Thr	Gly	Cys	Cys	Thr	Gly	Gly	Thr	Cys	
			675				680							685		
Ala	Ala	Ala	Gly	Gly	Cys	Thr	Thr	Cys	Thr	Ala	Cys	Cys	Cys	Cys	Ala	
			690				695							700		
Gly	Cys	Gly	Ala	Cys	Ala	Thr	Cys	Thr	Cys	Cys	Gly	Thr	Gly	Gly	Ala	

705	710	715	720
Gly Thr Gly Gly Gly	Ala Gly Ala Gly Cys	Ala Ala Thr Gly Gly Gly	
	725	730	735
Cys Ala Gly Cys Cys	Gly Gly Ala Gly Ala Ala Cys	Ala Ala Cys Thr	
	740	745	750
Ala Cys Ala Ala Gly	Ala Cys Cys Ala Cys Ala Cys	Cys Thr Cys Cys	
	755	760	765
Cys Ala Thr Gly Cys	Thr Gly Gly Ala Cys Thr Cys	Cys Gly Ala Cys	
	770	775	780
Gly Gly Cys Thr Cys	Cys Thr Thr Cys Thr Thr Cys	Cys Thr Cys Thr	
785	790	795	800
Ala Cys Ala Gly Cys	Ala Ala Gly Cys Thr Cys Ala Cys	Cys Gly Thr	
	805	810	815
Gly Gly Ala Cys Ala	Ala Gly Ala Gly Cys Ala Gly Gly	Thr Gly Gly	
	820	825	830
Cys Ala Gly Cys Ala	Gly Gly Gly Gly Ala Ala Cys Gly	Thr Cys Thr	
	835	840	845
Thr Cys Thr Cys Ala	Thr Gly Cys Thr Cys Cys Gly Thr	Gly Ala Thr	
	850	855	860
Gly Cys Ala Thr Gly	Ala Gly Gly Cys Thr Cys Thr Gly	Cys Ala Cys	
865	870	875	880
Ala Ala Cys Cys Ala	Cys Thr Ala Cys Ala Cys Ala Cys	Ala Gly Ala	
	885	890	895
Ala Gly Ala Gly Cys	Cys Thr Cys Thr Cys Cys Cys Thr	Gly Thr Cys	
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Thr Cys Cys Gly Gly	Gly Thr Ala Ala Ala		
	915	920	
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<211> 326			
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<213> 智人			
<400> 68			
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Phe Pro Glu Pro Val	Thr Val Ser Trp	Asn Ser Gly Ala	Leu Thr Ser
	35	40	45
Gly Val His Thr Phe	Pro Ala Val Leu	Gln Ser Ser Gly	Leu Tyr Ser

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

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<211> 981

<212> PRT

<213> 智人

<400> 69

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Cys	Ala	Thr	Cys	Cys	Gly	Thr	Cys	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Thr
			20					25					30		
Gly	Gly	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Cys	Thr	Cys	Cys	Ala	Gly	Gly
		35					40					45			
Ala	Gly	Cys	Ala	Cys	Cys	Thr	Cys	Cys	Gly	Ala	Gly	Ala	Gly	Cys	Ala
	50					55				60					
Cys	Ala	Gly	Cys	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Gly	Gly	Cys	Thr	Gly
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Cys	Cys	Thr	Gly	Gly	Thr	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Thr	Ala	Cys
			85					90					95		
Thr	Thr	Cys	Cys	Cys	Cys	Gly	Ala	Ala	Cys	Cys	Gly	Gly	Thr	Gly	Ala
		100						105					110		
Cys	Gly	Gly	Thr	Gly	Thr	Cys	Gly	Thr	Gly	Gly	Ala	Ala	Cys	Thr	Cys
	115						120					125			
Ala	Gly	Gly	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Ala	Cys	Cys	Ala	Gly	Cys
	130					135				140					
Gly	Gly	Cys	Gly	Thr	Gly	Cys	Ala	Cys	Ala	Cys	Cys	Thr	Thr	Cys	Cys
145					150				155					160	
Cys	Gly	Gly	Cys	Thr	Gly	Thr	Cys	Cys	Thr	Ala	Cys	Ala	Gly	Thr	Cys
			165					170					175		
Cys	Thr	Cys	Ala	Gly	Gly	Ala	Cys	Thr	Cys	Thr	Ala	Cys	Thr	Cys	Cys
		180						185					190		
Cys	Thr	Cys	Ala	Gly	Cys	Ala	Gly	Cys	Gly	Thr	Gly	Gly	Thr	Gly	Ala
	195						200					205			
Cys	Cys	Gly	Thr	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Ala	Gly	Cys	Ala	Gly
	210					215					220				
Cys	Thr	Thr	Gly	Gly	Gly	Cys	Ala	Cys	Gly	Ala	Ala	Gly	Ala	Cys	Cys
225					230				235					240	
Thr	Ala	Cys	Ala	Cys	Cys	Thr	Gly	Cys	Ala	Ala	Cys	Gly	Thr	Ala	Gly
			245					250					255		
Ala	Thr	Cys	Ala	Cys	Ala	Ala	Gly	Cys	Cys	Cys	Ala	Gly	Cys	Ala	Ala
		260					265					270			
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	275						280					285			
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Ala Thr Gly Gly Thr Cys Cys Cys Cys Cys Ala Thr Gly Cys Cys Cys																	
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Ala Thr Cys Ala Thr Gly Cys Cys Cys Cys Ala Gly Cys Ala Cys Cys Thr																	
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Gly Ala Gly Thr Thr Cys Cys Thr Gly Gly Gly Gly Gly Ala Cys																	
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Cys Ala Thr Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Gly Thr Thr																	
						355						360					365
Cys Cys Cys Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly																	
						370						375					380
Gly Ala Cys Ala Cys Thr Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr																	
385						390						395					400
Cys Cys Cys Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr																	
						405						410					415
Cys Ala Cys Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly																	
						420						425					430
Gly Ala Cys Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Ala Gly																	
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						450						455					460
Cys Ala Ala Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Thr																	
465						470						475					480
Gly Gly Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala																	
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Ala Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys																	
						500						505					510
Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys																	
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Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly Thr Gly																	
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Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys																	
545						550						555					560
Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys																	
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Thr Gly Gly Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly																	
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Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly Cys Ala Ala Gly Gly Thr																	
						595						600					605
Cys Thr Cys Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys																	

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Cys Ala Ala Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala		655
	660	665
Gly Ala Gly Cys Cys Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala		670
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705	710	715
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	740	745
Cys Thr Thr Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys		750
	755	760
Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly		765
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785	790	795
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Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys Cys Gly Thr Gly Cys		815
	820	825
Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala Cys Gly Gly Cys Thr Cys		830
	835	840
Cys Thr Thr Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys		845
	850	855
Ala Gly Gly Cys Thr Ala Ala Cys Cys Gly Thr Gly Gly Ala Cys Ala		860
865	870	875
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	885	890
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	900	905
Thr Gly Cys Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly		910
	915	920
		925

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

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 210 215 220
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 225 230 235 240
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 245 250 255
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 260 265 270
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 275 280 285
 Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
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 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 305 310 315 320
 Leu Ser Leu Ser Leu Gly Lys
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<210> 71

<211> 981

<212> PRT

<213> 智人

<400> 71

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 Ala Gly Cys Ala Cys Cys Thr Cys Cys Gly Ala Gly Ala Gly Cys Ala
 50 55 60
 Cys Ala Gly Cys Cys Gly Cys Cys Cys Thr Gly Gly Gly Cys Thr Gly
 65 70 75 80
 Cys Cys Thr Gly Gly Thr Cys Ala Ala Gly Gly Ala Cys Thr Ala Cys
 85 90 95
 Thr Thr Cys Cys Cys Cys Gly Ala Ala Cys Cys Gly Gly Thr Gly Ala
 100 105 110
 Cys Gly Gly Thr Gly Thr Cys Gly Thr Gly Gly Ala Ala Cys Thr Cys
 115 120 125
 Ala Gly Gly Cys Gly Cys Cys Cys Thr Gly Ala Cys Cys Ala Gly Cys
 130 135 140

Gly Gly Cys Gly Thr Gly Cys Ala Cys Ala Cys Cys Thr Thr Cys Cys			
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Cys Gly Gly Cys Thr Gly Thr Cys Cys Thr Ala Cys Ala Gly Thr Cys			
	165	170	175
Cys Thr Cys Ala Gly Gly Ala Cys Thr Cys Thr Ala Cys Thr Cys Cys			
	180	185	190
Cys Thr Cys Ala Gly Cys Ala Gly Cys Gly Thr Gly Gly Thr Gly Ala			
	195	200	205
Cys Cys Gly Thr Gly Cys Cys Cys Thr Cys Cys Ala Gly Cys Ala Gly			
	210	215	220
Cys Thr Thr Gly Gly Gly Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys			
225	230	235	240
Thr Ala Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Ala Gly			
	245	250	255
Ala Thr Cys Ala Cys Ala Ala Gly Cys Cys Cys Ala Gly Cys Ala Ala			
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Cys Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Gly			
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	290	295	300
Ala Thr Gly Gly Thr Cys Cys Cys Cys Cys Gly Thr Gly Cys Cys Cys			
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Ala Thr Cys Ala Thr Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Thr			
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Gly Ala Gly Thr Thr Cys Cys Thr Gly Gly Gly Gly Gly Gly Ala Cys			
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Cys Ala Thr Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Gly Thr Thr			
	355	360	365
Cys Cys Cys Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly			
	370	375	380
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Cys Cys Cys Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr			
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Cys Ala Cys Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly			
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Gly Ala Cys Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Ala Gly			
	435	440	445
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Gly Gly Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala		
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Ala Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys		
500	505	510
Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys		
515	520	525
Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly Thr Gly		
530	535	540
Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys		
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Cys Gly Thr Cys Gly Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys		
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Thr Gly Gly Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly		
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Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly Cys Ala Ala Gly Gly Thr		
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Cys Thr Cys Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys		
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Cys Cys Gly Thr Cys Cys Thr Cys Cys Ala Thr Cys Gly Ala Gly Ala		
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Ala Ala Cys Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala		
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Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly		
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Cys Thr Thr Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys		
755	760	765

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Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
50	55	60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
65	70	75 80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
	85	90 95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro		
	100	105 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
	115	120 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
	130	135 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp		
145	150	155 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
	165	170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp		
	180	185 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu		
	195	200 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg		
	210	215 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys		
225	230	235 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
	245	250 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
	260	265 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
	275	280 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser		
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<211> 981

<212> PRT

<213> 智人

<400> 73

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	340	345
Cys Ala Thr Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Gly Thr Thr		350
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Cys Cys Cys Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly		365
370	375	380
Gly Ala Cys Ala Cys Thr Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr		385
	390	395
Cys Cys Cys Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr		400
	405	410
Cys Ala Cys Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly		415
	420	425
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	450	455
Cys Ala Ala Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Thr		460
465	470	475
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	485	490
Ala Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys		495
	500	505
Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys		510
	515	520
Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly Thr Gly		525
	530	535
Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys		540
545	550	555
Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys		560
	565	570
Thr Gly Gly Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly		575
	580	585
Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly Cys Ala Ala Gly Gly Thr		590
	595	600
		605

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	675	680	685
Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Ala			
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Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly			
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Cys Thr Thr Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys			
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785	790	795	800
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Cys Thr Thr Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys			
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Thr Gly Cys Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly			

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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
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Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
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Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro		
100	105	110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
115	120	125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
130	135	140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp		
145	150	155
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
165	170	175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
180	185	190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu		

195	200	205
Pro Ser Ser Ile Glu Lys Thr	Ile Ser Lys Ala Lys Gly Gln Pro Arg	
210	215	220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys		
225	230	235
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
245	250	255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
260	265	270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
275	280	285
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser		
290	295	300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
305	310	315
Leu Ser Leu Ser Leu Gly Lys		
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<210> 75

<211> 981

<212> PRT

<213> 智人

<400> 75

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35 40 45
Ala Gly Cys Ala Cys Cys Thr Cys Cys Gly Ala Gly Ala Gly Cys Ala
50 55 60
Cys Gly Gly Cys Cys Gly Cys Cys Cys Thr Gly Gly Gly Cys Thr Gly
65 70 75 80
Cys Cys Thr Gly Gly Thr Cys Ala Ala Gly Gly Ala Cys Thr Ala Cys
85 90 95
Thr Thr Cys Cys Cys Cys Gly Ala Ala Cys Cys Ala Gly Thr Gly Ala
100 105 110
Cys Gly Gly Thr Gly Thr Cys Gly Thr Gly Gly Ala Ala Cys Thr Cys
115 120 125
Ala Gly Gly Cys Gly Cys Cys Cys Thr Gly Ala Cys Cys Ala Gly Cys

130	135	140
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145	150	155
Cys Gly Gly Cys Thr Gly Thr Cys Cys Thr Ala Cys Ala Gly Thr Cys		
165	170	175
Cys Thr Cys Ala Gly Gly Ala Cys Thr Cys Thr Ala Cys Thr Cys Cys		
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Cys Thr Cys Ala Gly Cys Ala Gly Cys Gly Thr Gly Gly Thr Gly Ala		
195	200	205
Cys Cys Gly Thr Gly Cys Cys Cys Thr Cys Cys Ala Gly Cys Ala Gly		
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Cys Thr Thr Gly Gly Gly Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys		
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Thr Ala Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Ala Gly		
245	250	255
Ala Thr Cys Ala Cys Ala Ala Gly Cys Cys Cys Ala Gly Cys Ala Ala		
260	265	270
Cys Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Gly		
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Ala Thr Gly Gly Thr Cys Cys Cys Cys Cys Ala Thr Gly Cys Cys Cys		
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Ala Cys Cys Ala Thr Gly Cys Cys Cys Ala Gly Cys Gly Cys Cys Thr		
325	330	335
Gly Ala Ala Thr Thr Thr Gly Ala Gly Gly Gly Gly Gly Ala Cys		
340	345	350
Cys Ala Thr Cys Ala Gly Thr Cys Thr Thr Cys Cys Thr Gly Thr Thr		
355	360	365
Cys Cys Cys Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly		
370	375	380
Gly Ala Cys Ala Cys Thr Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr		
385	390	395
Cys Cys Cys Gly Gly Ala Cys Cys Cys Cys Thr Gly Ala Gly Gly Thr		
405	410	415
Cys Ala Cys Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly		
420	425	430
Gly Ala Cys Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Ala Gly		
435	440	445

Ala Cys Cys Cys Cys Gly Ala Gly Gly Thr Cys Cys Ala Gly Thr Thr		
450	455	460
Cys Ala Ala Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Thr		
465	470	475
Gly Gly Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala		
485	490	495
Ala Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys		
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Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys		
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Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys		
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Cys Thr Cys Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys		
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Cys Cys Gly Thr Cys Ala Thr Cys Gly Ala Thr Cys Gly Ala Gly Ala		
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Cys Ala Ala Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala		
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Gly Ala Gly Cys Cys Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala		
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Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Ala		
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Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly		
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Cys Thr Thr Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys		

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Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly		
770	775	780
Ala Gly Ala Gly Cys Ala Ala Thr Gly Gly Gly Cys Ala Gly Cys Cys		
785	790	795
Gly Gly Ala Gly Ala Ala Cys Ala Ala Cys Thr Ala Cys Ala Ala Gly		800
805	810	815
Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys Cys Gly Thr Gly Cys		
820	825	830
Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala Cys Gly Gly Ala Thr Cys		
835	840	845
Cys Thr Thr Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys		
850	855	860
Ala Gly Gly Cys Thr Ala Ala Cys Cys Gly Thr Gly Gly Ala Cys Ala		
865	870	875
Ala Gly Ala Gly Cys Ala Gly Gly Thr Gly Gly Cys Ala Gly Gly Ala		
885	890	895
Gly Gly Gly Gly Ala Ala Thr Gly Thr Cys Thr Thr Cys Thr Cys Ala		
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Thr Gly Cys Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly		
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Ala Gly Gly Cys Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala		
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Cys Thr Ala Cys Ala Cys Ala Cys Ala Gly Ala Ala Gly Ala Gly Cys		
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Cys Cys Gly Cys Thr Gly Cys Cys Cys Thr Cys Gly Gly Cys Thr Gly		
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Thr Thr Thr Cys Cys Cys Gly Ala Gly Cys Cys Cys Gly Thr Gly Ala		
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Cys Gly Gly Gly Thr Gly Gly Ala Gly Ala Gly Cys Ala Ala Gly Thr		
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Ala Cys Gly Gly Cys Cys Cys Cys Cys Cys Thr Thr Gly Cys Cys Cys		
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Thr Cys Cys Thr Thr Gly Thr Cys Cys Thr Gly Cys Cys Cys Cys Thr		
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Cys Cys Cys Gly Gly Ala Cys Ala Cys Cys Cys Gly Ala Gly Gly Thr		
405	410	415
Gly Ala Cys Cys Thr Gly Thr Gly Thr Gly Gly Thr Cys Gly Thr Gly		
420	425	430
Gly Ala Cys Gly Thr Cys Ala Gly Cys Cys Ala Gly Gly Ala Gly Gly		
435	440	445
Ala Cys Cys Cys Cys Gly Ala Gly Gly Thr Gly Cys Ala Gly Thr Thr		
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Cys Ala Ala Cys Thr Gly Gly Thr Ala Thr Gly Thr Gly Gly Ala Cys		
465	470	475
Gly Gly Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Cys Ala		
485	490	495
Ala Thr Gly Cys Cys Ala Ala Ala Ala Cys Cys Ala Ala Gly Cys Cys		
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Cys Ala Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys		
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Ala Ala Thr Thr Cys Cys Ala Cys Cys Thr Ala Cys Ala Gly Gly Gly		
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Thr Gly Gly Thr Gly Ala Gly Cys Gly Thr Gly Cys Thr Gly Ala Cys		
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Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr Gly Ala Ala Gly Gly Gly		
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Ala Thr Thr Cys Thr Ala Cys Cys Cys Cys Thr Cys Cys Gly Ala Cys		
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785	790	795
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Cys Gly Gly Cys Thr Gly Ala Cys Ala Gly Thr Gly Gly Ala Cys Ala		
865	870	875
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Thr Gly Thr Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Cys Gly		
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Cys Thr Ala Cys Ala Cys Cys Cys Ala Gly Ala Ala Gly Ala Gly Cys		
945	950	955
Cys Thr Cys Thr Cys Cys Cys Thr Gly Thr Cys Cys Cys Thr Gly Gly		
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Cys Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Ala		
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Ala Gly Thr Ala Cys	Ala Ala Gly Thr Gly Cys	Ala Ala Gly Gly Thr			
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Cys Ala Gly Cys Ala Ala Thr	Ala Ala Gly Gly Gly Ala Cys	Thr Gly			
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Thr Ala Ala Ala Gly Gly Cys Cys	Ala Gly Cys Cys Cys Cys Gly Gly				
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675		680		685	
Cys Cys Cys Thr Gly Cys Cys Thr Cys Cys	Cys Ala Gly Cys Cys Ala				
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705		710		715	
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725		730		735	
Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr	Gly Ala Ala Gly Gly Gly				
740		745		750	
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Cys Gly Ala Gly Ala Ala Cys Ala Ala Thr	Thr Ala Thr Ala Ala Gly				
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Cys Thr Thr Cys Thr Thr Thr Cys Thr Gly	Thr Ala Cys Thr Cys Cys				
850		855		860	
Ala Gly Gly Cys Thr Gly Ala Cys Cys Gly	Thr Gly Gly Ala Thr Ala				
865		870		875	
				880	

Ala Gly Thr Cys Cys Ala Gly Gly Thr Gly Gly Cys Ala Gly Gly Ala
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Ala Gly Gly Cys Ala Ala Cys Gly Thr Gly Thr Thr Cys Ala Gly Cys
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Ala Gly Gly Cys Cys Cys Thr Gly Cys Ala Cys Ala Ala Thr Cys Ala
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Cys Thr Ala Cys Ala Cys Cys Cys Ala Gly Ala Ala Gly Thr Cys Cys
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<211> 327

<212> PRT

<213> 智人

<400> 78

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

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
	165	170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
	180	185 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu		
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Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg		
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Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys		
	225	230 235 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
	245	250 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
	260	265 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
	275	280 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser		
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<212> PRT

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<220>

<223> 合成恒定区

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Cys Ala Cys Gly Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly			
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Gly Ala Cys Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Ala Gly			
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Cys Ala Ala Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Thr			
465	470	475	480
Gly Gly Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala			
	485	490	495
Ala Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys			
	500	505	510
Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Thr Cys			
	515	520	525
Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly Thr Gly			
	530	535	540
Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr Cys Ala Cys			
545	550	555	560
Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys			
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Thr Gly Gly Cys Thr Gly Ala Ala Cys Gly Gly Cys Ala Ala Gly Gly			
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Cys Thr Cys Cys Ala Ala Cys Ala Ala Ala Gly Gly Cys Cys Thr Cys			
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Cys Cys Gly Thr Cys Ala Thr Cys Gly Ala Thr Cys Gly Ala Gly Ala			
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Cys Ala Ala Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala			
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	675	680	685
Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Ala			
	690	695	700

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	725	730	735
Cys Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly			
	740	745	750
Cys Thr Thr Cys Thr Ala Cys Cys Cys Cys Ala Gly Cys Gly Ala Cys			
	755	760	765
Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly Gly Gly			
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785	790	795	800
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	805	810	815
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	820	825	830
Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala Cys Gly Gly Ala Thr Cys			
	835	840	845
Cys Thr Thr Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Gly Cys			
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	885	890	895
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Thr Gly Cys Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly			
	915	920	925
Ala Gly Gly Cys Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala			
	930	935	940
Cys Thr Ala Cys Ala Cys Ala Cys Ala Gly Ala Ala Gly Ala Gly Cys			
945	950	955	960
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Gly Thr Ala Ala Ala			
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<211> 327

<212> PRT

<213> 智人

<400> 80

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			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
			35					40					45		
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
			50					55					60		
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
65						70				75					80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
						85				90					95
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro
						100				105					110
Pro	Val	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
						115				120					125
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
						130				135					140
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
145						150				155					160
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
						165				170					175
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
						180				185					190
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
						195				200					205
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
						210				215					220
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
225						230				235					240
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
						245				250					255
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
						260				265					270
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
						275				280					285
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325		
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Thr Ala Cys Cys Cys Cys Cys Gly Cys Gly Ala Gly Gly Cys Cys Ala		
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Thr Cys Cys Gly Gly Cys Ala Ala Cys Thr Cys Cys Cys Ala Gly Gly		
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Ala Ala Thr Cys Cys Gly Thr Gly Ala Cys Cys Gly Ala Gly Cys Ala		
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Ala Cys Cys Thr Ala Cys Thr Cys Cys Cys Thr Gly Thr Cys Cys Thr		
195 200 205		
Cys Cys Ala Cys Cys Cys Thr Gly Ala Cys Cys Cys Thr Gly Thr Cys		
210 215 220		
Cys Ala Ala Gly Gly Cys Cys Gly Ala Cys Thr Ala Cys Gly Ala Gly		

225	230	235	240
Ala Ala Gly Cys	Ala Cys Ala Ala Gly	Gly Thr Gly Thr	Ala Cys Gly
	245	250	255
Cys Cys Thr Gly	Cys Gly Ala Ala Gly	Thr Gly Ala Cys	Cys Cys Ala
	260	265	270
Cys Cys Ala Gly	Gly Gly Cys Cys Thr	Gly Thr Cys Thr	Ala Gly Cys
	275	280	285
Cys Cys Cys Gly	Thr Gly Ala Cys Cys	Ala Ala Gly Thr	Cys Thr Thr
	290	295	300
Thr Cys Ala Ala	Cys Cys Gly Gly Gly	Gly Cys Gly Ala	Gly Thr Gly
305	310	315	320
Thr			

<210> 82

<211> 107

<212> PRT

<213> 智人

<400> 82

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

<210> 83

<211> 321

<212> PRT

<213> 智人

<400> 83

Cys Gly Ala Ala	Cys Thr Gly Thr	Gly Gly Cys Thr	Gly Cys Ala Cys
1	5	10	15
Cys Ala Thr Cys	Thr Gly Thr Cys	Thr Thr Cys Ala	Thr Cys Thr Thr

20	25	30
Cys Cys Cys Gly Cys Cys Ala Thr Cys Thr Gly Ala Thr Gly Ala Gly		
35	40	45
Cys Ala Gly Thr Thr Gly Ala Ala Ala Thr Cys Thr Gly Gly Ala Ala		
50	55	60
Cys Thr Gly Cys Cys Thr Cys Thr Gly Thr Thr Gly Thr Gly Thr Gly		
65	70	75
Cys Cys Thr Gly Cys Thr Gly Ala Ala Thr Ala Ala Cys Thr Thr Cys		
85	90	95
Thr Ala Thr Cys Cys Cys Ala Gly Ala Gly Ala Gly Gly Cys Cys Ala		
100	105	110
Ala Ala Gly Thr Ala Cys Ala Gly Cys Gly Gly Ala Ala Gly Gly Thr		
115	120	125
Gly Gly Ala Thr Ala Ala Cys Gly Cys Cys Cys Thr Cys Cys Ala Ala		
130	135	140
Thr Cys Gly Gly Gly Thr Ala Ala Cys Thr Cys Cys Cys Ala Gly Gly		
145	150	155
Ala Gly Ala Gly Thr Gly Thr Cys Ala Cys Ala Gly Ala Gly Cys Ala		
165	170	175
Gly Gly Ala Gly Ala Gly Cys Ala Ala Gly Gly Ala Cys Ala Gly Cys		
180	185	190
Ala Cys Cys Thr Ala Cys Ala Gly Cys Cys Thr Cys Ala Gly Cys Ala		
195	200	205
Gly Cys Ala Cys Cys Cys Thr Gly Ala Cys Gly Cys Thr Gly Ala Gly		
210	215	220
Cys Ala Ala Ala Gly Cys Ala Gly Ala Cys Thr Ala Cys Gly Ala Gly		
225	230	235
Ala Ala Ala Cys Ala Cys Ala Ala Ala Gly Thr Cys Thr Ala Cys Gly		
245	250	255
Cys Cys Thr Gly Cys Gly Ala Ala Gly Thr Cys Ala Cys Cys Cys Ala		
260	265	270
Thr Cys Ala Gly Gly Gly Cys Cys Thr Gly Ala Gly Cys Thr Cys Gly		
275	280	285
Cys Cys Cys Gly Thr Cys Ala Cys Ala Ala Ala Gly Ala Gly Cys Thr		
290	295	300
Thr Cys Ala Ala Cys Ala Gly Gly Gly Gly Ala Gly Ala Gly Thr Gly		
305	310	315
Thr		320
<210> 84		

<211> 107

<212> PRT

<213> 智人

<400> 84

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

<210> 85

<211> 321

<212> PRT

<213> 智人

<400> 85

Cys	Gly	Ala	Ala	Cys	Thr	Gly	Thr	Gly	Gly	Cys	Thr	Gly	Cys	Ala	Cys
1				5				10					15		
Cys	Ala	Thr	Cys	Thr	Gly	Thr	Cys	Thr	Thr	Cys	Ala	Thr	Cys	Thr	Thr
			20					25					30		
Cys	Cys	Cys	Gly	Cys	Cys	Ala	Thr	Cys	Thr	Gly	Ala	Thr	Gly	Ala	Gly
		35					40					45			
Cys	Ala	Gly	Thr	Thr	Gly	Ala	Ala	Ala	Thr	Cys	Thr	Gly	Gly	Ala	Ala
	50					55				60					
Cys	Thr	Gly	Cys	Cys	Thr	Cys	Thr	Gly	Thr	Thr	Gly	Thr	Gly	Thr	Gly
65					70				75						80
Cys	Cys	Thr	Gly	Cys	Thr	Gly	Ala	Ala	Thr	Ala	Ala	Cys	Thr	Thr	Cys
			85					90					95		
Thr	Ala	Thr	Cys	Cys	Cys	Ala	Gly	Ala	Gly	Ala	Gly	Gly	Cys	Cys	Ala
			100					105					110		
Ala	Ala	Gly	Thr	Ala	Cys	Ala	Gly	Cys	Gly	Gly	Ala	Ala	Gly	Gly	Thr
			115					120					125		

Gly Gly Ala Thr Ala Ala Cys Gly Cys Cys Cys Thr Cys Cys Ala Ala															
130							135						140		
Thr Cys Gly Gly Gly Thr Ala Ala Cys Thr Cys Cys Cys Ala Gly Gly															
145							150						155		160
Ala Gly Ala Gly Thr Gly Thr Cys Ala Cys Ala Gly Ala Gly Cys Ala															
							165						170		175
Gly Gly Ala Gly Ala Gly Cys Ala Ala Gly Gly Ala Cys Ala Gly Cys															
							180						185		190
Ala Cys Cys Thr Ala Cys Ala Gly Cys Cys Thr Cys Ala Gly Cys Ala															
							195						200		205
Gly Cys Ala Cys Cys Cys Thr Gly Ala Cys Gly Cys Thr Gly Ala Gly															
							210						215		220
Cys Ala Ala Ala Gly Cys Ala Gly Ala Cys Thr Ala Cys Gly Ala Gly															
225							230						235		240
Ala Ala Ala Cys Ala Cys Ala Ala Ala Gly Thr Cys Thr Ala Cys Gly															
							245						250		255
Cys Cys Thr Gly Cys Gly Ala Ala Gly Thr Cys Ala Cys Cys Cys Ala															
							260						265		270
Thr Cys Ala Gly Gly Gly Cys Cys Thr Gly Ala Gly Cys Thr Cys Gly															
							275						280		285
Cys Cys Cys Gly Thr Cys Ala Cys Ala Ala Ala Gly Ala Gly Cys Thr															
							290						295		300
Thr Cys Ala Ala Cys Ala Gly Gly Gly Gly Ala Gly Ala Gly Thr Gly															
305							310						315		320
Thr															
<210> 86															
<211> 107															
<212> PRT															
<213> 智人															
<400> 86															
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu															
1							5						10		15
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe															
							20						25		30
Tyr Pro Arg Glu Ala Lys Val Gln Arg Lys Val Asp Asn Ala Leu Gln															
							35						40		45
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Glu Ser Lys Asp Ser															
							50						55		60
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu															

65					70					75					80
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
					85					90					95
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
					100					105					
<210> 87															
<211> 321															
<212> PRT															
<213> 智人															
<400> 87															
Cys	Gly	Ala	Ala	Cys	Thr	Gly	Thr	Gly	Gly	Cys	Thr	Gly	Cys	Ala	Cys
1				5					10					15	
Cys	Ala	Thr	Cys	Thr	Gly	Thr	Cys	Thr	Thr	Cys	Ala	Thr	Cys	Thr	Thr
				20					25				30		
Cys	Cys	Cys	Gly	Cys	Cys	Ala	Thr	Cys	Thr	Gly	Ala	Thr	Gly	Ala	Gly
			35					40					45		
Cys	Ala	Gly	Thr	Thr	Gly	Ala	Ala	Ala	Thr	Cys	Thr	Gly	Gly	Ala	Ala
			50					55				60			
Cys	Thr	Gly	Cys	Cys	Thr	Cys	Thr	Gly	Thr	Thr	Gly	Thr	Gly	Thr	Gly
65						70				75					80
Cys	Cys	Thr	Gly	Cys	Thr	Gly	Ala	Ala	Thr	Ala	Ala	Cys	Thr	Thr	Cys
						85				90					95
Thr	Ala	Thr	Cys	Cys	Cys	Ala	Gly	Ala	Gly	Ala	Gly	Gly	Cys	Cys	Ala
			100						105				110		
Ala	Ala	Gly	Thr	Ala	Cys	Ala	Gly	Thr	Gly	Gly	Ala	Ala	Gly	Gly	Thr
			115						120				125		
Gly	Gly	Ala	Thr	Ala	Ala	Cys	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Ala	Ala
			130						135				140		
Thr	Cys	Gly	Gly	Gly	Thr	Ala	Ala	Cys	Thr	Cys	Cys	Cys	Ala	Gly	Gly
145						150				155					160
Ala	Gly	Ala	Gly	Thr	Gly	Thr	Cys	Ala	Cys	Ala	Gly	Ala	Gly	Cys	Ala
						165				170				175	
Gly	Gly	Ala	Cys	Ala	Gly	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Ala	Gly	Cys
			180						185				190		
Ala	Cys	Cys	Thr	Ala	Cys	Ala	Gly	Cys	Cys	Thr	Cys	Ala	Gly	Cys	Ala
			195						200				205		
Gly	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Ala	Cys	Gly	Cys	Thr	Gly	Ala	Gly
			210						215				220		
Cys	Ala	Ala	Ala	Gly	Cys	Ala	Gly	Ala	Cys	Thr	Ala	Cys	Gly	Ala	Gly

