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(54) 发明名称

具有经过工程化的Fc结构域的抗CD40结合
分子及其治疗用途

(57) 摘要

本公开提供了CD40结合分子,所述CD40结合分子包括在铰链结构域中具有突变的经过工程化的人IgG结构域,例如人IgG1、IgG2和IgG4变体,所述经过工程化的人IgG结构域对一种或多种Fc γ 受体表现出改变的结合活性。本文还描述了用于使用所述CD40结合分子选择性激活或抑制受试者的免疫应答的方法。

1. 一种抗CD40抗体,其包含重链和轻链,其中所述重链包括如SEQ ID NO: 147所示的氨基酸序列,且所述轻链包括如SEQ ID NO: 146所示的氨基酸序列。
2. 一种药物组合物,其包括根据权利要求1所述的抗CD40抗体和药学上可接受的载体。
3. 根据权利要求1所述的抗CD40抗体在制备用于治疗受试者的CD40相关的癌症的药物中的用途。
4. 根据权利要求3所述的用途,其中所述抗CD40抗体与免疫调节试剂、化学治疗剂或其组合共同使用。
5. 根据权利要求4所述的用途,其中所述免疫调节试剂是治疗性疫苗或检查点抑制剂。
6. 根据权利要求5所述的用途,其中所述受试者正在接受包括检查点抑制剂、化学治疗剂或其组合的治疗方法。
7. 根据权利要求6所述的用途,其中所述检查点抑制剂是PD1抑制剂。

具有经过工程化的Fc结构域的抗CD40结合分子及其治疗用途

[0001] 相关申请

[0002] 本申请要求于2018年9月28日提交的国际专利申请第PCT/CN2018/0108285号的权益,所述国际专利申请通过引用整体并入本文。

背景技术

[0003] 分化簇40 (CD40) 是抗原呈递细胞 (APC) 激活所需的APC共刺激蛋白。CD40是肿瘤坏死因子 (TNF) -受体超家族的成员,并且对于各种免疫和炎症反应是必需的,所述免疫和炎症反应包含T细胞依赖性免疫球蛋白类别转换、记忆B细胞发育和生发中心形成。另外,CD40发现于肿瘤细胞,如B淋巴瘤的表面上,并且占有所有实体瘤的约70%。已经显示,其激活逆转对肿瘤特异性抗原的耐受性,从而导致抗原特异性抗肿瘤免疫。

[0004] Fc受体 (FcR) 是能够与抗体的Fc部分结合的免疫细胞表面蛋白的家族。存在若干种不同类型的Fc受体,包含Fc γ 受体、Fc α 受体、Fc ϵ 受体和新生儿Fc受体 (FcRn),所述受体与IgG、IgA、IgE和IgG抗体分别有不同的结合活性。Fc γ 受体亚家族包含Fc γ RI (CD64)、Fc γ RIIA (CD32a)、Fc γ RIIB (CD32b)、Fc γ RIIB (CD32c)、Fc γ RIIIA (CD16a) 和Fc γ RIIIB (CD16b)。Fc γ RI与IgG1抗体和IgG3抗体具有高结合亲和力,而其它Fc γ R与IgG抗体具有低结合亲和力。

[0005] 不同类型的Fc受体在免疫系统中发挥不同的作用。例如,表达在NK细胞和巨噬细胞上的Fc γ RIII受体与附着于受感染细胞或入侵病原体的抗体结合并且触发免疫细胞的抗体介导的吞噬作用 (ADCP) 或抗体依赖性细胞介导的细胞毒性 (ADCC),从而导致消除受感染细胞或入侵病原体。另一方面,表达在B细胞和树突细胞上的Fc γ RIIB受体可以在与IgG抗体结合时下调免疫细胞的活性。

[0006] 涉及激活的免疫细胞的治疗是用于消除如癌细胞等患病细胞的有前景的方法。然而,这种治疗方法常常会引起安全问题。例如,过度激活的免疫细胞将会导致不期望的细胞毒性,从而造成组织损伤。因此,开发有效且安全的新免疫疗法具有重大意义。

发明内容

[0007] 本公开至少部分地基于CD40结合分子 (例如,CD40激动剂或CD40拮抗剂) 的设计,其包括表现出所期望的铰链柔性和优选的Fc受体结合活性和/或选择性的经过工程化的(变体)Fc区 (例如,IgG1、IgG2或IgG4分子的经过工程化的Fc区),例如对Fc γ RIIB具有增强的结合亲和力和/或选择性或对一种或多种Fc γ R受体具有显著降低的结合亲和力。此类CD40结合分子可以用于调节需要治疗的受试者的免疫应答 (例如,选择性增强或选择性抑制免疫应答)。

[0008] 因此,本公开的一个方面提供了CD40结合分子 (例如,CD40激动剂或CD40拮抗剂),与野生型Fc区对应物相比,所述CD40结合分子包括CD40结合部分;以及抗体重链恒定区,所述抗体重链恒定区包括经过工程化的Fc区,其包括位置220-331中的任何位置处,例如位置228-329中的任何位置处的至少一个突变。编号系统是根据EU索引。

[0009] 在一些实施例中,CD40结合部分是CD40L的胞外结构域,其可以包括SEQ ID NO: 140的氨基酸序列。包括这种CD40结合部分的CD40结合分子可以是CD40激动剂。

[0010] 在其它实施例中,CD40结合部分可以是抗CD40抗体片段。在一个实施例中,抗CD40抗体片段包括重链和轻链,所述重链包括与本文所述的任何经过工程化的Fc区连接的重链可变区,所述轻链包括轻链可变区和轻链恒定区。

[0011] 在一些情况下,所述变体Fc区相对于野生型对应物可以对Fc γ RIIB具有增强的结合亲和力和/或选择性。在其它情况下,所述变体Fc区可以对一种或多种Fc γ R受体具有显著降低的结合亲和力。在一些实例中,所述变体Fc区对所有Fc γ R受体具有低结合活性或不具有结合活性。

[0012] 在一些实施例中,CD40结合分子可以包括IgG1分子(例如,人IgG1分子)的变体Fc区,其可以包括包含以下中的一种或多种的突变:(a)位置233-238(例如,234-238)内的氨基酸取代或缺失;(b)位置265处的取代;(c)位置267处的取代;(d)位置297处的取代;(e)位置328处的取代、位置329处的取代;或其组合。可替代地或另外,IgG1分子的Fc变体可以包括位置220、226、229、238、273、327、330和/或331处的一个或多个突变。在一个实例中,突变包括位置233-236中的任何位置处的取代、位置236-238中的一个或多个位置处的缺失或其组合。例如,位置233-235处的所述取代可以包括E233P、L234V、L234F、L234A、L235A和/或L235E。在一个实例中,突变包括位置236-238中的一个或多个位置处的缺失。在另一个实例中,位置238处的所述取代可以是P238S,位置265处的所述取代可以是D265A或其组合。在又一个实例中,所述取代位于位置267处并且是S267E。在另外的实例中,所述取代位于位置329处并且是P329G。在另外的实例中,所述突变可以包括位置265处的取代、位置297处的取代或其组合。例如,位置265处的所述取代可以是D265A,并且位置297处的所述取代可以是N297A。进一步地,位置220、226、229、327、330和331处的所述一个或多个取代可以是C220S、C226S、C229S、A327G、A330S和P331S。源自人IgG1的示例性变体Fc区可以是G1m1、G1m2、G1m17、G1m27、G1mAA、G1mAAG、G1N297A、G1m240和G1m40之一。

[0013] 在其它实施例中,CD40结合分子可以包括IgG2分子(例如,人IgG2分子)的Fc区,其可以包括包含以下中的一种或多种的突变:(a)位置237和238中的一个或多个位置的缺失;(b)位置265处的取代;(b)位置267处的取代;(c)位置297处的取代;(d)位置328处的取代;或其组合。在一些实例中,所述缺失位于位置237处或位于位置237和238两者处。可替代地或另外,IgG2分子的Fc变体可以包括至少一个突变,所述至少一个突变包括位置233-235、237、238、268、273、330和331中的一个或多个位置处的取代。例如,位置233-235、237、238、268、273、330和331中的一个或多个位置处的所述取代可以是P233E、V234A、V234L、A235L、A235S、G237A、P238S、H268A、H268Q、V273E、A330S和P331S。在一个实例中,所述取代位于位置267处并且是S267E。在另一个实例中,所述取代位于位置328处并且是L328F。在另外的实例中,所述突变可以包括位置265处的取代、位置297处的取代或其组合。例如,位置265处的所述取代可以是D265A,并且位置297处的所述取代可以是N297A。在一些特定实例中,源自IgG2的变体Fc区可以是G2m1、G2m17、G2m18、G2m19、G2m20、G2m27、G2m28、G2m29、G2m2040、G2m43、G2G4、G2mAA和G2m40之一。

[0014] 在又其它实施例中,CD40结合分子可以包括IgG4分子(例如,人IgG4分子)的Fc区,其可以包括(a)位置228处的氨基酸残基取代;(b)任何一个位置235-238处的取代或缺失;

(c) 位置265处的取代; (d) 位置267处的取代; (e) 位置297处的取代; (e) 位置328处的取代; 或其组合。在一个实例中, 位置228处的取代是S228P。在另一个实例中, 所述缺失位于位置236、237和238中的一个或多个位置处 (例如, 位于位置236和237两者处)。可替代地或另外, IgG4分子的Fc变体可以包括位置233-235、237和273中的一个或多个位置处的取代。例如, 一个或多个位置233-235、237和273处的取代可以是E233P、F234V、F234A、L235S、L235E、L235A、G237A和V273E。在另一个实例中, 位置267处的所述取代是S267E。在另外的实例中, 位置328处的所述取代是L328F。在另外的实例中, 所述突变可以包括位置265处的取代、位置297处的取代或其组合。例如, 位置265处的所述取代可以是D265A, 并且位置297处的所述取代可以是N297A。在一些特定实例中, 所述变体Fc区是G4m1、G4m2、G4m20、G4m28、G4m30、G4m41、G4m42、G4m46、G4mPE、G4mAA和G4m40之一。

[0015] 与野生型Fc区相比, 本文所述的变体Fc区中的任何变体Fc区可以对Fc γ RIIB表现出增强的结合活性和/或增强的选择性。可替代地, 本文所述的变体Fc区可以对任何Fc γ R受体具有低结合活性或不具有结合活性。在一些情况下, 所述变体Fc区可以对Fc γ RIIB表现出降低的结合亲和力。可替代地或另外, 所述变体Fc区与FcRn结合。

[0016] 本文所述的CD40结合分子中的任何CD40结合分子中的抗CD40抗体片段可以属于人抗体或人源化抗体。在一些实施例中, 抗CD40抗体是激动剂抗体。在一些实例中, 抗CD40抗体可以包括与SEQ ID NO:128中或19G6D6、36G7B8、13F1A7、9F12D9和17C5C2中的任何一个中的重链互补决定区 (HC CDR) 相同的HC CDR, 和/或与SEQ ID NO:129中或19G6D6、36G7B8、13F1A7、9F12D9和17C5C2中的任何一个中的轻链互补决定区 (LC CDR) 相同的LC CDR。在一个实例中, 抗体片段可以包括SEQ ID NO:128的重链可变区, 和/或SEQ ID NO:129的轻链可变区。在其它实例中, 抗体片段可以包括与19G6D6、36G7B8、13F1A7、9F12D9和17C5C2之一相同的重链可变区和/或相同的轻链可变区。

[0017] 另外, 本文提供了一种药物组合物, 其包括本文所述的CD40结合分子中的任何CD40结合分子和药学上可接受的载体。此类药物组合物可以用于选择性调节 (例如, 选择性激活或选择性抑制) 受试者的免疫应答。

[0018] 在又另一方面, 本公开提供了一种用于选择性调节 (例如, 选择性激活或选择性抑制) 受试者的免疫应答的方法, 所述方法包括向有需要的受试者施用有效量的本文所述的CD40结合分子。

[0019] 在本文所述的任何方法中, 所述受试者可以是患有或疑似患有癌症的人类患者, 并且所述CD40结合分子可以是CD40激动剂。示例性癌症包含肺癌、胃癌、肝癌、乳腺癌、皮肤癌、胰腺癌、脑癌、前列腺癌、膀胱癌、结肠直肠癌、肉瘤、骨癌、淋巴瘤和血液癌。

[0020] 可替代地, 所述受试者可以是患有或疑似患有免疫相关病症的人类患者, 并且所述CD40结合分子可以是CD40拮抗剂。示例性免疫病症包含自身免疫性疾病、免疫缺陷或过敏症。在一些实施例中, 用于治疗靶疾病是自身免疫性疾病。

[0021] 在又另一方面, 本公开提供了一种分离的抗CD40抗体, 其和选自以下组成的组的参考抗体与CD40的同一表位结合: 19G6D6、36G7B8、13F1A7、9F12D9和17C5C2, 或者与所述参考抗体竞争与所述表位结合。

[0022] 在一些实施例中, 所述抗体包括重链互补决定区1 (CDR1)、重链互补决定区2 (CDR2) 和重链互补决定区3 (CDR3), 所述重链CDR1、所述重链CDR2和所述重链CDR3共同与所

述参考抗体的相应重链CDR至少85%相同;和/或其中所述抗体包括轻链CDR1、轻链CDR2和轻链CDR3,所述轻链CDR1、所述轻链CDR2和所述轻链CDR3共同与所述参考抗体的相应轻链CDR至少85%相同。

[0023] 在另一个实施例中,相对于参考抗体的相应重链CDR,重链CDR1、重链CDR2和重链CDR3共同包括10个或更少氨基酸突变;和/或其中相对于参考抗体的相应轻链CDR,轻链CDR1、轻链CDR2和轻链CDR3共同包括10个或更少氨基酸突变。

[0024] 在一个实施例中,所述抗体包括重链可变区和/或轻链可变区,所述重链可变区与所述参考抗体的重链可变区至少85%相同,所述轻链可变区与所述参考抗体的轻链可变区至少85%相同。

[0025] 在一些实施例中,重链可变区相对于参考抗体的重链可变区包括10个或更少氨基酸残基突变;和/或并且相对于参考抗体的轻链可变区包括10个或更少氨基酸突变的轻链可变区。

[0026] 在一些实例中,本文公开的抗CD40抗体可以与所述参考抗体包括相同的重链可变区CDR和/或与所述参考抗体包括轻链可变区CDR。

[0027] 本文所述的任何抗CD40抗体可以是人抗体或人源化抗体。本文还提供了一种药物组合物,其包括本文所述的任何抗CD40抗体和药学上可接受的载体。

[0028] 进一步地,本公开的特征在于一种分离的核酸或核酸组,其编码或共同编码本文所述的任何CD40结合分子或任何抗CD40抗体。所述核酸或核酸组可以位于一个或两个载体,例如表达载体上。本文还提供了包括一种或多种此类载体的宿主细胞。

[0029] 本公开的特征还在于包括一种或多种本文所述的CD40结合分子和/或一种或多种本文公开的抗CD40抗体的药物组合物用于治疗本文所述的靶病症,或此类CD40结合分子和/或抗CD40抗体在制造用于治疗靶病症的药物中的用途。

[0030] 在以下描述中阐述了本发明的一个或多个实施例的细节。本发明的其它特征或优点将根据以下附图和对若干个实施例的详细描述并且还根据所附权利要求书变得显而易见。

附图说明

[0031] 图1A-1D是示出了如所指示的各种抗CD40抗体383IgG变体在如所指示的不同浓度下与CHO-K1细胞上表达的不同类型的Fc γ 受体的结合活性的图表。每种IgG变体的浓度从左到右为0.1 μ g/ml、0.3 μ g/ml、1 μ g/ml、3 μ g/ml、10 μ g/ml和30 μ g/ml。最右侧两个条(“仅2级抗体”和“空白”)充当对照。图1A:与Fc γ RI的结合亲和力。图1B:与Fc γ RII的结合亲和力。图1C:与Fc γ RIIB的结合亲和力。图1D:与Fc γ RIIIA的结合亲和力。

[0032] 图2是示出了在报告基因测定中,如IL8分泌所指示的许多抗CD40抗体383IgG变体对人CD40激活的刺激力的图表。每种IgG变体的浓度从左到右对应于:0.003 μ g/ml、0.01 μ g/ml、0.03 μ g/ml、0.1 μ g/ml、0.3 μ g/ml、1 μ g/ml、3 μ g/ml和10 μ g/ml。

[0033] 图3A-3D是示出了如所指示的许多抗CD40抗体383IgG变体与CHO-K1细胞上表达的不同类型的Fc γ 受体的结合活性的图表。每种抗CD40抗体383IgG变体的浓度从左到右为0.3 μ g/ml、1 μ g/ml、3 μ g/ml、10 μ g/ml和30 μ g/ml。最右侧两个条(“仅2级抗体”和“空白”)充当对照。图3A:与Fc γ RIIB的结合亲和力。图3B:与Fc γ RI的结合亲和力。图3C:与Fc γ RIIA的

结合亲和力。图3D：与Fc γ RIIB的结合亲和力。

[0034] 图4A-4F是图表，示出了在报告基因测定中通过IL8分泌指示的，由许多抗CD40抗体383IgG变体在溶液中和/或在与Fc γ RIIB表达性细胞共培养的情况下对人CD40激活的刺激。每种IgG变体的浓度从左到右对应于：0.003 μ g/ml、0.01 μ g/ml、0.03 μ g/ml、0.1 μ g/ml、0.3 μ g/ml和1 μ g/ml。虚线指示每个测定中的基线报告基因信号。图4A：IgG变体IgG1m2、IgG2m20、IgG1m40、IgG4m40。图4B：IgG变体IgG1m240、IgG2m2040、IgG4m41、IgG4m42、IgG2m43、IgG2m44和IgG4mAA。图4C：IgG变体IgG1 N297A、IgG2mAA、IgG2G4、IgG4mPE和IgG1mAA。图4D：IgG1m47、IgG1m48、IgG1m49、IgG1m50和IgG1mAA的IgG变体。图4E：IgG4m46和IgG4m30的IgG变体。图4F：IgG1m27、IgG2m19、IgG2m1、IgG4m2和IgG4m20的IgG变体。

[0035] 图5A-5D包含一组条形图，其示出了示例性抗CD40抗体383IgG变体的活性，所述活性通过抗体在溶液中（图5A和5B）或在与表达人Fc γ RIIB的CHO细胞共培养的情况下（图5C和5D）对来自健康供体的人树突细胞（DC）的激活来指示。DC激活由培养物上清液中的IL-8的条形图信号指示。

