(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 109689097 B
(45)授权公告日 2023.01.03

(21)申请号 201780045139.X
(22)申请日 2017.07.21
(65)同一申请的已公布的文献号
申请公布号 CN 109689097 A
(43)申请公布日 2019.04.26
(30)优先权数据
1612643.5 2016.07.21 GB
(85)PCT国际申请进入国家阶段日
2019.01.21
(86)PCT国际申请的申请数据
PCT/EP2017/068476 2017.07.21
(87)PCT国际申请的公布数据
WO2018/015535 EN 2018.01.25
(73)专利权人 医福斯治疗有限公司
地址 英国牛津
(72)发明人 O.维克兰德 A.格根斯 D.古普塔
(74)专利代理机构 中国专利代理(香港)有限公司 72001
专利代理师 罗文锋 李志强
(51)Int.Cl.
A61K 39/395(2006.01)

(56)对比文件
US 2012207754 A1,2012.08.16
WO 2015058148 A1,2015.04.23
WO 2014168548 A2,2014.10.16
US 2010267846 A1,2010.10.21
CN 101842490 A,2010.09.22
CN 103260640 A,2013.08.21
US 2004241176 A1,2004.12.02
US 2015093433 A1,2015.04.02
Philippe Nizard等.Anchoring antibodies to membranes using a diphtheria toxin T domain-ZZ fusion protein as a pH sensitive membrane anchor.《FEBS Letters》.1998,第433卷83-88.
Chien-Sheng Chen等.Protein G-liposomal nanovesicles as universal reagents for immunoassays.《Talanta》.2005,第67卷205-211.
(续)

审查员 夏向东

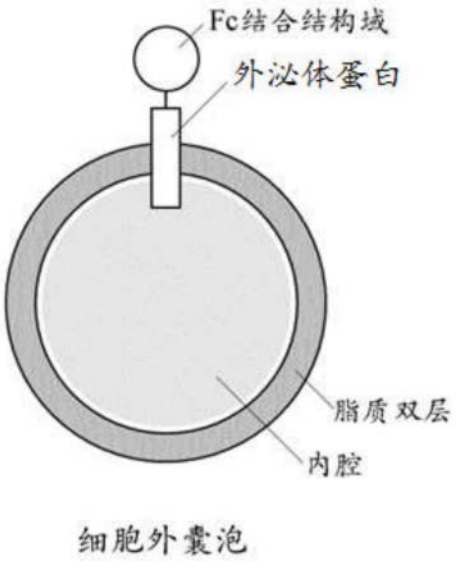
权利要求书3页 说明书29页
序列表97页 附图7页

(54)发明名称

包含具有FC结合能力的融合蛋白的细胞外囊泡

(57)摘要

本发明涉及细胞外囊泡(EV)治疗剂,其中所述EV包被有含有Fc结构域的蛋白质(如抗体)以用于i.a.靶向和治疗应用。所述EV的包被是经由对EV多肽进行本发明的蛋白质工程化而实现的。本发明因此涉及用于包被EV的方法、EV本身、以及这样的包被有含有Fc的蛋白质的EV的药物组合物和医学应用。



细胞外囊泡

CN 109689097 B

[转续页]

[接上页]

(56)对比文件

Michelle E. Hung等.Stabilization of Exosome-targeting Peptides via Engineered Glycosylation.《THE JOURNAL OF BIOLOGICAL CHEMISTRY》.2015,第290卷(第13期),8166-8172.

1.一种外泌体,所述外泌体包含至少一种融合蛋白,其中所述至少一种融合蛋白包含与至少一种人外泌体多肽融合的至少一种Fc结合多肽,并且其中所述至少一种Fc结合多肽展示在所述外泌体的外表面上,

进一步地其中所述至少一种Fc结合多肽选自由以下各项组成的组:蛋白A、蛋白G、蛋白A/G、蛋白L、蛋白LG、Z结构域、ZZ结构域、人类FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGRB、人类FCAMR、人类FCERA、人类FCAR、小鼠FCGRI、小鼠FCGRIIB、小鼠FCGRIII、小鼠FCGRIV、小鼠FCGRn、SPH肽、SPA肽、SPG2、SpA模拟物1、SpA模拟物2、SpA模拟物3、SpA模拟物4、SpA模拟物5、SpA模拟物6、SpA模拟物7、SpA模拟物8、SpA模拟物9、SpA模拟物10、Fcγ模拟物1、Fcγ模拟物2、以及其任何组合。

2.根据前述权利要求中任一项所述的外泌体,其中所述至少一种Fc结合多肽包含多于一个Fc结合区。

3.根据前述权利要求中任一项所述的外泌体,其中所述至少一种人外泌体多肽选自由以下各项组成的组:CD9、CD53、CD63、CD81、CD54、CD50、FLOT1、FLOT2、CD49d、CD71、CD133、CD138、CD235a、ALIX、多配体蛋白聚糖结合蛋白-1、多配体蛋白聚糖结合蛋白-2、Lamp2b、TSPAN8、TSPAN14、CD37、CD82、CD151、CD231、CD102、NOTCH1、NOTCH2、NOTCH3、NOTCH4、DLL1、DLL4、JAG1、JAG2、CD49d/ITGA4、ITGB5、ITGB6、ITGB7、CD11a、CD11b、CD11c、CD18/ITGB2、CD41、CD49b、CD49c、CD49e、CD51、CD61、CD104、Fc受体、白细胞介素受体、免疫球蛋白、CD2、CD3ε、CD3ζ、CD13、CD18、CD19、CD30、CD34、CD36、CD40、CD40L、CD44、CD45、CD45RA、CD47、CD86、CD110、CD111、CD115、CD117、CD125、CD135、CD184、CD200、CD279、CD273、CD274、CD362、EGFR、GLUR2、GLUR3、HLA-DM、L1CAM、LFA-1、Mac-1α、Mac-1β、STX3、TCRA、TCRB、TCRD、TCRG、VTI1A、VTI1B、其它人跨膜外泌体多肽、以及其任何组合。

4.根据前述权利要求中任一项所述的外泌体,其中所述至少一种Fc结合多肽与至少一种含有Fc的蛋白质结合。

5.根据前述权利要求中任一项所述的外泌体,其中所述外泌体具有与它结合的多个含有Fc的蛋白质,所述结合是经由所述Fc结合多肽与所述多个含有Fc的蛋白质的Fc结构域之间的相互作用而实现的,其中所述多个含有Fc的蛋白质可以是相同的或不同的。

6.根据权利要求4或5所述的外泌体,其中所述至少一种含有Fc的蛋白质是抗体和/或被工程化以包含Fc结构域的蛋白质。

7.根据权利要求6所述的外泌体,其中所述抗体是靶向抗体、治疗性抗体、抗体-药物缀合物(ADC)、或用于减少调理作用和/或免疫细胞介导的清除的抗体。

8.根据权利要求4至7中任一项所述的外泌体,其中所述外泌体具有与它结合的至少10个含有Fc的蛋白质。

9.一种(i)融合蛋白与(ii)含有Fc的蛋白质之间的非共价复合物,其特征在于所述融合蛋白包含与至少一种人外泌体多肽融合的至少一种Fc结合多肽,从而使所述Fc结合多肽展示在所述外泌体的外表面上,其中所述Fc结合多肽与所述含有Fc的蛋白质结合,进一步地其中所述至少一种Fc结合多肽选自由以下各项组成的组:蛋白A、蛋白G、蛋白A/G、蛋白L、蛋白LG、Z结构域、ZZ结构域、人类FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGRB、人类FCAMR、人类FCERA、人类FCAR、小鼠FCGRI、小鼠FCGRIIB、小鼠FCGRIII、小鼠FCGRIV、小鼠FCGRn、SPH肽、SPA肽、SPG2、SpA模拟物1、SpA模拟

物2、SpA模拟物3、SpA模拟物4、SpA模拟物5、SpA模拟物6、SpA模拟物7、SpA模拟物8、SpA模拟物9、SpA模拟物10、Fcγ模拟物1、Fcγ模拟物2、以及其任何组合。

10.根据权利要求9所述的非共价复合物，其中所述非共价复合物存在于外泌体的脂质膜中和/或外泌体内部。

11.一种药物组合物，所述药物组合物包含根据权利要求1至8中任一项所述的外泌体和/或根据权利要求9至10中任一项所述的非共价复合物、以及任选的药学上可接受的载体。

12.根据权利要求1至8中任一项所述的外泌体在制备药物中的用途。

13.一种用于使至少一种含有Fc的蛋白质与外泌体连接的方法，所述方法包括以下步骤：

(i)提供包含融合蛋白的外泌体，所述融合蛋白包含至少一种Fc结合多肽和至少一种人外泌体多肽；

(ii)使所述融合蛋白的Fc结合多肽结合所述至少一种含有Fc的蛋白质的Fc结构域，

进一步地其中所述至少一种Fc结合多肽选自由以下各项组成的组：蛋白A、蛋白G、蛋白A/G、蛋白L、蛋白LG、Z结构域、ZZ结构域、人类FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGRB、人类FCAMR、人类FCERA、人类FCAR、小鼠FCGRI、小鼠FCGRIIB、小鼠FCGRIII、小鼠FCGRIV、小鼠FCGRn、SPH肽、SPA肽、SPG2、SpA模拟物1、SpA模拟物2、SpA模拟物3、SpA模拟物4、SpA模拟物5、SpA模拟物6、SpA模拟物7、SpA模拟物8、SpA模拟物9、SpA模拟物10、Fcγ模拟物1、Fcγ模拟物2、以及其任何组合。

14.一种多肽构建体，所述多肽构建体包含融合蛋白，所述融合蛋白包含至少一种Fc结合多肽和至少一种人外泌体多肽，从而使所述Fc结合多肽展示在所述外泌体的外表面上；进一步地其中所述至少一种Fc结合多肽选自由以下各项组成的组：蛋白A、蛋白G、蛋白A/G、蛋白L、蛋白LG、Z结构域、ZZ结构域、人类FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGRB、人类FCAMR、人类FCERA、人类FCAR、小鼠FCGRI、小鼠FCGRIIB、小鼠FCGRIII、小鼠FCGRIV、小鼠FCGRn、SPH肽、SPA肽、SPG2、SpA模拟物1、SpA模拟物2、SpA模拟物3、SpA模拟物4、SpA模拟物5、SpA模拟物6、SpA模拟物7、SpA模拟物8、SpA模拟物9、SpA模拟物10、Fcγ模拟物1、Fcγ模拟物2、以及其任何组合。

15.一种多核苷酸构建体，所述多核苷酸构建体编码至少一种根据权利要求14所述的多肽构建体。

16.一种细胞，所述细胞包含至少一种根据权利要求14所述的多肽构建体、至少一种根据权利要求15所述的多核苷酸构建体、至少一种根据权利要求1至8中任一项所述的外泌体和/或至少一种根据权利要求9至10中任一项所述的非共价复合物。

17.一种用于将至少一种含有Fc的蛋白质递送到靶细胞的体外或离体方法，所述方法包括(i)使所述至少一种含有Fc的蛋白质的Fc结构域与包含在外泌体中的Fc结合多肽连接；以及(ii)使所述连接有所述至少一种含有Fc的蛋白质的外泌体与所述靶细胞接触；

进一步地其中所述至少一种Fc结合多肽选自由以下各项组成的组：蛋白A、蛋白G、蛋白A/G、蛋白L、蛋白LG、Z结构域、ZZ结构域、人类FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGRB、人类FCAMR、人类FCERA、人类FCAR、小鼠FCGRI、小鼠FCGRIIB、小鼠FCGRIII、小鼠FCGRIV、小鼠FCGRn、SPH肽、SPA肽、SPG2、SpA模拟物1、SpA模拟

物2、SpA模拟物3、SpA模拟物4、SpA模拟物5、SpA模拟物6、SpA模拟物7、SpA模拟物8、SpA模拟物9、SpA模拟物10、Fcγ模拟物1、Fcγ模拟物2、以及其任何组合。

18.根据权利要求17所述的方法，其中所述外泌体的Fc结合多肽是与至少一种人外泌体多肽的融合蛋白的一部分。

19.根据权利要求17至18中任一项所述的方法，其中将所述含有Fc的蛋白质递送到靶细胞中。

20.根据权利要求9至10中任一项所述的非共价复合物在制备药物中的用途。

21.根据权利要求11所述的药物组合物在制备药物中的用途。

包含具有FC结合能力的融合蛋白的细胞外囊泡

技术领域

[0001] 本发明涉及细胞外囊泡(EV)治疗剂,其中所述EV包被有包含Fc结构域的蛋白质(如抗体)以用于i.a.靶向和治疗应用。

背景技术

[0002] 蛋白质生物制剂常规用于治疗和/或预防广泛的疾病,包括癌症、遗传性病症以及自身免疫性疾病。当中可以发现当今许多轰动一时的药物的抗体和嵌合受体通常是以裸形式,即不使用任何递送载体来施用的。细胞外囊泡(EV)是由EV产生细胞释放到细胞外环境中的纳米级囊泡。EV,特别是外泌体已经被证实为能够将蛋白质生物制剂,如抗体和诱饵受体转运到靶细胞中,从而使得能够实现一种全新形式的先进生物治疗剂,其利用EV的特性与重组蛋白的特异性的组合。

[0003] 使用EV来递送蛋白质治疗剂与生物制剂的常规直接施用相比提供了许多优势。举例来说,当使用EV递送生物治疗剂时,它们受到保护而免于降解并且更稳定;EV构成了多价药物递送模式,其可以引起功效增强;EV可以改进蛋白质生物制剂的药物代谢动力学和药效动力学;EV可以靶向所关注的组织和细胞;EV可以具有反映它们的细胞起源的固有治疗作用;并且EV还使得能够穿透血脑屏障并且提高CNS递送。

[0004] 尽管具有它们所有的优势,但是将大而复杂的蛋白质生物制剂负载到EV中以随后向靶细胞递送尚未被证实是十分简单的。WO2013/084000和WO2014/168548这两者都描述了成功地将基于蛋白质的生物制剂(如抗体和诱饵受体)负载到EV中和EV上。WO2013/084000公开了所谓的将例如抗体内源性和外源性负载到诸如外泌体的EV中。外源性负载指的是经由在EV从培养物中的EV产生细胞中分离之后将蛋白质运载分子直接引入所述EV中来对EV进行负载。蛋白质的外源性引入可以如WO2013/084000中那样,在从亲本细胞中分离后,使用例如所关注的多肽的电穿孔或转染来进行。另一方面,内源性负载涉及如例如由WO2014/168548所教导,用编码所关注的治疗性蛋白质的多核苷酸构建体对EV产生细胞进行转染。WO2015/058148教导了所关注的蛋白质的内源性负载的实例,即用编码诸如CD64、CD32以及CD16的Fc受体的构建体对NK细胞进行遗传工程化。然而,对例如NK细胞进行遗传修饰以表达Fc受体并不是负载所关注的蛋白质的特别有效的方式,这是因为它将仅产生每个EV低数量的Fc受体。因此,由WO2015/058148所教导的方法完全没有解决与将EV用多种大而复杂的蛋白质生物制剂有效负载,特别是以可控的、可预测的、可按比例缩放的、以及有成本效益的方式有效负载相关的挑战。

发明内容

[0005] 因此,本发明的目的在于克服与将EV用蛋白质生物制剂负载,特别是负载抗体和包含Fc结构域的其它蛋白质以用于后续治疗应用相关的上述问题。此外,本发明旨在满足本领域内的其它现有需求,例如使得能够将EV用大量多种治疗性抗体、靶向抗体、或抗清除抗体和包含Fc结构域的其它蛋白质(天然包含或由于蛋白质工程化而包含)进行高亲和力

和高密度包被,以显著增强EV用于治疗性蛋白质递送的治疗潜力。

[0006] 本发明通过利用融合构建体实现了这些目的和其它目的,所述融合构建体包含与人类来源和/或非人类来源的Fc结合多肽(在本文常常被称为Fc结合剂)融合的外泌体蛋白。使用外泌体蛋白作为用于负载EV的模式使得能够在EV的表面上展示大量的Fc结合剂,这对于能够将EV用包含Fc结构域的蛋白质(在本文常常被称为含有Fc的蛋白质)致密包被是重要的,所述包含Fc结构域的蛋白质经由所述Fc结合剂与所述包含Fc结构域的蛋白质之间的相互作用与EV结合(在有利的实施方案中,这样的含有Fc的蛋白质可以是抗体)。可以融合到天然缺乏Fc结构域的蛋白质上的人类来源和/或哺乳动物来源的Fc结构域可以选自替代物的以下非限制性清单:人类IGHM(作为非限制性实例,登录号:P01871)、人类IGHA1(作为非限制性实例,登录号:P01876)、人类IGHA2(作为非限制性实例,登录号:P01877)、人类IGKC(作为非限制性实例,登录号:P01834)、人类IGHG1(作为非限制性实例,登录号:P01857)、人类IGHG2(作为非限制性实例,登录号:P01859)、人类IGHG3(作为非限制性实例,登录号:P01860)、人类IGHG4(作为非限制性实例,登录号:P01861)、人类IGHD(作为非限制性实例,登录号:P01880)、人类IGHE(作为非限制性实例,登录号:P01854)、以及其任何结构域、衍生物、或组合。使用非人类Fc结合多肽,如蛋白A/G以及所谓的Z结构域和二聚体ZZ结构域可以使得所述Fc结合剂与它的一个或多个相互作用配偶体,即含有Fc的蛋白质的Fc结构域之间的结合亲和力更高。此外,非人类Fc结合剂的尺寸常常小于人类Fc结合蛋白。另一方面,人类来源和/或哺乳动物来源的Fc结合蛋白和多肽结构域,如人类FCGRI(CD64)(作为非限制性实例,SEQ ID NO 31)、FCGR2A(CD32A)(作为非限制性实例,登录号:P12318)、FCGR2B(CD32B)(作为非限制性实例,登录号:P31994)、FCGR2C(CD32C)(作为非限制性实例,登录号:P31995)、FCGR3A(CD16A)(作为非限制性实例,登录号:P0837)、FCGR3B(CD16B)(作为非限制性实例,登录号:O75015)、FCAMR(作为非限制性实例,SEQ ID NO 28)、FCERA(作为非限制性实例,SEQ ID NO 30)、FCAR(作为非限制性实例,SEQ ID NO 29)、或小鼠FCGRI(作为非限制性实例,SEQ ID NO 79)、FCGRIIB(作为非限制性实例,SEQ ID NO 80)、FCGRIII(作为非限制性实例,SEQ ID NO 81)、FCGRIV(作为非限制性实例,SEQ ID NO 82)、FCGRn(作为非限制性实例,SEQ ID NO 83)可以提供优势,这是因为它们是哺乳动物蛋白质并且因而可以具有更小的免疫刺激性。无论如何,关键的是,对EV进行工程化以确保它们包含Fc结合多肽的融合构建体,而不仅仅是结合Fc结构域的过表达的蛋白质,以确保在EV上展示足够数量的Fc结合多肽并且使得能够进行可控的生产。

[0007] 此外,本发明的Fc结合多肽可以被工程化以小于天然表达的Fc结合蛋白,这使得更容易借助于与EV蛋白的融合构建体将它们引导到EV表面。此外,非人类Fc结合剂(其可以是例如细菌来源的)与人类Fc结合剂之间的一个显著差异是以下事实,即这样的非人类Fc结合剂在某些情况下可以同时结合多于一个Fc结构域,这可以引起包含Fc结构域的所关注的蛋白质对EV的表面包被增加。举例来说,蛋白A/G是源自于金黄色葡萄球菌(Staphylococcus aureus)的蛋白A与源自于停乳链球菌(Streptococcus dysgalactiae)的蛋白A之间的融合蛋白,其具有用于IgG抗体的Fc结构域的七个结合区。这种多价性可以使得多个包含Fc结构域的蛋白质,如抗体与每一个Fc结合剂(在这种情况下,是蛋白A/G)结合,从而使得EV能够被含有Fc结构域的蛋白质,如抗体更致密地包被。重要的是,将EV用Fc结合剂更致密地包被还可以例如使得例如抗体与它们的相应抗原之间的亲合力能够更高,

这意味着将增强与所关注的靶标的结合，这从靶向和/或治疗角度来看，可能是有益的。

[0008] 在一个方面，本发明涉及包含融合蛋白的EV，其中所述融合蛋白包含与外泌体多肽融合的至少一种基于多肽的Fc结合剂。由于与EV蛋白融合，因此所述Fc结合剂以高数量有效地展示在EV的表面上，从而使得能够将EV用含有Fc结构域的蛋白质，如抗体致密包被。将EV用抗体和包含Fc结构域的其它蛋白质(天然包含或由于分子生物学工程化而包含)包被出于以下几个原因是有利的：(1)靶向特定细胞类型、组织和/或器官的抗体或其它蛋白质代表了重新引导基于EV的治疗剂的分布和优化基于EV的治疗剂的递送的非常有用的方法；(2)与所关注的靶抗原相互作用的治疗性抗体或其它含有Fc结构域的蛋白质可以使用EV有效地递送到所关注的组织(例如递送到CNS或脑)；(3)在EV的表面上多重化的抗体或其它含有Fc结构域的蛋白质在结合靶标，如靶抗原方面可能显著更好；(4)EV是用于递送抗体-药物缀合物(ADC)或受体-药物缀合物的有利模式，这是因为ADC的多重化可以显著增强它们的治疗功效并且它们在EV上的存在意味着它们也可以进入靶细胞中；(5)包含Fc结合剂的EV促进含有Fc结构域的蛋白质的细胞内化，所述蛋白质诸如抗体、ADC或包含Fc结构域的基本上任何蛋白质(天然包含或由于工程化而包含)；以及(6)将EV用抗体或含有Fc结构域的蛋白质包被可以减少EV的调理作用和/或免疫介导的清除，这可能进而对它们的治疗活性是重要的。

[0009] 在另一个方面，本发明涉及根据本发明的融合蛋白与含有Fc结构域的蛋白质(如抗体和可以与Fc结构域融合的几乎任何生物药物，例如细胞内活性酶，如NPC1或核酸酶Cas9)之间的复合物。如上所述，所述融合蛋白包含与外泌体多肽融合的Fc结合多肽，并且所述Fc结合剂与所述复合物中的所述含有Fc结构域的蛋白质的Fc结构域结合，所述含有Fc结构域的蛋白质可以是所关注的任何蛋白质，例如抗体或包含Fc结构域的任何其它蛋白质(天然包含或由于所考虑的蛋白质的工程化而包含)。由于EV蛋白质的EV运输能力，因此融合蛋白与含有Fc结构域的蛋白质之间的这样的非共价复合物通常存在，例如锚定在EV的膜中，从而使得EV被多个含有Fc结构域的蛋白质包被，所述含有Fc结构域的蛋白质能够发挥它们的生物作用。所述复合物可以另外地或可选地存在于EV内部。

[0010] 在另一个方面，本发明涉及药物组合物，所述药物组合物包含根据本发明的EV和/或非共价复合物，如纳米颗粒复合物(即在内部、在外部和/或在EV膜中被多个至少一种类型的含有Fc的蛋白质修饰的EV)和药学上可接受的载体。在另外的方面，本发明因此还涉及EV、EV-蛋白质复合物、和/或包含这样的EV和EV-蛋白质复合物的药物组合物，其用于医学中，优选地用于治疗将受益于基于抗体或含有Fc结构域的蛋白质的治疗、基于ADC的治疗、和/或抗体介导的靶向的疾病。

[0011] 在另外的方面，本发明涉及用于产生能够与包含Fc结构域的蛋白质结合的EV的方法。这样的方法可以包括以下步骤：(i)向EV来源细胞中引入编码融合蛋白的多核苷酸构建体，所述融合蛋白包含至少一种Fc结合多肽和至少一种外泌体多肽；以及(ii)收获由所述EV来源细胞分泌的EV，所述EV包含所述所关注的融合蛋白。此外，本发明涉及用于将EV用包含Fc结构域的至少一种蛋白质包被的方法，所述方法包括以下步骤：(i)提供包含融合蛋白的EV，所述融合蛋白包含至少一种Fc结合剂和至少一种外泌体多肽；以及(ii)使所述融合蛋白的Fc结合剂结合包含Fc结构域的至少一种蛋白质的Fc结构域。

[0012] 最终，本发明还涉及包含至少一种Fc结合剂和至少一种外泌体多肽的融合蛋白、

以及编码这样的融合蛋白的多核苷酸构建体、以及包含这样的构建体的载体、EV和细胞。

附图说明

[0013] 图1:包含融合蛋白的EV的示意图,所述融合蛋白包含与Fc结合多肽(即Fc结合结构域)融合的外泌体蛋白。所述Fc结合剂能够结合例如抗体和/或包含Fc结构域的任何其它蛋白质,从而将EV转变成蛋白质治疗剂的多价递送载体。

[0014] 图2:EV的电子显微镜照片,包含Fc结合多肽的EV(A)被纳米金标记的抗体(即含有Fc的蛋白质)修饰,而缺乏Fc结合多肽的对照EV(B)没有与它们的表面结合的任何抗体。

[0015] 图3:流式细胞术数据,所述流式细胞术数据显示包含Fc结合多肽的EV结合所关注的含有Fc的蛋白质(人类IgG)。所述结合对于试剂盒中所包括的所有珠粒群体都是非常有效的,包括非特异性/同种型/阴性对照珠粒群体。

[0016] 图4:抗HER2抗体仅在高表达HER2的细胞系MDA-MB-361中与同种型对照修饰的EV和野生型EV相比增加抗体修饰的EV的摄取,而在低表达HER2的细胞系MDA-MB-231中不是这样。

[0017] 图5:与野生型EV或对照修饰的EV相反,依那西普(etanercept)包被的EV保护小鼠防止体重减轻,并且显示出比裸依那西普更高的活性,这可能是因为当依那西普被多重化时和/或当Fc结合多肽与它的Fc结构域结合时依那西普与TNFα之间的亲和力更高。

[0018] 图6:在经过Fc结合EV处理的细胞中明显存在荧光标记的抗体的信号,所述Fc结合EV已经与它们的包含Fc结构域的表面抗体连接,而在未处理的细胞(1)或对照EV处理的细胞(2)中不存在荧光信号,这是通过荧光显微镜术(A)和流式细胞术(B)测量的。这表明诸如抗体的含有Fc的蛋白质可以通过Fc结合EV细胞内递送,并且与EV结合显著增加细胞对抗体的摄取。

[0019] 图7:当通过Fc结合EV(即包含与至少一种外泌体多肽融合的至少一种Fc结合多肽的EV)将抗NFkB抗体递送到细胞中时成功抑制NFkB介导的细胞内信号。

[0020] 图8:对照EV以及用抗整合素-4a抗体进行单次处理在小鼠中显示出防止EAE发展的中度保护作用,而包被有相同的抗整合素-4a抗体的zz结构域EV几乎完全消除体内EAE的发展。

[0021] 图9:用于靶向基因组编辑的CRISPR-Cas9向导RNA复合物的细胞内递送,图表显示在经由Fc结合结构域-Lamp2b工程EV递送Fc Cas9向导RNA复合物之后的靶向基因组切割。

[0022] 图10:与Fc结构域融合并且与包含Fc结合多肽的HEK衍生的EV结合的溶酶体贮积症酶GBA的细胞内递送。

[0023] 图11:在用与Lamp2b-ZZ结构域EV的表面连接的负载siRNA的Ago2对U2OS细胞进行处理之后的细胞周期蛋白D水平,引起显著的靶标沉默。

具体实施方式

[0024] 本发明涉及关于包含融合蛋白的EV的各个方面和实施方案,所述融合蛋白包含与外泌体多肽融合的至少一种Fc结合剂,以使得能够将EV用抗体和其它含有Fc结构域的蛋白质致密包被,所述抗体和其它含有Fc结构域的蛋白质可以被所述Fc结合剂多价螯合并且用于治疗各种疾病和病症的治疗应用。

[0025] 为了方便和清楚起见，在下文收集和描述了本文使用的某些术语。除非另外定义，否则本文所用的所有技术和科学术语的含义与本发明所属领域的普通技术人员通常所了解的含义相同。

[0026] 在本发明的特征、方面、实施方案、或替代方案是用马库什组(Markush group)来描述的情况下，本领域技术人员将认识到的是，本发明也因此用马库什组的任何单个成员或成员的子组来描述。本领域技术人员将进一步认识到的是，本发明也因此用马库什组的单个成员或成员的子组的任何组合来描述。此外，应当指出的是，关于本发明的方面和/或实施方案中的一个所述的实施方案和特征在加以必要的变更的情况下也适用于本发明的所有其它方面和/或实施方案。举例来说，在本文关于包含含有Fc结合多肽的融合蛋白的EV所述的这样的Fc结合多肽应当被理解成公开了本文的所有其它方面、教导以及实施方案，与其相关，并且与其相容，例如涉及用于产生或包被EV的方法或涉及本文所述的多核苷酸和多肽构建体的方面和/或实施方案。此外，关于某些方面所述的某些实施方案，例如，如关于涉及治疗某些医学适应症的方面所述的包含含有Fc结合多肽和外泌体多肽的融合蛋白的EV的施用途径当然也可以与其它方面和/或实施方案相关，如涉及本发明的药物组合物和/或Fc结合多肽-含有Fc的蛋白质复合物的那些。此外，本文所鉴定的所有多肽和蛋白质都可以使用用于将多肽融合的常规策略自由地组合成融合蛋白。作为非限制性实例，本文所述的所有Fc结合多肽都可以与一种或多种外泌体多肽自由地组合成任何组合。此外，Fc结合多肽可以彼此组合以产生包含多于一种Fc结合多肽的构建体。此外，任何和所有特征(例如马库什组的任何和所有成员)都可以与任何和所有其它特征(例如任何其它马库什组的任何和所有成员)自由组合，例如任何Fc结合蛋白可以与任何含有Fc的蛋白质，如任何抗体组合，或任何外泌体多肽可以与任何Fc结合多肽组合。此外，当本文的教导涉及呈单个形式的EV(和/或EV锚定的融合蛋白-含有Fc的蛋白质复合物)和/或作为离散的天然纳米颗粒样囊泡的EV时，应当了解的是，所有这样的教导都同样关于和适用于多个EV和EV群体以及包被有含有Fc的蛋白质的EV。作为一般说明，根据本发明的Fc结合多肽、含有Fc的蛋白质(如抗体)、EV产生细胞来源、外泌体蛋白、以及所有其它方面、实施方案、和替代方案可以在不背离本发明的范围和精神的情况下自由组合成任何和所有可能的组合。此外，本发明的任何多肽或多核苷酸或任何多肽序列或多核苷酸序列(分别是氨基酸序列或核苷酸序列)可以与原始多肽、多核苷酸以及序列显著不同，只要任何给定分子保留实现与其相关的所期望的技术效果的能力即可。只要维持它们的生物学特性，根据本申请的多肽序列和/或多核苷酸序列就可以与天然序列相比相差多达50％(使用例如BLAST或ClustalW计算)，尽管尽可能高的序列同一性是优选的(例如60％、70％、80％、或例如90％或更高)。例如至少一种Fc结合多肽和至少一种外泌体蛋白的组合(融合)意味着对应多肽的某些片段可以被置换和/或修饰和/或所述序列可以因其它氨基酸段的插入而中断，这意味着与天然序列的差异可能是相当大的，只要保留关键特性(例如Fc结合特性、运输到外泌体的表面、治疗活性等)即可。类似的推理因此当然适用于编码这些多肽的多核苷酸序列。本文关于肽、多肽以及蛋白质提到的所有登录号和SEQ ID NO仅应当被看作是实例并且仅供参考，并且所有肽、多肽以及蛋白质都应当被给予它们的如本领域技术人员将对它们所了解的普通含义。因此，如上所述，本领域技术人员还将了解的是，本发明不仅包括本文提到的具体SEQ ID NO和/或登录号，而且还包括其变体和衍生物。本文提到的所有登录号都是根据2017年6月22

日版本的数据库的UniProtKB登录号，并且本文提到的所有蛋白质、多肽、肽、核苷酸以及多核苷酸都应当根据它们的如本领域技术人员所了解的常规含义来解释。

[0027] 术语"细胞外囊泡"或"EV"或"外泌体"在本文可互换使用并且应当被理解成涉及可以任何形式从细胞中获得的任何类型的囊泡，例如微囊泡(例如从细胞的质膜脱落的任何囊泡)、外泌体(例如源自于内溶酶体途径的任何囊泡)、凋亡小体(例如可从凋亡细胞中获得)、微粒(其可能源自于例如血小板)、核外粒体(可源自于例如血清中的中性粒细胞和单核白细胞)、前列腺体(prostatosome)(例如可从前列腺癌细胞中获得)、或心脏体(cardiosome)(例如可源自于心脏细胞)等。EV的尺寸可以显著变化，但是EV通常具有纳米级流体动力学半径，即小于1000nm的半径。显然，EV可以在体内、离体、以及体外源自于任何细胞类型。此外，所述术语还应当被理解为涉及细胞外囊泡模拟物、经由例如膜挤出、超声处理、或其它技术等获得的基于细胞膜的囊泡。对于本领域技术人员来说将清楚的是，当描述EV的医学和科学用途和应用时，本发明通常涉及多个EV，即EV的群体，其可能包含数千个、数百万个、数十亿个或甚至数万亿个EV。如可以从以下实验部分中看到的是，EV可以诸如每单位体积(例如每毫升)10^5个、10^8个、10^{10}个、10^{11}个、10^{12}个、10^{13}个、10^{14}个、10^{15}个、10^{18}个、10^{25}个、10^{30}个EV(常常被称作"颗粒")、或更大、更小或介于两者之间的任何其它数量的浓度存在。同样，术语"群体"应当被理解成包括构成这样的群体的多个实体，所述术语"群体"可以例如涉及包含外泌体多肽与Fc结合多肽之间的某种融合蛋白的EV，所述Fc结合多肽进而可以与所关注的含有Fc的蛋白质结合。换句话说，当以多个存在时，单个EV构成EV群体。因此，当然，本发明涉及单个EV和包含EV的群体这两者，如对于本领域技术人员来说将清楚的那样。当体内施用时EV的剂量当然可以根据待治疗的疾病、施用途径、所关注的含有Fc的蛋白质、EV上存在的任何靶向部分、药物制剂等而显著变化。此外，除了可以与EV表面结合的含有Fc的蛋白质之外，本发明的EV还可以包含另外的治疗剂。在一些实施方案中，所述另外的治疗剂可以是至少一种治疗性小分子药物。在一些实施方案中，所述治疗性小分子药物可以选自由以下各项组成的组：DNA损伤剂、抑制DNA合成的药剂、微管和微管蛋白结合剂、抗代谢物、氧化损伤诱导剂、抗血管生成剂、内分泌治疗、抗雌激素剂、免疫调节剂，如Toll样受体激动剂或拮抗剂；组蛋白脱乙酰酶抑制剂；信号转导抑制剂，如激酶抑制剂；热休克蛋白抑制剂、类视色素、生长因子受体抑制剂、抗有丝分裂化合物、抗炎剂、细胞周期调节剂、转录因子抑制剂、和细胞凋亡诱导剂、以及其任何组合。在另外的实施方案中，所述另外的治疗剂可以是基于治疗性核酸的药剂。这样的基于核酸的治疗剂可以选自包括以下各项的组：单链RNA或DNA、双链RNA或DNA、寡核苷酸，如siRNA；剪接转换RNA、CRISPR向导链、短发夹RNA(shRNA)、微小RNA、反义寡核苷酸、多核苷酸，如mRNA；质粒、或任何其它RNA或DNA载体。特别令人关注的是基于核酸的药剂，其是化学合成的和/或包含化学修饰的核苷酸，如2′-O-Me、2′-O-烯丙基、2′-O-MOE、2′-F、2′-CE、2′-EA 2′-FANA、LNA、CLNA、ENA、PNA、硫代磷酸酯、三环DNA等。在又另外的实施方案中，根据本发明的EV可以包含另外的治疗剂，所述另外的治疗剂可以是蛋白质和/或肽。这样的蛋白质和/或肽可以存在于EV内部、插入EV膜中或与EV膜缔合，或可以从EV突出到囊泡外环境中。这样的治疗性蛋白质和/或肽药剂可以选自包括以下各项的非限制性实例的组：抗体、胞内抗体、单链可变片段(scFv)、亲和体、双特异性和多特异性抗体或结合剂、亲和体、设计的锚蛋白重复蛋白(darpin)、受体、配体、用于例如酶替代治疗或基因编辑的酶、肿瘤抑制因子、病毒或细菌抑制剂、细胞组分蛋白、DNA

和/或RNA结合蛋白、DNA修复抑制剂、核酸酶、蛋白酶、整合酶、转录因子、生长因子、细胞凋亡抑制剂和诱导剂、毒素(例如假单胞菌外毒素)、结构蛋白、神经营养因子,如NT3/4、脑源性神经营养因子(BDNF)以及神经生长因子(NGF)和它的单个亚基,如2.5Sβ亚基;离子通道、膜转运蛋白、蛋白内稳态因子、参与细胞信号传导的蛋白质、翻译和转录相关蛋白、核苷酸结合蛋白、蛋白质结合蛋白、脂质结合蛋白、糖胺聚糖(GAG)和GAG结合蛋白、代谢蛋白、细胞应激调节蛋白、炎症和免疫系统调节蛋白、线粒体蛋白、以及热休克蛋白等。在一个优选的实施方案中,所述治疗剂可以是具有完整核酸酶活性的CRISPR相关(Cas)多肽(如Cas9(作为非限制性实例,登录号:Q99ZW2)),其与RNA链缔合(即携带它),所述RNA链使得所述Cas多肽一旦由EV递送就能够在靶细胞中实现它的核酸酶活性。或者,在另一个优选的实施方案中,Cas多肽可以是无催化活性的,以使得能够进行靶向遗传工程化。又另一个替代方案可以是任何其它类型的CRISPR效应物,如单RNA引导的核酸内切酶Cpf1(来自诸如氨基酸球菌属(Acidaminococcus)或毛螺旋菌科(Lachnospiraceae)的物种)(作为非限制性实例,登录号:U2UMQ6和A0Q7Q2)。另外的优选的实施方案包括选自包括以下各项的组的治疗性蛋白质:用于溶酶体贮积症的酶,例如葡萄糖脑苷脂酶,如伊米苷酶、α-半乳糖苷酶、α-L-艾杜糖苷酸酶、艾杜糖醛酸-2-硫酸酯酶和艾杜硫酶(idursulfase)、芳基硫酸酯酶、加硫酶(galsulfase)、酸性α葡萄糖苷酶、鞘磷脂酶、半乳糖脑苷脂酶、半乳糖神经酰胺酶、葡萄糖神经酰胺酶(作为非限制性实例,登录号:P04062)、神经酰胺酶、α-N-乙酰氨基半乳糖苷酶、β-半乳糖苷酶、溶酶体酸性脂肪酶、酸性鞘磷脂酶、NPC1(作为非限制性实例,登录号:O15118)、NPC2(作为非限制性实例,登录号:P61916)、乙酰肝素磺酰胺酶、N-乙酰氨基葡萄糖苷酶、乙酰肝素-α-氨基葡糖苷-N-乙酰转移酶、N-乙酰葡糖胺6-硫酸酯酶、半乳糖-6-硫酸硫酸酯酶、半乳糖-6-硫酸硫酸酯酶、透明质酸酶、α-N-乙酰神经氨酸酶、GlcNAc磷酸转移酶、粘脂蛋白1、棕榈酰蛋白硫酯酶、三肽基肽酶I、棕榈酰蛋白硫酯酶1、三肽基肽酶1、battenin(CLN3编码蛋白)、linclin、α-D-甘露糖苷酶、β-甘露糖苷酶、天冬氨酰氨基葡萄糖苷酶、α-L-岩藻糖苷酶、胱氨酸病蛋白(cystinosin)、组织蛋白酶K、唾液酸转运蛋白(sialin)、LAMP2、以及氨基己糖苷酶。在其它优选的实施方案中,所述治疗性蛋白质可以是例如调节炎症反应的细胞内蛋白,例如表观遗传蛋白,如甲基化酶和布罗莫结构域;或调节肌肉功能的细胞内蛋白,例如转录因子,如MyoD(作为非限制性实例,登录号:P15172)或Myf5;调节肌肉收缩性的蛋白质,例如肌球蛋白、肌动蛋白、钙/结合蛋白,如肌钙蛋白;或结构蛋白,如抗肌萎缩蛋白(dystrophin)(作为非限制性实例,登录号:P11532)、迷你抗肌萎缩蛋白(作为非限制性实例,登录号:P15172)、肌营养相关蛋白(utrophin)、肌联蛋白、伴肌动蛋白(nebulin)、抗肌萎缩蛋白相关蛋白,如异连蛋白(dystrobrevin)、互生蛋白(syntrophin)、中间丝蛋白(syncoilin)、肌间线蛋白(desmin)、肌聚糖蛋白(sarcoglycan)、肌养蛋白聚糖(dystroglycan)、肌长蛋白(sarcospan)、集聚蛋白(agrin)、和/或福山蛋白(fukutin)。重要的是,所有上述治疗性蛋白质都可以被工程化以含有Fc结构域,以使得能够与EV上存在的Fc结合多肽结合。另一个非限制性实例是Fc结构域融合到酶NPC1上以用于后续递送到靶细胞中。可以用于提高EV递送的含有Fc的蛋白质(例如Fc-Cas9或抗体)的细胞内生物活性的又另一个非限制性实例是使Fc结构域与以下各项融合:内体逃逸肽或蛋白质,如HA2;细胞穿膜肽(CPP),如TAT肽、转运素、穿膜素(peneratin)、聚赖氨酸、或gp41;霍乱毒素、志贺毒素、皂草素、白喉毒素肽等。在EV的表面上展示这样的内

体逃逸结构域可以增强向靶细胞中的内化和后续的内体逃逸。如何可以将Fc结构域融合到所关注的蛋白质上的有利的非限制性实例是将Fc结构域融合到Cas9、Cpf1、非切割Cas变体、或任何其它类型的基因编辑蛋白或核糖核蛋白(RNP)上以用于EV介导的向靶细胞中的递送。在一个优选的实施方案中,Fc结构域在N末端或C末端与Cas9融合,所述Cas9已经在体外预先负载单向导RNA(sgRNA)链(预先负载RNA的Cas形成所谓的核糖核蛋白(RNP)复合物)。然后使由此形成的所得的含有Fc结构域的RNP复合物由合适的EV的Fc结合多肽结合以使它们与EV表面连接,继而递送到靶细胞中。RNP复合物的形成可以通过不同的方式并且使用不同的RNA组分实现,如常规的单向导RNA、包含crRNA和tracrRNA这两者的合成向导RNA,任选地与发夹环、crRNA、tracrRNA、以及其各种组合相组合。用于同源定向重组或非同源末端连接或任何其它修复或置换机制的修复模板也可以被包括在预先形成的RNP中,然后可以使用Fc结构域-Fc结合多肽连接使其与EV连接。