225	230	235	240
Ala Ala Ala Cys	Ala Cys Ala Ala Ala Cys	Thr Cys Thr Ala Cys	Gly
	245	250	255
Cys Cys Thr Gly	Cys Gly Ala Ala Gly Thr Cys	Ala Cys Cys Cys	Ala
	260	265	270
Thr Cys Ala Gly	Gly Gly Cys Cys Thr Gly Ala Gly	Cys Thr Cys Gly	
	275	280	285
Cys Cys Cys Gly	Thr Cys Ala Cys Ala Ala Gly	Ala Gly Cys Thr	
	290	295	300
Thr Cys Ala Ala	Cys Ala Gly Gly Gly Gly Ala Gly	Ala Gly Thr Gly	
305	310	315	320
Thr			
<210> 88			
<211> 107			
<212> PRT			
<213> 智人			
<400> 88			
Arg Thr Val Ala	Ala Pro Ser Val Phe Ile Phe	Pro Pro Ser Asp	Glu
1	5	10	15
Gln Leu Lys Ser	Gly Thr Ala Ser Val Val Cys Leu Leu	Asn Asn Phe	
	20	25	30
Tyr Pro Arg Glu	Ala Lys Val Gln Trp Lys Val Asp	Asn Ala Leu Gln	
	35	40	45
Ser Gly Asn Ser	Gln Glu Ser Val Thr Glu Gln Asp	Ser Lys Asp Ser	
	50	55	60
Thr Tyr Ser Leu	Ser Ser Thr Leu Thr Leu Ser Lys	Ala Asp Tyr Glu	
65	70	75	80
Lys His Lys Leu	Tyr Ala Cys Glu Val Thr His Gln Gly	Leu Ser Ser	
	85	90	95
Pro Val Thr Lys	Ser Phe Asn Arg Gly Glu Cys		
	100	105	
<210> 89			
<211> 321			
<212> PRT			
<213> 智人			
<400> 89			
Cys Gly Ala Ala	Cys Thr Gly Thr Gly Gly Cys Thr	Gly Cys Ala Cys	
1	5	10	15
Cys Ala Thr Cys	Thr Gly Thr Cys Thr Thr Cys Ala	Thr Cys Thr Thr	

20	25	30
Cys Cys Cys Gly Cys Cys Ala Thr Cys Thr Gly Ala Thr Gly Ala Gly		
35	40	45
Cys Ala Gly Thr Thr Gly Ala Ala Ala Thr Cys Thr Gly Gly Ala Ala		
50	55	60
Cys Thr Gly Cys Cys Thr Cys Thr Gly Thr Thr Gly Thr Gly Thr Gly		
65	70	75
Cys Cys Thr Gly Cys Thr Gly Ala Ala Thr Ala Ala Cys Thr Thr Cys		
85	90	95
Thr Ala Thr Cys Cys Cys Ala Gly Ala Gly Ala Gly Gly Cys Cys Ala		
100	105	110
Ala Ala Gly Thr Ala Cys Ala Gly Thr Gly Gly Ala Ala Gly Gly Thr		
115	120	125
Gly Gly Ala Thr Ala Ala Cys Gly Cys Cys Cys Thr Cys Cys Ala Ala		
130	135	140
Thr Cys Gly Gly Gly Thr Ala Ala Cys Thr Cys Cys Cys Ala Gly Gly		
145	150	155
Ala Gly Ala Gly Thr Gly Thr Cys Ala Cys Ala Gly Ala Gly Cys Ala		
165	170	175
Gly Gly Ala Cys Ala Gly Cys Ala Ala Gly Gly Ala Cys Ala Gly Cys		
180	185	190
Ala Cys Cys Thr Ala Cys Ala Gly Cys Cys Thr Cys Ala Gly Cys Ala		
195	200	205
Ala Cys Ala Cys Cys Cys Thr Gly Ala Cys Gly Cys Thr Gly Ala Gly		
210	215	220
Cys Ala Ala Ala Gly Cys Ala Gly Ala Cys Thr Ala Cys Gly Ala Gly		
225	230	235
Ala Ala Ala Cys Ala Cys Ala Ala Ala Gly Thr Cys Thr Ala Cys Gly		
245	250	255
Cys Cys Thr Gly Cys Gly Ala Ala Gly Thr Cys Ala Cys Cys Cys Ala		
260	265	270
Thr Cys Ala Gly Gly Gly Cys Cys Thr Gly Ala Gly Cys Thr Cys Gly		
275	280	285
Cys Cys Cys Gly Thr Cys Ala Cys Ala Ala Ala Gly Ala Gly Cys Thr		
290	295	300
Thr Cys Ala Ala Cys Ala Gly Gly Gly Gly Ala Gly Ala Gly Thr Gly		
305	310	315
Cys		320
<210> 90		

<211> 107

<212> PRT

<213> 智人

<400> 90

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

<210> 91

<211> 312

<212> PRT

<213> 智人

<400> 91

Cys	Cys	Cys	Ala	Ala	Gly	Gly	Cys	Cys	Ala	Ala	Cys	Cys	Cys	Cys	Ala
1				5					10					15	
Cys	Gly	Gly	Thr	Cys	Ala	Cys	Thr	Cys	Thr	Gly	Thr	Thr	Cys	Cys	Cys
			20					25					30		
Gly	Cys	Cys	Cys	Thr	Cys	Cys	Thr	Cys	Thr	Gly	Ala	Gly	Gly	Ala	Gly
		35					40					45			
Cys	Thr	Cys	Cys	Ala	Ala	Gly	Cys	Cys	Ala	Ala	Cys	Ala	Ala	Gly	Gly
	50					55					60				
Cys	Cys	Ala	Cys	Ala	Cys	Thr	Ala	Gly	Thr	Gly	Thr	Gly	Thr	Cys	Thr
65					70					75					80
Gly	Ala	Thr	Cys	Ala	Gly	Thr	Gly	Ala	Cys	Thr	Thr	Cys	Thr	Ala	Cys
			85						90					95	
Cys	Cys	Gly	Gly	Gly	Ala	Gly	Cys	Thr	Gly	Thr	Gly	Ala	Cys	Ala	Gly
			100					105					110		
Thr	Gly	Gly	Cys	Thr	Thr	Gly	Gly	Ala	Ala	Gly	Gly	Cys	Ala	Gly	Ala
			115					120					125		

Thr Gly Gly Cys Ala Gly Cys Cys Cys Gly Thr Cys Ala Ala Gly															
130															
Gly Cys Gly Gly Gly Ala Gly Thr Gly Gly Ala Gly Ala Cys Gly Ala															
145															
Cys Cys Ala Ala Ala Cys Cys Cys Thr Cys Cys Ala Ala Ala Cys Ala															
Gly Ala Gly Cys Ala Ala Cys Ala Ala Cys Ala Ala Gly Thr Ala Cys															
Gly Cys Gly Gly Cys Cys Ala Gly Cys Ala Gly Cys Thr Ala Cys Cys															
Thr Gly Ala Gly Cys Cys Thr Gly Ala Cys Gly Cys Cys Cys Gly Ala															
Gly Cys Ala Gly Thr Gly Gly Ala Ala Gly Thr Cys Cys Cys Ala Cys															
Ala Gly Ala Ala Gly Cys Thr Ala Cys Ala Gly Cys Thr Gly Cys Cys															
Ala Gly Gly Thr Cys Ala Cys Gly Cys Ala Thr Gly Ala Ala Gly Gly															
Gly Ala Gly Cys Ala Cys Cys Gly Thr Gly Gly Ala Gly Ala Ala Gly															
Ala Cys Ala Gly Thr Gly Gly Cys Cys Cys Cys Thr Ala Cys Ala Gly															
Ala Ala Thr Gly Thr Thr Cys Ala															
305															
<210> 92															
<211> 104															
<212> PRT															
<213> 智人															
<400> 92															
Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu															
1															
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr															
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys															
Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr															
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His															

Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys
				85					90					95	
Thr	Val	Ala	Pro	Thr	Glu	Cys	Ser								
				100											
<210> 93															
<211> 318															
<212> PRT															
<213> 智人															
<400> 93															
Gly	Gly	Thr	Cys	Ala	Gly	Cys	Cys	Cys	Ala	Ala	Gly	Gly	Cys	Cys	Ala
1				5					10					15	
Ala	Cys	Cys	Cys	Cys	Ala	Cys	Thr	Gly	Thr	Cys	Ala	Cys	Thr	Cys	Thr
			20					25					30		
Gly	Thr	Thr	Cys	Cys	Cys	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Thr	Cys	Thr
		35					40					45			
Gly	Ala	Gly	Gly	Ala	Gly	Cys	Thr	Cys	Cys	Ala	Ala	Gly	Cys	Cys	Ala
	50					55				60					
Ala	Cys	Ala	Ala	Gly	Gly	Cys	Cys	Ala	Cys	Ala	Cys	Thr	Ala	Gly	Thr
65					70				75					80	
Gly	Thr	Gly	Thr	Cys	Thr	Gly	Ala	Thr	Cys	Ala	Gly	Thr	Gly	Ala	Cys
				85					90					95	
Thr	Thr	Cys	Thr	Ala	Cys	Cys	Cys	Gly	Gly	Gly	Ala	Gly	Cys	Thr	Gly
			100					105					110		
Thr	Gly	Ala	Cys	Ala	Gly	Thr	Gly	Gly	Cys	Cys	Thr	Gly	Gly	Ala	Ala
		115					120					125			
Gly	Gly	Cys	Ala	Gly	Ala	Thr	Gly	Gly	Cys	Ala	Gly	Cys	Cys	Cys	Cys
	130						135				140				
Gly	Thr	Cys	Ala	Ala	Gly	Gly	Cys	Gly	Gly	Gly	Ala	Gly	Thr	Gly	Gly
145					150					155				160	
Ala	Gly	Ala	Cys	Cys	Ala	Cys	Cys	Ala	Ala	Ala	Cys	Cys	Cys	Thr	Cys
				165					170					175	
Cys	Ala	Ala	Ala	Cys	Ala	Gly	Ala	Gly	Cys	Ala	Ala	Cys	Ala	Ala	Cys
			180					185					190		
Ala	Ala	Gly	Thr	Ala	Cys	Gly	Cys	Gly	Gly	Cys	Cys	Ala	Gly	Cys	Ala
		195					200					205			
Gly	Cys	Thr	Ala	Cys	Cys	Thr	Gly	Ala	Gly	Cys	Cys	Thr	Gly	Ala	Cys
	210						215				220				
Gly	Cys	Cys	Cys	Gly	Ala	Gly	Cys	Ala	Gly	Thr	Gly	Gly	Ala	Ala	Gly
225					230					235				240	

Thr Cys Cys Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr Ala Cys Ala		
245	250	255
Gly Cys Thr Gly Cys Cys Ala Gly Gly Thr Cys Ala Cys Gly Cys Ala		
260	265	270
Thr Gly Ala Ala Gly Gly Gly Ala Gly Cys Ala Cys Cys Gly Thr Gly		
275	280	285
Gly Ala Gly Ala Ala Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Cys		
290	295	300
Cys Thr Ala Cys Ala Gly Ala Ala Thr Gly Thr Thr Cys Ala		
305	310	315
<210> 94		
<211> 318		
<212> PRT		
<213> 智人		
<400> 94		
Gly Gly Thr Cys Ala Gly Cys Cys Cys Ala Ala Gly Gly Cys Cys Ala		
1	5	10
Ala Cys Cys Cys Cys Ala Cys Thr Gly Thr Cys Ala Cys Thr Cys Thr		
20	25	30
Gly Thr Thr Cys Cys Cys Gly Cys Cys Cys Thr Cys Cys Thr Cys Thr		
35	40	45
Gly Ala Gly Gly Ala Gly Cys Thr Cys Cys Ala Ala Gly Cys Cys Ala		
50	55	60
Ala Cys Ala Ala Gly Gly Cys Cys Ala Cys Ala Cys Thr Ala Gly Thr		
65	70	75
Gly Thr Gly Thr Cys Thr Gly Ala Thr Cys Ala Gly Thr Gly Ala Cys		
85	90	95
Thr Thr Cys Thr Ala Cys Cys Cys Gly Gly Gly Ala Gly Cys Thr Gly		
100	105	110
Thr Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Thr Gly Gly Ala Ala		
115	120	125
Gly Gly Cys Ala Gly Ala Thr Gly Gly Cys Ala Gly Cys Cys Cys Cys		
130	135	140
Gly Thr Cys Ala Ala Gly Gly Cys Gly Gly Gly Ala Gly Thr Gly Gly		
145	150	155
Ala Gly Ala Cys Cys Ala Cys Cys Ala Ala Ala Cys Cys Cys Thr Cys		
165	170	175
Cys Ala Ala Ala Cys Ala Gly Ala Gly Cys Ala Ala Cys Ala Ala Cys		
180	185	190

Ala Ala Gly Thr Ala Cys Gly Cys Gly Gly Cys Cys Ala Gly Cys Ala		
195	200	205
Gly Cys Thr Ala Cys Cys Thr Gly Ala Gly Cys Cys Thr Gly Ala Cys		
210	215	220
Gly Cys Cys Cys Gly Ala Gly Cys Ala Gly Thr Gly Gly Ala Ala Gly		
225	230	235
240		
Thr Cys Cys Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr Ala Cys Ala		
245	250	255
Gly Cys Thr Gly Cys Cys Ala Gly Gly Thr Cys Ala Cys Gly Cys Ala		
260	265	270
Thr Gly Ala Ala Gly Gly Gly Ala Gly Cys Ala Cys Cys Gly Thr Gly		
275	280	285
Gly Ala Gly Ala Ala Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Cys		
290	295	300
Cys Thr Ala Cys Ala Gly Ala Ala Thr Gly Thr Thr Cys Ala		
305	310	315

<210> 95

<211> 106

<212> PRT

<213> 智人

<400> 95

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

<210> 96

<211> 318

<212> PRT

<213> 智人

<400> 96

Gly	Gly	Cys	Cys	Ala	Gly	Cys	Cys	Thr	Ala	Ala	Gly	Gly	Cys	Cys	Gly
1				5					10					15	
Cys	Thr	Cys	Cys	Thr	Thr	Cys	Thr	Gly	Thr	Gly	Ala	Cys	Cys	Cys	Thr
				20				25						30	
Gly	Thr	Thr	Cys	Cys	Cys	Cys	Cys	Cys	Ala	Thr	Cys	Cys	Thr	Cys	Cys
			35					40					45		
Gly	Ala	Gly	Gly	Ala	Ala	Cys	Thr	Gly	Cys	Ala	Gly	Gly	Cys	Thr	Ala
			50				55						60		
Ala	Cys	Ala	Ala	Gly	Gly	Cys	Cys	Ala	Cys	Cys	Cys	Thr	Cys	Gly	Thr
65					70				75						80
Gly	Thr	Gly	Cys	Cys	Thr	Gly	Ala	Thr	Cys	Ala	Gly	Cys	Gly	Ala	Cys
					85				90						95
Thr	Thr	Cys	Thr	Ala	Cys	Cys	Cys	Thr	Gly	Gly	Cys	Gly	Cys	Cys	Gly
			100						105					110	
Thr	Gly	Ala	Cys	Cys	Gly	Thr	Gly	Gly	Cys	Cys	Thr	Gly	Gly	Ala	Ala
			115						120					125	
Gly	Gly	Cys	Thr	Gly	Ala	Thr	Ala	Gly	Cys	Thr	Cys	Thr	Cys	Cys	Thr
			130					135						140	
Gly	Thr	Gly	Ala	Ala	Gly	Gly	Cys	Cys	Gly	Gly	Cys	Gly	Thr	Gly	Gly
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					165						170				175
Cys	Ala	Ala	Gly	Cys	Ala	Gly	Thr	Cys	Cys	Ala	Ala	Cys	Ala	Ala	Cys
			180						185					190	
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			195						200					205	
Cys	Cys	Thr	Ala	Cys	Cys	Thr	Gly	Thr	Cys	Cys	Cys	Thr	Gly	Ala	Cys
			210						215					220	
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225					230						235				240
Thr	Cys	Cys	Cys	Ala	Cys	Cys	Gly	Gly	Thr	Cys	Cys	Thr	Ala	Cys	Ala
					245						250				255
Gly	Cys	Thr	Gly	Cys	Cys	Ala	Ala	Gly	Thr	Gly	Ala	Cys	Cys	Cys	Ala
			260						265					270	
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 Thr Cys Cys Cys Ala Cys Cys Gly Gly Thr Cys Cys Thr Ala Cys Thr
 245 250 255

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

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Phe Tyr Pro Gly Pro Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro		
35	40	45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn		
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Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys		
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Ala Cys Ala Ala Gly Gly Cys Cys Ala Cys Ala Cys Thr Gly Gly Thr		
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		80

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				85						90					95		
Thr Thr Cys Thr Ala Cys Cys Cys Gly Gly Gly Ala Gly Cys Cys Gly																	
				100						105					110		
Thr Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Thr Gly Gly Ala Ala																	
				115						120					125		
Gly Gly Cys Ala Gly Ala Thr Ala Gly Cys Ala Gly Cys Cys Cys Cys																	
				130						135					140		
Gly Thr Cys Ala Ala Gly Gly Cys Gly Gly Gly Ala Gly Thr Gly Gly																	
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Ala Gly Ala Cys Cys Ala Cys Cys Ala Cys Ala Cys Cys Cys Thr Cys																	
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Cys Ala Ala Ala Cys Ala Ala Ala Gly Cys Ala Ala Cys Ala Ala Cys																	
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				210						215					220		
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				20				25				30			
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65				70				75				80			
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Thr	Gly	Ala	Cys	Ala	Gly	Thr	Gly	Gly	Cys	Cys	Thr	Gly	Gly	Ala	Ala
115				120				125							
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130				135				140							
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				165				170				175			
Cys	Ala	Ala	Ala	Cys	Ala	Ala	Ala	Gly	Cys	Ala	Ala	Cys	Ala	Ala	Cys
180				185				190							

Ala Ala Gly Thr Ala Cys Gly Cys Gly Gly Cys Cys Ala Gly Cys Ala		
195	200	205
Gly Cys Thr Ala Cys Cys Thr Gly Ala Gly Cys Cys Thr Gly Ala Cys		
210	215	220
Gly Cys Cys Thr Gly Ala Gly Cys Ala Gly Thr Gly Gly Ala Ala Gly		
225	230	235
240		
Thr Cys Cys Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr Ala Cys Ala		
245	250	255
Gly Cys Thr Gly Cys Cys Ala Gly Gly Thr Cys Ala Cys Gly Cys Ala		
260	265	270
Thr Gly Ala Ala Gly Gly Gly Ala Gly Cys Ala Cys Cys Gly Thr Gly		
275	280	285
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Cys Thr Ala Cys Ala Gly Ala Ala Thr Gly Thr Thr Cys Ala		
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Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro		
35	40	45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn		
50	55	60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys		
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				20					25					30	
Gly	Thr	Thr	Cys	Cys	Cys	Gly	Cys	Cys	Cys	Thr	Cys	Cys	Thr	Cys	Thr
				35					40					45	
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				50					55					60	
Ala	Cys	Ala	Ala	Gly	Gly	Cys	Cys	Ala	Cys	Ala	Cys	Thr	Gly	Gly	Thr
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									85					90	
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									180					185	
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									210					215	
Gly	Cys	Cys	Thr	Gly	Ala	Gly	Cys	Ala	Gly	Thr	Gly	Gly	Ala	Ala	Gly
225									230					235	
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									275					280	
Gly	Ala	Gly	Ala	Ala	Gly	Ala	Cys	Ala	Gly	Thr	Gly	Gly	Cys	Cys	Cys
									290					295	
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 Phe Tyr Pro Gly Ala Val Lys Val Ala Trp Lys Ala Asp Gly Ser Pro
 35 40 45
 Val Asn Thr Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
 50 55 60
 Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
 65 70 75 80
 Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
 85 90 95
 Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
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 35 40 45
 Gly Ala Gly Gly Ala Gly Cys Thr Thr Cys Ala Ala Gly Cys Cys Ala
 50 55 60
 Ala Cys Ala Ala Gly Gly Cys Cys Ala Cys Ala Cys Thr Gly Gly Thr
 65 70 75 80
 Gly Thr Gly Thr Cys Thr Cys Gly Thr Ala Ala Gly Thr Gly Ala Cys
 85 90 95
 Thr Thr Cys Thr Ala Cys Cys Cys Gly Gly Gly Ala Gly Cys Cys Gly

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

50	55	60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys		
65	70	75
Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val		
85	90	95
Glu Lys Thr Val Ala Pro Ala Glu Cys Ser		
100	105	
<210> 113		
<211> 318		
<212> PRT		
<213> 智人		
<400> 113		
Gly Gly Thr Cys Ala Gly Cys Cys Cys Ala Ala Gly Gly Cys Thr Gly		
1	5	10
Cys Cys Cys Cys Cys Thr Cys Gly Gly Thr Cys Ala Cys Thr Cys Thr		
20	25	30
Gly Thr Thr Cys Cys Cys Ala Cys Cys Cys Thr Cys Cys Thr Cys Thr		
35	40	45
Gly Ala Gly Gly Ala Gly Cys Thr Thr Cys Ala Ala Gly Cys Cys Ala		
50	55	60
Ala Cys Ala Ala Gly Gly Cys Cys Ala Cys Ala Cys Thr Gly Gly Thr		
65	70	75
Gly Thr Gly Thr Cys Thr Cys Gly Thr Ala Ala Gly Thr Gly Ala Cys		
85	90	95
Thr Thr Cys Ala Ala Cys Cys Cys Gly Gly Gly Ala Gly Cys Cys Gly		
100	105	110
Thr Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Thr Gly Gly Ala Ala		
115	120	125
Gly Gly Cys Ala Gly Ala Thr Gly Gly Cys Ala Gly Cys Cys Cys Cys		
130	135	140
Gly Thr Cys Ala Ala Gly Gly Thr Gly Gly Gly Ala Gly Thr Gly Gly		
145	150	155
Ala Gly Ala Cys Cys Ala Cys Cys Ala Ala Ala Cys Cys Cys Thr Cys		
165	170	175
Cys Ala Ala Ala Cys Ala Ala Ala Gly Cys Ala Ala Cys Ala Ala Cys		
180	185	190
Ala Ala Gly Thr Ala Thr Gly Cys Gly Gly Cys Cys Ala Gly Cys Ala		
195	200	205
Gly Cys Thr Ala Cys Cys Thr Gly Ala Gly Cys Cys Thr Gly Ala Cys		

210	215	220
Gly Cys Cys Cys Gly Ala Gly Cys Ala Gly Thr Gly Gly Ala Ala Gly		
225	230	235
Thr Cys Cys Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr Ala Cys Ala		240
	245	250
Gly Cys Thr Gly Cys Cys Gly Gly Gly Thr Cys Ala Cys Gly Cys Ala		255
	260	265
Thr Gly Ala Ala Gly Gly Gly Ala Gly Cys Ala Cys Cys Gly Thr Gly		270
	275	280
Gly Ala Gly Ala Ala Gly Ala Cys Ala Gly Thr Gly Gly Cys Cys Cys		285
	290	295
Cys Thr Gly Cys Ala Gly Ala Ala Thr Gly Cys Thr Cys Thr		300
305	310	315
<210> 114		
<211> 106		
<212> PRT		
<213> 智人		
<400> 114		
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser		
1	5	10
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Val Ser Asp		15
	20	25
Phe Asn Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro		30
	35	40
Val Lys Val Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn		45
	50	55
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys		60
65	70	75
Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val		80
	85	90
Glu Lys Thr Val Ala Pro Ala Glu Cys Ser		95
	100	105