[0036] 图6A-6B是示出了如所指示的抗CD40抗体383IgG变体与CHO-K1细胞上表达的人CD40的结合活性的图表。每种IgG变体的浓度从左到右为0.01 μ g/ml、0.1 μ g/ml、1 μ g/ml和10 μ g/ml。最右侧三个条（“赫赛汀（Herceptin）”、“仅2级抗体”和“空白”）充当对照。图6A：如所指示的许多抗CD40抗体383IgG变体。图6B：如所指示的许多抗CD40抗体383IgG变体。

[0037] 图7A-7B是示出了小鼠肿瘤模型中如所指示的各种抗CD40抗体383IgG变体的肿瘤生长曲线的图表。图7A：示出了纯合子B-hCD40 C57BL6小鼠中在抗体处理之后的不同时间点处的肿瘤体积变化的图表。示出了肿瘤大小的平均值 $\pm$ SEM。图7B：是示出了如纯合子B-hCD40 C57BL6小鼠中所示在抗体处理之后血清丙氨酸转氨酶（ALT，在肝损伤时释放到血清中的肝酶）水平的图表。示出了肿瘤大小的平均值 $\pm$ SEM。

具体实施方式

[0038] 本文提供了CD40结合分子（例如，CD40激动剂或CD40拮抗剂），其包括CD40结合部分（例如，CD40配体的胞外结构域或抗CD40抗体片段）和经过工程化（变体）的Fc区，其可以对一种或多种Fc受体具有改变的结合亲和力和/或特异性，例如对Fc γ RIIB具有增强的结合亲和力、对Fc γ RIIB具有增强的结合特异性和/或对一种或多种Fc γ R具有显著降低的结合亲和力（例如，对所有Fc γ R受体具有低结合活性或不具有结合活性）。

[0039] 预期此类CD40结合分子会表现出出乎意料的优越治疗活性。例如，预期具有对Fc γ RIIB具有增强的结合亲和力的变体Fc区的CD40结合分子将表现出增强的激动活性，并且预期具有对Fc γ RIIB具有增强的结合特异性的变体Fc区的CD40结合分子相对于野生型对应物将表现出更高的肿瘤选择性。进一步地，对Fc γ R受体具有低结合亲和力或无结合亲和力的CD40结合分子将有助于激活肿瘤微环境中的CD40阳性免疫细胞和/或阻断免疫病症中的CD40阳性免疫细胞。

[0040] 因此，本文描述了用于设计CD40结合分子的方法，所述CD40结合分子包括CD40结合部分和经过工程化的Fc区（Fc变体），所述经过工程化的Fc区可以是IgG分子（例如，IgG1、IgG2和IgG4分子，如人IgG1、人IgG2和人IgG4分子），以及其用于调节免疫应答的用途。这种Fc变体相对于野生型对应物可以对Fc γ RIIB（CD32B）具有增强的结合亲和力和/或相对于

其它Fc受体,如Fc γ RIII (CD16) 具有增强的结合选择性。可替代地,这种Fc变体相对于野生型对应物可以对一种或多种Fc γ R受体(例如,对所有Fc γ R受体)具有显著降低的结合亲和力。“显著降低”意指Fc变体对Fc γ R受体的结合亲和力比野生型对应物对同一Fc γ R受体的结合亲和力低至少60%(例如,低70%、低80%、低90%、低95%、低98%或低99%)。在一些实例中,Fc变体可以对所有Fc γ R受体具有低结合亲和力或无结合亲和力,即结合亲和力不能通过常规测定来检测或结合亲和力是显著低的,这样使得将不触发显著的生物活性。

[0041] I. CD40结合分子

[0042] 本文描述了CD40结合分子,其包括与经过工程化的Fc区连接的CD40结合部分,所述经过工程化的Fc区对如本文所述的一种或多种Fc受体具有改变的结合亲和力和/或特异性。此类CD40结合分子可以是CD40激动剂,其能够在与细胞表面CD40结合时触发由CD40/CD40L介导的信号传导。可替代地,本文所述的CD40结合分子是CD40拮抗剂,其能够在与细胞表面CD40结合时抑制由CD40/CD40L介导的信号传导。当向需要治疗的受试者施用,CD40结合分子可用于调节(选择性调节)免疫应答。

[0043] (i) CD40结合部分

[0044] 本文所述的CD40结合部分可以是与CD40,例如人CD40结合的任何肽或多肽。CD40是本领域熟知的免疫细胞受体。例如,NCBI GenBank登录号P25942.1和AAB08705.1分别提供了人和小鼠CD40的信息。下面提供了示例性人CD40多肽的氨基酸序列。

[0045] 人CD40:

[0046] MVRLPLQCVLWGCLLTAVHPEPPTACREKQYLINSQCCSLCQPGQKLVS DCTEFTETEC LPCGESEFLDTWNRETHCHQH KYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCVLHRSCSPGFGVKQIATGVSDTICEPCPVGFFSNVSSAFEKCHPWTSCETKDLVVQQAGTNKTDVVC GPQDRLRALVVIPIIFGILFAILLVLVFIKKVAKKPTNKAPHPKQEPQEINFPDDLPGSNTAAPVQETLHGCQPVTQEDGKESRISVQERQ (SEQ ID NO:141)

[0047] 来自其它物种的CD40多肽是本领域已知的,并且可以使用人类序列或小鼠序列作为查询从公开可获得的基因数据库,例如GenBank获得。

[0048] 在一些实施例中,CD40结合部分可以是包括CD40配体(CD40L或CD154)的胞外结构域的多肽。CD40L是在T细胞表面上表达的膜糖蛋白。已经显示分子在细胞因子存在的情况下刺激B细胞增殖和免疫球蛋白的分泌。另外,CD40L可以在外周血单核细胞中诱导细胞因子产生和杀肿瘤活性。CD40L的序列和其胞外结构域是本领域熟知的。例如,NCBI GenBank登录号NP_000065.1(胞外结构域,氨基酸47-261)提供了人CD40L的信息。下面提供了示例性人CD40L的胞外结构域的氨基酸序列。

[0049] 人CD40L(胞外结构域):

[0050] HRRLDKIEDERNLHEDFVFMKTIQRCNTGERSLSLLNCEEIKSQFEGFVKDIMLNKEETK KENSFEMQKGDQNPQIAAHVISEASSKTTSVLQWAEKGYTMSNNLVTLENGKQLTVKRQGLYYIYAQVTFCSNREASSQAPFIASLCLKSPGRFERILLRAANTHSSAKPCGQQSIHLGGVFELQPGASVFNVTDP SQVSHGTGFTSFGLLKL (SEQ ID NO:140)

[0051] 来自其它物种的CD40L多肽是本领域已知的,并且可以使用人序列作为查询从公开可获得的基因数据库,例如GenBank获得。

[0052] 在其它实施例中,本文所述的CD40结合部分可以包括抗CD40抗体。如本文所使用的,术语“抗CD40抗体”是指能够与CD40多肽结合的任何抗体,其可以具有合适的来源,例如

人或非人哺乳动物(例如,小鼠、大鼠、兔、灵长类动物,如猴等)。

[0053] 本文所述的抗CD40抗体包括重链和任选地轻链,所述重链包括与本文所述的任何Fc变体连接的重链可变结构域,所述轻链包括轻链可变区和轻链恒定区。重链可变区(V_H)和任选地轻链可变区(V_L)通常参与抗原(在这种情况下是CD40)结合。

[0054] V_H 和 V_L 区可以进一步细分为高变区,也称为“互补决定区”(“CDR”),其散布有更保守的被称为“框架区”(“FR”)的区。每个 V_H 和 V_L 通常由按以下顺序从氨基端到羧基端布置的三个CDR和四个FR构成:FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。框架区和CDR的范围可以使用本领域已知的方法,例如通过Kabat定义、Chothia定义、AbM定义和/或接触定义来精确地鉴定,所有所述定义均是本领域熟知的。参见例如,Kabat,E.A.等人,(1991)《免疫学上关注的蛋白质的序列(Sequences of Proteins of Immunological Interest)》,第五版,美国卫生与公众服务部(U.S.Department of Health and Human Services),NIH公开号91-3242;Chothia等人,(1989)《自然(Nature)》342:877;Chothia,C.等人(1987),《分子生物学杂志(J.Mol.Biol.)》196:901-917;Al-lazikani等人,(1997)《分子生物学杂志(J.Molec.Biol.)》273:927-948;和Almagro,《分子识别杂志(J.Mol.Recognit.)》17:132-143(2004)。还参见hgmp.mrc.ac.uk和bioinf.org.uk/abs。

[0055] 在一些实施例中,本文所述的抗CD40抗体可以结合并抑制CD40的活性至少50%(例如,60%、70%、80%、90%、95%或更高,包含其中的任何增量)。提供抑制剂效力的量度的表观抑制常数(K_{iapp} 或 $K_{i,app}$)与降低酶活性所需的抑制剂浓度相关并且不依赖于酶浓度。本文所述的抗CD40抗体的抑制活性可以通过本领域已知的常规方法确定。

[0056] 抗体的 K_i^{app} 值可以通过测量不同浓度的抗体对反应程度(例如,酶活性)的抑制作用来确定;将作为抑制剂浓度的函数的伪一阶速率常数(v)的变化拟合到修正的莫里森等式(Morrison equation)(等式1)得到表观 K_i 值的估计值。对于竞争性抑制剂,可以根据从 K_i^{app} 与底物浓度的绘图的线性回归分析中提取的y截距获得 K_i^{app} 。

$$[0057] \quad v = A \cdot \frac{([E] - [I] - K_i^{app}) + \sqrt{([E] - [I] - K_i^{app})^2 + 4[E] \cdot K_i^{app}}}{2} \quad (\text{等式 1})$$

[0058] 其中A等于 v_0/E ,在抑制剂(I)不存在的情况下酶反应的初始速度(v_0)除以总酶浓度(E)。

[0059] 在一些实施例中,本文所述的抗CD40抗体对于靶抗原或抗原表位的 K_i^{app} 值可以为1000、900、800、700、600、500、400、300、200、100、50、40、30、20、19、18、17、16、15、14、13、12、11、10、9、8、7、6、5pM或更小。在一些实施例中,任何抗CD40抗体可以进一步亲和力成熟以减少抗体对靶抗原或其抗原表位的 K_i^{app} 。

[0060] 在一些情况下,抗CD40抗体可以将CD40/CD40L相互作用触发的信号传导抑制至少50%(例如,60%、70%、80%、90%、95%或更高,包含其中的任何增量)。这种抑制活性可以通过常规方法或本文所述的测定来确定。

[0061] 本文所述的抗体可以是鼠、大鼠、人类或任何其它来源(包含嵌合抗体或人源化抗体)。此类抗体是非天然存在的,即在没有人行为(例如,用所期望的抗原或其片段免疫此类动物或从抗体文库中分离)的情况下将不会在动物中产生。

[0062] 在一些实施例中,抗CD40抗体是人源化抗体,其可以具有下文或本文其它地方所述的一种或多种要素或特性。人源化抗体是指为特异性嵌合免疫球蛋白、免疫球蛋白链或

其含有衍生自非人免疫球蛋白的最小序列的抗原结合片段的非人(例如,鼠)抗体的形式。通常,人源化抗体是来自接受者的CDR的残基被来自如小鼠、大鼠或兔等具有期望特异性、亲和力和能力的非人物种(供体抗体)的CDR的残基替代的人免疫球蛋白(接受者抗体)。在一些情况下,人免疫球蛋白的Fv框架区(FR)残基被对应的非人残基替代。此外,人源化抗体可以包括既未在接受者抗体中发现也未在导入的CDR或框架序列中发现但被包含在内以进一步精化和优化抗体性能的残基。在一些情况下,人源化抗体可以包括至少一个并且通常两个可变结构域中的基本上所有可变结构域,其中所有或基本上所有CDR区对应于非人免疫球蛋白的那些区,并且所有或基本上所有FR区是人免疫球蛋白共有序列的那些区。人源化抗体最佳地还将包括免疫球蛋白恒定区或结构域(Fc)的至少一部分,通常是人免疫球蛋白恒定区或结构域的至少一部分。抗体可以具有如W0 99/58572中所描述的修饰的Fc区。其它形式的人源化抗体具有关于原始抗体改变的一个或多个CDR(一个、两个、三个、四个、五个或六个),也称为“源自”来自原始抗体的一个或多个CDR的一个或多个CDR。人源化抗体还可以涉及亲和力成熟。

[0063] 用于构建人源化抗体的方法也是本领域熟知的。参见例如Queen等人,《美国国家科学院院刊(Proc.Natl.Acad.Sci.USA)》,86:10029-10033(1989)。在一个实例中,按照本领域已知的方法对亲本非人抗体的 V_H 和 V_L 可变区进行三维分子建模分析。接下来,使用相同的分子建模分析来鉴定被预测对形成正确CDR结构具有重要性的框架氨基酸残基。平行地,使用亲本 V_H 和 V_L 序列作为搜索查询来从任何抗体基因数据库中鉴定具有与亲本非人抗体的氨基酸序列同源的氨基酸序列的人 V_H 链和人 V_L 链。然后选择人 V_H 受体基因和人 V_L 受体基因。

[0064] 可以用来自亲本非人抗体或其功能变体的CDR区替代所选人受体基因内的CDR区。在必要时,可以使用在亲本链的框架区内被预测在与CDR区相互作用时具有重要性的残基来取代人受体基因中的对应残基。

[0065] 在一些实施例中,本文所述的抗CD40抗体与对应的靶抗原或其表位,例如CD40抗原或表位特异性结合。与抗原或表位“特异性结合”的抗体是本领域充分理解的术语。如果分子与特定靶抗原比其与替代性靶标更频繁地、更快速地、持续时间更长地和/或亲和力更大地反应,则所述分子被称为表现出“特异性结合”。如果抗体比与其它物质亲和力更大地、亲合力更高地、更容易地和/或持续时间更长地结合,则所述抗体与靶抗原或表位“特异性结合”。例如,与抗原(CD40)或其中的抗原表位特异性(或优先地)结合的抗体是这样的抗体:所述抗体与这种靶抗原比与其它抗原或同一抗原中的其它表位亲和力更大地、亲合力更高地、更容易地和/或持续时间更长地结合。利用这个定义还应理解,例如,与第一靶抗原特异性结合的抗体可以或可以不与第二靶抗原特异性结合或优先地结合。如此,“特异性结合”或“优先结合”不一定需要(尽管其可以包含)排他结合。在一些实例中,与靶抗原或其表位“特异性结合”的抗体可以不与其它抗原或同一抗原中的其它表位结合(即,在常规方法中仅可以检测基线结合活性)。在一些实施例中,本文所述的抗CD40抗体与CD40特异性结合。可替代地/另外,相对于小鼠对应物,本文所述的抗CD40抗体与人CD40或其片段特异性结合,或反之亦然(例如,如在相同的测定条件下的同一测定中确定的,对一种抗原的结合亲和力比对另一种抗原的结合亲和力高至少10倍)。在其它情况下,本文所述的抗CD40抗体可以与人和非人CD40(例如,小鼠)交叉反应,例如对人和非人CD40的结合亲和力差异小于5倍,例如小于2倍,或基本上类似。

[0066] 在一些实施例中,本文所述的抗CD40抗体对靶抗原(例如,CD40)或其抗原表位具有合适的结合亲和力。如本文所使用的,“结合亲和力”是指表观缔合常数或 K_A 。 K_A 是解离常数(K_D)的倒数。本文所述的抗CD40抗体对于靶抗原或抗原表位的结合亲和力(K_D)可以为至少 10^{-5} 、 10^{-6} 、 10^{-7} 、 10^{-8} 、 10^{-9} 、 10^{-10} M或更低。增大的结合亲和力对应于减小的 K_D 。抗体相对于第二抗原对第一抗原的更高亲和力结合可以通过比用于结合第二抗原的 K_A (或数值 K_D)更高的用于结合第一抗原的 K_A (或更小的数值 K_D)来指示。在这种情况下,所述抗体相对于第二抗原(例如,第二构象或其模拟物中的相同的第一蛋白质;或第二蛋白质)对第一抗原(例如,第一构象或其模拟物中的第一蛋白质)具有特异性。结合亲和力的差异(例如,对于特异性或其它比较)可以为至少1.5倍、2倍、3倍、4倍、5倍、10倍、15倍、20倍、37.5倍、50倍、70倍、80倍、91倍、100倍、500倍、1000倍、10,000倍或 10^5 倍。在一些实施例中,任何抗CD40抗体可以进一步亲和力成熟以增加抗体对靶抗原或其抗原表位的结合亲和力。

[0067] 可以通过各种方法来确定结合亲和力(或结合特异性),包含平衡透析、平衡结合、凝胶过滤、ELISA、表面等离子共振或光谱学(例如,使用荧光测定)。用于评估结合亲和力的示例性条件为处于HBS-P缓冲液(10mM HEPES pH7.4,150mM NaCl,0.005% (v/v)表面活性剂P20)中。这些技术可以用于根据靶蛋白浓度测量结合的结合蛋白的浓度。结合的结合蛋白的浓度([结合(Bound)])通常通过以下等式与游离靶蛋白([游离(Free)])的浓度相关:

[0068] $[结合] = [游离] / (K_d + [游离])$

[0069] 然而,并不总是需要对 K_A 进行精确测定,因为有时例如通过功能性测定,例如体外或体内测定中的活性足以获得对亲和力的定量测量、获得对亲和力的定性测量或者获得对亲和力的推断,所述亲和力例如是使用如ELISA或FACS分析等方法确定的、与 K_A 成正比并且因此可以用于比较,如确定更高的亲和力是否例如高2倍。

[0070] 下文提供了示例抗CD40抗体383(V_H 和 V_L 氨基酸序列;CDR以粗体字表示): V_H :

[0071] QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTGYYMH**WVRQAPGQGLEWMG**WINPDSGGTNYAQKFQGR**VTMTDR
DTSISTAYMELNRLRSDDTAVYYCARD**QDPLGYCTNGVCSYFDY**WGQGTLLTVSS (SEQ ID NO: 128)

[0072] V_L :

[0073] DIQMTQSPSSVSASVGDRVTITCRAS**QGIYSWLAWYQ**KPGKAPNLLIY**TASTLQ**SGVPSRFSGSGSGTDFT
LTISSLQPEDFATYYC**QQANIFPLT**FGGGTKVEIK (SEQ ID NO: 129)