[0028] 如本文所述的术语"抗体"和"mAb"和"Ab"应当被理解为包括完整抗体(即全抗体)以及其具有抗原结合特性的任何衍生物。常规上,抗体指的是包含由二硫键相互连接的至少两条重(H)链和两条轻(L)链的糖蛋白、或其抗原结合部分。每一条重链包含重链可变区(在本文缩写为V_H)和重链恒定区。每一条轻链包含轻链可变区(在本文缩写为V_L)和轻链恒定区。重链和轻链的可变区含有与抗原相互作用的结合结构域。V_H区和V_L区可以进一步细分成被称为互补决定区(CDR)的高变区,与被称为框架区(FR)的更保守的区域交替。重要的是,出于本发明的目的,所关注的抗体优选地具有Fc结构域或其衍生物,所述Fc结构域或其衍生物可以与本发明的Fc结合多肽结合以使得能够包被EV表面。用于本发明中的抗体可以是单克隆抗体(mAb)或多克隆抗体,优选地是mAb。在本发明中特别有用的抗体可以是嵌合抗体、CDR移植抗体、纳米抗体、人类或人源化抗体或其任何衍生物,只要它可以由Fc结合多肽结合即可,所述Fc结合多肽通常包含在根据本发明的融合蛋白中。抗体的产生在本发明的范围之外,但是通常,单克隆抗体和多克隆抗体这两者都是由实验性非人类哺乳动物,如山羊、兔、美洲驼、骆驼科动物、大鼠或小鼠产生的,但是合适的抗体也可以是其它产生方法的结果,例如Kohler和Milstein的标准体细胞杂交技术。在例如小鼠中产生杂交瘤是非常完善的程序并且可以使用本领域公知的技术实现。用于本发明中的抗体可以是人类抗体、人源化抗体、和/或任何类型的嵌合抗体。如本文所用的术语"人类抗体"意图包括具有可变区的抗体,其中框架区和CDR区这两者都源自于人类生殖系免疫球蛋白序列。用于本发明中的人类抗体可以包括并非由人类生殖系免疫球蛋白序列编码的氨基酸残基(例如在体外通过随机诱变或位点特异性诱变或在体内通过体细胞突变引入的突变)。术语"抗体衍生物"指的是抗体的任何修饰形式,例如具有以任何方式修饰的氨基酸序列的抗体、或抗体和另外的药剂或抗体的缀合物、双特异性抗体、多特异性抗体、抗体结构域等。术语"人源化抗体"指的是如下抗体,其中源自于另一种哺乳动物物种,如小鼠、骆驼科动物、美洲驼等的CDR序列已经移植到人类框架序列上。可以在人类框架序列内进行另外的框架区修饰。根据本发明的抗体可以包括所有同种型和亚型,如IgG(例如IgG1、IgG2、IgG3、IgG4、IgG2a、IgG2d、以及IgG2c)、IgA、IgM、IgM、IgD等、以及其单体、二聚体、和低聚物。此外,根据本发明的抗体在展示在EV上时可以具有以下几种功能:(1)抗体可以靶向特定的细胞类型、组织、和/或器官以重新引导基于EV的治疗剂的分布和优化基于EV的治疗剂的递送;(2)与所关注的靶抗原相互作用的治疗性抗体可以使用EV有效地递送到所关注的组织(例如递送到CNS

或脑)；(3)EV表面上多重化的抗体在结合靶抗原方面可以是显著更好的；(4)抗体-药物缀合物(ADC)可以在EV上被多重化以显著增强它们的治疗功效；(5)由Fc结合多肽结合的抗体对靶标可以具有更高的亲和力；(6)包被到根据本发明的EV上的抗体可以细胞内递送；以及(7)将EV用抗体包被可以减少EV的调理作用和/或免疫介导的清除，这可能进而对治疗活性是重要的。

[0029] 术语"含有Fc的蛋白质"和"包含Fc结构域的蛋白质"和"含Fc结构域的蛋白质"和"含有Fc结构域的蛋白质"和"Fc结构域蛋白"和类似术语在本文可互换使用并且应当被理解为涉及任何蛋白质、多肽、或肽(即包含氨基酸序列的任何分子)，其天然包含至少一个Fc结构域或由于对所考虑的蛋白质进行工程化以引入Fc结构域而包含至少一个Fc结构域。Fc表示"可结晶片段"，它是抗体尾区的名称。然而，也可以形成Fc结构域并且将其用于其它蛋白质上，而不仅仅是抗体。这样的含有Fc结构域的蛋白质的非限制性实例包括抗体和抗体衍生物、Fc修饰的诱饵受体和/或信号转导蛋白，如IL1、IL2、IL3、IL4、IL5、IL6(如信号转导蛋白gp130(作为非限制性实例，登录号:P40189))、IL7、IL8、IL9、IL10、IL11、IL12、IL13、IL14、IL15、IL17(如IL17R，其中作为非限制性实例，登录号:Q96F46)、IL23(如IL23R，其中作为非限制性实例，登录号:Q5VWK5)等的白细胞介素诱饵受体、含有Fc结构域的双特异性和多特异性结合剂、任何类型的含有Fc结构域的受体或配体、用于例如酶替代治疗或基因编辑的Fc结构域修饰的酶、上面已经移植有Fc结构域的核酸酶，如Cas和Cas9；与Fc结构域融合的肿瘤抑制因子等。可以与天然缺乏Fc结构域的所关注的蛋白质融合的合适的Fc结构域包括以下非限制性实例:人类IGHM(作为非限制性实例，登录号:P01871)、人类IGHA1(作为非限制性实例，登录号:P01876)、人类IGHA2(作为非限制性实例，登录号:P01877)、人类IGKC(作为非限制性实例，登录号:P01834)、人类IGHG1(作为非限制性实例，登录号:P01857)、人类IGHG2(作为非限制性实例，登录号:P01859)、人类IGHG3(作为非限制性实例，登录号:P01860)、人类IGHG4(作为非限制性实例，登录号:P01861)、人类IGHD(作为非限制性实例，登录号:P01880)、人类IGHE(作为非限制性实例，登录号:P01854)、以及其任何结构域、衍生物、或组合。基本上，所关注的任何蛋白质可以被修饰以包含Fc结构域。上面可以引入有Fc结构域的蛋白质的非限制性实例包括例如肿瘤抑制因子、病毒或细菌抑制剂、细胞组分蛋白、DNA和/或RNA结合蛋白、DNA修复抑制剂、核酸酶、蛋白酶、整合酶、转录因子、生长因子、细胞凋亡抑制剂和诱导剂、毒素(例如假单胞菌外毒素)、结构蛋白、神经营养因子，如NT3/4、脑源性神经营养因子(BDNF)以及神经生长因子(NGF)和它的单个亚基，如2.5Sβ亚基；离子通道、膜转运蛋白、蛋白内稳态因子、参与细胞信号传导的蛋白质、翻译和转录相关蛋白、核苷酸结合蛋白、蛋白质结合蛋白、脂质结合蛋白、糖胺聚糖(GAG)和GAG结合蛋白、代谢蛋白、细胞应激调节蛋白、炎症和免疫系统调节蛋白、线粒体蛋白、以及热休克蛋白等。所关注的蛋白质的上述清单不是详尽的并且其它蛋白质也可能是相关的，只要所述蛋白质包含Fc结构域即可或只要有可能将所考虑的蛋白质进行工程化以包含Fc结构域即可。这样的将蛋白质进行工程化以引入Fc结构域的一个非限制性实例包括将Fc结构域添加到诱饵受体中，例如将Fc结构域添加到Cas酶或Cas9酶上以用于生物活性递送到靶细胞中以使得能够进行基因编辑。这样的将蛋白质进行工程化以引入Fc结构域的另一个非限制性实例包括将Fc结构域添加到用于酶替代治疗的酶上(例如Fc结构域-葡萄糖脑苷脂酶或Fc结构域-α-半乳糖苷酶或Fc结构域-NPC1)。可商购获得的Fc结构域修饰的蛋白质的公知实例是依那西

普,其是用于治疗各种自身免疫性疾病的生物药物,包含融合到TNF受体2上的IgG的Fc结构域。因此,如从上文可以清楚地看出,根据本发明的含有Fc结构域的蛋白质可以基本上是天然含有Fc结构域或由于引入Fc结构域而含有Fc结构域的任何所关注的蛋白质。

[0030] 含有Fc的蛋白质在本文常常被描述为与EV和/或Fc结合多肽"连接"。或者,EV有时被称为被含有Fc的蛋白质"包被"或被称为具有"与它们的表面结合"或"与它们的表面连接"的含有Fc的蛋白质。这些术语在Fc结合多肽与Fc结构域之间的常规相互作用的背景下应当被理解为这两种多肽以产生在Fc结合剂与Fc结构域之间形成的化学键(通常是非共价键)的方式彼此相互作用。因此,这通常意味着包含Fc结合多肽的EV因此具有借助于化学键与它连接的含有Fc的蛋白质的Fc结构域。如本领域技术人员所将了解的那样,当在EV表面上发生结合时,EV因此可以具有与它结合(连接)的多个这样的含有Fc的蛋白质,从而产生包被形式。

[0031] 术语"Fc结合多肽"和"Fc结合蛋白(Fc binding protein)"和"Fc结合剂"和"Fc结合蛋白(Fc-binding protein)"和"结合剂"在本文可互换使用并且应当被理解为涉及可以结合任何所关注的蛋白质的Fc结构域的任何蛋白质、多肽或肽(即包含氨基酸序列的任何分子)。通常,本发明的Fc结合多肽源自于人类或非人类(例如哺乳动物来源、细菌等)的各种来源,它们对各种抗体同种型、亚型、以及种类(例如IgG(在IgG的情况下,作为非限制性实例,IgG1、IgG2、IgG3、IgG4、IgG2a、IgG2d、和/或IgG2c)、IgA、IgM、IgM、IgD等)的Fc结构域具有高亲和力,并且它们可以与EV蛋白融合。除了由本申请所提到的其它Fc结合多肽之外,根据本发明的Fc结合多肽的非限制性实例还包括蛋白A(作为非限制性实例,SEQ ID NO 77)、蛋白G(作为非限制性实例,SEQ ID NO 78)、蛋白A/G(作为非限制性实例,SEQ ID NO 72)、Z结构域(作为非限制性实例,SEQ ID NO 73)、ZZ结构域(作为非限制性实例的SEQ ID NO 73的两个可操作连接的拷贝,即作为非限制性实例,SEQ ID NO 74)、人类FCGRI(作为非限制性实例,SEQ ID NO 31)、人类FCGRIIA(作为非限制性实例,SEQ ID NO 33)、人类FCGRIIB(作为非限制性实例,登录号:31994)、人类FCGRIIC(作为非限制性实例,登录号:31995)、人类FCGRIIIA(作为非限制性实例,登录号:P08637)、人类FCGR3B(作为非限制性实例,登录号:O75015)、人类FCAMR(作为非限制性实例,SEQ ID NO 28)、人类FCERA、人类FCAR、小鼠FCGRI(作为非限制性实例,SEQ ID NO 79)、小鼠FCGRIIB(作为非限制性实例,SEQ ID NO 80)、小鼠FCGRIII(作为非限制性实例,SEQ ID NO 81)、小鼠FCGRIV(作为非限制性实例,SEQ ID NO 82)、小鼠FCGRn(作为非限制性实例,SEQ ID NO 83)、以及其各种组合、衍生物、或替代物。

[0032] 术语"EV蛋白"和"EV多肽"和"外泌体多肽"和"外泌体蛋白"在本文可互换使用并且应当被理解为涉及可以用于将多肽构建体(除了EV蛋白之外,其通常还包含Fc结合多肽)转运到合适的囊泡结构,即转运到合适的EV的任何多肽。更确切地说,这些术语应当被理解为包括使得能够将融合蛋白构建体转运、运输或穿梭到囊泡结构,如EV的任何多肽。这样的外泌体多肽的实例是例如CD9(作为非限制性实例,SEQ ID NO 1)、CD53(作为非限制性实例,SEQ ID NO 2)、CD63(作为非限制性实例,SEQ ID NO 3)、CD81(作为非限制性实例,SEQ ID NO 4)、CD54(作为非限制性实例,SEQ ID NO 5)、CD50(作为非限制性实例,SEQ ID NO 6)、FLOT1(作为非限制性实例,SEQ ID NO 7)、FLOT2(作为非限制性实例,SEQ ID NO 8)、CD49d(作为非限制性实例,SEQ ID NO 9)、CD71(也被称为转铁蛋白受体)(作为非限制性实

例,SEQ ID NO 10)和它的内体分选结构域,即转铁蛋白受体内体分选结构域(作为非限制性实例,SEQ ID NO 23)、CD133(作为非限制性实例,SEQ ID NO 11)、CD138(多配体蛋白聚糖-1)(作为非限制性实例,SEQ ID NO 12)、CD235a(作为非限制性实例,SEQ ID NO 13)、ALIX(作为非限制性实例,SEQ ID NO 14)、多配体蛋白聚糖结合蛋白-1(作为非限制性实例,SEQ ID NO 15)、多配体蛋白聚糖结合蛋白-2(作为非限制性实例,SEQ ID NO 16)、Lamp2b(作为非限制性实例,SEQ ID NO 17)、多配体蛋白聚糖-2(作为非限制性实例,SEQ ID NO 20)、多配体蛋白聚糖-3(作为非限制性实例,SEQ ID NO 21)、多配体蛋白聚糖-4(作为非限制性实例,SEQ ID NO 22)、TSPAN8、TSPAN14、CD37、CD82、CD151、CD231、CD102、NOTCH1、NOTCH2、NOTCH3、NOTCH4、DLL1、DLL4、JAG1、JAG2、CD49d/ITGA4、ITGB5、ITGB6、ITGB7、CD11a、CD11b、CD11c、CD18/ITGB2、CD41、CD49b、CD49c、CD49e、CD51、CD61、CD104、Fc受体、白细胞介素受体、免疫球蛋白、MHC-I组分或MHC-II组分、CD2、CD3ε、CD3ζ、CD13、CD18、CD19(作为非限制性实例,SEQ ID NO 26)、CD30(作为非限制性实例,SEQ ID NO 27)、TSG101、CD34、CD36、CD40、CD40L、CD44、CD45、CD45RA、CD47、CD86、CD110、CD111、CD115、CD117、CD125、CD135、CD184、CD200、CD279、CD273、CD274、CD362、COL6A1、AGRN、EGFR、GAPDH、GLUR2、GLUR3、HLA-DM、HSPG2、L1CAM、LAMB1、LAMC1、LFA-1、LGALS3BP、Mac-1α、Mac-1β、MFGE8、SLIT2、STX3、TCRA、TCRB、TCRD、TCRG、VTI1A、VTI1B、其它外泌体多肽、以及其任何组合,但是能够将多肽构建体转运到EV的许多其它多肽被包括在本发明的范围内。通常,在本发明的许多实施方案中,至少一种外泌体多肽与至少一种Fc结合多肽融合,以形成存在于EV中的融合蛋白。这样的融合蛋白还可以包含各种其它组分以优化它们的一种或多种功能,包括接头、跨膜结构域、胞质结构域、多聚化结构域等。

[0033] 术语"来源细胞"或"EV来源细胞"或"亲本细胞"或"细胞来源"或"EV产生细胞"或任何其它类似术语应当被理解为涉及能够在合适的条件下,例如在悬浮培养中或在贴壁培养中或在任何其它类型的培养系统中产生EV的任何类型的细胞。根据本发明的来源细胞还可以包括在体内产生外泌体的细胞。根据本发明的来源细胞可以选自广泛的细胞和细胞系,例如间充质干细胞或基质细胞或成纤维细胞(可从例如骨髓、脂肪组织、脐带胶样组织(Wharton's jelly)、围产期组织、牙蕾、脐带血、皮肤组织等获得)、羊膜细胞,更确切地说是任选地表达各种早期标志物的羊膜上皮细胞;髓系抑制细胞、M2极化巨噬细胞、脂肪细胞、内皮细胞、成纤维细胞等。特别令人关注的细胞系包括人类脐带内皮细胞(HUVEC)、人类胚肾(HEK)细胞、内皮细胞系,如微血管或淋巴管内皮细胞;软骨细胞、不同来源的MSC、气道或肺泡上皮细胞、成纤维细胞、内皮细胞等。此外,免疫细胞,如B细胞、T细胞、NK细胞、巨噬细胞、单核白细胞、树突状细胞(DC)也在本发明的范围内,并且能够产生EV的基本上任何类型的细胞也被包括在本文中。一般来说,EV可以源自于基本上任何细胞来源,无论它是原代细胞来源还是永生化细胞系。EV来源细胞可以是任何胚胎干细胞、胎儿干细胞、以及成体干细胞类型,包括诱导多潜能干细胞(iPSC)和通过任何方法获得的其它干细胞。当治疗神经系统疾病时,可以考虑使用例如原代神经元、星形胶质细胞、少突胶质细胞、小胶质细胞、以及神经祖细胞作为来源细胞。来源细胞在性质上对于待治疗的患者来说可以是同种异体的、自体的、或甚至异种的,即所述细胞可以来自患者本身或来自无关、匹配或不匹配的供体。在某些情况下,从医学角度来看,同种异体细胞可能是优选的,这是因为它们可以提供免疫调节作用,这可能不可从患有某种适应症的患者的自体细胞获得。举例来说,在治疗全

身性、外周和/或神经系统炎症的情况下，同种异体MSC可能是优选的，这是因为可从这些细胞获得的EV可以使得能够经由例如巨噬细胞和/或中性粒细胞表型转换(分别从促炎性M1表型或N1表型转换成抗炎性M2表型或N2表型)来进行免疫调节。

[0034] 在第一个方面，本发明涉及包含融合蛋白的EV，其中所述融合蛋白包含与外泌体多肽融合的至少一种Fc结合多肽。由于与EV蛋白融合，因此Fc结合多肽被有效地转运到EV并且以高数量展示在EV的表面上，这使得能够随后将EV用各种类型的含有Fc的蛋白质包被，所述含有Fc的蛋白质通常是具有Fc结构域的治疗性蛋白质、靶向抗体、治疗性抗体、抗体-药物缀合物、和/或在体内被动结合或有意选择以减少免疫细胞的调理作用和识别(以延长EV的循环时间)的抗体。

[0035] 因此，在一个实施方案中，根据第一个方面的EV具有与它结合的多个含有Fc的蛋白质，所述结合是经由Fc结合多肽与所述多个含有Fc的蛋白质的Fc结构域之间的相互作用而实现的，其中所述多个含有Fc的蛋白质可以是相同的或不同的。所述EV可以经由Fc结合剂与包含Fc结构域的至少一种蛋白质之间的非共价相互作用而包被有多个包含Fc结构域的蛋白质。所述多个可以是至少10个、至少20个或至少30个包含Fc结构域的蛋白质。

[0036] 在本发明的一个实施方案中，所述Fc结合剂是非人类来源的，它们可以例如从细菌、病毒、或非人类哺乳动物获得。在另一个实施方案中，所述Fc结合剂是人类或哺乳动物来源的。在优选的实施方案中，所述至少一种Fc结合多肽可以选自包括以下各项的组：蛋白A(作为非限制性实例，SEQ ID NO 77)、蛋白G(作为非限制性实例，SEQ ID NO 78)、蛋白A/G(作为非限制性实例，SEQ ID NO 72)、Z结构域(作为非限制性实例，SEQ ID NO 73)、ZZ结构域(作为非限制性实例，SEQ ID NO 74)、蛋白L(作为非限制性实例，pdb id no 1HEZ)、蛋白LG、人类FCGRI(作为非限制性实例，SEQ ID NO 31)、人类FCGR2A(作为非限制性实例，登录号：P12318)、人类FCGR2B(作为非限制性实例，登录号：P31994)、人类FCGR2C(作为非限制性实例，登录号：P31994)、人类FCGR3A(作为非限制性实例，登录号：P08637)、人类FCGR3B(作为非限制性实例，登录号：O75015)、人类FCGRB(作为非限制性实例，登录号：Q92637)(作为非限制性实例，SEQ ID NO 32)、人类FCAMR(作为非限制性实例，SEQ ID NO 28)、人类FCERA(作为非限制性实例，SEQ ID NO 30)、人类FCAR(作为非限制性实例，SEQ ID NO 29)、小鼠FCGRI(作为非限制性实例，SEQ ID NO 79)、小鼠FCGRIIB(作为非限制性实例，SEQ ID NO 80)、小鼠FCGRIII(作为非限制性实例，SEQ ID NO 81)、小鼠FCGRIV(作为非限制性实例，SEQ ID NO 82)、小鼠FCGRn(作为非限制性实例，SEQ ID NO 83)、以及上述Fc结合多肽中的任一种的任何组合。已经由例如噬菌体展示筛选和经由生物信息学获得的其它合适的Fc结合多肽包括Fc结合肽SPH(作为非限制性实例，SEQ ID NO 57)、SPA(作为非限制性实例，SEQ ID NO 58)、SPG2(作为非限制性实例，SEQ ID NO 59)、SpA模拟物1(作为非限制性实例，SEQ ID NO 60)、SpA模拟物2(作为非限制性实例，SEQ ID NO 61)、SpA模拟物3(作为非限制性实例，SEQ ID NO 62)、SpA模拟物4(作为非限制性实例，SEQ ID NO 63)、SpA模拟物5(作为非限制性实例，SEQ ID NO 64)、SpA模拟物6(作为非限制性实例，SEQ ID NO 65)、SpA模拟物7(作为非限制性实例，SEQ ID NO 66)、SpA模拟物8(作为非限制性实例，SEQ ID NO 69)、SpA模拟物9(作为非限制性实例，SEQ ID NO 70)、SpA模拟物10(作为非限制性实例，SEQ ID NO 71)、Fcγ模拟物1(作为非限制性实例，SEQ ID NO 67)、以及Fcγ模拟物2(作为非限制性实例，SEQ ID NO 68)、以及其任何组合或衍生物。用于特定构建体的最合适的Fc结合多肽的

选择在很大程度上取决于所期望的结合特征、亲和力、当与外泌体多肽融合时Fc结合多肽的取向、以及各种其它因素。

[0037] 蛋白A/G是包含7个Fc结合结构域EDABC-C1C3的重组遗传工程蛋白，其中蛋白A部分是从金黄色葡萄球菌片段E、D、A、B以及C获得的，并且蛋白G部分是从链球菌片段C1和C3获得的。有利的是，蛋白A/G(作为非限制性实例，SEQ ID NO 72)比单独的蛋白A(作为非限制性实例，SEQ ID NO 77)或蛋白G(作为非限制性实例，SEQ ID NO 78)具有更广泛的结合能力并且它对来自各种物种的抗体具有广泛的结合亲和力。蛋白A/G结合各种人类、小鼠以及大鼠IgG亚类，如人类IgG1、IgG2、IgG3、IgG4；小鼠IgG2a、IgG2b、IgG3；以及大鼠IgG2a、IgG2c。此外，蛋白A/G结合来自牛、山羊、绵羊、马、兔、豚鼠、猪、狗以及猫的总IgG。蛋白A/G已经被工程化以去除细胞壁结合区、细胞膜结合区以及白蛋白结合区以使得能够与所关注的蛋白质的Fc结构域进行强结合。因此，在根据本发明的有利的实施方案中，Fc结合剂包含多于一个Fc结合区，蛋白A、蛋白G、以及蛋白A/G也是这样。在一个替代性实施方案中，Fc结合剂可以倍增以使得能够与所关注的抗体的多于一个拷贝结合。举例来说，短Z结构域Fc结合剂可以经由可操作的连接以多于一个拷贝包括在融合蛋白中，从而允许与多于一个Fc结构域结合。通过这种方式，有可能不仅在单独的融合蛋白之间，而且还在一个单一的融合蛋白内，将抗体和其它含有Fc结构域的蛋白质多重化，从而可以结合多于一个抗体。举例来说，当将Fc结合多肽引入属于四次跨膜蛋白家族的EV蛋白(如CD63)中时，可能有利的是，将一个Fc结合剂插入在蛋白质的一个环上并且将另一个Fc结合剂(其可以是相同的或不同的)插入在蛋白质的另一个环上。Fc结合剂可以被放置在面向内和/或面向外的环上，这取决于含有Fc的蛋白质是意图负载到EV的内腔中还是负载到EV的表面上。根据本发明的融合蛋白的一些非限制性实例可以如下示意性地描述(以下符号不应当被视为说明任何C末端和/或N末端方向，它仅意图用于说明目的)：

[0038] 外泌体多肽-Fc结合多肽-Fc结合多肽

[0039] 外泌体多肽结构域-Fc结合多肽-外泌体多肽结构域-Fc结合多肽

[0040] 外泌体多肽结构域-Fc结合多肽A-外泌体多肽结构域-Fc结合多肽B

[0041] 在一些实施方案中，包含外泌体多肽和Fc结合多肽的融合蛋白还可以含有另外的多肽、多肽结构域或序列。这些另外的多肽结构域可以发挥各种功能，例如这些结构域可以(i)有助于增强融合蛋白的EV表面展示；(ii)引起融合蛋白聚簇，从而提高Fc结合多肽的亲合力；(iii)充当接头以优化外泌体多肽与Fc结合多肽之间的相互作用；和/或(iv)提高在EV膜中的锚定、以及各种其它功能。可以有利地部分或全部包括在本发明的融合蛋白中的两种这样的另外的多肽是gp130(作为非限制性实例，SEQ ID NO 18)和肿瘤坏死因子受体1(TNFR1)(作为非限制性实例，SEQ ID NO 19)。具体来说，这些另外的多肽的跨膜结构域对于优化向EV膜中的插入和Fc结合多肽的展示可能是非常有用的。总之，各种跨膜结构域作为融合蛋白中的另外的结构域可能是非常有利的。举例来说，当使用外泌体蛋白多配体蛋白聚糖结合蛋白时，非常有利的是，在融合蛋白的多配体蛋白聚糖结合蛋白与Fc结合多肽之间插入另外的多肽结构域，如TNFR的跨膜结构域或gp130的跨膜结构域。另外的其它结构域可以包括多聚化结构域，如fold-on结构域、亮氨酸拉链结构域和/或三聚化结构域，以增加表面展示和/或亲合力。其非限制性示意性实例示于下文中：

[0042] 多配体蛋白聚糖结合蛋白-胞质TNRF-Foldon三聚化结构域-跨膜TNFR结构域-Z结

构域-细胞外TNFR结构域

[0043] 多配体蛋白聚糖-亮氨酸拉链结构域-gp130胞质结构域-gp130跨膜结构域-Fc结合多肽-gp130细胞外结构域

[0044] 在另一个实施方案中，外泌体多肽可以选自包括以下各项的组：CD9、CD53、CD63、CD81、CD54、CD50、FLOT1、FLOT2、CD49d、CD71、CD133、CD138、CD235a、ALIX、多配体蛋白聚糖结合蛋白-1、多配体蛋白聚糖结合蛋白-2、Lamp2b、TSPAN8、多配体蛋白聚糖-1、多配体蛋白聚糖-2、多配体蛋白聚糖-3、多配体蛋白聚糖-4、TSPAN14、CD37、CD82(作为非限制性实例，SEQ ID NO 24)、CD151、CD231、CD102、NOTCH1、NOTCH2、NOTCH3、NOTCH4、DLL1、DLL4、JAG1、JAG2、CD49d/ITGA4、ITGB5、ITGB6、ITGB7、CD11a、CD11b、CD11c、CD18/ITGB2、CD41、CD49b、CD49c、CD49e、CD51、CD61、CD104、Fc受体、白细胞介素受体、免疫球蛋白、MHC-I组分或MHC-II组分、CD2、CD3ε、CD3ζ、CD13、CD18、CD19、CD30、CD34、CD36、CD40、CD40L、CD44、CD45、CD45RA、CD47、CD86、CD110、CD111、CD115、CD117、CD125、CD135、CD184、CD200、CD279、CD273、CD274、CD362、COL6A1、AGRN、EGFR、GAPDH、GLUR2、GLUR3、HLA-DM、HSPG2、L1CAM、LAMB1、LAMC1、LFA-1、LGALS3BP、Mac-1α、Mac-1β、MFGE8(作为非限制性实例，SEQ ID NO 25)、SLIT2、STX3、TCRA、TCRB、TCRD、TCRG、VTI1A、VTI1B、其它外泌体多肽、以及其任何组合。

[0045] 根据本发明的特别有利的融合蛋白可以包含人类外泌体蛋白CD63、CD81、CD9、CD71(转铁蛋白受体)、Lamp2、以及多配体蛋白聚糖结合蛋白，其与以下Fc结合多肽的至少一个拷贝融合：Z结构域、蛋白A、蛋白G、蛋白A/G、FCGRI、人类FCGR2A、人类FCGR2B、人类FCGR2C、人类FCGR3A、人类FCGR3B、人类FCGR3C、人类FCAMR、人类FCAR、以及人类FCERA。确切地说，使两个Z结构域与EV蛋白CD63(作为非限制性实例，SEQ ID NO 3)融合会产生非常强效的Fc结合剂，其由于Z结构域的小尺寸和CD63的高EV表面表达而在EV的表面上大量展示。Fc结合剂在EV的外表面上展示当然是优选的以使得能够外源性结合含有Fc结构域的所关注的蛋白质。在CD63-ZZ结构域融合蛋白的情况下，Z结构域可以插入CD63的第一环和第二环中，以使得能够在CD63锚定到EV膜中之后在外EV表面上展示。此外，如上所述，合适的另外的多肽和多肽结构域和接头也可以被包括在融合蛋白中，所述融合蛋白通常包含外泌体多肽和Fc结合多肽。这些另外的多肽包括来自各种细胞因子受体(如TNFR1和TNFR2)、IL6信号转导蛋白gp130、以及各种其它细胞因子和细胞因子相关多肽的结构域。在某些情况下，细胞因子和细胞因子相关多肽(如各种细胞因子受体)可能单独能够将Fc结合多肽转运到EV。特别有用的接头是多个小而具有柔性的氨基酸和/或小而具有柔性的氨基酸的组合，如甘氨酸(G)和丝氨酸(S)，通常表示为GS，例如2×GS或4×GS。也可以在C末端和N末端添加用于简化纯化和测定的His标签，并且也可以添加各种荧光蛋白，如GFP。以下是融合蛋白的特别有利的非限制性实例，所述融合蛋白包含至少一种外泌体多肽和至少一种Fc结合多肽，其常常经由接头连接并且任选地包括一种或多种另外的多肽或多肽结构域：

[0046] • CD81-蛋白A/G CD81第二环(作为非限制性实例，SEQ ID NO 75)

[0047] • CD9-ZZ结构域CD9第二环(作为非限制性实例，SEQ ID NO 76)

[0048] • FCAR细胞外结构域-2×GGGgS接头-Lamp2b(作为非限制性实例，SEQ ID NO 55)

[0049] • FCAR细胞外结构域-4×GS接头-Lamp2b(作为非限制性实例，SEQ ID NO 54)

[0050] • FCGR1A细胞外结构域-2×GGGgS接头-Lamp2b(作为非限制性实例，SEQ ID NO 49)

[0051] • FCGR1A细胞外结构域-4×GS接头-Lamp2b(作为非限制性实例,SEQ ID NO 48)

[0052] • FcRN细胞外结构域-4×GS接头-Lamp2b(作为非限制性实例,SEQ ID NO 39)

[0053] • FcRN-2×GGGgS接头-Lamp2b(作为非限制性实例,SEQ ID NO 40)

[0054] • Gp130细胞外结构域-2×GGGGS接头-FCAR细胞外结构域-Gp130跨膜结构域-亮氨酸拉链-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 52)

[0055] • Gp130细胞外结构域-2×GGGGS接头-FCGR1A细胞外结构域-Gp130跨膜结构域-亮氨酸拉链-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 46)

[0056] • Gp130细胞外结构域-2×GGGGS接头-FcRN细胞外结构域-Gp130跨膜结构域-亮氨酸拉链-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 43)

[0057] • Gp130细胞外结构域-2×GGGGS接头-Z结构域-Gp130跨膜结构域-亮氨酸拉链-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 34)

[0058] • 转铁蛋白受体-2×GGGGS接头-FCAR细胞外结构域(作为非限制性实例,SEQ ID NO 56)

[0059] • 转铁蛋白受体-2×GGGGS接头-FCGR1A细胞外结构域(作为非限制性实例,SEQ ID NO 50)

[0060] • 转铁蛋白受体-2×GGGGS接头-FcRN细胞外结构域(作为非限制性实例,SEQ ID NO 41)

[0061] • 转铁蛋白受体-2×GGGGS接头-Z结构域(作为非限制性实例,SEQ ID NO 38)

[0062] • CD63-FCAR细胞外结构域CD63第一环和CD63第二环(作为非限制性实例,SEQ ID NO 53)

[0063] • CD63-FCGR1A细胞外结构域CD63第一环和CD63第二环(作为非限制性实例,SEQ ID NO 47)

[0064] • CD63-FcRN细胞外结构域CD63第一环和CD63第二环(作为非限制性实例,SEQ ID NO 44)

[0065] • CD63-Z结构域CD63第一环和CD63第二环(作为非限制性实例,SEQ ID NO 35)

[0066] • TNFR细胞外结构域-2×GGGGS接头-FCAR细胞外结构域-TNFR跨膜结构域-foldon-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 51)

[0067] • TNFR细胞外结构域-2×GGGGS接头-FCGR1A细胞外结构域-TNFR跨膜结构域-foldon-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 45)

[0068] • TNFR细胞外结构域-2×GGGGS接头-FcRN细胞外结构域-TNFR跨膜结构域-foldon-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 42)

[0069] • TNFR细胞外结构域-2×GGGGS接头-Z结构域-TNFR跨膜结构域-foldon-N末端多配体蛋白聚糖结合蛋白(作为非限制性实例,SEQ ID NO 33)

[0070] • Z结构域-2×GGGgS接头-Lamp2b(作为非限制性实例,SEQ ID NO 37)

[0071] • Z结构域-4×GS接头-Lamp2b(作为非限制性实例,SEQ ID NO 36)

[0072] • 转铁蛋白受体-蛋白AG(作为非限制性实例,可操作地与作为非限制性实例的SEQ ID NO 72融合的SEQ ID NO 10)

[0073] 上述融合蛋白仅仅是本发明允许的许多工程化可能性的实例,并且因而,它们仅仅是本发明的非限制性实施方案。根据本发明的融合蛋白的所有组分都可以自由组合,例

如,所述融合蛋白可以含有一个或几个外泌体多肽,其可以被放置在融合蛋白的C末端、N末端、或这两者、或任何位置处。此外,所述融合蛋白还可以含有一个或几个Fc结合多肽,其可以被放置在融合蛋白的C末端、N末端、或这两者、或例如跨膜部分的任何环中的一个或多个上、或任何位置处。为了清楚起见,在单个构建体中可以包含多于一种类型的外泌体多肽和多于一种类型的Fc结合多肽。此外,可以包括另外的氨基酸段,如接头(常常包含氨基酸甘氨酸和丝氨酸)和His标签以简化纯化、测定以及可视化。此外,在融合蛋白序列中的任何位置处还可以包括其它肽和多肽结构域。举例来说,可以有利地包括来自各种细胞因子受体的各种结构域和区域,例如TNFR1、TNFR2、IL17R、IL23R、gp130、IL6R等的各种结构域。

[0074] 在另一个实施方案中,Fc结合多肽可以如上所述与包含Fc结构域的任何蛋白质结合,所述蛋白质不仅可以是抗体,而且还可以是包含Fc结构域的其它蛋白质,它们可以是天然存在的和工程化的含有Fc结构域的蛋白质,如上文在几个实例中提到的蛋白质。有利的是,本发明产生包被有多个包含Fc结构域的蛋白质的EV,所述包被是经由Fc结合多肽与至少一种含有Fc的蛋白质之间的相互作用而实现的。Fc结合剂与含有Fc的蛋白质之间的相互作用通常是基于Fc结合多肽与含有Fc的蛋白质的Fc结构域之间的非共价键。当然,一个单一的EV可以包被有多于一种类型的含有Fc结构域的蛋白质。在一个非限制性实例中,Fc结合EV包被有沿PD1轴靶向合适的靶标的一种抗体,而另一种抗体沿CTLA4轴靶向合适的靶标。在另一个非限制性实例中,Fc结合EV包被有靶向肿瘤细胞表面受体的抗体和与Fc结构域融合的Cas9。正如通常情况那样,一个单一的EV也可以包含很多个一种单一类型的含有Fc结构域的蛋白质,如一种类型的单克隆抗体。靶向抗体、治疗性抗体、含有Fc的所关注的非抗体治疗性蛋白质、抗体-药物缀合物(ADC)、以及用于减少调理作用和/或免疫细胞介导的清除的抗体的各种组合构成本发明的优选的实施方案。在有利的实施方案中,根据本发明的EV包被有多个包含Fc结构域的蛋白质。举例来说,当使用高表达的EV蛋白,如CD63或CD81或多配体蛋白聚糖结合蛋白时,可以实现EV表面的非常致密的包被。因此,本发明可以包被有至少10个包含Fc结构域的蛋白质,优选地至少20个包含Fc结构域的蛋白质,甚至更优选地至少30个包含Fc结构域的蛋白质。这些蛋白质可以是相同蛋白质的拷贝(例如50个依那西普分子包被一个EV)或多于一种蛋白质的拷贝(例如30个依那西普分子和30个gp130-Fc结构域融合蛋白包被一个EV)。通过选择EV蛋白和Fc结合剂的最佳组合,有可能进一步增加展示,在某些情况下,有可能将EV用多于50个包含Fc结构域的蛋白质,或甚至多于约75个包含Fc结构域的蛋白质包被。

[0075] 在另一个方面,本发明还涉及包含展示多肽与Fc结合多肽之间的融合蛋白的细胞。展示多肽通常可以是跨膜蛋白。各种外泌体多肽可以用于该目的,并且常规的细胞跨膜蛋白,如T细胞受体跨膜结构域;白细胞介素受体、转铁蛋白受体、锡蛋白、肌脂蛋白、受磷蛋白、以及各种其它膜蛋白,如通道和同向转运蛋白/内向转运蛋白也可以用于该目的,它们可以将Fc结合多肽转运到细胞膜以用于在细胞膜的外部或内部展示,这取决于所关注的含有Fc的蛋白质将要存在于细胞内部还是展示在细胞表面上。在一个优选的实施方案中,含有Fc的蛋白质是抗体并且所述细胞是预期用于细胞治疗的细胞,如嵌合抗原受体(CAR)T细胞。使用这种方法,细胞可以靶向所关注的特定组织,在CAR-T细胞的情况下,所述所关注的组织可能是肿瘤组织。在免疫调节细胞,如MSC的情况下,所述所关注的组织可能是炎症和/或损伤的部位。本文的所有抗体和其它含有Fc的蛋白质出于与对于EV相同的原因同样适用

于展示在细胞上。

[0076] 在另一个方面，本发明涉及一种复合物，所述复合物是在融合蛋白与包含Fc结构域的蛋白质之间形成的，所述融合蛋白包含(i)外泌体多肽和(ii)Fc结合多肽。根据本发明的EV因此通常包含多个这样的复合物，并且通常，更高数量的这样的复合物在EV上展示而没有与例如空间位阻相关的问题，从治疗和/或靶向观点来看，所述EV变得更强效。这样的融合蛋白-含有Fc的蛋白质复合物通常存在于EV的脂质膜中，这是借助于介导向外泌体膜中的转运和锚定的外泌体蛋白的存在而实现的。然而，所述复合物也可以存在于其它脂质膜中，例如细胞膜或细胞器的膜。根据本发明的EV还与含有Fc的蛋白质形成一种类型的纳米颗粒复合物。通常，如上所述，包含Fc结合多肽的每一个EV与多个含有Fc的蛋白质结合，这产生包被(修饰)有和/或含有多个所关注的含有Fc的蛋白质的EV。其实例是允许经由与抗体一起孵育而与这样的抗体结合的Fc结合EV在它们的表面上被多个抗体修饰，例如每个EV至少10个抗体，或更经常，每个EV至少20个或30个抗体。因此，这种EV-抗体复合物构成一种类型的纳米颗粒复合物，其对于靶向、治疗、以及细胞内递送具有显著的效用。

[0077] 重要的是，本发明还提供了一种以内源性方式将含有Fc的蛋白质负载到EV中的方法。这样的内源性负载方法包括使以下各项在EV产生细胞中共表达：(i)包含外泌体多肽和Fc结合多肽的融合蛋白；以及(ii)包含Fc结构域的所关注的蛋白质。与Fc结合结构域融合的外泌体多肽使得能够将融合蛋白主动分选到EV产生细胞中的EV中，并且Fc结合蛋白的存在使得所述融合蛋白能够将含有Fc的蛋白质拖曳(转运)到EV中。如上所述，各种外泌体蛋白可以用于将融合蛋白分选到EV中，特别是在内源性负载的情况下，蛋白质的选择是非常重要的。可溶性EV蛋白，如Alix和多配体蛋白聚糖结合蛋白可以适用于负载意图可溶于靶环境中的含有Fc的蛋白质，如优选地可溶于靶细胞内的Cas9。然而，含有Fc的蛋白质的内源性负载也可以使用跨膜和/或膜相关EV蛋白，如CD9、CD81、CD63等来实现。当使用膜结合的外泌体蛋白进行内源性负载时，Fc结合多肽改为被放置在EV膜的内腔侧上的环上而不是囊泡外侧上，从而使得能够进行内腔负载而不是囊泡外负载。根据本发明的EV因此通常包含多个这样的融合蛋白-含有Fc结构域的蛋白质复合物(″多个″应当被理解为涉及相同的含有Fc结构域的蛋白质的多个拷贝或几个不同的含有Fc结构域的蛋白质)，其在内部或外部锚定在EV膜中或与EV膜缔合，或在EV的内腔中呈基本上可溶形式。

[0078] 在另一个方面，本发明涉及用于产生EV的方法，所述EV能够与包含Fc结构域的蛋白质结合，如抗体和被工程化以包含Fc结构域的蛋白质。这样的方法通常包括以下步骤：(i)向EV来源细胞中引入编码融合蛋白的多核苷酸构建体，所述融合蛋白包含至少一种Fc结合多肽和至少一种外泌体多肽；以及(ii)收集已经由所述EV产生来源细胞分泌的EV，其中所述EV包含已经从所述多核苷酸构建体表达的融合蛋白。在后续的步骤中，可以使用合适的纯化技术将包含融合蛋白的EV纯化，继而使其暴露于含有Fc结构域的蛋白质，如抗体，以使得能够经由Fc结合多肽与所关注的蛋白质的Fc结构域之间的相互作用来结合含有Fc的蛋白质。如上所述，在一个替代性实施方案中，步骤(i)还可以包括在相同的EV来源细胞中从多核苷酸构建体表达所关注的含有Fc的蛋白质，从而实现EV的内源性负载。所述融合蛋白(在外泌体多肽与Fc结合多肽之间)和含有Fc的蛋白质可以从同一多核苷酸构建体或不同的多核苷酸构建体表达，这取决于构建体设计。

[0079] 在又另一个方面，本发明涉及一种用于使至少一种包含Fc结构域的蛋白质，如抗

体与EV连接的方法。在一个实施方案中，所述方法用于将EV用所述至少一种包含Fc结构域的蛋白质包被。这样的方法包括以下步骤：(i)提供包含融合蛋白的EV，所述融合蛋白包含与至少一种外泌体多肽融合的至少一种Fc结合蛋白；以及(ii)使所述融合蛋白的Fc结合蛋白结合至少一种包含Fc结构域的蛋白质的Fc结构域。用于产生根据本发明的包含融合蛋白的EV的EV来源细胞可以用产生携带融合蛋白-含有Fc的蛋白质复合物的EV所需的多核苷酸构建体稳定转染或瞬时转染。稳定的转染是有利的，这是因为它能够建立主细胞库(MCB)和工作细胞库(WCB)。然而，瞬时转染在某些情况下也是有利的，例如当评估不同的构建体时或例如当快速建立包括从患者自身的EV产生细胞获得的EV的自体治疗时。