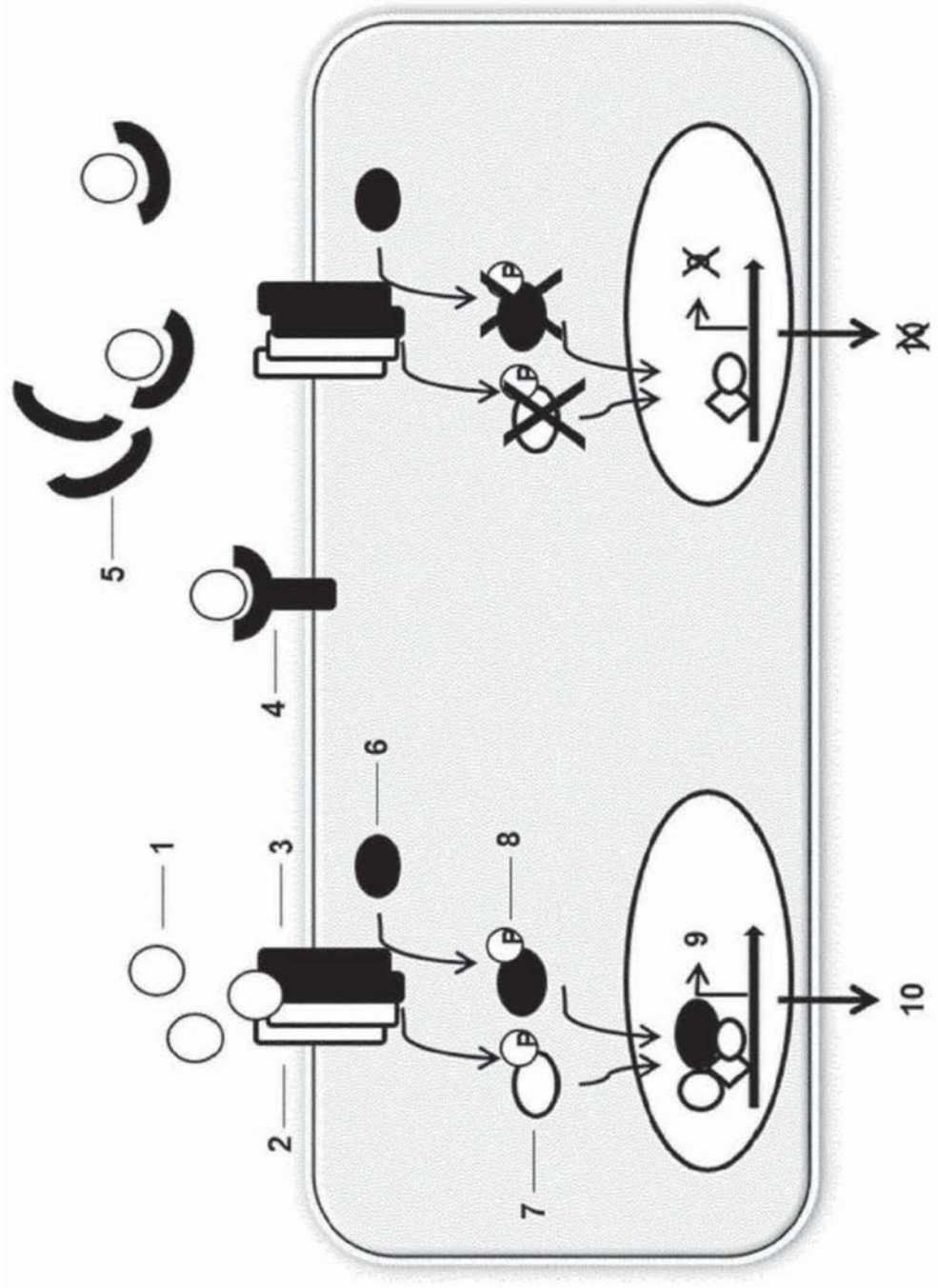


图1

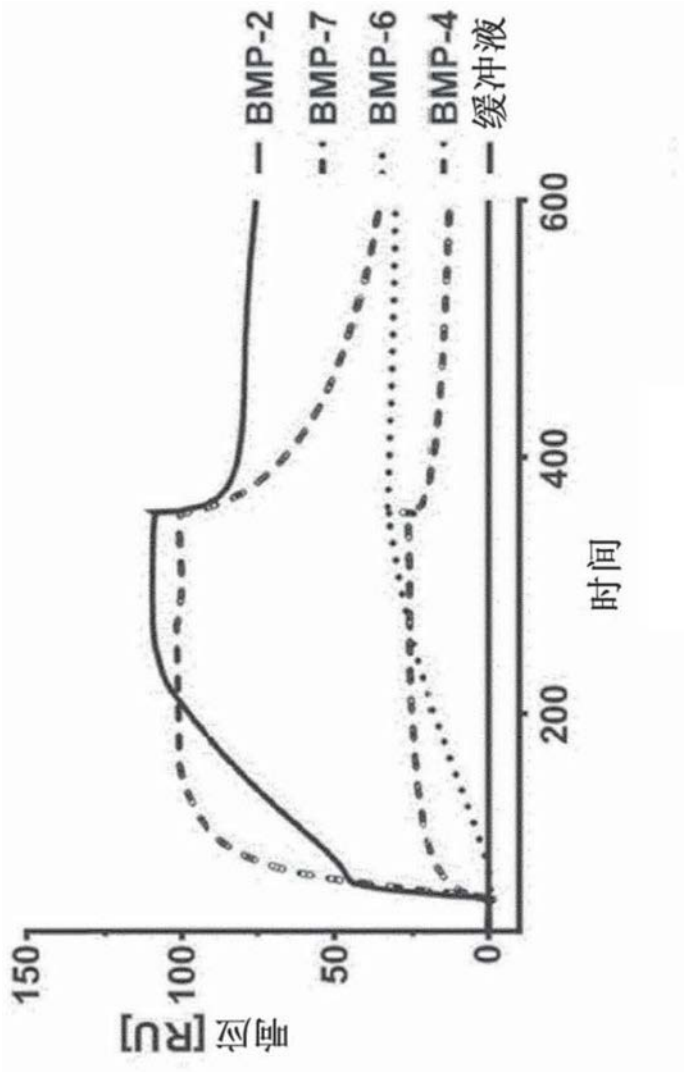


图2a

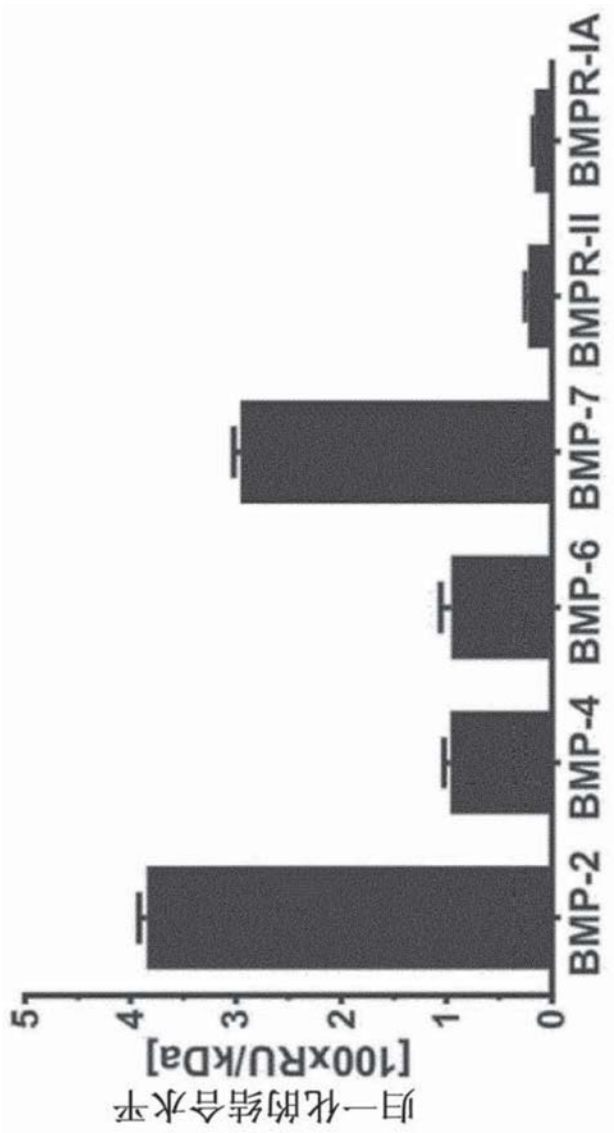


图2b

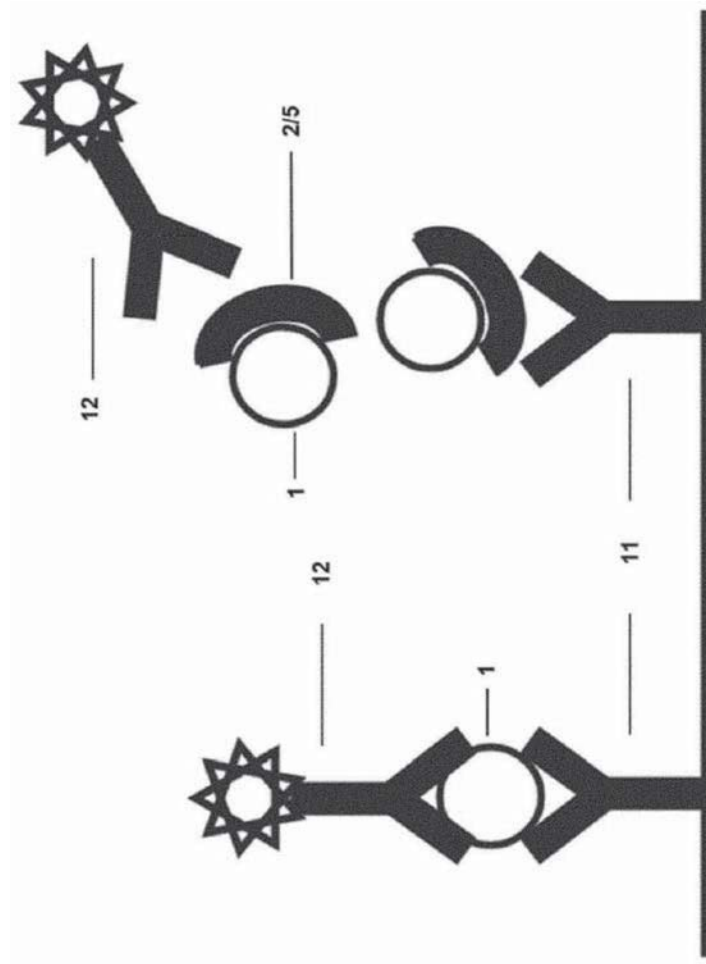


图3a

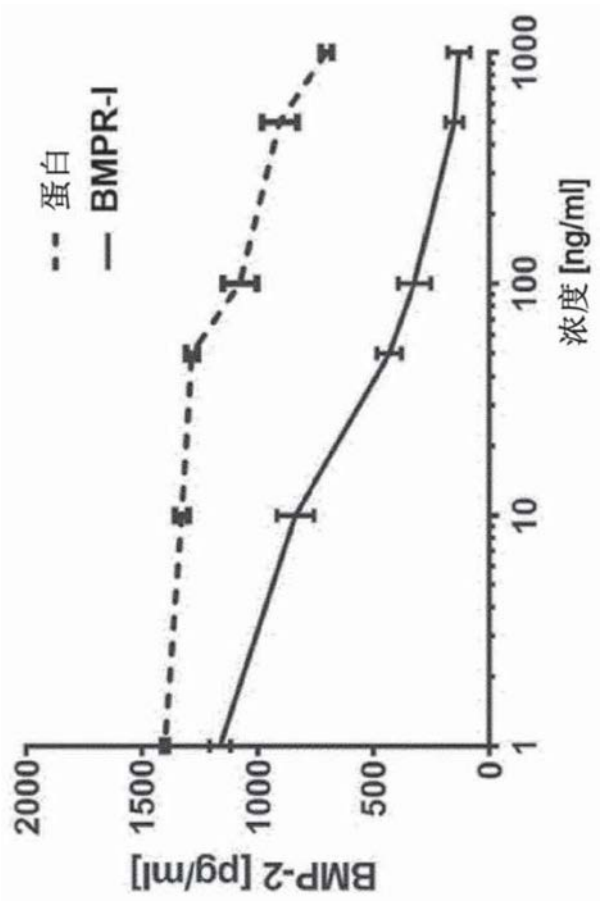


图3b

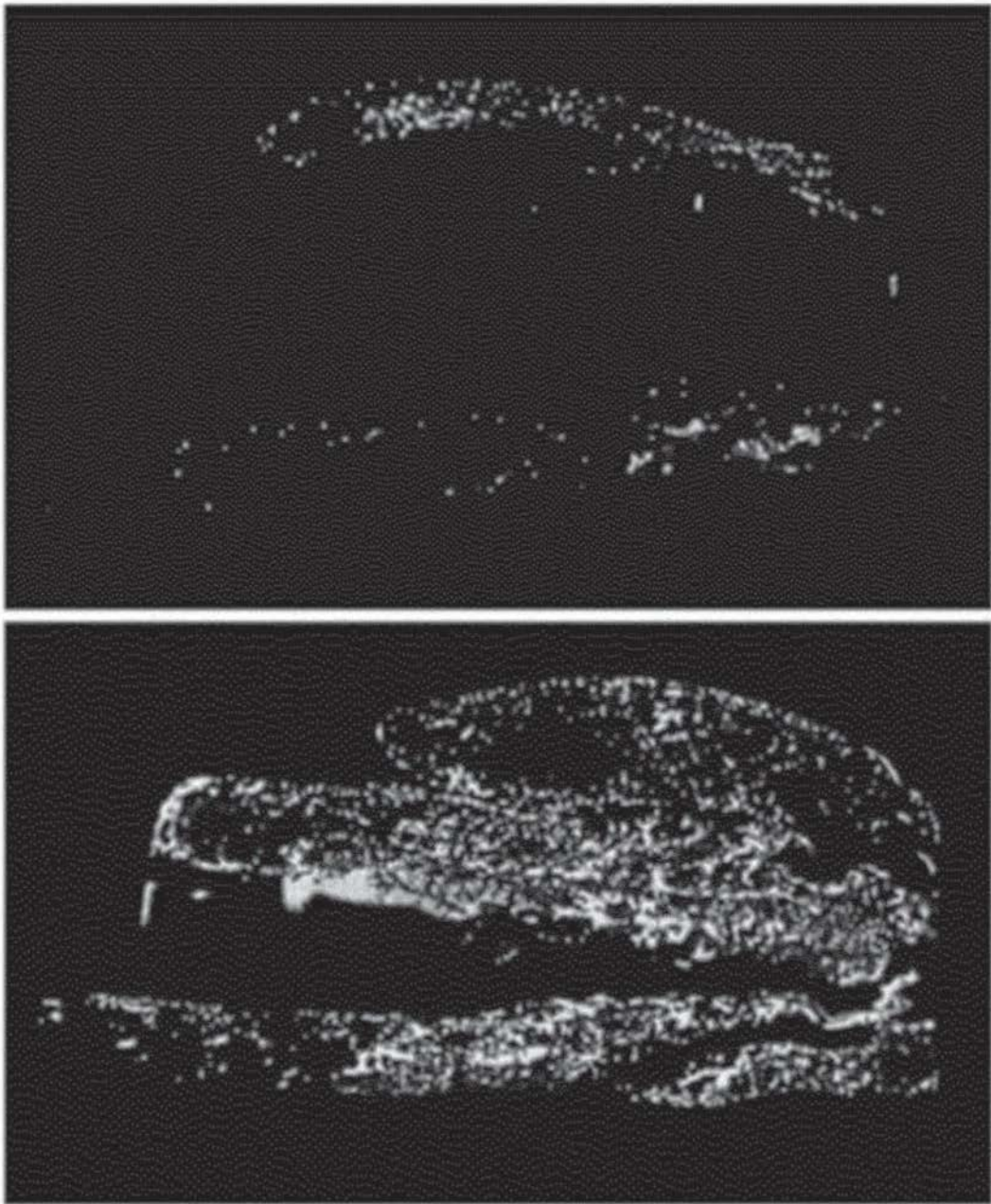


图4a

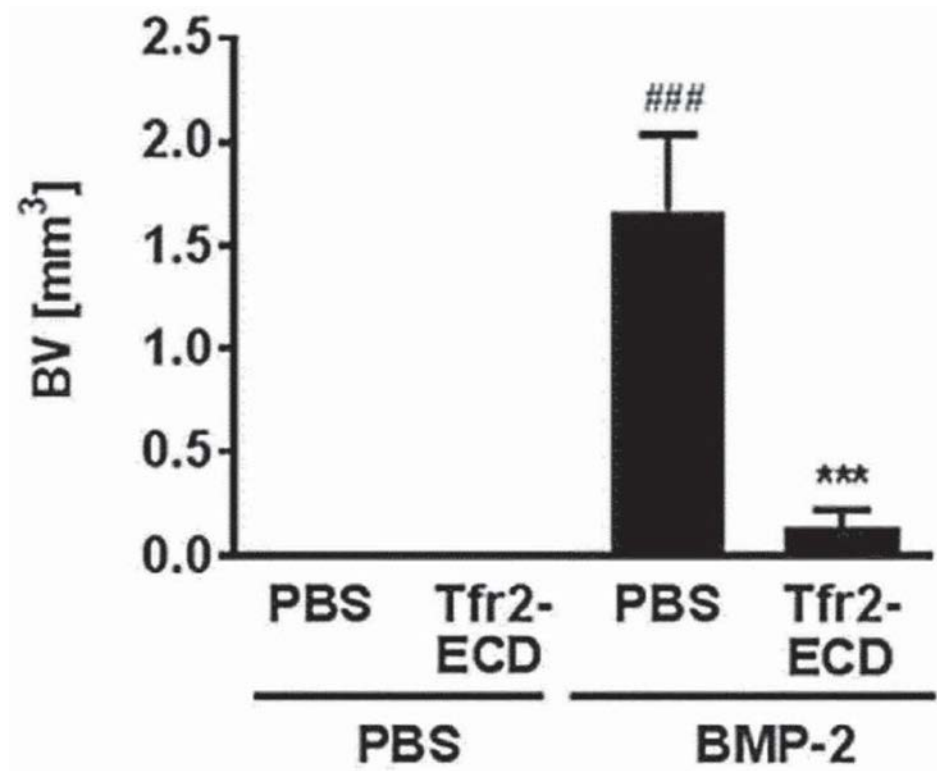


图4b

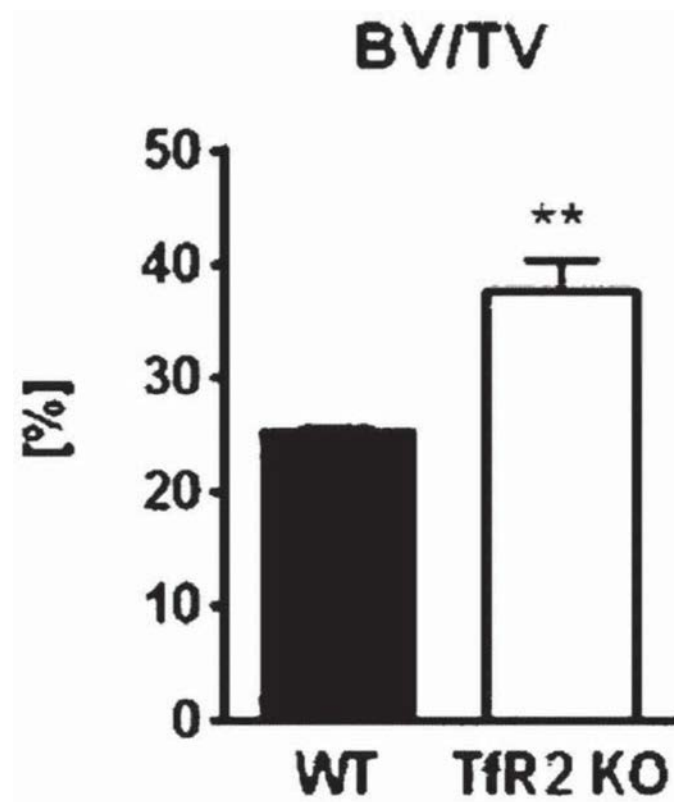


图5

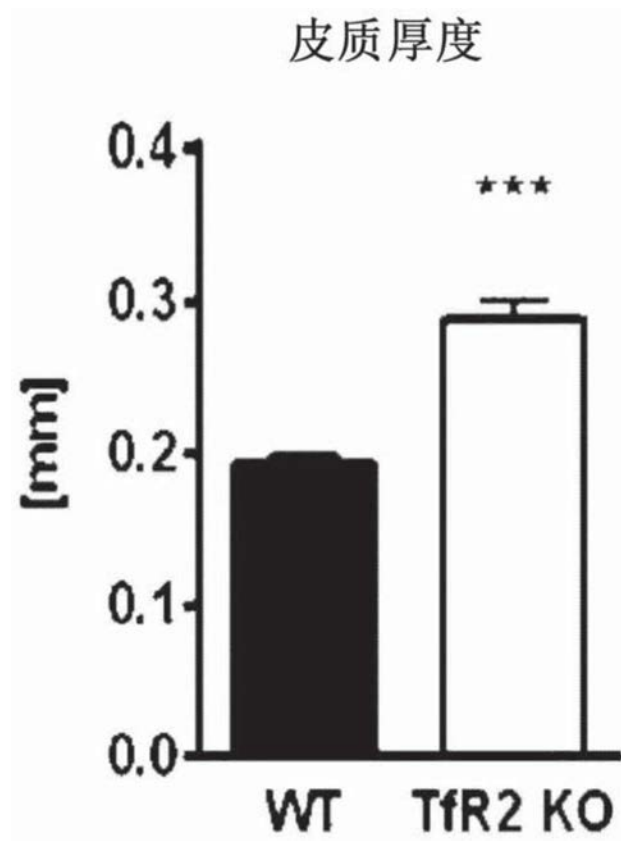


图6

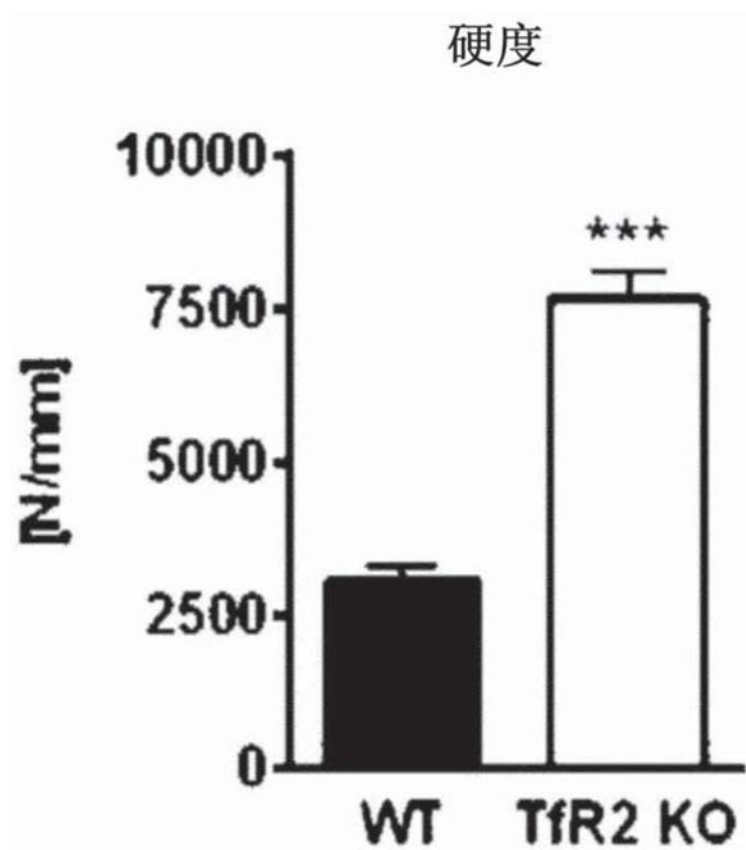


图7

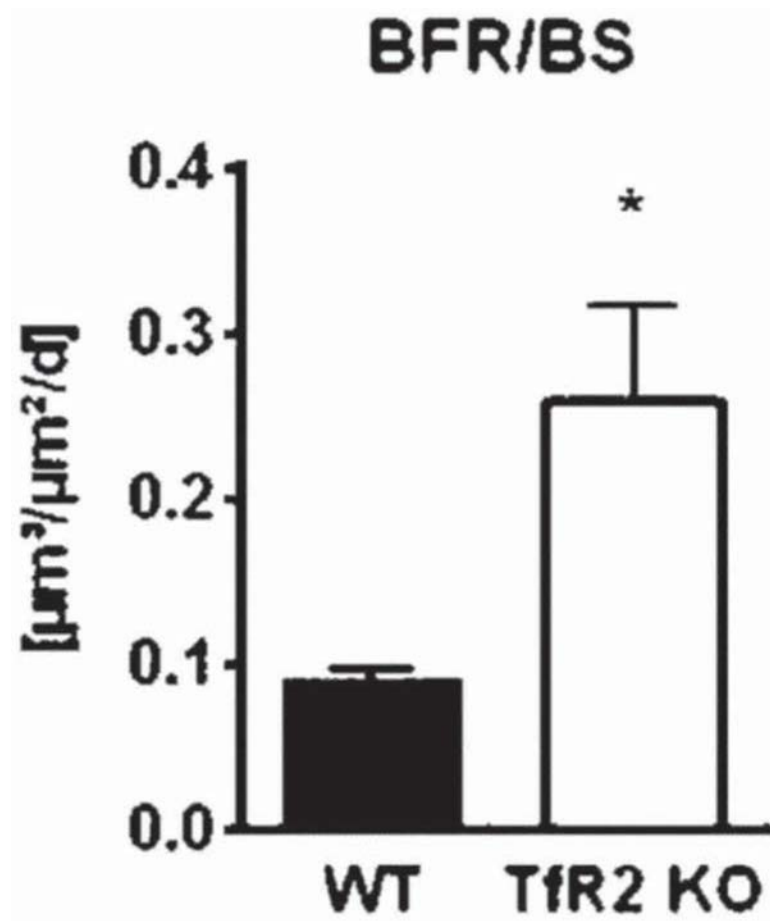


图8