[0074] 下文提供了另外的示例性抗CD40抗体(CDR以粗体字表示)。

[0075] 19G6D6

[0076] V_H :

[0077] EVQLQQSGPELVKPGASVKIPCKAS**GYTFTDYNM**DWVKQSHGKSLEWIGD**INPNNDISIYNQKFRG**KATLTVDKSS
STAYMELRSLTSEDTA VYYCAR**RFAY**WGQGTLLTVSA (SEQ ID NO: 130)

[0078] V_L :

[0079] DVVMTQIPLSLPVSIGDQASISCR**SSQSLVSYGNTYL**HWFLQKPGQSPKLLIY**NVSNRFS**GVDPDRFSGSGSGTDFT
TLRISRVEAEDLGVYFC**SQGTHVPWT**FGGGTKLEIK (SEQ ID NO: 131)

[0080] 36G7B8

[0081] V_H :

[0082] QVQLQQPGAELVRPGASVKLSCKAS**GYIFISYWI**HWLQRPGRGLEWIG**RIDPNNGG**TKYNEKFRYKASLTVDKSS
STAYMQLSSLTSEDSAVYYCTK**GVITTLVAGDY**WGQGTLLTVSS
(SEQ ID NO: 132)

- [0083] V_L :
DIQMTQSPASLSASLGSETVSI**ECLASEDISNDL**AWYQQKSGKSPQLLIY**FVDRLLD**GVPSRFSGSGSGTRHSLKIS
- [0084] GMQPEDEADYFC**QQSYKYPPT**FGGGTKLELK (SEQ ID NO: 133)
- [0085] 13F1A7
- [0086] V_H :
EVQILETGGGLVKPGGSLRLSCATS**GFNFNDSE**MNWVRQAPGKLEWVA**QIRNKNYNYATYYTESLE**GRVTISRDD
- [0087] SKSRVYLQVSSLRAEDSAVYYCTSY**YYDGFADYFDY**WGQGMVTVSS (SEQ ID NO: 134)
- [0088] V_L :
EIVLTQSPPTMAASPGEKITITC**SASSSISSNYL**HWYQQKPGSSPKVLIY**RTSNLAS**GVPPVRFSGSGSGTSYSLTI
- [0089] GTMEADVATYYC**QQGSSIPY**TFGGGTKLEIK (SEQ ID NO: 135)
- [0090] 9F12D9
- [0091] V_H :
EVHLVESGGGLVQPGRSLKLSAAS**GFTFTNYGL**HWIRQAPTGLEWVA**SISPSGGVTTYRDSVKGR**FTISRDNKG
- [0092] TTLHLQMSLRS EDTATYYCAL**PFLGWGGANWIA**HWGQGLTVTVSS (SEQ ID NO: 136)
- [0093] V_L :
DIKVTQSPSFLSASVGDRATIN**CASQNLNKYL**NWYQQKPGEPKLLIY**NTDNL**YTGIPSRFSGSGSVADFTLTIS
- [0094] GLQPEDVATYFC**MQHNVRRT**FGGGTKLELK (SEQ ID NO: 137)
- [0095] 17C5C2
- [0096] V_H :
EVHILETGGGLVKPGGSLGLSCTTS**GFNFNDYFM**NWVRQAPGKLEWVA**QIRNGNYDYAAYYAESLE**GRVTISRDD
- [0097] SKSSVNLQVSSLRAEDTAIYYCTSY**YYDGHFDYFDN**WGHGVMVTVSS (SEQ ID NO: 138)
- [0098] V_L :
DIKMTQSPSFLSASVGDSVTFT**CASQNIYIYL**NWYQQKFGAPKLLIY**NTNNLQT**GIPSRFSGSGSESGTVFTLTIS
- [0099] SLQPEDVATYFC**LQHSSRRT**FGGGTKLELK (SEQ ID NO: 139)

[0100] 在一些实施例中,本文所述的抗CD40抗体和本文所述的任何示例性抗体与同一表位结合,或者与示例性抗体竞争与CD40抗原结合。

[0101] “表位”是指靶抗原上被抗体识别并结合的位点。位点可以完全由氨基酸组分构成、完全由蛋白质的氨基酸的化学修饰(例如,糖基部分)构成或由其组合构成。重叠表位包含至少一个共同的氨基酸残基。表位可以是线性的,其长度通常为6-15个氨基酸。可替代地,表位可以是构象的。可以通过常规技术,例如表位作图方法(参见例如以下描述)来确定抗体与其结合的表位。与本文所述的示例性抗体相同的表位结合的抗体可以与示例性抗体完全相同的表位或基本上重叠的表位(例如,含有少于3个非重叠氨基酸残基、少于2个非重叠氨基酸残基或仅1个非重叠氨基酸残基)结合。可以通过本领域熟知的竞争测定来确定两种抗体是否彼此竞争与同源抗原结合。

[0102] 在一些实施例中,本文公开的抗CD40抗体包括与以下序列中的重链和轻链CDR相同的重链和轻链CDR:(a) SEQ ID NO:128和SEQ ID NO:129;(b) SEQ ID NO:130和SEQ ID NO:131(19G6D6);(c) SEQ ID NO:132和SEQ ID NO:133(36G7B8);(d) SEQ ID NO:134和SEQ ID NO:135(13F1A7);(e) SEQ ID NO:136和SEQ ID NO:137(9F12D9)或(f) SEQ ID NO:138和SEQ ID NO:139(17C5C2)。在一些实例中,抗CD40抗体包括以下序列的重链可变结构域:SEQ ID NO:128、SEQ ID NO:130、SEQ ID NO:132、SEQ ID NO:134、SEQ ID NO:136或SEQ ID NO:

138,和/或以下序列的轻链可变结构域:SEQ ID NO:129、SEQ ID NO:131、SEQ ID NO:133、SEQ ID NO:135、SEQ ID NO:137或SEQ ID NO:139。

[0103] 本文公开的示例性抗CD40抗体中的任何一种的功能变体也在本公开的范围。此类功能变体在结构和功能两者上基本上类似于示例性抗CD40抗体中的任何一种。功能变体包括与示例性抗CD40抗体中的任何一种基本上相同的V_H和V_L CDR。例如,其可以在抗体的总CDR区(共同地)中仅包括至多10个(例如,10个、9个、8个、7个、6个、5个、4个、3个、2个或1个)氨基酸残基变异,并且以基本上类似的亲和力与CD40的相同表位(例如,具有相同顺序的K_D值)结合。可替代地或另外,氨基酸残基变异是保守氨基酸残基取代。如本文所使用的,“保守氨基酸取代”是指不改变进行氨基酸取代的蛋白质的相对电荷或大小特性的氨基酸取代。可以根据用于改变本领域的普通技术人员已知的多肽序列的方法来制备变体,所述方法如编制这种方法的参考文献中发现的,所述参考文献例如,《分子克隆:实验室手册(Molecular Cloning:A Laboratory Manual)》,J.Sambrook等人编辑,第二版,冷泉港实验室出版社(Cold Spring Harbor Laboratory Press),冷泉港,纽约,1989或《分子生物学实验室指南(Current Protocols in Molecular Biology)》,F.M.Ausubel等人编辑,约翰威利父子出版公司(John Wiley&Sons,Inc.),纽约。氨基酸的保守取代包含在以下组中的氨基酸之间进行的取代:(a)M、I、L、V;(b)F、Y、W;(c)K、R、H;(d)A、G;(e)S、T;(f)Q、N;以及(g)E、D。

[0104] 在一些实施例中,本文所述的抗CD40抗体可以包括重链CDR,其组合(共同地)与以下序列中的重链CDR具有至少80%(例如,80%、85%、90%、95%、96%、97%、98%、99%和其中的任何增量百分比)序列同一性:SEQ ID NO:128、SEQ ID NO:130、SEQ ID NO:132、SEQ ID NO:134、SEQ ID NO:136或SEQ ID NO:138。可替代地或另外,抗CD40抗体可以包括轻链CDR,其共同地与以下序列中的轻链CDR具有至少80%(例如,85%、90%、95%、96%、97%、98%、99%和其中的任何增量百分比)序列同一性:SEQ ID NO:129、SEQ ID NO:131、SEQ ID NO:133、SEQ ID NO:135、SEQ ID NO:137或SEQ ID NO:139。

[0105] 在一些实施例中,本文所述的抗CD40抗体可以包括重链可变结构域和/或轻链可变结构域,所述重链可变结构域与SEQ ID NO:128、130、132、134、136或138至少80%(例如,85%、90%、95%、96%、97%、98%、99%和其中的任何增量百分比)相同,所述轻链可变结构域与SEQ ID NO:129、131、133、135、137或139至少80%(例如,85%、90%、95%、96%、97%、98%、99%和其中的任何增量百分比)相同。

[0106] 使用Karlin和Altschul,《美国国家科学院院刊》,87:2264-68,1990的算法来确定两个氨基酸序列的“同一性百分比”,所述算法如Karlin和Altschul,《美国国家科学院院刊》,90:5873-77,1993中那样进行修改。此类算法并入Altschul等人,《分子生物学杂志》215:403-10,1990的NBLAST和XBLAST程序(2.0版)中。可以用XBLAST程序(分值=50,字长=3)来执行BLAST蛋白质检索以获得与所关注蛋白质分子同源的氨基酸序列。当两个序列之间存在空位时,可以利用如Altschul等人,《核酸研究(Nucleic Acids Res.)》,25(17):3389-3402,1997中描述的带空位BLAST(Gapped BLAST)。当利用BLAST程序和带空位BLAST程序时,可以使用相应程序(例如,XBLAST和NBLAST)的默认参数。

[0107] (ii)经过工程化的Fc区

[0108] 本文所述的CD40结合分子包括经修饰的重链恒定区,其中Fc结构域被修饰以调节

其对如Fc γ R等Fc受体的结合亲和力和/或特异性。

[0109] 在一些实施例中,本文所述的CD40结合分子中的Fc变体相对于其野生型对应物对Fc γ RIIB具有增强的选择性。对Fc γ RIIB具有选择性、与Fc γ RIIB选择性结合或与Fc γ RIIB特异性结合的Fc片段是本领域中充分理解的术语。如果分子与特定靶抗原(例如,Fc γ RIIB受体)比其与替代性靶标(例如,Fc γ RIII受体)更频繁地、更快速地、持续时间更长地和/或亲和力更大地反应,则称分子表现出“选择性结合”或“特异性结合”。如果Fc片段比其与其它Fc受体亲和力更大地、亲合力更高地、更容易地和/或持续时间更长地结合,则Fc片段与Fc受体“特异性结合”。例如,与Fc γ RIIB特异性(或优先地)结合的Fc片段是这样的Fc片段:所述Fc片段与这种Fc受体比与其它Fc受体亲和力更大地、亲合力更高地、更容易地和/或持续时间更长地结合。利用这个定义还应理解,例如,与第一Fc受体选择性或特异性结合的Fc片段可以与或不与第二Fc受体特异性或优先地结合。如此,“选择性结合”、“特异性结合”或“优先结合”不一定需要(尽管其可以包含)排他结合。在一些实例中,与靶Fc受体(例如,Fc γ RIIB)“选择性结合”或“特异性结合”的Fc片段可能不与其它Fc受体结合(即,无法通过常规方法检测到的结合)。在其它实施例中,变体Fc片段不与任何Fc γ R结合。

[0110] 下表1中给出了IgG1、IgG2和IgG4与不同Fc受体的相对结合亲和力。

[0111] 表1.人和小鼠免疫球蛋白与Fc受体的相对结合亲和力

	人				小鼠			
	Fc γ R	IgG1	IgG2	IgG4	Fc γ R	IgG1	IgG2a	IgG2b
[0112]	I	++++	-	++++	I	-	++++	++++
	IIA (H131)	+++	++	++	III	++	++	++
	IIA (R131)	+++	+	++				
	IIB	++	+/-	++	IIB	+++	++	+++
	IIIA (V158)	+++	+	++	IV	-	+++	++
	IIIA (F158)	++	+/-	++				

[0113] 本文所述的Fc变体相对于其野生型对应物(引入突变以产生Fc变体的野生型亲本Fc区)可以对Fc γ RIIB具有增强的选择性。这种Fc变体对Fc γ RIIB相对于其对另一种Fc受体(例如,Fc γ RIII)的相对结合活性高于野生型对应物对Fc γ RIIB相对于其对其它Fc受体(例如,Fc γ RIII)的相对结合活性。Fc变体可以对Fc γ RIIB具有增强的结合活性和/或与另一种Fc受体(例如,Fc γ RIII)具有降低的结合活性。在一些实施例中,本文所述的Fc变体可以对Fc γ RIIB和另一种Fc受体(例如,Fc γ RIII)两者均具有降低的结合活性;然而,对其它Fc受体(例如,Fc γ RIII)的降低的结合活性的水平大于对Fc γ RIIB的降低的结合活性的水平。

[0114] 在一些实施例中,本文所述的Fc变体对于Fc γ RIIB具有合适的结合亲和力,例如相比于Fc变体源自的野生型亲本Fc增强的结合亲和力。如本文所使用的,“结合亲和力”是指表观缔合常数或 K_A 。 K_A 是解离常数(K_D)的倒数。本文所述的Fc变体对于Fc γ RIIB的结合亲和力(K_D)可以为至少 10^{-5} 、 10^{-6} 、 10^{-7} 、 10^{-8} 、 10^{-9} 、 10^{-10} M或更低。增大的结合亲和力对应于减小的 K_D 。Fc片段对第一Fc受体的亲和力结合相对于其对第二Fc受体更高可以通过用于结合第一Fc受体的 K_A (或数值 K_D)比用于结合第二Fc受体的 K_A (或数值 K_D)更高(或更小)来指示。在这种情况下,Fc变体相对于第二Fc受体对第一Fc受体具有特异性。在一些实施例中,与对Fc γ RIII(Fc γ RIIIA或Fc γ RIIB)的结合亲和力相比,本文所述的Fc变体对Fc γ RIIB具有更高的结合亲和力(更高的 K_A 或更小的 K_D)。结合亲和力的差异(例如,对于特异性或其它比较)

可以为至少1.5倍、2倍、3倍、4倍、5倍、10倍、15倍、20倍、37.5倍、50倍、70倍、80倍、91倍、100倍、500倍、1000倍、10,000倍或 10^5 倍。

[0115] 在一些实施例中,可以根据对应的小鼠IgG,例如小鼠IgG1中的氨基酸残基,通过使野生型人IgG1、IgG2或IgG4 Fc片段中的一个或多个氨基酸残基发生突变来设计本文所述的Fc变体。下文提供了人和小鼠IgG(分别为hIgG和mIgG)的序列比较(SEQ ID NO:60-64,从上到下,各自表示对应Fc区的片段211-245、260-278和320-332的组合):

	21-	22-	23-	24-	...26-	27-	...32-	33-
	12345678	9012345	6789 0123456789012345...0123456	7 89012	3 45678...01234567	8 9012		
	上部		核心下部		CH2			
[0116]	hIgG1	VDDKVEPK-SCDKTHT	CPPC PAPELLGGPSVFLFPP...	TCVVVDVSHEDPEVKFNWY...	KCKVSNKALPAPI			
	hIgG2	VDKTVVERK-CC-V-E-	CPPC PAPPVA-GPSVFLFPP...	TCVVVDVSHEDPEVQFNWY...	KCKVSNKGLPAPI			
	hIgG4	VDKRVESKYG----	PPCPSC PAPEFLGGPSVFLFPP...	TCVVVDVSQEDPEVQFNWY...	KCKVSNKGLPSSI			
	mIgG1	VDDKIVPR-DC--G	CKPCIC TVPEVS---SVFIFPP...	TCVVVDISKDDPEVQFSWF...	KCRVNSAAFPAPI			
	mIgG2a	VDDKIEPRGPTIKP	CPPCKC PAPNLLGGPSVFIFFPP...	TCVVVDVSEDDPDVQISWF...	KCKVNNKDLAPAI			

[0117] 下文提供了野生型鼠IgG1和IgG2 Fc片段以及具有降低的Fc γ R结合的示例性Fc变体的氨基酸序列:

[0118] 野生型小鼠IgG1 Fc片段的氨基酸序列:

[0119] VDDKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLITITLTPKVTCVVVDISKDDPEVQFSWFVDDVE
VHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMA
KDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLVNQQSNWEAGNTFTCSVLHEGLHNH
HTEKSLSHSPGK (SEQ ID NO:142)

[0120] 野生型小鼠IgG2a Fc片段的氨基酸序列:

[0121] VDDKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFFPKIKDVLIMISLPIVTCVVVDVSEDDPDVQISW
FVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQQDWMSGKEFKCKVNNKDLAPAIERTISKPKGSVRAPQVYVLP
PEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSYFMYSKLRVEKKNWVERNSYSCSVVH
EGLHNHHTTKSFSRTPGK (SEQ ID NO:143)

[0122] 突变小鼠IgG1mDANA Fc片段的氨基酸序列:

[0123] VDDKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLITITLTPKVTCVVVAISKDDPEVQFSWFVDDVE
VHTAQTQPREEQFASTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMA
KDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLVNQQSNWEAGNTFTCSVLHEGLHNH
HTEKSLSHSPGK (SEQ ID NO:144)

[0124] 突变小鼠IgG2a1mDANA Fc片段的氨基酸序列:

[0125] VDDKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFFPKIKDVLIMISLPIVTCVVVAVSEDDPDVQISW
FVNNVEVHTAQTQTHREDYASTLRVVSALPIQHQQDWMSGKEFKCKVNNKDLAPAIERTISKPKGSVRAPQVYVLP
PEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSYFMYSKLRVEKKNWVERNSYSCSVVH
EGLHNHHTTKSFSRTPGK (SEQ ID NO:145)

[0126] 在一些实施例中,本文所述的Fc变体是包括Fc片段的铰链结构域中的一个或多个突变(例如,氨基酸取代、缺失或添加)的人IgG1、G2或G4 Fc变体。人IgG在铰链结构域中含有核心基序CPPC或CPSC(根据EU索引,位置226-229)。位置216到225被视为铰链结构域的上部,并且位置230-238被视为铰链结构域的下部。除非明确指示,否则本文所使用的编号系统是根据EU索引。在一些实例中,所述一个或多个突变可以位于铰链结构域的上部。可替代地或另外,所述一个或多个突变可以位于铰链结构域的下部。在一些实施例中,本文公开的