[0080] 在另一个方面，本发明涉及用于在体外、离体或体内将所关注的蛋白质递送到靶细胞的细胞内环境中的方法。这样的方法包括以下步骤：(i)提供包含至少一种Fc结合多肽的EV；(ii)使所述包含Fc结合多肽的EV与含有Fc的蛋白质接触，以使得EV中所包含的Fc结合多肽与含有Fc的蛋白质的Fc结构域之间能够结合；以及(iii)使EV与一种或多种含有Fc的蛋白质之间形成的复合物(即经由Fc结合多肽与Fc结构域之间的相互作用而连接有至少一种含有Fc的蛋白质的EV)与一种或多种靶细胞接触。在一个优选的实施方案中，在融合蛋白中包含Fc结合多肽以及至少一种外泌体多肽，但是任选地还包含其它多肽和结构域。由于EV内化到靶细胞中的独特能力，因此含有Fc的蛋白质也将被内化。这是非常有利的并且开放了细胞内空间以递送几乎任何基于蛋白质的治疗剂。如上所述，含有Fc的蛋白质的EV介导的内化在体内和体外都发生，并且这些方法因此可以对治疗开发具有显著的影响，而且也用于研究和诊断目的。

[0081] 在另一个方面，本发明涉及EV用作抗体和其它所关注的含有Fc结构域的蛋白质的递送载体的用途。此外，本发明还提供了与含有Fc的蛋白质连接的EV用作其它所关注的治疗剂的递送载体的用途。作为非限制性实例，在表面上连接有靶向抗体的EV还可以含有另外的治疗剂，所述另外的治疗剂可以存在于EV内部和/或EV膜中。举例来说，抗体包被的EV可以用于将RNA治疗剂运载物(如mRNA、siRNA、寡核苷酸等)递送到靶细胞、组织和/或器官中。在另一个非限制性实例中，在表面上连接有含有Fc的靶向蛋白(如已经被工程化以含有Fc结构域的scFv)并且在EV内部或在EV膜中/上包含治疗性蛋白质，如用于基因编辑的Cas9，任选地连同CRISPR RNA向导链一起的EV。

[0082] 在另外的方面，本发明的方法还可以包括使EV来源细胞暴露于血清饥饿、缺氧、巴弗洛霉素(bafilomycin)、或细胞因子，如TNF-α和/或IFN-γ，以影响所得的EV的产量或特性。EV的生产规模和时间线将在很大程度上取决于EV产生细胞或细胞系并且因此可以由本领域技术人员相应地进行调整。根据本发明的方法还可以包括EV纯化步骤，其可以在将包含融合蛋白的EV与待连接到(例如包被到)EV上的含有Fc结构域的蛋白质(如抗体)共孵育之前进行。EV可以经由选自包括以下各项的一组技术的程序纯化：液相色谱法(LC)、高效液相色谱法(HPLC)、珠粒洗脱色谱法、旋转过滤、切向流过滤(TFF)、中空纤维过滤、离心、免疫沉淀、流场分级分离、透析、基于微流体的分离等、或其任何组合。在一个有利的实施方案中，使用过滤(优选地是超滤(UF)、切向流过滤或中空纤维过滤)和尺寸排阻液相色谱法(LC)或珠粒洗脱色谱法的顺序组合进行EV的纯化。纯化步骤的这种组合产生优化的纯化，这进而产生优越的治疗活性。此外，与常规用于纯化外泌体的超速离心(UC)相比，顺序的过滤-色谱法显著更快并且有可能按比例放大到更高的制造量，这是在现有技术中占主导地

位的当前UC方法的显著缺点。另一种有利的纯化方法是切向流过滤(TFF),其提供可按比例缩放性和纯度,并且可以与任何其它类型的纯化技术组合。

[0083] 在又另一个方面,本发明涉及药物组合物,所述药物组合物包含根据本发明的EV,所述EV通常呈EV群体的形式。通常,根据本发明的药物组合物包含一种类型的治疗性EV(即包含某种类型的融合蛋白并且被一种或多种类型的含有Fc的蛋白质包被的EV群体,所述含有Fc的蛋白质诸如抗体;Cas9-Fc融合蛋白和Fc-RNP融合复合物;与Fc结构域融合的溶酶体贮积症酶等),其与至少一种药学上可接受的赋形剂一起配制。然而,在单一药物组合物中当然可以包含多于一种类型的EV群体,例如在期望组合抗体治疗的情况下。然而,当然,如上所述,单个EV或单个EV群体可以包含与EV表面结合的多于一个含有Fc的蛋白质(例如抗体)。所述至少一种药学上可接受的赋形剂可以选自包括以下各项的组:任何药学上可接受的材料、组合物或媒介物,例如固体或液体填充剂、稀释剂、赋形剂、载体、溶剂或封装材料,其可以参与例如悬浮EV群体、维持EV群体的活性、或将EV群体从一个器官或身体的一部分携带或转运到另一个器官或身体的另一部分(例如从血液到所关注的任何组织和/或器官和/或身体部分)。

[0084] 本发明还涉及EV的美容应用。因此,本发明可以涉及皮肤护理产品,如霜膏、洗剂、凝胶、乳液、软膏、糊剂、粉剂、搽剂、防晒剂、洗发剂等,其包含合适的EV以改善和/或缓解诸如皮肤干燥、皱纹、皱褶、起皱和/或皮肤褶痕的症状和问题。在一个实施方案中,EV(携带与例如所关注的抗体结合的融合蛋白)是从具有再生特性的合适的EV产生细胞来源(例如MSC)获得的,其被包含在美容霜膏、洗剂或凝胶中以用于皱纹、褶皱、皱褶、起皱和/或皮肤褶痕的美容或治疗缓解。

[0085] 在又另一个方面,本发明涉及用于医学的根据本发明的EV。当然,当包含与所关注的蛋白质(如抗体)的Fc结构域结合的融合蛋白的EV用于医学时,它实际上通常是正使用的EV的群体。向患者施用的EV的剂量将取决于例如已经包被在EV表面上的所关注的抗体的数量、待治疗或缓解的疾病或症状、施用途径、治疗性蛋白质本身的药理作用、EV的固有特性、任何靶向抗体或其它靶向实体的存在、以及本领域技术人员已知的各种其它相关参数。

[0086] 携带含有Fc的蛋白质的本发明的EV可以用于几个不同的治疗和药物方面。在一个实施方案中,EV被靶向特定细胞类型、组织、和/或器官的抗体或其它含有Fc的蛋白质覆盖。这是使EV(除了含有Fc的蛋白质之外,其还可以包含其它药剂)靶向所关注的组织的非常强效的方式,并且可以代表靶向药物递送中的阶跃变化。在另一个实施方案中,与所关注的靶抗原相互作用的治疗性抗体或其它含有Fc结构域的蛋白质可以使用具有穿过生物屏障的能力的EV有效地递送到通常难以到达的所关注的组织。这种方法可以例如使得能够将单克隆抗体递送到中枢神经系统或脑中。在又另一个实施方案中,将EV用含有Fc的蛋白质包被是将所关注的含有Fc的蛋白质进行多重化的方式,以增强或影响它的靶标亲合力或它与所关注的靶标结合的构象。在又另一个实施方案中,根据本发明的EV使得能够提高抗体-药物缀合物(ADC)或受体-药物缀合物的递送和功效,这是因为ADC的多重化可以显著增强它们的治疗功效并且它们在EV上的存在意味着它们也可以进入靶细胞中。在另一个实施方案中,EV进入靶细胞中的能力意味着本发明的EV打开了整个细胞内空间并且使得可通过基本上任何包含Fc结构域的蛋白质和/或上面可以融合Fc结构域的任何蛋白质(如用于酶替代治疗的酶;核酸酶,如Cas9;或肿瘤抑制因子,如p53、pVHL、APC、CD95、ST5、YPEL3、ST7、以及

ST14中的任-种)进行给药。

[0087] 根据本发明的EV和其EV群体因此可以用于预防和/或治疗目的,例如用于预防和/或治疗和/或缓解各种疾病和病症。其中可以施用根据本发明的EV的疾病的非限制性实例包括克罗恩氏病(Crohn′s disease)、溃疡性结肠炎、强直性脊柱炎、类风湿性关节炎、多发性硬化症、系统性红斑狼疮、类肉瘤病、特发性肺纤维化、银屑病、肿瘤坏死因子(TNF)受体相关周期性综合征(TRAPS)、白细胞介素-1受体拮抗因子缺乏症(DIRA)、子宫内膜异位症、自身免疫性肝炎、硬皮病、肌炎、中风、急性脊髓损伤、血管炎、格林-巴利综合征(Guillain-Barré syndrome)、急性心肌梗塞、ARDS、败血病、脑膜炎、脑炎、肝衰竭、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪肝病(NAFLD)、肾衰竭、心力衰竭或任何急性或慢性器官衰竭和相关潜在病因学、移植物抗宿主病、杜氏肌营养不良症(Duchenne muscular dystrophy)和其它肌营养不良症、溶酶体贮积病,如戈谢病(Gaucher disease)、法布里病(Fabry′s disease)、MPS I、MPS II(亨特氏综合征(Hunter syndrome))和MPS III、尼-皮二氏病(Niemann-Pick disease)、庞贝氏病(Pompe disease)等;神经退行性疾病,包括阿尔茨海默氏病(Alzheimer′s disease)、帕金森氏病(Parkinson′s disease)、亨廷顿氏病(Huntington′s disease)和其它三核苷酸重复序列相关疾病、痴呆;ALS、癌症诱发的恶病质、厌食、2型糖尿病、以及各种癌症。几乎所有类型的癌症都是本发明的相关疾病靶标,例如急性成淋巴细胞性白血病(ALL)、急性髓系白血病、肾上腺皮质癌、AIDS相关癌症、AIDS相关淋巴瘤、肛门癌、阑尾癌、星形细胞瘤、小脑或大脑基底细胞癌、胆管癌、膀胱癌、骨肿瘤、脑干神经胶质瘤、脑癌、脑肿瘤(小脑星形细胞瘤、大脑星形细胞瘤/恶性神经胶质瘤、室管膜瘤、成神经管细胞瘤、幕上原始神经外胚层肿瘤、视觉通路和下丘脑神经胶质瘤)、乳腺癌、支气管腺瘤/类癌、伯基特氏淋巴瘤(Burkitt′s lymphoma)、类癌肿瘤(儿童期、胃肠道)、原发灶不明癌、中枢神经系统淋巴瘤、小脑星形细胞瘤/恶性神经胶质瘤、宫颈癌、慢性淋巴细胞性白血病、慢性骨髓性白血病、慢性骨髓增生性病症、结肠癌、皮肤T细胞淋巴瘤、结缔组织增生性小圆细胞肿瘤、子宫内膜癌、室管膜瘤、食道癌、颅外生殖细胞肿瘤、性腺外生殖细胞肿瘤、肝外胆管癌、眼癌(眼内黑色素瘤、成视网膜细胞瘤)、胆囊癌、胃(Gastric/Stomach)癌、胃肠道类癌肿瘤、胃肠道间质瘤(GIST)、生殖细胞肿瘤(颅外、性腺外、或卵巢)、妊娠期滋养细胞肿瘤、神经胶质瘤(脑干神经胶质瘤、大脑星形细胞瘤、视觉通路和下丘脑神经胶质瘤)、胃类癌、毛细胞白血病、头颈部癌、心脏癌、肝细胞癌(肝癌)、霍奇金淋巴瘤(Hodgkin lymphoma)、下咽癌、眼内黑色素瘤、胰岛细胞癌(内分泌胰腺)、卡波西氏肉瘤(Kaposi sarcoma)、肾癌(肾细胞癌)、喉癌、白血病((急性成淋巴细胞性(也被称作急性淋巴细胞性白血病)、急性髓系(也被称作急性骨髓性白血病)、慢性淋巴细胞性(也被称作慢性淋巴细胞性白血病)、慢性骨髓性(也被称作慢性髓系白血病)、毛细胞白血病))、唇和口腔癌、脂肪肉瘤、肝癌(原发性)、肺癌(非小细胞、小细胞)、淋巴瘤、AIDS相关淋巴瘤、伯基特氏淋巴瘤、皮肤T细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、成神经管细胞瘤、梅克尔细胞癌(Merkel Cell Carcinoma)、间皮瘤、原发灶不明的颈部转移性鳞癌、口腔癌、多发性内分泌腺瘤综合征、多发性骨髓瘤/浆细胞瘤、蕈样真菌病、骨髓增生异常/骨髓增生性疾病、骨髓性白血病、慢性髓系白血病(急性、慢性)、骨髓瘤、鼻腔和鼻旁窦癌、鼻咽癌、成神经细胞瘤、口腔癌、口咽癌、骨肉瘤/骨恶性纤维组织细胞瘤、卵巢癌、卵巢上皮癌(表面上皮-间质瘤)、卵巢生殖细胞肿瘤、卵巢低度恶性潜能肿瘤、胰腺癌、胰岛细胞癌、甲状旁腺癌、阴茎

癌、咽癌、嗜铬细胞瘤、松果体星形细胞瘤、松果体生殖细胞瘤、成松果体细胞瘤和幕上原始神经外胚层肿瘤、垂体腺瘤、胸膜肺母细胞瘤、前列腺癌、直肠癌、肾细胞癌(肾癌)、成视网膜细胞瘤、横纹肌肉瘤、唾液腺癌、肉瘤(尤文氏家族肿瘤肉瘤(Ewing family of tumors sarcoma)、卡波西氏肉瘤、软组织肉瘤、子宫肉瘤)、塞扎里综合征(Sézary syndrome)、皮肤癌(非黑色素瘤、黑色素瘤)、小肠癌、鳞状细胞癌、颈部鳞癌、胃癌、幕上原始神经外胚层肿瘤、睾丸癌、咽喉癌、胸腺瘤和胸腺癌、甲状腺癌、肾盂和输尿管的移行细胞癌、尿道癌、子宫癌、子宫肉瘤、阴道癌、外阴癌、瓦尔登斯特伦巨球蛋白血症(Waldenström macroglobulinemia)、和/或肾母细胞瘤(Wilm′s tumor)。

[0088] 根据本发明的EV可以经由各种不同的施用途径向人类或动物受试者施用,例如经耳(耳部)、颊面、结膜、皮肤、牙齿、电渗、宫颈内、窦内、气管内、肠内、硬膜外、羊膜外、体外、血液透析、浸润、间质、腹内、羊膜内、动脉内、关节内、胆道内、支气管内、囊内、心内、软骨内、尾部内、海绵体内、腔内、脑内、脑池内、角膜内、冠内(牙齿)、冠状动脉内、阴茎海绵体内、真皮内、椎间盘内、导管内、十二指肠内、硬膜内、表皮内、食道内、胃内、牙龈内、回肠内、病灶内、管腔内、淋巴管内、髓内、脑膜内、肌内、眼内、卵巢内、心包内、腹膜内、胸膜内、前列腺内、肺内、窦内、脊柱内、滑膜内、腱内、睾丸内、鞘内、胸内、小管内、肿瘤内、鼓室内、子宫内、血管内、静脉内、静脉内推注、静脉内滴注、心室内、膀胱内、玻璃体内、离子电渗疗法、灌注、经喉、经鼻、鼻胃、封闭敷料技术、眼科、口服、口咽、其它、肠胃外、经皮、关节周、硬膜外、神经周、牙周、经直肠、呼吸道(吸入)、眼球后、软组织、蛛网膜下、结膜下、皮下、舌下、粘膜下、局部、透皮、经粘膜、经胎盘、经气管、经鼓室、输尿管、尿道、和/或阴道施用、和/或上述施用途径的任何组合,其通常取决于待治疗的疾病和/或抗体或EV群体本身的特征。

[0089] 根据本发明的合适的靶向抗体可以靶向源自于例如肿瘤、实体器官、身体结构、细胞或组织类型的抗原。可以由靶向抗体靶向的抗原的来源的非限制性实例包括肝、肺、肾、心脏、胰腺、肾上腺、甲状腺、甲状旁腺、脑,包括所有脑区域(例如丘脑、下丘脑、纹状体等);血脑屏障、CNS、PNS、骨髓、皮肤、血管系统、淋巴系统(包括脾)、关节、眼睛、肌肉组织、炎症部位、损伤部位、以及细胞类型,如脂肪细胞、肌细胞(成肌细胞和肌管)、卫星细胞、心脏细胞、内皮细胞、成纤维细胞、肝细胞、肾细胞、周细胞、神经元、胶质细胞、星形胶质细胞、少突胶质细胞、巨噬细胞、DC细胞、B细胞、T细胞、NK细胞、软骨细胞、成骨细胞、骨细胞、上皮细胞、红细胞、早期祖细胞,如多能造血干细胞/血胚细胞、髓系祖细胞、淋巴祖细胞等。与靶向癌症相关的抗原的非限制性实例包括腺癌抗原、甲胎蛋白、BAFF、C242抗原、CA-125、碳酸酐酶9(CA-IX)、二唾液酸神经节苷脂(GD2)、4-IBB、5T4、CD22、CD221、CD23(IgE受体)、CD28、CD30(TNFRSF8)、CD33、CD4、CD40、CD44 v6、CD51、CD52、CD56、CD74、CD80、CEA、CNTO888、CTLA-4、DR5、EGFR、EpCAM、CD3、FAP、纤连蛋白胞外结构域-B、叶酸受体1、GD2、GD3神经节苷脂、糖蛋白75、GPNMB、HER2/neu、HGF、人类分散因子受体激酶、IGF-1受体、IGF-I、IgG1、LI-CAM、IL-13、IL-6、胰岛素样生长因子I受体、整合素α5 β1、整合素αv β3、豆荚蛋白、MORAb-009、MS4A1、MUC1、粘蛋白CanAg、C-MET、CCR4、CD 152、CD 10、CD 19、CD20、CD200、N-羟乙酰神经氨酸、NPC-IC、PDGF-R a、PDL192、磷脂酰丝氨酸、肿瘤抗原CTAA16.88、VEGF-A、VEGFR-1、VEGFR2、波形蛋白、RANKL、RON、ROR1、SCH 900105、SDC1、SLAMF7、TAG-72、生腱蛋白C、TGFβ2、TGF-β、TRAIL-R1、TRAIL-R2、叶酸受体、转铁蛋白受体以及其任何组合。

[0090] 根据本发明的包被EV以防止或减少调理作用和/或免疫细胞介导的EV清除的抗体

或其它含有Fc结构域的蛋白质可以是基本上任何含有Fc的蛋白质，如抗体，其天然地存在于血清或任何其它体液中。这些抗体因此可以是任何类型的，例如IgG、IgA、IgM、IgE和/或IgD，但是包含Fc结构域并且具有在体内防止EV的调理作用的能力的任何其它蛋白质也可以用于包被EV。因此，可以主动或被动进行EV的包被以避免或减少免疫清除，其中主动包被可以涉及在体内施用之前将所考虑的EV用合适的包含Fc结构域的蛋白质修饰。用于该目的的合适的含有Fc的蛋白质包括与Fc结构域融合的因子H和/或因子I。因子H和因子I是补体系统的负调节剂(通过抑制C3转化成C3b)，从而当与Fc结构域融合并且经由Fc结合多肽与融合蛋白的Fc结构域之间的结合而与EV表面连接时，引起EV清除减少。另一方面，被动包被可能需要允许所考虑的EV用它的可用的未结合的Fc结合剂在体内多价螯合蛋白质。

[0091] 在另一个实施方案中，根据本发明的治疗性和/或靶向抗体的合适的非限制性实例可以是以下各项中的任一种或多种:阿巴伏单抗(Abagovomab)、阿昔单抗(Abciximab)、阿克序单抗(Actoxumab)、阿达木单抗(Adalimumab)、阿德木单抗(Adecatumumab)、阿多-曲妥珠单抗-艾美坦辛(Adotrastuzumab emtansine)、阿度奴单抗(Aducanumab)、阿非莫单抗(Afelimomab)、阿托珠单抗(Afutuzumab)、阿珠单抗(Alacizumab)、阿仑单抗(Alemtuzumab)、阿利库单抗(Alirocumab)、喷替酸阿妥莫单抗(Altumomab pentetate)、阿麦妥昔单抗(Amatuximab)、马安莫单抗(Anatumomab mafenatox)、安弗鲁单抗(Anifrolumab)、安芦珠单抗(Anrukinzumab)、阿泊珠单抗(Apolizumab)、阿西莫单抗(Arcitumomab)、阿塞珠单抗(Aselizumab)、阿特珠单抗(Atezolizumab)、阿堤努单抗(Atinumab)、阿利单抗(Atlizumab)、阿托木单抗(Atorolimuma)、阿维单抗(Avelumab)、巴匹珠单抗(Bapineuzumab)、巴利昔单抗(Basiliximab)、巴维昔单抗(Bavituximab)、贝妥莫单抗(Bectumomab)、贝利单抗(Belimumab)、本雷利珠单抗(Benralizumab)、柏替木单抗(Bertilimumab)、贝索单抗(Besilesomab)、贝伐单抗(Bevacizumab)、贝洛序单抗(Bezlotoxumab)、比西单抗(Biciromab)、比马单抗(Bimagrumab)、莫比伐珠单抗(Bivatuzumab mertansine)、博纳吐单抗(Blinatumomab)、博索珠单抗(Blosozumab)、本妥昔单抗-维度汀(Brentuximab vedotin)、布雷奴单抗(Briakinumab)、布罗达单抗(Brodalumab)、卡那单抗(Canakinumab)、莫坎妥珠单抗(Cantuzumab mertansine)、拉坎妥珠单抗(Cantuzumab ravtansine)、卡普赛珠单抗(Caplacizumab)、卡罗单抗喷地肽(Capromab pendetide)、卡鲁单抗(Carlumab)、卡妥索单抗(Catumaxomab)、cBR96-多柔比星免疫缀合物、西利珠单抗(Cedelizumab)、聚乙二醇化赛妥珠单抗(Certolizumab pegol)、西妥昔单抗(Cetuximab)、泊西他珠单抗(Citatuzumab bogatox)、西妥木单抗(Cixutumumab)、克莱赞珠单抗(Clazakizumab)、克立昔单抗(Clenoliximab)、替可利妥珠单抗(Clivatuzumab tetraxetan)、可那木单抗(Conatumumab)、可丝珠单抗(Concizumab)、克仁珠单抗(Crenezumab)、CR6261、达西珠单抗(Dacetuzumab)、达利珠单抗(Daclizumab)、达罗妥珠单抗(Dalotuzumab)、达雷木单抗(Daratumumab)、登西珠单抗(Demcizumab)、地诺单抗(Denosumab)、地莫单抗(Detumomab)、地努图希单抗(Dinutuximab)、阿托度单抗(Dorlimomab aritox)、德罗图单抗(Drozitumab)、杜利妥单抗(Duligotumab)、度匹鲁单抗(Dupilumab)、度伐鲁单抗(Durvalumab)、杜氏图单抗(Dusigitumab)、依美昔单抗(Ecromeximab)、艾库组单抗(Eculizumab)、埃巴单抗(Edobacomab)、依决洛单抗(Edrecolomab)、依法利珠单抗(Efalizumab)、依夫单抗(Efungumab)、依德鲁单抗

(Eldelumab)、埃罗妥珠单抗(Elotuzumab)、艾西莫单抗(Elsilimomab)、依那妥珠单抗(Enavatuzumab)、聚乙二醇化恩莫单抗(Enlimomab pegol)、依诺珠单抗(Enokizumab)、恩曲单抗(Enoticumab)、恩司昔单抗(Ensituximab)、西依匹妥莫单抗(Epitumomab cituxetan)、依帕珠单抗(Epratuzumab)、厄利珠单抗(Erlizumab)、厄马索单抗(Ertumaxomab)、依那西普、埃达珠单抗(Etaracizumab)、埃图力珠单抗(Etrolizumab)、依伏库单抗(Evolocumab)、艾韦单抗(Exbivirumab)、法索单抗(Fanolesomab)、法拉莫单抗(Faralimomab)、法利珠单抗(Farletuzumab)、法希姆单抗(Fasinumab)、FBTA05、非维珠单抗(Felvizumab)、非扎奴单抗(Fezakinumab)、芬克拉妥珠单抗(Ficlatuzumab)、芬妥木单抗(Figitumumab)、弗兰托单抗(Flanvotumab)、芳妥珠单抗(Fontolizumab)、弗罗鲁单抗(Foralumab)、福拉韦单抗(Foravirumab)、夫苏木单抗(Fresolimumab)、弗兰单抗(Fulranumab)、弗妥昔单抗(Futuximab)、加利昔单抗(Galiximab)、盖尼塔单抗(Ganitumab)、更汀芦单抗(Gantenerumab)、加维莫单抗(Gavilimomab)、吉妥珠单抗奥唑米星(Gemtuzumab ozogamicin)、吉伏珠单抗(Gevokizumab)、吉瑞妥昔单抗(Girentuximab)、戈利巴图木单抗-维度汀(Glembatumumab vedotin)、戈利木单抗(Golimumab)、戈利昔单抗(Gomiliximab)、古塞库单抗(Guselkumab)、伊巴珠单抗(Ibalizumab)、替坦异贝莫单抗(Ibritumomab tiuxetan)、依库单抗(Icrucumab)、伊戈伏单抗(Igovomab)、IMAB362、英西单抗(Imciromab)、英加妥珠单抗(Imgatuzumab)、英克拉库单抗(Inclacumab)、拉茚达昔单抗(Indatuximab ravtansine)、英夫利昔单抗(Infliximab)、英妥木单抗(Intetumumab)、伊诺莫单抗(Inolimomab)、伊珠单抗奥唑米星(Inotuzumab ozogamicin)、伊匹木单抗(Ipilimumab)、伊妥木单抗(Iratumumab)、依托珠单抗(Itolizumab)、艾塞吉珠单抗(Ixekizumab)、凯利昔单抗(Keliximab)、拉贝珠单抗(Labetuzumab)、拉姆利珠单抗(Lambrolizumab)、拉姆帕力珠单抗(Lampalizumab)、来金珠单抗(Lebrikizumab)、来马索单抗(Lemalesomab)、乐德木单抗(Lerdelimumab)、来沙木单抗(Lexatumumab)、利韦单抗(Libivirumab)、利格珠单抗(Ligelizumab)、林妥珠单抗(Lintuzumab)、利丽单抗(Lirilumab)、罗德希珠单抗(Lodelcizumab)、莫洛伏珠单抗(Lorvotuzumab mertansine)、鲁卡木单抗(Lucatumumab)、鲁昔单抗(Lumiliximab)、马帕木单抗(Mapatumumab)、马妥昔单抗(Margetuximab)、马司莫单抗(Maslimomab)、马利木单抗(Mavrilimumab)、马妥珠单抗(Matuzumab)、美泊利单抗(Mepolizumab)、美替木单抗(Metelimumab)、米拉珠单抗(Milatuzumab)、明瑞莫单抗(Minretumomab)、米妥莫单抗(Mitumomab)、莫加利珠单抗(Mogamulizumab)、莫罗木单抗(Morolimumab)、莫维珠单抗(Motavizumab)、帕西妥莫单抗(Moxetumomab pasudotox)、莫罗单抗-CD3(Muromonab-CD3)、他那可单抗(Nacolomab tafenatox)、那米鲁单抗(Namilumab)、伊那莫单抗(Naptumomab estafenatox)、纳那妥单抗(Namatumab)、那他珠单抗(Natalizumab)、奈巴库单抗(Nebacumab)、奈昔木单抗(Necitumumab)、奈瑞莫单抗(Nerelimomab)、奈瓦库单抗(Nesvacumab)、尼妥珠单抗(Nimotuzumab)、纳武单抗(Nivolumab)、巯诺莫单抗(Nofetumomab merpentan)、奥卡拉妥珠单抗(Ocaratuzumab)、奥瑞珠单抗(Ocrelizumab)、奥度莫单抗(Odulimomab)、奥法木单抗(Ofatumumab)、奥拉单抗(Olaratumab)、奥鲁凯珠单抗(Olokizumab)、奥马珠单抗(Omalizumab)、奥那妥珠单抗(Onartuzumab)、奥妥希珠单抗(Ontuxizumab)、莫奥珠单抗(Oportuzumab monatox)、奥戈伏单抗(Oregovomab)、奥泰单抗(Orticumab)、奥昔珠单抗

(Otelixizumab)、奥乐妥珠单抗(Otlertuzumab)、欧西鲁单抗(Oxelumab)、奥扎尼珠单抗(Ozanezumab)、奥佐利珠单抗(Ozoralizumab)、帕昔单抗(Pagibaximab)、帕利珠单抗(Palivizumab)、帕尼单抗(Panitumumab)、帕尼库单抗(Pankomab)、帕诺库单抗(Panobacumab)、帕沙珠单抗(Parsatuzumab)、帕考珠单抗(Pascolizumab)、帕特立珠单抗(Pateclizumab)、帕图单抗(Patritumab)、派姆单抗(Pembrolizumab)、培图莫单抗(Pemtumomab)、帕科珠单抗(Perakizumab)、帕妥珠单抗(Pertuzumab)、培克珠单抗(Pexelizumab)、匹迪丽珠单抗(Pidilizumab)、匹那珠单抗-维度汀(Pinatuzumab vedotin)、平妥莫单抗(Pintumomab)、普拉库鲁单抗(Placulumab)、泊拉珠单抗-维度汀(Polatuzumab vedotin)、普恩珠单抗(Ponezumab)、普立昔单抗(Priliximab)、普陀昔单抗(Pritoxaximab)、普立木单抗(Pritumumab)、PRO 140、坤立珠单抗(Quilizumab)、雷库图单抗(Racotumomab)、雷德图单抗(Radretumab)、雷韦单抗(Rafivirumab)、雷莫芦单抗(Ramucirumab)、雷珠单抗(Ranibizumab)、雷昔库单抗(Raxibacumab)、瑞加韦单抗(Regavirumab)、瑞利珠单抗(Reslizumab)、利妥木单抗(Rilotumumab)、利克珠单抗(Risankizumab)、利妥昔单抗(Rituximab)、罗妥木单抗(Robatumumab)、罗勒杜单抗(Roledumab)、罗姆苏珠单抗(Romosozumab)、罗利珠单抗(Rontalizumab)、罗维珠单抗(Rovelizumab)、鲁利珠单抗(Ruplizumab)、萨马利珠单抗(Samalizumab)、沙鲁单抗(Sarilumab)、沙妥莫单抗喷地肽(Satumomab pendetide)、苏金单抗(Secukinumab)、司里班妥单抗(Seribantumab)、斯图希单抗(Setoxaximab)、司韦单抗(Sevirumab)、西罗珠单抗(Sibrotuzumab)、西法木单抗(Sifalimumab)、司妥昔单抗(Siltuximab)、西姆妥珠单抗(Simtuzumab)、西利珠单抗(Siplizumab)、希瑞库单抗(Sirukumab)、苏兰珠单抗(Solanezumab)、索利托单抗(Solitomab)、索耐珠单抗(Sonepcizumab)、松妥珠单抗(Sontuzumab)、司他芦单抗(Stamulumab)、硫索单抗(Sulesomab)、索维单抗(Suvizumab)、他巴卢单抗(Tabalumab)、替他珠单抗(Tacatuzumab tetraxetan)、他度珠单抗(Tadocizumab)、他利珠单抗(Talizumab)、他尼珠单抗(Tanezumab)、帕他莫单抗(Taplitumomab paptox)、替非珠单抗(Tefibazumab)、阿替莫单抗(Telimomab aritox)、替妥莫单抗(Tenatumomab)、替奈昔单抗(Teneliximab)、替利珠单抗(Teplizumab)、替普单抗(Teprotumumab)、替西木单抗(Ticilimumab)、蒂尔他昔单抗(Tildrakizumab)、替加珠单抗(Tigatuzumab)、托珠单抗(Tocilizumab)、托利珠单抗(Toralizumab)、托西莫单抗(Tositumomab)、百克沙(Bexxar)、托维图单抗(Tovetumab)、曲洛青木单抗(Tralokinumab)、曲妥珠单抗(Trastuzumab)、曲加立珠单抗(Tregalizumab)、替西木单抗(Tremelimumab)、妥克妥珠单抗-西莫白介素(Tucotuzumab celmoleukin)、妥韦单抗(Tuvirumab)、乌妥昔单抗(Ublituximab)、优卢单抗(Urelumab)、乌珠单抗(Urtoxazumab)、优特克单抗(Ustekinumab)、万替珠单抗(Vantictumab)、伐利昔单抗(Vapaliximab)、瓦替利珠单抗(Vatelizumab)、维多珠单抗(Vedolizumab)、维妥珠单抗(Veltuzumab)、维帕莫单抗(Vepalimomab)、维西库单抗(Vesencumab)、维西珠单抗(Visilizumab)、伏洛昔单抗(Volociximab)、伏司妥珠单抗-马佛多汀(Vorsetuzumab mafodotin)、伏妥昔单抗(Votumumab)、扎鲁木单抗(Zalutumumab)、扎木单抗(Zanolimumab)、扎妥昔单抗(Zatuximab)、齐拉木单抗(Ziralimumab)、阿佐莫单抗(Zolimomab aritox)、或其任何组合。重要的是,本发明提供了任何抗体的递送,无论它的靶标在细胞内和/或细胞外。本发明

的EV有效内化抗体的能力代表了单克隆抗体发展中的阶跃变化并且可以使得能够靶向靶细胞的整个细胞内隔室内的抗原和靶标。重要的是,根据本发明的抗体和含有Fc的蛋白质可以有利地被标记以用于检测和成像目的,例如使用荧光团、MRI剂、PET剂、放射剂、酶、纳米颗粒、金属、有机和无机化合物等。

[0092] 应当了解的是,可以在不脱离本发明的范围的情况下对上述示例性方面、实施方案、替代方案、以及变化方案进行修改。现在将通过所附实施例进一步举例说明本发明,所述实施例当然也可以在不脱离本发明的范围和精神的情况下进行相当大的修改。

[0093] 实验部分

[0094] 材料和方法

[0095] 构建体设计和克隆:已经构建了包含至少一种外泌体多肽和至少一种Fc结合多肽的各种融合蛋白,将其克隆到载体中并且在几种不同的EV产生细胞来源中产生。通常通过合成产生ORF并且将其克隆到哺乳动物表达载体pSF-CAG-Amp中。简单地说,根据制造商的说明书(NEB公司),用酶NotI和SalI消化合成的DNA和载体质粒。根据制造商的说明书(NEB公司),使用T4连接酶将限制的纯化的DNA片段连接在一起。通过在补充氨苄西林(ampicillin)的平板上进行细菌转化来选择成功的连接事件。根据制造商的说明书,通过'大量制备法(maxi-prep)'产生用于转染的质粒。

[0096] 在含有Fc的蛋白质在表达融合蛋白的相同的EV产生细胞来源中内源性产生的情况下,购买ORF序列(傲锐东源科技公司(Origene Technologies,Inc.))并且将其扩增和克隆到pIRES双顺反子表达载体(Clonetech Laboratories公司)的MSC A位点中以使得在翻译时,外泌体多肽在一个构建体中与Fc结合多肽融合,而所关注的含有Fc的蛋白质被单独翻译(从单独的构建体或从同一构建体)并且转运到待在EV产生细胞来源中形成的EV中。使用NEBuilder高保真度DNA组装克隆试剂盒(NEB公司)进行大部分的克隆并且使用桑格测序(Sanger sequencing)(Source BioScience公司)确认。pIRES载体使得能够同时双顺反子表达这两个转基因,从而确保EV产生细胞将同时表达融合蛋白和所关注的含有Fc的蛋白质这两者。根据制造商的建议,将质粒转化到NEB 5-α感受态大肠杆菌细胞(NEB公司)中并且在振荡孵育箱中培养过夜。根据制造商的说明书,使用'大量制备质粒DNA纯化试剂盒'(快而精公司(Qiagen))分离和纯化质粒。

[0097] • 细胞培养和转染

[0098] 根据实验设计和测定,在某些情况下,在常规的二维细胞培养物中进行非病毒瞬时转染和外泌体产生,而在其它情况下,使用病毒介导的转导来产生稳定的细胞系,通常将其培养在不同类型的生物反应器中。为简明起见,在本文仅提到几个实例。

[0099] 通常将HEK293T细胞接种到15cm培养皿(每个培养皿9×10^6个细胞)中并且在如由ATCC所推荐的含有血清的DMEM中静置过夜。第二天,将细胞用直接添加到细胞上的脂质复合DNA瞬时转染。简单地说,将DNA和聚乙烯亚胺(PEI)分别在OptiMEM中孵育5分钟,之后在室温下组合在一起20分钟。将脂质复合DNA和细胞共孵育6小时,之后,将条件培养基更换成OptiMEM,持续48小时。在培养皿、烧瓶以及其它细胞培养容器中评价的其它细胞和细胞系包括骨髓来源的间充质基质细胞(BM-MSC)和脐带胶样组织来源的MSC(WJ-MSC)、羊膜细胞、成纤维细胞、各种内皮和上皮细胞、以及各种免疫细胞和细胞系。

[0100] 在病毒转导和产生用于融合蛋白和所关注的含有Fc的蛋白质的各种组合的稳定

细胞系的情况下，通常使用慢病毒(LV)对细胞来源进行病毒转导，如BM-MSC、WJ-MSC、成纤维细胞、羊膜细胞、成纤维细胞、各种内皮和上皮细胞。通常，在感染之前24小时，将100.000个细胞(例如成纤维细胞、MSC等)或200.000个细胞(例如HEK293T)平板接种在6孔板中。添加2μL的LV和任选的凝聚胺(Polybrene)(或海地美溴铵(hexadimethrine bromide)，孔中的最终浓度是8μg/mL)，并且在转导后24小时，将转导细胞的细胞培养基更换成新鲜的完全培养基。在转导后72小时，进行嘌呤霉素选择(4μg/ml-6μg/ml)，通常持续7天，继而分析包含外泌体多肽和Fc结合多肽的融合蛋白构建体的稳定表达。

[0101] 在二维培养物中或在生物反应器(通常是中空纤维生物反应器或搅拌釜式生物反应器)中培养稳定的细胞，随后收获条件培养基以用于外泌体制备。进行各种制备和纯化步骤。标准工作流程包括以下步骤：预先清除上清液；基于过滤进行浓缩；基于色谱法去除蛋白质污染物；以及任选地在合适的缓冲液中配制所得的外泌体组合物以用于体外和/或体内测定。

[0102] • 测定和分析

[0103] 蛋白质印迹法是评价EV中融合蛋白的富集的非常方便的分析方法。简单地说，根据制造商的说明书(英杰公司(Invitrogen)，Novex PAGE 4%-12%凝胶)进行SDS-PAGE，其中每个孔上样1×10^{10}个外泌体和20μg的细胞裂解物。根据制造商的说明书(Immobilon，英杰公司)将蛋白质从SDS-PAGE凝胶转移到PVDF膜。将膜在Odyssey封闭缓冲液(Licor公司)中封闭并且根据供应商的说明书(一抗：艾博抗公司(Abcam)，二抗：Licor公司)用针对Fc结合多肽和/或外泌体蛋白的抗体探测。将分子探针在680nm和800nm波长处可视化。

[0104] 对于EV尺寸确定，使用配备有分析软件的NanoSight仪器进行纳米颗粒跟踪分析(NTA)。对于所有记录，我们使用13或15的照相机级别和自动功能以用于所有采集后设置。电子显微镜术和荧光显微镜术经常用于了解细胞内位置和释放以及定量和分析EV。

[0105] 使用多种方法来分离和纯化EV，通常使用过滤(如TFF)和LC(特别是珠粒洗脱LC)的组合。通常，收集合有EV的培养基并且以300g进行低速旋转5分钟，继而进行2000g旋转10分钟以去除较大的颗粒和细胞碎片。然后用0.22μm注射式过滤器过滤上清液并且进行不同的纯化步骤。使用具有100kDa截止过滤器的Vivaflow 50R切向流(TFF)装置(赛多利斯公司(Sartorius))或具有100kDa或300kDa截止中空纤维过滤器的KR2i TFF系统(SpectrumLabs公司)将大体积渗滤和浓缩到约20ml。随后将预浓缩的培养基加到与ÄKTAprime plus或ÄKTA Pure 25色谱系统(通用电气医疗集团生命科学部(GE Healthcare Life Sciences))连接的珠粒洗脱柱(HiScreen或HiTrap Capto Core 700柱，通用电气医疗集团生命科学部)上。根据制造商的说明书选择用于柱平衡的流速设置、样品加载以及柱就地清洗程序。根据UV吸光度色谱图收集样品并且使用Amicon Ultra-15 10kDa分子量截止旋转过滤器(密理博公司(Millipore))浓缩到100μl的最终体积并且储存在-80℃以用于进一步的下游分析。为了评估蛋白质和RNA洗脱曲线，使用KR2i TFF系统，使用100kDa和300kDa中空纤维过滤器浓缩和渗滤培养基并且在Tricorn 10/300琼脂糖凝胶4快速流动(S4FF)柱(通用电气医疗集团生命科学部)上分析样品。

[0106] • 实施例

[0107] 实施例1：使IgG与包含Fc结合多肽的EV(Fc结合EV)结合

[0108] 使用300kd中空纤维柱进行切向流过滤来从来自工程化的HEK293T细胞(对照或稳定表达Gp130细胞外结构域-2×GGGGS接头-Z结构域-Gp130跨膜结构域-亮氨酸拉链-N末端多配体蛋白聚糖结合蛋白-His标签的Fc结合构建体)的条件培养基中分离EV,继而使用10kd旋转过滤器进行超滤以浓缩。然后使用电子显微镜术和流式细胞术评估Fc结合EV对IgG的结合能力。

[0109] 对于电子显微镜术,在37℃将1×10^9个EV与和金纳米颗粒缀合的兔抗山羊10nm抗体一起孵育2小时。如图2中所示,Fc结合EV(A)被纳米金标记的抗体(即含有Fc的蛋白质)修饰,而对照EV(B)没有结合任何抗体。

[0110] 对于流式细胞术,将1×10^8个EV在轨道振荡器上以450rpm在120μl的PBS中与来自人类MACSPlex外泌体试剂盒(美天旎生物技术公司(Miltenyi Biotec),订单号:130-108-813)的15μl抗体包被的捕捉珠粒一起孵育过夜,持续16小时。在洗涤之后,将3μg的AlexaFluor647缀合的人类IgG Fc片段(杰克逊实验室公司(Jackson Laboratories),目录号009-600-008)添加到没有EV的对照(A)、对照EV(B)、或Fc结合EV(多配体蛋白聚糖结合蛋白-gp130-z结构域-gp130)(C)中。在室温下孵育1小时之后,洗掉未结合的Fc片段并且经由流式细胞术分析样品。在图3中,对应的左侧点图示出了使用B1-A(激发:488nm,发射滤光片:500nm-550nm;面积)或B2-A(激发:488nm,发射滤光片:565nm-605nm,面积)参数的硬染色的捕捉珠粒群体。对应的右图示出了R1-A(激发:635nm,发射滤光片:655nm-730nm,面积)或B2-A参数,证实了仅在(C)中AlexaFluor647标记的Fc片段与EV结合,所述EV已经与捕捉珠粒结合。图3显示Fc结合EV与AlexaFluor647标记的Fc片段(人类IgG)结合并且也非常有效地与试剂盒中所包括的由制造商在所有捕捉珠粒群体上包被的所有39种不同抗体的Fc结构域结合,包括两个阴性对照珠粒群体在内。