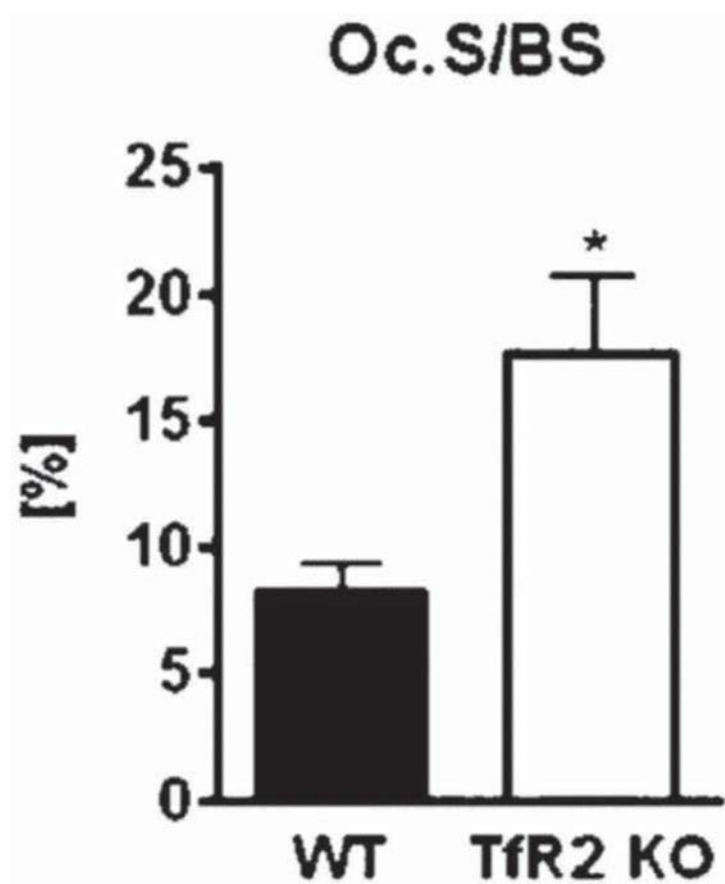


图9

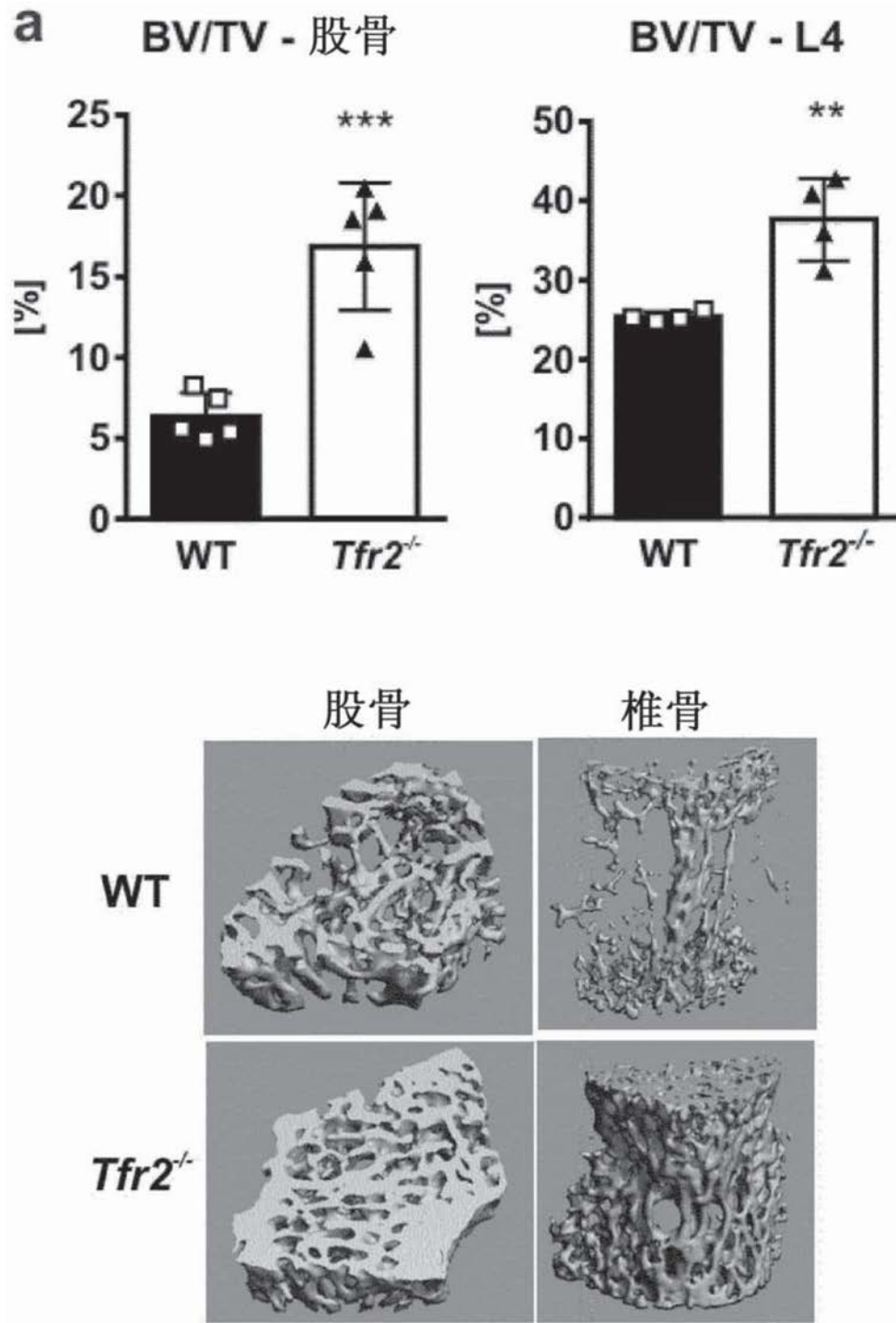


图10a

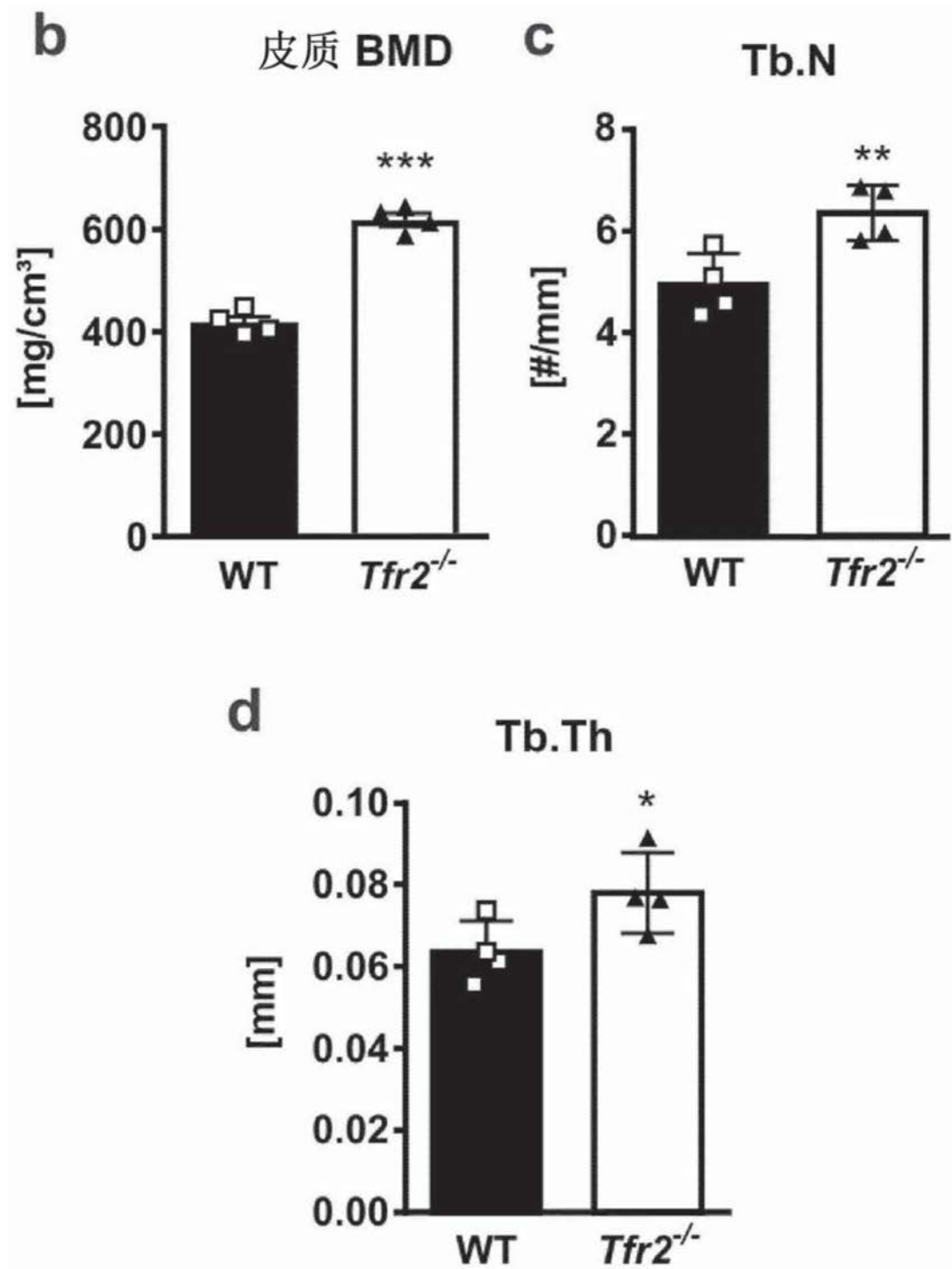


图10b-d

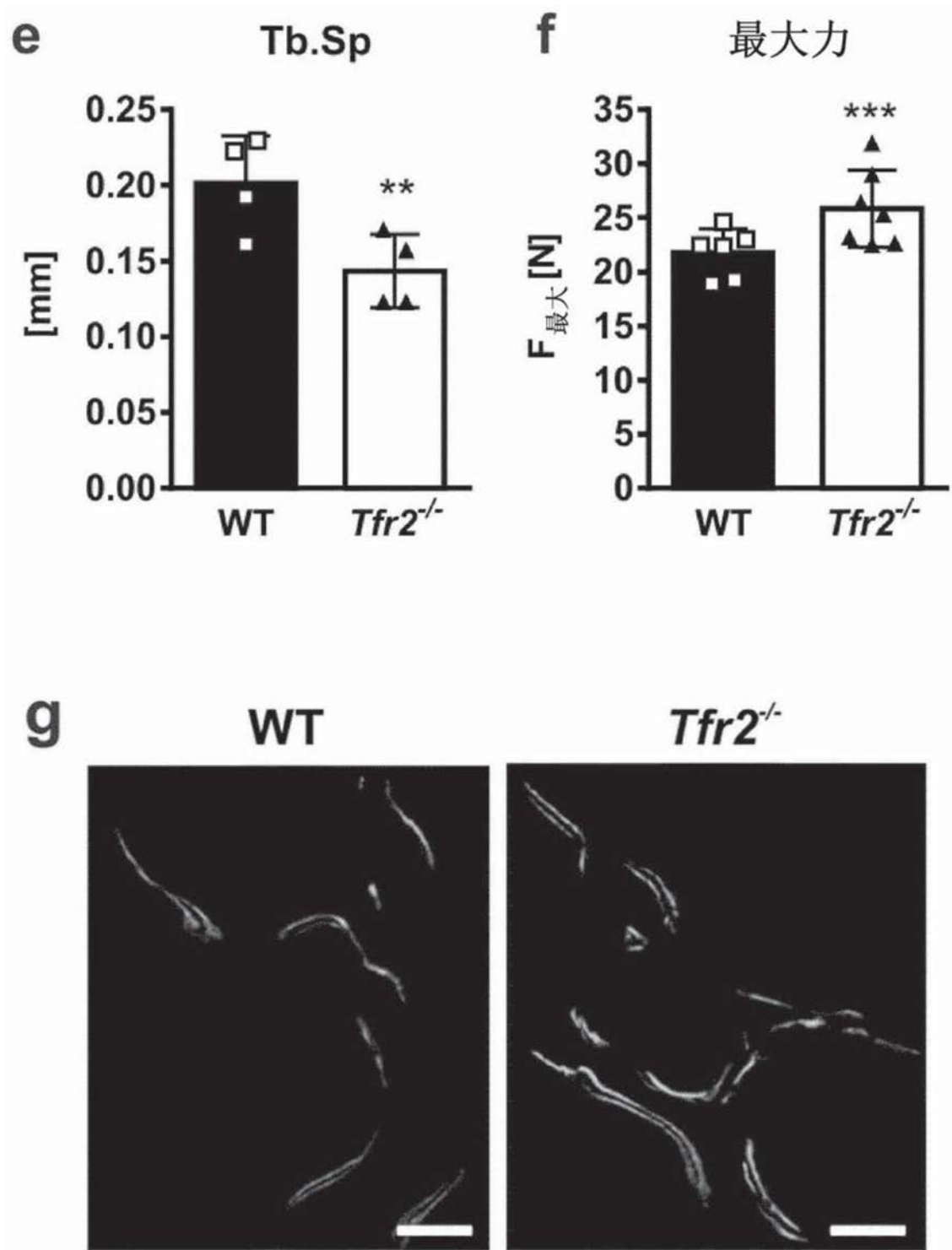


图10e-g

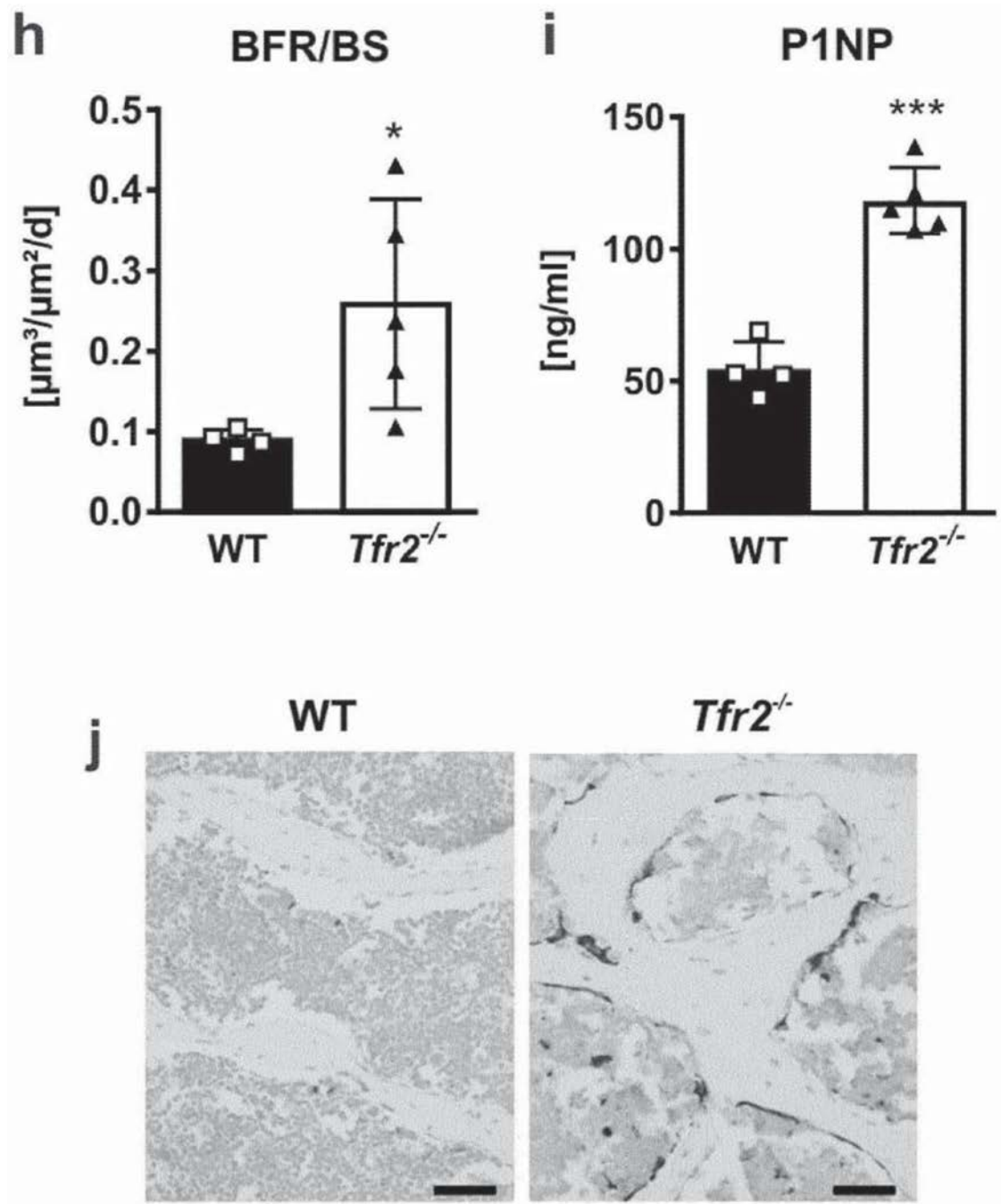


图10h-j

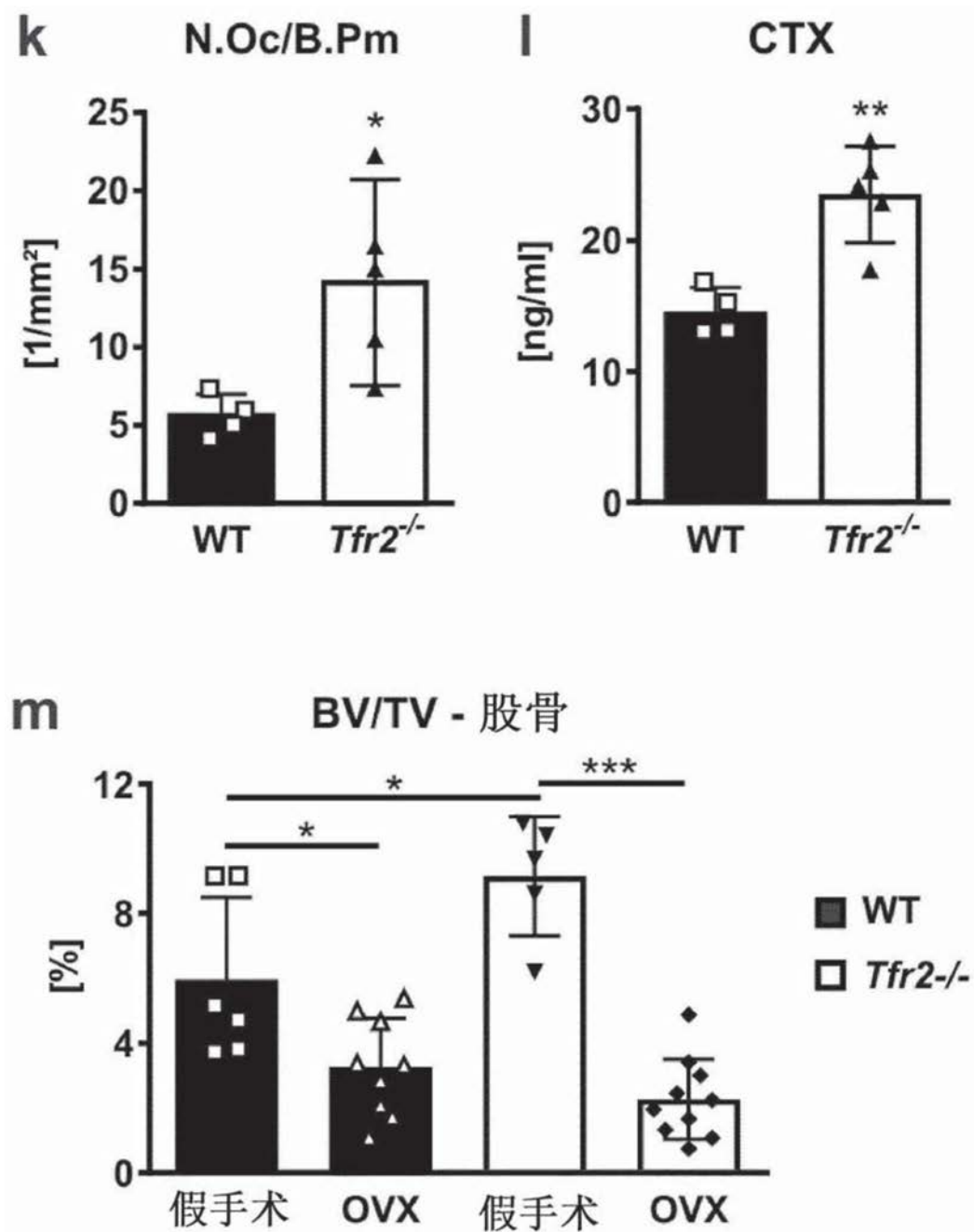


图10k-m

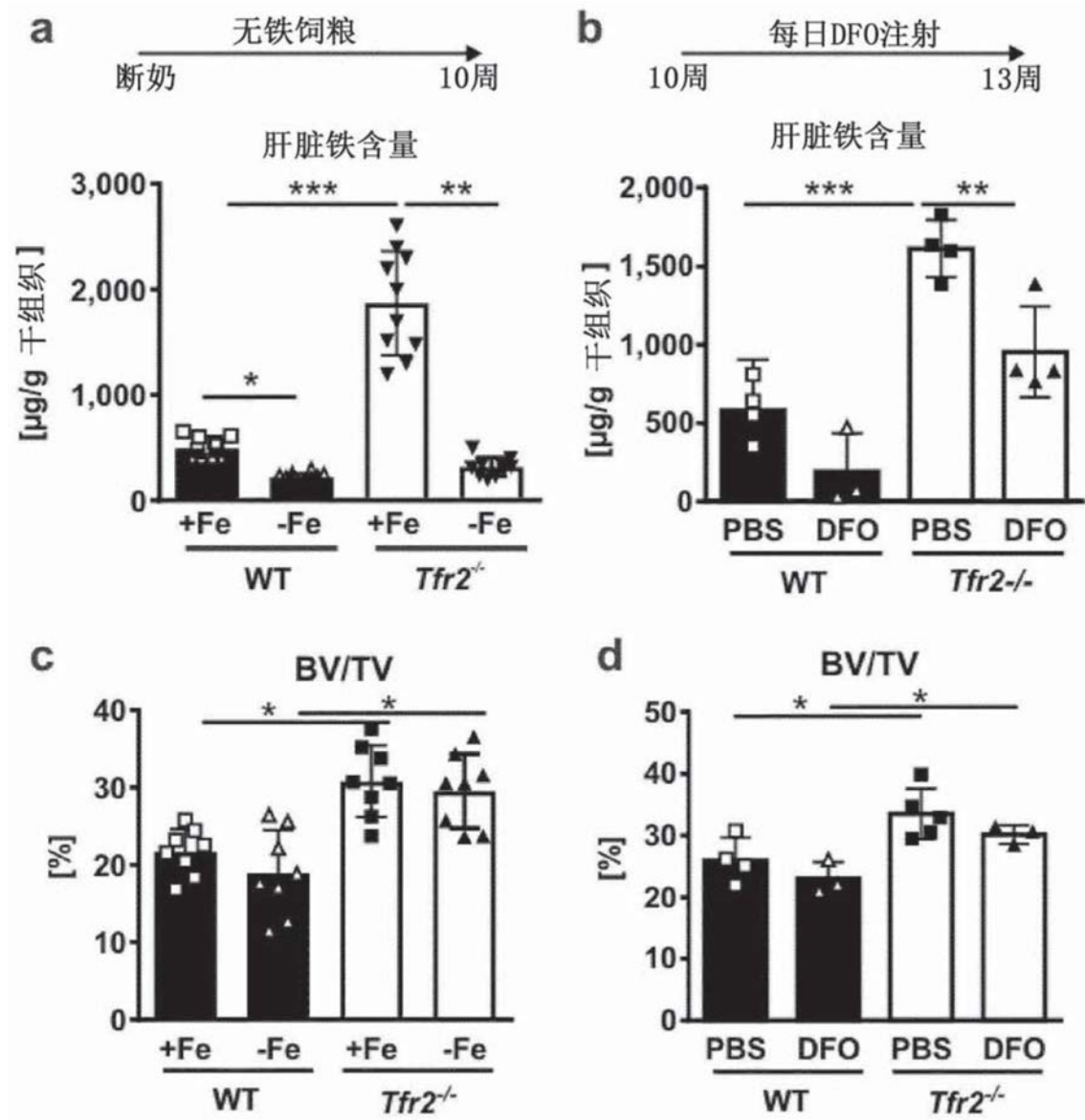


图11a-d

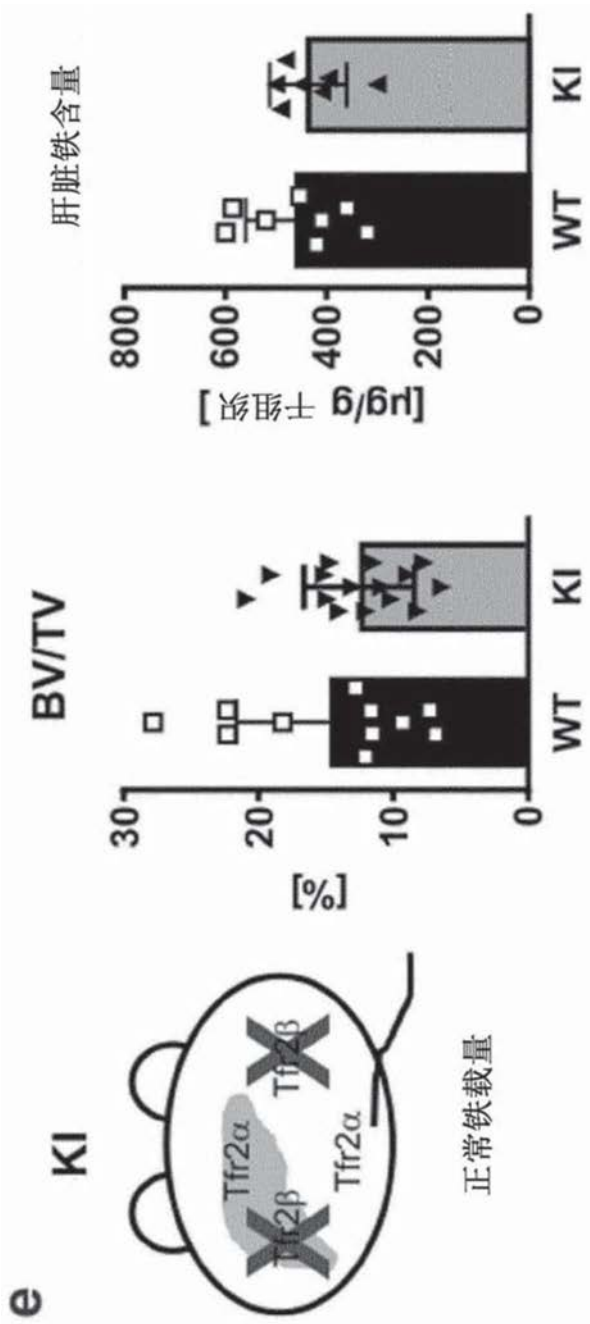


图11e

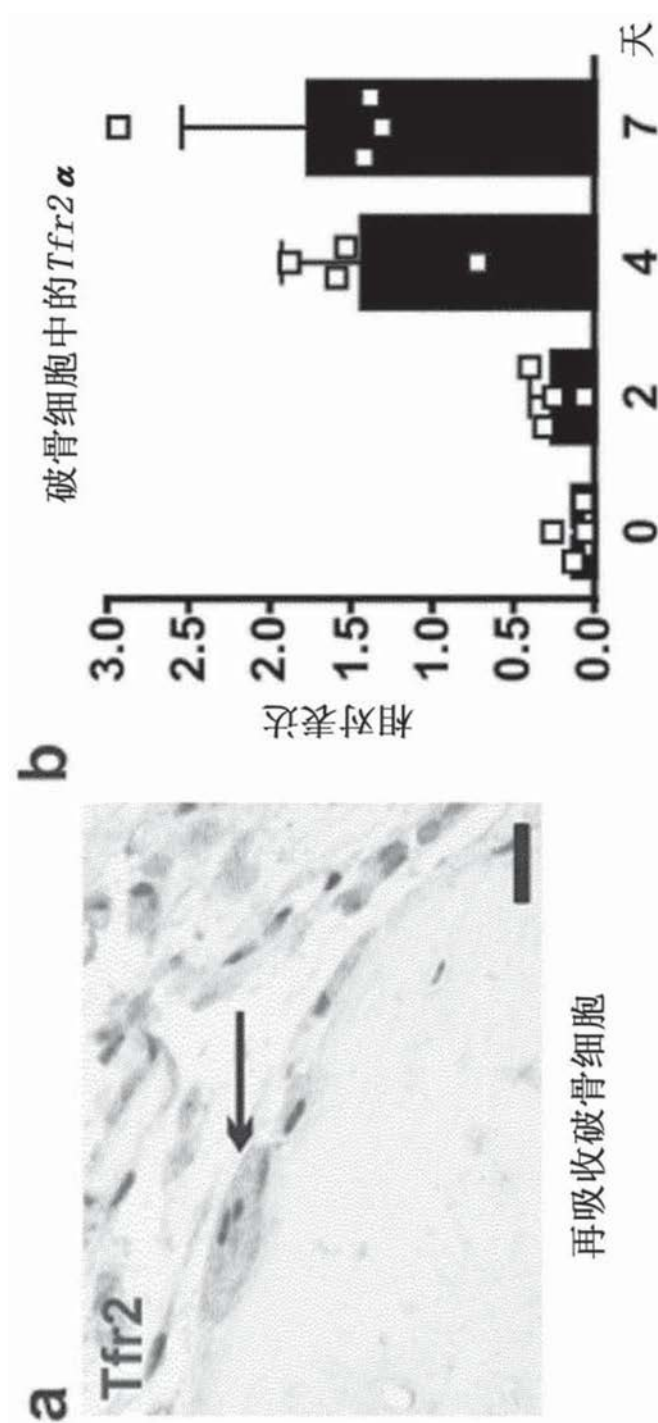


图12a-b

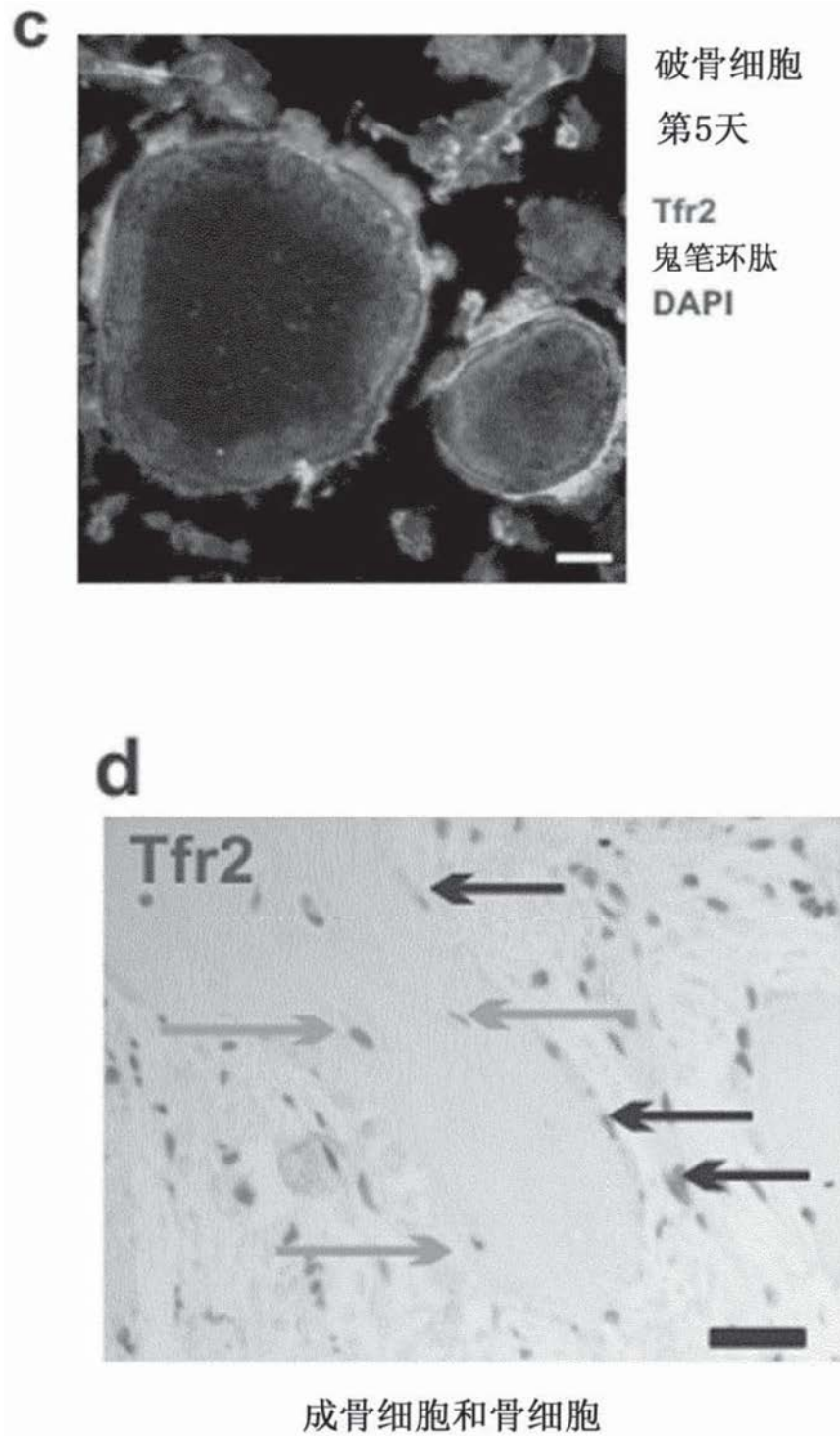


图12c-d

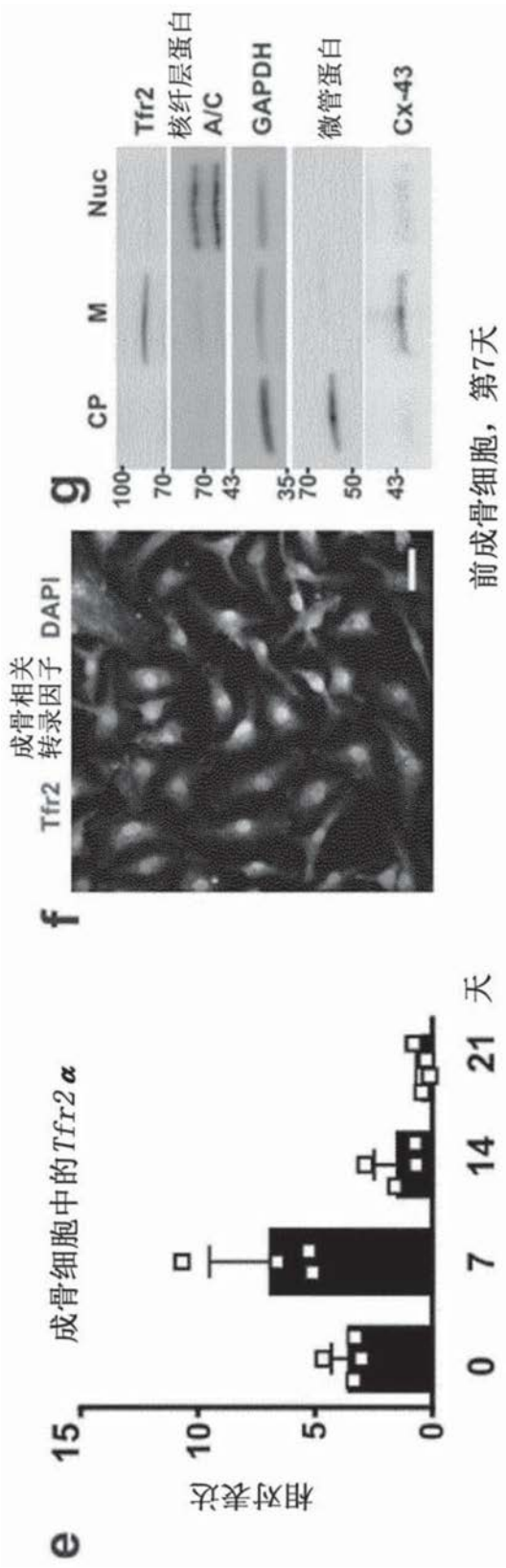