任何抗CD40分子的Fc区可以包括位置220-331的任何位置处,优选地在位置228-329的任何位置处的至少一个突变。与其天然对应物相比,此类Fc变体可以对Fc受体(例如,Fc γ IIB、Fc γ RI、Fc γ RIIA或Fc γ RIIIA)中的一种或多种具有改变的结合亲和力和/或特异性。

[0127] 在一些实施例中,可以根据小鼠IgG1的铰链结构域中的对应氨基酸残基进行人IgG Fc的突变。例如,小鼠IgG1在位置236-238处不含有GGP基序。因此,这个GGP基序中的残基中的一个或多个残基可以从人IgG1、IgG2或IgG4 Fc片段中缺失以产生本文所述的Fc变体。

[0128] 可替代地或另外,人Fc变体可以在铰链结构域的上部、下部或两者中含有一个或多个氨基酸取代。例如,Fc变体可以包括位置233、234、235和/或236中的一个或多个位置处的一个或多个氨基酸取代。这种氨基酸取代可以与本文所提到的GGP基序(236-238)中的一个或多个GGP基序的缺失组合。可以将这些突变引入到人IgG2或IgG4 Fc片段中以产生本文所述的Fc变体。在一些实例中,本文所述的Fc变体在位置236-238中的一个或多个位置(例如,236、237、238或其任何组合)处含有缺失。

[0129] 本文所述的铰链结构域中的突变中的任何突变可以与参与与Fc受体相互作用的一个或多个位置处的突变(例如,氨基酸取代)组合。这种位置包含但不限于位置265、267、273、297和327-331或其组合。在那些位置处的示例性氨基酸取代包含D265A、S267E、V273E、N297A、L328F、P329G、A330S和/或P331S。

[0130] 在一些实施例中,本文公开的Fc变体可以源自IgG1分子(例如,人IgG1)并且在位置220、226、229、234-238、265、267、297和327-331中的一个或多个位置处的位置处含有一个或多个突变。例如,Fc变体可以包括位置234-238内的取代或缺失、位置265处的取代(例如,D265A)、位置267处的取代(例如,S267E)、位置297处的取代(例如,N297A)、位置328处的取代(例如,L328F)、位置329处的取代(例如,P329G)或其组合。可替代地或另外,Fc变体可以包括在位置220(例如,C220S)、226(例如,C226S)、229(例如,C229S)、327(例如,A327G)、330(例如,A330S)和331(例如,P331S)中的一个或多个位置处的取代。在一些情况下,源自IgG1分子的Fc变体可以包括位置236-238中的一个或多个位置处的缺失。

[0131] 在一些实施例中,本文公开的Fc变体可以源自IgG2分子(例如,人IgG2)并且在位置233-235、237-238、265-268、273、297、328、330和331中的一个或多个位置处含有一个或多个突变。在一些实例中,这种Fc变体可以包括位置237-238内的缺失(例如,位置237处的缺失或位置237和238两者的缺失)、位置265处的取代(例如,D265A)、位置267处的取代(例如,S267E)、位置297处的取代(例如,N297A)、位置328处的取代(例如,L328F)或其组合。可替代地或另外,源自IgG2分子的Fc变体可以包括在位置233-235、237、238、268、273、330和331(例如,P233E、V234A、V234L、A235L、A235S、G237A、P238S、H268A、H268Q、V273E、A330S和P331S)中的一个或多个位置处的取代。

[0132] 在又其它实施例中,本文公开的Fc变体可以源自IgG4分子(例如,人IgG4),并且在228、233-238、265、267、273、297和328处含有一个或多个突变。在一些实例中,这种Fc变体可以包括位置228处的取代(例如,S228P)、位置235-238中的任何位置处的取代或缺失(例如,位置236-238之一(例如,位置236和位置237)处的缺失)、位置265处的取代(例如,D265A)、位置267处的取代(例如,S267E)、位置273处的取代(例如,V273E)、位置297处的取代(例如,N297A)、位置328处的取代(例如,L328F)或其组合。可替代地或另外,Fc变体可以

包括位置233-235和237 (例如, E233P、F234V、F234A、L235S、L235E、L235A和G237A) 中的一个或多个位置处的取代。

[0133] 源自在位置265、267、273、297、328和/或329处含有一个或多个突变的IgG2或IgG4分子的Fc变体也在本公开的范围。此类突变可以包含这些位置,例如D265A、S267E、V273E、N297A、L328F和/或P329G中的一个或多个位置处的氨基酸取代。

[0134] 在一些情况下,本文公开的任何Fc变体可以进一步包括位置309处的突变,例如取代(例如,V309L)。这种Fc变体可以源自IgG2分子(例如,人IgG2)。在一些实施例中,位置309处的突变可以与位置234、268、330和331中的一个或多个位置处的突变组合。此类Fc变体的实例包含G2m43。

[0135] 在一些实施例中,本文所述的Fc变体可以包括与其野生型对应物的氨基酸序列至少85%相同(例如,90%、95%、98%、99%或更高)的氨基酸序列(例如,本文所述的野生型人IgG1、IgG2或IgG4的Fc片段)。

[0136] 在一个实例中,本文所述的Fc变体中的氨基酸残基取代是保守氨基酸残基取代。

[0137] 下文提供了示出示例性位置的序列比对,在所述示例性位置中,可以将突变引入到hIgG1、hIgG2和IgG4中以产生本公开的各种Fc变体。

[0138] 人IgG1变体相对于野生型人IgG1的序列比对 (SEQ ID NO:70-88、163-168和215, 从上到下):

	21-	22-	23-	24-	...26-	27-	...32-	33-
	12345678	9012345	6789 0123456789012345...	0123456	7 89012	3 45678...	01234567	8 9012
	<u>上部</u>		<u>核心下部</u>	<u>CH2</u>				
[0139]	hIgG1	VDKKVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m1	KVEPK-SCDKTHT CPPC PAPELL---SVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m2	KVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m-2	KKVEPK-CD- v-e CPPC PAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m-4	KKVEPKY G --- pp CPPC PAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m5	KVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVVDVSHEDPE e KFNWY...KCKVSNKALPAPI						
	hIgG1m7	KVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m8	KVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1m9	KVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1m15	KVEPK-SCDKTHT CPPC PAPELL---SVFLFPP...TCVVVDVSHEDPE e KFNWY...KCKVSNKALPAPI						
	hIgG1m17	KVEPK-SCDKTHT CPPC PAPELL---SVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m18	KVEPK-SCDKTHT CPPC PAPELL---SVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1m19	KVEPK-SCDKTHT CPPC PAPELL---SVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1m25	KVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVVDVSHEDPE e KFNWY...KCKVSNKALPAPI						
	hIgG1m27	KVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKALPAPI						
[0140]	hIgG1m28	KVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1m29	KVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVVDV e HEDPEVKFNWY...KCKVSNKAL f PAPI						
	hIgG1mA	KKVEPK-SCDKTHT CPPC PAPE aa GGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1mAG	KKVEPK-SCDKTHT CPPC PAPE aa GGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKAL g API						
	hIgG1m40	VDKKVEPK-SCDKTHT CPPC PAPELLGGPSVFLFPP...TCVVV a VSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m45	VDKKVEPK-SCDKTHT CPPC PAPE pva -GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m240	VDKKVEPK-SCDKTHT CPPC PAPELL-GPSVFLFPP...TCVVV a VSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m47	VDKKVEPK-SCDKTHT CPPC PAPE pva -GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNK g L ss i						
	hIgG1m48	VDKKVEPK- ss DKTHT sPPs PAPELLGG ss SVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m49	VDKKVEPK-SCDKTHT sPPs PAPE pva GGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI						
	hIgG1m50	VDKKVEPK-SCDKTHT CPPC PAPE egg GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKAL ps						

[0141] 人IgG2变体相对于野生型人IgG2的序列比对(SEQ ID NO:89-105和169-173,从上到下):

	21- 12345678	22- 9012345	23- 67890123456789012345	24- 67890123456789012345	...26- 01234567	27- 789012345678	...32- 012345678	33- 89012
	上部	核心下部	CH2					
hIgG2	VDK	TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m1		TVERK-CC-V-E-CP	PPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m-1	KT	VERK-SCDKTHTCP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m2		TVERK-CC-V-E-CP	PPCPAPPVflgGPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m-4	KT	VERKYG---PP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m5		TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m7		TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m8		TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m9		TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m10		TVERK-CC-V-E-CP	PPCPAPPVes---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m15		TVERK-CC-V-E-CP	PPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m17		TVERK-CC-V-E-CP	PPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m18		TVERK-CC-V-E-CP	PPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m19		TVERK-CC-V-E-CP	PPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m20		TVERK-CC-V-E-CP	PPCPAPPVA---PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m27		TVERK-CC-V-E-CP	PPCPAPPVA---PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m28		TVERK-CC-V-E-CP	PPCPAPPVA---PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m40	VDK	TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m43	VDK	TVERK-CC-V-E-CP	PPCPAPPaa-asSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2m44	VDK	TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2mAA	VDK	TVERK-CC-V-E-CP	PPCPAPPaa-aGPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
G2m2040	VDK	TVERK-CC-V-E-CP	PPCPAPPVA---PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					
hIgG2G4	VDK	TVERK-CC-V-E-CP	PPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI					

[0143] 人IgG4变体相对于野生型人IgG4的序列比对 (SEQ ID NO:65、106-127和174-177, 从上到下)

	21- 12345678	22- 9012345	23- 67890123456789012345	24- 67890123456789012345	...26- 01234567	27- 789012345678	...32- 012345678	33- 89012
	上部	核心下部	CH2					
hIgG4	VDK	RVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m1		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m-1		KRVESK---SCDKTHTCP	PPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m2		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m-2		KRVESK-CC-v-e-CP	PPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m3		KRVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m4		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m5		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m7		KRVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m8		KRVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m9		KRVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m10		KRVESKYG---PP	CPSCPAPEVs---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m15		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m17		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m18		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m19		KRVESKYG---PP	CPSCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m20		KRVESKYG---PP	CPSCPAPEFLG---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m25		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m27		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m28		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m29		KRVESKYG---PP	CPSCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m30		KRVESKYG---PP	CPSCPAPEFL---PSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4mPE		KRVESKYG---PP	CPSCPAPEFEGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m40	VDK	RVESKYG---PP	CPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m41	VDK	RVESKYG---PP	CPSCAPPvaggGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m42	VDK	RVESKYG---PP	CPSCAPPvaggGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4m46	VDK	RVESKYG---PP	CPSCPAPEaLgaPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					
hIgG4mAA	VDK	RVESKYG---PP	CPSCPAPEaaGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI					

[0146] 下文提供了野生型人IgG1、IgG2和IgG4 Fc片段的氨基酸序列以及许多示例性hIgG1、hIgG2和hIgG4 Fc变体 (基于EU编号, 位置221及以后位置):

[0147] 野生型人IgG1 Fc片段的氨基酸序列:

[0148] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY

VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:1)

[0149] 野生型人IgG2 Fc片段的氨基酸序列:

[0150] VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:2)

[0151] 野生型人IgG4 Fc片段的氨基酸序列:

[0152] VDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:3)

[0153] 人IgG4 S228P Fc变体的氨基酸序列:

[0154] VDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:4)

[0155] 示例性人IgG1 Fc变体的氨基酸序列:

[0156] G1m1:

[0157] VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:5)

[0158] G1m2:

[0159] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:6)

[0160] G1m-2:

[0161] VDKKVEPKCCVECPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:7)

[0162] G1m-4:

[0163] VDKKVEPKYGPCCPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:8)

[0164] G1m5:

[0165] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEEKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:9)

[0166] G1m7:

[0167] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVEHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:10)

[0168] G1m8:

[0169] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:11)

[0170] G1m9:

[0171] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVEHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:12)

[0172] G1m15:

[0173] VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEEKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:13)

[0174] G1m17:

[0175] VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVDVEHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:14)

[0176] G1m18:

[0177] VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:15)

[0178] G1m19:

[0179] VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVDVEHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH

NHYTQKSLSLSPGK (SEQ ID NO:16)

[0180] G1m25:

[0181] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:17)

[0182] G1m27:

[0183] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:18)

[0184] G1m28:

[0185] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFAPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:19)

[0186] G1m29:

[0187] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFAPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:20)

[0188] G1mAA:

[0189] VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:21)

[0190] G1mAG:

[0191] VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:22)

[0192] G1m40:

[0193] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:160)

[0194] G1m45

[0195] VDKKVEPKSCDKTHTCPPCPAP_{pva}GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR

EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:178)

[0196] G1m240

[0197] VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVAVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:179)

[0198] G1 N297A

[0199] VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV
VDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:180)

[0200] G1m47

[0201] VDKKVEPKSCDKTHTCPPCPAP_{pva}GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK_{gLPs s} IEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK (SEQ ID NO:181)

[0202] G1m48

[0203] VDKKVEPKS_sDKTHT_sPP_sPAP_{pva}ELLGG_sSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:182)

[0204] G1m49

[0205] VDKKVEPKSCDKTHT_sPP_sPAP_{pva}GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:183)

[0206] G1m50

[0207] VDKKVEPKSCDKTHTCPPCPAPE_feGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP_as IEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO:184)

[0208] 示例性人IgG2 Fc变体的氨基酸序列:

[0209] G2m1:

[0210] VDKTVERKCCVECPAPPVAVSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:23) G2m-1:

[0211] VDKTVERKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYV

DGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO:24)

[0212] G2m2:

[0213] VDKTVERKCCVECPCPPAPPFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO:25)

[0214] G2m-4:

[0215] VDKTVERKYGPCPPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:26)

[0216] G2m5:

[0217] VDKTVERKCCVECPCPPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:27)

[0218] G2m7:

[0219] VDKTVERKCCVECPCPPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:28)

[0220] G2m8:

[0221] VDKTVERKCCVECPCPPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:29)

[0222] G2m9:

[0223] VDKTVERKCCVECPCPPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:30)

[0224] G2m10:

[0225] VDKTVERKCCVECPCPAPEVSSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
HYTQKSLSLSPGK (SEQ ID NO:31)

[0226] G2m15:

[0227] VDKTVERKCCVECPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:32)

[0228] G2m17:

[0229] VDKTVERKCCVECPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:33)

[0230] G2m18:

[0231] VDKTVERKCCVECPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:34)

[0232] G2m19:

[0233] VDKTVERKCCVECPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:35)

[0234] G2m20:

[0235] VDKTVERKCCVECPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:36)

[0236] G2m27:

[0237] VDKTVERKCCVECPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:37)

[0238] G2m28:

[0239] VDKTVERKCCVECPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:38)

[0240] G2m40:

[0241] VDKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFASTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:161)

[0242] G2m43

[0243] VDKTVERKCCVECPPCAPPaaasSVFLFPPKPKDTLMISRTPEVTCVVVDVSaEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTV1HQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:185)

[0244] G2m44

[0245] VDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSqEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTV1HQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:186)

[0246] G2mAA

[0247] VDKTVERKCCVECPPCAPPaaaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO:213)

[0248] G2m2040

[0249] VDKTVERKCCVECPPCAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFASTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:187)

[0250] G2G4

[0251] VDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLGK (SEQ ID NO:188)

[0252] 示例性人IgG4 Fc变体的氨基酸序列:

[0253] G4m1:

[0254] VDKRVESKYGPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTKSLSLSLGK (SEQ ID NO:39)

[0255] G4m-1:

[0256] VDKRVESKCDKTHTPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVM
HEALHNHYTKSLSLSLGK (SEQ ID NO:40)

[0257] G4m2:

[0258] VDKRVESKYGPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM

TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN
HYTQKSLSLSLGK (SEQ ID NO:41)

[0259] G4m-2:

[0260] VDKRVESKCCVEPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV
DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
LHNHYTQKSLSLSLGK (SEQ ID NO:42)

[0261] G4m3:

[0262] VDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:43)

[0263] G4m4:

[0264] VDKRVESKYGPPCPPCAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY
TQKSLSLSLGK (SEQ ID NO:44)

[0265] G4m5:

[0266] VDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:45)

[0267] G4m7:

[0268] VDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:46)

[0269] G4m8:

[0270] VDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:47)

[0271] G4m9:

[0272] VDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:48)

[0273] G4m10:

[0274] VDKRVESKYGPPCPPCAPEVSSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV

HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSEIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY
TQKSLSLSLGK (SEQ ID NO:49)

[0275] G4m17:

[0276] VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY
TQKSLSLSLGK (SEQ ID NO:50)

[0277] G4m18:

[0278] VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSEIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY
TQKSLSLSLGK (SEQ ID NO:51)

[0279] G4m19:

[0280] VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSEIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY
TQKSLSLSLGK (SEQ ID NO:52)

[0281] G4m20:

[0282] VDKRVESKYGPPCPPCPAPEFLGVSFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNH
YTQKSLSLSLGK (SEQ ID NO:53)

[0283] G4m25:

[0284] VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN
HYTQKSLSLSLGK (SEQ ID NO:54)

[0285] G4m27:

[0286] VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN
HYTQKSLSLSLGK (SEQ ID NO:55)

[0287] G4m28:

[0288] VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSEIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN
HYTQKSLSLSLGK (SEQ ID NO:56)

[0289] G4m29:

[0290] VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN
HYTQKSLSLSLGK (SEQ ID NO:57)

[0291] G4m30:

[0292] VDKRVESKYGPPCPPCPAPEFLPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNH
YTQKSLSLSLGK (SEQ ID NO:58)

[0293] G4mPE:

[0294] VDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:59)

[0295] G4m40:

[0296] VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFASTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:162)

[0297] G4m41

[0298] VDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:189)

[0299] G4m42

[0300] VDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:190)

[0301] G4m46

[0302] VDKRVESKYGPPCPPCPAPEaLGaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKaYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:191)

[0303] G4mAA

[0304] VDKRVESKYGPPCPPCPAPEaaGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALH
NHYTQKSLSLSLGK (SEQ ID NO:192)