[0111] 实施例2:用于递送抗HER2抗体的FCGR1A Lamp2B EV

[0112] 使用超滤和尺寸排阻色谱法从HEK293T细胞(稳定表达FCGR1A细胞外结构域-4×GS接头-Lamp2b或它们的野生型对照)中分离EV。将EV用PKH26红色荧光染料标记,并且通过将EV和抗体在37℃共孵育1小时来用抗HER2抗体或它的同种型对照修饰。通过尺寸排阻色谱法去除未结合的抗体。使用流式细胞术在低表达HER2的细胞系MDA-MB-231中和在高表达HER2的细胞系MDA-MB-361中对抗体修饰的EV的摄取进行表征。图4显示抗HER2抗体仅在高表达HER2的细胞系MDA-MB-361中与同种型对照修饰的EV和野生型EV相比增加修饰的EV的摄取,而在低表达HER2的细胞系MDA-MB-231中不是这样。使用表达CD63-ZZ融合蛋白的EV获得类似的结果。

[0113] 实施例3:包含CD81-蛋白A/G融合蛋白的EV对依那西普的递送

[0114] 使用超滤和尺寸排阻色谱法从HEK293T细胞(稳定表达CD81-蛋白A/G CD81第二环融合蛋白或它们的野生型对照)中分离EV。通过将EV和依那西普在37℃共孵育1小时来将EV用依那西普或对照抗体修饰。通过尺寸排阻色谱法去除未结合的依那西普。为了研究依那西普修饰的EV的抗炎作用,使用经过充分研究的TNBS诱发的结肠炎小鼠模型。该模型模拟了与IBD患者相关的肠道炎症、细胞因子风暴和体重减轻。将24只小鼠分成四个处理组,每组有6只小鼠。在诱发结肠炎之前1周,通过在皮肤上施用150μl的含有2%TNBS的橄榄油乙酸盐溶液来对小鼠进行预致敏。然后通过给予100μl在40%乙醇中含有1.5%TNBS的溶液的直肠输注来诱发结肠炎。在诱发结肠炎后立即,在尾静脉中静脉内施用200μl的10E10个EV/

g的EV。图5显示与野生型EV或对照修饰的EV相反，依那西普包被的EV保护小鼠防止体重减轻，并且显示出比裸依那西普更高的活性，这可能是因为当依那西普被多重化时和/或当Fc结合多肽与它的Fc结构域结合时依那西普与TNFα之间的亲和力更高。

[0115] 实施例4：抗体经由Fc结合EV的细胞内摄取和递送

[0116] 使用超滤和尺寸排阻色谱法从脐带胶样组织来源的MSC(稳定表达TNFR细胞外结构域-2×GGGGS接头-Z结构域-TNFR跨膜结构域-foldon-N末端多配体蛋白聚糖结合蛋白融合蛋白或对照)的条件培养基中分离EV。为了研究Fc结合EV是否可以用于细胞内递送Ab，将4×10^11个EV在400μl中与总共3μg的AlexaFluor488标记的抗Lamin B2 IgG[abcam ab200426，兔单克隆EPR9701(B)]一起孵育16小时(过夜)。对于摄取实验，将Huh7细胞以每孔30,000个细胞平板接种到48孔板中并且孵育16小时，之后添加0.675×10^11个抗体标记的EV。将细胞在加湿气氛中在37℃和5％CO_2下孵育2小时，之后对它们进行胰蛋白酶消化并且通过荧光显微镜术(A)和流式细胞术(B)分析，如图6;A)中所示，显示了与相衬图像合并的绿色荧光信号。B)中的直方图示出了x轴上对数刻度上的绿色荧光强度和y轴上的归一化频率。1：没有经过任何抗体或EV处理的HuH7细胞。2：经过与抗Lamin B2抗体一起孵育的对照EV处理的HuH7细胞。3：经过与抗Lamin B2抗体一起孵育的Fc结合EV处理的HuH7细胞。图6显示在经过Fc结合EV加上抗体处理的细胞中明显存在荧光抗体的信号，而在未处理细胞(1)或对照EV处理的细胞(2)中不存在荧光信号。这表明抗体可以经由Fc结合EV细胞内递送，并且与EV结合显著增加了细胞对抗体的摄取。

[0117] 为了证实功能性细胞内递送，将抗NFkB抗体(抗NFkB-Ab)与对应的EV在37℃一起孵育1小时。将报告细胞系，即稳定表达NFkB-荧光素酶的HEK细胞用5ng/ml的hTNF-α和EV-Ab混合物处理。在处理6小时之后，测量荧光素酶活性。图7显示了当通过Fc结合EV递送抗NFkB-ab时的成功抑制。

[0118] 实施例5：使用被抗整合素-4-α-Ab修饰的Fc结合EV治疗EAE

[0119] 通过在免疫接种后两天并且在同一天皮下注射100μl的MOG_{35-55}-CFA乳液并且腹膜内注射400ng的百日咳毒素对C57BL/6小鼠诱发实验性自身免疫性脑炎(EAE)。如实施例1中所述，从骨髓来源的MSC(稳定表达CD9-ZZ(融合构建体，包含与作为非限制性实例的SEQ ID NO 74可操作地连接的作为非限制性实例的SEQ ID NO 1)结构域融合蛋白或它们的野生型对照)的条件培养基中分离EV。将抗整合素-4-α抗体(Ab)与对应的EV(zzEV或对照EV)一起孵育。在第7天时在存在或不存在EV的情况下向EAE小鼠注射抗整合素-4a-Ab。图8显示对照EV以及抗整合素-4a-Ab本身显示出中度的防止EAE发展的保护作用，而与抗整合素-4a-Ab一起孵育的zzEV显示出对EAE发展的几乎完全抑制。

[0120] 实施例6：通过使用Fc结合EV递送Fc-Cas9核酸内切酶进行靶向基因组缺失

[0121] 如实施例1中所述，从获自脂肪细胞(稳定转染FCGR1A细胞外结构域-4×GS接头-Lamp2b融合蛋白或作为对照的Lamp2b GFP)的细胞培养基中纯化EV。使用不同量的EV(100μg、500μg、2.5mg、5mg以及10mg)，而靶向HPRT的Fc(IGHG1)标记的Cas9向导RNA复合物(所谓的RNP复合物)的量保持在100μg。Cas9复合物与EV的最终重量比分别是1:1、1:5、1:25、1:50以及1:100并且在22℃孵育60分钟。使用1:5的Cas9复合物与EV的重量比获得了Cas9在EV上的最大负载，通过超滤去除游离的Cas9复合物。然后使用负载Cas9的Fc+脂肪细胞-EV以不同的浓度处理Huh7细胞。在24小时之后，收获细胞并且根据制造商的方案使用GeneArt基因

组切割检测试剂盒(赛默科技公司(Thermo scientific))以制备样品基因组切割测定并且在2%琼脂糖凝胶上进行电泳。然后使用Image J软件定量插入缺失。图9显示靶细胞中的剂量依赖性基因编辑。还在相同的设置中评价了各种其它对的Fc结合多肽和与Cas9融合的Fc结构域。还在相同的设置中评价了人类FCAMR(IgA和IgM结合)、人类FCGR3A(IgG结合)、以及人类FCGRB(IgG结合),它们与CD83融合并且与和几种不同的人类Fc结构域(例如IGHM、IGHA1、IGHG1等)融合的Cas9组合。总之,所有构建体都显示出基因编辑活性,但是与FCGR1A细胞外结构域-4×GS接头-Lamp2b融合蛋白相比,具有更低的效能(数据未示)。

[0122] 实施例7:使用人类Fc/pH值感受蛋白G复合物用可溶性溶酶体蛋白修饰EV

[0123] 评价与各种外泌体蛋白,如CD63、Lamp2、以及转铁蛋白受体融合的蛋白G的C2结构域的表达和EV展示水平。为了促进溶酶体蛋白拴系到EV的表面,使人类Fc结构域(源自于IgG)(hFc)与酶GBA的N末端或C末端融合。在N末端融合构建体的情况下,在GBA原生的信号肽之后插入hFc结构域。使这两种构建体共表达引起EV对GBA的显著富集,比野生型GBA的过表达更多。除了蛋白G的野生型C2结构域之外,pH值感受C2结构域也以先前所述的方式展示在EV表面上。虽然pH值感受C2结构域具有有效结合人类Fc区的能力,但是在pH 4下,复合物形成的亲和力下降超过一千倍。在由pH值感受C2结构域EV修饰的GBA被细胞摄取后,它们被运输到溶酶体隔室。在所述隔室的低pH值内,拴系的GBA和pH值感受c2结构域解离,从而有助于游离的未拴系的GBA在溶酶体的内腔内存在。

[0124] 在37℃将从产生野生型外泌体、蛋白G的C2结构域修饰的外泌体或蛋白G的pH值感受C2结构域修饰的外泌体的Hek293T细胞中分离的条件培养基与来自表达野生型GBA或人类Fc-GBA融合体的Hek293T细胞的条件培养基组合1小时。此外,进行共孵育,其中将条件培养基酸化到pH 4。然后通过超滤和珠粒洗脱色谱法分离EV。为了评估外泌体拴系的GBA的水平,通过蛋白质印迹法分析纯化的囊泡并且探测GBA的存在。为了评估携带GBA的外泌体的GBA活性,将患者来源的GBA缺陷型成纤维细胞与GBA富集的外泌体共孵育并且在48小时后分析葡萄糖神经酰胺水平。图10显示了该实验的结果:WT:野生型Hek293t外泌体;GBA:野生型GBA;hFc-GBA:人类Fc片段-GBA融合体;PG:用蛋白G的C2结构域修饰的外泌体;PGpH:用pH值感受蛋白G的C2结构域修饰的外泌体。n=3。在类似的实验中,还在相同的设置中评价了作为Fc结合多肽的蛋白L和蛋白LG,产生类似的结果(数据未示)。

[0125] 实施例8:包被有与人类Fc结构域融合的负载siRNA的Ago2的EV产生包含Lamp2b与Fc结合多肽ZZ之间的融合蛋白的EV并且使用超滤和珠粒洗脱色谱法从Hek293T细胞中分离。使hFc-Ago2融合蛋白在Hek293T细胞中表达并且通过亲和色谱法分离,之后,将所述融合蛋白在分子过量的针对细胞周期蛋白D的siRNA中孵育过夜。通过第二轮的亲和纯化去除过量的siRNA。将5×10^6个负载的EV与10^5个U2OS细胞共孵育过夜,之后在48小时之后,收获细胞并且评估细胞周期蛋白D水平。对于体内研究,将1×10^6个A549细胞与1:1比率的基质胶混合并且皮下注射到NCRNU小鼠体内。每隔一天,使用尾静脉施用,用10^7个负载siRNA的外泌体对荷瘤小鼠进行处理。在研究过程中,使用卡尺测量来计算肿瘤体积。在用展示在Lamp2b-ZZ结构域EV表面上的负载siRNA的Ago2处理U2OS细胞之后的细胞周期蛋白D水平显示出显著的靶标沉默,如图11中所示。对于+ve对照,直接转染siCyclin D。hFc表示外泌体表面展示;siCyclin表示抗细胞周期蛋白D siRNA;siScr:乱序序列。n=3。

序列表

<110> Evox Therapeutics Ltd
<120> 胞外囊泡的表面装饰
<130> Evox8
<140> PCT/EP2017/068476
<141> 2017-07-21
<150> GB1612643.5
<151> 2016-07-21
<160> 83
<170> PatentIn 版本 3.5
<210> 1
<211> 227
<212> PRT
<213> 人类(Homo sapiens)
<400> 1

[0001]

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

<210> 2
<211> 219
<212> PRT
<213> 人类
<400> 2

```
Met Gly Met Ser Ser Leu Lys Leu Leu Lys Tyr Val Leu Phe Phe Phe
1               5                  10                  15
Asn Leu Leu Phe Trp Ile Cys Gly Cys Cys Ile Leu Gly Phe Gly Ile
```

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

<210> 3

[0002] <211> 237

<212> PRT

<213> 人类

<400> 3

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

180 185 190
Lys Ile Gly Gly Trp Leu Arg Lys Asn Val Leu Val Val Ala Ala Ala
195 200 205
Ala Leu Gly Ile Ala Phe Val Glu Val Leu Gly Ile Val Phe Ala Cys
210 215 220
Cys Leu Val Lys Ser Ile Arg Ser Gly Tyr Glu Val Met
225 230 235

<210> 4
<211> 236
<212> PRT
<213> 人类
<400> 4

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

[0003] Phe Val Asn Lys Asp Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp
115 120 125
Gln Ala Leu Gln Gln Ala Val Val Asp Asp Asp Ala Asn Asn Ala Lys
130 135 140
Ala Val Val Lys Thr Phe His Glu Thr Leu Asp Cys Cys Gly Ser Ser
145 150 155 160
Thr Leu Thr Ala Leu Thr Thr Ser Val Leu Lys Asn Asn Leu Cys Pro
165 170 175
Ser Gly Ser Asn Ile Ile Ser Asn Leu Phe Lys Glu Asp Cys His Gln
180 185 190
Lys Ile Asp Asp Leu Phe Ser Gly Lys Leu Tyr Leu Ile Gly Ile Ala
195 200 205
Ala Ile Val Val Ala Val Ile Met Ile Phe Glu Met Ile Leu Ser Met
210 215 220
Val Leu Cys Cys Gly Ile Arg Asn Ser Ser Val Tyr
225 230 235

<210> 5
<211> 532
<212> PRT
<213> 人类
<400> 5

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

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

[0004] Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly Asn Asp Ser Phe Ser Ala
260 265 270
Lys Ala Ser Val Ser Val Thr Ala Glu Asp Glu Gly Thr Gln Arg Leu
275 280 285
Thr Cys Ala Val Ile Leu Gly Asn Gln Ser Gln Glu Thr Leu Gln Thr
290 295 300
Val Thr Ile Tyr Ser Phe Pro Ala Pro Asn Val Ile Leu Thr Lys Pro
305 310 315 320
Glu Val Ser Glu Gly Thr Glu Val Thr Val Lys Cys Glu Ala His Pro
325 330 335
Arg Ala Lys Val Thr Leu Asn Gly Val Pro Ala Gln Pro Leu Gly Pro
340 345 350
Arg Ala Gln Leu Leu Leu Lys Ala Thr Pro Glu Asp Asn Gly Arg Ser
355 360 365
Phe Ser Cys Ser Ala Thr Leu Glu Val Ala Gly Gln Leu Ile His Lys
370 375 380
Asn Gln Thr Arg Glu Leu Arg Val Leu Tyr Gly Pro Arg Leu Asp Glu
385 390 395 400
Arg Asp Cys Pro Gly Asn Trp Thr Trp Pro Glu Asn Ser Gln Gln Thr
405 410 415
Pro Met Cys Gln Ala Trp Gly Asn Pro Leu Pro Glu Leu Lys Cys Leu
420 425 430
Lys Asp Gly Thr Phe Pro Leu Pro Ile Gly Glu Ser Val Thr Val Thr
435 440 445
Arg Asp Leu Glu Gly Thr Tyr Leu Cys Arg Ala Arg Ser Thr Gln Gly
450 455 460
Glu Val Thr Arg Lys Val Thr Val Asn Val Leu Ser Pro Arg Tyr Glu

```
465                 470                 475                 480
Ile Val Ile Ile Thr Val Val Ala Ala Ala Val Ile Met Gly Thr Ala
                485                 490                 495
Gly Leu Ser Thr Tyr Leu Tyr Asn Arg Gln Arg Lys Ile Lys Lys Tyr
            500                 505                 510
Arg Leu Gln Gln Ala Gln Lys Gly Thr Pro Met Lys Pro Asn Thr Gln
        515                 520                 525
Ala Thr Pro Pro
    530
<210>  6
<211>  547
<212>  PRT
<213>  人类
<400>  6
Met Ala Thr Met Val Pro Ser Val Leu Trp Pro Arg Ala Cys Trp Thr
1               5                   10                  15
Leu Leu Val Cys Cys Leu Leu Thr Pro Gly Val Gln Gly Gln Glu Phe
            20                  25                  30
Leu Leu Arg Val Glu Pro Gln Asn Pro Val Leu Ser Ala Gly Gly Ser
        35                  40                  45
Leu Phe Val Asn Cys Ser Thr Asp Cys Pro Ser Ser Glu Lys Ile Ala
    50                  55                  60
Leu Glu Thr Ser Leu Ser Lys Glu Leu Val Ala Ser Gly Met Gly Trp
65                  70                  75                  80
Ala Ala Phe Asn Leu Ser Asn Val Thr Gly Asn Ser Arg Ile Leu Cys
                85                  90                  95
Ser Val Tyr Cys Asn Gly Ser Gln Ile Thr Gly Ser Ser Asn Ile Thr
            100                 105                 110
Val Tyr Arg Leu Pro Glu Arg Val Glu Leu Ala Pro Leu Pro Pro Trp
        115                 120                 125
Gln Pro Val Gly Gln Asn Phe Thr Leu Arg Cys Gln Val Glu Asp Gly
    130                 135                 140
Ser Pro Arg Thr Ser Leu Thr Val Val Leu Leu Arg Trp Glu Glu Glu
145                 150                 155                 160
Leu Ser Arg Gln Pro Ala Val Glu Glu Pro Ala Glu Val Thr Ala Thr
                165                 170                 175
Val Leu Ala Ser Arg Asp Asp His Gly Ala Pro Phe Ser Cys Arg Thr
            180                 185                 190
Glu Leu Asp Met Gln Pro Gln Gly Leu Gly Leu Phe Val Asn Thr Ser
        195                 200                 205
Ala Pro Arg Gln Leu Arg Thr Phe Val Leu Pro Val Thr Pro Pro Arg
    210                 215                 220
Leu Val Ala Pro Arg Phe Leu Glu Val Glu Thr Ser Trp Pro Val Asp
225                 230                 235                 240
Cys Thr Leu Asp Gly Leu Phe Pro Ala Ser Glu Ala Gln Val Tyr Leu
                245                 250                 255
Ala Leu Gly Asp Gln Met Leu Asn Ala Thr Val Met Asn His Gly Asp
            260                 265                 270
Thr Leu Thr Ala Thr Ala Thr Ala Thr Ala Arg Ala Asp Gln Glu Gly
        275                 280                 285
Ala Arg Glu Ile Val Cys Asn Val Thr Leu Gly Gly Glu Arg Arg Glu
    290                 295                 300
Ala Arg Glu Asn Leu Thr Val Phe Ser Phe Leu Gly Pro Ile Val Asn
```

[0005]

305 310 315 320
Leu Ser Glu Pro Thr Ala His Glu Gly Ser Thr Val Thr Val Ser Cys
325 330 335
Met Ala Gly Ala Arg Val Gln Val Thr Leu Asp Gly Val Pro Ala Ala
340 345 350
Ala Pro Gly Gln Pro Ala Gln Leu Gln Leu Asn Ala Thr Glu Ser Asp
355 360 365
Asp Gly Arg Ser Phe Phe Cys Ser Ala Thr Leu Glu Val Asp Gly Glu
370 375 380
Phe Leu His Arg Asn Ser Ser Val Gln Leu Arg Val Leu Tyr Gly Pro
385 390 395 400
Lys Ile Asp Arg Ala Thr Cys Pro Gln His Leu Lys Trp Lys Asp Lys
405 410 415
Thr Arg His Val Leu Gln Cys Gln Ala Arg Gly Asn Pro Tyr Pro Glu
420 425 430
Leu Arg Cys Leu Lys Glu Gly Ser Ser Arg Glu Val Pro Val Gly Ile
435 440 445
Pro Phe Phe Val Asn Val Thr His Asn Gly Thr Tyr Gln Cys Gln Ala
450 455 460
Ser Ser Ser Arg Gly Lys Tyr Thr Leu Val Val Val Met Asp Ile Glu
465 470 475 480
Ala Gly Ser Ser His Phe Val Pro Val Phe Val Ala Val Leu Leu Thr
485 490 495
Leu Gly Val Val Thr Ile Val Leu Ala Leu Met Tyr Val Phe Arg Glu
500 505 510
His Gln Arg Ser Gly Ser Tyr His Val Arg Glu Glu Ser Thr Tyr Leu
[0006] 515 520 525
Pro Leu Thr Ser Met Gln Pro Thr Glu Ala Met Gly Glu Glu Pro Ser
530 535 540
Arg Ala Glu
545

<210> 7
<211> 427
<212> PRT
<213> 人类
<400> 7

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

130 135 140
Ser Val Val Ser Tyr Thr Leu Lys Asp Ile His Asp Asp Gln Asp Tyr
145 150 155 160
Leu His Ser Leu Gly Lys Ala Arg Thr Ala Gln Val Gln Lys Asp Ala
165 170 175
Arg Ile Gly Glu Ala Glu Ala Lys Arg Asp Ala Gly Ile Arg Glu Ala
180 185 190
Lys Ala Lys Gln Glu Lys Val Ser Ala Gln Tyr Leu Ser Glu Ile Glu
195 200 205
Met Ala Lys Ala Gln Arg Asp Tyr Glu Leu Lys Lys Ala Ala Tyr Asp
210 215 220
Ile Glu Val Asn Thr Arg Arg Ala Gln Ala Asp Leu Ala Tyr Gln Leu
225 230 235 240
Gln Val Ala Lys Thr Lys Gln Gln Ile Glu Glu Gln Arg Val Gln Val
245 250 255
Gln Val Val Glu Arg Ala Gln Gln Val Ala Val Gln Glu Gln Glu Ile
260 265 270
Ala Arg Arg Glu Lys Glu Leu Glu Ala Arg Val Arg Lys Pro Ala Glu
275 280 285
Ala Glu Arg Tyr Lys Leu Glu Arg Leu Ala Glu Ala Glu Lys Ser Gln
290 295 300
Leu Ile Met Gln Ala Glu Ala Glu Ala Ala Ser Val Arg Met Arg Gly
305 310 315 320
Glu Ala Glu Ala Phe Ala Ile Gly Ala Arg Ala Arg Ala Glu Ala Glu
325 330 335
Gln Met Ala Lys Lys Ala Glu Ala Phe Gln Leu Tyr Gln Glu Ala Ala
[0007] 340 345 350
Gln Leu Asp Met Leu Leu Glu Lys Leu Pro Gln Val Ala Glu Glu Ile
355 360 365
Ser Gly Pro Leu Thr Ser Ala Asn Lys Ile Thr Leu Val Ser Ser Gly
370 375 380
Ser Gly Thr Met Gly Ala Ala Lys Val Thr Gly Glu Val Leu Asp Ile
385 390 395 400
Leu Thr Arg Leu Pro Glu Ser Val Glu Arg Leu Thr Gly Val Ser Ile
405 410 415
Ser Gln Val Asn His Lys Pro Leu Arg Thr Ala
420 425

<210> 8
<211> 427
<212> PRT
<213> 人类
<400> 8

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

85 90 95
Asp Ile Lys Asn Val Val Leu Gln Thr Leu Glu Gly His Leu Arg Ser
100 105 110
Ile Leu Gly Thr Leu Thr Val Glu Gln Ile Tyr Gln Asp Arg Asp Gln
115 120 125
Phe Ala Lys Leu Val Arg Glu Val Ala Ala Pro Asp Val Gly Arg Met
130 135 140
Gly Ile Glu Ile Leu Ser Phe Thr Ile Lys Asp Val Tyr Asp Lys Val
145 150 155 160
Asp Tyr Leu Ser Ser Leu Gly Lys Thr Gln Thr Ala Val Val Gln Arg
165 170 175
Asp Ala Asp Ile Gly Val Ala Glu Ala Glu Arg Asp Ala Gly Ile Arg
180 185 190
Glu Ala Glu Cys Lys Lys Glu Met Leu Asp Val Lys Phe Met Ala Asp
195 200 205
Thr Lys Ile Ala Asp Ser Lys Arg Ala Phe Glu Leu Gln Lys Ser Ala
210 215 220
Phe Ser Glu Glu Val Asn Ile Lys Thr Ala Glu Ala Gln Leu Ala Tyr
225 230 235 240
Glu Leu Gln Gly Ala Arg Glu Gln Gln Lys Ile Arg Gln Glu Glu Ile
245 250 255
Glu Ile Glu Val Val Gln Arg Lys Lys Gln Ile Ala Val Glu Ala Gln
260 265 270
Glu Ile Leu Arg Thr Asp Lys Glu Leu Ile Ala Thr Val Arg Arg Pro
275 280 285
Ala Glu Ala Glu Ala His Arg Ile Gln Gln Ile Ala Glu Gly Glu Lys
[0008] 290 295 300
Val Lys Gln Val Leu Leu Ala Gln Ala Glu Ala Glu Lys Ile Arg Lys
305 310 315 320
Ile Gly Glu Ala Glu Ala Ala Val Ile Glu Ala Met Gly Lys Ala Glu
325 330 335
Ala Glu Arg Met Lys Leu Lys Ala Glu Ala Tyr Gln Lys Tyr Gly Asp
340 345 350
Ala Ala Lys Met Ala Leu Val Leu Glu Ala Leu Pro Gln Ile Ala Ala
355 360 365
Lys Ile Ala Ala Pro Leu Thr Lys Val Asp Glu Ile Val Val Leu Ser
370 375 380
Gly Asp Asn Ser Lys Val Thr Ser Glu Val Asn Arg Leu Leu Ala Glu
385 390 395 400
Leu Pro Ala Ser Val His Ala Leu Thr Gly Val Asp Leu Ser Lys Ile
405 410 415
Pro Leu Ile Lys Lys Ala Thr Gly Val Gln Val
420 425

<210> 9
<211> 1032
<212> PRT
<213> 人类
<400> 9

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

```
          35                  40                  45
Asn Thr Leu Phe Gly Tyr Ser Val Val Leu His Ser His Gly Ala Asn
      50                  55                  60
Arg Trp Leu Leu Val Gly Ala Pro Thr Ala Asn Trp Leu Ala Asn Ala
65                  70                  75                  80
Ser Val Ile Asn Pro Gly Ala Ile Tyr Arg Cys Arg Ile Gly Lys Asn
                  85                  90                  95
Pro Gly Gln Thr Cys Glu Gln Leu Gln Leu Gly Ser Pro Asn Gly Glu
             100                 105                 110
Pro Cys Gly Lys Thr Cys Leu Glu Glu Arg Asp Asn Gln Trp Leu Gly
         115                 120                 125
Val Thr Leu Ser Arg Gln Pro Gly Glu Asn Gly Ser Ile Val Thr Cys
     130                 135                 140
Gly His Arg Trp Lys Asn Ile Phe Tyr Ile Lys Asn Glu Asn Lys Leu
145                 150                 155                 160
Pro Thr Gly Gly Cys Tyr Gly Val Pro Pro Asp Leu Arg Thr Glu Leu
                 165                 170                 175
Ser Lys Arg Ile Ala Pro Cys Tyr Gln Asp Tyr Val Lys Lys Phe Gly
             180                 185                 190
Glu Asn Phe Ala Ser Cys Gln Ala Gly Ile Ser Ser Phe Tyr Thr Lys
         195                 200                 205
Asp Leu Ile Val Met Gly Ala Pro Gly Ser Ser Tyr Trp Thr Gly Ser
     210                 215                 220
Leu Phe Val Tyr Asn Ile Thr Thr Asn Lys Tyr Lys Ala Phe Leu Asp
225                 230                 235                 240
Lys Gln Asn Gln Val Lys Phe Gly Ser Tyr Leu Gly Tyr Ser Val Gly
                 245                 250                 255
Ala Gly His Phe Arg Ser Gln His Thr Thr Glu Val Val Gly Gly Ala
             260                 265                 270
Pro Gln His Glu Gln Ile Gly Lys Ala Tyr Ile Phe Ser Ile Asp Glu
         275                 280                 285
Lys Glu Leu Asn Ile Leu His Glu Met Lys Gly Lys Lys Leu Gly Ser
     290                 295                 300
Tyr Phe Gly Ala Ser Val Cys Ala Val Asp Leu Asn Ala Asp Gly Phe
305                 310                 315                 320
Ser Asp Leu Leu Val Gly Ala Pro Met Gln Ser Thr Ile Arg Glu Glu
                 325                 330                 335
Gly Arg Val Phe Val Tyr Ile Asn Ser Gly Ser Gly Ala Val Met Asn
             340                 345                 350
Ala Met Glu Thr Asn Leu Val Gly Ser Asp Lys Tyr Ala Ala Arg Phe
         355                 360                 365
Gly Glu Ser Ile Val Asn Leu Gly Asp Ile Asp Asn Asp Gly Phe Glu
     370                 375                 380
Asp Val Ala Ile Gly Ala Pro Gln Glu Asp Asp Leu Gln Gly Ala Ile
385                 390                 395                 400
Tyr Ile Tyr Asn Gly Arg Ala Asp Gly Ile Ser Ser Thr Phe Ser Gln
                 405                 410                 415
Arg Ile Glu Gly Leu Gln Ile Ser Lys Ser Leu Ser Met Phe Gly Gln
             420                 425                 430
Ser Ile Ser Gly Gln Ile Asp Ala Asp Asn Asn Gly Tyr Val Asp Val
         435                 440                 445
Ala Val Gly Ala Phe Arg Ser Asp Ser Ala Val Leu Leu Arg Thr Arg
     450                 455                 460
```

[0009]

Pro Val Val Ile Val Asp Ala Ser Leu Ser His Pro Glu Ser Val Asn
465 470 475 480
Arg Thr Lys Phe Asp Cys Val Glu Asn Gly Trp Pro Ser Val Cys Ile
485 490 495
Asp Leu Thr Leu Cys Phe Ser Tyr Lys Gly Lys Glu Val Pro Gly Tyr
500 505 510
Ile Val Leu Phe Tyr Asn Met Ser Leu Asp Val Asn Arg Lys Ala Glu
515 520 525
Ser Pro Pro Arg Phe Tyr Phe Ser Ser Asn Gly Thr Ser Asp Val Ile
530 535 540
Thr Gly Ser Ile Gln Val Ser Ser Arg Glu Ala Asn Cys Arg Thr His
545 550 555 560
Gln Ala Phe Met Arg Lys Asp Val Arg Asp Ile Leu Thr Pro Ile Gln
565 570 575
Ile Glu Ala Ala Tyr His Leu Gly Pro His Val Ile Ser Lys Arg Ser
580 585 590
Thr Glu Glu Phe Pro Pro Leu Gln Pro Ile Leu Gln Gln Lys Lys Glu
595 600 605
Lys Asp Ile Met Lys Lys Thr Ile Asn Phe Ala Arg Phe Cys Ala His
610 615 620
Glu Asn Cys Ser Ala Asp Leu Gln Val Ser Ala Lys Ile Gly Phe Leu
625 630 635 640
Lys Pro His Glu Asn Lys Thr Tyr Leu Ala Val Gly Ser Met Lys Thr
645 650 655
Leu Met Leu Asn Val Ser Leu Phe Asn Ala Gly Asp Asp Ala Tyr Glu
660 665 670

[0010] Thr Thr Leu His Val Lys Leu Pro Val Gly Leu Tyr Phe Ile Lys Ile
675 680 685
Leu Glu Leu Glu Glu Lys Gln Ile Asn Cys Glu Val Thr Asp Asn Ser
690 695 700
Gly Val Val Gln Leu Asp Cys Ser Ile Gly Tyr Ile Tyr Val Asp His
705 710 715 720
Leu Ser Arg Ile Asp Ile Ser Phe Leu Leu Asp Val Ser Ser Leu Ser
725 730 735
Arg Ala Glu Glu Asp Leu Ser Ile Thr Val His Ala Thr Cys Glu Asn
740 745 750
Glu Glu Glu Met Asp Asn Leu Lys His Ser Arg Val Thr Val Ala Ile
755 760 765
Pro Leu Lys Tyr Glu Val Lys Leu Thr Val His Gly Phe Val Asn Pro
770 775 780
Thr Ser Phe Val Tyr Gly Ser Asn Asp Glu Asn Glu Pro Glu Thr Cys
785 790 795 800
Met Val Glu Lys Met Asn Leu Thr Phe His Val Ile Asn Thr Gly Asn
805 810 815
Ser Met Ala Pro Asn Val Ser Val Glu Ile Met Val Pro Asn Ser Phe
820 825 830
Ser Pro Gln Thr Asp Lys Leu Phe Asn Ile Leu Asp Val Gln Thr Thr
835 840 845
Thr Gly Glu Cys His Phe Glu Asn Tyr Gln Arg Val Cys Ala Leu Glu
850 855 860
Gln Gln Lys Ser Ala Met Gln Thr Leu Lys Gly Ile Val Arg Phe Leu
865 870 875 880
Ser Lys Thr Asp Lys Arg Leu Leu Tyr Cys Ile Lys Ala Asp Pro His

885 890 895
Cys Leu Asn Phe Leu Cys Asn Phe Gly Lys Met Glu Ser Gly Lys Glu
900 905 910
Ala Ser Val His Ile Gln Leu Glu Gly Arg Pro Ser Ile Leu Glu Met
915 920 925
Asp Glu Thr Ser Ala Leu Lys Phe Glu Ile Arg Ala Thr Gly Phe Pro
930 935 940
Glu Pro Asn Pro Arg Val Ile Glu Leu Asn Lys Asp Glu Asn Val Ala
945 950 955 960
His Val Leu Leu Glu Gly Leu His His Gln Arg Pro Lys Arg Tyr Phe
965 970 975
Thr Ile Val Ile Ile Ser Ser Ser Leu Leu Leu Gly Leu Ile Val Leu
980 985 990
Leu Leu Ile Ser Tyr Val Met Trp Lys Ala Gly Phe Phe Lys Arg Gln
995 1000 1005
Tyr Lys Ser Ile Leu Gln Glu Glu Asn Arg Arg Asp Ser Trp Ser
1010 1015 1020
Tyr Ile Asn Ser Lys Ser Asn Asp Asp
1025 1030

<210> 10
<211> 760
<212> PRT
<213> 人类
<400> 10

Met Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu
1 5 10 15

[0011] Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
20 25 30
Asn Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala
35 40 45
Asp Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly
50 55 60
Ser Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly
65 70 75 80
Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
85 90 95
Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro
100 105 110
Gly Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys
115 120 125
Arg Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile
130 135 140
Lys Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln
145 150 155 160
Lys Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe
165 170 175
Lys Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val
180 185 190
Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg
195 200 205
Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys
210 215 220
Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys

[0012]

```
225                 230                 235                 240
Lys Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile
                245                 250                 255
Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
            260                 265                 270
Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
        275                 280                 285
Pro Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly
    290                 295                 300
Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
305                 310                 315                 320
Phe Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr
                325                 330                 335
Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
            340                 345                 350
Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser
        355                 360                 365
Glu Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile
    370                 375                 380
Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
385                 390                 395                 400
His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
                405                 410                 415
Ala Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met
            420                 425                 430
Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
        435                 440                 445
Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
    450                 455                 460
Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
465                 470                 475                 480
Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
                485                 490                 495
Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn
            500                 505                 510
Val Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp
        515                 520                 525
Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
    530                 535                 540
Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
545                 550                 555                 560
Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu
                565                 570                 575
Ile Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu
            580                 585                 590
Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn
        595                 600                 605
Leu Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp
    610                 615                 620
Leu Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln
625                 630                 635                 640
Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
                645                 650                 655
```

Thr Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys
660 665 670
Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro
675 680 685
Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
690 695 700
Gly Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys
705 710 715 720
Gln Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
725 730 735
Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
740 745 750
Val Trp Asp Ile Asp Asn Glu Phe
755 760

<210> 11
<211> 865
<212> PRT
<213> 人类
<400> 11

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

[0013]

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

Met Asn Ser Thr Leu Lys Ser Leu His Gln Gln Ser Thr Gln Leu Ser
275 280 285
Ser Ser Leu Thr Ser Val Lys Thr Ser Leu Arg Ser Ser Leu Asn Asp
290 295 300
Pro Leu Cys Leu Val His Pro Ser Ser Glu Thr Cys Asn Ser Ile Arg
305 310 315 320
Leu Ser Leu Ser Gln Leu Asn Ser Asn Pro Glu Leu Arg Gln Leu Pro
325 330 335
Pro Val Asp Ala Glu Leu Asp Asn Val Asn Asn Val Leu Arg Thr Asp
340 345 350
Leu Asp Gly Leu Val Gln Gln Gly Tyr Gln Ser Leu Asn Asp Ile Pro
355 360 365
Asp Arg Val Gln Arg Gln Thr Thr Thr Val Val Ala Gly Ile Lys Arg
370 375 380
Val Leu Asn Ser Ile Gly Ser Asp Ile Asp Asn Val Thr Gln Arg Leu
385 390 395 400
Pro Ile Gln Asp Ile Leu Ser Ala Phe Ser Val Tyr Val Asn Asn Thr
405 410 415
Glu Ser Tyr Ile His Arg Asn Leu Pro Thr Leu Glu Glu Tyr Asp Ser
420 425 430
Tyr Trp Trp Leu Gly Gly Leu Val Ile Cys Ser Leu Leu Thr Leu Ile
435 440 445
Val Ile Phe Tyr Tyr Leu Gly Leu Leu Cys Gly Val Cys Gly Tyr Asp
450 455 460
Arg His Ala Thr Pro Thr Thr Arg Gly Cys Val Ser Asn Thr Gly Gly
465 470 475 480

[0014] Val Phe Leu Met Val Gly Val Gly Leu Ser Phe Leu Phe Cys Trp Ile
485 490 495
Leu Met Ile Ile Val Val Leu Thr Phe Val Phe Gly Ala Asn Val Glu
500 505 510
Lys Leu Ile Cys Glu Pro Tyr Thr Ser Lys Glu Leu Phe Arg Val Leu
515 520 525
Asp Thr Pro Tyr Leu Leu Asn Glu Asp Trp Glu Tyr Tyr Leu Ser Gly
530 535 540
Lys Leu Phe Asn Lys Ser Lys Met Lys Leu Thr Phe Glu Gln Val Tyr
545 550 555 560
Ser Asp Cys Lys Lys Asn Arg Gly Thr Tyr Gly Thr Leu His Leu Gln
565 570 575
Asn Ser Phe Asn Ile Ser Glu His Leu Asn Ile Asn Glu His Thr Gly
580 585 590
Ser Ile Ser Ser Glu Leu Glu Ser Leu Lys Val Asn Leu Asn Ile Phe
595 600 605
Leu Leu Gly Ala Ala Gly Arg Lys Asn Leu Gln Asp Phe Ala Ala Cys
610 615 620
Gly Ile Asp Arg Met Asn Tyr Asp Ser Tyr Leu Ala Gln Thr Gly Lys
625 630 635 640
Ser Pro Ala Gly Val Asn Leu Leu Ser Phe Ala Tyr Asp Leu Glu Ala
645 650 655
Lys Ala Asn Ser Leu Pro Pro Gly Asn Leu Arg Asn Ser Leu Lys Arg
660 665 670
Asp Ala Gln Thr Ile Lys Thr Ile His Gln Gln Arg Val Leu Pro Ile
675 680 685
Glu Gln Ser Leu Ser Thr Leu Tyr Gln Ser Val Lys Ile Leu Gln Arg

690 695 700
Thr Gly Asn Gly Leu Leu Glu Arg Val Thr Arg Ile Leu Ala Ser Leu
705 710 715 720
Asp Phe Ala Gln Asn Phe Ile Thr Asn Asn Thr Ser Ser Val Ile Ile
725 730 735
Glu Glu Thr Lys Lys Tyr Gly Arg Thr Ile Ile Gly Tyr Phe Glu His
740 745 750
Tyr Leu Gln Trp Ile Glu Phe Ser Ile Ser Glu Lys Val Ala Ser Cys
755 760 765
Lys Pro Val Ala Thr Ala Leu Asp Thr Ala Val Asp Val Phe Leu Cys
770 775 780
Ser Tyr Ile Ile Asp Pro Leu Asn Leu Phe Trp Phe Gly Ile Gly Lys
785 790 795 800
Ala Thr Val Phe Leu Leu Pro Ala Leu Ile Phe Ala Val Lys Leu Ala
805 810 815
Lys Tyr Tyr Arg Arg Met Asp Ser Glu Asp Val Tyr Asp Asp Val Glu
820 825 830
Thr Ile Pro Met Lys Asn Met Glu Asn Gly Asn Asn Gly Tyr His Lys
835 840 845
Asp His Val Tyr Gly Ile His Asn Pro Val Met Thr Ser Pro Ser Gln
850 855 860
His
865

<210> 12
<211> 310
<212> PRT
[0015] <213> 人类
<400> 12

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

195 200 205
Gln Asp Phe Thr Phe Glu Thr Ser Gly Glu Asn Thr Ala Val Val Ala
210 215 220
Val Glu Pro Asp Arg Arg Asn Gln Ser Pro Val Asp Gln Gly Ala Thr
225 230 235 240
Gly Ala Ser Gln Gly Leu Leu Asp Arg Lys Glu Val Leu Gly Gly Val
245 250 255
Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly
260 265 270
Phe Met Leu Tyr Arg Met Lys Lys Lys Asp Glu Gly Ser Tyr Ser Leu
275 280 285
Glu Glu Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys
290 295 300
Gln Glu Glu Phe Tyr Ala
305 310

<210> 13
<211> 150
<212> PRT
<213> 人类
<400> 13

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

[0016]

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

<210> 14
<211> 867
<212> PRT
<213> 人类
<400> 14

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

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

[0017]

Ile Ala Arg Leu Gln His Ala Ala Glu Leu Ile Lys Thr Val Ala Ser
275 280 285
Arg Tyr Asp Glu Tyr Val Asn Val Lys Asp Phe Ser Asp Lys Ile Asn
290 295 300
Arg Ala Leu Ala Ala Ala Lys Lys Asp Asn Asp Phe Ile Tyr His Asp
305 310 315 320
Arg Val Pro Asp Leu Lys Asp Leu Asp Pro Ile Gly Lys Ala Thr Leu
325 330 335
Val Lys Ser Thr Pro Val Asn Val Pro Ile Ser Gln Lys Phe Thr Asp
340 345 350
Leu Phe Glu Lys Met Val Pro Val Ser Val Gln Gln Ser Leu Ala Ala
355 360 365
Tyr Asn Gln Arg Lys Ala Asp Leu Val Asn Arg Ser Ile Ala Gln Met
370 375 380
Arg Glu Ala Thr Thr Leu Ala Asn Gly Val Leu Ala Ser Leu Asn Leu
385 390 395 400
Pro Ala Ala Ile Glu Asp Val Ser Gly Asp Thr Val Pro Gln Ser Ile
405 410 415
Leu Thr Lys Ser Arg Ser Val Ile Glu Gln Gly Gly Ile Gln Thr Val
420 425 430
Asp Gln Leu Ile Lys Glu Leu Pro Glu Leu Leu Gln Arg Asn Arg Glu
435 440 445
Ile Leu Asp Glu Ser Leu Arg Leu Leu Asp Glu Glu Glu Ala Thr Asp
450 455 460
Asn Asp Leu Arg Ala Lys Phe Lys Glu Arg Trp Gln Arg Thr Pro Ser
465 470 475 480
Asn Glu Leu Tyr Lys Pro Leu Arg Ala Glu Gly Thr Asn Phe Arg Thr