图12e-g

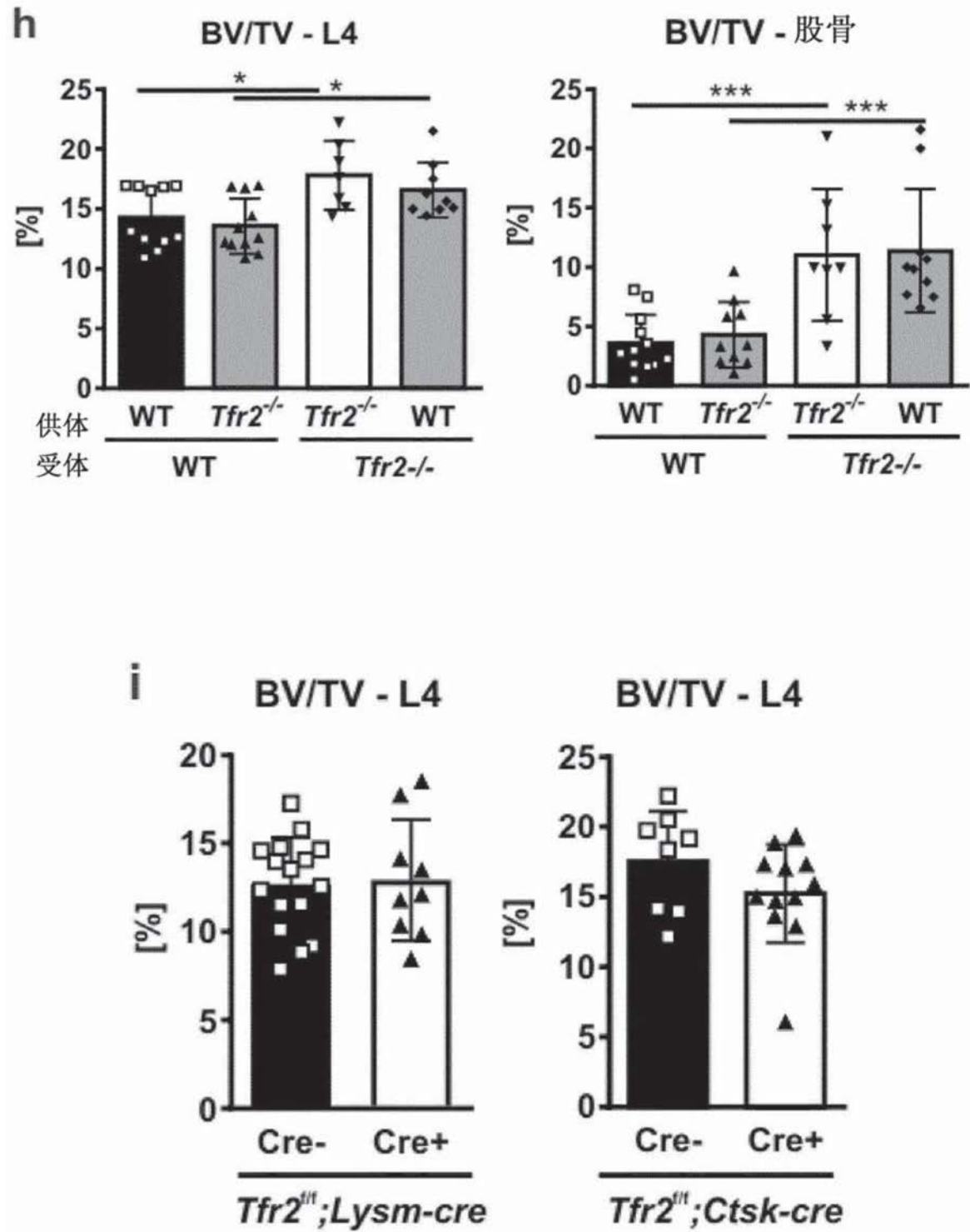


图12h-i

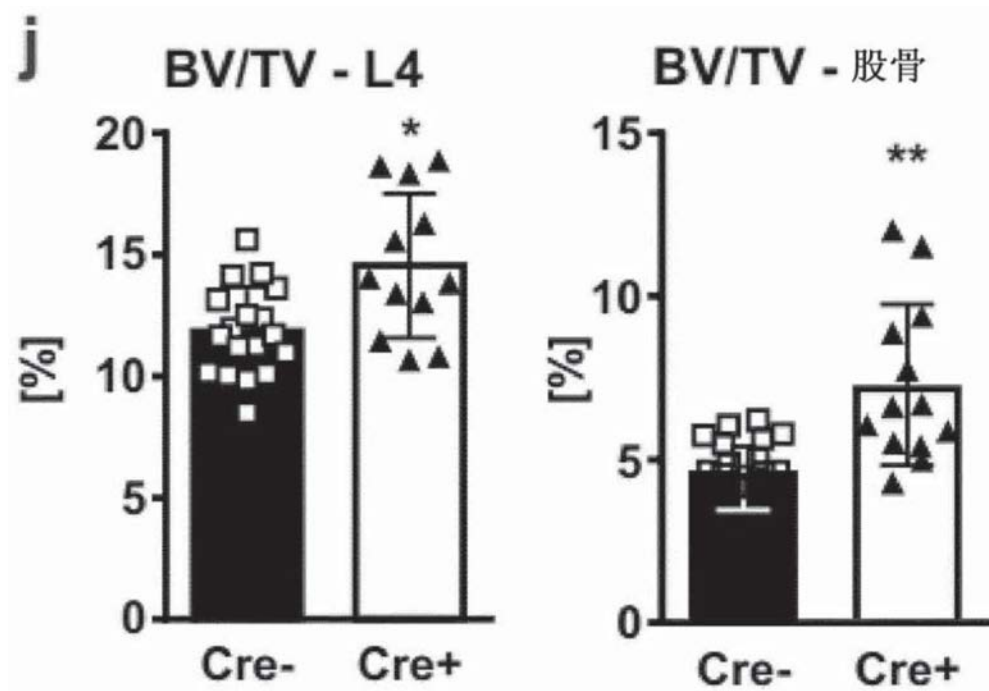


图12j

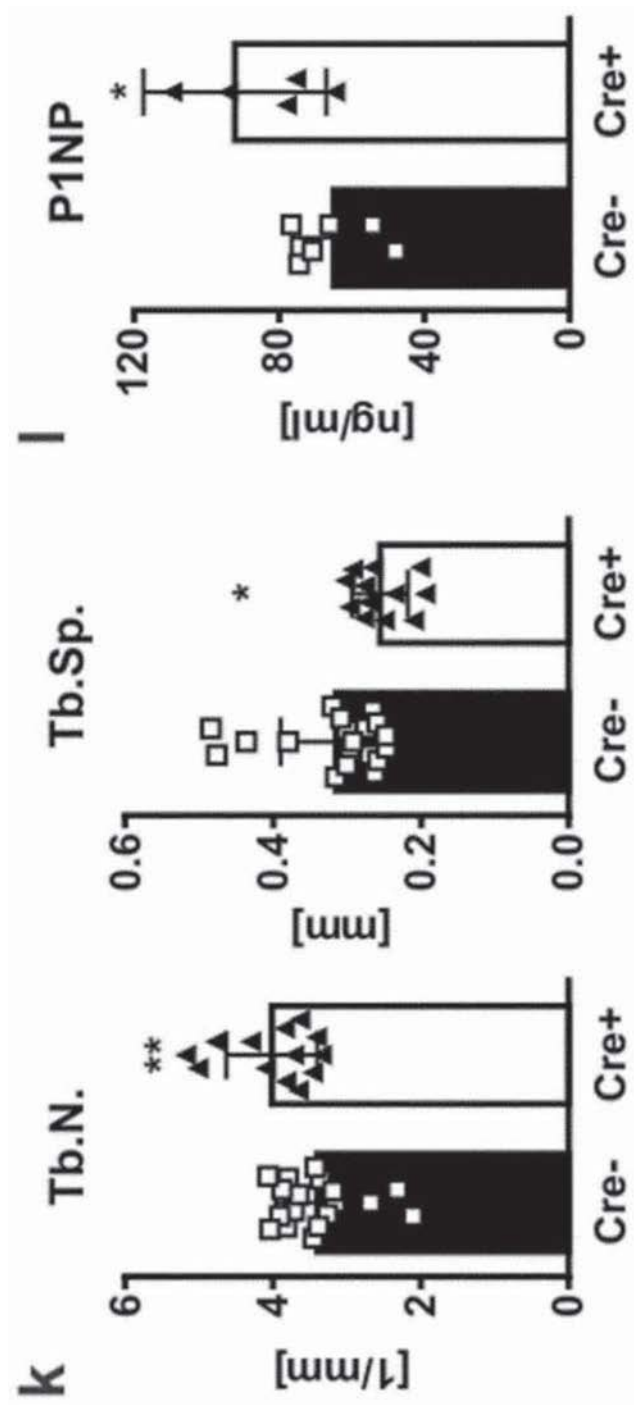


图12k-1

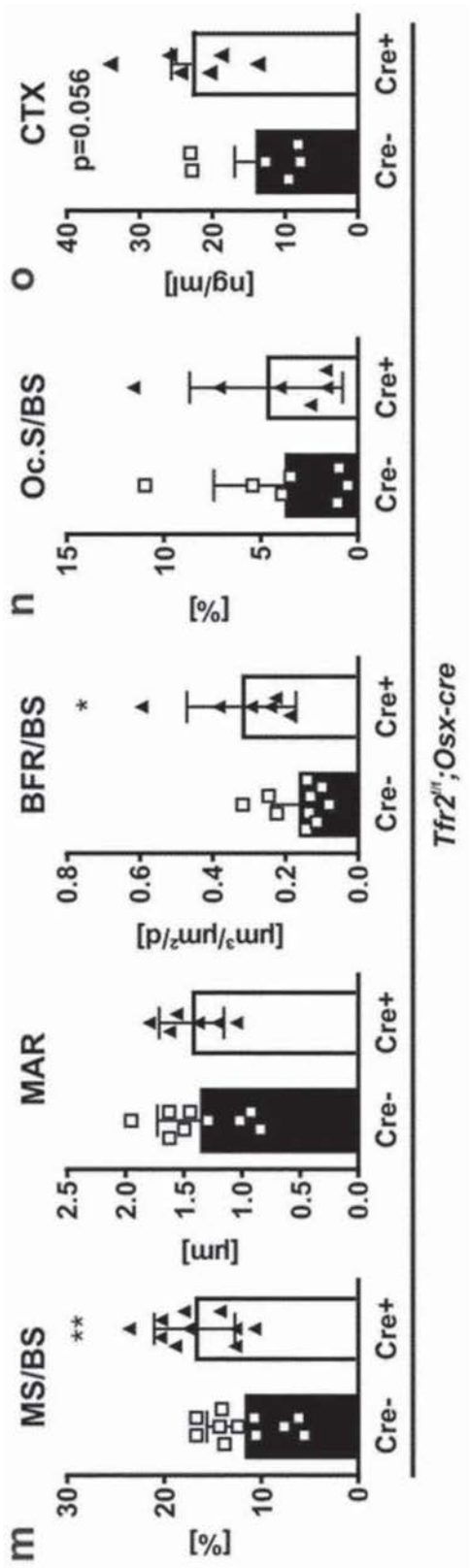


图12m-o

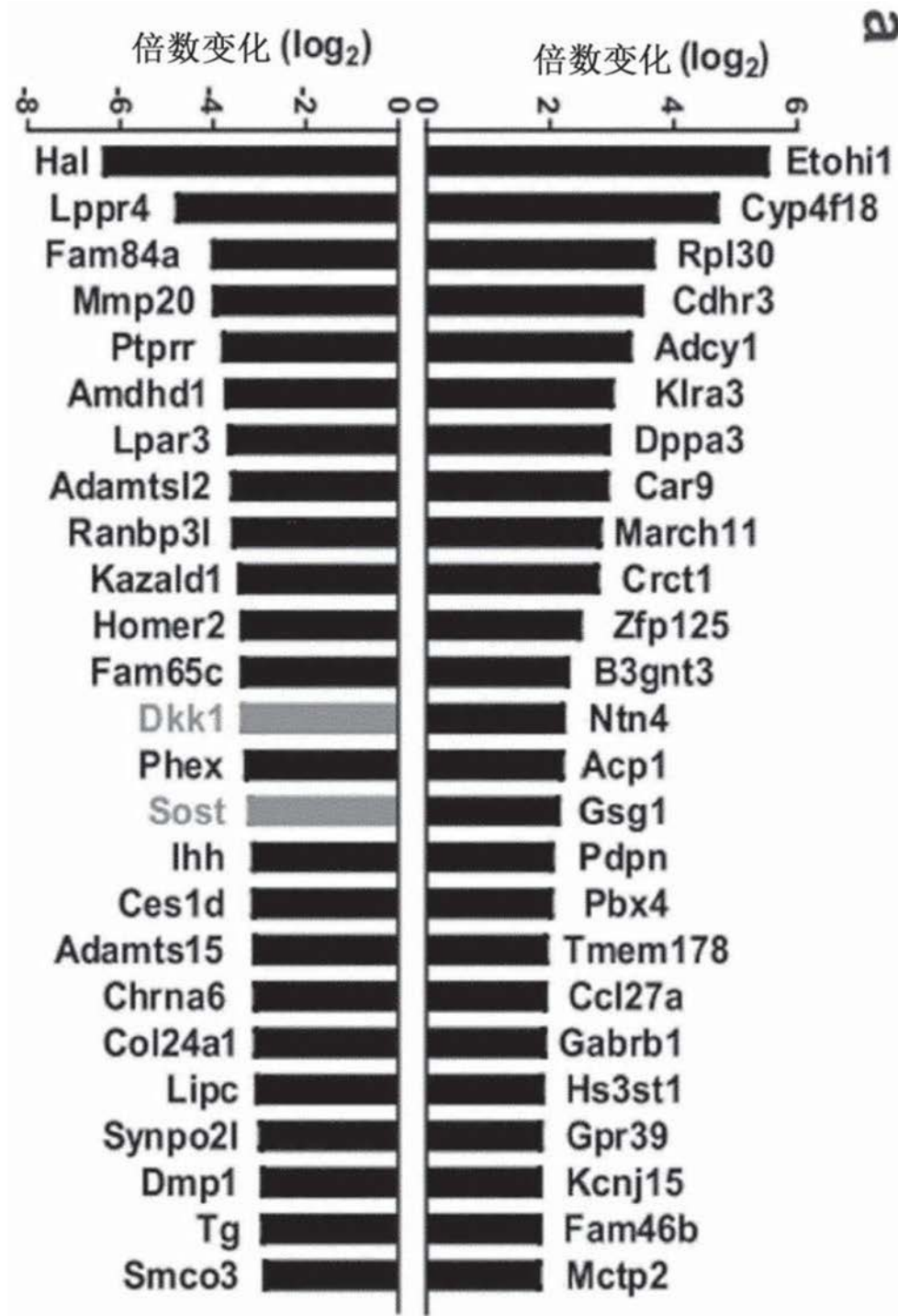


图13a

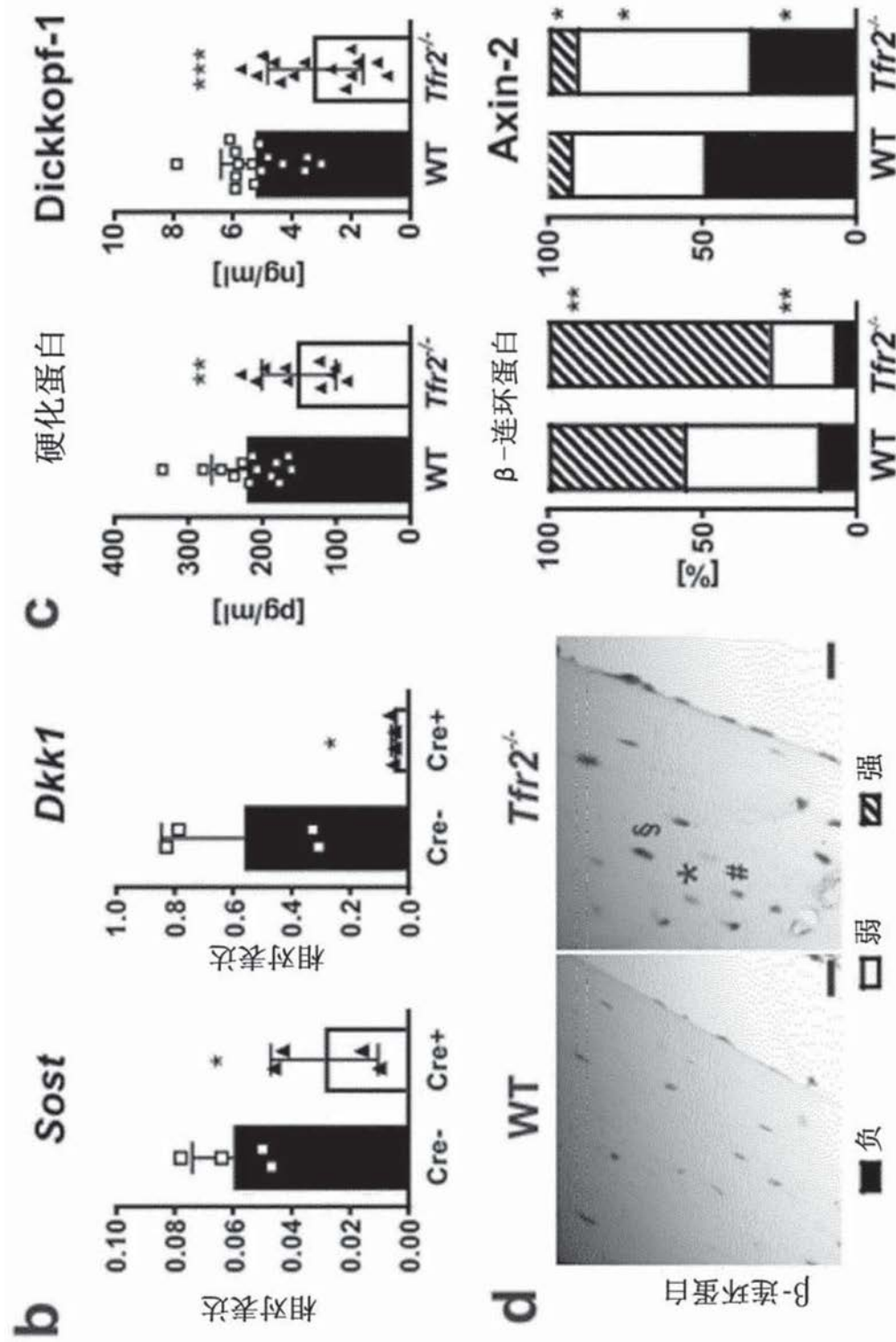


图13b-d

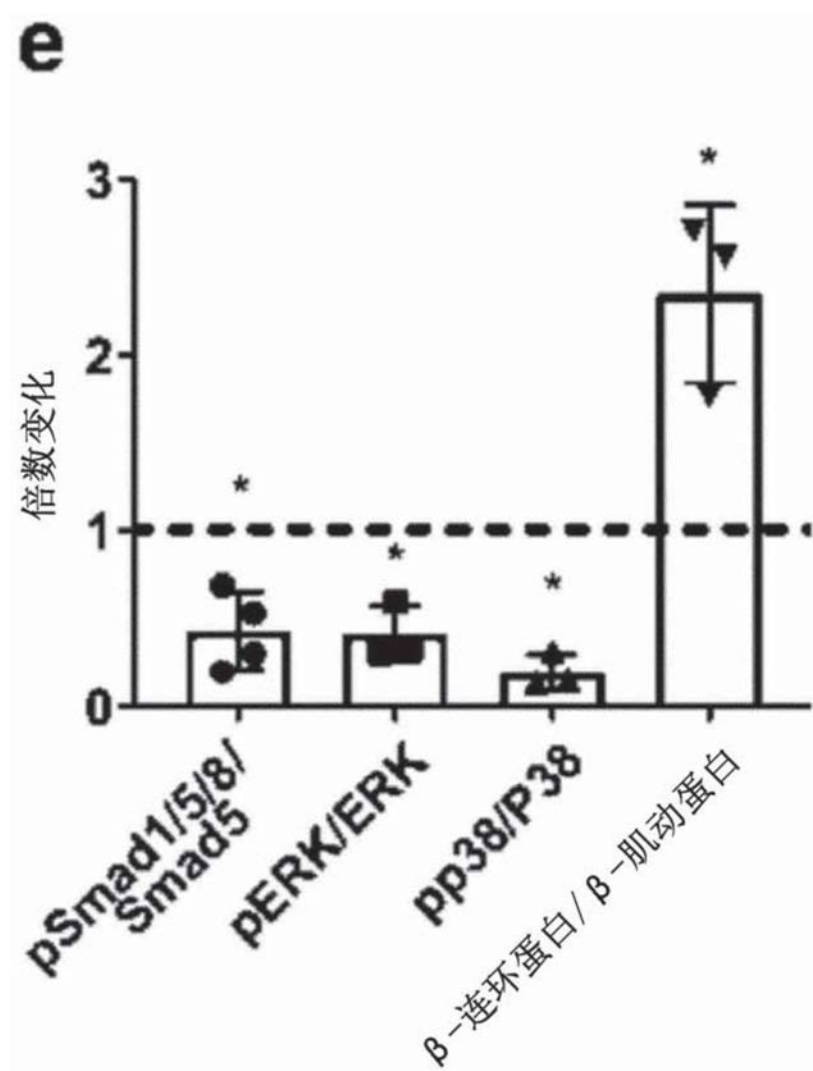


图13e

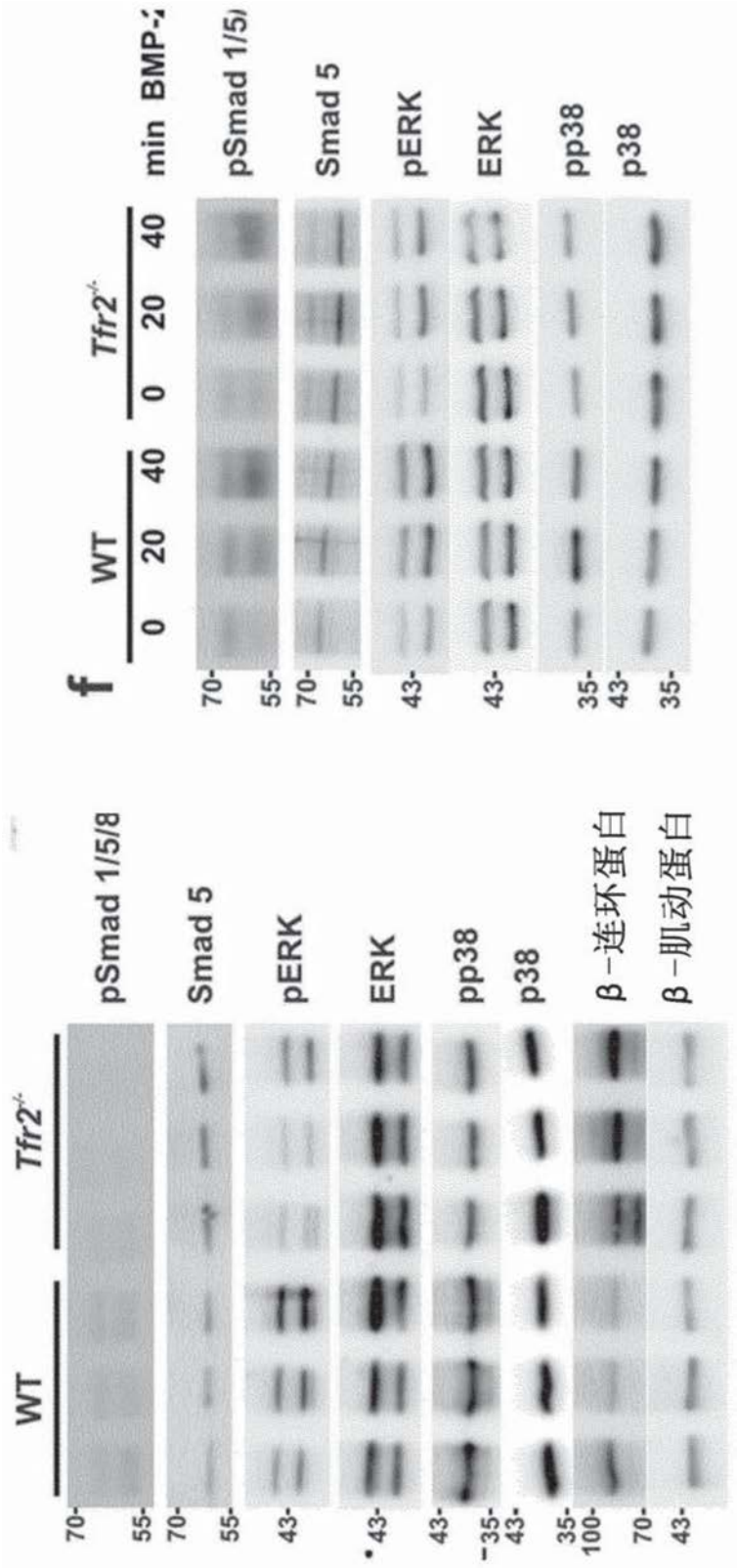


图13f

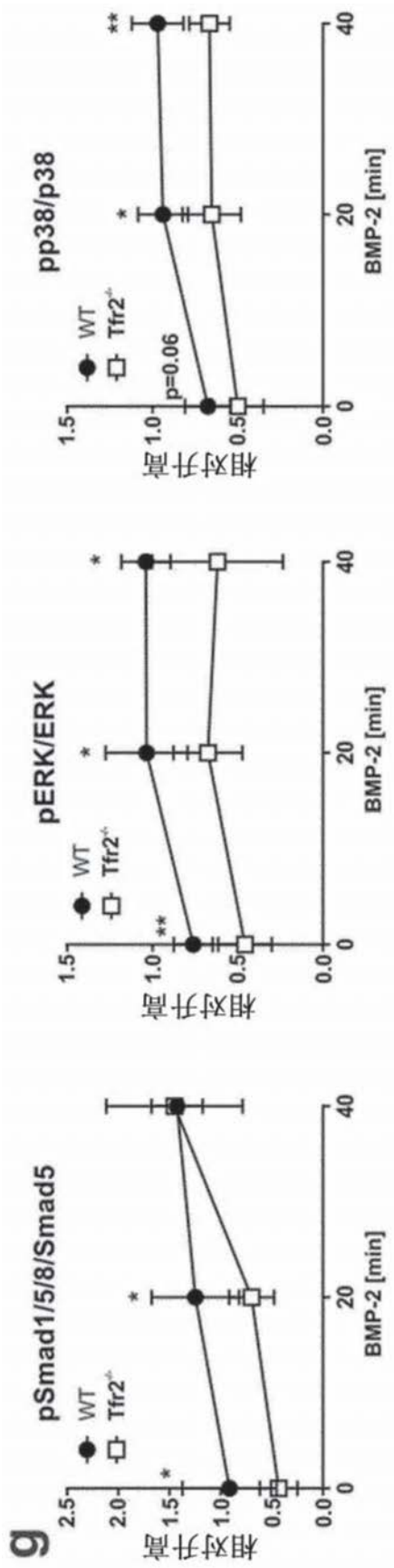


图13g

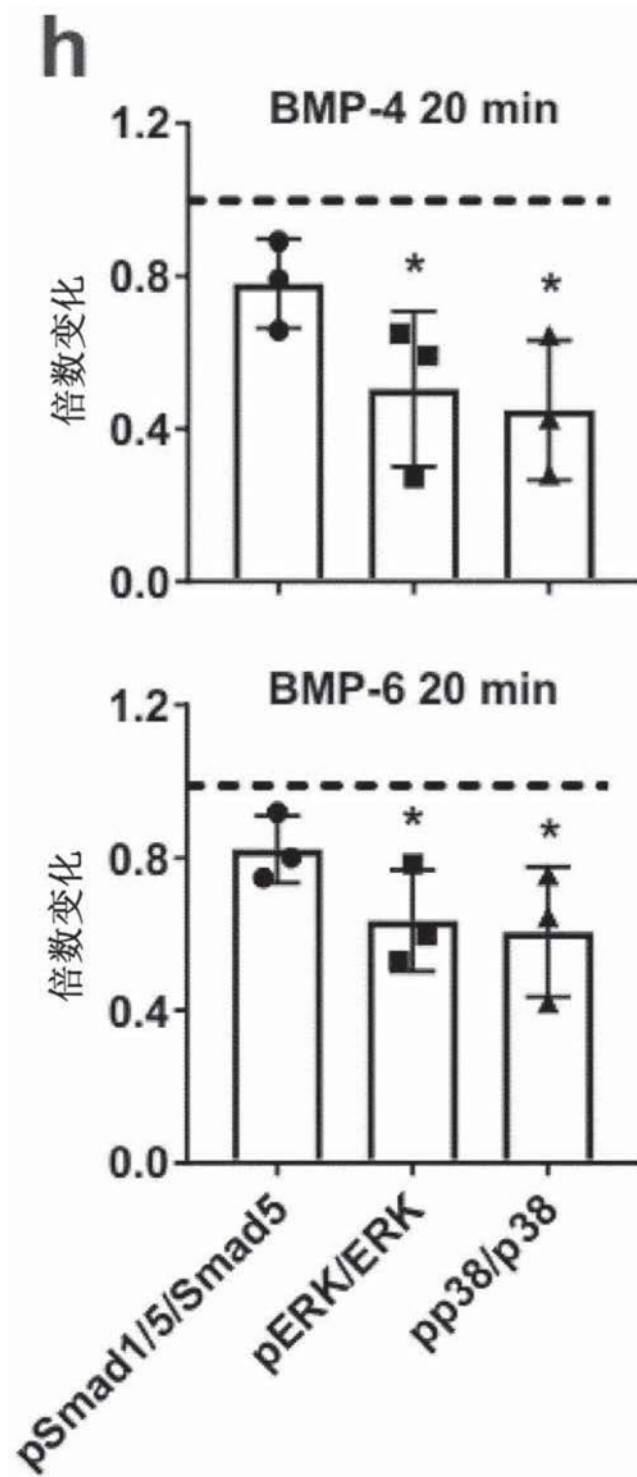


图13h