[0305] 本文所述的Fc变体与野生型对应物相比可以对Fc γ RIIB表现出增强的结合活性。实例包含G2m2、G2m5、G2m7、G2m8、G2m9、G2m19、G2m44、G1m7、G1m9、G1m27、G1m45、G1m47、G1m49、G1m50、G4m7、G4m46和G4mPE。可替代地或另外，Fc变体与其野生型对应物相比可以对Fc γ RIIB具有增强的选择性，例如G2m1、G2m20、G2m43、G2m44、G2G4、G2mAA、G1m2、G1m15、G1m17、G1m18、G1m19、G1m27、G1m28、G1m29、G4m1、G4m2、G4m7、G4m8、G4m9、G4m20、G4m25、G4m27、G4m28、G4m30、G4m46和G4mPE。此类Fc变体可以保留与FcRn的结合活性。这些Fc变体可以用于构建能够使免疫受体和Fc γ RIIB受体交联的本文所述的治疗剂。

[0306] 可替代地，如本文所述的某些Fc变体可以对Fc γ RIIB具有选择性和/或对任何Fc γ R具有明显的低结合活性或不具有结合活性。实例包含G1m2、G1m25、G1m40、G1mAAG、G1m240、G2m1、G2m20、G2m40、G2m2040、G4m5、G4m18、G4m19、G4m20、G4m30、G4m40、G4m41和G4m42。此类Fc变体可以保留与FcRn的结合活性。由于亲合力效应，含有此类Fc变体的治疗剂(例如，抗体)可能能够使免疫受体和Fc γ RIIB受体交联。

[0307] 下表2-4中提供了示例性Fc变体与其野生型对应物相比的结合亲和力/特异性变化。“N/A”指示无可用数据。当发现Fc变体的结合活性与野生型对应物相比为“无变化”时，这意味着如在相同实验条件下通过同一测定指示的，Fc变体与野生型对应物之间的结合活性不存在显著变异。当Fc变体的结合活性相对于其野生型对应物“增大”或“减小”时，这意味着如在相同实验条件下通过同一测定确定的，Fc变体的结合活性高于或低于野生型对应物的结合活性，并且如本领域的技术人员已知的，变异是显著的(例如，生物学上显著的)。当Fc变体的结合活性相对于其野生型对应物“略微增大”或“略微减小”时，这意味着如在相同实验条件下通过同一测定确定的，Fc变体的结合活性高于或低于野生型对应物的结合活性，并且变异在统计学上是显著的但处于有限水平(例如，高达10%)。

[0308] 表2. 人IgG1突变体相对于野生型人IgG1的Fc γ R结合活性

[0309]

	相对于野生型对应物的结合活性变化					
IgG1 突变体	FcγRI	FcγRIIA (H131)	FcγRIIA (R131)	FcγRIIB	FcγRIIC	FcγRIII
G1m1	减小	减小	减小	减小	减小	减小
G1m2	减小	减小	减小	减小	减小	减小
G1m-2	无变化	N/A	N/A	无变化	N/A	无变化
G1m-4	无变化	N/A	N/A	无变化	N/A	无变化
G1m5	增大	增大	增大	无变化	增大	略微减小
G1m7	增大	增大	增大	增大	增大	略微减小
G1m8	增大	略微减小	无变化	增大	略微增大	略微减小
G1m9	增大	减小	增大	增大	增大	无变化
G1m15	减小	减小	减小	减小	减小	减小
G1m17	减小	减小	减小	减小	减小	减小
G1m18	减小	减小	无变化	减小	减小	减小
G1m19	减小	增大	增大	增大	增大	减小
G1m25	减小	减小	减小	减小	减小	减小
G1m27	减小	减小	减小	增大	减小	减小
G1m28	减小	减小	减小	减小	减小	减小
G1m29	减小	减小	增大	增大	增大	减小
G1mAA	减小	N/A	减小	减小	N/A	减小
G1mAAG	减小	N/A	减小	减小	N/A	减小
G1m240	减小	N/A	减小	减小	N/A	减小
G1m45	减小	N/A	减小	减小	N/A	减小
G1 N297A	减小	N/A	减小	减小	N/A	减小
G1m47	减小	N/A	减小	减小	N/A	减小
G1m48	减小	N/A	减小	减小	N/A	减小
G1m49	减小	N/A	减小	减小	N/A	减小
G1m50	减小	N/A	减小	减小	N/A	减小

[0310] 表3. 人IgG2突变体相对于野生型人IgG2的Fc γ R结合活性

[0311]

	相对于野生型对应物的结合活性变化					
IgG2 突变体	FcγRI	FcγRIIA (H131)	FcγRIIA (R131)	FcγRIIB	FcγRIIC	FcγRIII
G2m1	无变化	减小	减小	减小	无变化	无变化
G2m2	增大	减小	无变化	增大	无变化	无变化

[0312]

G2m10	无变化	减小	无变化	略微减小	无变化	无变化
G2m5	略微增大	减小	无变化	减小	无变化	无变化
G2m7	无变化	略微增大	增大	增大	略微增大	无变化
G2m8	无变化	减小	无变化	无变化	无变化	无变化
G2m9	无变化	无变化	增大	增大	增大	无变化
G2m-1	增大	N/A	N/A	减小	N/A	无变化
G2m-4	增大	N/A	N/A	减小	N/A	无变化
G2m15	无变化	N/A	N/A	减小	N/A	无变化
G2m17	无变化	N/A	增大	无变化	增大	无变化
G2m18	略微增大	N/A	无变化	减小	无变化	无变化
G2m19	无变化	N/A	增大	增大	无变化	无变化
G2m20	无变化	N/A	无变化	减小	无变化	无变化
G2m27	略微增大	N/A	N/A	增大	N/A	无变化
G2m28	无变化	N/A	N/A	增大	N/A	无变化
G2m2040	减小	N/A	减小	减小	N/A	减小
G2m43	无变化	N/A	减小	减小	N/A	减小
G2m44	无变化	N/A	减小	无变化	N/A	减小
G2mAA	无变化	N/A	减小	无变化	N/A	减小
G2G4	减小	N/A	减小	无变化	N/A	减小

[0313] 表4. 人IgG4突变体相对于野生型人IgG4的Fc γ R结合活性

[0314]

IgG4 突变体	相对于野生型对应物的结合活性变化					
	Fc γ RI	Fc γ RIIA (H131)	Fc γ RIIA (R131)	Fc γ RIIB	Fc γ RIIC	Fc γ RIII
G4m1	减小	增大	无变化	略微减小	略微增大	无变化
G4m2	减小	无变化	减小	略微减小	无变化	无变化
G4m10	减小	无变化	减小	减小	无变化	无变化
G4m20	减小	无变化	减小	减小	无变化	无变化
G4m3	减小	无变化	无变化	减小	无变化	无变化
G4m7	无变化	增大	增大	增大	增大	略微增大
G4m8	无变化	无变化	增大	略微增大	无变化	无变化
G4m9	无变化	无变化	增大	增大	增大	无变化
G4m17	减小	无变化	增大	增大	增大	增大
G4m18	减小	无变化	无变化	减小	无变化	增大
G4m19	减小	无变化	无变化	减小	无变化	略微增大
G4m25	减小	无变化	增大	略微减小	无变化	增大
G4m27	减小	无变化	无变化	减小	无变化	略微增大
G4m28	减小	无变化	略微增大	增大	增大	无变化
G4m29	减小	无变化	增大	增大	增大	略微增大
G4m4	减小	无变化	无变化	减小	无变化	无变化
G4m-1	无变化	N/A	N/A	无变化	N/A	无变化
G4m-2	无变化	N/A	N/A	减小	N/A	无变化

[0315]

G4mPE	减小	N/A	N/A	略微减小	无变化	无变化
G4m30	减小	N/A	无变化	减小	无变化	无变化
G4m40	减小	N/A	减小	减小	N/A	减小
G4m41	减小	N/A	减小	减小	N/A	减小
G4m42	减小	N/A	减小	减小	N/A	减小
G4mAA	减小	N/A	减小	减小	N/A	减小
G4m46	减小	N/A	减小	减小	N/A	减小

[0316] 本文所述的Fc变体可以按照本文所提供的指导进行设计并且通过常规重组技术

产生。Fc变体对各种Fc受体的结合亲和力和特异性可以通过常规方法来确定。还参见下面的实例。

[0317] 在具体实例中,本文公开的CD40结合分子(抗CD40分子)可以维持IgG1亲本的铰链区、含有一个或多个突变(例如,根据如以上所讨论的小鼠IgG1,在位置236-238处的一个或多个缺失),所述一个或多个突变导致与Fc受体(如Fc γ R2B)的结合亲和力降低但维持与Fc受体的残余结合活性。具有此类性质的示例性Fc变体包括但不限于G1m2、G4m20、G4m30和G4m46。此类抗CD分子中的CD40结合部分可以源自激动抗CD40抗体。此类CD40结合部分可以源自本文公开的抗CD40抗体383。在一些情况下,CD40结合部分与抗体383包括相同的V_H和V_L CDR。在一些实例中,CD40结合部分可以与抗体383包括相同的VH和/或VL链(分别为SEQ ID NO:128和129)。可替代地,CD40结合部分可以是本文公开的抗体383的功能变体。此类CD40结合分子将具有如以下实例中所证明的许多有利特征。实例包含在体内增强的抗肿瘤功效以及改善的治疗窗和减少的副作用(例如,较少的肝脏毒性),这可以归因于基线CD40激动活性和残余的Fc γ RIIB结合活性。预期过高的CD40激动剂活性和/或Fc γ RIIB结合活性会诱导副作用,如细胞毒性。

[0318] 在其它具体实例中,本文公开的CD40结合分子可以包括源自IgG2的Fc变体结构域(例如,维持IgG2铰链)并且根据小鼠对应物含有位置236-238中的一个或多个位置处的一个或多个突变(例如,缺失或取代),以降低与Fc受体的结合亲和力,特别是与Fc γ RIIB的结合亲和力。在一些情况下,此类Fc变体具有位置236-238中的一个或多个位置处的缺失。可替代地或另外,Fc变体可以具有位置234、237、238、268或其组合处的取代。此类Fc变体可以含有参与与Fc受体结合的一个或多个位置处的另外的突变,所述位置例如位置265(例如,D265A)。Fc变体可以维持与Fc受体,如Fc γ RIIB的残余结合活性(例如,G2m20和G2m43)。可替代地,Fc变体可以不与Fc受体,如Fc γ RIIB结合(例如,G2m40)。此类抗CD分子中的CD40结合部分可以源自激动抗CD40抗体。此类CD40结合部分可以源自本文公开的抗CD40抗体383。在一些情况下,CD40结合部分与抗体383包括相同的V_H和V_L CDR。在一些实例中,CD40结合部分可以与抗体383包括相同的VH和/或VL链(分别为SEQ ID NO:128和129)。可替代地,CD40结合部分可以是本文公开的抗体383的功能变体。此类CD40结合分子将具有如以下实例中所证明的许多有利特征。实例包含在体内增强的抗肿瘤功效以及改善的治疗窗和减少的副作用(例如,较少的肝脏毒性),这可以归因于基线CD40激动活性和残余Fc γ RIIB结合活性的组合(例如,383-IghuG2m20)或相对高的CD40激动活性和与Fc γ RIIB无结合的组合(例如,383-IghuG2m40)。

[0319] 除了本文所述的FACS结合测定之外,Fc变体对Fc γ 受体的活性可以在替代性测定中进行检查。例如,可以使用在与Fc γ RIIB表达性细胞共培养或不与其共培养的情况下进行的CD40报告基因测定来证明受体交联和激活的效果。由于抗体与两个靶标(例如,CD40和Fc γ RIIB)同时结合产生的亲合力效应,所以此测定对检测Fc γ RIIB结合更敏感。可通过FACS检测到的最小或无明显结合可以在报告基因测定中显示阳性结果。

[0320] II. 包括Fc变体的CD40结合分子的制备

[0321] 本文所述的CD40结合分子可以通过常规方法,例如重组技术来制备。以下是一些实例。

[0322] 对于包括CD40L的胞外结构域的CD40结合分子,CD40L胞外结构域的编码序列可以

与合适的Fc变体的编码序列框内融合。可以将完整CD40结合分子的编码序列克隆到合适的表达载体中,可以将所述表达载体引入到合适的宿主细胞进行蛋白质表达。

[0323] 可以通过本领域已知的任何方法制备与CD40结合的抗体。参见例如,Harlow和Lane, (1998),《抗体:实验室手册 (Antibodies: A Laboratory Manual)》,冷泉港实验室,纽约。在一些实施例中,可以通过常规杂交瘤技术制备对CD40或其胞外结构域具有特异性的抗体。可以使用任选地与如KLH等载体蛋白偶联的全长靶受体或片段来使宿主动物免疫,以生成与所述抗原结合的抗体。如本文进一步描述的,宿主动物的免疫途径和方案通常与用于抗体刺激和产生的已建立的和常规的技术保持一致。用于产生小鼠抗体、人源化抗体和人抗体的通用技术是本领域已知的并且在本文中进行描述。设想的是,可以操纵包含人类在内的任何哺乳动物受试者或来自其的产生抗体的细胞以充当用于产生哺乳动物(包含人)杂交瘤细胞系的基础。通常,对宿主动物腹膜内、肌肉内、口服、皮下、足底内和/或皮内接种一定量的免疫原,包含如本文所述的免疫原。

[0324] 可以使用Kohler, B. 和Milstein, C. (1975)《自然》256:495-497或如Buck, D.W. 等人,《体外 (In Vitro)》,18:377-381 (1982) 所修改的一般体细胞杂交技术由淋巴细胞和永生化骨髓瘤细胞来制备杂交瘤。可以在杂交中使用可用的骨髓瘤系,所述骨髓瘤系包括但不限于X63-Ag8.653和来自美国加利福尼亚州圣地亚哥索尔克研究所细胞分布中心 (Salk Institute, Cell Distribution Center, San Diego, Calif., USA) 的那些骨髓瘤系。通常,所述技术涉及使用如聚乙二醇等融合剂或通过本领域的技术人员熟知的电气装置来融合骨髓瘤细胞和淋巴样细胞。融合之后,将细胞从融合培养基中分离并且在如次黄嘌呤-氨基蝶呤-胸苷 (HAT) 培养基等选择性生长培养基中生长,以消除未杂交的亲本细胞。可以使用补充有或不含血清的本文所述的任何培养基培养分泌单克隆抗体的杂交瘤。作为细胞融合技术的另一个替代性方案,可以使用EBV永生化B细胞来产生本文所述的抗免疫细胞受体单克隆抗体。使杂交瘤膨胀并在需要时进行亚克隆,并且通过常规免疫测定程序(例如,放射免疫测定、酶免疫测定或荧光免疫测定)来测定上清液的抗免疫原活性。

[0325] 可以用作抗体的来源的杂交瘤涵盖所有衍生物、产生能够调节靶免疫细胞受体的活性的单克隆抗体的亲本杂交瘤的子代细胞。可以使用已知程序在体外或体内生长产生这种抗体的杂交瘤。在需要时,可以通过如硫酸铵沉淀、凝胶电泳、透析、色谱法和超滤等常规免疫球蛋白纯化程序来从培养基或体液中分离单克隆抗体。可以例如通过在由附着于固相的免疫原制成的吸附剂上运行制剂并且从免疫原中洗脱或释放期望抗体来去除不期望的活性(如果存在的话)。用靶抗原或含有靶氨基酸序列的片段使宿主动物免疫可以产生抗体(例如,单克隆抗体)群,所述靶氨基酸序列使用双功能制剂或衍生化制剂(例如,马来酰亚胺基苯甲酰基磺基琥珀酰亚胺酯(通过半胱氨酸残基进行缀合)、N-羟基琥珀酰亚胺(通过赖氨酸残基进行缀合)、戊二醛、琥珀酸酐、SOCl₂或R₁N=C=NR,其中R和R₁是不同的烷基)来与在待免疫物种中产生免疫原性的蛋白质(例如,钥孔虫凝集素、血清白蛋白、牛甲状腺球蛋白或大豆胰蛋白酶抑制剂)缀合。

[0326] 如果需要,可以对所关注(例如,通过杂交瘤产生)抗体(单克隆抗体或多克隆抗体)进行测序,并且然后将多核苷酸序列克隆到载体中,以供本文所述的抗CD40抗体的进一步构建。可以在载体中将对所关注抗体进行编码的序列维持在宿主细胞中并且然后可以使宿主细胞膨胀并冷冻以供将来使用。

[0327] 在替代性方案中,多核苷酸序列可以用于基因操纵以使抗体“人源化”或改善亲和力(亲和力成熟)或抗体的其它特性。例如,如果将抗体用于人类的临床试验和治疗,则可以将恒定区工程化成更类似于人恒定区以避免免疫应答。可以期望对抗体序列进行基因操纵,以获得与靶抗原更大的亲和力和在抑制或激活免疫细胞受体的活性方面更大的功效。对本领域的技术人员而言将显而易见的是,可以对抗体进行一种或多种多核苷酸改变,并且所述一种或多种多核苷酸改变仍维持其与靶受体的结合特异性。

[0328] 在其它实施例中,可以通过使用已经被工程化以表达特异性人免疫球蛋白的可商购获得的小鼠来获得完全人抗体。被设计成产生更期望的(例如,完全人抗体)或更稳健的免疫应答的转基因动物也可以用于生成人源化抗体或人抗体。这种技术的实例为来自安进公司(Amgen, Inc.) (弗里蒙特,加利福尼亚州)的Xenomouse^{RTM}以及来自Medarex公司(普林斯顿,新泽西州)的HuMAb-Mouse^{RTM}和TC MouseTM。在另一个替代性方案中,可以通过噬菌体展示或酵母技术重组地制备抗体。参见例如美国专利第5,565,332号;第5,580,717号;第5,733,743号;和第6,265,150号;以及Winter等人,(1994)《免疫学年鉴(Annu.Rev.Immunol.)》12:433-455。

[0329] 可替代地,可以将如噬菌体展示技术(McCafferty等人,(1990)《自然》348:552-553)、酵母展示技术或哺乳动物细胞展示技术等抗体文库技术用于如对靶免疫受体具有特异性的人抗体等分离的抗体。

[0330] 用于构建人源化抗体的方法也是本领域熟知的。参见例如Queen等人,《美国国家科学院院刊》,86:10029-10033 (1989)。在一个实例中,按照本领域已知的方法对亲本非人抗体的V_H和V_L可变区进行三维分子建模分析。接下来,使用相同的分子建模分析来鉴定被预测对形成正确CDR结构具有重要性的框架氨基酸残基。平行地,使用亲本VH和VL序列作为搜索查询来从任何抗体基因数据库中鉴定具有与亲本非人抗体的氨基酸序列同源的氨基酸序列的人VH链和人VL链。然后选择人VH受体基因和人VL受体基因。