485 490 495
Val Leu Asp Lys Ala Val Gln Ala Asp Gly Gln Val Lys Glu Cys Tyr
500 505 510
Gln Ser His Arg Asp Thr Ile Val Leu Leu Cys Lys Pro Glu Pro Glu
515 520 525
Leu Asn Ala Ala Ile Pro Ser Ala Asn Pro Ala Lys Thr Met Gln Gly
530 535 540
Ser Glu Val Val Asn Val Leu Lys Ser Leu Leu Ser Asn Leu Asp Glu
545 550 555 560
Val Lys Lys Glu Arg Glu Gly Leu Glu Asn Asp Leu Lys Ser Val Asn
565 570 575
Phe Asp Met Thr Ser Lys Phe Leu Thr Ala Leu Ala Gln Asp Gly Val
580 585 590
Ile Asn Glu Glu Ala Leu Ser Val Thr Glu Leu Asp Arg Val Tyr Gly
595 600 605
Gly Leu Thr Thr Lys Val Gln Glu Ser Leu Lys Lys Gln Glu Gly Leu
610 615 620
Leu Lys Asn Ile Gln Val Ser His Gln Glu Phe Ser Lys Met Lys Gln
625 630 635 640
Ser Asn Asn Glu Ala Asn Leu Arg Glu Glu Val Leu Lys Asn Leu Ala
645 650 655
Thr Ala Tyr Asp Asn Phe Val Glu Leu Val Ala Asn Leu Lys Glu Gly
660 665 670
Thr Lys Phe Tyr Asn Glu Leu Thr Glu Ile Leu Val Arg Phe Gln Asn
675 680 685
Lys Cys Ser Asp Ile Val Phe Ala Arg Lys Thr Glu Arg Asp Glu Leu
[0018] 690 695 700
Leu Lys Asp Leu Gln Gln Ser Ile Ala Arg Glu Pro Ser Ala Pro Ser
705 710 715 720
Ile Pro Thr Pro Ala Tyr Gln Ser Ser Pro Ala Gly Gly His Ala Pro
725 730 735
Thr Pro Pro Thr Pro Ala Pro Arg Thr Met Pro Pro Thr Lys Pro Gln
740 745 750
Pro Pro Ala Arg Pro Pro Pro Pro Val Leu Pro Ala Asn Arg Ala Pro
755 760 765
Ser Ala Thr Ala Pro Ser Pro Val Gly Ala Gly Thr Ala Ala Pro Ala
770 775 780
Pro Ser Gln Thr Pro Gly Ser Ala Pro Pro Pro Gln Ala Gln Gly Pro
785 790 795 800
Pro Tyr Pro Thr Tyr Pro Gly Tyr Pro Gly Tyr Cys Gln Met Pro Met
805 810 815
Pro Met Gly Tyr Asn Pro Tyr Ala Tyr Gly Gln Tyr Asn Met Pro Tyr
820 825 830
Pro Pro Val Tyr His Gln Ser Pro Gly Gln Ala Pro Tyr Pro Gly Pro
835 840 845
Gln Gln Pro Ser Tyr Pro Phe Pro Gln Pro Pro Gln Gln Ser Tyr Tyr
850 855 860
Pro Gln Gln
865
<210> 15
<211> 297
<212> PRT
<213> 人类

<400> 15

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

[0019]

<210> 16
<211> 292
<212> PRT
<213> 人类
<400> 16

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

65 70 75 80
Pro Gly Pro Gly Gln Met Val Ala Pro Val Thr Gly Tyr Ser Leu Gly
85 90 95
Val Arg Arg Ala Glu Ile Lys Pro Gly Val Arg Glu Ile His Leu Cys
100 105 110
Lys Asp Glu Arg Gly Lys Thr Gly Leu Arg Leu Arg Lys Val Asp Gln
115 120 125
Gly Leu Phe Val Gln Leu Val Gln Ala Asn Thr Pro Ala Ser Leu Val
130 135 140
Gly Leu Arg Phe Gly Asp Gln Leu Leu Gln Ile Asp Gly Arg Asp Cys
145 150 155 160
Ala Gly Trp Ser Ser His Lys Ala His Gln Val Val Lys Lys Ala Ser
165 170 175
Gly Asp Lys Ile Val Val Val Val Arg Asp Arg Pro Phe Gln Arg Thr
180 185 190
Val Thr Met His Lys Asp Ser Met Gly His Val Gly Phe Val Ile Lys
195 200 205
Lys Gly Lys Ile Val Ser Leu Val Lys Gly Ser Ser Ala Ala Arg Asn
210 215 220
Gly Leu Leu Thr Asn His Tyr Val Cys Glu Val Asp Gly Gln Asn Val
225 230 235 240
Ile Gly Leu Lys Asp Lys Lys Ile Met Glu Ile Leu Ala Thr Ala Gly
245 250 255
Asn Val Val Thr Leu Thr Ile Ile Pro Ser Val Ile Tyr Glu His Met
260 265 270
Val Lys Lys Leu Pro Pro Val Leu Leu His His Thr Met Asp His Ser
[0020] 275 280 285
Ile Pro Asp Ala
290

<210> 17
<211> 410
<212> PRT
<213> 人类
<400> 17

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

145 150 155 160
Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe
165 170 175
Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp
180 185 190
Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
195 200 205
Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser
210 215 220
Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln
225 230 235 240
Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro
245 250 255
Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu
260 265 270
Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val
275 280 285
Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr
290 295 300
Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr
305 310 315 320
Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr
325 330 335
Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val
340 345 350
Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys
[0021] 355 360 365
Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala
370 375 380
Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu
385 390 395 400
Lys His His His Ala Gly Tyr Glu Gln Phe
405 410

<210> 18
<211> 918
<212> PRT
<213> 人类
<400> 18
Met Leu Thr Leu Gln Thr Trp Leu Val Gln Ala Leu Phe Ile Phe Leu
1 5 10 15
Thr Thr Glu Ser Thr Gly Glu Leu Leu Asp Pro Cys Gly Tyr Ile Ser
20 25 30
Pro Glu Ser Pro Val Val Gln Leu His Ser Asn Phe Thr Ala Val Cys
35 40 45
Val Leu Lys Glu Lys Cys Met Asp Tyr Phe His Val Asn Ala Asn Tyr
50 55 60
Ile Val Trp Lys Thr Asn His Phe Thr Ile Pro Lys Glu Gln Tyr Thr
65 70 75 80
Ile Ile Asn Arg Thr Ala Ser Ser Val Thr Phe Thr Asp Ile Ala Ser
85 90 95
Leu Asn Ile Gln Leu Thr Cys Asn Ile Leu Thr Phe Gly Gln Leu Glu
100 105 110
Gln Asn Val Tyr Gly Ile Thr Ile Ile Ser Gly Leu Pro Pro Glu Lys

```
          115                 120                 125
Pro Lys Asn Leu Ser Cys Ile Val Asn Glu Gly Lys Lys Met Arg Cys
      130                 135                 140
Glu Trp Asp Arg Gly Arg Glu Thr His Leu Glu Thr Asn Phe Thr Leu
145                 150                 155                 160
Lys Ser Glu Trp Ala Thr His Lys Phe Ala Asp Cys Lys Ala Lys Arg
                  165                 170                 175
Asp Thr Pro Thr Ser Cys Thr Val Asp Tyr Ser Thr Val Tyr Phe Val
              180                 185                 190
Asn Ile Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Thr
          195                 200                 205
Ser Asp His Ile Asn Phe Asp Pro Val Tyr Lys Val Lys Pro Asn Pro
      210                 215                 220
Pro His Asn Leu Ser Val Ile Asn Ser Glu Glu Leu Ser Ser Ile Leu
225                 230                 235                 240
Lys Leu Thr Trp Thr Asn Pro Ser Ile Lys Ser Val Ile Ile Leu Lys
                  245                 250                 255
Tyr Asn Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ser Gln Ile
              260                 265                 270
Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln Asp
          275                 280                 285
Leu Lys Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Cys Met Lys Glu
      290                 295                 300
Asp Gly Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Ile
305                 310                 315                 320
Thr Tyr Glu Asp Arg Pro Ser Lys Ala Pro Ser Phe Trp Tyr Lys Ile
```

[0022]

```
                  325                 330                 335
Asp Pro Ser His Thr Gln Gly Tyr Arg Thr Val Gln Leu Val Trp Lys
              340                 345                 350
Thr Leu Pro Pro Phe Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val
          355                 360                 365
Thr Leu Thr Arg Trp Lys Ser His Leu Gln Asn Tyr Thr Val Asn Ala
      370                 375                 380
Thr Lys Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Val Ala Thr Leu
385                 390                 395                 400
Thr Val Arg Asn Leu Val Gly Lys Ser Asp Ala Ala Val Leu Thr Ile
                  405                 410                 415
Pro Ala Cys Asp Phe Gln Ala Thr His Pro Val Met Asp Leu Lys Ala
              420                 425                 430
Phe Pro Lys Asp Asn Met Leu Trp Val Glu Trp Thr Thr Pro Arg Glu
          435                 440                 445
Ser Val Lys Lys Tyr Ile Leu Glu Trp Cys Val Leu Ser Asp Lys Ala
      450                 455                 460
Pro Cys Ile Thr Asp Trp Gln Gln Glu Asp Gly Thr Val His Arg Thr
465                 470                 475                 480
Tyr Leu Arg Gly Asn Leu Ala Glu Ser Lys Cys Tyr Leu Ile Thr Val
                  485                 490                 495
Thr Pro Val Tyr Ala Asp Gly Pro Gly Ser Pro Glu Ser Ile Lys Ala
              500                 505                 510
Tyr Leu Lys Gln Ala Pro Pro Ser Lys Gly Pro Thr Val Arg Thr Lys
          515                 520                 525
Lys Val Gly Lys Asn Glu Ala Val Leu Glu Trp Asp Gln Leu Pro Val
      530                 535                 540
```

Asp Val Gln Asn Gly Phe Ile Arg Asn Tyr Thr Ile Phe Tyr Arg Thr
545 550 555 560
Ile Ile Gly Asn Glu Thr Ala Val Asn Val Asp Ser Ser His Thr Glu
565 570 575
Tyr Thr Leu Ser Ser Leu Thr Ser Asp Thr Leu Tyr Met Val Arg Met
580 585 590
Ala Ala Tyr Thr Asp Glu Gly Gly Lys Asp Gly Pro Glu Phe Thr Phe
595 600 605
Thr Thr Pro Lys Phe Ala Gln Gly Glu Ile Glu Ala Ile Val Val Pro
610 615 620
Val Cys Leu Ala Phe Leu Leu Thr Thr Leu Leu Gly Val Leu Phe Cys
625 630 635 640
Phe Asn Lys Arg Asp Leu Ile Lys Lys His Ile Trp Pro Asn Val Pro
645 650 655
Asp Pro Ser Lys Ser His Ile Ala Gln Trp Ser Pro His Thr Pro Pro
660 665 670
Arg His Asn Phe Asn Ser Lys Asp Gln Met Tyr Ser Asp Gly Asn Phe
675 680 685
Thr Asp Val Ser Val Val Glu Ile Glu Ala Asn Asp Lys Lys Pro Phe
690 695 700
Pro Glu Asp Leu Lys Ser Leu Asp Leu Phe Lys Lys Glu Lys Ile Asn
705 710 715 720
Thr Glu Gly His Ser Ser Gly Ile Gly Gly Ser Ser Cys Met Ser Ser
725 730 735
Ser Arg Pro Ser Ile Ser Ser Ser Asp Glu Asn Glu Ser Ser Gln Asn
740 745 750

[0023] Thr Ser Ser Thr Val Gln Tyr Ser Thr Val Val His Ser Gly Tyr Arg
755 760 765
His Gln Val Pro Ser Val Gln Val Phe Ser Arg Ser Glu Ser Thr Gln
770 775 780
Pro Leu Leu Asp Ser Glu Glu Arg Pro Glu Asp Leu Gln Leu Val Asp
785 790 795 800
His Val Asp Gly Gly Asp Gly Ile Leu Pro Arg Gln Gln Tyr Phe Lys
805 810 815
Gln Asn Cys Ser Gln His Glu Ser Ser Pro Asp Ile Ser His Phe Glu
820 825 830
Arg Ser Lys Gln Val Ser Ser Val Asn Glu Glu Asp Phe Val Arg Leu
835 840 845
Lys Gln Gln Ile Ser Asp His Ile Ser Gln Ser Cys Gly Ser Gly Gln
850 855 860
Met Lys Met Phe Gln Glu Val Ser Ala Ala Asp Ala Phe Gly Pro Gly
865 870 875 880
Thr Glu Gly Gln Val Glu Arg Phe Glu Thr Val Gly Met Glu Ala Ala
885 890 895
Thr Asp Glu Gly Met Pro Lys Ser Tyr Leu Pro Gln Thr Val Arg Gln
900 905 910
Gly Gly Tyr Met Pro Gln
915

<210> 19
<211> 455
<212> PRT
<213> 人类
<400> 19

```
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
1               5                  10                  15
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
            20                  25                  30
His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
        35                  40                  45
Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65                  70                  75                  80
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
                85                  90                  95
Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
            100                 105                 110
Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
        115                 120                 125
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
    130                 135                 140
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145                 150                 155                 160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190
Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205
Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu
    210                 215                 220
Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys
225                 230                 235                 240
Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu
                245                 250                 255
Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser
            260                 265                 270
Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val
        275                 280                 285
Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys
    290                 295                 300
Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly
305                 310                 315                 320
Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn
                325                 330                 335
Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
            340                 345                 350
Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
        355                 360                 365
Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
    370                 375                 380
Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
385                 390                 395                 400
Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
                405                 410                 415
Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
```

[0024]

420 425 430
Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
435 440 445
Pro Ala Pro Ser Leu Leu Arg
450 455
<210> 20
<211> 201
<212> PRT
<213> 人类
<400> 20
Met Arg Arg Ala Trp Ile Leu Leu Thr Leu Gly Leu Val Ala Cys Val
1 5 10 15
Ser Ala Glu Ser Arg Ala Glu Leu Thr Ser Asp Lys Asp Met Tyr Leu
20 25 30
Asp Asn Ser Ser Ile Glu Glu Ala Ser Gly Val Tyr Pro Ile Asp Asp
35 40 45
Asp Asp Tyr Ala Ser Ala Ser Gly Ser Gly Ala Asp Glu Asp Val Glu
50 55 60
Ser Pro Glu Leu Thr Thr Ser Arg Pro Leu Pro Lys Ile Leu Leu Thr
65 70 75 80
Ser Ala Ala Pro Lys Val Glu Thr Thr Thr Leu Asn Ile Gln Asn Lys
85 90 95
Ile Pro Ala Gln Thr Lys Ser Pro Glu Glu Thr Asp Lys Glu Lys Val
100 105 110
His Leu Ser Asp Ser Glu Arg Lys Met Asp Pro Ala Glu Glu Asp Thr
115 120 125
[0025] Asn Val Tyr Thr Glu Lys His Ser Asp Ser Leu Phe Lys Arg Thr Glu
130 135 140
Val Leu Ala Ala Val Ile Ala Gly Gly Val Ile Gly Phe Leu Phe Ala
145 150 155 160
Ile Phe Leu Ile Leu Leu Leu Val Tyr Arg Met Arg Lys Lys Asp Glu
165 170 175
Gly Ser Tyr Asp Leu Gly Glu Arg Lys Pro Ser Ser Ala Ala Tyr Gln
180 185 190
Lys Ala Pro Thr Lys Glu Phe Tyr Ala
195 200
<210> 21
<211> 442
<212> PRT
<213> 人类
<400> 21
Met Lys Pro Gly Pro Pro His Arg Ala Gly Ala Ala His Gly Ala Gly
1 5 10 15
Ala Gly Ala Gly Ala Ala Ala Gly Pro Gly Ala Arg Gly Leu Leu Leu
20 25 30
Pro Pro Leu Leu Leu Leu Leu Leu Ala Gly Arg Ala Ala Gly Ala Gln
35 40 45
Arg Trp Arg Ser Glu Asn Phe Glu Arg Pro Val Asp Leu Glu Gly Ser
50 55 60
Gly Asp Asp Asp Ser Phe Pro Asp Asp Glu Leu Asp Asp Leu Tyr Ser
65 70 75 80
Gly Ser Gly Ser Gly Tyr Phe Glu Gln Glu Ser Gly Ile Glu Thr Ala
85 90 95

Met Arg Phe Ser Pro Asp Val Ala Leu Ala Val Ser Thr Thr Pro Ala
100 105 110
Val Leu Pro Thr Thr Asn Ile Gln Pro Val Gly Thr Pro Phe Glu Glu
115 120 125
Leu Pro Ser Glu Arg Pro Thr Leu Glu Pro Ala Thr Ser Pro Leu Val
130 135 140
Val Thr Glu Val Pro Glu Glu Pro Ser Gln Arg Ala Thr Thr Val Ser
145 150 155 160
Thr Thr Met Ala Thr Thr Ala Ala Thr Ser Thr Gly Asp Pro Thr Val
165 170 175
Ala Thr Val Pro Ala Thr Val Ala Thr Ala Thr Pro Ser Thr Pro Ala
180 185 190
Ala Pro Pro Phe Thr Ala Thr Thr Ala Val Ile Arg Thr Thr Gly Val
195 200 205
Arg Arg Leu Leu Pro Leu Pro Leu Thr Thr Val Ala Thr Ala Arg Ala
210 215 220
Thr Thr Pro Glu Ala Pro Ser Pro Pro Thr Thr Ala Ala Val Leu Asp
225 230 235 240
Thr Glu Ala Pro Thr Pro Arg Leu Val Ser Thr Ala Thr Ser Arg Pro
245 250 255
Arg Ala Leu Pro Arg Pro Ala Thr Thr Gln Glu Pro Asp Ile Pro Glu
260 265 270
Arg Ser Thr Leu Pro Leu Gly Thr Thr Ala Pro Gly Pro Thr Glu Val
275 280 285
Ala Gln Thr Pro Thr Pro Glu Thr Phe Leu Thr Thr Ile Arg Asp Glu
290 295 300

[0026] Pro Glu Val Pro Val Ser Gly Gly Pro Ser Gly Asp Phe Glu Leu Pro
305 310 315 320
Glu Glu Glu Thr Thr Gln Pro Asp Thr Ala Asn Glu Val Val Ala Val
325 330 335
Gly Gly Ala Ala Ala Lys Ala Ser Ser Pro Pro Gly Thr Leu Pro Lys
340 345 350
Gly Ala Arg Pro Gly Pro Gly Leu Leu Asp Asn Ala Ile Asp Ser Gly
355 360 365
Ser Ser Ala Ala Gln Leu Pro Gln Lys Ser Ile Leu Glu Arg Lys Glu
370 375 380
Val Leu Val Ala Val Ile Val Gly Gly Val Val Gly Ala Leu Phe Ala
385 390 395 400
Ala Phe Leu Val Thr Leu Leu Ile Tyr Arg Met Lys Lys Lys Asp Glu
405 410 415
Gly Ser Tyr Thr Leu Glu Glu Pro Lys Gln Ala Ser Val Thr Tyr Gln
420 425 430
Lys Pro Asp Lys Gln Glu Glu Phe Tyr Ala
435 440

<210> 22
<211> 198
<212> PRT
<213> 人类
<400> 22
Met Ala Pro Ala Arg Leu Phe Ala Leu Leu Leu Phe Phe Val Gly Gly
1 5 10 15
Val Ala Glu Ser Ile Arg Glu Thr Glu Val Ile Asp Pro Gln Asp Leu
20 25 30

Leu Glu Gly Arg Tyr Phe Ser Gly Ala Leu Pro Asp Asp Glu Asp Val
35 40 45
Val Gly Pro Gly Gln Glu Ser Asp Asp Phe Glu Leu Ser Gly Ser Gly
50 55 60
Asp Leu Asp Asp Leu Glu Asp Ser Met Ile Gly Pro Glu Val Val His
65 70 75 80
Pro Leu Val Pro Leu Asp Asn His Ile Pro Glu Arg Ala Gly Ser Gly
85 90 95
Ser Gln Val Pro Thr Glu Pro Lys Lys Leu Glu Glu Asn Glu Val Ile
100 105 110
Pro Lys Arg Ile Ser Pro Val Glu Glu Ser Glu Asp Val Ser Asn Lys
115 120 125
Val Ser Met Ser Ser Thr Val Gln Gly Ser Asn Ile Phe Glu Arg Thr
130 135 140
Glu Val Leu Ala Ala Leu Ile Val Gly Gly Ile Val Gly Ile Leu Phe
145 150 155 160
Ala Val Phe Leu Ile Leu Leu Leu Met Tyr Arg Met Lys Lys Lys Asp
165 170 175
Glu Gly Ser Tyr Asp Leu Gly Lys Lys Pro Ile Tyr Lys Lys Ala Pro
180 185 190
Thr Asn Glu Phe Tyr Ala
195

<210> 23
<211> 59
<212> PRT
<213> 人类

[0027] <400> 23

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

<210> 24
<211> 267
<212> PRT
<213> 人类

<400> 24

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

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

<210> 25
<211> 387
<212> PRT
<213> 人类
<400> 25

[0028]
Met Pro Arg Pro Arg Leu Leu Ala Ala Leu Cys Gly Ala Leu Leu Cys
1 5 10 15
Ala Pro Ser Leu Leu Val Ala Leu Asp Ile Cys Ser Lys Asn Pro Cys
20 25 30
His Asn Gly Gly Leu Cys Glu Glu Ile Ser Gln Glu Val Arg Gly Asp
35 40 45
Val Phe Pro Ser Tyr Thr Cys Thr Cys Leu Lys Gly Tyr Ala Gly Asn
50 55 60
His Cys Glu Thr Lys Cys Val Glu Pro Leu Gly Met Glu Asn Gly Asn
65 70 75 80
Ile Ala Asn Ser Gln Ile Ala Ala Ser Ser Val Arg Val Thr Phe Leu
85 90 95
Gly Leu Gln His Trp Val Pro Glu Leu Ala Arg Leu Asn Arg Ala Gly
100 105 110
Met Val Asn Ala Trp Thr Pro Ser Ser Asn Asp Asp Asn Pro Trp Ile
115 120 125
Gln Val Asn Leu Leu Arg Arg Met Trp Val Thr Gly Val Val Thr Gln
130 135 140
Gly Ala Ser Arg Leu Ala Ser His Glu Tyr Leu Lys Ala Phe Lys Val
145 150 155 160
Ala Tyr Ser Leu Asn Gly His Glu Phe Asp Phe Ile His Asp Val Asn
165 170 175
Lys Lys His Lys Glu Phe Val Gly Asn Trp Asn Lys Asn Ala Val His
180 185 190
Val Asn Leu Phe Glu Thr Pro Val Glu Ala Gln Tyr Val Arg Leu Tyr
195 200 205
Pro Thr Ser Cys His Thr Ala Cys Thr Leu Arg Phe Glu Leu Leu Gly

210 215 220
Cys Glu Leu Asn Gly Cys Ala Asn Pro Leu Gly Leu Lys Asn Asn Ser
225 230 235 240
Ile Pro Asp Lys Gln Ile Thr Ala Ser Ser Ser Tyr Lys Thr Trp Gly
245 250 255
Leu His Leu Phe Ser Trp Asn Pro Ser Tyr Ala Arg Leu Asp Lys Gln
260 265 270
Gly Asn Phe Asn Ala Trp Val Ala Gly Ser Tyr Gly Asn Asp Gln Trp
275 280 285
Leu Gln Val Asp Leu Gly Ser Ser Lys Glu Val Thr Gly Ile Ile Thr
290 295 300
Gln Gly Ala Arg Asn Phe Gly Ser Val Gln Phe Val Ala Ser Tyr Lys
305 310 315 320
Val Ala Tyr Ser Asn Asp Ser Ala Asn Trp Thr Glu Tyr Gln Asp Pro
325 330 335
Arg Thr Gly Ser Ser Lys Ile Phe Pro Gly Asn Trp Asp Asn His Ser
340 345 350
His Lys Lys Asn Leu Phe Glu Thr Pro Ile Leu Ala Arg Tyr Val Arg
355 360 365
Ile Leu Pro Val Ala Trp His Asn Arg Ile Ala Leu Arg Leu Glu Leu
370 375 380
Leu Gly Cys
385

<210> 26
<211> 556
<212> PRT
[0029] <213> 人类
<400> 26

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

195 200 205
Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
210 215 220
Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225 230 235 240
Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
245 250 255
Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
260 265 270
Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
275 280 285
Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
290 295 300
Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305 310 315 320
Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
325 330 335
Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
340 345 350
Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
355 360 365
Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
370 375 380
Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385 390 395 400
Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
[0030] 405 410 415
Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
420 425 430
Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
435 440 445
Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
450 455 460
Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465 470 475 480
Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Gly
485 490 495
Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro Gln
500 505 510
Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp Ala
515 520 525
Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala Trp
530 535 540
Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545 550 555
<210> 27
<211> 595
<212> PRT
<213> 人类
<400> 27
Met Arg Val Leu Leu Ala Ala Leu Gly Leu Leu Phe Leu Gly Ala Leu
1 5 10 15
Arg Ala Phe Pro Gln Asp Arg Pro Phe Glu Asp Thr Cys His Gly Asn

```
                20                  25                  30
Pro Ser His Tyr Tyr Asp Lys Ala Val Arg Arg Cys Cys Tyr Arg Cys
        35                  40                  45
Pro Met Gly Leu Phe Pro Thr Gln Gln Cys Pro Gln Arg Pro Thr Asp
    50                  55                  60
Cys Arg Lys Gln Cys Glu Pro Asp Tyr Tyr Leu Asp Glu Ala Asp Arg
65                  70                  75                  80
Cys Thr Ala Cys Val Thr Cys Ser Arg Asp Asp Leu Val Glu Lys Thr
                85                  90                  95
Pro Cys Ala Trp Asn Ser Ser Arg Val Cys Glu Cys Arg Pro Gly Met
            100                 105                 110
Phe Cys Ser Thr Ser Ala Val Asn Ser Cys Ala Arg Cys Phe Phe His
        115                 120                 125
Ser Val Cys Pro Ala Gly Met Ile Val Lys Phe Pro Gly Thr Ala Gln
    130                 135                 140
Lys Asn Thr Val Cys Glu Pro Ala Ser Pro Gly Val Ser Pro Ala Cys
145                 150                 155                 160
Ala Ser Pro Glu Asn Cys Lys Glu Pro Ser Ser Gly Thr Ile Pro Gln
                165                 170                 175
Ala Lys Pro Thr Pro Val Ser Pro Ala Thr Ser Ser Ala Ser Thr Met
            180                 185                 190
Pro Val Arg Gly Gly Thr Arg Leu Ala Gln Glu Ala Ala Ser Lys Leu
        195                 200                 205
Thr Arg Ala Pro Asp Ser Pro Ser Ser Val Gly Arg Pro Ser Ser Asp
    210                 215                 220
Pro Gly Leu Ser Pro Thr Gln Pro Cys Pro Glu Gly Ser Gly Asp Cys
225                 230                 235                 240
Arg Lys Gln Cys Glu Pro Asp Tyr Tyr Leu Asp Glu Ala Gly Arg Cys
                245                 250                 255
Thr Ala Cys Val Ser Cys Ser Arg Asp Asp Leu Val Glu Lys Thr Pro
            260                 265                 270
Cys Ala Trp Asn Ser Ser Arg Thr Cys Glu Cys Arg Pro Gly Met Ile
        275                 280                 285
Cys Ala Thr Ser Ala Thr Asn Ser Cys Ala Arg Cys Val Pro Tyr Pro
    290                 295                 300
Ile Cys Ala Ala Glu Thr Val Thr Lys Pro Gln Asp Met Ala Glu Lys
305                 310                 315                 320
Asp Thr Thr Phe Glu Ala Pro Pro Leu Gly Thr Gln Pro Asp Cys Asn
                325                 330                 335
Pro Thr Pro Glu Asn Gly Glu Ala Pro Ala Ser Thr Ser Pro Thr Gln
            340                 345                 350
Ser Leu Leu Val Asp Ser Gln Ala Ser Lys Thr Leu Pro Ile Pro Thr
        355                 360                 365
Ser Ala Pro Val Ala Leu Ser Ser Thr Gly Lys Pro Val Leu Asp Ala
    370                 375                 380
Gly Pro Val Leu Phe Trp Val Ile Leu Val Leu Val Val Val Val Gly
385                 390                 395                 400
Ser Ser Ala Phe Leu Leu Cys His Arg Arg Ala Cys Arg Lys Arg Ile
                405                 410                 415
Arg Gln Lys Leu His Leu Cys Tyr Pro Val Gln Thr Ser Gln Pro Lys
            420                 425                 430
Leu Glu Leu Val Asp Ser Arg Pro Arg Arg Ser Ser Thr Gln Leu Arg
        435                 440                 445
```

[0031]

Ser Gly Ala Ser Val Thr Glu Pro Val Ala Glu Glu Arg Gly Leu Met
450 455 460
Ser Gln Pro Leu Met Glu Thr Cys His Ser Val Gly Ala Ala Tyr Leu
465 470 475 480
Glu Ser Leu Pro Leu Gln Asp Ala Ser Pro Ala Gly Gly Pro Ser Ser
485 490 495
Pro Arg Asp Leu Pro Glu Pro Arg Val Ser Thr Glu His Thr Asn Asn
500 505 510
Lys Ile Glu Lys Ile Tyr Ile Met Lys Ala Asp Thr Val Ile Val Gly
515 520 525
Thr Val Lys Ala Glu Leu Pro Glu Gly Arg Gly Leu Ala Gly Pro Ala
530 535 540
Glu Pro Glu Leu Glu Glu Glu Leu Glu Ala Asp His Thr Pro His Tyr
545 550 555 560
Pro Glu Gln Glu Thr Glu Pro Pro Leu Gly Ser Cys Ser Asp Val Met
565 570 575
Leu Ser Val Glu Glu Glu Gly Lys Glu Asp Pro Leu Pro Thr Ala Ala
580 585 590
Ser Gly Lys
595

<210> 28
<211> 532
<212> PRT
<213> 人类
<400> 28

[0032]
Met Pro Leu Phe Leu Ile Leu Cys Leu Leu Gln Gly Ser Ser Phe Ala
1 5 10 15
Leu Pro Gln Lys Arg Pro His Pro Arg Trp Leu Trp Glu Gly Ser Leu
20 25 30
Pro Ser Arg Thr His Leu Arg Ala Met Gly Thr Leu Arg Pro Ser Ser
35 40 45
Pro Leu Cys Trp Arg Glu Glu Ser Ser Phe Ala Ala Pro Asn Ser Leu
50 55 60
Lys Gly Ser Arg Leu Val Ser Gly Glu Pro Gly Gly Ala Val Thr Ile
65 70 75 80
Gln Cys His Tyr Ala Pro Ser Ser Val Asn Arg His Gln Arg Lys Tyr
85 90 95
Trp Cys Arg Leu Gly Pro Pro Arg Trp Ile Cys Gln Thr Ile Val Ser
100 105 110
Thr Asn Gln Tyr Thr His His Arg Tyr Arg Asp Arg Val Ala Leu Thr
115 120 125
Asp Phe Pro Gln Arg Gly Leu Phe Val Val Arg Leu Ser Gln Leu Ser
130 135 140
Pro Asp Asp Ile Gly Cys Tyr Leu Cys Gly Ile Gly Ser Glu Asn Asn
145 150 155 160
Met Leu Phe Leu Ser Met Asn Leu Thr Ile Ser Ala Gly Pro Ala Ser
165 170 175
Thr Leu Pro Thr Ala Thr Pro Ala Ala Gly Glu Leu Thr Met Arg Ser
180 185 190
Tyr Gly Thr Ala Ser Pro Val Ala Asn Arg Trp Thr Pro Gly Thr Thr
195 200 205
Gln Thr Leu Gly Gln Gly Thr Ala Trp Asp Thr Val Ala Ser Thr Pro
210 215 220

Gly Thr Ser Lys Thr Thr Ala Ser Ala Glu Gly Arg Arg Thr Pro Gly
225 230 235 240
Ala Thr Arg Pro Ala Ala Pro Gly Thr Gly Ser Trp Ala Glu Gly Ser
245 250 255
Val Lys Ala Pro Ala Pro Ile Pro Glu Ser Pro Pro Ser Lys Ser Arg
260 265 270
Ser Met Ser Asn Thr Thr Glu Gly Val Trp Glu Gly Thr Arg Ser Ser
275 280 285
Val Thr Asn Arg Ala Arg Ala Ser Lys Asp Arg Arg Glu Met Thr Thr
290 295 300
Thr Lys Ala Asp Arg Pro Arg Glu Asp Ile Glu Gly Val Arg Ile Ala
305 310 315 320
Leu Asp Ala Ala Lys Lys Val Leu Gly Thr Ile Gly Pro Pro Ala Leu
325 330 335
Val Ser Glu Thr Leu Ala Trp Glu Ile Leu Pro Gln Ala Thr Pro Val
340 345 350
Ser Lys Gln Gln Ser Gln Gly Ser Ile Gly Glu Thr Thr Pro Ala Ala
355 360 365
Gly Met Trp Thr Leu Gly Thr Pro Ala Ala Asp Val Trp Ile Leu Gly
370 375 380
Thr Pro Ala Ala Asp Val Trp Thr Ser Met Glu Ala Ala Ser Gly Glu
385 390 395 400
Gly Ser Ala Ala Gly Asp Leu Asp Ala Ala Thr Gly Asp Arg Gly Pro
405 410 415
Gln Ala Thr Leu Ser Gln Thr Pro Ala Val Gly Pro Trp Gly Pro Pro
420 425 430

[0033] Gly Lys Glu Ser Ser Val Lys Arg Thr Phe Pro Glu Asp Glu Ser Ser
435 440 445
Ser Arg Thr Leu Ala Pro Val Ser Thr Met Leu Ala Leu Phe Met Leu
450 455 460
Met Ala Leu Val Leu Leu Gln Arg Lys Leu Trp Arg Arg Arg Thr Ser
465 470 475 480
Gln Glu Ala Glu Arg Val Thr Leu Ile Gln Met Thr His Phe Leu Glu
485 490 495
Val Asn Pro Gln Ala Asp Gln Leu Pro His Val Glu Arg Lys Met Leu
500 505 510
Gln Asp Asp Ser Leu Pro Ala Gly Ala Ser Leu Thr Ala Pro Glu Arg
515 520 525
Asn Pro Gly Pro
530

<210> 29
<211> 287
<212> PRT
<213> 人类
<400> 29

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

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

[0034] Cys Gln Pro Gly Leu Thr Phe Ala Arg Thr Pro Ser Val Cys Lys
275 280 285

<210> 30
<211> 86
<212> PRT
<213> 人类
<400> 30
Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Leu Val Glu Gln Ala
1 5 10 15
Ala Ala Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu
20 25 30
Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile
35 40 45
Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Asp Gly Val
50 55 60
Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys
65 70 75 80
His Glu Lys Pro Pro Gln
85

<210> 31
<211> 374
<212> PRT
<213> 人类
<400> 31
Met Trp Phe Leu Thr Thr Leu Leu Leu Trp Val Pro Val Asp Gly Gln
1 5 10 15
Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val Ser

20 25 30
Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu
35 40 45
Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln
50 55 60
Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp Ser
65 70 75 80
Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Ile
85 90 95
Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser Ser Arg
100 105 110
Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys
115 120 125
Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe
130 135 140
Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile
145 150 155 160
Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His Arg Tyr
165 170 175
Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro Ala Pro
180 185 190
Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn Leu Val
195 200 205
Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly Leu Gln
210 215 220
Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg Asn
[0035] 225 230 235 240
Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp Ser Gly
245 250 255
Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly Asn Val Leu Lys Arg
260 265 270
Ser Pro Glu Leu Glu Leu Gln Val Leu Gly Leu Gln Leu Pro Thr Pro
275 280 285
Val Trp Phe His Val Leu Phe Tyr Leu Ala Val Gly Ile Met Phe Leu
290 295 300
Val Asn Thr Val Leu Trp Val Thr Ile Arg Lys Glu Leu Lys Arg Lys
305 310 315 320
Lys Lys Trp Asp Leu Glu Ile Ser Leu Asp Ser Gly His Glu Lys Lys
325 330 335
Val Ile Ser Ser Leu Gln Glu Asp Arg His Leu Glu Glu Glu Leu Lys
340 345 350
Cys Gln Glu Gln Lys Glu Glu Gln Leu Gln Glu Gly Val His Arg Lys
355 360 365
Glu Pro Gln Gly Ala Thr
370

<210> 32
<211> 280
<212> PRT
<213> 人类
<400> 32
Met Trp Phe Leu Thr Thr Leu Leu Leu Trp Val Pro Val Asp Gly Gln
1 5 10 15
Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val Ser

20 25 30
Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu
35 40 45
Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln
50 55 60
Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp Ser
65 70 75 80
Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Ile
85 90 95
Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser Ser Arg
100 105 110
Val Phe Met Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys
115 120 125
Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe
130 135 140
Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile
145 150 155 160
Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His Arg Tyr
165 170 175
Thr Ser Ala Gly Ile Ser Gln Tyr Thr Val Lys Gly Leu Gln Leu Pro
180 185 190
Thr Pro Val Trp Phe His Val Leu Phe Tyr Leu Ala Val Gly Ile Met
195 200 205
Phe Leu Val Asn Thr Val Leu Trp Val Thr Ile Arg Lys Glu Leu Lys
210 215 220
Arg Lys Lys Lys Trp Asn Leu Glu Ile Ser Leu Asp Ser Gly His Glu
[0036] 225 230 235 240
Lys Lys Val Ile Ser Ser Leu Gln Glu Asp Arg His Leu Glu Glu Glu
245 250 255
Leu Lys Cys Gln Glu Gln Lys Glu Glu Gln Leu Gln Glu Gly Val His
260 265 270
Arg Lys Glu Pro Gln Gly Ala Thr
275 280

<210> 33
<211> 416
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 33

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

100 105 110
Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145 150 155 160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
165 170 175
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
180 185 190
Lys Leu Cys Leu Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
195 200 205
Arg Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile
210 215 220
Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln
225 230 235 240
Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala
245 250 255
Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Pro Gln Gly Thr Glu Asp
260 265 270
Ser Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys
275 280 285
Leu Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp
290 295 300
Lys Gly Thr Asn Gly Gly Gly Gly Ser Gly Arg Gly Tyr Ile Pro Glu
[0037] 305 310 315 320
Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys Asp Gly Glu Trp Val
325 330 335
Phe Leu Ser Thr Phe Leu Ser Pro Ala Asn Gly Gly Gly Gly Ser Gly
340 345 350
Arg Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys Val Asp Lys Val Ile
355 360 365
Gln Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala Asn Pro Ala Ile Leu
370 375 380
Ser Glu Ala Ser Ala Pro Ile Pro His Asp Gly Asn Leu Tyr Pro Arg
385 390 395 400
Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu Ser Leu Glu Gly Gly
405 410 415

<210> 34
<211> 836
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 34
Met Ser Ala Pro Arg Ile Trp Leu Ala Gln Ala Leu Leu Phe Phe Leu
1 5 10 15
Thr Thr Glu Ser Ile Gly Gln Leu Leu Glu Pro Cys Gly Tyr Ile Tyr
20 25 30
Pro Glu Phe Pro Val Val Gln Arg Gly Ser Asn Phe Thr Ala Ile Cys
35 40 45
Val Leu Lys Glu Ala Cys Leu Gln His Tyr Tyr Val Asn Ala Ser Tyr

```
     50                  55                  60
Ile Val Trp Lys Thr Asn His Ala Ala Val Pro Arg Glu Gln Val Thr
65                  70                  75                  80
Val Ile Asn Arg Thr Thr Ser Ser Val Thr Phe Thr Asp Val Val Leu
                85                  90                  95
Pro Ser Val Gln Leu Thr Cys Asn Ile Leu Ser Phe Gly Gln Ile Glu
            100                 105                 110
Gln Asn Val Tyr Gly Val Thr Met Leu Ser Gly Phe Pro Pro Asp Lys
        115                 120                 125
Pro Thr Asn Leu Thr Cys Ile Val Asn Glu Gly Lys Asn Met Leu Cys
    130                 135                 140
Gln Trp Asp Pro Gly Arg Glu Thr Tyr Leu Glu Thr Asn Tyr Thr Leu
145                 150                 155                 160
Lys Ser Glu Trp Ala Thr Glu Lys Phe Pro Asp Cys Gln Ser Lys His
                165                 170                 175
Gly Thr Ser Cys Met Val Ser Tyr Met Pro Thr Tyr Tyr Val Asn Ile
            180                 185                 190
Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Ser Ser Glu
        195                 200                 205
Ser Ile Asn Phe Asp Pro Val Asp Lys Val Lys Pro Thr Pro Pro Tyr
    210                 215                 220
Asn Leu Ser Val Thr Asn Ser Glu Glu Leu Ser Ser Ile Leu Lys Leu
225                 230                 235                 240
Ser Trp Val Ser Ser Gly Leu Gly Gly Leu Leu Asp Leu Lys Ser Asp
                245                 250                 255
Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ile Gln Val Pro Leu
            260                 265                 270
Glu Asp Thr Met Ser Pro Arg Thr Ser Phe Thr Val Gln Asp Leu Lys
        275                 280                 285
Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Ser Ile Lys Asp Ser Gly
    290                 295                 300
Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Thr Thr Tyr
305                 310                 315                 320
Glu Asp Arg Pro Ser Arg Pro Pro Ser Phe Trp Tyr Lys Thr Asn Pro
                325                 330                 335
Ser His Gly Gln Glu Tyr Arg Ser Val Arg Leu Ile Trp Lys Ala Leu
            340                 345                 350
Pro Leu Ser Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val Ile Leu
        355                 360                 365
Thr Gln Ser Lys Ser Val Ser Gln Thr Tyr Thr Val Thr Gly Thr Glu
    370                 375                 380
Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Val Ala Ser Leu Ala Ala
385                 390                 395                 400
Arg Asn Lys Val Gly Lys Ser Ala Ala Ala Val Leu Thr Ile Pro Ser
                405                 410                 415
Pro His Val Thr Ala Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg
            420                 425                 430
Met Lys Gln Lys Lys Leu Val Gly Glu Arg Gly Ser Gly Ser Gly Ser
        435                 440                 445
Gly Ser Gly Ser Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe
    450                 455                 460
Tyr Glu Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala
465                 470                 475                 480
```

[0038]

Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu
485 490 495
Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Ala Ala Pro
500 505 510
Ala Arg Gly Pro Thr Val Arg Thr Lys Lys Val Gly Lys Asn Glu Ala
515 520 525
Val Leu Ala Trp Asp Gln Ile Pro Val Asp Asp Gln Asn Gly Phe Ile
530 535 540
Arg Asn Tyr Ser Ile Ser Tyr Arg Thr Ser Val Gly Lys Glu Met Val
545 550 555 560
Val His Val Asp Ser Ser His Thr Glu Tyr Thr Leu Ser Ser Leu Ser
565 570 575
Ser Asp Thr Leu Tyr Met Val Arg Met Ala Ala Tyr Thr Asp Glu Gly
580 585 590
Gly Lys Asp Gly Pro Glu Phe Thr Phe Thr Thr Pro Lys Phe Ala Gln
595 600 605
Gly Glu Ile Glu Ala Ile Val Val Pro Val Cys Leu Ala Phe Leu Leu
610 615 620
Thr Thr Leu Leu Gly Val Leu Phe Cys Phe Asn Lys Arg Asp Leu Ile
625 630 635 640
Lys Lys His Ile Trp Pro Asn Val Pro Asp Pro Ser Lys Ser His Ile
645 650 655
Ala Gln Trp Ser Pro His Thr Pro Pro Arg His Asn Phe Asn Ser Lys
660 665 670
Asp Gln Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg Met Lys Gln
675 680 685