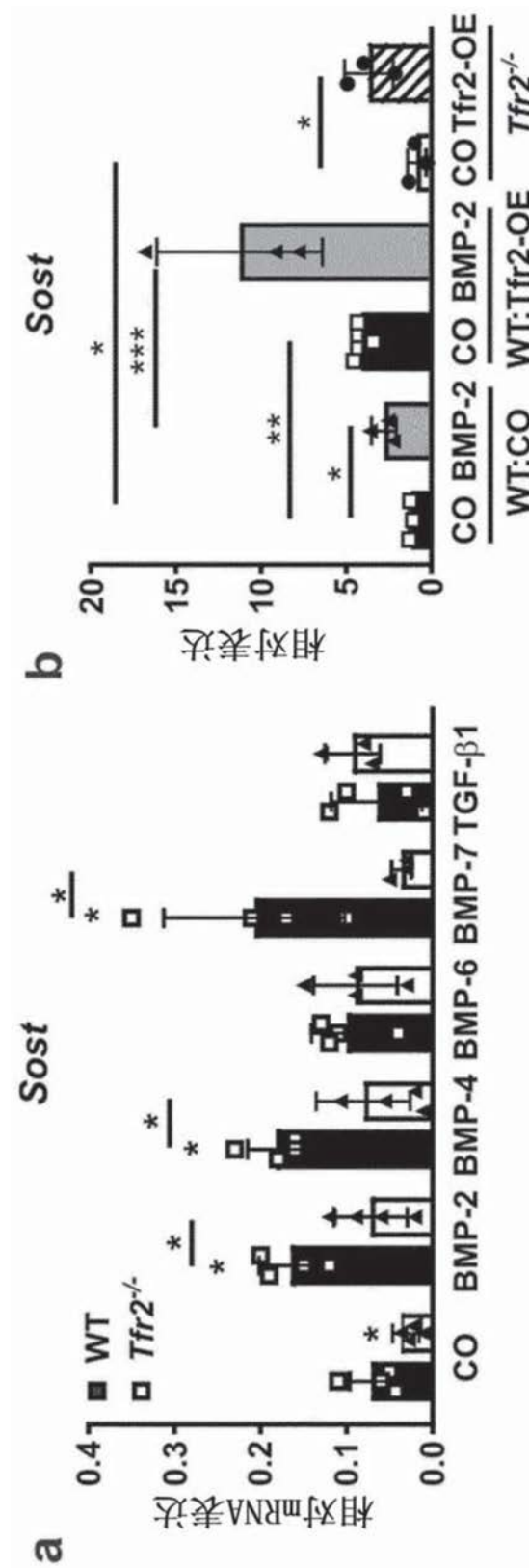


图14a-b

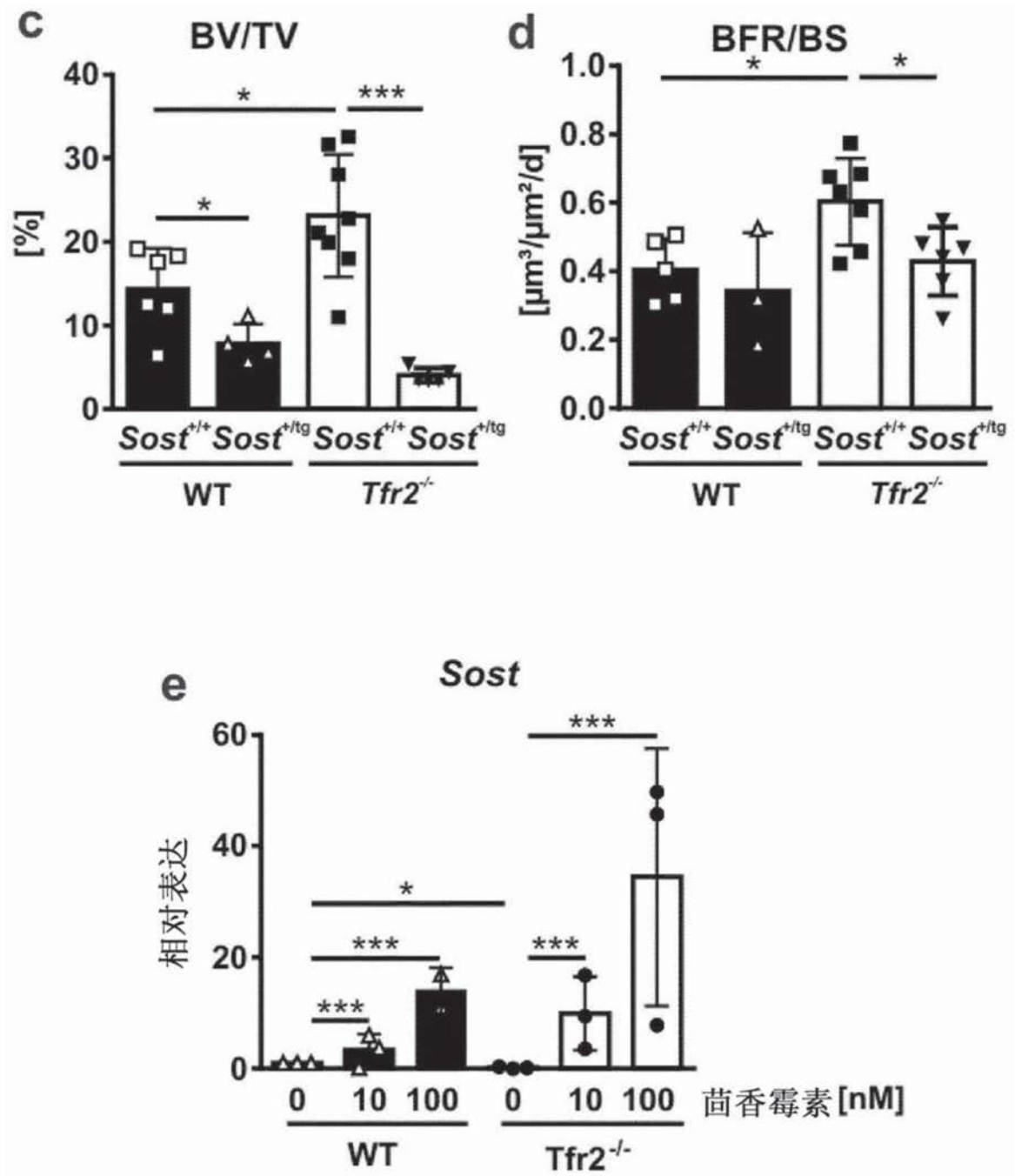


图14c-e

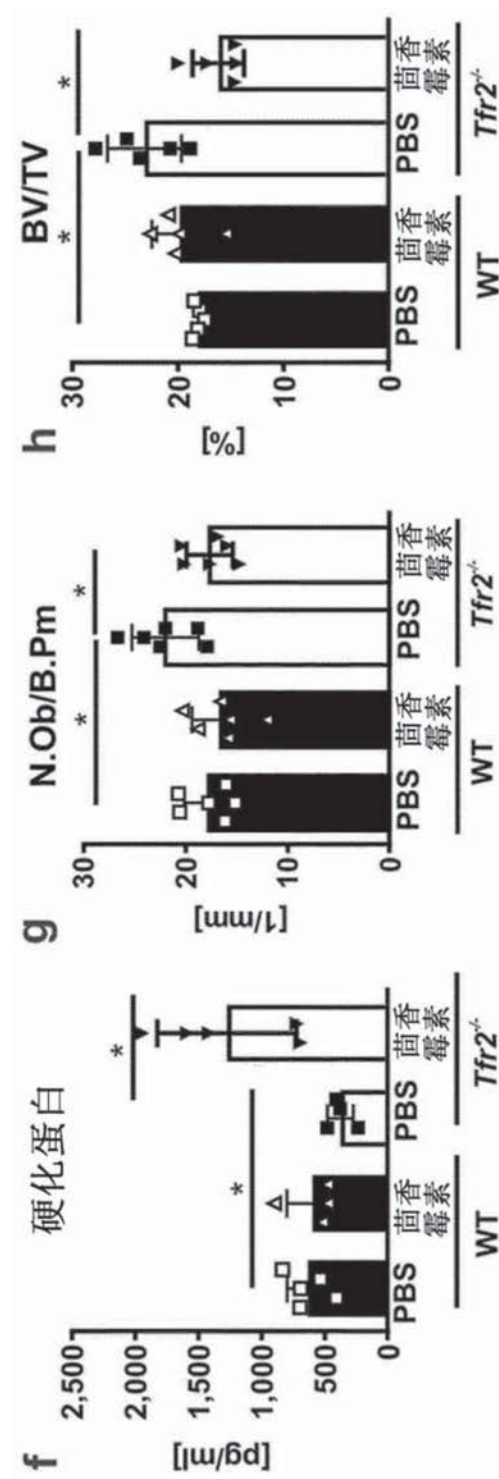


图14f-h

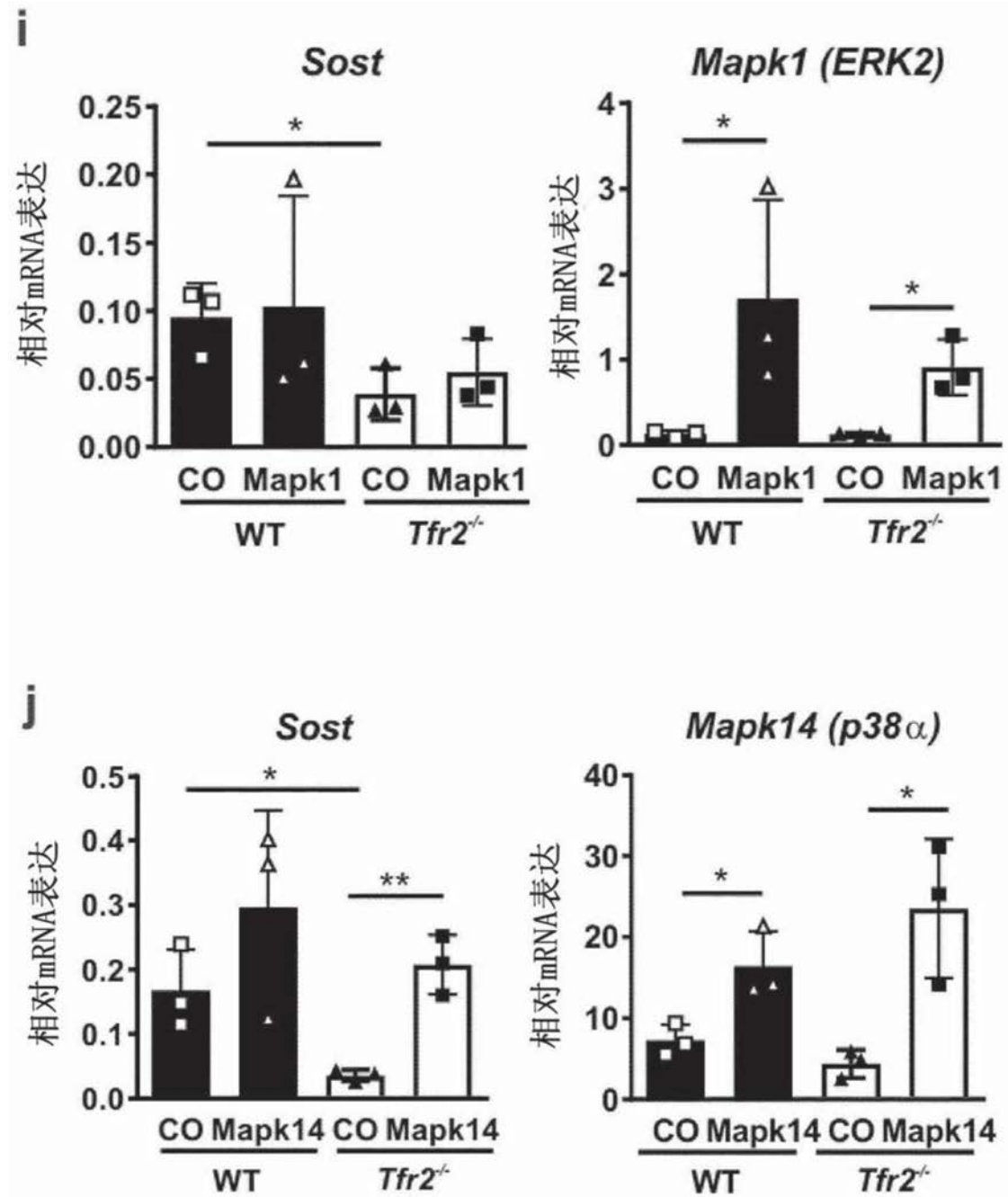


图14i-j

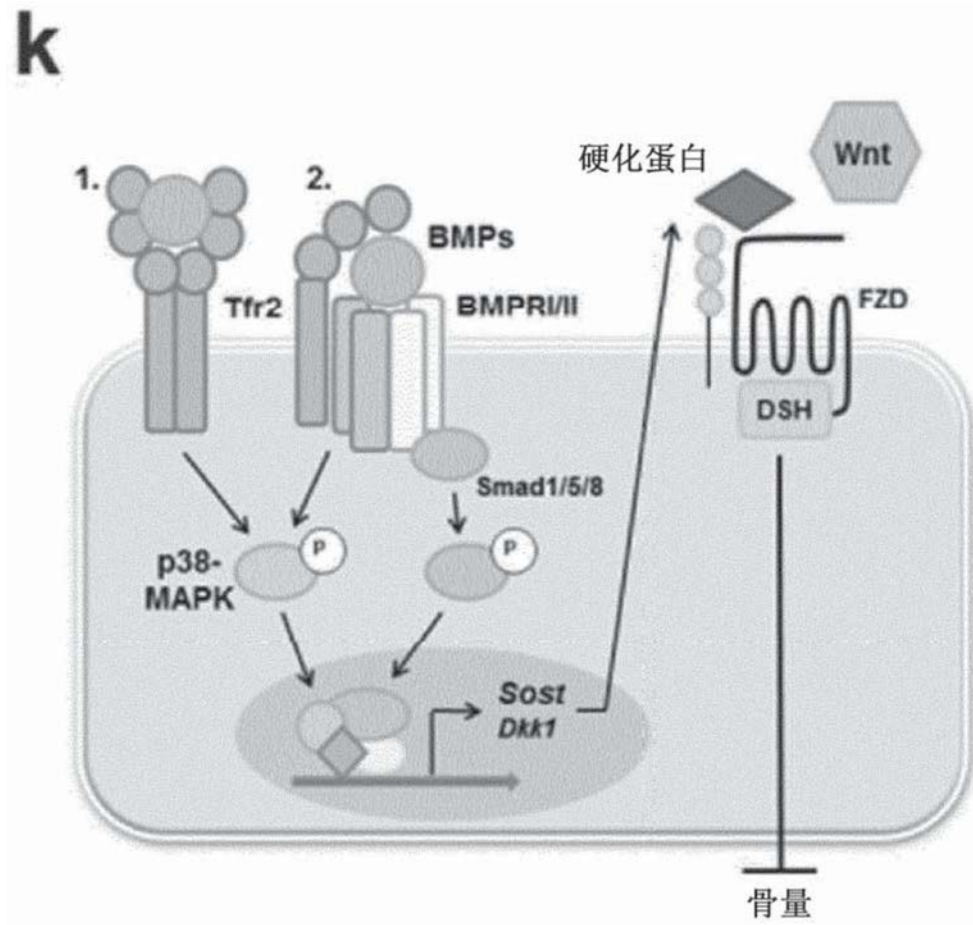


图14k

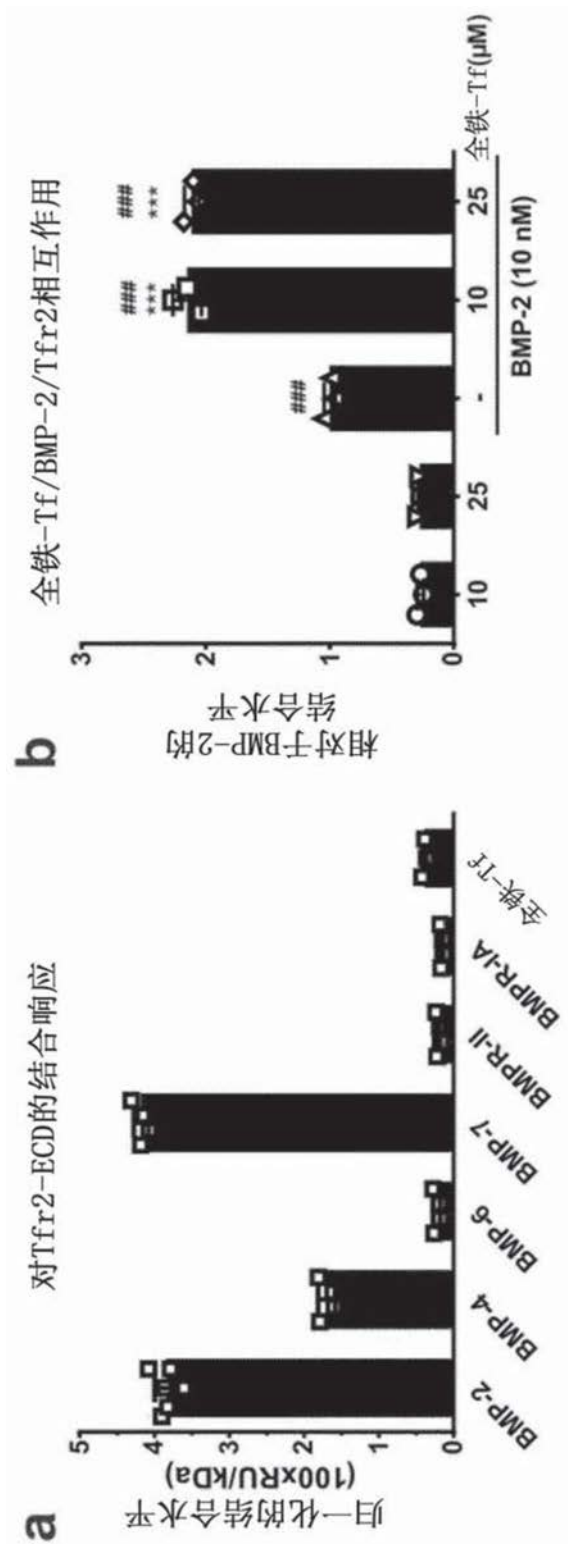


图15a-b

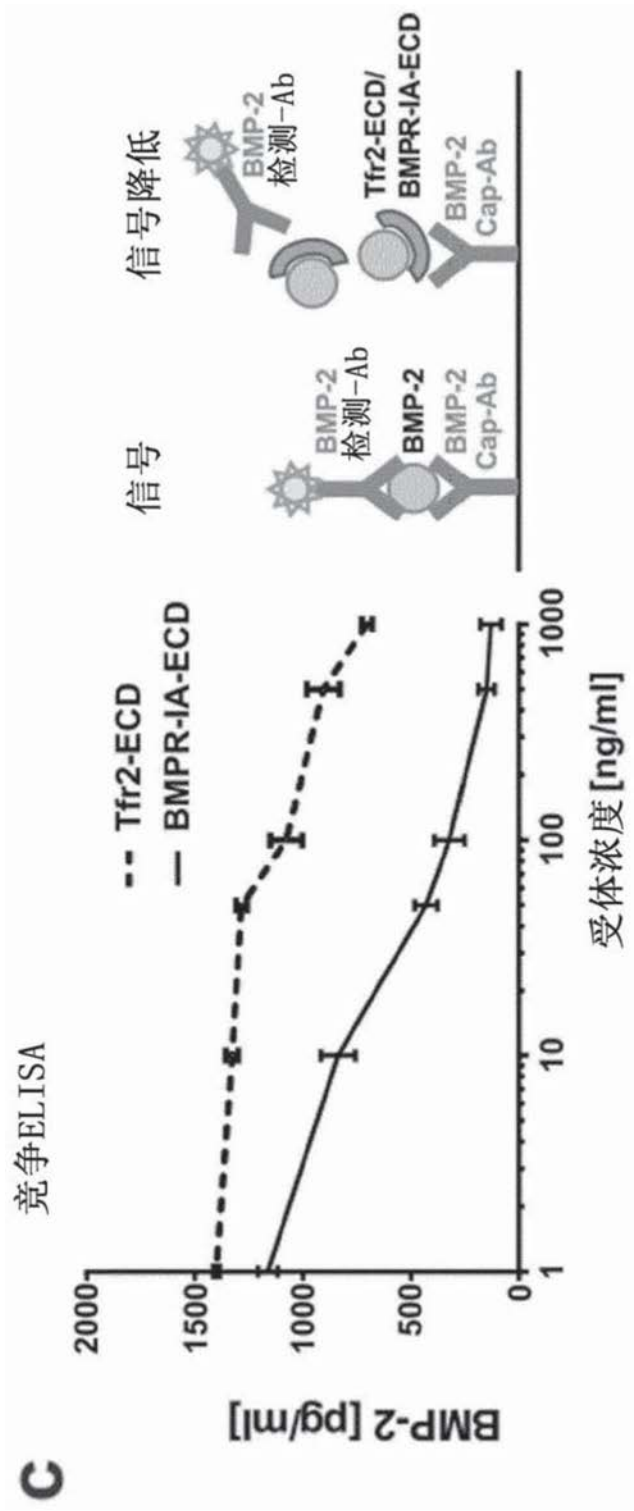


图15c

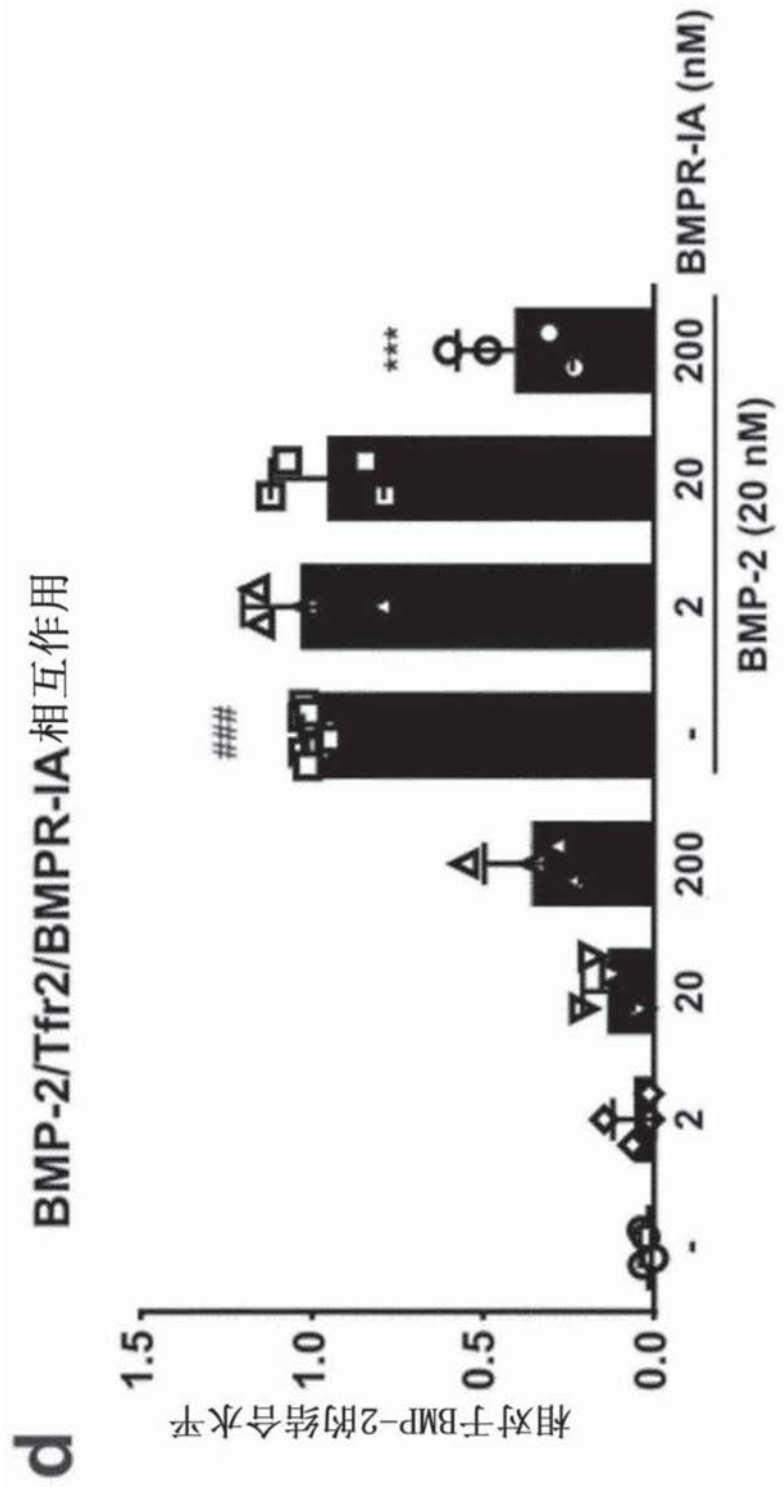


图15d

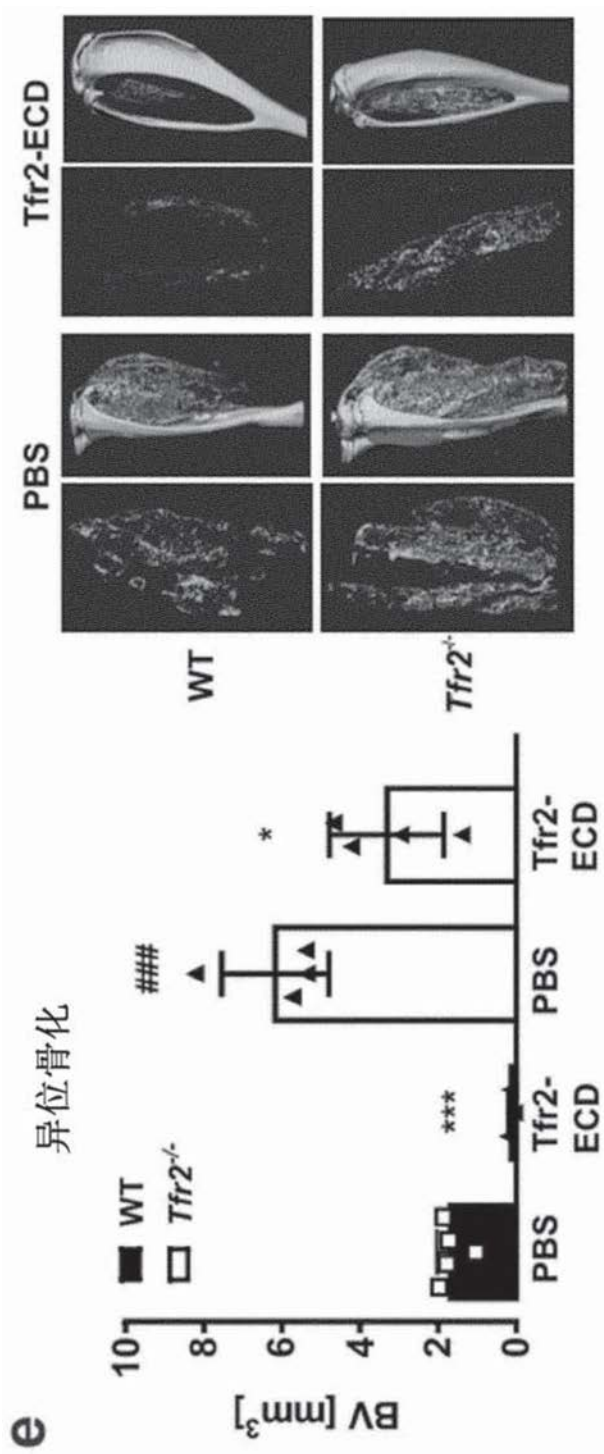


图15e

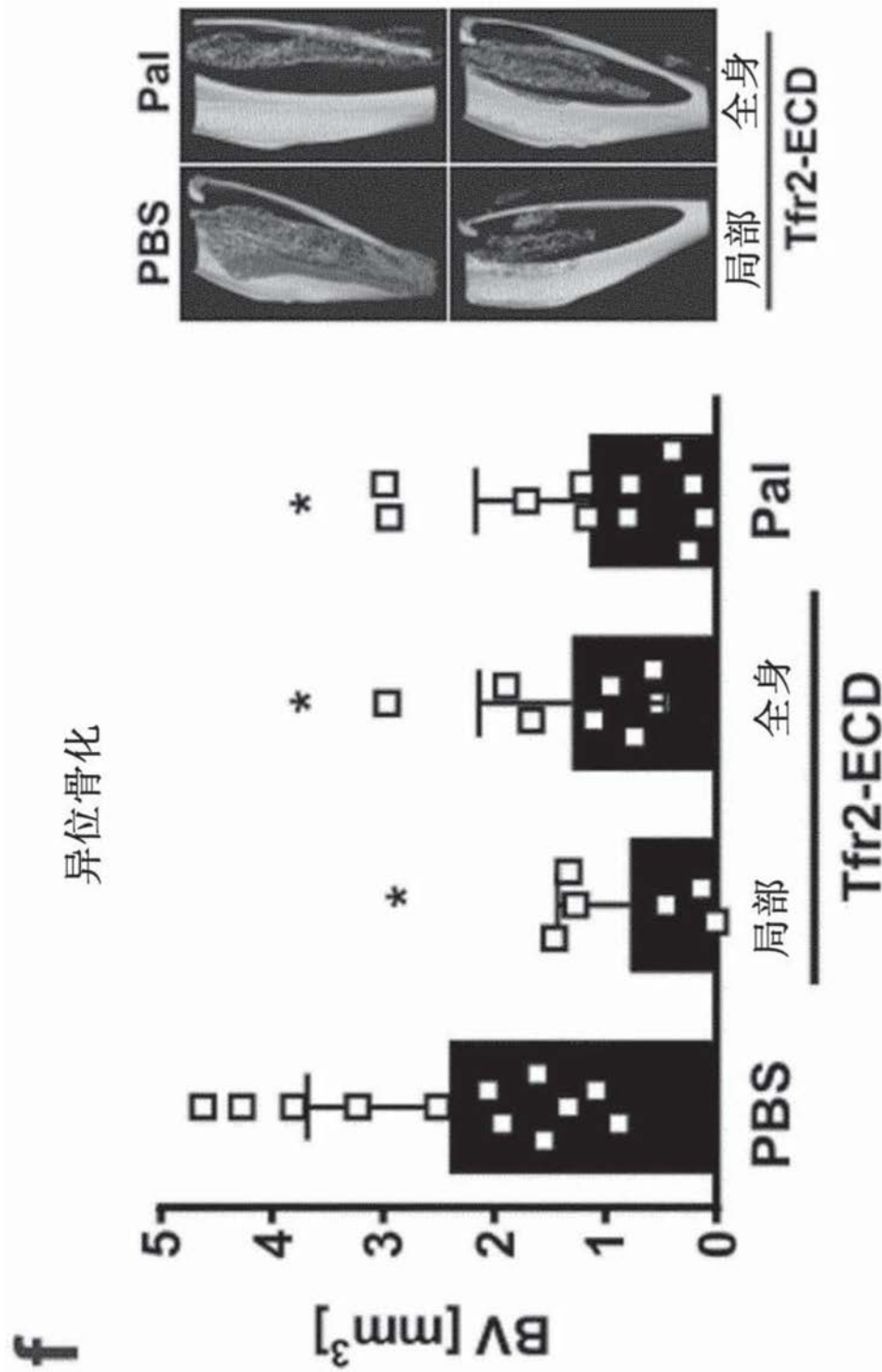


图15f

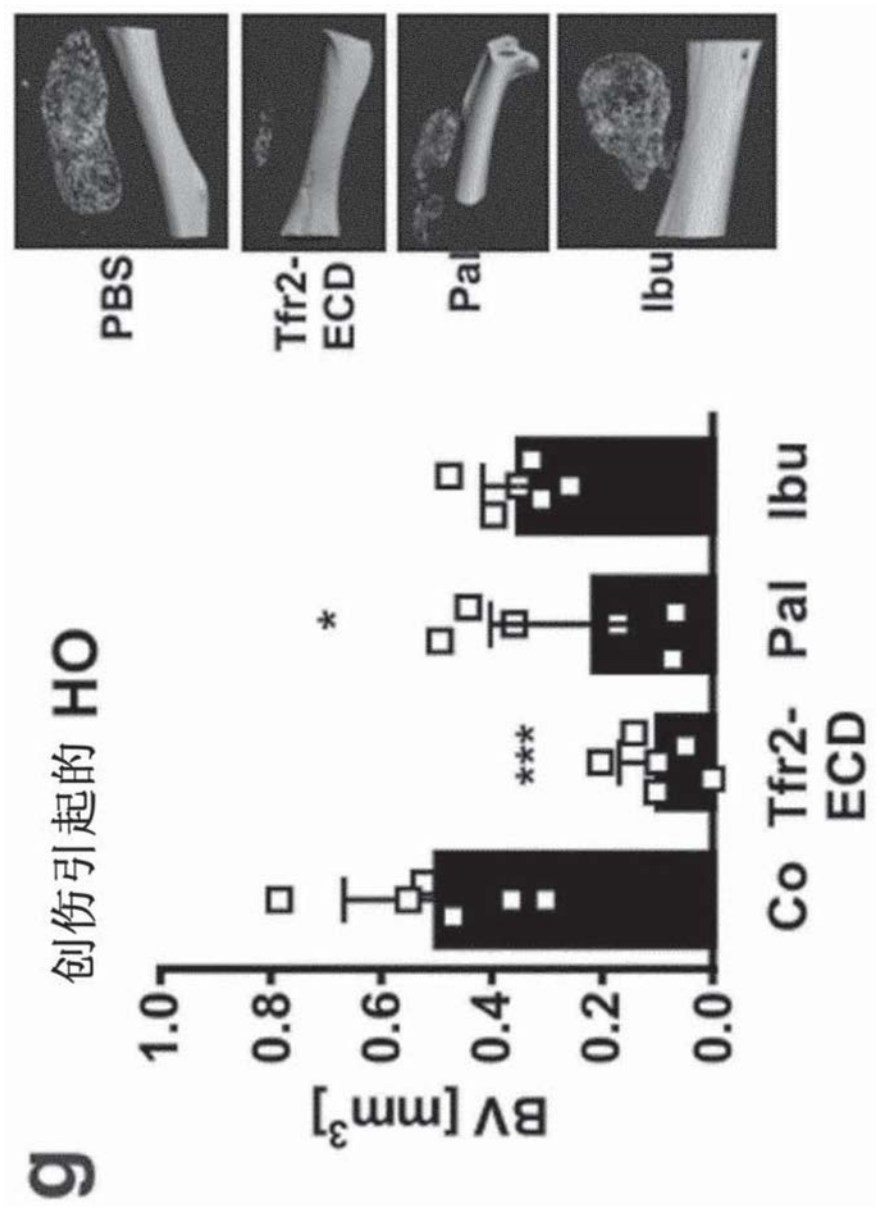


图15g