[0331] 可以用来自亲本非人抗体或其功能变体的CDR区替代所选人受体基因内的CDR区。在必要时,可以使用在亲本链的框架区内被预测在与CDR区相互作用时具有重要性的残基(参见以上描述)来取代人受体基因中的对应残基。

[0332] 一旦获得能够与靶免疫细胞受体结合的抗体,其重链的编码序列可以与合适的Fc变体的编码序列框内融合,其可以通过常规重组技术与FcγRIIB选择性结合或不与任何FcγR结合,例如本文所述的任何Fc变体。在一些情况下,首先研究抗体用于激活其所结合的免疫细胞受体的激动作用。可以选择这种激动抗体用于制备本文所述的CD40结合分子以增强激动作用。

[0333] 在其它情况下,首先研究抗体用于抑制其所结合的免疫细胞受体的拮抗作用。可以选择这种拮抗抗体用于制备本文所述的CD40结合分子以下调免疫应答。可替代地,可以选择对任何Fc受体具有低结合活性或不具有结合活性的Fc变体用于制备CD40拮抗剂。

[0334] 本文所述的所得抗体分子或CD40结合分子可以通过如下所例示的常规重组技术产生。可以将对本文所述的CD40结合分子的抗体或多肽的重链和轻链进行编码的核酸克隆到一个表达载体中,每个核苷酸序列与合适的启动子可操作地连接。在一个实例中,对重链和轻链进行编码的核苷酸序列中的每个核苷酸序列与不同的启动子可操作地连接。可替代地,对重链和轻链进行编码的核苷酸序列可以与单个启动子可操作地连接,使得重链和轻

链两者均从同一启动子表达。在必要时,可以在对重链和轻链进行编码的序列之间插入内部核糖体进入位点(IRES)。

[0335] 在一些实例中,将对抗体的两条链进行编码的核苷酸序列克隆到两个载体中,所述载体可以被引入到相同或不同的细胞中。当在不同的细胞中表达这两条链时,其中的每条链均可以从表达这种链的宿主细胞中分离,并且分离的重链和轻链可以混合并在允许形成抗体的合适条件下温育。

[0336] 通常,可以使用本领域已知的方法将对抗体的一条或所有链进行编码的核酸序列克隆到合适的表达载体中、与合适的启动子可操作地连接。例如,可以在合适条件下使核苷酸序列和载体与限制酶相接触,以在每个分子上产生可以彼此配对并且用连接酶连接在一起的互补端。可替代地,可以将合成核酸连接子与基因的末端连接。这些合成连接子含有对应于载体中的特定限制性位点的核酸序列。表达载体/启动子的选择将取决于用于产生抗体的宿主细胞的类型。

[0337] 可以使用各种启动子来表达本文所述的抗体,所述启动子包含但不限于巨细胞病毒(CMV)中间早期启动子、如劳斯肉瘤(Rous sarcoma)病毒LTR、HIV-LTR、HTLV-1LTR等病毒LTR、猿猴病毒40(SV40)早期启动子、大肠杆菌(E.coli) lac UV5启动子和单纯性疱疹tk病毒启动子。

[0338] 还可以使用可调节的启动子。这些可调节的启动子包含使用来自大肠杆菌的lac阻遏物作为转录调节剂对携带有lac操纵基因的哺乳动物细胞启动子的转录进行调节的那些启动子[Brown,M.等人,《细胞(Cell)》,49:603-612(1987)]、使用四环素阻遏物(tetR)的那些启动子[Gossen,M.和Bujard,H.,《美国国家科学院院刊》89:5547-5551(1992);Yao,F.等人,《人类基因疗法(Human Gene Therapy)》,9:1939-1950(1998);Shockett,P.等人,《美国国家科学院院刊》,92:6522-6526(1995)]。其它系统包含FK506二聚体、使用雌二醇(astradiol)的VP16或p65、RU486、二元酚米乐甾酮(diphenol murislerone)或雷帕霉素(rapamycin)。诱导型系统可从英杰公司(Invitrogen)、克隆技术公司(Clontech)和阿瑞雅德公司(Ariad)获得。

[0339] 可以使用包含具有操纵子的阻遏物的可调节启动子。在一个实施例中,来自大肠杆菌的lac阻遏物可以用作转录调节剂对携带有lac操纵基因的哺乳动物细胞启动子的转录进行调节[M.Brown等人,《细胞》,49:603-612(1987)];Gossen和Bujard(1992);[M.Gossen等人,《美国国家科学院院刊》,89:5547-5551(1992)],所述携带有lac操纵基因的哺乳动物细胞启动子将四环素阻遏物(tetR)与转录激活子(VP 16)组合,以产生tetR-哺乳动物细胞转录激活子融合蛋白tTa(tetR-VP 16),携带有tetO的哺乳动物启动子源自人巨细胞病毒(hCMV)主要立即早期启动子以用于产生tetR-tet操纵基因系统来控制哺乳动物细胞中的基因表达。在一个实施例中,使用四环素诱导型开关。当四环素操纵基因适当地定位在CMV启动子的TATA元件下游时,四环素阻遏物(tetR)而非tetR-哺乳动物细胞转录因子融合衍生物可以单独用作强效反式调节剂来调节哺乳动物细胞中的基因表达(Yao等人,《人类基因疗法》)。这个四环素诱导型开关的一个特别的优点是其不需要使用四环素阻遏物-哺乳动物细胞反式激活子或阻遏物融合蛋白来实现其可调节作用,在一些情况下,所述四环素阻遏物-哺乳动物细胞反式激活子或阻遏物融合蛋白可能对细胞有毒(Gossen等人,《美国国家科学院院刊》,89:5547-5551(1992);Shockett等人,《美国国家科学院院刊》,

92:6522-6526(1995))。

[0340] 另外,载体可以含有例如以下中的一些或全部:可选标志基因,如用于在哺乳动物细胞中选择稳定或瞬时转染子的新霉素基因;用于高水平转录的来自人CMV的立即早期基因的增强子/启动子序列;用于mRNA稳定性的来自SV40的转录终止和RNA加工信号;用于适当的游离型复制的SV40多瘤复制起点和ColE1;内部核糖体结合位点(IRES)、通用多克隆位点;以及用于正义和反义RNA的体外转录的T7和SP6 RNA启动子。用于产生含有转基因的载体的合适的载体和方法是本领域熟知并且可获得的。

[0341] 可用于实践本文所述的方法的聚腺苷酸化信号的实例包括但不限于人胶原I聚腺苷酸化信号、人胶原II聚腺苷酸化信号和SV40聚腺苷酸化信号。

[0342] 可以将包括对抗体中的任何抗体进行编码的核酸的一个或多个载体(例如,表达载体)引入到合适的宿主细胞中以用于产生抗体。可以在合适的条件下培养宿主细胞以用于表达抗体或其任何多肽链。可以通过常规方法,例如亲和力纯化通过培养的细胞(例如,来自细胞或培养上清液)来回收这种抗体或其多肽链。如果有必要,可以在合适的条件下在允许产生抗体的合适时间段内温育抗体的多肽链。

[0343] 在一些实施例中,用于制备本文所述的抗体的方法涉及对如本文所述的抗体的重链和轻链进行编码的重组表达载体。可以通过常规方法,例如磷酸钙介导的转染将重组表达载体引入到合适的宿主细胞(例如,dhfr-CHO细胞)中。可以选择并在允许表达形成抗体的这两条多肽链的合适条件下培养阳性转化体宿主细胞,这两条多肽链可以从细胞或从培养基中回收。在必要时,可以在允许形成抗体的合适条件下培育从宿主细胞中回收的这两条链。

[0344] 在一个实例中,提供了两种重组表达载体,一种重组表达载体对抗免疫细胞受体抗体的重链进行编码并且另一种重组表达载体对同一抗体的轻链进行编码。可以通过常规方法,例如磷酸钙介导的转染将这两种重组表达载体都引入到合适的宿主细胞(例如,dhfr-CHO细胞)中。可替代地,可以将表达载体中的每种表达载体均引入到合适的宿主细胞中。可以选择并在允许表达抗体的多肽链的合适条件下培养阳性转化体。在将这两种表达载体引入到相同的宿主细胞中时,可以从宿主细胞或从培养基中回收其中产生的抗体。如果有必要,可以从宿主细胞或从培养基中回收多肽链,并且然后在允许形成抗体的合适条件下温育多肽链。当将这两种表达载体引入到不同的宿主细胞中时,所述两种表达载体中的每种表达载体可以从对应的宿主细胞或从对应的培养基中回收。然后可以在合适的条件下温育这两条多肽链以用于形成抗体。

[0345] 使用标准分子生物学技术来制备重组表达载体、转染宿主细胞、选择转化体、培养宿主细胞以及从培养基中回收抗体。例如,可以用蛋白质A或蛋白质G偶联基质通过亲和色谱法来分离一些抗体。

[0346] 可以使用本领域已知的或本文所述的测定来验证本文所述的抗体的生物活性。

[0347] III. 药物组合物

[0348] 本公开提供了包括本文所述的CD40结合分子或任何抗CD40抗体的药物组合物及其用于调节由CD40/CD40L信号传导触发的免疫应答的用途。如本文所述的这种CD40结合分子或还如本文所述的抗CD40抗体可以用于治疗如癌症或免疫相关病症等疾病。

[0349] 如本文所述的CD40结合分子或抗CD40抗体可以与药学上可接受的载体(赋形剂)

混合,以形成用于治疗靶疾病的药物组合物。“可接受的”意指载体必须与组合物的活性成分相容(并且优选地,能够稳定活性成分)并且对待治疗的受试者无害。药学上可接受的赋形剂(载体)包含缓冲液,所述缓冲液是本领域熟知的。参见例如,《雷明顿:药学科学与实践(Remington:The Science and Practice of Pharmacy)》第20版,(2000),利平科特·威廉姆斯&威尔金斯公司(Lippincott Williams and Wilkins),K.E.Hoover编辑。

[0350] 用于本发明方法的药物组合物可以包括冻干调配物或水溶液形式的药学上可接受的载体、赋形剂或稳定剂。(《雷明顿:药学科学与实践》第20版,(2000),利平科特·威廉姆斯&威尔金斯公司,K.E.Hoover编辑)。可接受的载体、赋形剂或稳定剂在所使用的剂量和浓度下对接受者无毒,并且可以包括:缓冲液,如磷酸盐、柠檬酸盐和其它有机酸;抗氧化剂,包含抗坏血酸和甲硫氨酸;防腐剂(如十八烷基二甲基苄基氯化铵;氯化六甲双铵;苯扎氯铵;苄索氯铵;苯酚、丁醇或苯甲醇;对羟基苯甲酸烷基酯,如对羟基苯甲酸甲酯或对羟基苯甲酸丙酯;儿茶酚;间苯二酚;环己醇;3-戊醇;以及间甲酚);低分子量(少于约10个残基)的多肽;蛋白质,如血清白蛋白、明胶或免疫球蛋白;亲水性聚合物,如聚乙烯吡咯烷酮;氨基酸,如甘氨酸、谷氨酰胺、天冬酰胺、组氨酸、精氨酸或赖氨酸;单糖、双糖和其它碳水化合物,包含葡萄糖、甘露糖或葡聚糖;螯合剂,如EDTA;糖,如蔗糖、甘露醇、海藻糖或山梨醇;成盐抗衡离子,如钠;金属络合物(例如,Zn-蛋白络合物);和/或非离子表面活性剂,如TWEEN™、PLURONICS™或聚乙二醇(PEG)。

[0351] 在一些实例中,本文所述的药物组合物包括含有抗体(或编码核酸)的脂质体,所述脂质体可以通过本领域已知的方法制备,如以下文献中所描述的方法:Epstein等人,《美国国家科学院院刊》82:3688(1985);Hwang等人,《美国国家科学院院刊》77:4030(1980);以及美国专利第4,485,045号和第4,544,545号。美国专利第5,013,556号中公开了具有增强的循环时间的脂质体。可以用包括磷脂酰胆碱、胆固醇和PEG衍生化磷脂酰乙醇胺(PEG-PE)的脂质组合物来通过反相蒸发法生成特别有用的脂质体。通过具有限定孔径的过滤器将脂质体挤出以产生具有期望直径的脂质体。

[0352] 还可以将CD40结合分子、抗CD40抗体或一种或多种编码核酸包埋在例如通过凝聚法技术或通过界面聚合制备的微胶囊(例如,分别是羟甲基纤维素或明胶微胶囊和聚(甲基丙烯酸甲酯)微胶囊)中、胶状药物递送系统(例如,脂质体、白蛋白微球、微乳剂、纳米颗粒和纳米胶囊)中或粗乳液中。这些技术都是本领域已知的,参见例如,《雷明顿:药学科学与实践》第20版,马克出版公司(Mack Publishing)(2000)。

[0353] 在其它实例中,可以以缓释型格式调配本文所述的药物组合物。缓释型制剂的合适的实例包含含有抗体的固体疏水性聚合物的半渗透基质,所述基质呈成型制品,例如薄膜或微胶囊的形式。缓释型基质的实例包含聚酯、水凝胶(例如,聚(2-羟乙基-甲基丙烯酸酯)或聚(乙烯醇))、聚交酯(美国专利第3,773,919号)、L-谷氨酸和L-谷氨酸-7-乙酯的共聚物、不可降解的乙烯-乙酸乙烯酯共聚物、如LUPRON DEPOT™(由乳酸-乙醇酸共聚物和乙酸亮丙瑞林构成的可注射微球体)等可降解的乳酸-乙醇酸共聚物、乙酸异丁酸蔗糖酯和聚-D-(-)-3-羟基丁酸。

[0354] 用于体内施用的药物组合物必须是无菌的。这通过例如无菌过滤膜过滤而容易地实现。通常将治疗性抗体组合物放置在具有无菌进口端的容器中,例如,具有可被皮下注射针刺穿的塞子的静脉内溶液袋或小瓶中。

[0355] 本文所述的药物组合物可以采用单位剂型,如片剂、丸剂、胶囊剂、粉剂、颗粒剂、溶液或悬浮液或栓剂,以用于口服、肠胃外或直肠施用或者通过吸入或吹入施用。

[0356] 为了制备如片剂等固体组合物,可以将主要活性成分与药物载体例如常规压片成分(如玉米淀粉、乳糖、蔗糖、山梨醇、滑石、硬脂酸、硬脂酸镁、磷酸二钙或树胶)和如水等其它药物稀释剂混合,以形成含有本发明的化合物的均相混合物固体预调配组合物或无毒的其药学上可接受的盐。在称这些预调配组合物均相时,这意指活性成分均匀地分散在整个组合物中,使得组合物可以容易地细分成等效单位剂型,如片剂、丸剂和胶囊剂。然后将这个固体预调配组合物细分成上述类型的单位剂型,所述单位剂型含有0.1到约500mg的本发明的活性成分。可以包覆或以其它方式配混新组合物的片剂或丸剂以提供给延长作用的优点的剂型。例如,片剂或丸剂可以包括内剂量组分和外剂量组分,后者在前者之上采用包膜的形式。这两种组分可以通过肠溶层分开,所述肠溶层用于抵抗胃中的崩解并且允许内组分完整地传递进入十二指肠或被延迟释放。多种材料可以用于这种肠溶层或包衣,这种材料包含多种聚合酸以及聚合酸与如虫胶、十六醇和乙酸纤维素等此类材料的混合物。

[0357] 合适的表面活性剂具体地包含非离子剂,如聚氧乙烯山梨聚糖(例如,TweenTM 20、40、60、80或85)和其它山梨聚糖(例如,SpanTM 20、40、60、80或85)。具有表面活性剂的组合物将方便地包括介于0.05%与5%之间的表面活性剂,并且可以介于0.1%与2.5%之间。应当理解,如果有必要,可以添加其它成分,例如甘露醇或其它药学上可接受的媒剂。

[0358] 可以使用如IntralipidTM、LiposynTM、InfonutrolTM、LipofundinTM和LipiphysanTM等可商购获得的脂肪乳剂来制备合适的乳剂。活性成分可以溶解在预混合的乳剂组合物中,或者可替代地,活性成分可以溶解在油(例如,大豆油、红花油、棉籽油、芝麻油、玉米油或杏仁油)和在与磷脂(例如卵磷脂、大豆磷脂或大豆卵磷脂)和水混合时形成的乳剂中。应当理解,可以添加其它成分,例如甘油或葡萄糖,以调整乳剂的张力。合适的乳剂通常将含有高达20%的油,例如,介于5%与20%之间。脂肪乳剂可以包括介于0.1与1.0 μ m之间、具体地0.1与0.5 μ m之间的脂肪滴,并且pH范围为5.5到8.0。

[0359] 乳剂组合物可以是通过将抗体与IntralipidTM或其组分(大豆油、卵磷脂、甘油和水)混合而制备的那些乳剂组合物。

[0360] 用于吸入或吹入的药物组合物包含药学上可接受的水性或有机溶剂或其混合物中的溶液和悬浮液以及粉末。液体或固体组合物可以含有如上文所列出的合适的药学上可接受的赋形剂。在一些实施例中,通过口服或鼻腔呼吸途径施用组合物以产生局部或全身作用。

[0361] 可以通过使用气体来雾化优选地无菌的药学上可接受的溶剂中的组合物。可以直接从雾化装置中呼吸雾化溶液,或者雾化装置可以附着到面罩、帐篷或间歇正压呼吸机。可以从以适当方式递送调配物的装置优选地通过口服或鼻腔施用溶液、悬浮液或粉末组合物。

[0362] IV. 治疗应用

[0363] 本文公开的CD40结合分子中的任何CD40结合分子或抗CD40抗体可以用于调节(例如,增强或抑制)针对侵入性病原体 and/或患病细胞如癌细胞的免疫应答。

[0364] 为了实践本文所公开的方法,可以通过合适的途径向需要治疗的受试者(例如,人)施用有效量的本文所述的药物组合物,所述合适的途径如静脉内施用(例如,如团注或

通过一段时间内的连续输注)、通过肌肉内、腹膜内、脑脊髓内、皮下、关节内、滑膜内、鞘内、口服、吸入或局部途径。包含喷射雾化器和超声雾化器的用于液体调配物的可商购获得的雾化器可用于施用。液体调配物可以直接雾化并且冻干粉可以在重构之后雾化。可替代地,本文所述的抗体可以使用碳氟化合物调配物和计量吸入器来雾化或者作为冻干粉和研磨粉吸入。