[0039]
Leu Glu Asp Lys Val Glu Glu Leu Leu Ser Lys Asn Tyr His Leu Glu
690 695 700
Asn Glu Val Ala Arg Leu Lys Lys Leu Val Gly Glu Arg Gly Ser Gly
705 710 715 720
Ser Gly Ser Gly Ser Gly Ser Ser Leu Tyr Pro Ser Leu Glu Asp Leu
725 730 735
Lys Val Asp Lys Val Ile Gln Ala Gln Thr Ala Tyr Ser Ala Asn Pro
740 745 750
Ala Ser Gln Ala Phe Val Leu Val Asp Ala Ser Ala Ala Leu Pro Pro
755 760 765
Asp Gly Asn Leu Tyr Pro Lys Leu Tyr Pro Glu Leu Ser Gln Tyr Met
770 775 780
Gly Leu Ser Leu Asn Glu Ala Glu Ile Cys Glu Ser Met Pro Met Val
785 790 795 800
Ser Gly Ala Pro Ala Gln Gly Gln Leu Val Ala Arg Pro Ser Ser Val
805 810 815
Asn Tyr Met Val Ala Pro Val Thr Gly Asn Asp Ala Gly Ile Arg Arg
820 825 830
Ala Glu Ile Lys
835

<210> 35
<211> 359
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 35

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

[0040]

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

<210> 36
<211> 532
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 36

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

[0041]

Pro Asp Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala
210 215 220
Ile Arg Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr
225 230 235 240
Leu Glu Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln
245 250 255
Ala Phe Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp
260 265 270
Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro
275 280 285
Ser Pro Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr
290 295 300
Tyr Ser Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly
305 310 315 320
Leu Gln Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile
325 330 335
Asn Pro Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala
340 345 350
Leu Leu Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe
355 360 365
Ala Val Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser
370 375 380
Met Tyr Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu
385 390 395 400
Ser Tyr Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu
405 410 415
Gln Thr Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu

420 425 430
Arg Val Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln
435 440 445
Asp Cys Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala Val Gly
450 455 460
Ala Ala Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile
465 470 475 480
Gly Leu Lys His His His Ala Gly Tyr Glu Gln Phe Gly Ser Gly Ser
485 490 495
Gly Ser Gly Ser Gly Ser Gly Ser Thr Gly Gly Ser Arg Thr Gly Ser
500 505 510
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Gly His His His His
515 520 525
His His His His
530

<210> 37
<211> 514
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 37
Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15
Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Lys Ser Ser Val
20 25 30

[0042]
Gly Arg Gln Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr
35 40 45
Glu Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe
50 55 60
Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala
65 70 75 80
Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Gly Gly Gly Gly
85 90 95
Ser Gly Gly Gly Gly Ser Leu Glu Leu Asn Leu Thr Asp Ser Glu Asn
100 105 110
Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met Asn Phe Thr Val Arg Tyr
115 120 125
Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val Thr Ile Ser Asp His Gly
130 135 140
Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly Asp Asp Gln Asn Gly Pro
145 150 155 160
Lys Ile Ala Val Gln Phe Gly Pro Gly Phe Ser Trp Ile Ala Asn Phe
165 170 175
Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp Ser Val Ser Phe Ser Tyr
180 185 190
Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp Ala Glu Asp Lys Gly Ile
195 200 205
Leu Thr Val Asp Glu Leu Leu Ala Ile Arg Ile Pro Leu Asn Asp Leu
210 215 220
Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu Lys Asn Asp Val Val Gln
225 230 235 240
His Tyr Trp Asp Val Leu Val Gln Ala Phe Val Gln Asn Gly Thr Val

245 250 255
Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala
260 265 270
Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro
275 280 285
Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val Asn Asn Gly Asn Asp
290 295 300
Thr Cys Leu Leu Ala Thr Met Gly Leu Gln Leu Asn Ile Thr Gln Asp
305 310 315 320
Lys Val Ala Ser Val Ile Asn Ile Asn Pro Asn Thr Thr His Ser Thr
325 330 335
Gly Ser Cys Arg Ser His Thr Ala Leu Leu Arg Leu Asn Ser Ser Thr
340 345 350
Ile Lys Tyr Leu Asp Phe Val Phe Ala Val Lys Asn Glu Asn Arg Phe
355 360 365
Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr Leu Val Asn Gly Ser Val
370 375 380
Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr Trp Asp Ala Pro Leu Gly
385 390 395 400
Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr Val Ser Val Ser Gly Ala
405 410 415
Phe Gln Ile Asn Thr Phe Asp Leu Arg Val Gln Pro Phe Asn Val Thr
420 425 430
Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys Ser Ala Asp Asp Asp Asn
435 440 445
Phe Leu Val Pro Ile Ala Val Gly Ala Ala Leu Ala Gly Val Leu Ile
[0043] 450 455 460
Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu Lys His His His Ala Gly
465 470 475 480
Tyr Glu Gln Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
485 490 495
Thr Gly Gly Ser Arg Thr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
500 505 510
Gly Ser

<210> 38
<211> 826
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 38
Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu Pro
1 5 10 15
Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp Asn
20 25 30
Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala Asp
35 40 45
Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly Ser
50 55 60
Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly Phe
65 70 75 80
Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr Glu

85 90 95
Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro Gly
100 105 110
Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys Arg
115 120 125
Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile Lys
130 135 140
Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln Lys
145 150 155 160
Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe Lys
165 170 175
Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val Lys
180 185 190
Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu
195 200 205
Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala
210 215 220
Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys
225 230 235 240
Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile Val
245 250 255
Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser
260 265 270
Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro
275 280 285
Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly Thr
[0044] 290 295 300
Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe
305 310 315 320
Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile
325 330 335
Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys
340 345 350
Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser Glu
355 360 365
Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile Lys
370 375 380
Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp His
385 390 395 400
Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala Ala
405 410 415
Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met Phe
420 425 430
Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile Ile
435 440 445
Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr Glu
450 455 460
Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr Tyr
465 470 475 480
Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val Ser
485 490 495
Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn Val
500 505 510

Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp Ala
515 520 525
Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe Leu
530 535 540
Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp Thr
545 550 555 560
Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu Ile
565 570 575
Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu Val
580 585 590
Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn Leu
595 600 605
Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp Leu
610 615 620
Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln Trp
625 630 635 640
Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu Thr
645 650 655
Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys Lys
660 665 670
Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro Tyr
675 680 685
Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser Gly
690 695 700
Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys Gln
705 710 715 720

[0045]

Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala Leu
725 730 735
Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp Val
740 745 750
Trp Asp Ile Asp Asn Glu Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly
755 760 765
Ser Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile
770 775 780
Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln
785 790 795 800
Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala
805 810 815
Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys
820 825

<210> 39
<211> 726
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 39
Met Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala Val Ser
1 5 10 15
Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp Leu Gly
20 25 30
Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu Ala Glu Pro
35 40 45

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

[0046] Gly Gly Ser Gly Ser Gly Ser Val Cys Phe Arg Leu Phe Pro Val Pro
260 265 270
Gly Ser Gly Leu Val Leu Val Cys Leu Val Leu Gly Ala Val Arg Ser
275 280 285
Tyr Ala Lys Ser Ser Val Gly Arg Gln Gly Ser Gly Ser Gly Ser Gly
290 295 300
Leu Glu Leu Asn Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala
305 310 315 320
Lys Trp Gln Met Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr
325 330 335
Tyr Lys Thr Val Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly
340 345 350
Ser Ile Cys Gly Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe
355 360 365
Gly Pro Gly Phe Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr
370 375 380
Tyr Ser Ile Asp Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr
385 390 395 400
Thr Phe Pro Asp Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu
405 410 415
Leu Ala Ile Arg Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu
420 425 430
Ser Thr Leu Glu Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu
435 440 445
Val Gln Ala Phe Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu
450 455 460
Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr

465 470 475 480
Val Pro Ser Pro Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala
485 490 495
Gly Thr Tyr Ser Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr
500 505 510
Met Gly Leu Gln Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile
515 520 525
Asn Ile Asn Pro Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His
530 535 540
Thr Ala Leu Leu Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe
545 550 555 560
Val Phe Ala Val Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn
565 570 575
Ile Ser Met Tyr Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn
580 585 590
Asn Leu Ser Tyr Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn
595 600 605
Lys Glu Gln Thr Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe
610 615 620
Asp Leu Arg Val Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr
625 630 635 640
Ala Gln Asp Cys Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala
645 650 655
Val Gly Ala Ala Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr
660 665 670
Phe Ile Gly Leu Lys His His His Ala Gly Tyr Glu Gln Phe Gly Ser
[0047] 675 680 685
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr Gly Gly Ser Arg Thr
690 695 700
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Gly His His
705 710 715 720
His His His His His His
725

<210> 40
<211> 710
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 40
Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15
Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Lys Ser Ser Val
20 25 30
Gly Arg Gln Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala
35 40 45
Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp
50 55 60
Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu Ala
65 70 75 80
Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr Trp
85 90 95
Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu Glu

100 105 110
Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly Leu
115 120 125
Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala Lys
130 135 140
Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln Gly
145 150 155 160
Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg Trp
165 170 175
Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu Phe
180 185 190
Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly Asn
195 200 205
Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Ser
210 215 220
Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr Pro
225 230 235 240
Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly Thr
245 250 255
Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala Ser
260 265 270
Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Gly Gly
275 280 285
Gly Gly Ser Gly Gly Gly Gly Ser Leu Glu Leu Asn Leu Thr Asp Ser
290 295 300
Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met Asn Phe Thr Val
[0048] 305 310 315 320
Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val Thr Ile Ser Asp
325 330 335
His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly Asp Asp Gln Asn
340 345 350
Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe Ser Trp Ile Ala
355 360 365
Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp Ser Val Ser Phe
370 375 380
Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp Ala Glu Asp Lys
385 390 395 400
Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg Ile Pro Leu Asn
405 410 415
Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu Lys Asn Asp Val
420 425 430
Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe Val Gln Asn Gly
435 440 445
Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr
450 455 460
Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro
465 470 475 480
Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val Asn Asn Gly
485 490 495
Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln Leu Asn Ile Thr
500 505 510
Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro Asn Thr Thr His
515 520 525

Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu Arg Leu Asn Ser
530 535 540
Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val Lys Asn Glu Asn
545 550 555 560
Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr Leu Val Asn Gly
565 570 575
Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr Trp Asp Ala Pro
580 585 590
Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr Val Ser Val Ser
595 600 605
Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val Gln Pro Phe Asn
610 615 620
Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys Ser Ala Asp Asp
625 630 635 640
Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala Leu Ala Gly Val
645 650 655
Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu Lys His His His
660 665 670
Ala Gly Tyr Glu Gln Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
675 680 685
Gly Ser Thr Gly Gly Ser Arg Thr Gly Ser Gly Ser Gly Ser Gly Ser
690 695 700
Gly Ser Gly Ser Pro Gly
705 710

<210> 41
<211> 1020
[0049] <212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 41
Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu Pro
1 5 10 15
Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp Asn
20 25 30
Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala Asp
35 40 45
Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly Ser
50 55 60
Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly Phe
65 70 75 80
Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr Glu
85 90 95
Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro Gly
100 105 110
Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys Arg
115 120 125
Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile Lys
130 135 140
Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln Lys
145 150 155 160
Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe Lys
165 170 175

Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val Lys
180 185 190
Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu
195 200 205
Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala
210 215 220
Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys
225 230 235 240
Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile Val
245 250 255
Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser
260 265 270
Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro
275 280 285
Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly Thr
290 295 300
Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe
305 310 315 320
Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile
325 330 335
Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys
340 345 350
Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser Glu
355 360 365
Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile Lys
370 375 380

[0050] Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp His
385 390 395 400
Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala Ala
405 410 415
Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met Phe
420 425 430
Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile Ile
435 440 445
Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr Glu
450 455 460
Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr Tyr
465 470 475 480
Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val Ser
485 490 495
Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn Val
500 505 510
Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp Ala
515 520 525
Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe Leu
530 535 540
Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp Thr
545 550 555 560
Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu Ile
565 570 575
Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu Val
580 585 590
Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn Leu

595 600 605
Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp Leu
610 615 620
Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln Trp
625 630 635 640
Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu Thr
645 650 655
Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys Lys
660 665 670
Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro Tyr
675 680 685
Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser Gly
690 695 700
Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys Gln
705 710 715 720
Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala Leu
725 730 735
Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp Val
740 745 750
Trp Asp Ile Asp Asn Glu Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly
755 760 765
Ser Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala Val Ser
770 775 780
Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp Leu Gly
785 790 795 800
Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu Ala Glu Pro
[0051] 805 810 815
Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys
820 825 830
Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu Glu Ala Phe
835 840 845
Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly Leu Leu Gly
850 855 860
Cys Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala Lys Phe Ala
865 870 875 880
Leu Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln Gly Thr Trp
885 890 895
Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg Trp Gln Gln
900 905 910
Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu Phe Ser Cys
915 920 925
Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly Asn Leu Glu
930 935 940
Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Ser Ser Pro
945 950 955 960
Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr Pro Pro Glu
965 970 975
Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly Thr Gly Gln
980 985 990
Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala Ser Ser Ser
995 1000 1005
Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys
1010 1015 1020

<210> 42
<211> 610
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 42

Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
1 5 10 15
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30
His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
35 40 45
Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65 70 75 80
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
85 90 95
Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
100 105 110
Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
[0052] 145 150 155 160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
165 170 175
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
180 185 190
Lys Leu Cys Leu Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
195 200 205
Arg Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala Val Ser
210 215 220
Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp Leu Gly
225 230 235 240
Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu Ala Glu Pro
245 250 255
Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys
260 265 270
Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu Glu Ala Phe
275 280 285
Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly Leu Leu Gly
290 295 300
Cys Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala Lys Phe Ala
305 310 315 320
Leu Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln Gly Thr Trp
325 330 335
Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg Trp Gln Gln
340 345 350
Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu Phe Ser Cys
355 360 365

Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly Asn Leu Glu
370 375 380
Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Ser Ser Pro
385 390 395 400
Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr Pro Pro Glu
405 410 415
Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly Thr Gly Gln
420 425 430
Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala Ser Ser Ser
435 440 445
Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Pro Gln Gly Thr
450 455 460
Glu Asp Ser Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly
465 470 475 480
Leu Cys Leu Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln
485 490 495
Arg Trp Lys Gly Thr Asn Gly Gly Gly Gly Ser Gly Arg Gly Tyr Ile
500 505 510
Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys Asp Gly Glu
515 520 525
Trp Val Phe Leu Ser Thr Phe Leu Ser Pro Ala Asn Gly Gly Gly Gly
530 535 540
Ser Gly Arg Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys Val Asp Lys
545 550 555 560
Val Ile Gln Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala Asn Pro Ala
565 570 575

[0053] Ile Leu Ser Glu Ala Ser Ala Pro Ile Pro His Asp Gly Asn Leu Tyr
580 585 590
Pro Arg Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu Ser Leu Glu
595 600 605
Gly Gly
610

<210> 43
<211> 1030
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 43
Met Ser Ala Pro Arg Ile Trp Leu Ala Gln Ala Leu Leu Phe Phe Leu
1 5 10 15
Thr Thr Glu Ser Ile Gly Gln Leu Leu Glu Pro Cys Gly Tyr Ile Tyr
20 25 30
Pro Glu Phe Pro Val Val Gln Arg Gly Ser Asn Phe Thr Ala Ile Cys
35 40 45
Val Leu Lys Glu Ala Cys Leu Gln His Tyr Tyr Val Asn Ala Ser Tyr
50 55 60
Ile Val Trp Lys Thr Asn His Ala Ala Val Pro Arg Glu Gln Val Thr
65 70 75 80
Val Ile Asn Arg Thr Thr Ser Ser Val Thr Phe Thr Asp Val Val Leu
85 90 95
Pro Ser Val Gln Leu Thr Cys Asn Ile Leu Ser Phe Gly Gln Ile Glu
100 105 110

Gln Asn Val Tyr Gly Val Thr Met Leu Ser Gly Phe Pro Pro Asp Lys
115 120 125
Pro Thr Asn Leu Thr Cys Ile Val Asn Glu Gly Lys Asn Met Leu Cys
130 135 140
Gln Trp Asp Pro Gly Arg Glu Thr Tyr Leu Glu Thr Asn Tyr Thr Leu
145 150 155 160
Lys Ser Glu Trp Ala Thr Glu Lys Phe Pro Asp Cys Gln Ser Lys His
165 170 175
Gly Thr Ser Cys Met Val Ser Tyr Met Pro Thr Tyr Tyr Val Asn Ile
180 185 190
Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Ser Ser Glu
195 200 205
Ser Ile Asn Phe Asp Pro Val Asp Lys Val Lys Pro Thr Pro Pro Tyr
210 215 220
Asn Leu Ser Val Thr Asn Ser Glu Glu Leu Ser Ser Ile Leu Lys Leu
225 230 235 240
Ser Trp Val Ser Ser Gly Leu Gly Gly Leu Leu Asp Leu Lys Ser Asp
245 250 255
Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ile Gln Val Pro Leu
260 265 270
Glu Asp Thr Met Ser Pro Arg Thr Ser Phe Thr Val Gln Asp Leu Lys
275 280 285
Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Ser Ile Lys Asp Ser Gly
290 295 300
Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Thr Thr Tyr
305 310 315 320

[0054] Glu Asp Arg Pro Ser Arg Pro Pro Ser Phe Trp Tyr Lys Thr Asn Pro
325 330 335
Ser His Gly Gln Glu Tyr Arg Ser Val Arg Leu Ile Trp Lys Ala Leu
340 345 350
Pro Leu Ser Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val Ile Leu
355 360 365
Thr Gln Ser Lys Ser Val Ser Gln Thr Tyr Thr Val Thr Gly Thr Glu
370 375 380
Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Val Ala Ser Leu Ala Ala
385 390 395 400
Arg Asn Lys Val Gly Lys Ser Ala Ala Ala Val Leu Thr Ile Pro Ser
405 410 415
Pro His Val Thr Ala Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg
420 425 430
Met Lys Gln Lys Lys Leu Val Gly Glu Arg Gly Ser Gly Ser Gly Ser
435 440 445
Gly Ser Gly Ser Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr
450 455 460
Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly
465 470 475 480
Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu
485 490 495
Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr
500 505 510
Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu
515 520 525
Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly

530 535 540
Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala
545 550 555 560
Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln
565 570 575
Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg
580 585 590
Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu
595 600 605
Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly
610 615 620
Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro
625 630 635 640
Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr
645 650 655
Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly
660 665 670
Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala
675 680 685
Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Ala
690 695 700
Ala Pro Ala Arg Gly Pro Thr Val Arg Thr Lys Lys Val Gly Lys Asn
705 710 715 720
Glu Ala Val Leu Ala Trp Asp Gln Ile Pro Val Asp Asp Gln Asn Gly
725 730 735
Phe Ile Arg Asn Tyr Ser Ile Ser Tyr Arg Thr Ser Val Gly Lys Glu
[0055] 740 745 750
Met Val Val His Val Asp Ser Ser His Thr Glu Tyr Thr Leu Ser Ser
755 760 765
Leu Ser Ser Asp Thr Leu Tyr Met Val Arg Met Ala Ala Tyr Thr Asp
770 775 780
Glu Gly Gly Lys Asp Gly Pro Glu Phe Thr Phe Thr Thr Pro Lys Phe
785 790 795 800
Ala Gln Gly Glu Ile Glu Ala Ile Val Val Pro Val Cys Leu Ala Phe
805 810 815
Leu Leu Thr Thr Leu Leu Gly Val Leu Phe Cys Phe Asn Lys Arg Asp
820 825 830
Leu Ile Lys Lys His Ile Trp Pro Asn Val Pro Asp Pro Ser Lys Ser
835 840 845
His Ile Ala Gln Trp Ser Pro His Thr Pro Pro Arg His Asn Phe Asn
850 855 860
Ser Lys Asp Gln Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg Met
865 870 875 880
Lys Gln Leu Glu Asp Lys Val Glu Glu Leu Leu Ser Lys Asn Tyr His
885 890 895
Leu Glu Asn Glu Val Ala Arg Leu Lys Lys Leu Val Gly Glu Arg Gly
900 905 910
Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Leu Tyr Pro Ser Leu Glu
915 920 925
Asp Leu Lys Val Asp Lys Val Ile Gln Ala Gln Thr Ala Tyr Ser Ala
930 935 940
Asn Pro Ala Ser Gln Ala Phe Val Leu Val Asp Ala Ser Ala Ala Leu
945 950 955 960

Pro Pro Asp Gly Asn Leu Tyr Pro Lys Leu Tyr Pro Glu Leu Ser Gln
965 970 975
Tyr Met Gly Leu Ser Leu Asn Glu Ala Glu Ile Cys Glu Ser Met Pro
980 985 990
Met Val Ser Gly Ala Pro Ala Gln Gly Gln Leu Val Ala Arg Pro Ser
995 1000 1005
Ser Val Asn Tyr Met Val Ala Pro Val Thr Gly Asn Asp Ala Gly
1010 1015 1020
Ile Arg Arg Ala Glu Ile Lys
1025 1030

<210> 44
<211> 747
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 44

Ala Val Glu Gly Gly Met Lys Cys Val Lys Phe Leu Leu Tyr Val Leu
1 5 10 15
Leu Leu Ala Phe Cys Ala Cys Ala Val Gly Leu Ile Ala Val Gly Val
20 25 30
Gly Ala Gln Leu Val Leu Ser Gln Thr Gly Thr Ala Glu Ser His Leu
35 40 45
Ser Leu Leu Tyr His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr
50 55 60
Pro Ala Phe Trp Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser
[0056] 65 70 75 80
Tyr Asn Ser Leu Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp
85 90 95
Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg
100 105 110
Ile Lys Glu Lys Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys
115 120 125
Gly Pro Tyr Thr Leu Gln Gly Leu Leu Gly Cys Glu Leu Gly Pro Asp
130 135 140
Asn Thr Ser Val Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe
145 150 155 160
Met Asn Phe Asp Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu
165 170 175
Ala Leu Ala Ile Ser Gln Arg Trp Gln Gln Gln Asp Lys Ala Ala Asn
180 185 190
Lys Glu Leu Thr Phe Leu Leu Phe Ser Cys Pro His Arg Leu Arg Glu
195 200 205
His Leu Glu Arg Gly Arg Gly Asn Leu Glu Trp Lys Glu Pro Pro Ser
210 215 220
Met Arg Leu Lys Ala Arg Pro Ser Ser Pro Gly Phe Ser Val Leu Thr
225 230 235 240
Cys Ser Ala Phe Ser Phe Tyr Pro Pro Glu Leu Gln Leu Arg Phe Leu
245 250 255
Arg Asn Gly Leu Ala Ala Gly Thr Gly Gln Gly Asp Phe Gly Pro Asn
260 265 270
Ser Asp Gly Ser Phe His Ala Ser Ser Ser Leu Thr Val Lys Ser Gly
275 280 285

```
Asp Glu His His Tyr Cys Gly Thr Ile Ile Gln Gly Ala Thr Pro Gly
    290                 295                 300
Ser Leu Leu Pro Val Val Ile Ile Ala Val Gly Val Phe Leu Phe Leu
305                 310                 315                 320
Val Ala Phe Val Gly Cys Cys Gly Ala Cys Lys Glu Asn Tyr Cys Leu
                325                 330                 335
Met Ile Thr Phe Ala Ile Phe Leu Ser Leu Ile Met Leu Val Glu Val
            340                 345                 350
Ala Ala Ala Ile Ala Gly Tyr Val Phe Arg Asp Lys Val Met Ser Glu
        355                 360                 365
Phe Asn Asn Asn Phe Arg Gln Gln Met Glu Asn Tyr Pro Lys Asn Asn
    370                 375                 380
His Thr Ala Ser Ile Leu Asp Arg Met Gln Ala Asp Phe Lys Cys Cys
385                 390                 395                 400
Gly Ala Gly Ser Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr
                405                 410                 415
Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly
            420                 425                 430
Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu
        435                 440                 445
Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr
    450                 455                 460
Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu
465                 470                 475                 480
Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly
                485                 490                 495
```

[0057]

```
Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala
            500                 505                 510
Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln
        515                 520                 525
Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg
    530                 535                 540
Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu
545                 550                 555                 560
Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly
                565                 570                 575
Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro
            580                 585                 590
Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr
        595                 600                 605
Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly
    610                 615                 620
Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala
625                 630                 635                 640
Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Gly
                645                 650                 655
Ser Ala Asn Tyr Thr Asp Trp Glu Lys Ile Pro Ser Met Ser Lys Asn
            660                 665                 670
Arg Val Pro Asp Ser Cys Cys Ile Asn Val Thr Val Gly Cys Gly Ile
        675                 680                 685
Asn Phe Asn Glu Lys Ala Ile His Lys Glu Gly Cys Val Glu Lys Ile
    690                 695                 700
Gly Gly Trp Leu Arg Lys Asn Val Leu Val Val Ala Ala Ala Ala Leu
```

705 710 715 720
Gly Ile Ala Phe Val Glu Val Leu Gly Ile Val Phe Ala Cys Cys Leu
725 730 735
Val Lys Ser Ile Arg Ser Gly Tyr Glu Val Met
740 745

<210> 45
<211> 610
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 45

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

[0058] Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145 150 155 160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
165 170 175
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
180 185 190
Lys Leu Cys Leu Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
195 200 205
Arg Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp
210 215 220
Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu
225 230 235 240
His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala
245 250 255
Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn
260 265 270
Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp
275 280 285
Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser
290 295 300
Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala
305 310 315 320
Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys

325 330 335
Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr
340 345 350
Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His
355 360 365
Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro
370 375 380
Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn
385 390 395 400
Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly
405 410 415
Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly
420 425 430
Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp
435 440 445
Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Pro Gln Gly Thr
450 455 460
Glu Asp Ser Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly
465 470 475 480
Leu Cys Leu Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln
485 490 495
Arg Trp Lys Gly Thr Asn Gly Gly Gly Gly Ser Gly Arg Gly Tyr Ile
500 505 510
Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys Asp Gly Glu
515 520 525
Trp Val Phe Leu Ser Thr Phe Leu Ser Pro Ala Asn Gly Gly Gly Gly
[0059] 530 535 540
Ser Gly Arg Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys Val Asp Lys
545 550 555 560
Val Ile Gln Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala Asn Pro Ala
565 570 575
Ile Leu Ser Glu Ala Ser Ala Pro Ile Pro His Asp Gly Asn Leu Tyr
580 585 590
Pro Arg Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu Ser Leu Glu
595 600 605
Gly Gly
610
<210> 46
<211> 1030
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 46
Met Ser Ala Pro Arg Ile Trp Leu Ala Gln Ala Leu Leu Phe Phe Leu
1 5 10 15
Thr Thr Glu Ser Ile Gly Gln Leu Leu Glu Pro Cys Gly Tyr Ile Tyr
20 25 30
Pro Glu Phe Pro Val Val Gln Arg Gly Ser Asn Phe Thr Ala Ile Cys
35 40 45
Val Leu Lys Glu Ala Cys Leu Gln His Tyr Tyr Val Asn Ala Ser Tyr
50 55 60
Ile Val Trp Lys Thr Asn His Ala Ala Val Pro Arg Glu Gln Val Thr

65 70 75 80
Val Ile Asn Arg Thr Thr Ser Ser Val Thr Phe Thr Asp Val Val Leu
85 90 95
Pro Ser Val Gln Leu Thr Cys Asn Ile Leu Ser Phe Gly Gln Ile Glu
100 105 110
Gln Asn Val Tyr Gly Val Thr Met Leu Ser Gly Phe Pro Pro Asp Lys
115 120 125
Pro Thr Asn Leu Thr Cys Ile Val Asn Glu Gly Lys Asn Met Leu Cys
130 135 140
Gln Trp Asp Pro Gly Arg Glu Thr Tyr Leu Glu Thr Asn Tyr Thr Leu
145 150 155 160
Lys Ser Glu Trp Ala Thr Glu Lys Phe Pro Asp Cys Gln Ser Lys His
165 170 175
Gly Thr Ser Cys Met Val Ser Tyr Met Pro Thr Tyr Tyr Val Asn Ile
180 185 190
Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Ser Ser Glu
195 200 205
Ser Ile Asn Phe Asp Pro Val Asp Lys Val Lys Pro Thr Pro Pro Tyr
210 215 220
Asn Leu Ser Val Thr Asn Ser Glu Glu Leu Ser Ser Ile Leu Lys Leu
225 230 235 240
Ser Trp Val Ser Ser Gly Leu Gly Gly Leu Leu Asp Leu Lys Ser Asp
245 250 255
Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ile Gln Val Pro Leu
260 265 270
Glu Asp Thr Met Ser Pro Arg Thr Ser Phe Thr Val Gln Asp Leu Lys
[0060] 275 280 285
Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Ser Ile Lys Asp Ser Gly
290 295 300
Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Thr Thr Tyr
305 310 315 320
Glu Asp Arg Pro Ser Arg Pro Pro Ser Phe Trp Tyr Lys Thr Asn Pro
325 330 335
Ser His Gly Gln Glu Tyr Arg Ser Val Arg Leu Ile Trp Lys Ala Leu
340 345 350
Pro Leu Ser Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val Ile Leu
355 360 365
Thr Gln Ser Lys Ser Val Ser Gln Thr Tyr Thr Val Thr Gly Thr Glu
370 375 380
Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Val Ala Ser Leu Ala Ala
385 390 395 400
Arg Asn Lys Val Gly Lys Ser Ala Ala Ala Val Leu Thr Ile Pro Ser
405 410 415
Pro His Val Thr Ala Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg
420 425 430
Met Lys Gln Lys Lys Leu Val Gly Glu Arg Gly Ser Gly Ser Gly Ser
435 440 445
Gly Ser Gly Ser Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln
450 455 460
Pro Pro Trp Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys
465 470 475 480
Glu Val Leu His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn
485 490 495

Gly Thr Ala Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala
500 505 510
Ser Val Asn Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly
515 520 525
Arg Ser Asp Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu
530 535 540
Gln Val Ser Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg
545 550 555 560
Cys His Ala Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg
565 570 575
Asn Gly Lys Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile
580 585 590
Leu Lys Thr Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met
595 600 605
Gly Lys His Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu
610 615 620
Leu Phe Pro Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu
625 630 635 640
Glu Gly Asn Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln
645 650 655
Arg Pro Gly Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr
660 665 670
Leu Arg Gly Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg
675 680 685
Arg Glu Asp Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Ala
690 695 700

[0061]
Ala Pro Ala Arg Gly Pro Thr Val Arg Thr Lys Lys Val Gly Lys Asn
705 710 715 720
Glu Ala Val Leu Ala Trp Asp Gln Ile Pro Val Asp Asp Gln Asn Gly
725 730 735
Phe Ile Arg Asn Tyr Ser Ile Ser Tyr Arg Thr Ser Val Gly Lys Glu
740 745 750
Met Val Val His Val Asp Ser Ser His Thr Glu Tyr Thr Leu Ser Ser
755 760 765
Leu Ser Ser Asp Thr Leu Tyr Met Val Arg Met Ala Ala Tyr Thr Asp
770 775 780
Glu Gly Gly Lys Asp Gly Pro Glu Phe Thr Phe Thr Thr Pro Lys Phe
785 790 795 800
Ala Gln Gly Glu Ile Glu Ala Ile Val Val Pro Val Cys Leu Ala Phe
805 810 815
Leu Leu Thr Thr Leu Leu Gly Val Leu Phe Cys Phe Asn Lys Arg Asp
820 825 830
Leu Ile Lys Lys His Ile Trp Pro Asn Val Pro Asp Pro Ser Lys Ser
835 840 845
His Ile Ala Gln Trp Ser Pro His Thr Pro Pro Arg His Asn Phe Asn
850 855 860
Ser Lys Asp Gln Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg Met
865 870 875 880
Lys Gln Leu Glu Asp Lys Val Glu Glu Leu Leu Ser Lys Asn Tyr His
885 890 895
Leu Glu Asn Glu Val Ala Arg Leu Lys Lys Leu Val Gly Glu Arg Gly
900 905 910
Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Leu Tyr Pro Ser Leu Glu

915 920 925
Asp Leu Lys Val Asp Lys Val Ile Gln Ala Gln Thr Ala Tyr Ser Ala
930 935 940
Asn Pro Ala Ser Gln Ala Phe Val Leu Val Asp Ala Ser Ala Ala Leu
945 950 955 960
Pro Pro Asp Gly Asn Leu Tyr Pro Lys Leu Tyr Pro Glu Leu Ser Gln
965 970 975
Tyr Met Gly Leu Ser Leu Asn Glu Ala Glu Ile Cys Glu Ser Met Pro
980 985 990
Met Val Ser Gly Ala Pro Ala Gln Gly Gln Leu Val Ala Arg Pro Ser
995 1000 1005
Ser Val Asn Tyr Met Val Ala Pro Val Thr Gly Asn Asp Ala Gly
1010 1015 1020
Ile Arg Arg Ala Glu Ile Lys
1025 1030

<210> 47
<211> 747
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 47
Ala Val Glu Gly Gly Met Lys Cys Val Lys Phe Leu Leu Tyr Val Leu
1 5 10 15
Leu Leu Ala Phe Cys Ala Cys Ala Val Gly Leu Ile Ala Val Gly Val
20 25 30

[0062] Gly Ala Gln Leu Val Leu Ser Gln Thr Gly Thr Gln Val Asp Thr Thr
35 40 45
Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val Ser Val Phe Gln Glu
50 55 60
Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu Pro Gly Ser Ser
65 70 75 80
Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln Thr Ser Thr Pro
85 90 95
Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp Ser Gly Glu Tyr Arg
100 105 110
Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Ile Gln Leu Glu Ile
115 120 125
His Arg Gly Trp Leu Leu Leu Gln Val Ser Ser Arg Val Phe Thr Glu
130 135 140
Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys Asp Lys Leu Val
145 150 155 160
Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe Lys Phe Phe His
165 170 175
Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile Ser His Asn Gly
180 185 190
Thr Tyr His Cys Ser Gly Met Gly Lys His Arg Tyr Thr Ser Ala Gly
195 200 205
Ile Ser Val Thr Val Lys Glu Leu Phe Pro Ala Pro Val Leu Asn Ala
210 215 220
Ser Val Thr Ser Pro Leu Leu Glu Gly Asn Leu Val Thr Leu Ser Cys
225 230 235 240
Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly Leu Gln Leu Tyr Phe Ser

245 250 255
Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg Asn Thr Ser Ser Glu
260 265 270
Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp Ser Gly Leu Tyr Trp Cys
275 280 285
Glu Ala Ala Thr Glu Asp Gly Thr Ile Ile Gln Gly Ala Thr Pro Gly
290 295 300
Ser Leu Leu Pro Val Val Ile Ile Ala Val Gly Val Phe Leu Phe Leu
305 310 315 320
Val Ala Phe Val Gly Cys Cys Gly Ala Cys Lys Glu Asn Tyr Cys Leu
325 330 335
Met Ile Thr Phe Ala Ile Phe Leu Ser Leu Ile Met Leu Val Glu Val
340 345 350
Ala Ala Ala Ile Ala Gly Tyr Val Phe Arg Asp Lys Val Met Ser Glu
355 360 365
Phe Asn Asn Asn Phe Arg Gln Gln Met Glu Asn Tyr Pro Lys Asn Asn
370 375 380
His Thr Ala Ser Ile Leu Asp Arg Met Gln Ala Asp Phe Lys Cys Cys
385 390 395 400
Gly Ala Gly Ser Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln
405 410 415
Pro Pro Trp Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys
420 425 430
Glu Val Leu His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn
435 440 445
Gly Thr Ala Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala
[0063] 450 455 460
Ser Val Asn Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly
465 470 475 480
Arg Ser Asp Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu
485 490 495
Gln Val Ser Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg
500 505 510
Cys His Ala Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg
515 520 525
Asn Gly Lys Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile
530 535 540
Leu Lys Thr Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met
545 550 555 560
Gly Lys His Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu
565 570 575
Leu Phe Pro Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu
580 585 590
Glu Gly Asn Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln
595 600 605
Arg Pro Gly Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr
610 615 620
Leu Arg Gly Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg
625 630 635 640
Arg Glu Asp Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly
645 650 655
Ser Ala Asn Tyr Thr Asp Trp Glu Lys Ile Pro Ser Met Ser Lys Asn
660 665 670

Arg Val Pro Asp Ser Cys Cys Ile Asn Val Thr Val Gly Cys Gly Ile
675 680 685
Asn Phe Asn Glu Lys Ala Ile His Lys Glu Gly Cys Val Glu Lys Ile
690 695 700
Gly Gly Trp Leu Arg Lys Asn Val Leu Val Val Ala Ala Ala Ala Leu
705 710 715 720
Gly Ile Ala Phe Val Glu Val Leu Gly Ile Val Phe Ala Cys Cys Leu
725 730 735
Val Lys Ser Ile Arg Ser Gly Tyr Glu Val Met
740 745

<210> 48
<211> 726
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 48

Met Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp
1 5 10 15
Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu
20 25 30
His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala
35 40 45
Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn
50 55 60
Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp
[0064] 65 70 75 80
Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser
85 90 95
Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala
100 105 110
Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys
115 120 125
Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr
130 135 140
Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His
145 150 155 160
Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro
165 170 175
Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn
180 185 190
Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly
195 200 205
Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly
210 215 220
Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp
225 230 235 240
Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly Ser Gly Ser
245 250 255
Gly Gly Ser Gly Ser Gly Ser Val Cys Phe Arg Leu Phe Pro Val Pro
260 265 270
Gly Ser Gly Leu Val Leu Val Cys Leu Val Leu Gly Ala Val Arg Ser
275 280 285

Tyr Ala Lys Ser Ser Val Gly Arg Gln Gly Ser Gly Ser Gly Ser Gly
290 295 300
Leu Glu Leu Asn Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala
305 310 315 320
Lys Trp Gln Met Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr
325 330 335
Tyr Lys Thr Val Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly
340 345 350
Ser Ile Cys Gly Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe
355 360 365
Gly Pro Gly Phe Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr
370 375 380
Tyr Ser Ile Asp Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr
385 390 395 400
Thr Phe Pro Asp Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu
405 410 415
Leu Ala Ile Arg Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu
420 425 430
Ser Thr Leu Glu Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu
435 440 445
Val Gln Ala Phe Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu
450 455 460
Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr
465 470 475 480
Val Pro Ser Pro Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala
485 490 495

[0065] Gly Thr Tyr Ser Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr
500 505 510
Met Gly Leu Gln Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile
515 520 525
Asn Ile Asn Pro Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His
530 535 540
Thr Ala Leu Leu Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe
545 550 555 560
Val Phe Ala Val Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn
565 570 575
Ile Ser Met Tyr Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn
580 585 590
Asn Leu Ser Tyr Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn
595 600 605
Lys Glu Gln Thr Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe
610 615 620
Asp Leu Arg Val Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr
625 630 635 640
Ala Gln Asp Cys Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala
645 650 655
Val Gly Ala Ala Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr
660 665 670
Phe Ile Gly Leu Lys His His His Ala Gly Tyr Glu Gln Phe Gly Ser
675 680 685
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr Gly Gly Ser Arg Thr
690 695 700
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Gly His His

705 710 715 720
His His His His His His
725

<210> 49
<211> 710
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 49

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15
Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Lys Ser Ser Val
20 25 30
Gly Arg Gln Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro
35 40 45
Pro Trp Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu
50 55 60
Val Leu His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly
65 70 75 80
Thr Ala Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser
85 90 95
Val Asn Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg
100 105 110
Ser Asp Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln
115 120 125
[0066] Val Ser Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys
130 135 140
His Ala Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn
145 150 155 160
Gly Lys Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu
165 170 175
Lys Thr Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly
180 185 190
Lys His Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu
195 200 205
Phe Pro Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu
210 215 220
Gly Asn Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg
225 230 235 240
Pro Gly Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu
245 250 255
Arg Gly Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg
260 265 270
Glu Asp Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly Gly
275 280 285
Gly Gly Ser Gly Gly Gly Gly Ser Leu Glu Leu Asn Leu Thr Asp Ser
290 295 300
Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met Asn Phe Thr Val
305 310 315 320
Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val Thr Ile Ser Asp
325 330 335
His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly Asp Asp Gln Asn

340 345 350
Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe Ser Trp Ile Ala
355 360 365
Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp Ser Val Ser Phe
370 375 380
Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp Ala Glu Asp Lys
385 390 395 400
Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg Ile Pro Leu Asn
405 410 415
Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu Lys Asn Asp Val
420 425 430
Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe Val Gln Asn Gly
435 440 445
Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr
450 455 460
Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro
465 470 475 480
Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val Asn Asn Gly
485 490 495
Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln Leu Asn Ile Thr
500 505 510
Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro Asn Thr Thr His
515 520 525
Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu Arg Leu Asn Ser
530 535 540
Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val Lys Asn Glu Asn
[0067] 545 550 555 560
Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr Leu Val Asn Gly
565 570 575
Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr Trp Asp Ala Pro
580 585 590
Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr Val Ser Val Ser
595 600 605
Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val Gln Pro Phe Asn
610 615 620
Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys Ser Ala Asp Asp
625 630 635 640
Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala Leu Ala Gly Val
645 650 655
Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu Lys His His His
660 665 670
Ala Gly Tyr Glu Gln Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
675 680 685
Gly Ser Thr Gly Gly Ser Arg Thr Gly Ser Gly Ser Gly Ser Gly Ser
690 695 700
Gly Ser Gly Ser Pro Gly
705 710

<210> 50
<211> 1020
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列

<400> 50

Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu Pro
1 5 10 15
Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp Asn
20 25 30
Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala Asp
35 40 45
Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly Ser
50 55 60
Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly Phe
65 70 75 80
Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr Glu
85 90 95
Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro Gly
100 105 110
Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys Arg
115 120 125
Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile Lys
130 135 140
Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln Lys
145 150 155 160
Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe Lys
165 170 175
Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val Lys
180 185 190
Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu
[0068] 195 200 205
Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala
210 215 220
Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys
225 230 235 240
Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile Val
245 250 255
Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser
260 265 270
Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro
275 280 285
Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly Thr
290 295 300
Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe
305 310 315 320
Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile
325 330 335
Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys
340 345 350
Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser Glu
355 360 365
Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile Lys
370 375 380
Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp His
385 390 395 400
Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala Ala
405 410 415

Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met Phe
420 425 430
Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile Ile
435 440 445
Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr Glu
450 455 460
Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr Tyr
465 470 475 480
Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val Ser
485 490 495
Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn Val
500 505 510
Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp Ala
515 520 525
Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe Leu
530 535 540
Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp Thr
545 550 555 560
Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu Ile
565 570 575
Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu Val
580 585 590
Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn Leu
595 600 605
Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp Leu
610 615 620

[0069]

Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln Trp
625 630 635 640
Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu Thr
645 650 655
Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys Lys
660 665 670
Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro Tyr
675 680 685
Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser Gly
690 695 700
Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys Gln
705 710 715 720
Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala Leu
725 730 735
Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp Val
740 745 750
Trp Asp Ile Asp Asn Glu Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly
755 760 765
Ser Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp
770 775 780
Val Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu
785 790 795 800
His Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala
805 810 815
Thr Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn
820 825 830
Asp Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp

835 840 845
Pro Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser
850 855 860
Ser Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala
865 870 875 880
Trp Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys
885 890 895
Ala Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr
900 905 910
Asn Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His
915 920 925
Arg Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro
930 935 940
Ala Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn
945 950 955 960
Leu Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly
965 970 975
Leu Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly
980 985 990
Arg Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp
995 1000 1005
Ser Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp
1010 1015 1020
<210> 51
<211> 565
<212> PRT
[0070] <213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 51
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
1 5 10 15
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30
His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
35 40 45
Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65 70 75 80
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
85 90 95
Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
100 105 110
Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145 150 155 160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
165 170 175
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr

180 185 190

Lys Leu Cys Leu Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
195 200 205

Arg Gln Glu Gly Asp Phe Pro Met Pro Phe Ile Ser Ala Lys Ser Ser
210 215 220

Pro Val Ile Pro Leu Asp Gly Ser Val Lys Ile Gln Cys Gln Ala Ile
225 230 235 240

Arg Glu Ala Tyr Leu Thr Gln Leu Met Ile Ile Lys Asn Ser Thr Tyr
245 250 255

Arg Glu Ile Gly Arg Arg Leu Lys Phe Trp Asn Glu Thr Asp Pro Glu
260 265 270

Phe Val Ile Asp His Met Asp Ala Asn Lys Ala Gly Arg Tyr Gln Cys
275 280 285

Gln Tyr Arg Ile Gly His Tyr Arg Phe Arg Tyr Ser Asp Thr Leu Glu
290 295 300

Leu Val Val Thr Gly Leu Tyr Gly Lys Pro Phe Leu Ser Ala Asp Arg
305 310 315 320

Gly Leu Val Leu Met Pro Gly Glu Asn Ile Ser Leu Thr Cys Ser Ser
325 330 335

Ala His Ile Pro Phe Asp Arg Phe Ser Leu Ala Lys Glu Gly Glu Leu
340 345 350

Ser Leu Pro Gln His Gln Ser Gly Glu His Pro Ala Asn Phe Ser Leu
355 360 365

Gly Pro Val Asp Leu Asn Val Ser Gly Ile Tyr Arg Cys Tyr Gly Trp
370 375 380

Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe Pro Ser Asn Ala Leu Glu
[0071] 385 390 395 400

Leu Val Val Thr Asp Ser Ile His Gln Asp Tyr Thr Thr Gln Asn Pro
405 410 415

Gln Gly Thr Glu Asp Ser Gly Thr Thr Val Leu Leu Pro Leu Val Ile
420 425 430

Phe Phe Gly Leu Cys Leu Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr
435 440 445

Arg Tyr Gln Arg Trp Lys Gly Thr Asn Gly Gly Gly Gly Ser Gly Arg
450 455 460

Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys
465 470 475 480

Asp Gly Glu Trp Val Phe Leu Ser Thr Phe Leu Ser Pro Ala Asn Gly
485 490 495

Gly Gly Gly Ser Gly Arg Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys
500 505 510

Val Asp Lys Val Ile Gln Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala
515 520 525

Asn Pro Ala Ile Leu Ser Glu Ala Ser Ala Pro Ile Pro His Asp Gly
530 535 540

Asn Leu Tyr Pro Arg Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu
545 550 555 560

Ser Leu Glu Gly Gly
565

<210> 52
<211> 985
<212> PRT
<213> 人工序列

<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 52

Met Ser Ala Pro Arg Ile Trp Leu Ala Gln Ala Leu Leu Phe Phe Leu
1 5 10 15
Thr Thr Glu Ser Ile Gly Gln Leu Leu Glu Pro Cys Gly Tyr Ile Tyr
20 25 30
Pro Glu Phe Pro Val Val Gln Arg Gly Ser Asn Phe Thr Ala Ile Cys
35 40 45
Val Leu Lys Glu Ala Cys Leu Gln His Tyr Tyr Val Asn Ala Ser Tyr
50 55 60
Ile Val Trp Lys Thr Asn His Ala Ala Val Pro Arg Glu Gln Val Thr
65 70 75 80
Val Ile Asn Arg Thr Thr Ser Ser Val Thr Phe Thr Asp Val Val Leu
85 90 95
Pro Ser Val Gln Leu Thr Cys Asn Ile Leu Ser Phe Gly Gln Ile Glu
100 105 110
Gln Asn Val Tyr Gly Val Thr Met Leu Ser Gly Phe Pro Pro Asp Lys
115 120 125
Pro Thr Asn Leu Thr Cys Ile Val Asn Glu Gly Lys Asn Met Leu Cys
130 135 140
Gln Trp Asp Pro Gly Arg Glu Thr Tyr Leu Glu Thr Asn Tyr Thr Leu
145 150 155 160
Lys Ser Glu Trp Ala Thr Glu Lys Phe Pro Asp Cys Gln Ser Lys His
165 170 175
Gly Thr Ser Cys Met Val Ser Tyr Met Pro Thr Tyr Tyr Val Asn Ile
[0072] 180 185 190
Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Val Ser Ser Glu
195 200 205
Ser Ile Asn Phe Asp Pro Val Asp Lys Val Lys Pro Thr Pro Pro Tyr
210 215 220
Asn Leu Ser Val Thr Asn Ser Glu Glu Leu Ser Ser Ile Leu Lys Leu
225 230 235 240
Ser Trp Val Ser Ser Gly Leu Gly Gly Leu Leu Asp Leu Lys Ser Asp
245 250 255
Ile Gln Tyr Arg Thr Lys Asp Ala Ser Thr Trp Ile Gln Val Pro Leu
260 265 270
Glu Asp Thr Met Ser Pro Arg Thr Ser Phe Thr Val Gln Asp Leu Lys
275 280 285
Pro Phe Thr Glu Tyr Val Phe Arg Ile Arg Ser Ile Lys Asp Ser Gly
290 295 300
Lys Gly Tyr Trp Ser Asp Trp Ser Glu Glu Ala Ser Gly Thr Thr Tyr
305 310 315 320
Glu Asp Arg Pro Ser Arg Pro Pro Ser Phe Trp Tyr Lys Thr Asn Pro
325 330 335
Ser His Gly Gln Glu Tyr Arg Ser Val Arg Leu Ile Trp Lys Ala Leu
340 345 350
Pro Leu Ser Glu Ala Asn Gly Lys Ile Leu Asp Tyr Glu Val Ile Leu
355 360 365
Thr Gln Ser Lys Ser Val Ser Gln Thr Tyr Thr Val Thr Gly Thr Glu
370 375 380
Leu Thr Val Asn Leu Thr Asn Asp Arg Tyr Val Ala Ser Leu Ala Ala
385 390 395 400

Arg Asn Lys Val Gly Lys Ser Ala Ala Ala Val Leu Thr Ile Pro Ser
405 410 415
Pro His Val Thr Ala Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Arg
420 425 430
Met Lys Gln Lys Lys Leu Val Gly Glu Arg Gly Ser Gly Ser Gly Ser
435 440 445
Gly Ser Gly Ser Gln Glu Gly Asp Phe Pro Met Pro Phe Ile Ser Ala
450 455 460
Lys Ser Ser Pro Val Ile Pro Leu Asp Gly Ser Val Lys Ile Gln Cys
465 470 475 480
Gln Ala Ile Arg Glu Ala Tyr Leu Thr Gln Leu Met Ile Ile Lys Asn
485 490 495
Ser Thr Tyr Arg Glu Ile Gly Arg Arg Leu Lys Phe Trp Asn Glu Thr
500 505 510
Asp Pro Glu Phe Val Ile Asp His Met Asp Ala Asn Lys Ala Gly Arg
515 520 525
Tyr Gln Cys Gln Tyr Arg Ile Gly His Tyr Arg Phe Arg Tyr Ser Asp
530 535 540
Thr Leu Glu Leu Val Val Thr Gly Leu Tyr Gly Lys Pro Phe Leu Ser
545 550 555 560
Ala Asp Arg Gly Leu Val Leu Met Pro Gly Glu Asn Ile Ser Leu Thr
565 570 575
Cys Ser Ser Ala His Ile Pro Phe Asp Arg Phe Ser Leu Ala Lys Glu
580 585 590
Gly Glu Leu Ser Leu Pro Gln His Gln Ser Gly Glu His Pro Ala Asn
595 600 605

[0073]

Phe Ser Leu Gly Pro Val Asp Leu Asn Val Ser Gly Ile Tyr Arg Cys
610 615 620
Tyr Gly Trp Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe Pro Ser Asn
625 630 635 640
Ala Leu Glu Leu Val Val Thr Asp Ser Ile His Gln Asp Tyr Thr Thr
645 650 655
Gln Asn Ala Ala Pro Ala Arg Gly Pro Thr Val Arg Thr Lys Lys Val
660 665 670
Gly Lys Asn Glu Ala Val Leu Ala Trp Asp Gln Ile Pro Val Asp Asp
675 680 685
Gln Asn Gly Phe Ile Arg Asn Tyr Ser Ile Ser Tyr Arg Thr Ser Val
690 695 700
Gly Lys Glu Met Val Val His Val Asp Ser Ser His Thr Glu Tyr Thr
705 710 715 720
Leu Ser Ser Leu Ser Ser Asp Thr Leu Tyr Met Val Arg Met Ala Ala
725 730 735
Tyr Thr Asp Glu Gly Gly Lys Asp Gly Pro Glu Phe Thr Phe Thr Thr
740 745 750
Pro Lys Phe Ala Gln Gly Glu Ile Glu Ala Ile Val Val Pro Val Cys
755 760 765
Leu Ala Phe Leu Leu Thr Thr Leu Leu Gly Val Leu Phe Cys Phe Asn
770 775 780
Lys Arg Asp Leu Ile Lys Lys His Ile Trp Pro Asn Val Pro Asp Pro
785 790 795 800
Ser Lys Ser His Ile Ala Gln Trp Ser Pro His Thr Pro Pro Arg His
805 810 815
Asn Phe Asn Ser Lys Asp Gln Gly Ser Gly Ser Gly Ser Gly Ser Gly

820 825 830
Ser Arg Met Lys Gln Leu Glu Asp Lys Val Glu Glu Leu Leu Ser Lys
835 840 845
Asn Tyr His Leu Glu Asn Glu Val Ala Arg Leu Lys Lys Leu Val Gly
850 855 860
Glu Arg Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Leu Tyr Pro
865 870 875 880
Ser Leu Glu Asp Leu Lys Val Asp Lys Val Ile Gln Ala Gln Thr Ala
885 890 895
Tyr Ser Ala Asn Pro Ala Ser Gln Ala Phe Val Leu Val Asp Ala Ser
900 905 910
Ala Ala Leu Pro Pro Asp Gly Asn Leu Tyr Pro Lys Leu Tyr Pro Glu
915 920 925
Leu Ser Gln Tyr Met Gly Leu Ser Leu Asn Glu Ala Glu Ile Cys Glu
930 935 940
Ser Met Pro Met Val Ser Gly Ala Pro Ala Gln Gly Gln Leu Val Ala
945 950 955 960
Arg Pro Ser Ser Val Asn Tyr Met Val Ala Pro Val Thr Gly Asn Asp
965 970 975
Ala Gly Ile Arg Arg Ala Glu Ile Lys
980 985

<210> 53
<211> 657
<212> PRT
<213> 人工序列
<220>
[0074] <223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 53
Ala Val Glu Gly Gly Met Lys Cys Val Lys Phe Leu Leu Tyr Val Leu
1 5 10 15
Leu Leu Ala Phe Cys Ala Cys Ala Val Gly Leu Ile Ala Val Gly Val
20 25 30
Gly Ala Gln Leu Val Leu Ser Gln Thr Gly Thr Gln Glu Gly Asp Phe
35 40 45
Pro Met Pro Phe Ile Ser Ala Lys Ser Ser Pro Val Ile Pro Leu Asp
50 55 60
Gly Ser Val Lys Ile Gln Cys Gln Ala Ile Arg Glu Ala Tyr Leu Thr
65 70 75 80
Gln Leu Met Ile Ile Lys Asn Ser Thr Tyr Arg Glu Ile Gly Arg Arg
85 90 95
Leu Lys Phe Trp Asn Glu Thr Asp Pro Glu Phe Val Ile Asp His Met
100 105 110
Asp Ala Asn Lys Ala Gly Arg Tyr Gln Cys Gln Tyr Arg Ile Gly His
115 120 125
Tyr Arg Phe Arg Tyr Ser Asp Thr Leu Glu Leu Val Val Thr Gly Leu
130 135 140
Tyr Gly Lys Pro Phe Leu Ser Ala Asp Arg Gly Leu Val Leu Met Pro
145 150 155 160
Gly Glu Asn Ile Ser Leu Thr Cys Ser Ser Ala His Ile Pro Phe Asp
165 170 175
Arg Phe Ser Leu Ala Lys Glu Gly Glu Leu Ser Leu Pro Gln His Gln
180 185 190
Ser Gly Glu His Pro Ala Asn Phe Ser Leu Gly Pro Val Asp Leu Asn

```
          195                 200                 205
Val Ser Gly Ile Tyr Arg Cys Tyr Gly Trp Tyr Asn Arg Ser Pro Tyr
      210                 215                 220
Leu Trp Ser Phe Pro Ser Asn Ala Leu Glu Leu Val Val Thr Asp Ser
225                 230                 235                 240
Ile His Gln Asp Tyr Thr Thr Gln Asn Gly Thr Ile Ile Gln Gly Ala
                245                 250                 255
Thr Pro Gly Ser Leu Leu Pro Val Val Ile Ile Ala Val Gly Val Phe
            260                 265                 270
Leu Phe Leu Val Ala Phe Val Gly Cys Cys Gly Ala Cys Lys Glu Asn
          275                 280                 285
Tyr Cys Leu Met Ile Thr Phe Ala Ile Phe Leu Ser Leu Ile Met Leu
      290                 295                 300
Val Glu Val Ala Ala Ala Ile Ala Gly Tyr Val Phe Arg Asp Lys Val
305                 310                 315                 320
Met Ser Glu Phe Asn Asn Asn Phe Arg Gln Gln Met Glu Asn Tyr Pro
                325                 330                 335
Lys Asn Asn His Thr Ala Ser Ile Leu Asp Arg Met Gln Ala Asp Phe
            340                 345                 350
Lys Cys Cys Gly Ala Gly Ser Gln Glu Gly Asp Phe Pro Met Pro Phe
          355                 360                 365
Ile Ser Ala Lys Ser Ser Pro Val Ile Pro Leu Asp Gly Ser Val Lys
      370                 375                 380
Ile Gln Cys Gln Ala Ile Arg Glu Ala Tyr Leu Thr Gln Leu Met Ile
385                 390                 395                 400
Ile Lys Asn Ser Thr Tyr Arg Glu Ile Gly Arg Arg Leu Lys Phe Trp
                405                 410                 415
Asn Glu Thr Asp Pro Glu Phe Val Ile Asp His Met Asp Ala Asn Lys
            420                 425                 430
Ala Gly Arg Tyr Gln Cys Gln Tyr Arg Ile Gly His Tyr Arg Phe Arg
          435                 440                 445
Tyr Ser Asp Thr Leu Glu Leu Val Val Thr Gly Leu Tyr Gly Lys Pro
      450                 455                 460
Phe Leu Ser Ala Asp Arg Gly Leu Val Leu Met Pro Gly Glu Asn Ile
465                 470                 475                 480
Ser Leu Thr Cys Ser Ser Ala His Ile Pro Phe Asp Arg Phe Ser Leu
                485                 490                 495
Ala Lys Glu Gly Glu Leu Ser Leu Pro Gln His Gln Ser Gly Glu His
            500                 505                 510
Pro Ala Asn Phe Ser Leu Gly Pro Val Asp Leu Asn Val Ser Gly Ile
          515                 520                 525
Tyr Arg Cys Tyr Gly Trp Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe
      530                 535                 540
Pro Ser Asn Ala Leu Glu Leu Val Val Thr Asp Ser Ile His Gln Asp
545                 550                 555                 560
Tyr Thr Thr Gln Asn Gly Ser Ala Asn Tyr Thr Asp Trp Glu Lys Ile
                565                 570                 575
Pro Ser Met Ser Lys Asn Arg Val Pro Asp Ser Cys Cys Ile Asn Val
            580                 585                 590
Thr Val Gly Cys Gly Ile Asn Phe Asn Glu Lys Ala Ile His Lys Glu
          595                 600                 605
Gly Cys Val Glu Lys Ile Gly Gly Trp Leu Arg Lys Asn Val Leu Val
      610                 615                 620
```

[0075]

Val Ala Ala Ala Ala Leu Gly Ile Ala Phe Val Glu Val Leu Gly Ile
625 630 635 640
Val Phe Ala Cys Cys Leu Val Lys Ser Ile Arg Ser Gly Tyr Glu Val
645 650 655
Met

<210> 54
<211> 681
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 54
Met Gln Glu Gly Asp Phe Pro Met Pro Phe Ile Ser Ala Lys Ser Ser
1 5 10 15
Pro Val Ile Pro Leu Asp Gly Ser Val Lys Ile Gln Cys Gln Ala Ile
20 25 30
Arg Glu Ala Tyr Leu Thr Gln Leu Met Ile Ile Lys Asn Ser Thr Tyr
35 40 45
Arg Glu Ile Gly Arg Arg Leu Lys Phe Trp Asn Glu Thr Asp Pro Glu
50 55 60
Phe Val Ile Asp His Met Asp Ala Asn Lys Ala Gly Arg Tyr Gln Cys
65 70 75 80
Gln Tyr Arg Ile Gly His Tyr Arg Phe Arg Tyr Ser Asp Thr Leu Glu
85 90 95
Leu Val Val Thr Gly Leu Tyr Gly Lys Pro Phe Leu Ser Ala Asp Arg
[0076] 100 105 110
Gly Leu Val Leu Met Pro Gly Glu Asn Ile Ser Leu Thr Cys Ser Ser
115 120 125
Ala His Ile Pro Phe Asp Arg Phe Ser Leu Ala Lys Glu Gly Glu Leu
130 135 140
Ser Leu Pro Gln His Gln Ser Gly Glu His Pro Ala Asn Phe Ser Leu
145 150 155 160
Gly Pro Val Asp Leu Asn Val Ser Gly Ile Tyr Arg Cys Tyr Gly Trp
165 170 175
Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe Pro Ser Asn Ala Leu Glu
180 185 190
Leu Val Val Thr Asp Ser Ile His Gln Asp Tyr Thr Thr Gln Asn Gly
195 200 205
Ser Gly Ser Gly Gly Ser Gly Ser Gly Ser Val Cys Phe Arg Leu Phe
210 215 220
Pro Val Pro Gly Ser Gly Leu Val Leu Val Cys Leu Val Leu Gly Ala
225 230 235 240
Val Arg Ser Tyr Ala Lys Ser Ser Val Gly Arg Gln Gly Ser Gly Ser
245 250 255
Gly Ser Gly Leu Glu Leu Asn Leu Thr Asp Ser Glu Asn Ala Thr Cys
260 265 270
Leu Tyr Ala Lys Trp Gln Met Asn Phe Thr Val Arg Tyr Glu Thr Thr
275 280 285
Asn Lys Thr Tyr Lys Thr Val Thr Ile Ser Asp His Gly Thr Val Thr
290 295 300
Tyr Asn Gly Ser Ile Cys Gly Asp Asp Gln Asn Gly Pro Lys Ile Ala
305 310 315 320

Val Gln Phe Gly Pro Gly Phe Ser Trp Ile Ala Asn Phe Thr Lys Ala
325 330 335
Ala Ser Thr Tyr Ser Ile Asp Ser Val Ser Phe Ser Tyr Asn Thr Gly
340 345 350
Asp Asn Thr Thr Phe Pro Asp Ala Glu Asp Lys Gly Ile Leu Thr Val
355 360 365
Asp Glu Leu Leu Ala Ile Arg Ile Pro Leu Asn Asp Leu Phe Arg Cys
370 375 380
Asn Ser Leu Ser Thr Leu Glu Lys Asn Asp Val Val Gln His Tyr Trp
385 390 395 400
Asp Val Leu Val Gln Ala Phe Val Gln Asn Gly Thr Val Ser Thr Asn
405 410 415
Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile
420 425 430
His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro Lys Glu Lys
435 440 445
Pro Glu Ala Gly Thr Tyr Ser Val Asn Asn Gly Asn Asp Thr Cys Leu
450 455 460
Leu Ala Thr Met Gly Leu Gln Leu Asn Ile Thr Gln Asp Lys Val Ala
465 470 475 480
Ser Val Ile Asn Ile Asn Pro Asn Thr Thr His Ser Thr Gly Ser Cys
485 490 495
Arg Ser His Thr Ala Leu Leu Arg Leu Asn Ser Ser Thr Ile Lys Tyr
500 505 510
Leu Asp Phe Val Phe Ala Val Lys Asn Glu Asn Arg Phe Tyr Leu Lys
515 520 525

[0077]

Glu Val Asn Ile Ser Met Tyr Leu Val Asn Gly Ser Val Phe Ser Ile
530 535 540
Ala Asn Asn Asn Leu Ser Tyr Trp Asp Ala Pro Leu Gly Ser Ser Tyr
545 550 555 560
Met Cys Asn Lys Glu Gln Thr Val Ser Val Ser Gly Ala Phe Gln Ile
565 570 575
Asn Thr Phe Asp Leu Arg Val Gln Pro Phe Asn Val Thr Gln Gly Lys
580 585 590
Tyr Ser Thr Ala Gln Asp Cys Ser Ala Asp Asp Asp Asn Phe Leu Val
595 600 605
Pro Ile Ala Val Gly Ala Ala Leu Ala Gly Val Leu Ile Leu Val Leu
610 615 620
Leu Ala Tyr Phe Ile Gly Leu Lys His His His Ala Gly Tyr Glu Gln
625 630 635 640
Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr Gly Gly
645 650 655
Ser Arg Thr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro
660 665 670
Gly His His His His His His His His
675 680

<210> 55
<211> 665
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 55

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

[0078]

Gly Trp Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe Pro Ser Asn Ala
210 215 220
Leu Glu Leu Val Val Thr Asp Ser Ile His Gln Asp Tyr Thr Thr Gln
225 230 235 240
Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Glu Leu Asn Leu
245 250 255
Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met Asn
260 265 270
Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val Thr
275 280 285
Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly Asp
290 295 300
Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe Ser
305 310 315 320
Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp Ser
325 330 335
Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp Ala
340 345 350
Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg Ile
355 360 365
Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu Lys
370 375 380
Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe Val
385 390 395 400
Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys
405 410 415
Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr

420 425 430
Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val
435 440 445
Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln Leu
450 455 460
Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro Asn
465 470 475 480
Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu Arg
485 490 495
Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val Lys
500 505 510
Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr Leu
515 520 525
Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr Trp
530 535 540
Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr Val
545 550 555 560
Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val Gln
565 570 575
Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys Ser
580 585 590
Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala Leu
595 600 605
Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu Lys
610 615 620
His His His Ala Gly Tyr Glu Gln Phe Gly Ser Gly Ser Gly Ser Gly
[0079] 625 630 635 640
Ser Gly Ser Gly Ser Thr Gly Gly Ser Arg Thr Gly Ser Gly Ser Gly
645 650 655
Ser Gly Ser Gly Ser Gly Ser Pro Gly
660 665

<210> 56
<211> 975
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 56
Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu Pro
1 5 10 15
Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp Asn
20 25 30
Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala Asp
35 40 45
Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly Ser
50 55 60
Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly Phe
65 70 75 80
Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr Glu
85 90 95
Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro Gly
100 105 110
Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys Arg

```
          115                 120                 125
Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile Lys
      130                 135                 140
Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln Lys
145                 150                 155                 160
Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe Lys
                  165                 170                 175
Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val Lys
              180                 185                 190
Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg Leu
          195                 200                 205
Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys Ala
      210                 215                 220
Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys Lys
225                 230                 235                 240
Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile Val
                  245                 250                 255
Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu Ser
              260                 265                 270
Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe Pro
          275                 280                 285
Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly Thr
      290                 295                 300
Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln Phe
305                 310                 315                 320
Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr Ile
                  325                 330                 335
Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp Cys
              340                 345                 350
Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser Glu
          355                 360                 365
Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile Lys
      370                 375                 380
Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp His
385                 390                 395                 400
Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala Ala
                  405                 410                 415
Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met Phe
              420                 425                 430
Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile Ile
          435                 440                 445
Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr Glu
      450                 455                 460
Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr Tyr
465                 470                 475                 480
Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val Ser
                  485                 490                 495
Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn Val
              500                 505                 510
Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp Ala
          515                 520                 525
Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe Leu
      530                 535                 540
```

[0080]

Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp Thr
545 550 555 560
Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu Ile
565 570 575
Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu Val
580 585 590
Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn Leu
595 600 605
Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp Leu
610 615 620
Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln Trp
625 630 635 640
Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu Thr
645 650 655
Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys Lys
660 665 670
Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro Tyr
675 680 685
Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser Gly
690 695 700
Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys Gln
705 710 715 720
Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala Leu
725 730 735
Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp Val
740 745 750

[0081] Trp Asp Ile Asp Asn Glu Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly
755 760 765
Ser Gln Glu Gly Asp Phe Pro Met Pro Phe Ile Ser Ala Lys Ser Ser
770 775 780
Pro Val Ile Pro Leu Asp Gly Ser Val Lys Ile Gln Cys Gln Ala Ile
785 790 795 800
Arg Glu Ala Tyr Leu Thr Gln Leu Met Ile Ile Lys Asn Ser Thr Tyr
805 810 815
Arg Glu Ile Gly Arg Arg Leu Lys Phe Trp Asn Glu Thr Asp Pro Glu
820 825 830
Phe Val Ile Asp His Met Asp Ala Asn Lys Ala Gly Arg Tyr Gln Cys
835 840 845
Gln Tyr Arg Ile Gly His Tyr Arg Phe Arg Tyr Ser Asp Thr Leu Glu
850 855 860
Leu Val Val Thr Gly Leu Tyr Gly Lys Pro Phe Leu Ser Ala Asp Arg
865 870 875 880
Gly Leu Val Leu Met Pro Gly Glu Asn Ile Ser Leu Thr Cys Ser Ser
885 890 895
Ala His Ile Pro Phe Asp Arg Phe Ser Leu Ala Lys Glu Gly Glu Leu
900 905 910
Ser Leu Pro Gln His Gln Ser Gly Glu His Pro Ala Asn Phe Ser Leu
915 920 925
Gly Pro Val Asp Leu Asn Val Ser Gly Ile Tyr Arg Cys Tyr Gly Trp
930 935 940
Tyr Asn Arg Ser Pro Tyr Leu Trp Ser Phe Pro Ser Asn Ala Leu Glu
945 950 955 960
Leu Val Val Thr Asp Ser Ile His Gln Asp Tyr Thr Thr Gln Asn

965 970 975

<210> 57
<211> 376
<212> PRT
<213> 酿脓链球菌(Streptococcus pyogenes)
<400> 57

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

[0082] Ile Ser Glu Ala Ser Arg Lys Ser Leu Ser Arg Asp Leu Glu Ala Ser
165 170 175
Arg Ala Ala Lys Lys Asp Leu Glu Ala Glu His Gln Lys Leu Glu Ala
180 185 190
Glu His Gln Lys Leu Lys Glu Asp Lys Gln Ile Ser Asp Ala Ser Arg
195 200 205
Gln Gly Leu Ser Arg Asp Leu Glu Ala Ser Arg Ala Ala Lys Lys Glu
210 215 220
Leu Glu Ala Asn His Gln Lys Leu Glu Ala Glu His Gln Lys Leu Lys
225 230 235 240
Glu Asp Lys Gln Ile Ser Asp Ala Ser Arg Gln Gly Leu Ser Arg Asp
245 250 255
Leu Glu Ala Ser Arg Ala Ala Lys Lys Glu Leu Glu Ala Asn His Gln
260 265 270
Lys Leu Glu Ala Glu Ala Lys Ala Leu Lys Glu Gln Leu Ala Lys Gln
275 280 285
Ala Glu Glu Leu Ala Lys Leu Arg Ala Gly Lys Ala Ser Asp Ser Gln
290 295 300
Thr Pro Asp Thr Lys Pro Gly Asn Lys Ala Val Pro Gly Lys Gly Gln
305 310 315 320
Ala Pro Gln Ala Gly Thr Lys Pro Asn Gln Asn Lys Ala Pro Met Lys
325 330 335
Glu Thr Lys Arg Gln Leu Pro Ser Thr Gly Glu Thr Ala Asn Pro Phe
340 345 350
Phe Thr Ala Ala Ala Leu Thr Val Met Ala Thr Ala Gly Val Ala Ala
355 360 365
Val Val Lys Arg Lys Glu Glu Asn

370 375

<210> 58
<211> 450
<212> PRT
<213> 金黄色葡萄球菌（Staphylococcus aureus）
<400> 58

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

[0083]

Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn
165 170 175
Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser
180 185 190
Gln Ser Ala Asn Leu Leu Ser Glu Ala Lys Lys Leu Asn Glu Ser Gln
195 200 205
Ala Pro Lys Ala Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe
210 215 220
Tyr Glu Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly
225 230 235 240
Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Val Ser Lys Glu Ile Leu
245 250 255
Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Glu Glu Asp
260 265 270
Asn Lys Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp
275 280 285
Gly Asn Lys Pro Gly Lys Glu Asp Asn Lys Lys Pro Gly Lys Glu Asp
290 295 300
Gly Asn Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp
305 310 315 320
Gly Asn Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp
325 330 335
Gly Asn Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp
340 345 350
Gly Asn Gly Val His Val Val Lys Pro Gly Asp Thr Val Asn Asp Ile
355 360 365
Ala Lys Ala Asn Gly Thr Thr Ala Asp Lys Ile Ala Ala Asp Asn Lys

370 375 380
Leu Ala Asp Lys Asn Met Ile Lys Pro Gly Gln Glu Leu Val Val Asp
385 390 395 400
Lys Lys Gln Pro Ala Asn His Ala Asp Ala Asn Lys Ala Gln Ala Leu
405 410 415
Pro Glu Thr Gly Glu Glu Asn Pro Phe Ile Gly Thr Thr Val Phe Gly
420 425 430
Gly Leu Ser Leu Ala Leu Gly Ala Ala Leu Leu Ala Gly Arg Arg Arg
435 440 445
Glu Leu
450

<210> 59
<211> 593
<212> PRT
<213> 链球菌属 (Streptococcus sp)
<400> 59

Met Glu Lys Glu Lys Lys Val Lys Tyr Phe Leu Arg Lys Ser Ala Phe
1 5 10 15
Gly Leu Ala Ser Val Ser Ala Ala Phe Leu Val Gly Ser Thr Val Phe
20 25 30
Ala Val Asp Ser Pro Ile Glu Asp Thr Pro Ile Ile Arg Asn Gly Gly
35 40 45
Glu Leu Thr Asn Leu Leu Gly Asn Ser Glu Thr Thr Leu Ala Leu Arg
50 55 60
Asn Glu Glu Ser Ala Thr Ala Asp Leu Thr Ala Ala Ala Val Ala Asp
65 70 75 80
[0084] Thr Val Ala Ala Ala Ala Ala Glu Asn Ala Gly Ala Ala Ala Trp Glu
85 90 95
Ala Ala Ala Ala Ala Asp Ala Leu Ala Lys Ala Lys Ala Asp Ala Leu
100 105 110
Lys Glu Phe Asn Lys Tyr Gly Val Ser Asp Tyr Tyr Lys Asn Leu Ile
115 120 125
Asn Asn Ala Lys Thr Val Glu Gly Val Lys Asp Leu Gln Ala Gln Val
130 135 140
Val Glu Ser Ala Lys Lys Ala Arg Ile Ser Glu Ala Thr Asp Gly Leu
145 150 155 160
Ser Asp Phe Leu Lys Ser Gln Thr Pro Ala Glu Asp Thr Val Lys Ser
165 170 175
Ile Glu Leu Ala Glu Ala Lys Val Leu Ala Asn Arg Glu Leu Asp Lys
180 185 190
Tyr Gly Val Ser Asp Tyr His Lys Asn Leu Ile Asn Asn Ala Lys Thr
195 200 205
Val Glu Gly Val Lys Asp Leu Gln Ala Gln Val Val Glu Ser Ala Lys
210 215 220
Lys Ala Arg Ile Ser Glu Ala Thr Asp Gly Leu Ser Asp Phe Leu Lys
225 230 235 240
Ser Gln Thr Pro Ala Glu Asp Thr Val Lys Ser Ile Glu Leu Ala Glu
245 250 255
Ala Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp
260 265 270
Tyr Tyr Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys
275 280 285
Ala Leu Ile Asp Glu Ile Leu Ala Ala Leu Pro Lys Thr Asp Thr Tyr

290 295 300
Lys Leu Ile Leu Asn Gly Lys Thr Leu Lys Gly Glu Thr Thr Thr Glu
305 310 315 320
Ala Val Asp Ala Ala Thr Ala Glu Lys Val Phe Lys Gln Tyr Ala Asn
325 330 335
Asp Asn Gly Val Asp Gly Glu Trp Thr Tyr Asp Asp Ala Thr Lys Thr
340 345 350
Phe Thr Val Thr Glu Lys Pro Glu Val Ile Asp Ala Ser Glu Leu Thr
355 360 365
Pro Ala Val Thr Thr Tyr Lys Leu Val Ile Asn Gly Lys Thr Leu Lys
370 375 380
Gly Glu Thr Thr Thr Glu Ala Val Asp Ala Ala Thr Ala Glu Lys Val
385 390 395 400
Phe Lys Gln Tyr Ala Asn Asp Asn Gly Val Asp Gly Glu Trp Thr Tyr
405 410 415
Asp Asp Ala Thr Lys Thr Phe Thr Val Thr Glu Lys Pro Glu Val Ile
420 425 430
Asp Ala Ser Glu Leu Thr Pro Ala Val Thr Thr Tyr Lys Leu Val Ile
435 440 445
Asn Gly Lys Thr Leu Lys Gly Glu Thr Thr Thr Lys Ala Val Asp Ala
450 455 460
Glu Thr Ala Glu Lys Ala Phe Lys Gln Tyr Ala Asn Asp Asn Gly Val
465 470 475 480
Asp Gly Val Trp Thr Tyr Asp Asp Ala Thr Lys Thr Phe Thr Val Thr
485 490 495
Glu Met Val Thr Glu Val Pro Gly Asp Ala Pro Thr Glu Pro Glu Lys
[0085] 500 505 510
Pro Glu Ala Ser Ile Pro Leu Val Pro Leu Thr Pro Ala Thr Pro Ile
515 520 525
Ala Lys Asp Asp Ala Lys Lys Asp Asp Thr Lys Lys Glu Asp Ala Lys
530 535 540
Lys Pro Glu Ala Lys Lys Glu Asp Ala Lys Lys Ala Glu Thr Leu Pro
545 550 555 560
Thr Thr Gly Glu Gly Ser Asn Pro Phe Phe Thr Ala Ala Ala Leu Ala
565 570 575
Val Met Ala Gly Ala Gly Ala Leu Ala Val Ala Ser Lys Arg Lys Glu
580 585 590
Asp

<210> 60
<211> 10
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为SpA模拟物1的Fc结合肽
<400> 60
Thr Trp Lys Thr Ser Arg Ile Ser Ile Phe
1 5 10
<210> 61
<211> 13
<212> PRT
<213> 人工序列
<220> 结合

<223> 称为SpA模拟物2的Fc结合肽
<400> 61
Asp Cys Ala Trp His Leu Gly Glu Leu Val Trp Cys Thr
1 5 10
<210> 62
<211> 10
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为SpA模拟物3的Fc结合肽
<400> 62
Phe Gly Arg Leu Val Ser Ser Ile Arg Tyr
1 5 10
<210> 63
<211> 12
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为SpA模拟物4的Fc结合肽
<400> 63
Glu Pro Ile His Arg Ser Thr Leu Thr Ala Leu Leu
1 5 10
<210> 64
<211> 6
<212> PRT
<213> 人工序列
[0086] <220> 结合
<223> 称为SpA模拟物5的Fc结合肽
<400> 64
His Trp Arg Gly Trp Val
1 5
<210> 65
<211> 6
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为SpA模拟物6的Fc结合肽
<400> 65
His Tyr Phe Lys Phe Asp
1 5
<210> 66
<211> 6
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为SpA模拟物7的Fc结合肽
<400> 66
His Phe Arg Arg His Leu
1 5
<210> 67
<211> 8
<212> PRT
<213> 人工序列

<220> 结合
<223> 称为 Fcγ 模拟物 1 的 Fc 结合肽
<400> 67
Asn Lys Phe Arg Gly Lys Tyr Lys
1 5
<210> 68
<211> 8
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为 Fcγ 模拟物 2 的 Fc 结合肽
<400> 68
Asn Ala Arg Lys Phe Tyr Lys Gly
1 5
<210> 69
<211> 8
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为 SpA 模拟物 8 的 Fc 结合肽
<400> 69
Phe Tyr Trp His Cys Leu Asp Glu
1 5
<210> 70
<211> 8
<212> PRT
[0087] <213> 人工序列
<220> 结合
<223> Fc 结合肽 称为 SpA 模拟物 9
<400> 70
Phe Tyr Cys His Trp Ala Leu Glu
1 5
<210> 71
<211> 8
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为 SpA 模拟物 10 的 Fc 结合肽
<400> 71
Phe Tyr Cys His Thr Ile Asp Glu
1 5
<210> 72
<211> 429
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为蛋白 A/G 的 Fc 结合多肽
<400> 72
Asn Ala Ala Gln His Asp Glu Ala Gln Gln Asn Ala Phe Tyr Gln Val
1 5 10 15
Leu Asn Met Pro Asn Leu Asn Ala Asp Gln Arg Asn Gly Phe Ile Gln
20 25 30
Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Val Leu Gly Glu Ala

35 40 45

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

[0088]

Leu Thr Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp
260 265 270
Pro Ser Val Ser Lys Glu Ile Leu Ala Glu Ala Lys Lys Leu Asn Asp
275 280 285
Ala Gln Ala Pro Lys Glu Glu Asp Ser Leu Glu Gly Ser Gly Ser Gly
290 295 300
Thr Tyr Lys Leu Ile Leu Asn Gly Lys Thr Leu Lys Gly Glu Thr Thr
305 310 315 320
Thr Glu Ala Val Asp Ala Ala Thr Ala Glu Lys Val Phe Lys Gln Tyr
325 330 335
Ala Asn Asp Asn Gly Val Asp Gly Glu Trp Thr Tyr Asp Asp Ala Thr
340 345 350
Lys Thr Phe Thr Val Thr Glu Lys Pro Glu Val Ile Asp Ala Ser Glu
355 360 365
Leu Thr Pro Ala Val Thr Thr Tyr Lys Leu Val Ile Asn Gly Lys Thr
370 375 380
Leu Lys Gly Glu Thr Thr Thr Lys Ala Val Asp Ala Glu Thr Ala Glu
385 390 395 400
Lys Ala Phe Lys Gln Tyr Ala Asn Asp Asn Gly Val Asp Gly Val Trp
405 410 415
Thr Tyr Asp Asp Ala Thr Lys Thr Phe Thr Val Thr Glu
420 425

<210> 73
<211> 57
<212> PRT
<213> 人工序列

<220> 结合
<223> 称为 Z 结构域的 Fc 结合多肽
<400> 73
Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu
1 5 10 15
His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser
20 25 30
Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys
35 40 45
Lys Leu Asn Asp Ala Gln Ala Pro Lys
50 55
<210> 74
<211> 114
<212> PRT
<213> 人工序列
<220> 结合
<223> 称为 ZZ 结构域的 Fc 结合多肽
<400> 74
Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu
1 5 10 15
His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser
20 25 30
Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys
35 40 45
Lys Leu Asn Asp Ala Gln Ala Pro Lys Asp Asn Lys Phe Asn Lys Glu
50 55 60
[0089] Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Asn Glu
65 70 75 80
Glu Gln Arg Asn Ala Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln
85 90 95
Ser Ala Asn Leu Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala
100 105 110
Pro Lys

<210> 75
<211> 665
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 75
Met Gly Val Glu Gly Cys Thr Lys Cys Ile Lys Tyr Leu Leu Phe Val
1 5 10 15
Phe Asn Phe Val Phe Trp Leu Ala Gly Gly Val Ile Leu Gly Val Ala
20 25 30
Leu Trp Leu Arg His Asp Pro Gln Thr Thr Asn Leu Leu Tyr Leu Glu
35 40 45
Leu Gly Asp Lys Pro Ala Pro Asn Thr Phe Tyr Val Gly Ile Tyr Ile
50 55 60
Leu Ile Ala Val Gly Ala Val Met Met Phe Val Gly Phe Leu Gly Cys
65 70 75 80
Tyr Gly Ala Ile Gln Glu Ser Gln Cys Leu Leu Gly Thr Phe Phe Thr
85 90 95

Cys Leu Val Ile Leu Phe Ala Cys Glu Val Ala Ala Gly Ile Trp Gly
100 105 110
Phe Val Asn Lys Asp Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp
115 120 125
Gln Ala Leu Gln Gln Ala Val Val Asp Asp Asp Ala Asn Asn Ala Lys
130 135 140
Ala Val Val Lys Thr Phe His Glu Thr Leu Asp Cys Cys Gly Ser Ser
145 150 155 160
Thr Leu Thr Ala Leu Thr Thr Ser Asn Ala Ala Gln His Asp Glu Ala
165 170 175
Gln Gln Asn Ala Phe Tyr Gln Val Leu Asn Met Pro Asn Leu Asn Ala
180 185 190
Asp Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln
195 200 205
Ser Ala Asn Val Leu Gly Glu Ala Gln Lys Leu Asn Asp Ser Gln Ala
210 215 220
Pro Lys Ala Asp Ala Gln Gln Asn Asn Phe Asn Lys Asp Gln Gln Ser
225 230 235 240
Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn Glu Ala Gln Arg
245 250 255
Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Thr Asn
260 265 270
Val Leu Gly Glu Ala Lys Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala
275 280 285
Asp Asn Asn Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu
290 295 300

[0090]
Asn Met Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser
305 310 315 320
Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ser Glu Ala Lys
325 330 335
Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala Asp Asn Lys Phe Asn Lys
340 345 350
Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Asn
355 360 365
Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser
370 375 380
Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln
385 390 395 400
Ala Pro Lys Ala Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe
405 410 415
Tyr Glu Ile Leu His Leu Pro Asn Leu Thr Glu Glu Gln Arg Asn Gly
420 425 430
Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Val Ser Lys Glu Ile Leu
435 440 445
Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Glu Glu Asp
450 455 460
Ser Leu Glu Gly Ser Gly Ser Gly Thr Tyr Lys Leu Ile Leu Asn Gly
465 470 475 480
Lys Thr Leu Lys Gly Glu Thr Thr Thr Glu Ala Val Asp Ala Ala Thr
485 490 495
Ala Glu Lys Val Phe Lys Gln Tyr Ala Asn Asp Asn Gly Val Asp Gly
500 505 510
Glu Trp Thr Tyr Asp Asp Ala Thr Lys Thr Phe Thr Val Thr Glu Lys