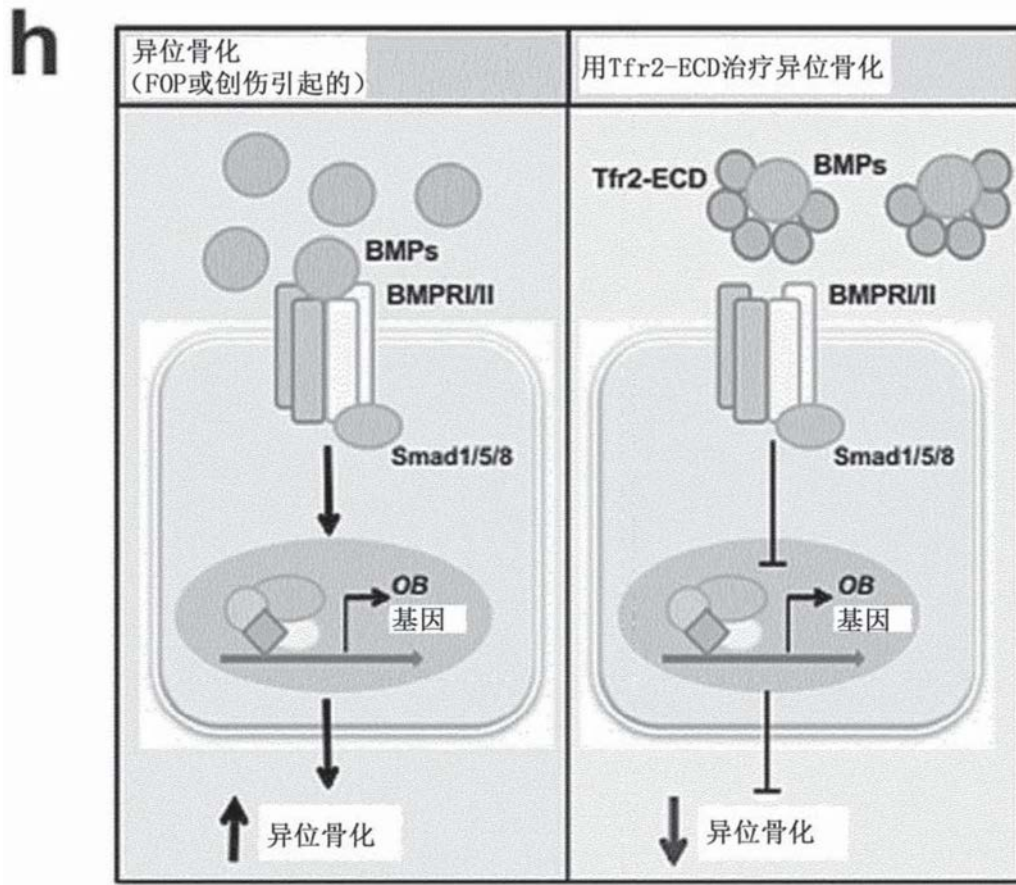


图15h

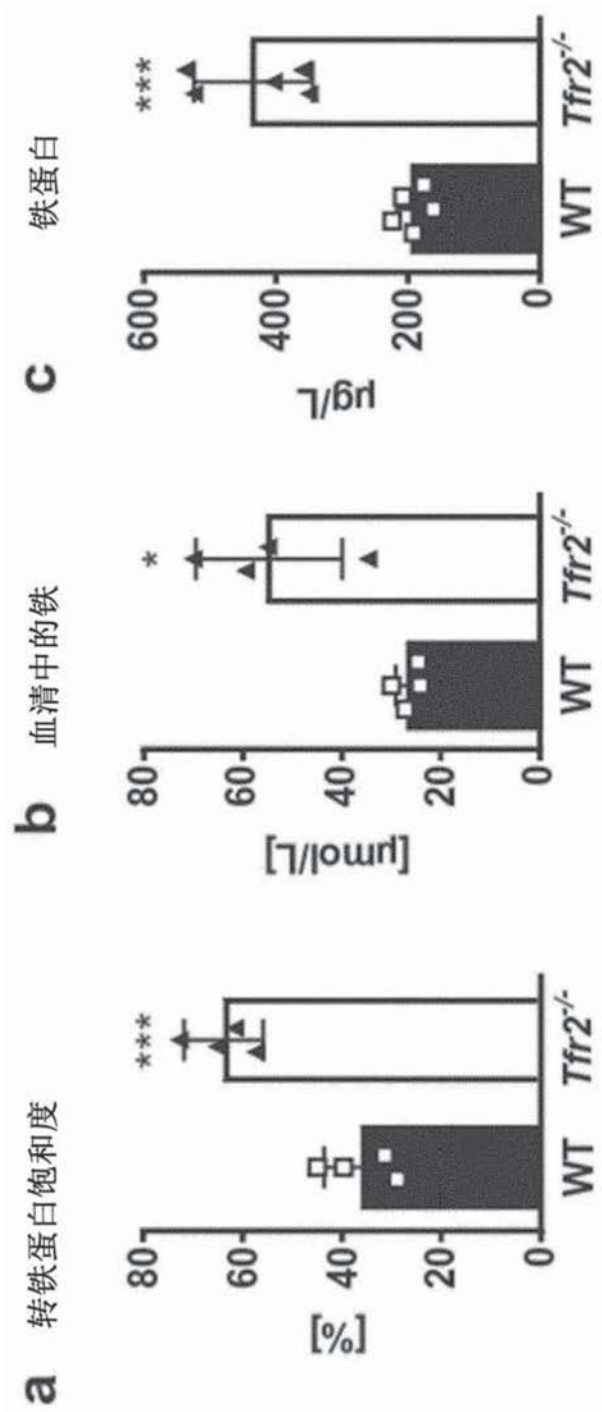


图16a-c

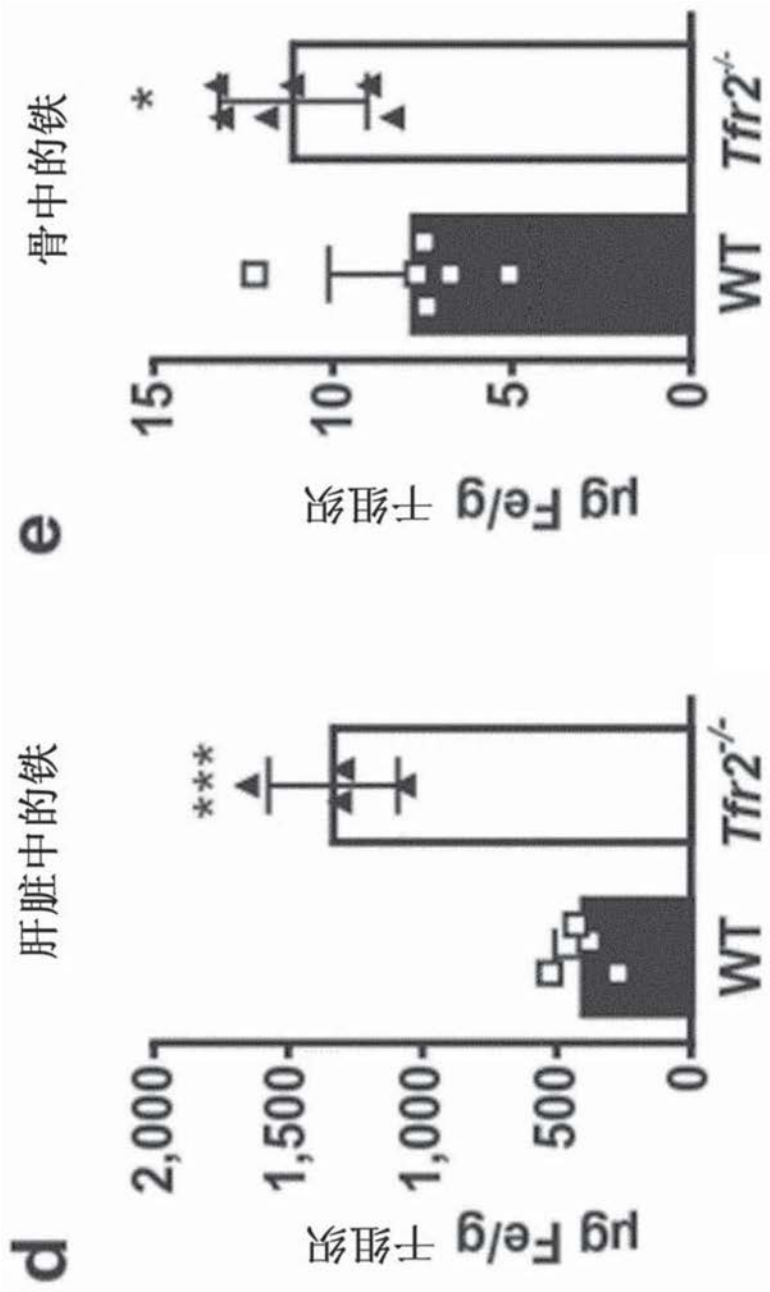


图16d-e

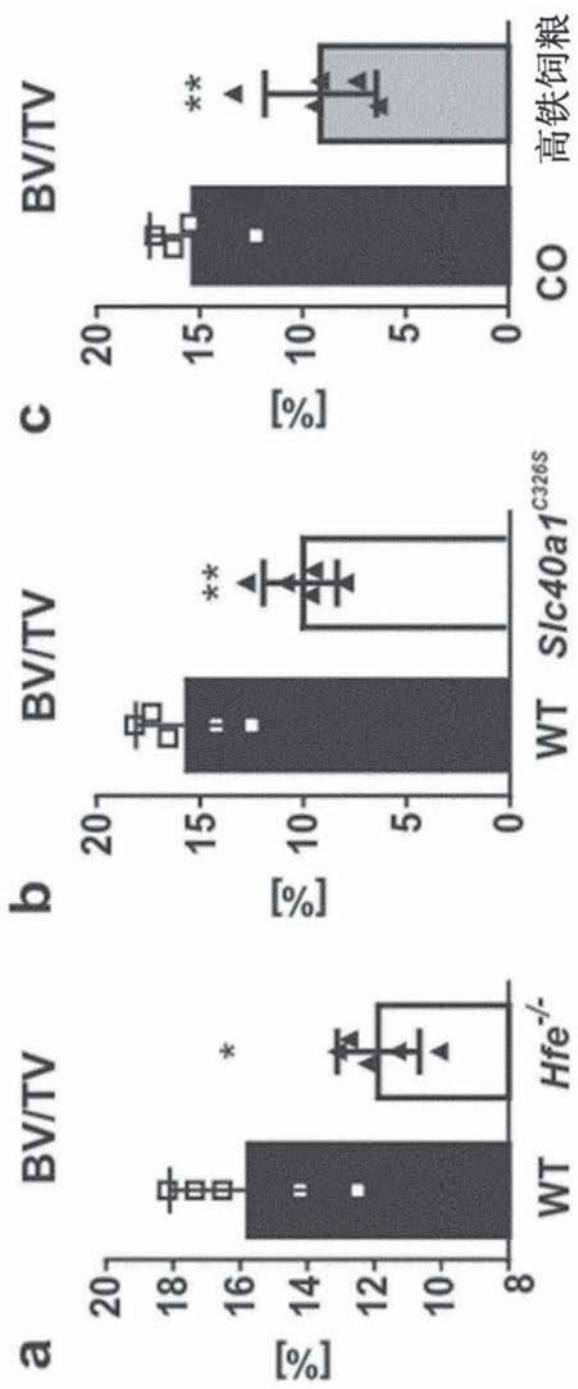


图17a-c

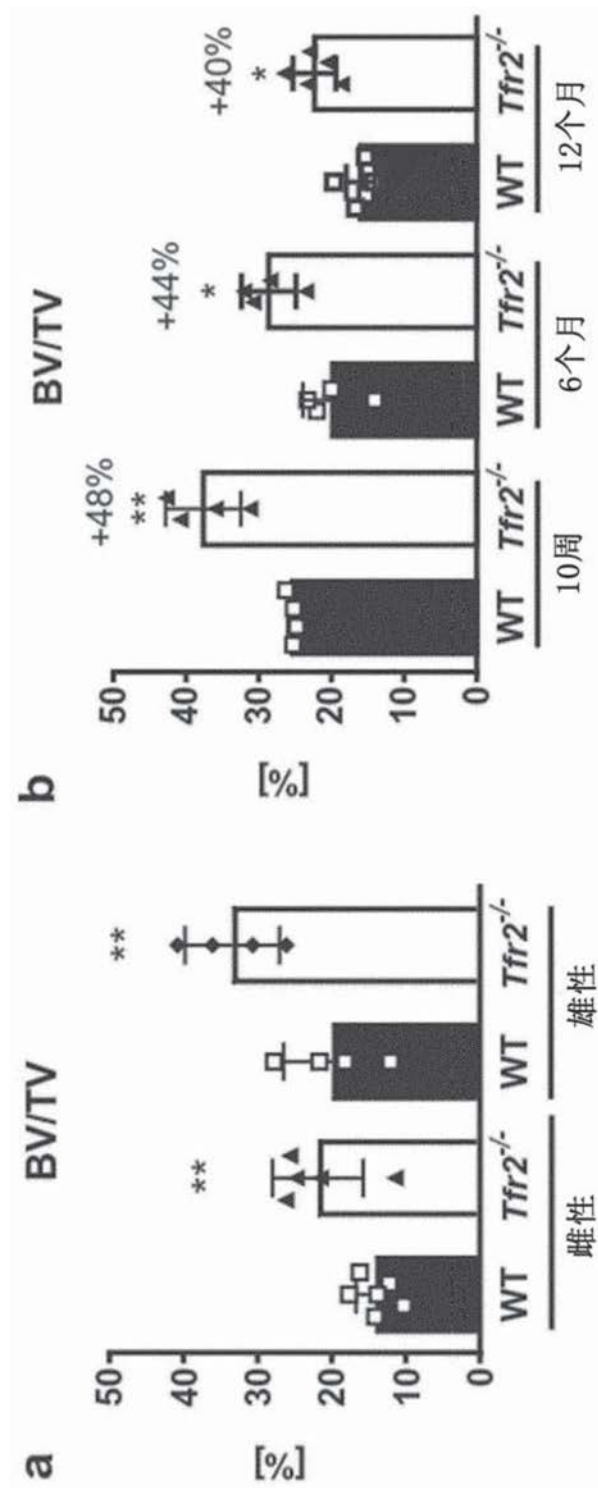


图18a-b

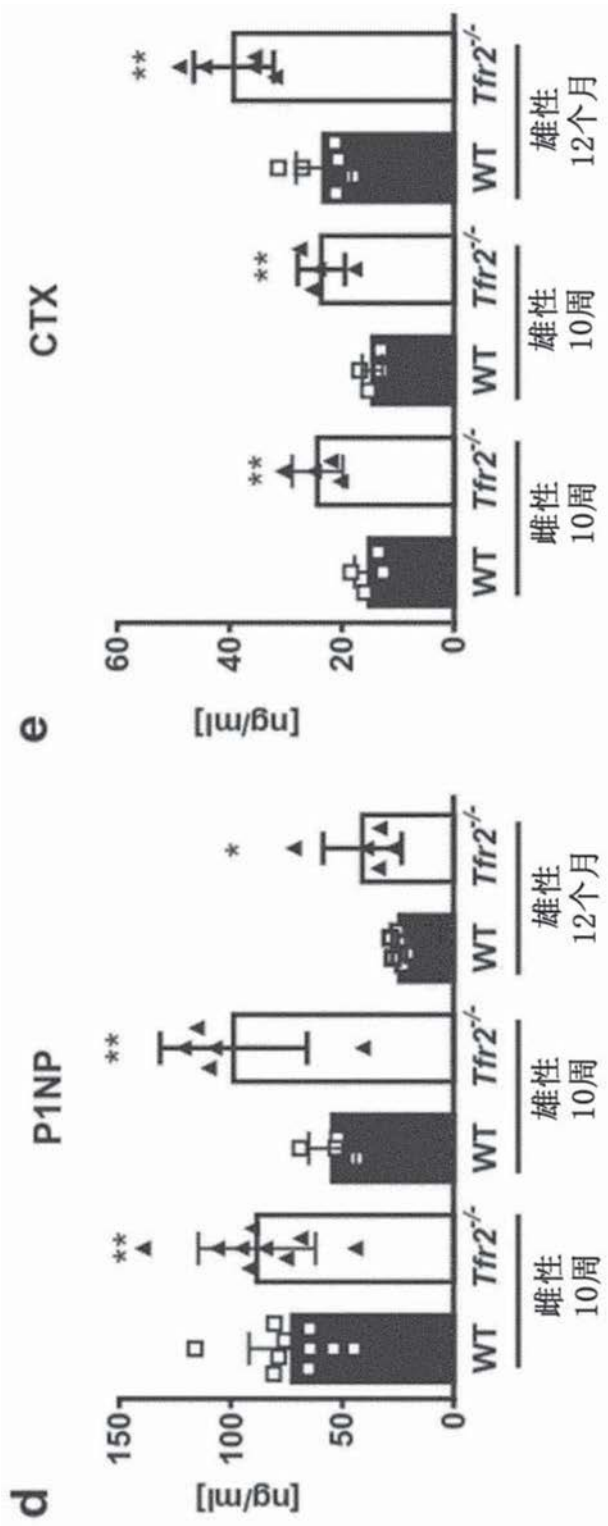


图18d-e

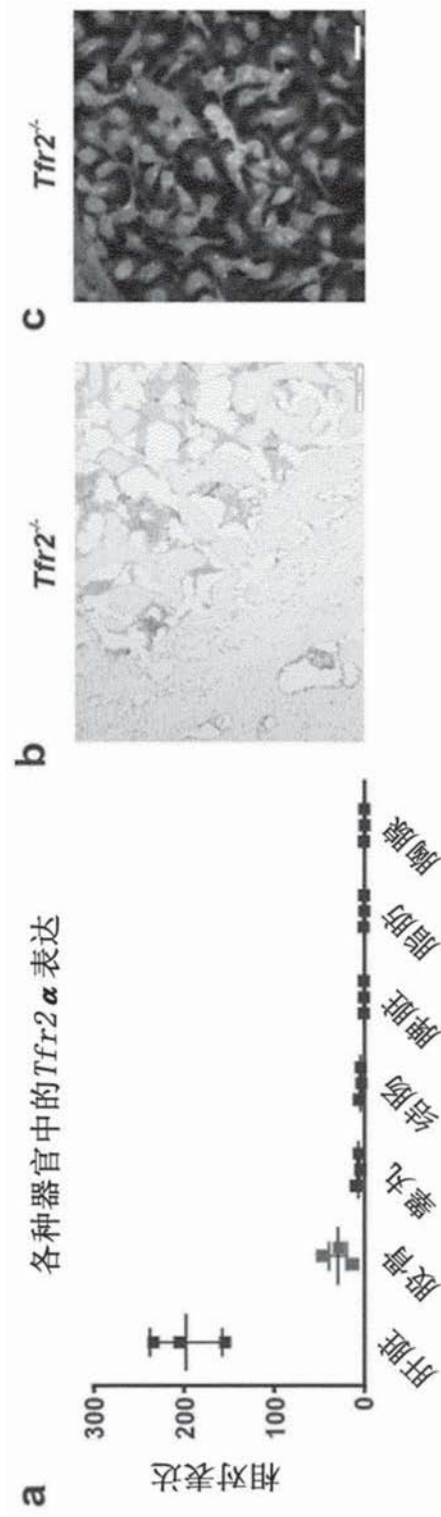


图19a-c

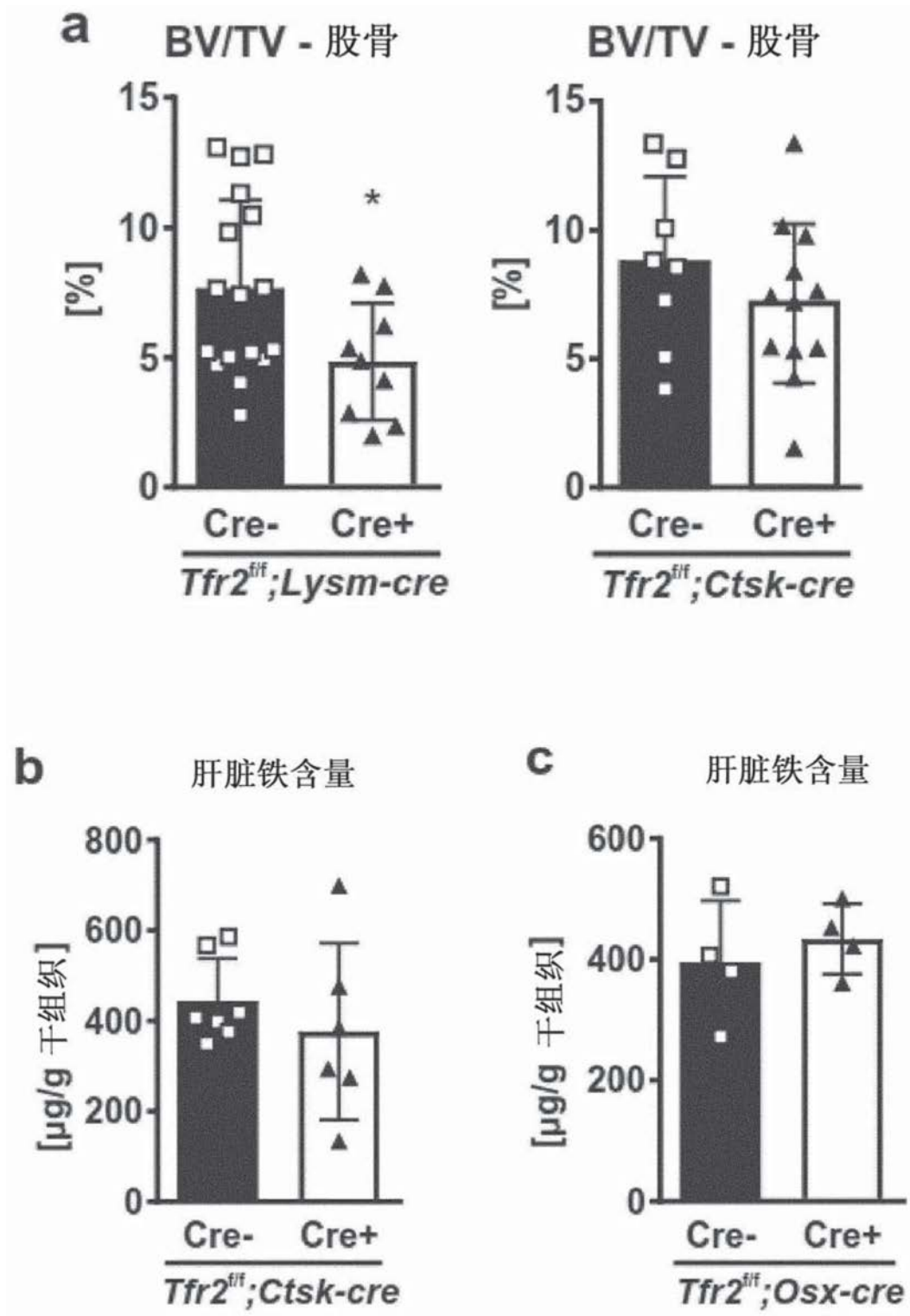


图20a-c

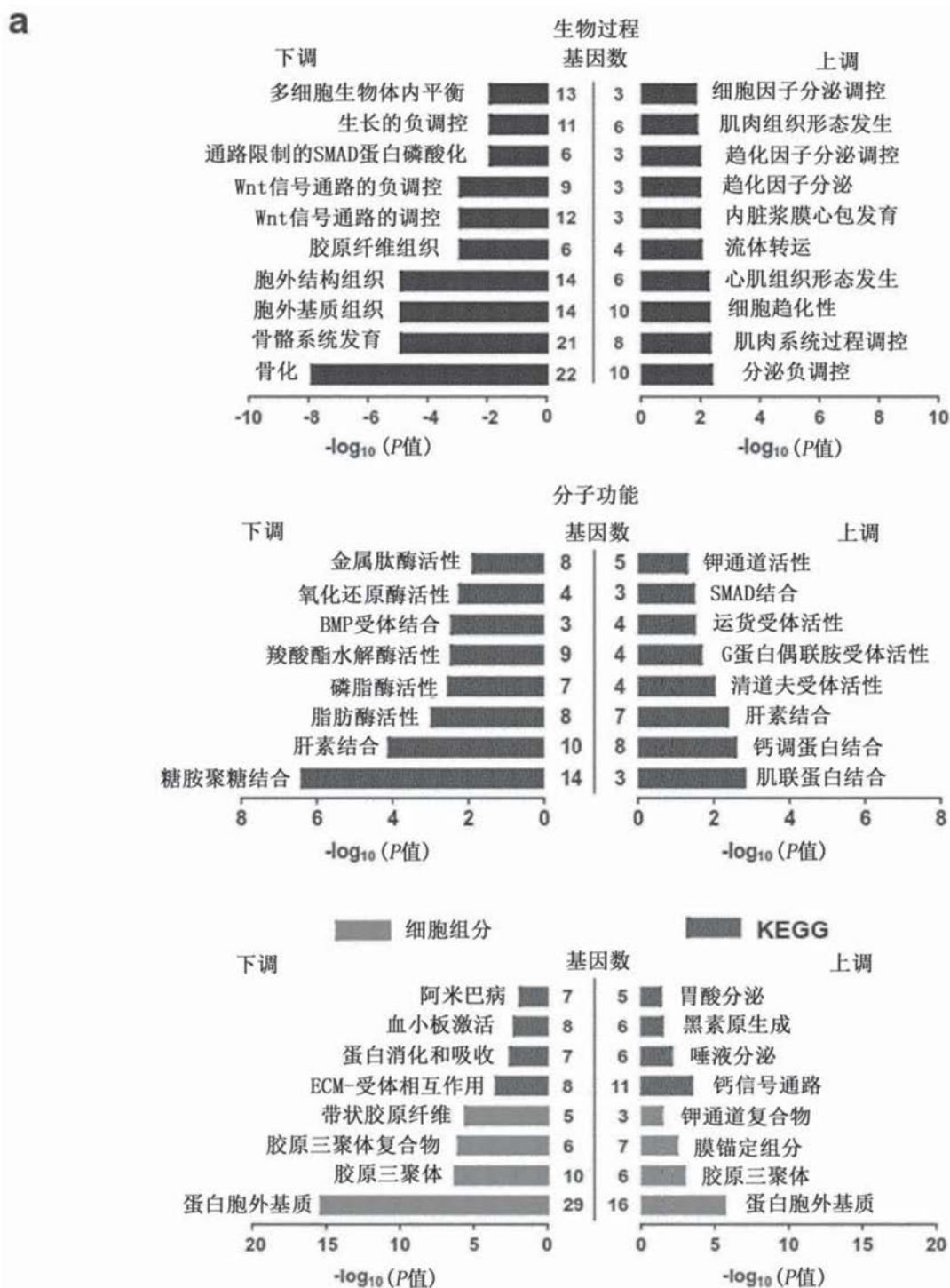
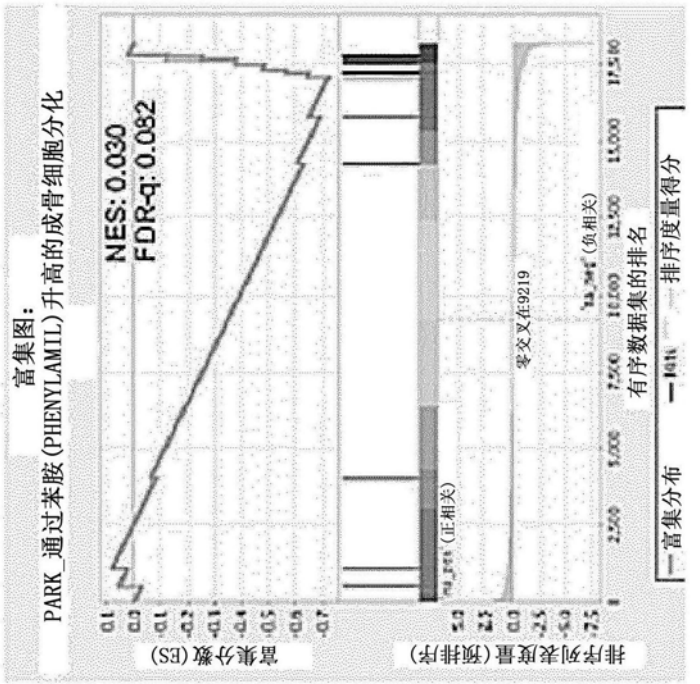
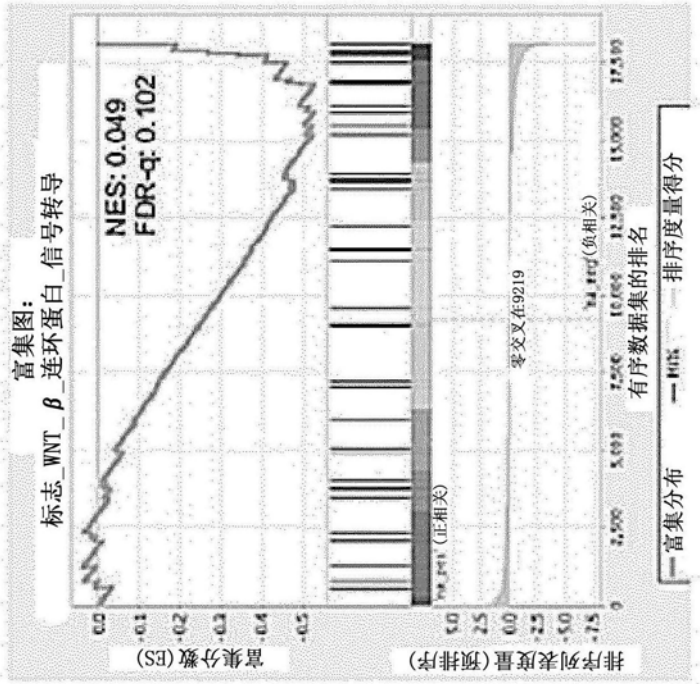