[0365] 待通过本文所述的方法治疗的受试者可以是哺乳动物,更优选地是人。哺乳动物包含但不限于家畜、运动动物(sport animal)、宠物、灵长类动物、马、狗、猫、小鼠和大鼠。

[0366] 在一些情况下,受试者是患有如癌症等细胞介导的疾病或病症或者处于患有如癌症等细胞介导的疾病或病症的风险中的人类患者,所述癌症包含但不限于肺癌、胃癌(stomach cancer)、肝癌、乳腺癌、皮肤癌、胰腺癌、脑癌、前列腺癌、膀胱癌或结肠直肠癌。另外的示例性癌症包含但不限于乳腺癌;胆管癌;膀胱癌;脑癌,包含成胶质细胞瘤和成神经管细胞瘤;宫颈癌;绒毛膜癌;结肠癌;子宫内膜癌;食道癌;胃癌(gastric cancer);血液肿瘤,包含急性淋巴细胞白血病和骨髓性白血病,例如B细胞CLL;T细胞急性成淋巴细胞性白血病/淋巴瘤;毛细胞白血病;慢性骨髓性白血病,多发性骨髓瘤;AIDS相关白血病和成人T细胞白血病/淋巴瘤;上皮内肿瘤,包含博文氏病(Bowen's disease)和佩吉特氏病(Paget's disease);肝癌;肺癌;淋巴瘤,包含霍奇金氏病(Hodgkin's disease)和淋巴细胞性淋巴瘤;成神经细胞瘤;口腔癌,包含鳞状细胞癌;卵巢癌,包含由以下引起的那些:上皮细胞、基质细胞、生殖细胞和间充质细胞;胰腺癌;前列腺癌;直肠癌;肉瘤,包含平滑肌肉瘤、横纹肌肉瘤、脂肪肉瘤、纤维肉瘤和骨肉瘤;皮肤癌,包含黑色素瘤、梅克尔细胞癌(Merkel cell carcinoma)、卡波西肉瘤(Kaposi's sarcoma)、基底细胞癌和鳞状细胞癌;睾丸癌,包含胚组织瘤,如精原细胞瘤、非精原细胞瘤(畸胎瘤、绒毛膜癌)、间质瘤和生殖细胞肿瘤;甲状腺癌,包含甲状腺腺癌和髓样癌;和肾癌,包含腺癌和威尔姆氏肿瘤(Wilms tumor)。患有癌症的受试者可以通过常规医学检查,例如实验室测试、器官功能测试、CT扫描或超声波来鉴定。在一些实施例中,通过本文所述的方法待治疗的受试者可以是已经经历或正经受抗癌疗法(例如,化学疗法、放射疗法、免疫疗法或外科手术)的人癌症患者。

[0367] 在其它情况下,受试者是患有免疫相关病症或处于免疫相关病症风险的人类患者。免疫相关病症是指免疫系统的功能障碍,包含自身免疫性疾病、免疫缺陷和/或过敏症。在一个实施例中,免疫相关病症是自身免疫性疾病。免疫相关病症的实例包含但不限于类风湿性关节炎(RA)、系统性红斑狼疮(SLE)、重症肌无力(MG)、格雷夫氏病(Graves' Disease)、特发性血小板减少性紫癜(ITP)、格林-巴利综合征(Guillain-Barre Syndrome)、自身免疫性心肌炎、膜性肾小球肾炎、糖尿病、I型或II型糖尿病、多发性硬化症、雷诺氏综合征(Reynaud's syndrome)、自身免疫性甲状腺炎、胃炎、乳糜泻、白癜风、肝炎、原发性胆汁性肝硬化、炎症性肠病、脊椎关节病变、实验性自身免疫性脑脊髓炎、免疫性中性粒细胞减少症、青少年型糖尿病、和与常见于结核病、结节病和多肌炎中的由细胞因子、T淋巴细胞介导的迟发型超敏反应相关的免疫应答、多动脉炎、皮肤血管炎、天疱疮、类天疱疮(pemphigoid)、古德帕斯彻氏综合征(Goodpasture's syndrome)、川崎氏病(Kawasaki's disease)、系统性硬化症、抗磷脂综合征、干燥综合征(Sjogren's syndrome)、移植物抗宿主(GVH)疾病和免疫性血小板减少症。患有免疫相关病症的受试者可以通过常规医学检查(例如,用实验室测试)来鉴定。在一些实施例中,通过本文所述的方

法待治疗的受试者可以是患有免疫相关病症的人类受试者,所述人类受试者已经经历或正经受免疫相关病症治疗,例如免疫抑制介导、激素替代疗法、输血、抗炎药物和/或疼痛药物。

[0368] 如本文所使用的,“有效量”是指单独地或与一种或多种其它活性剂组合地赋予受试者治疗效果所需的每种活性剂的量。在一些实施例中,治疗效果是调节(例如,激活)靶免疫受体,从而触发或增强受体介导的免疫应答。确定抗体的量是否达到治疗效果对于本领域的技术人员而言将会是显而易见的。如本领域的技术人员所认识到的,有效量有所不同,这取决于正在治疗的特定病状、病状的严重程度、包含年龄、身体状况、大小、性别和体重在内的个体患者参数、治疗持续时间、同时疗法的性质(如果有的话)、具体施用途径和在健康从业者的知识和专业技能内的相似因素。这些因素是本领域的普通技术人员所熟知的并且可以仅通过常规实验来解决。通常优选使用个别组分或其组合的最大剂量,也就是说,根据合理的医学判断的最高安全剂量。

[0369] 如半衰期等经验性考虑通常将有助于确定剂量。例如,可以使用如人源化抗体或完全人抗体等与人免疫系统相容的分子来延长抗体的半衰期并且防止抗体受到宿主的免疫系统的攻击。施用频率可以在治疗过程中确定并进行调整,并且通常但不一定是基于靶疾病/病症的治疗和/或抑制和/或改善和/或延迟。可替代地,抗体的持续连续释放调配物可以是适当的。用于实现持续释放的各种调配物和装置是本领域已知的。

[0370] 在一个实例中,本文所述的CD40结合分子或抗CD40抗体的剂量可以在给予一次或多次抗体施用的个体中凭经验确定。给予个体递增剂量的激动剂。为了评估激动剂的功效,可以遵循疾病/病症的指标。

[0371] 通常,对于施用任何治疗剂,如本文所述的CD40结合分子或抗CD40抗体,初始候选剂量可以为约2mg/kg。出于本公开的目的,典型的日剂量的范围根据上述因素可以为约0.1 μ g/kg到3 μ g/kg、到30 μ g/kg、到300 μ g/kg、到3mg/kg、到30mg/kg、到100mg/kg或更多中的任何剂量。对于在若干天或更长时间内的重复施用,根据病状持续治疗,直至出现期望的症状抑制或直至达到足以减轻靶疾病或病症或其症状的治疗水平。示例性给药方案包括施用约2mg/kg的初始剂量,随后施用约1mg/kg的抗体的每周维持剂量,或者随后每隔一周施用约1mg/kg的维持剂量。然而,根据从业者希望实现的药代动力学衰变模式,其它剂量方案可能是有用的。例如,设想每周给药一到四次。在一些实施例中,可以使用的给药范围为约3 μ g/mg到约2mg/kg(如约3 μ g/mg、约10 μ g/mg、约30 μ g/mg、约100 μ g/mg、约300 μ g/mg、约1mg/kg和约2mg/kg)。在一些实施例中,给药频率为每周一次、每2周一次、每4周一次、每5周一次、每6周一次、每7周一次、每8周一次、每9周一次或每10周一次;或每月一次、每2个月一次或每3个月一次或更久一次。通过常规技术和测定,容易地监测这一疗法的进展。给药方案(包含使用的治疗剂)可以随时间推移而变化。

[0372] 在一些实施例中,对于正常体重的成年患者,可以施用的剂量范围为约0.3到5.00mg/kg。在一些实例中,如本文所述的抗体等治疗剂的剂量可以为10mg/kg。特定的给药方案,即剂量、定时和重复,将取决于特定个体和所述个体的病史以及个别药剂的性质(如药剂的半衰期和本领域所熟知的其它考虑)。

[0373] 出于本公开的目的,本文所述的CD40结合分子或抗CD40抗体的适当剂量将取决于所采用的特异性抗体、抗体和/或非抗体肽(或其组合物)、疾病/病症的类型和严重程度、

CD40结合分子或抗CD40抗体是否出于预防或治疗目的而施用、既往疗法、患者的临床病史和对激动剂的应答以及主治医生的判定。通常,临床医生将施用CD40结合分子或抗CD40抗体,直至达到实现期望结果的剂量。在一些实施例中,期望结果是血栓形成的减少。确定剂量是否产生期望结果的方法对于本领域的技术人员而言将会是显而易见的。一种或多种CD40结合分子或抗CD40抗体的施用可以是连续或间歇的,这取决于例如接受者的生理状况、施用目的是治疗性的还是预防性的以及熟练从业者已知的其它因素。CD40结合分子或抗CD40抗体的施用可以在预选时间段内基本上是连续的,或者可以例如在发展靶疾病或病症之前、期间或之后采用一系列间隔剂量。

[0374] 如本文所使用的,术语“治疗”是指向受试者施加或施用包含一种或多种活性剂的组合物,所述受试者患有靶疾病或病症、疾病/病症的症状或对疾病/症状有易感性,其目的是治疗、治愈、减轻、缓解、改变、补救、改善、改进或影响病症、疾病的症状或对疾病或病症的易感性。

[0375] 减轻靶疾病/病症包含延迟疾病的发展或进展或者降低疾病严重程度。减轻疾病不一定需要治愈效果。如本文所使用的,“延迟”靶疾病或病症的发展意指推迟、阻碍、减缓、放缓、稳定和/或延缓疾病的进展。这种延迟可以具有不同的时间长度,这取决于疾病的历史和/或正在治疗的个体。“延迟”或减轻疾病的发展或者延迟疾病的发作的方法是降低在给定时间帧内发展疾病的一种或多种症状的可能性和/或与不使用所述方法相比在给定时间帧内降低症状的程度的方法。这种比较通常是基于临床研究,使用足以给出统计学上显著的结果的许多受试者。

[0376] 疾病的“发展”或“进展”意指疾病的初始表现和/或后续进展。疾病的发展可以是可检测到的并且可以使用如本领域熟知的标准临床技术进行评估。然而,发展还指可能无法检测到的进展。出于本公开的目的,发展或进展是指症状的生物学过程。“发展”包含发生、复发和发作。如本文所使用的,靶疾病或病症的“发作”或“发生”包含初始发作和/或复发。

[0377] 在一些实施例中,在体内以足以激活靶受体的活性至少20%(例如,30%、40%、50%、60%、70%、80%、90%或更大)的量向需要治疗的受试者施用本文所述的抗体。

[0378] 根据待治疗的疾病的类型或疾病的位点,可以使用医学领域的普通技术人员已知的常规方法来向受试者施用药物组合物。这种组合物还可以通过其它常规途径施用,例如口服、肠胃外、通过吸入喷雾、局部、直肠、鼻腔、颊、阴道或通过植入式储药器施用。如本文所使用的术语“肠胃外”包含皮下、皮内、静脉内、肌肉内、关节内、动脉内、滑膜内、胸骨内、鞘内、病灶内和颅内注射或输注技术。另外,可以通过可注射的贮库施用途向受试者施用组合物,如使用1个月、3个月或6个月贮库可注射或可生物降解材料和方法。在一些实例中,眼内或玻璃体内施用药物组合物。

[0379] 可注射组合物可以含有各种载体,如植物油、二甲基乙酰胺、二甲基甲酰胺、乳酸乙酯、碳酸乙酯、肉豆蔻酸异丙酯、乙醇和多元醇(甘油、丙二醇、液体聚乙二醇等)。对于静脉内注射,可以通过滴注方法施用水溶性抗体,由此输注含有抗体和生理学上可接受的赋形剂的药物调配物。生理学上可接受的赋形剂可以包含例如5%葡萄糖、0.9%盐水、林格氏溶液(Ringer's solution)或其它合适的赋形剂。肌肉内制剂(例如,抗体的合适的可溶性盐形式的无菌调配物)可以在如注射用水、0.9%盐水或5%葡萄糖溶液等药物赋形剂中溶

解和施用。

[0380] 本文所述的方法中使用的特定给药方案,即剂量、定时和重复,将取决于特定受试者和所述受试者的病史。

[0381] 在一些实施例中,可以向需要治疗的受试者施用多于一种抗体或抗体与另一种合适的治疗剂的组合。CD40结合分子或抗CD40抗体还可以与用于增强和/或补充药剂有效性的其它药剂结合使用。

[0382] 可以通过本领域熟知的方法对靶疾病/病症的治疗功效进行评估。

[0383] 本文所述的治疗剂可以与用于如癌症等靶疾病的其它类型的疗法结合使用。另外的抗癌疗法包含化学疗法、外科手术、辐射、基因疗法等。当使用第二治疗剂时,这种药剂可以与本文所述的CD40结合分子或抗CD40抗体同时或依次(以任何顺序)施用。

[0384] 当与另外的治疗剂共同施用时,可以根据相加作用或协同效应降低每种药剂的合适的治疗有效剂量。

[0385] 本公开的治疗可以与其它免疫调节治疗组合,所述其它免疫调节治疗如例如治疗性疫苗(包含但不限于GVAX、基于DC的疫苗等)或检查点抑制剂(包含但不限于阻断CTLA4、PD1、LAG3、TIM3等的药剂)。可替代地,本公开的治疗可以与以下组合:化学治疗剂,例如嘧啶类似物(5-氟尿嘧啶、氟尿苷、卡培他滨(capecitabine)、吉西他滨(gemcitabine)和阿糖胞苷)、嘌呤类似物、叶酸拮抗剂和相关抑制剂(巯基嘌呤、巯鸟嘌呤、喷司他丁(pentostatin)和2-氯脱氧腺苷(克拉屈滨(cladribine)));抗增殖/抗有丝分裂剂,包含如长春花生物碱(长春碱、长春新碱和长春瑞滨)等天然产物、如紫杉烷(紫杉醇、多西他赛(docetaxel))、长春新碱、长春碱、诺考达唑(nocodazole)、埃博霉素(epothilone)和诺维本(navelbine)等微管破坏剂、表鬼臼毒素(依托泊苷(etoposide)、替尼泊苷(teniposide))、DNA损伤剂(放线菌素、安吡啶(amsacrine)、蒽环霉素(anthracycline)、博来霉素(bleomycin)、白消安(busulfan)、喜树碱(camptothecin)、卡铂、苯丁酸氮芥(chlorambucil)、顺铂、环磷酰胺(cyclophosphamide)、环磷酰胺(cytosan)、更生霉素(dactinomycin)、柔红霉素(daunorubicin)、多柔比星(doxorubicin)、表柔比星(epirubicin)、六甲甲基蜜胺(hexamethylnelamine)、奥沙利铂(oxaliplatin)、异环磷酰胺、美法仑(melphalan)、二氯甲基二乙胺(merchlorehtamine)、丝裂霉素(mitomycin)、米托蒽醌(mitoxantrone)、亚硝基脲、普卡霉素(plicamycin)、丙卡巴肼(procarbazine)、紫杉酚(taxol)、泰索帝(taxotere)、替尼泊苷、三乙烯硫代磷酰胺(triethylenethiophosphoramidate)和依托泊苷(VP16));抗生素,如更生霉素(放线菌素D)、柔红霉素、多柔比星(阿霉素(adriamycin))、伊达比星(idarubicin)、蒽环霉素、米托蒽醌、博来霉素、普卡霉素(光神霉素(mithramycin))和丝裂霉素;酶(系统地代谢L-天冬酰胺并且剥夺不具有合成其自身的天冬酰胺的能力的细胞的L-天冬酰胺酶);抗血小板剂;抗增殖/抗有丝分裂烷化剂,如氮芥(二氯甲基二乙胺、环磷酰胺和类似物、美法仑、苯丁酸氮芥)、乙烯亚胺和甲基三聚氰胺(六甲基三聚氰胺和噻替派)、烷基磺酸盐-白消安、亚硝基脲(卡莫司汀(carmustine)(BCNU)和类似物、链脲霉素(streptozocin))、三氮烯-达卡巴嗪(trazenes-dacarbazine)(DTIC);抗增殖/抗有丝分裂抗代谢物,如叶酸类似物(甲氨蝶呤);铂配位络合物(顺铂、卡铂)、丙卡巴肼、羟基脲、米托坦(mitotane)、氨基鲁米特(aminoglutethimide);激素、激素类似物(雌激素、三苯氧胺(tamoxifen)、戈舍瑞林

(goserelin)、比卡鲁胺(bicalutamide)、尼鲁米特(nilutamide))和芳香酶抑制剂(来曲唑(letrozole)、阿那曲唑(anastrozole));抗凝血剂(肝素、合成肝素盐和其它凝血酶抑制剂);纤维蛋白溶解剂(如组织纤溶酶原激活剂、链激酶和尿激酶)、阿司匹林(aspirin)、双嘧达莫(dipyridamole)、噻氯匹定(ticlopidine)、氯吡格雷(clopidogrel)、阿昔单抗(abciximab);抗迁移剂;抗分泌剂(贝莱维定(breveldin));免疫抑制剂(环孢菌素(cyclosporine)、他克莫司(tacrolimus)(FK-506)、西罗莫司(sirrolimus)(雷帕霉素(rapamycin))、硫唑嘌呤、霉酚酸酯);抗血管生成化合物(例如,TNP-470、染料木黄酮、贝伐单抗(bevacizumab))和生长因子抑制剂(例如,成纤维细胞生长因子(FGF)抑制剂);血管紧张素受体阻断剂;一氧化氮供体;反义寡核苷酸;抗体(曲妥珠单抗(trastuzumab));细胞周期抑制剂和分化诱导剂(维甲酸(tretinoin));mTOR抑制剂、拓扑异构酶抑制剂(多柔比星(阿霉素)、安吡啶、喜树碱、柔红霉素、更生霉素、京尼平苷(eniposide)、表柔比星、依托泊苷、伊达比星和米托蒽醌、托泊替康(topotecan)、伊立替康(irinotecan))、皮质类固醇(可的松(cortisone)、地塞米松(dexamethasone)、氢化可的松(hydrocortisone)、甲基强的松龙(methylprednisolone)、强的松(prednisone)和泼尼松龙(prednisolone));生长因子信号转导酶抑制剂;线粒体功能障碍诱导剂和胱天蛋白酶激活剂;以及染色质破坏剂。