515 520 525
Pro Glu Val Ile Asp Ala Ser Glu Leu Thr Pro Ala Val Thr Thr Tyr
530 535 540
Lys Leu Val Ile Asn Gly Lys Thr Leu Lys Gly Glu Thr Thr Thr Lys
545 550 555 560
Ala Val Asp Ala Glu Thr Ala Glu Lys Ala Phe Lys Gln Tyr Ala Asn
565 570 575
Asp Asn Gly Val Asp Gly Val Trp Thr Tyr Asp Asp Ala Thr Lys Thr
580 585 590
Phe Thr Val Thr Glu Val Leu Lys Asn Asn Leu Cys Pro Ser Gly Ser
595 600 605
Asn Ile Ile Ser Asn Leu Phe Lys Glu Asp Cys His Gln Lys Ile Asp
610 615 620
Asp Leu Phe Ser Gly Lys Leu Tyr Leu Ile Gly Ile Ala Ala Ile Val
625 630 635 640
Val Ala Val Ile Met Ile Phe Glu Met Ile Leu Ser Met Val Leu Cys
645 650 655
Cys Gly Ile Arg Asn Ser Ser Val Tyr
660 665

<210> 76
<211> 342
<212> PRT
<213> 人工序列
<220>
<223> 包含至少一种体外多肽和至少一种 Fc 结合多肽的人工序列
<400> 76

[0091]
Met Pro Val Lys Gly Gly Thr Lys Cys Ile Lys Tyr Leu Leu Phe Gly
1 5 10 15
Phe Asn Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly
20 25 30
Leu Trp Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu
35 40 45
Thr Asn Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile
50 55 60
Gly Ala Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly
65 70 75 80
Ala Val Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu
85 90 95
Leu Val Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser
100 105 110
His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
115 120 125
Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
130 135 140
Ala Ile His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu
145 150 155 160
Gln Phe Ile Ser Asp Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala
165 170 175
Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn
180 185 190
Ala Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu
195 200 205
Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Asp Asn

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

<210> 77
<211> 296
<212> PRT
<213> 金黄色葡萄球菌
<400> 77

Asn Ala Ala Gln His Asp Glu Ala Gln Gln Asn Ala Phe Tyr Gln Val
1 5 10 15
Leu Asn Met Pro Asn Leu Asn Ala Asp Gln Arg Asn Gly Phe Ile Gln
20 25 30
[0092] Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Val Leu Gly Glu Ala
35 40 45
Gln Lys Leu Asn Asp Ser Gln Ala Pro Lys Ala Asp Ala Gln Gln Asn
50 55 60
Asn Phe Asn Lys Asp Gln Gln Ser Ala Phe Tyr Glu Ile Leu Asn Met
65 70 75 80
Pro Asn Leu Asn Glu Ala Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys
85 90 95
Asp Asp Pro Ser Gln Ser Thr Asn Val Leu Gly Glu Ala Lys Lys Leu
100 105 110
Asn Glu Ser Gln Ala Pro Lys Ala Asp Asn Asn Phe Asn Lys Glu Gln
115 120 125
Gln Asn Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn Glu Glu
130 135 140
Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser
145 150 155 160
Ala Asn Leu Leu Ser Glu Ala Lys Lys Leu Asn Glu Ser Gln Ala Pro
165 170 175
Lys Ala Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu
180 185 190
Ile Leu His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly Phe Ile
195 200 205
Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu
210 215 220
Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Ala Asp Asn Lys Phe
225 230 235 240
Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn

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

<210> 78
<211> 125
<212> PRT
<213> 停乳链球菌(Streptococcus dysgalactiae)
<400> 78
Thr Tyr Lys Leu Ile Leu Asn Gly Lys Thr Leu Lys Gly Glu Thr Thr
1 5 10 15
Thr Glu Ala Val Asp Ala Ala Thr Ala Glu Lys Val Phe Lys Gln Tyr
20 25 30
Ala Asn Asp Asn Gly Val Asp Gly Glu Trp Thr Tyr Asp Asp Ala Thr
35 40 45
Lys Thr Phe Thr Val Thr Glu Lys Pro Glu Val Ile Asp Ala Ser Glu
50 55 60
Leu Thr Pro Ala Val Thr Thr Tyr Lys Leu Val Ile Asn Gly Lys Thr
65 70 75 80
Leu Lys Gly Glu Thr Thr Thr Lys Ala Val Asp Ala Glu Thr Ala Glu
85 90 95
Lys Ala Phe Lys Gln Tyr Ala Asn Asp Asn Gly Val Asp Gly Val Trp
100 105 110
[0093] Thr Tyr Asp Asp Ala Thr Lys Thr Phe Thr Val Thr Glu
115 120 125

<210> 79
<211> 404
<212> PRT
<213> 小家鼠(Mus musculus)
<400> 79
Met Ile Leu Thr Ser Phe Gly Asp Asp Met Trp Leu Leu Thr Thr Leu
1 5 10 15
Leu Leu Trp Val Pro Val Gly Gly Glu Val Val Asn Ala Thr Lys Ala
20 25 30
Val Ile Thr Leu Gln Pro Pro Trp Val Ser Ile Phe Gln Lys Glu Asn
35 40 45
Val Thr Leu Trp Cys Glu Gly Pro His Leu Pro Gly Asp Ser Ser Thr
50 55 60
Gln Trp Phe Ile Asn Gly Thr Ala Val Gln Ile Ser Thr Pro Ser Tyr
65 70 75 80
Ser Ile Pro Glu Ala Ser Phe Gln Asp Ser Gly Glu Tyr Arg Cys Gln
85 90 95
Ile Gly Ser Ser Met Pro Ser Asp Pro Val Gln Leu Gln Ile His Asn
100 105 110
Asp Trp Leu Leu Leu Gln Ala Ser Arg Arg Val Leu Thr Glu Gly Glu
115 120 125
Pro Leu Ala Leu Arg Cys His Gly Trp Lys Asn Lys Leu Val Tyr Asn
130 135 140
Val Val Phe Tyr Arg Asn Gly Lys Ser Phe Gln Phe Ser Ser Asp Ser
145 150 155 160

Glu Val Ala Ile Leu Lys Thr Asn Leu Ser His Ser Gly Ile Tyr His
165 170 175
Cys Ser Gly Thr Gly Arg His Arg Tyr Thr Ser Ala Gly Val Ser Ile
180 185 190
Thr Val Lys Glu Leu Phe Thr Thr Pro Val Leu Arg Ala Ser Val Ser
195 200 205
Ser Pro Phe Pro Glu Gly Ser Leu Val Thr Leu Asn Cys Glu Thr Asn
210 215 220
Leu Leu Leu Gln Arg Pro Gly Leu Gln Leu His Phe Ser Phe Tyr Val
225 230 235 240
Gly Ser Lys Ile Leu Glu Tyr Arg Asn Thr Ser Ser Glu Tyr His Ile
245 250 255
Ala Arg Ala Glu Arg Glu Asp Ala Gly Phe Tyr Trp Cys Glu Val Ala
260 265 270
Thr Glu Asp Ser Ser Val Leu Lys Arg Ser Pro Glu Leu Glu Leu Gln
275 280 285
Val Leu Gly Pro Gln Ser Ser Ala Pro Val Trp Phe His Ile Leu Phe
290 295 300
Tyr Leu Ser Val Gly Ile Met Phe Ser Leu Asn Thr Val Leu Tyr Val
305 310 315 320
Lys Ile His Arg Leu Gln Arg Glu Lys Lys Tyr Asn Leu Glu Val Pro
325 330 335
Leu Val Ser Glu Gln Gly Lys Lys Ala Asn Ser Phe Gln Gln Val Arg
340 345 350
Ser Asp Gly Val Tyr Glu Glu Val Thr Ala Thr Ala Ser Gln Thr Thr
355 360 365

[0094] Pro Lys Glu Ala Pro Asp Gly Pro Arg Ser Ser Val Gly Asp Cys Gly
370 375 380
Pro Glu Gln Pro Glu Pro Leu Pro Pro Ser Asp Ser Thr Gly Ala Gln
385 390 395 400
Thr Ser Gln Ser

<210> 80
<211> 330
<212> PRT
<213> 小家鼠
<400> 80
Met Glu Ser Asn Trp Thr Val His Val Phe Ser Arg Thr Leu Cys His
1 5 10 15
Met Leu Leu Trp Thr Ala Val Leu Asn Leu Ala Ala Gly Thr His Asp
20 25 30
Leu Pro Lys Ala Val Val Lys Leu Glu Pro Pro Trp Ile Gln Val Leu
35 40 45
Lys Glu Asp Thr Val Thr Leu Thr Cys Glu Gly Thr His Asn Pro Gly
50 55 60
Asn Ser Ser Thr Gln Trp Phe His Asn Gly Arg Ser Ile Arg Ser Gln
65 70 75 80
Val Gln Ala Ser Tyr Thr Phe Lys Ala Thr Val Asn Asp Ser Gly Glu
85 90 95
Tyr Arg Cys Gln Met Glu Gln Thr Arg Leu Ser Asp Pro Val Asp Leu
100 105 110
Gly Val Ile Ser Asp Trp Leu Leu Leu Gln Thr Pro Gln Leu Val Phe
115 120 125

Leu Glu Gly Glu Thr Ile Thr Leu Arg Cys His Ser Trp Arg Asn Lys
130 135 140
Leu Leu Asn Arg Ile Ser Phe Phe His Asn Glu Lys Ser Val Arg Tyr
145 150 155 160
His His Tyr Ser Ser Asn Phe Ser Ile Pro Lys Ala Asn His Ser His
165 170 175
Ser Gly Asp Tyr Tyr Cys Lys Gly Ser Leu Gly Arg Thr Leu His Gln
180 185 190
Ser Lys Pro Val Thr Ile Thr Val Gln Gly Pro Lys Ser Ser Arg Ser
195 200 205
Leu Pro Val Leu Thr Ile Val Ala Ala Val Thr Gly Ile Ala Val Ala
210 215 220
Ala Ile Val Ile Ile Leu Val Ser Leu Val Tyr Leu Lys Lys Lys Gln
225 230 235 240
Val Pro Ala Leu Pro Gly Asn Pro Asp His Arg Glu Met Gly Glu Thr
245 250 255
Leu Pro Glu Glu Val Gly Glu Tyr Arg Gln Pro Ser Gly Gly Ser Val
260 265 270
Pro Val Ser Pro Gly Pro Pro Ser Gly Leu Glu Pro Thr Ser Ser Ser
275 280 285
Pro Tyr Asn Pro Pro Asp Leu Glu Glu Ala Ala Lys Thr Glu Ala Glu
290 295 300
Asn Thr Ile Thr Tyr Ser Leu Leu Lys His Pro Glu Ala Leu Asp Glu
305 310 315 320
Glu Thr Glu His Asp Tyr Gln Asn His Ile
325 330

[0095] <210> 81
<211> 261
<212> PRT
<213> 小家鼠
<400> 81
Met Phe Gln Asn Ala His Ser Gly Ser Gln Trp Leu Leu Pro Pro Leu
1 5 10 15
Thr Ile Leu Leu Leu Phe Ala Phe Ala Asp Arg Gln Ser Ala Ala Leu
20 25 30
Pro Lys Ala Val Val Lys Leu Asp Pro Pro Trp Ile Gln Val Leu Lys
35 40 45
Glu Asp Met Val Thr Leu Met Cys Glu Gly Thr His Asn Pro Gly Asn
50 55 60
Ser Ser Thr Gln Trp Phe His Asn Gly Arg Ser Ile Arg Ser Gln Val
65 70 75 80
Gln Ala Ser Tyr Thr Phe Lys Ala Thr Val Asn Asp Ser Gly Glu Tyr
85 90 95
Arg Cys Gln Met Glu Gln Thr Arg Leu Ser Asp Pro Val Asp Leu Gly
100 105 110
Val Ile Ser Asp Trp Leu Leu Leu Gln Thr Pro Gln Arg Val Phe Leu
115 120 125
Glu Gly Glu Thr Ile Thr Leu Arg Cys His Ser Trp Arg Asn Lys Leu
130 135 140
Leu Asn Arg Ile Ser Phe Phe His Asn Glu Lys Ser Val Arg Tyr His
145 150 155 160
His Tyr Lys Ser Asn Phe Ser Ile Pro Lys Ala Asn His Ser His Ser
165 170 175

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

<210> 82
<211> 249
<212> PRT
<213> 小家鼠
<400> 82

Met Trp Gln Leu Leu Leu Pro Thr Ala Leu Val Leu Thr Ala Phe Ser
1 5 10 15
Gly Ile Gln Ala Gly Leu Gln Lys Ala Val Val Asn Leu Asp Pro Lys
20 25 30
Trp Val Arg Val Leu Glu Glu Asp Ser Val Thr Leu Arg Cys Gln Gly
35 40 45
Thr Phe Ser Pro Glu Asp Asn Ser Ile Lys Trp Phe His Asn Glu Ser
50 55 60
Leu Ile Pro His Gln Asp Ala Asn Tyr Val Ile Gln Ser Ala Arg Val
[0096] 65 70 75 80
Lys Asp Ser Gly Met Tyr Arg Cys Gln Thr Ala Leu Ser Thr Ile Ser
85 90 95
Asp Pro Val Gln Leu Glu Val His Met Gly Trp Leu Leu Leu Gln Thr
100 105 110
Thr Lys Trp Leu Phe Gln Glu Gly Asp Pro Ile His Leu Arg Cys His
115 120 125
Ser Trp Gln Asn Arg Pro Val Arg Lys Val Thr Tyr Leu Gln Asn Gly
130 135 140
Lys Gly Lys Lys Tyr Phe His Glu Asn Ser Glu Leu Leu Ile Pro Lys
145 150 155 160
Ala Thr His Asn Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Ile Gly
165 170 175
His Asn Asn Lys Ser Ser Ala Ser Phe Arg Ile Ser Leu Gly Asp Pro
180 185 190
Gly Ser Pro Ser Met Phe Pro Pro Trp His Gln Ile Thr Phe Cys Leu
195 200 205
Leu Ile Gly Leu Leu Phe Ala Ile Asp Thr Val Leu Tyr Phe Ser Val
210 215 220
Arg Arg Gly Leu Gln Ser Pro Val Ala Asp Tyr Glu Glu Pro Lys Ile
225 230 235 240
Gln Trp Ser Lys Glu Pro Gln Asp Lys
245

<210> 83
<211> 365
<212> PRT
<213> 小家鼠

<400> 83

Met Gly Met Pro Leu Pro Trp Ala Leu Ser Leu Leu Leu Val Leu Leu
1 5 10 15
Pro Gln Thr Trp Gly Ser Glu Thr Arg Pro Pro Leu Met Tyr His Leu
20 25 30
Thr Ala Val Ser Asn Pro Ser Thr Gly Leu Pro Ser Phe Trp Ala Thr
35 40 45
Gly Trp Leu Gly Pro Gln Gln Tyr Leu Thr Tyr Asn Ser Leu Arg Gln
50 55 60
Glu Ala Asp Pro Cys Gly Ala Trp Met Trp Glu Asn Gln Val Ser Trp
65 70 75 80
Tyr Trp Glu Lys Glu Thr Thr Asp Leu Lys Ser Lys Glu Gln Leu Phe
85 90 95
Leu Glu Ala Leu Lys Thr Leu Glu Lys Ile Leu Asn Gly Thr Tyr Thr
100 105 110
Leu Gln Gly Leu Leu Gly Cys Glu Leu Ala Ser Asp Asn Ser Ser Val
115 120 125
Pro Thr Ala Val Phe Ala Leu Asn Gly Glu Glu Phe Met Lys Phe Asn
130 135 140
Pro Arg Ile Gly Asn Trp Thr Gly Glu Trp Pro Glu Thr Glu Ile Val
145 150 155 160
Ala Asn Leu Trp Met Lys Gln Pro Asp Ala Ala Arg Lys Glu Ser Glu
165 170 175
[0097] Phe Leu Leu Asn Ser Cys Pro Glu Arg Leu Leu Gly His Leu Glu Arg
180 185 190
Gly Arg Arg Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
195 200 205
Ala Arg Pro Gly Asn Ser Gly Ser Ser Val Leu Thr Cys Ala Ala Phe
210 215 220
Ser Phe Tyr Pro Pro Glu Leu Lys Phe Arg Phe Leu Arg Asn Gly Leu
225 230 235 240
Ala Ser Gly Ser Gly Asn Cys Ser Thr Gly Pro Asn Gly Asp Gly Ser
245 250 255
Phe His Ala Trp Ser Leu Leu Glu Val Lys Arg Gly Asp Glu His His
260 265 270
Tyr Gln Cys Gln Val Glu His Glu Gly Leu Ala Gln Pro Leu Thr Val
275 280 285
Asp Leu Asp Ser Ser Ala Arg Ser Ser Val Pro Val Val Gly Ile Val
290 295 300
Leu Gly Leu Leu Leu Val Val Val Ala Ile Ala Gly Gly Val Leu Leu
305 310 315 320
Trp Gly Arg Met Arg Ser Gly Leu Pro Ala Pro Trp Leu Ser Leu Ser
325 330 335
Gly Asp Asp Ser Gly Asp Leu Leu Pro Gly Gly Asn Leu Pro Pro Glu
340 345 350
Ala Glu Pro Gln Gly Ala Asn Ala Phe Pro Ala Thr Ser
355 360 365



图1

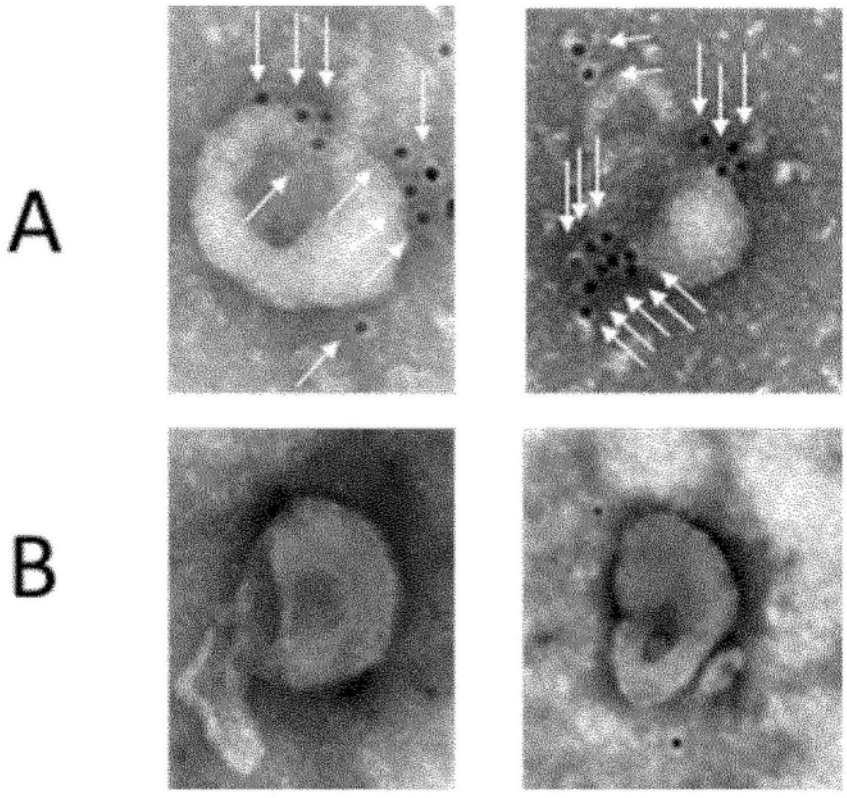


图2

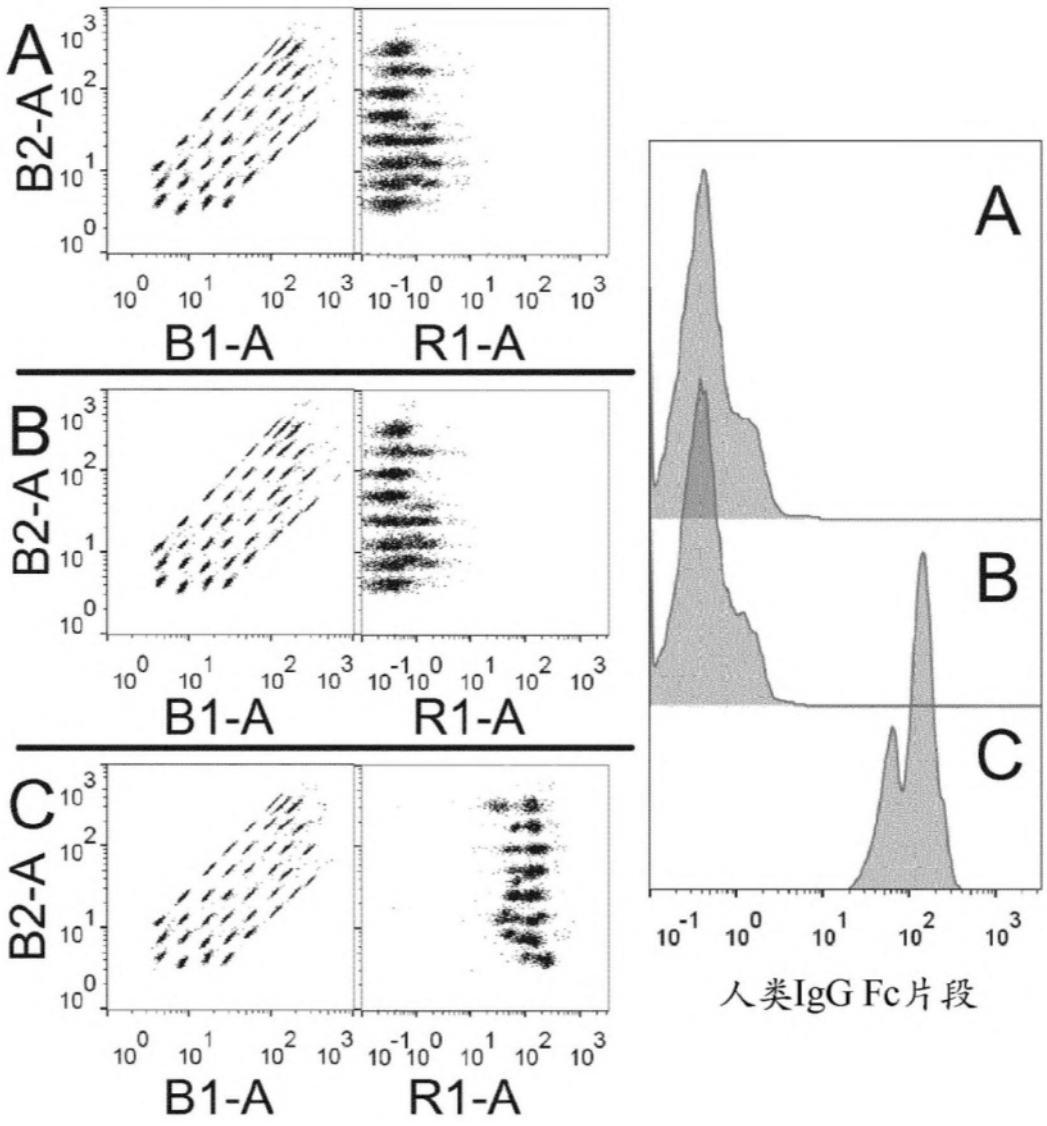


图3

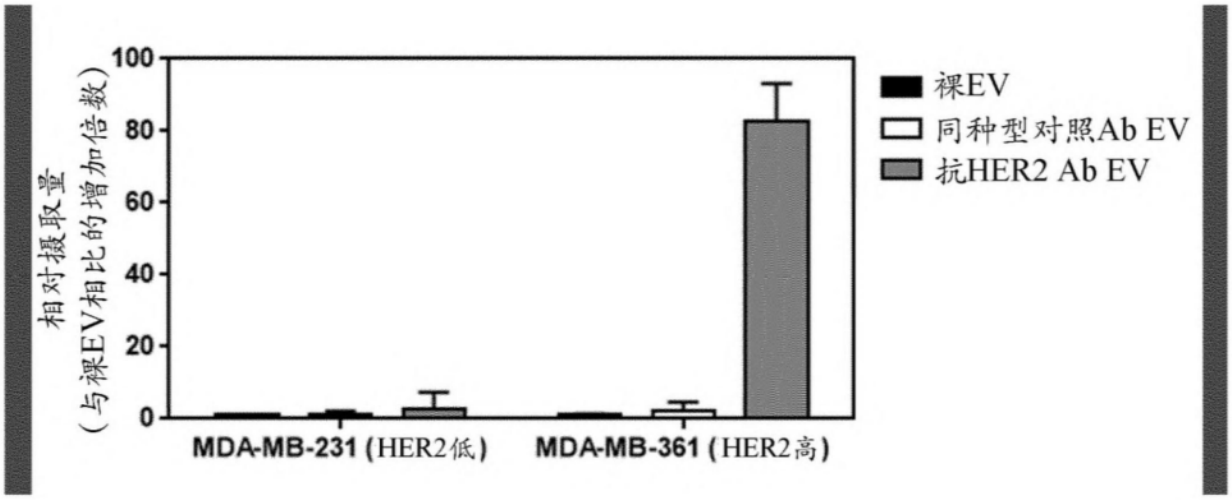

相对摄取量
（与裸EV相比的增加倍数）
100
80
60
40
20
0
MDA-MB-231 (HER2低)
MDA-MB-361 (HER2高)
裸EV
同种型对照Ab EV
抗HER2 Ab EV

图4

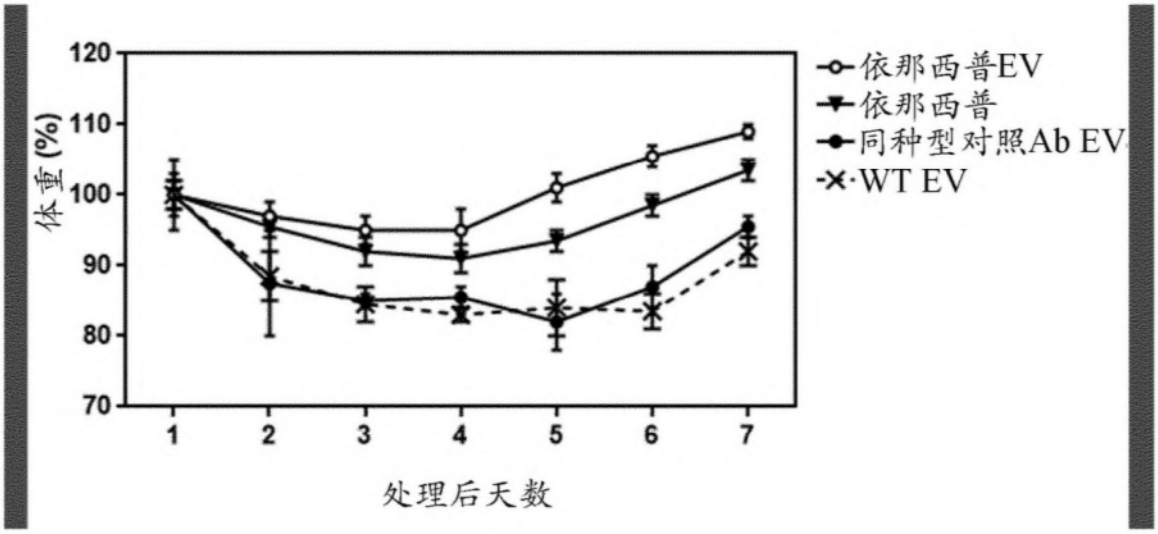

体重 (%)
120
110
100
90
80
70
1
2
3
4
5
6
7
处理后天数
依那西普EV
依那西普
同种型对照Ab EV
WT EV

图5

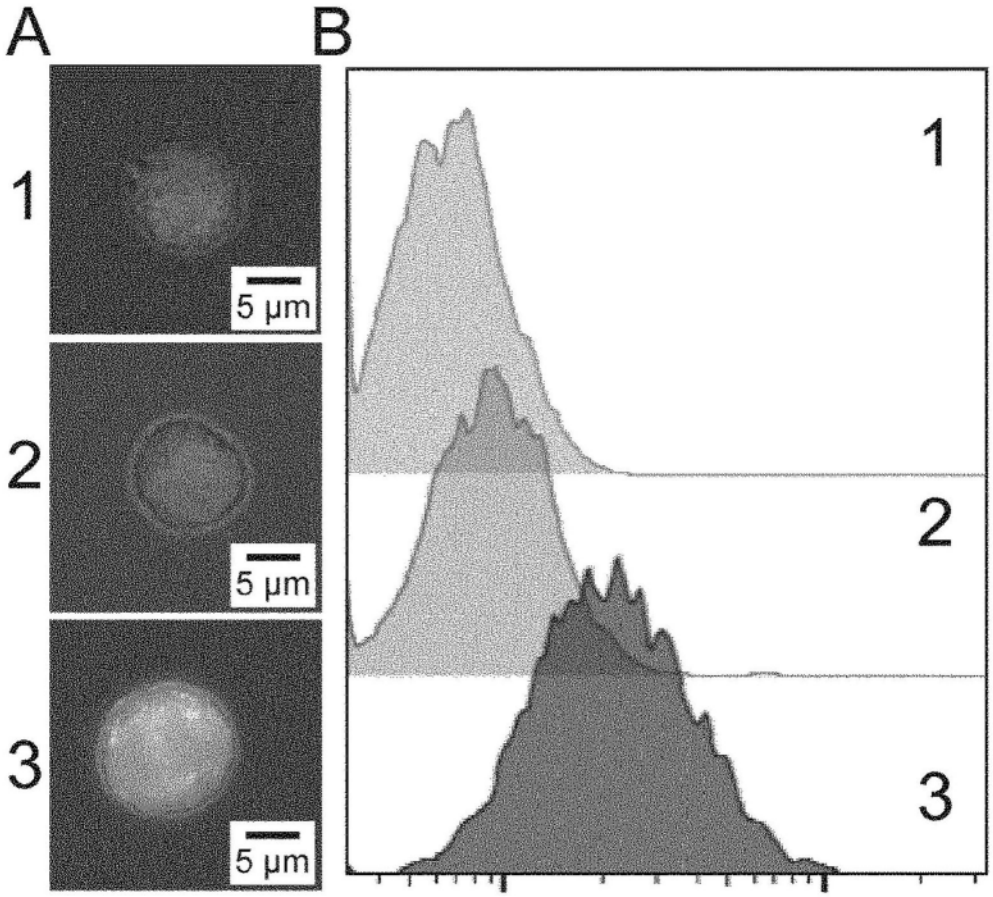


图6

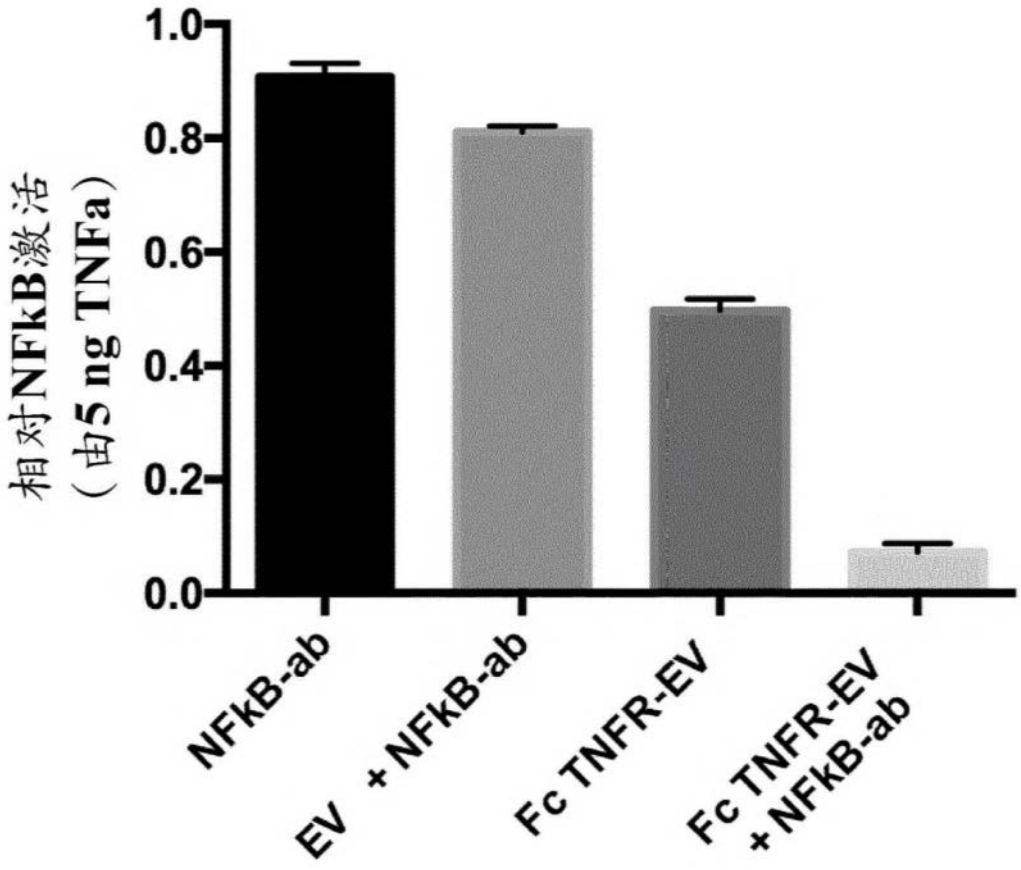

相对NFkB激活
（由5 ng TNFa）
1.0
0.8
0.6
0.4
0.2
0.0
NFkB-ab
EV + NFkB-ab
Fc TNFR-EV
Fc TNFR-EV
+NFkB-ab

图7

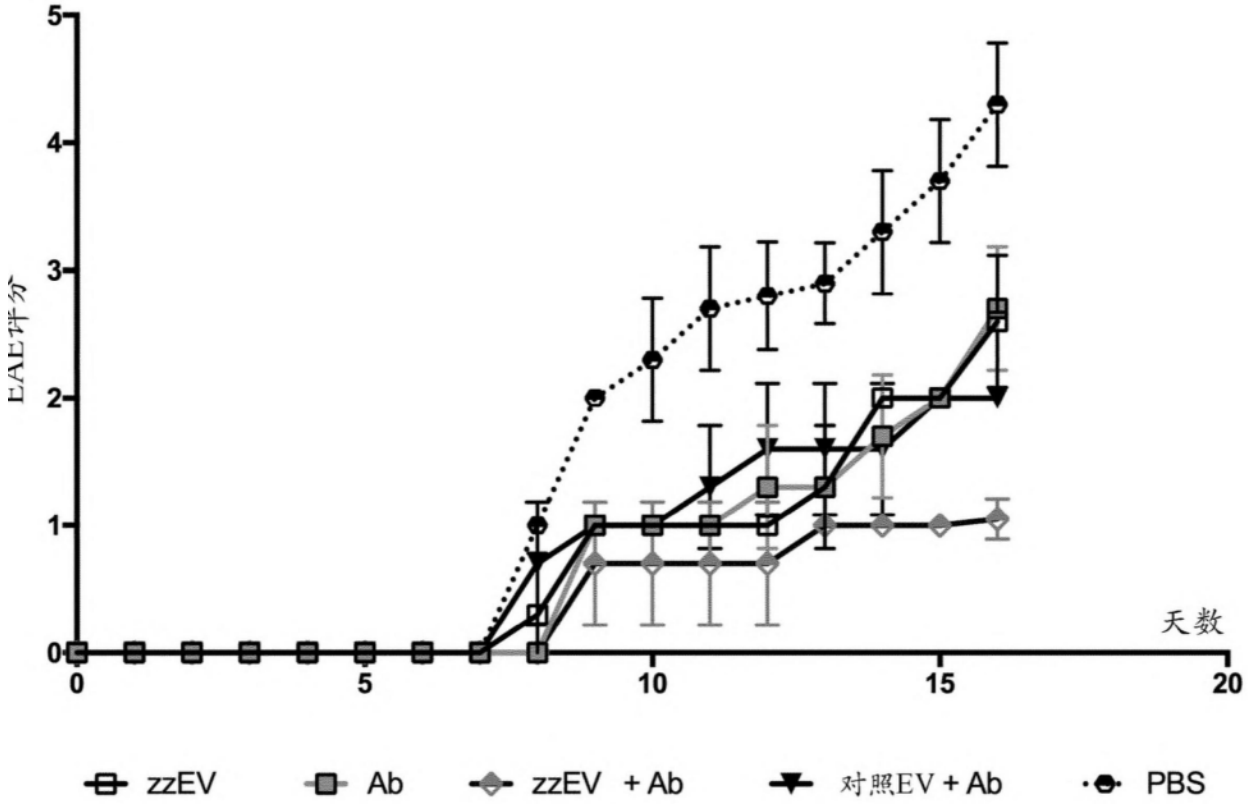

EAE评分
天数
0
1
2
3
4
5
0
5
10
15
20
zzEV
Ab
zzEV + Ab
对照EV + Ab
PBS

图8

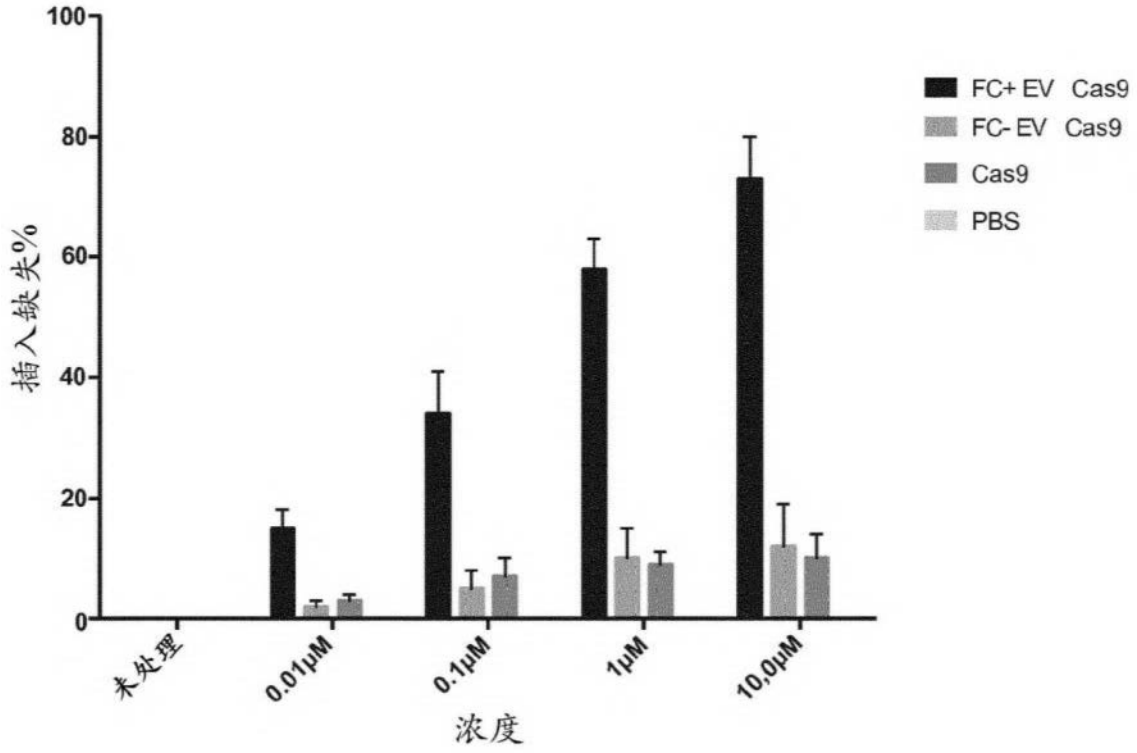

插入缺失%
浓度
0
20
40
60
80
100
未处理
0.01μM
0.1μM
1μM
10.0μM
FC+ EV Cas9
FC- EV Cas9
Cas9
PBS

图9

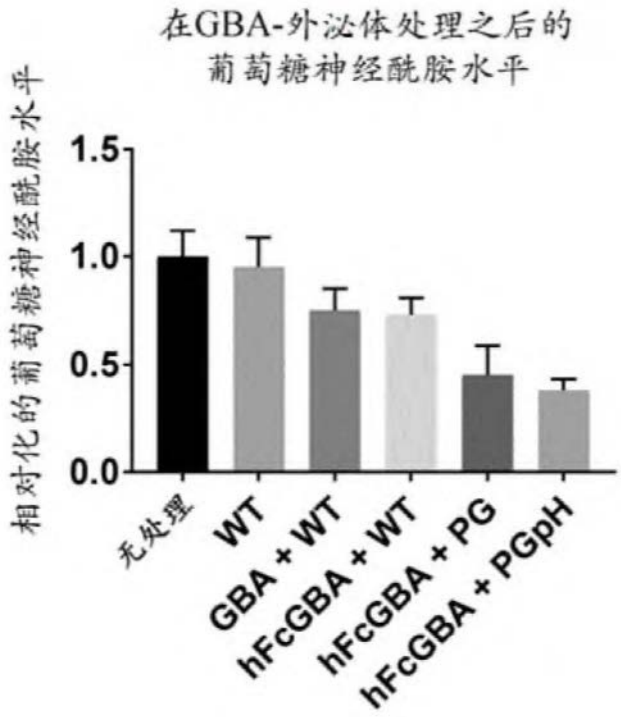

在GBA-外泌体处理之后的
葡萄糖神经酰胺水平
相对化的葡萄糖神经酰胺水平
1.5
1.0
0.5
0.0
无处理
WT
GBA + WT
hFcGBA + WT
hFcGBA + PG
hFcGBA + PGpH

图10

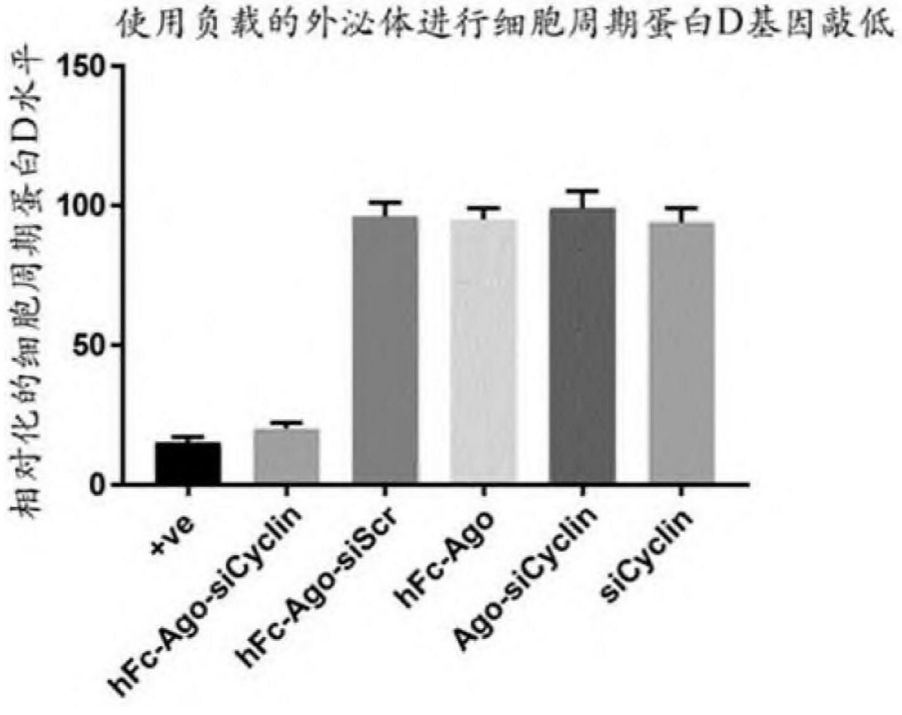

使用负载的外泌体进行细胞周期蛋白D基因敲低
相对化的细胞周期蛋白D水平
150
100
50
0
+ve
hFc-Ago-siCyclin
hFc-Ago-siScr
hFc-Ago
Ago-siCyclin
siCyclin

图11