图21a

b



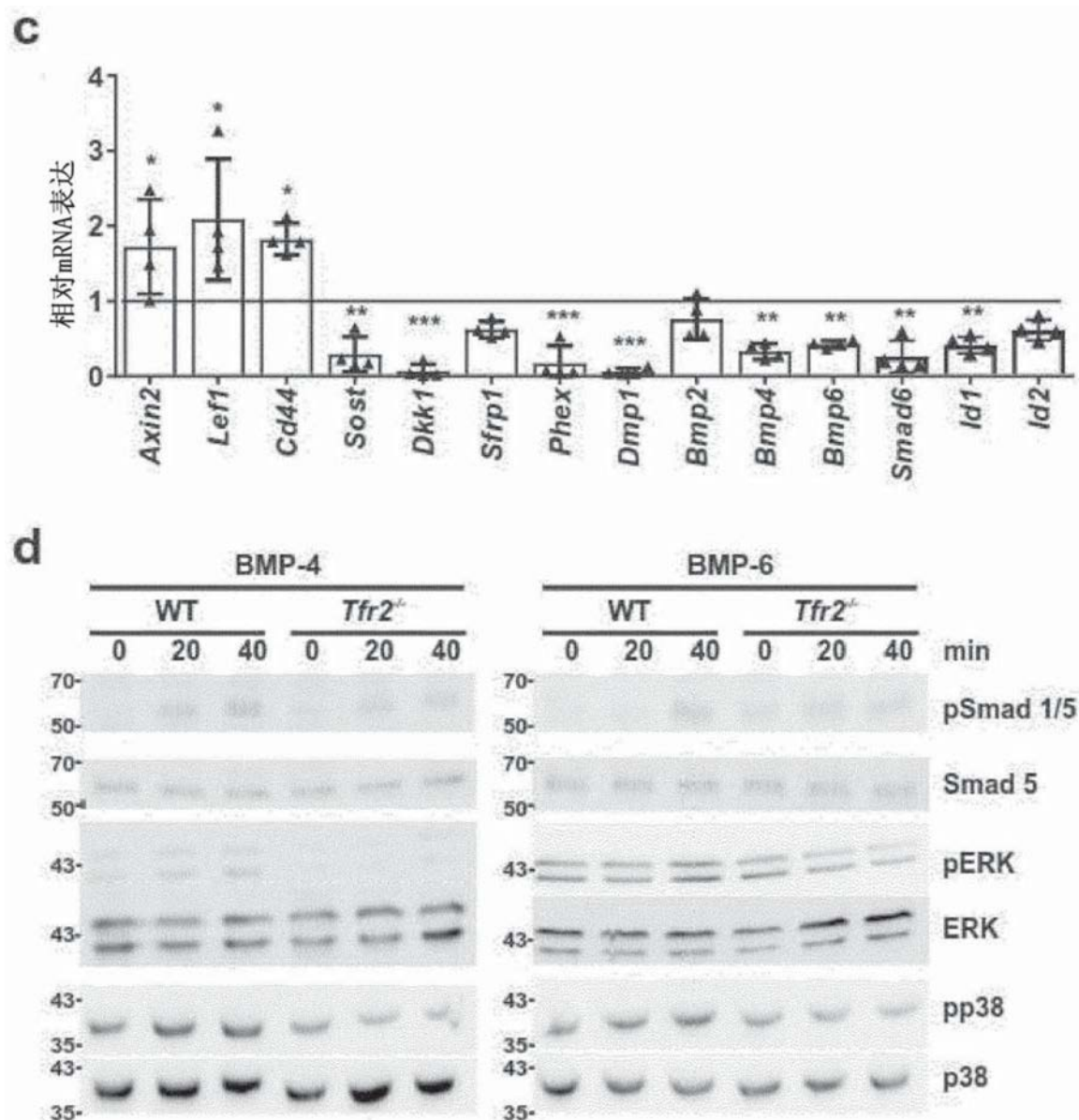


图21c-d

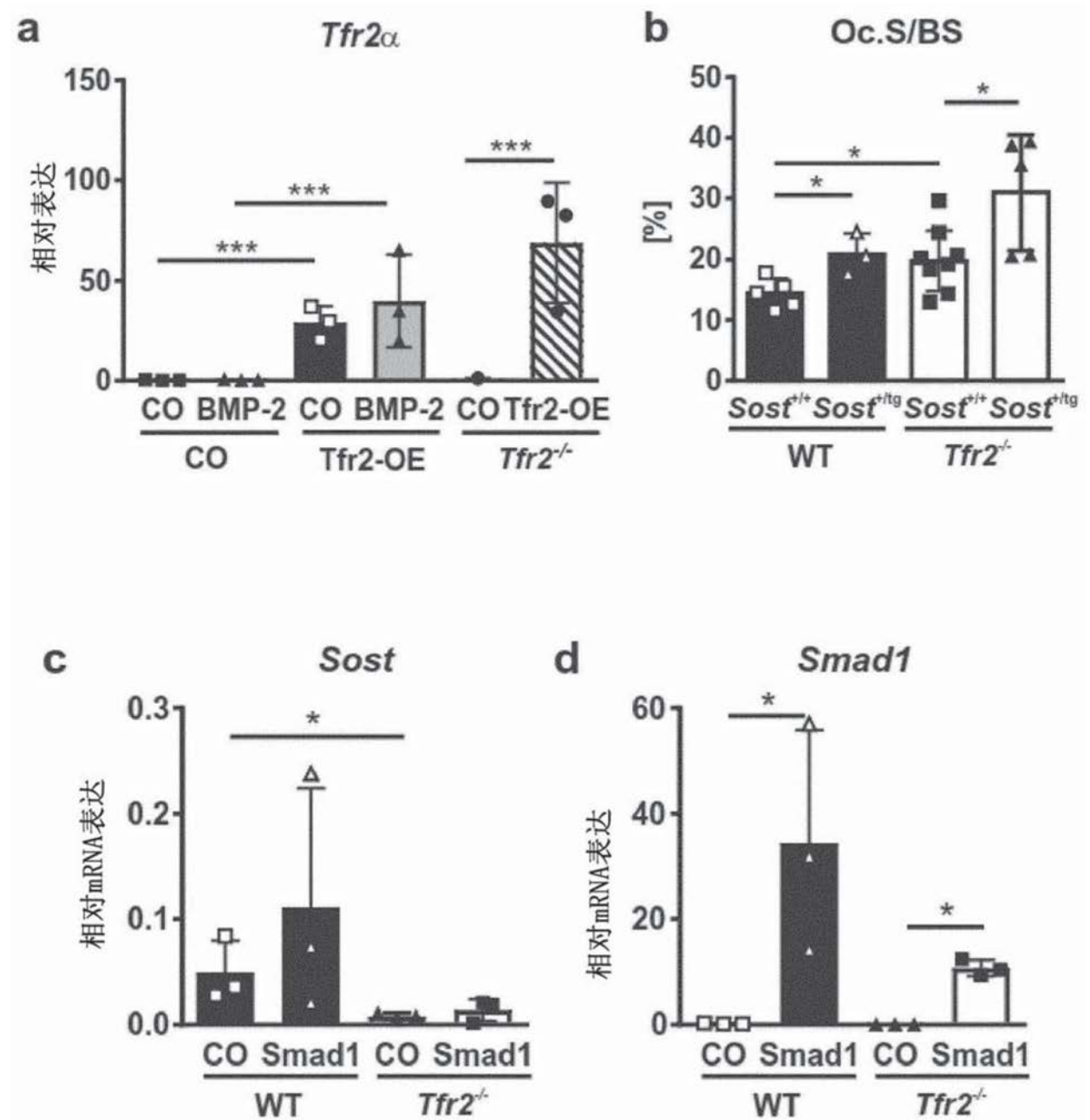


图22a-d

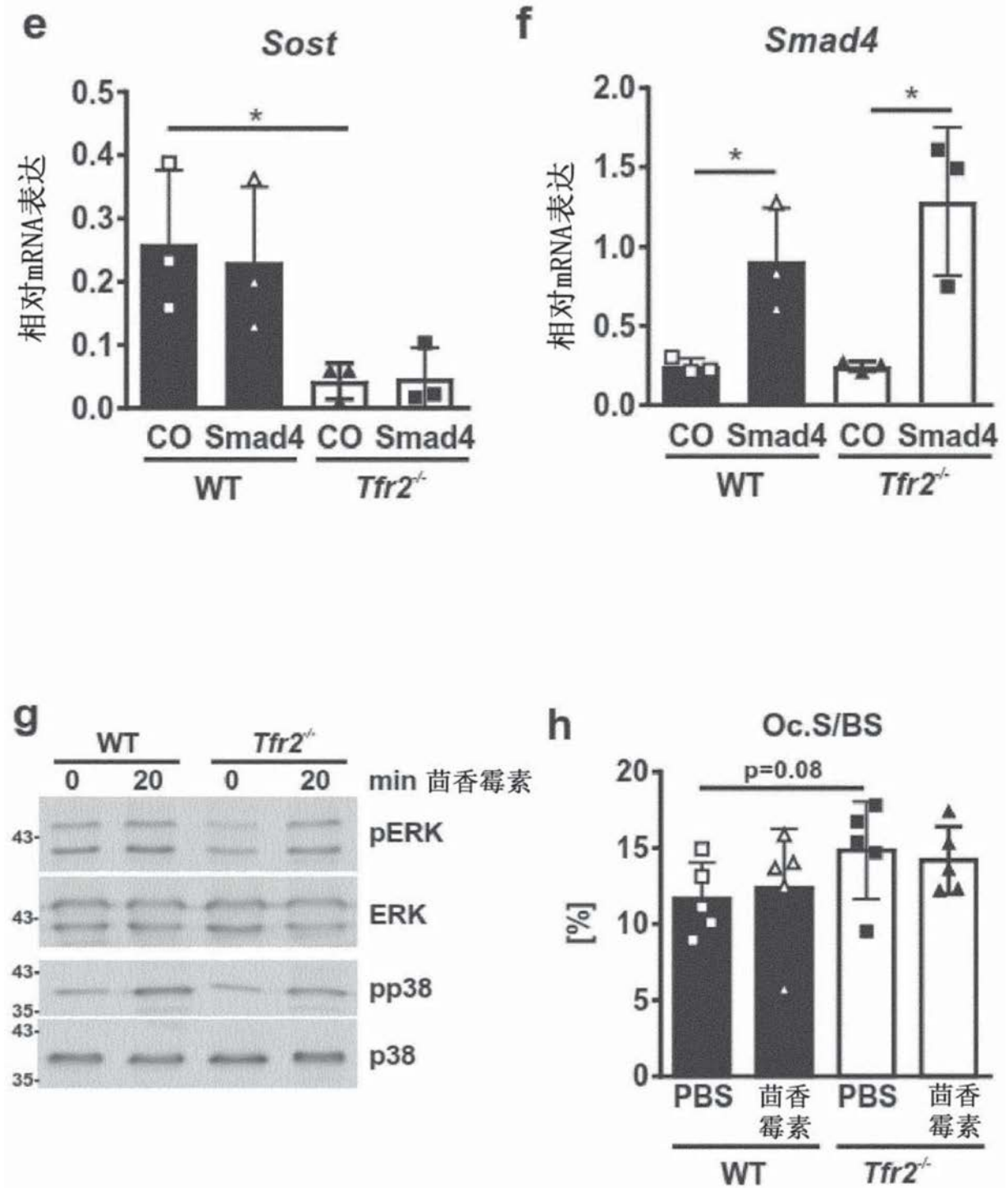


图22e-h

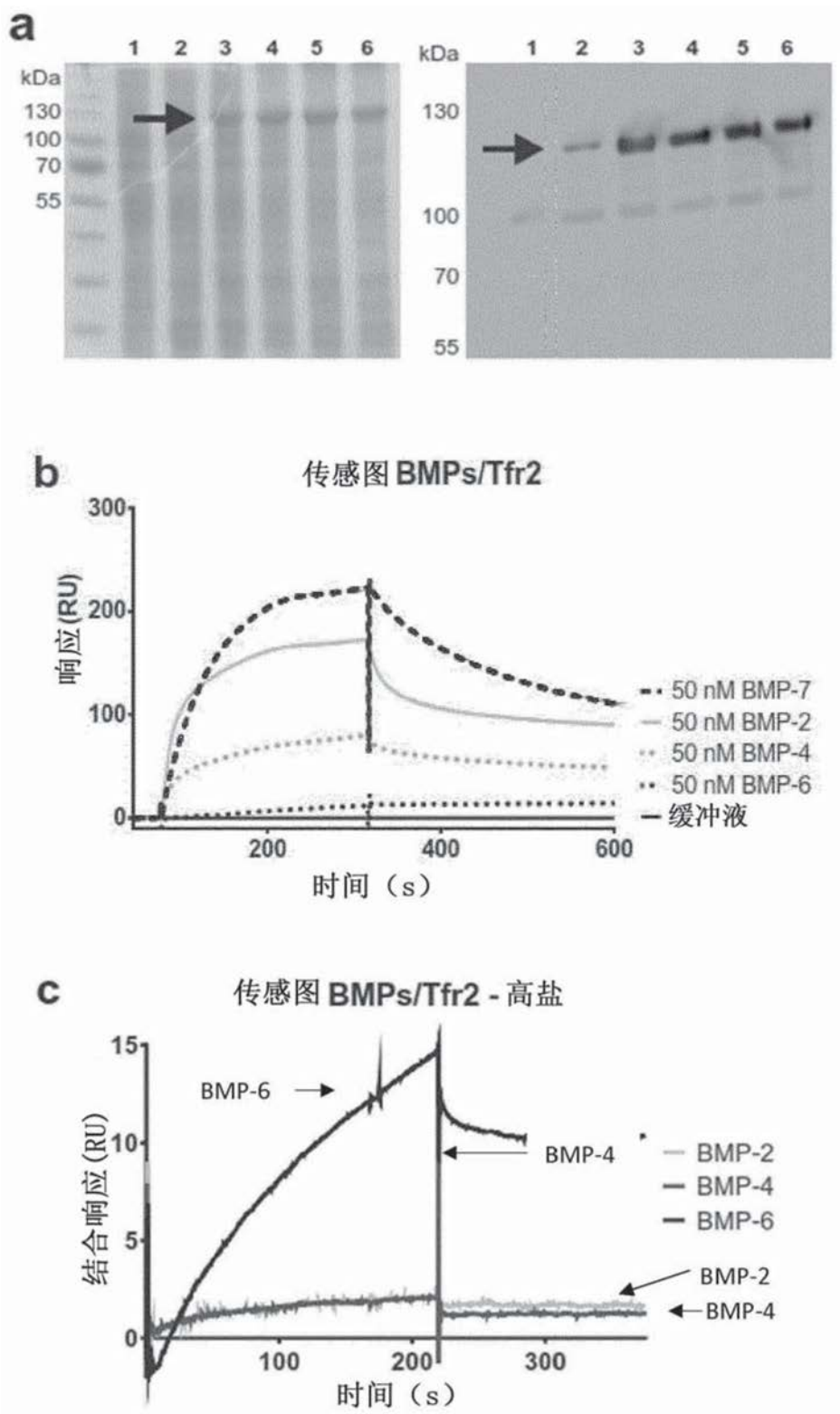


图23a-c

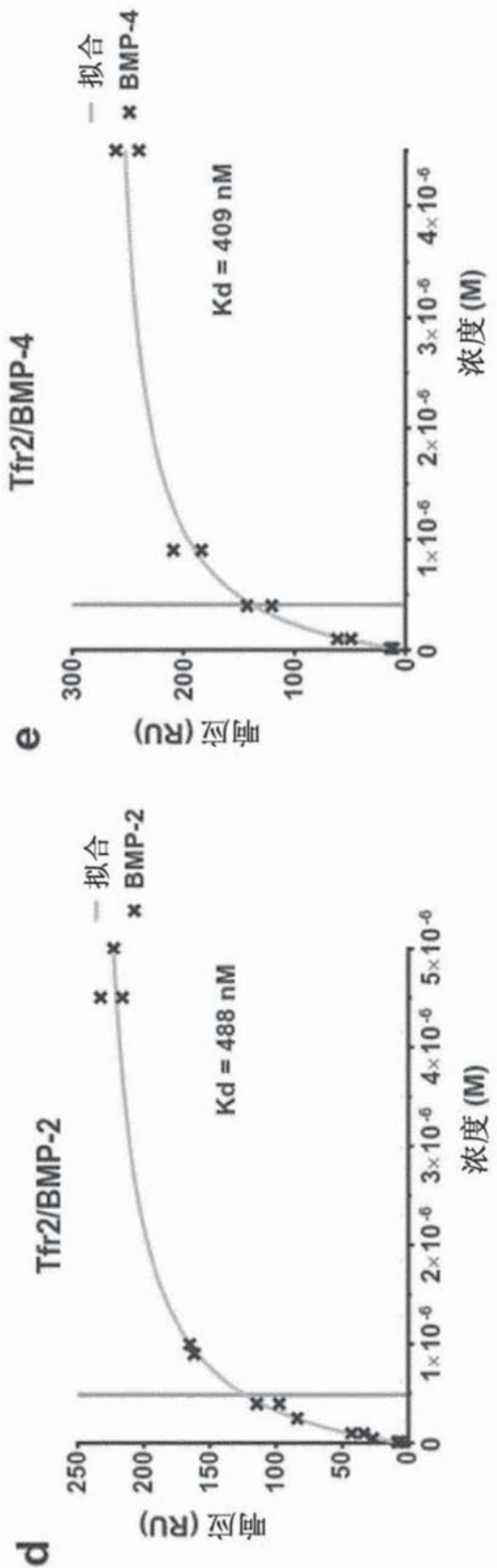


图23d-e

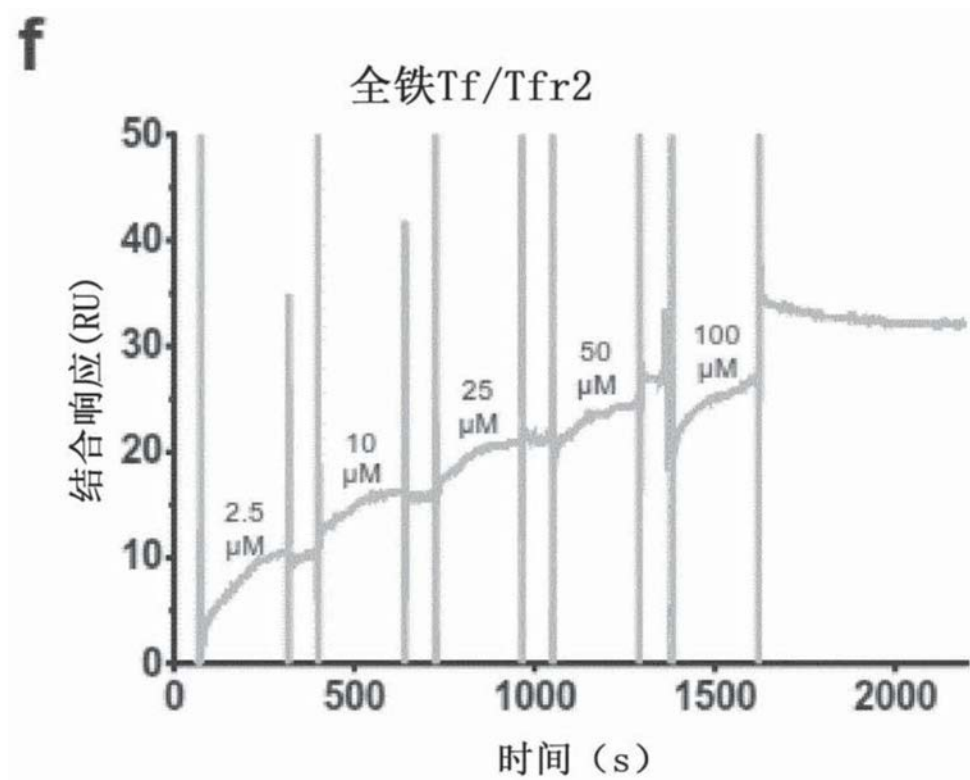


图23f

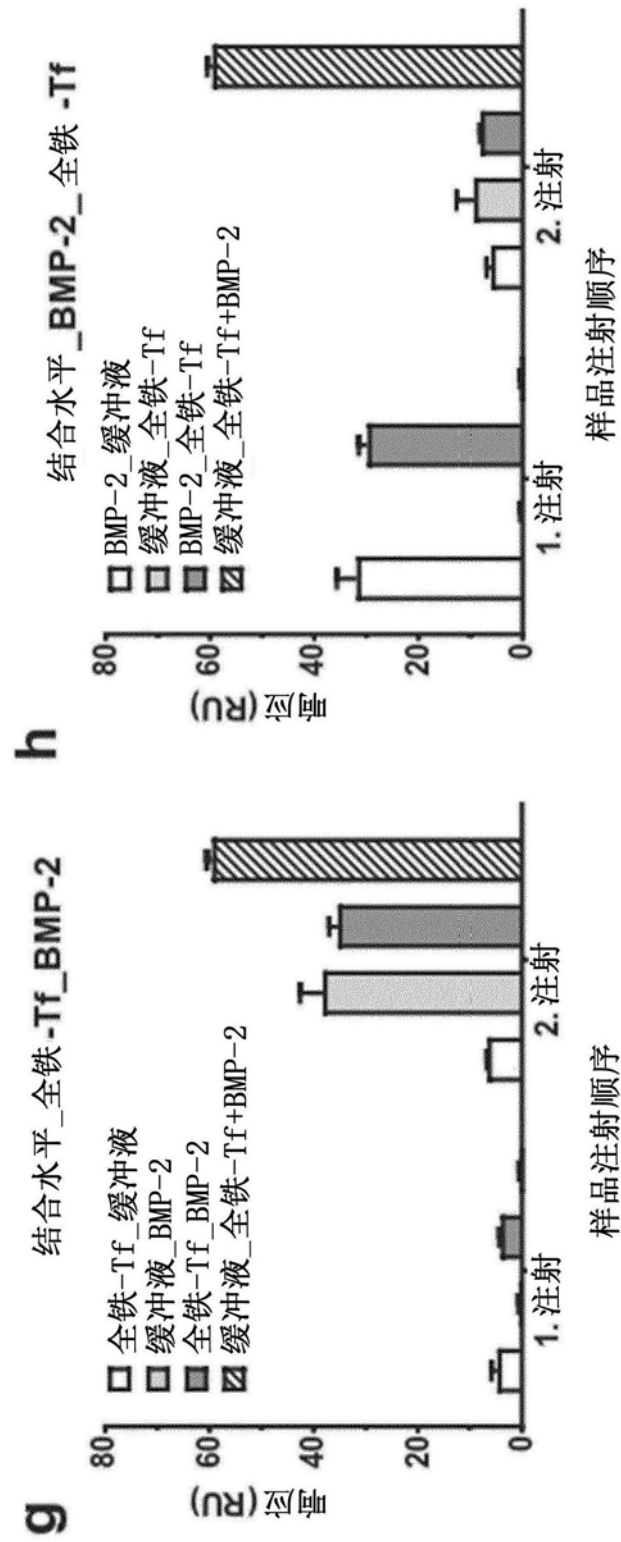


图23g-h

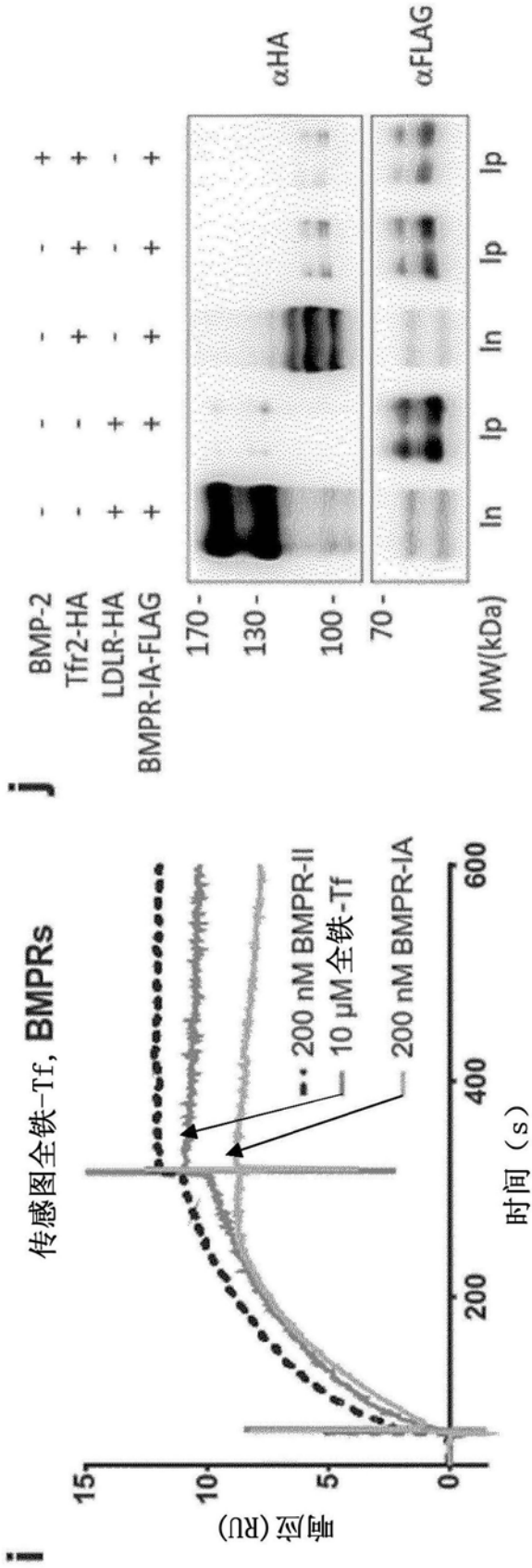


图23i-j

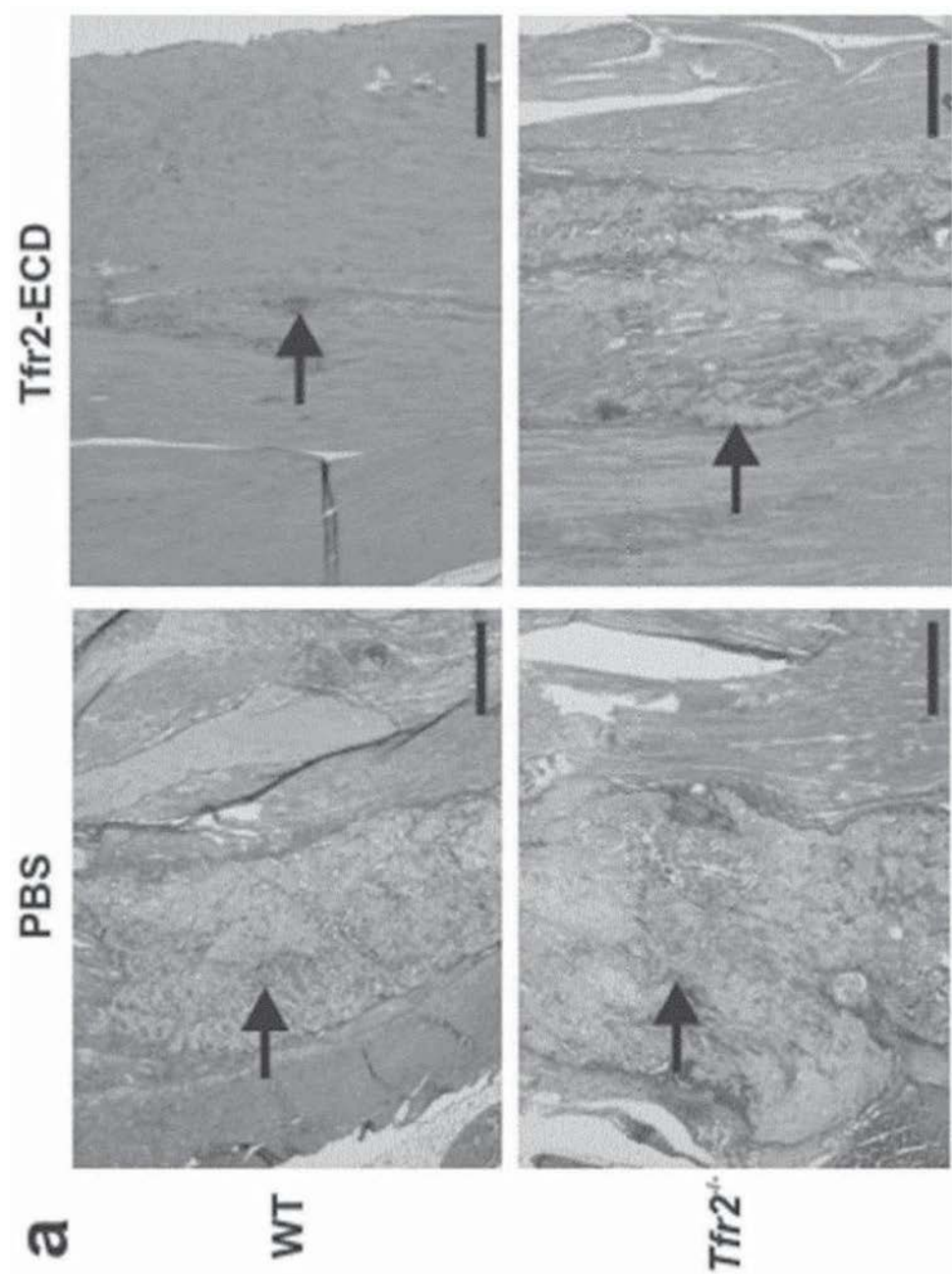


图24a

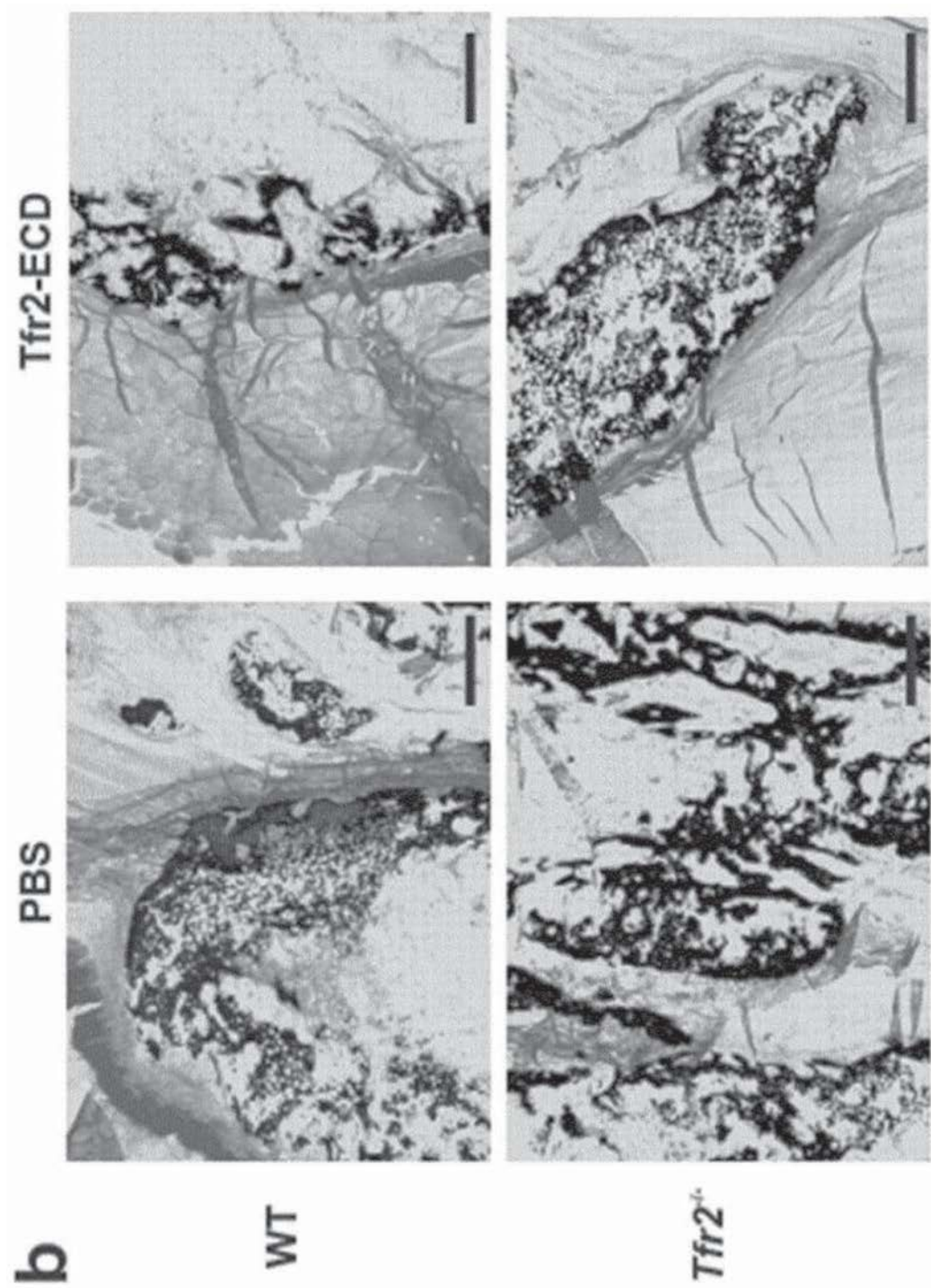


图24b

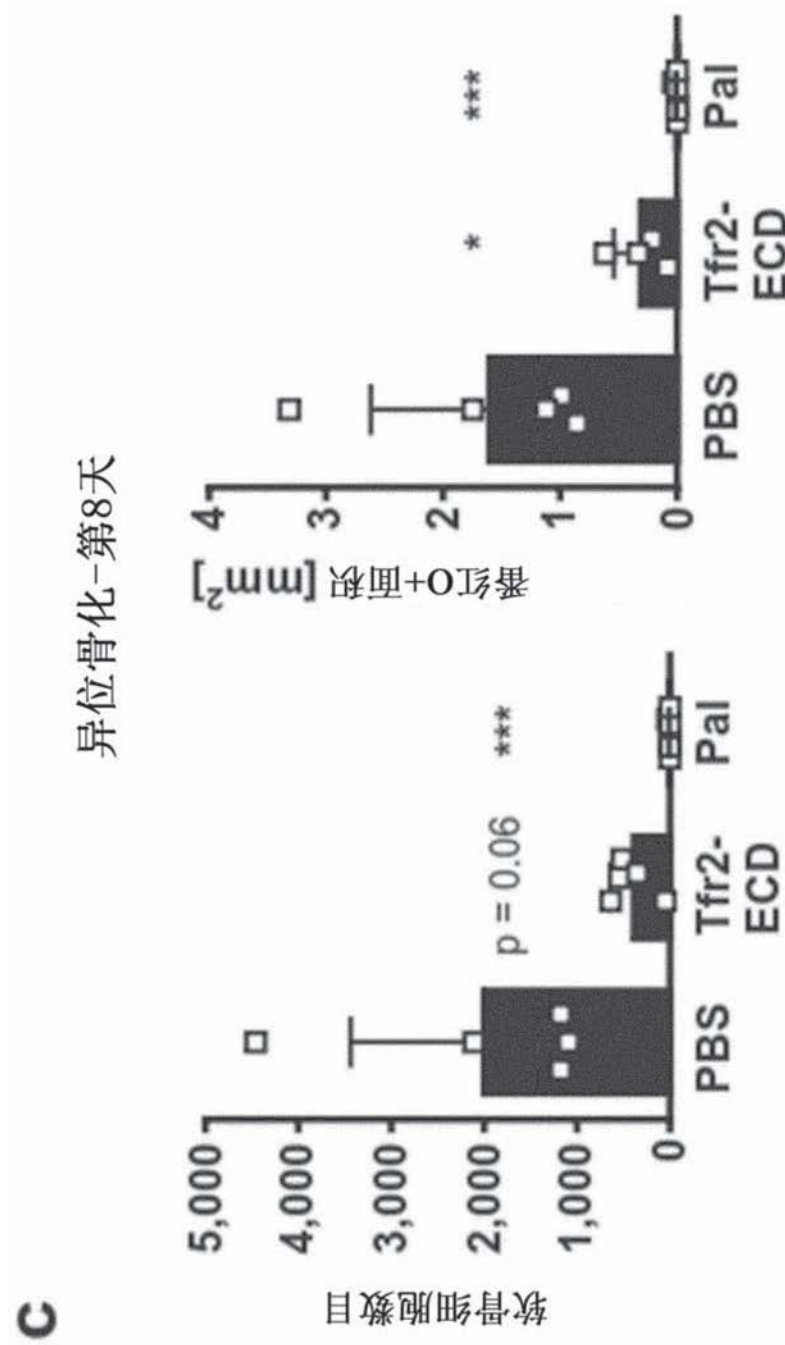


图24c

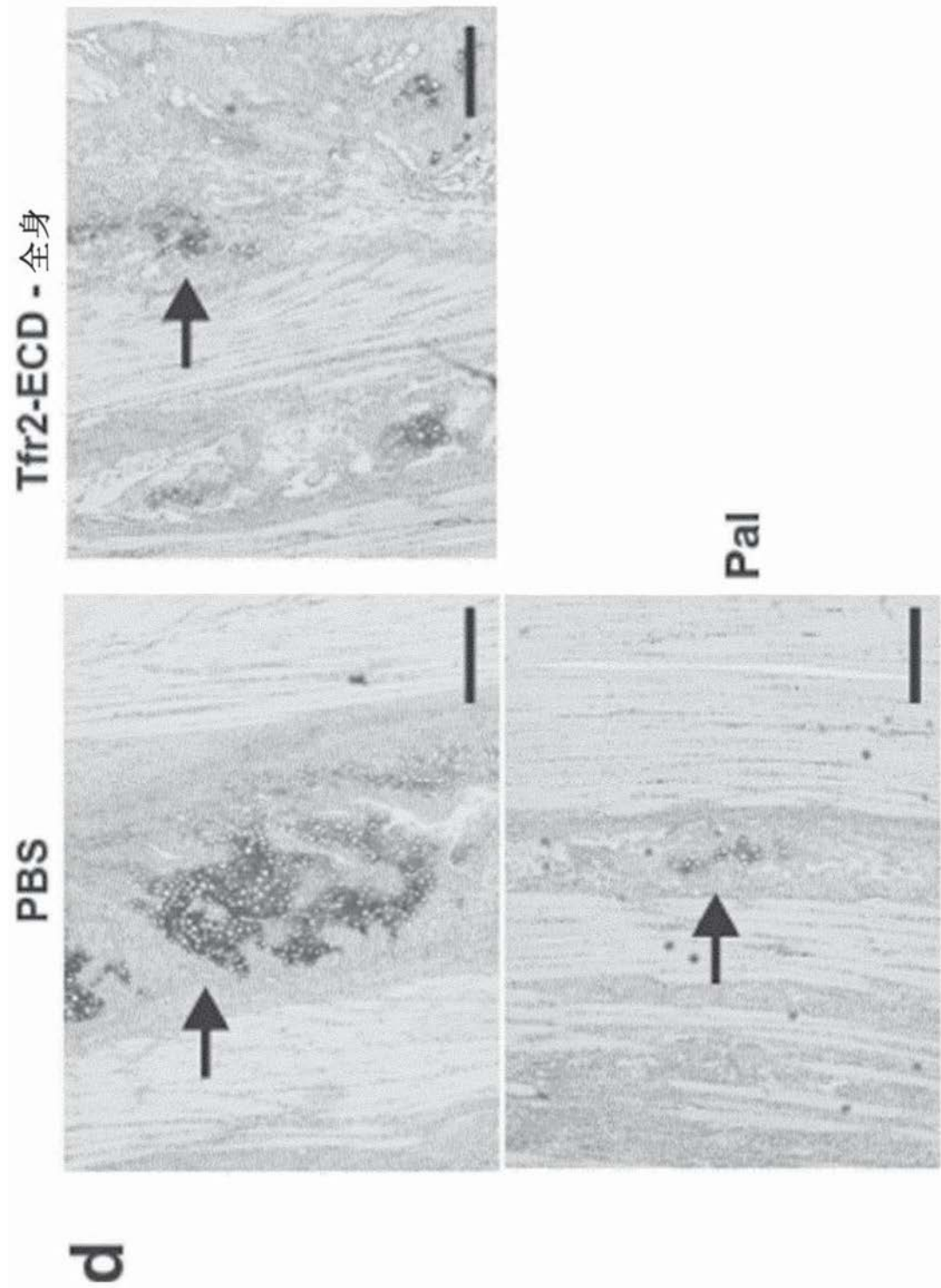


图24d