[0386] 关于另外的有用药剂的实例,还参见:《内科医生案头参考(Physician's Desk Reference)》,补充第59版,(2005),Thomson P D R, Montvale N.J.;Gennaro等人编辑,《雷明顿药理学科学与实践》,补充第20版,(2000),马里兰州巴尔的摩的利平科特·威廉姆斯&威尔金斯公司(Lippincott Williams and Wilkins,Baltimore Md.);Braunwald等人编辑,《哈里森内科医学原理(Harrison's Principles of Internal Medicine)》,补充第15版,(2001),麦格劳·希尔公司(McGraw Hill),纽约;Berkow等人编辑,《默克诊断与疗法手册(The Merck Manual of Diagnosis and Therapy)》,(1992),默克研究实验室(Merck Research Laboratories),拉威(Rahway),新泽西州(N.J.)。

[0387] V. 试剂盒

[0388] 本公开还提供了用于使用本文所述的任何CD40结合分子或抗CD40抗体增强期望免疫应答的试剂盒。

[0389] 在一些实施例中,试剂盒可以包括用于根据本文所述的任何方法使用的说明书。包含的说明书可以包括对施用用于治疗、延迟发作或减轻如本文所述的那些靶疾病等靶疾病的治疗剂的描述。试剂盒可以进一步包括对基于鉴定个体是否患有靶疾病来选择适于治疗的所述个体的描述。在仍其它实施例中,说明书包括对向具有靶疾病风险的个体施用如抗体等治疗剂的描述。

[0390] 与治疗剂的使用有关的说明书通常包含关于用于预期治疗的剂量、给药方案和施用途径的信息。容器可以是单位剂量、散装包装(例如,多剂量包装)或亚单位剂量。本发明的试剂盒中提供的说明书通常是在标签或包装插页(例如,包含在试剂盒中的纸张)上的书面说明,但机器可读说明书(例如,磁性或光学存储盘上携带的说明书)也是可接受的。

[0391] 标签或包装插页指示组合物用于治疗、延迟发作和/或减轻如癌症等靶疾病或病症。可以提供说明书以用于实践本文所述的任何方法。

[0392] 本发明的试剂盒采用合适的包装。合适的包装包含但不限于小瓶、瓶、广口瓶、软包装(例如,密封的密拉(Mylar)或塑料袋)等。还设想了与具体装置(如吸入器、鼻腔施用装

置(例如,雾化器)或输注装置(如微型泵))组合使用的包装。试剂盒可以具有无菌进口端(例如,容器可以是具有可被皮下注射针刺穿的塞子的静脉内溶液袋或小瓶)。容器也可以具有无菌进口端(例如,容器可以是具有可被皮下注射针刺穿的塞子的静脉内溶液袋或小瓶)。组合物中的至少一种活性剂是如本文所述的那些治疗剂的治疗剂。

[0393] 试剂盒可以任选地提供如缓冲液等另外的组分以及解释性信息。通常,试剂盒包括容器和在容器上或与容器相关的标签或一个或多个包装插页。在一些实施例中,本发明提供了包括上文所述的试剂盒的内容物的制品。

[0394] 一般技术

[0395] 除非另有指示,否则本发明的实践将采用在本领域技术范围内的分子生物学(包含重组技术)、微生物学、细胞生物学、生物化学和免疫学的常规技术。此类技术在如以下文献中有充分解释:《分子克隆:实验室手册(Molecular Cloning:A Laboratory Manual)》,第二版(Sambrook等人,1989),冷泉港出版社;《寡核苷酸合成(Oligonucleotide Synthesis)》(M.J.Gait编辑,1984);《分子生物学方法(Methods in Molecular Biology)》,胡玛纳出版社(Humana Press);《细胞生物学:实验室手册(Cell Biology:A Laboratory Notebook)》(J.E.Cellis编辑,1998),学术出版社;《动物细胞培养(Animal Cell Culture)》(R.I.Freshney编辑,1987);《细胞和组织培养导论(Introduction to Cell and Tissue Culture)》(J.P.Mather和P.E.Roberts,1998),普莱南出版社(Plenum Press);《细胞和组织培养:实验室程序(Cell and Tissue Culture:Laboratory Procedures)》(A.Doyle,J.B.Griffiths和D.G.Newell编辑,1993-8),约翰·威利父子出版公司(J.Wiley and Sons);《酶学方法(Methods in Enzymology)》(学术出版社有限公司);《实验免疫学手册(Handbook of Experimental Immunology)》(D.M.Weir和C.C.Blackwell编辑);《哺乳动物细胞的基因转移载体(Gene Transfer Vectors for Mammalian Cells)》(J.M.Miller和M.P.Calos编辑,1987);《分子生物学实验指南(Current Protocols in Molecular Biology)》(F.M.Ausubel等人编辑,1987);《PCR:聚合酶链反应(PCR:The Polymerase Chain Reaction)》(Mullis等人编辑,1994);《免疫学实验指南(Current Protocols in Immunology)》(J.E.Coligan等人编辑,1991);《精编分子生物学实验指南(Short Protocols in Molecular Biology)》(约翰·威利父子出版公司,1999);《免疫生物学(Immunobiology)》(C.A.Janeway和P.Travers,1997);《抗体(Antibodies)》(P.Finch,1997);《抗体:实用方法(Antibodies:a practical approach)》(D.Catty.编辑,IRL出版社,1988-1989);《单克隆抗体:实用方法(Monoclonal antibodies:a practical approach)》(P.Shepherd和C.Dean编辑,牛津大学出版社(Oxford University Press),2000);《使用抗体:实验室手册(Using antibodies:a laboratory manual)》(E.Harlow和D.Lane(冷泉港实验室出版社,1999));《抗体》(M.Zanetti和J.D.Capra编辑,哈伍德学术出版社(Harwood Academic Publishers),1995)。

[0396] 无需进一步详细阐述,相信本领域的技术人员可以基于以上描述在最大程度上利用本发明。因此,以下具体实施例应被解释为仅是说明性的,并且不以任何方式限制本公开的其余部分。出于本文所提及的目的或主题,本文所引用的所有出版物均通过引用并入。

[0397] 实例1.具有经过工程化的Fc区的抗CD40抗体

[0398] 合成并且克隆对具有不同重链CH1和Fc区或人 κ 轻链恒定区的抗CD40抗体可变结

构域进行编码的cDNA序列。用含有对应的重链序列和轻链序列的质粒进行CHO瞬时表达。这些抗体通过蛋白质A亲和色谱法进行纯化。下文提供了重链(HC)和轻链(LC)的氨基酸序列:

[0399] 383-huIgG LC

[0400] DIQMTQSPSSVSASVGDRTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:146)

[0401] 383-huIgG1m2 HC

[0402] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:147)

[0403] 383-huIgG1m27 HC

[0404] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:148)

[0405] 383-huIgG2m1 HC

[0406] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVSCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:149)

[0407] 383-huIgG2m19 HC

[0408] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVSCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:150)

[0409] 383-huIgG2m20 HC

[0410] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV
DKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPR
EEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQGGNVFSCSVMEALHNHYTQKSLSLS
PGK (SEQ ID NO:151)

[0411] 383-huIgG4m2 HC

[0412] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKV
DKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPR
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLS
SLGK (SEQ ID NO:152)

[0413] 383-huIgG4m20 HC

[0414] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKV
DKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPR
EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLS
LGK (SEQ ID NO:153)

[0415] 383-huIgG4m30 HC

[0416] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKV
DKRVESKYGPPCPPCPAPEFLPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPR
EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLS
LGK (SEQ ID NO:154)

[0417] 383-msIgG LC

[0418] DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSG
TDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI
NVKWKIDGSERQNGVLNSWTDQDSKSTYSMSSTLTCLKDEYERHNSYTCEATHKSTSTSPIVKSFNREK (SEQ ID
NO:155)

[0419] 383-msIgG1 DANA HC

[0420] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV

TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTLTVTVSSASTTPPSVYPLAPGSAAQ
TNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSSETVTCNVAHPASSTKVD
KKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLITITLTPKVTVCVVVAISKDDPEVQFSWFVDDVEVHTAQTQPRE
EQFASTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMI
TDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLVNQQSNWEAGNTFTCSVLHEGLHNHHTTEKSLSHSP
GK (SEQ ID NO:156)

[0421] 383-msIgG1 HC

[0422] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTLTVTVSSASTTPPSVYPLAPGSAAQ
TNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSSETVTCNVAHPASSTKVD
KKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLITITLTPKVTVCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPRE
EQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMI
TDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLVNQQSNWEAGNTFTCSVLHEGLHNHHTTEKSLSHSP
GK (SEQ ID NO:157)

[0423] 383-msIgG2a DANA HC

[0424] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTLTVTVSSASTTAPSVYPLAPVCGDT
TGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVD
KKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFFPKIKDVLMIISLPIVTCVVVAIVEDDPDVQISWVFNNEVHTA
QTQTHREDYASTLRVVSALPIQHQQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEEEMTKKQV
TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSGYSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTK
SFSRTPGK (SEQ ID NO:158)

[0425] 383-msIgG2a HC

[0426] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTLTVTVSSASTTAPSVYPLAPVCGDT
TGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVD
KKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFFPKIKDVLMIISLPIVTCVVVDVEDDPDVQISWVFNNEVHTA
QTQTHREDYNSTLRVVSALPIQHQQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEEEMTKKQV
TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSGYSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTK
SFSRTPGK (SEQ ID NO:159)

[0427] 制备另外的Fc突变体,并且下文提供了重链(HC)的氨基酸序列(上文提供了轻链(LC)序列):

[0428] 383-huIgG1 HC

[0429] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSTSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK

SLSLSPGK (SEQ ID NO:207)

[0430] 383-huIgG2 HC

[0431] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSNFGTQTYTCNVDHKPSNTKV
DKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSGDSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSL
SPGK (SEQ ID NO:208)

[0432] 383-huIgG4SP HC

[0433] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDHKPSNTKV
DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:209)

[0434] 383-huIgG1mAA

[0435] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQK
SLSLSPGK (SEQ ID NO:210)

[0436] 383-huIgG1m40 HC

[0437] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVaVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQY_aSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQK
SLSLSPGK (SEQ ID NO:193)

[0438] 383-huIgG1m45 HC

[0439] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAP_{pva}GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS

LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:194)

[0440] 383-huIg G1m240 HC

[0441] QVQLVQSGAEVKKPGASVKVSCKASGYFTFTGYIMHWVRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVAVVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:195)

[0442] 383-huIgG1 N297A

[0443] QVQLVQSGAEVKKPGASVKVSCKASGYFTFTGYIMHWVRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK
LSLSPGK (SEQ ID NO:196)

[0444] 383-huIgG1m47 HC

[0445] QVQLVQSGAEVKKPGASVKVSCKASGYFTFTGYIMHWVRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAP_{pva}GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK_{gLPss}IEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:197)

[0446] 383-huIgG1m48 HC

[0447] QVQLVQSGAEVKKPGASVKVSCKASGYFTFTGYIMHWVRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKS_sDKTHT_sPP_sPAPELLGG_sSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK
LSLSPGK (SEQ ID NO:198)

[0448] 383-huIgG1m49 HC

[0449] QVQLVQSGAEVKKPGASVKVSCKASGYFTFTGYIMHWVRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHT_sPP_sPAP_{pva}GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA

KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO:199)

[0450] 383-huIgG1m50 HC

[0451] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPEf_eGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAsIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO:214)

[0452] 383-huIgG1mAAG

[0453] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO:211)

[0454] 383-huIgG2m40 HC

[0455] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKTVERKCCVECPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFASTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTPPMLSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO:200)

[0456] 383-huIgG2m43 HC

[0457] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKTVERKCCVECPAPPaaasSVFLFPPKPKDTLMISRTPEVTCVVVDVSaEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTPPMLSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO:201)

[0458] 383-huIgG2m44 HC

[0459] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV

DKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSqEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVIHQDWLNGKEYKCKVSNKGLPssIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSL
SPGK (SEQ ID NO:202)

[0460] 383-huIgG2mAA HC

[0461] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTTLTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKTVERKCCVECPPCPAPPaaaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSL
SPGK (SEQ ID NO:203)

[0462] 383-huIgG2m2040 HC

[0463] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTTLTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVAVSHEDPEVQFNWYVDGVEVHNAKTKPR
EEQFASTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLS
PGK (SEQ ID NO:204)

[0464] 383-huIgG2G4 HC

[0465] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTTLTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSL
SLGK (SEQ ID NO:205)

[0466] 383-huIgG4m40 HC

[0467] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTTLTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVAVSQEDPEVQFNWYVDGVEVHNAKTK
PREEQFASTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:206)

[0468] 383-huIgG4m41 HC

[0469] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWRQAPGQGLEWMGWINPDSSGGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGGTTLTVSSASTKGPSVFPLAPSSKST

SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVAVSVQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVVHQDNLGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:66)

[0470] 383-huIgG4m42 HC

[0471] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHVVRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVAVSVQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDNLGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:67)

[0472] 383-huIgG4m46 HC

[0473] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHVVRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKRVESKYGPPCPPCPAPEaLGaPSVFLFPPKPKDTLMISRTPEVTCVAVDVQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDNLGKaYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:68)

[0474] 383-huIgG4mPE HC

[0475] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHVVRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPCSRST
SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKV
DKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVAVDVQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDNLGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:212)

[0476] 383-huIgG4mAA HC

[0477] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHVVRQAPGQGLEWMGWINPDSSGTNYAQKFQGRV
TMRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKRVESKYGPPCPPCPAPEaaGGPSVFLFPPKPKDTLMISRTPEVTCVAVDVQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDNLGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLS
LSLGK (SEQ ID NO:69)

[0478] 实例2.具有Fc突变体的CD40抗体与细胞Fc γ R的结合活性的确定

[0479] 为了确定IgG突变体中CD40活性与细胞Fc受体的结合活性,使用本领域已知的慢

病毒递送系统将CHO细胞基因工程化,以表达人Fc γ R(Fc γ RI、Fc γ RIIA、Fc γ RIIB和Fc γ RIII)。

[0480] 使用本文公开的抗CD40抗体383作为示例性抗CD40部分,按照本文的公开内容设计和构建许多抗CD40 IgG Fc突变体,包含383-msIgG1、383-msIgG1 DANA、383-msIgG2a、383-msIgG2a DANA、383-hIgG2、对照huIgG1、383-huIgG1m27、383-huIgG2m19、383-huIgG1m2、383-huIgG2m1、383-huIgG2m20、383-huIgG4m2、383-huIgG4m20、383-huIgG4m30、383-huIgG1mAA和383-huIgG4SP(上文提供的氨基酸序列)。这些IgG突变体在上铰链结构域、下铰链结构域或CH2结构域内含有突变。

[0481] 关于IgG突变体与不同Fc γ R的结合的FACS分析,使用胰蛋白酶-EDTA收获Fc γ R过表达性CHO细胞,并且将其悬浮在冷染色缓冲液(含3%BSA的PBS)中。向细胞中添加在染色缓冲液中稀释的测试IgG突变体。将混合物在4℃下温育2小时,并且然后用冷染色缓冲液洗涤两次并重悬于带PE标记的抗人IgG中,之后在4℃下温育2小时。将混合物用染色缓冲液洗涤两次并重悬于含2%PFA的PBS中以进行FACS。

[0482] 如图1A-1D和3A-3D所示,许多抗CD40人IgG1、IgG2和IgG4突变体显示出与细胞表面上表达的Fc γ R的结合活性,而其它突变体对所检查的Fc γ R未显示明显的发现。结合性质变化的概述列于上表2-4中。

[0483] 实例3.具有经过工程化的Fc区的CD40抗体显示出差异CD40激动剂活性

[0484] 为了确定IgG突变体的激动剂活性,开发了CD40报告基因测定,其涉及报告细胞过表达性人CD40 T细胞。将这种GS-H2-huCD40报告细胞重悬于测定缓冲液中,并且用台盼蓝确定细胞密度和存活力。用测定缓冲液(含有1%FBS的MEM)将细胞悬浮液稀释到 1×10^4 个细胞/mL。以100微升/孔添加细胞,使得在测定板(Nunc,目录号167425)中最终细胞数量为1000个细胞/孔。在测定缓冲液中以2x最终浓度制备测试样品的连续工作稀释液。以100微升/孔测试样品以2x最终浓度向测定板添加样品。将测定板在37℃、5%CO₂温育箱中温育18-20小时。温育18-20小时之后,从测定板的每个孔中收集8 μ l上清液并且将其添加到HTRF检测测定板(Nunc)中。使用人IL-8测定试剂盒(Cisbio,目录号62IL8PEB)进行人白介素8(CD40激活的报告基因)检测测定。具体地,使用16 μ l的测定体积。使用Tecan F200pro的时间分辨荧光读取结果,并且记录相对光单位数据。

[0485] 如图2和图4A-4E所示,所有所测试的抗CD40抗体IgG突变体刺激人CD40激活,如由IL8的分泌所证明的。由于每种抗体同种型结构的铰链柔性,CD40激活的量级受其中所含有的Fc变体的影响。

[0486] 还在与Fc γ RIIB表达性CHO细胞共培养的情况下进行CD40报告基因测定,并且结果示于图4A-4D中。在微环境中所测试的抗体分子与CD40和Fc γ R2B同时结合将由于亲合力效应而影响个体结合,所述亲合力效应是指个体非共价结合相互作用的多个亲和力的累积强度。抗体显示出与所述抗体与Fc γ RIIB的结合活性相关的增加的活性。注意到,具有对Fc γ RIIB的结合很弱或不明显的Fc变体的抗体在共培养报告基因测定中表现出增强的激动剂活性,这表明报告基因测定的更高灵敏度可能归因于亲合力效应。因此,抗体的Fc结构可以影响具有相同可变结构域的抗体的激动剂活性。

[0487] 实例4.树突细胞(DC)功能测定中的抗CD40抗体IgG突变体的表征

[0488] 如上述实例所述,体外测试包括各种Fc突变体的示例性抗CD40抗体Ig变体的CD40

结合活性和激动活性,以及如实例6所述在体内测试抗肿瘤功效和毒性。其在激活人树突细胞中的活性如下进行。

[0489] 将来自健康供体的冷冻的人PBMC(澳赛尔斯公司(Allcells),目录号PB005F)解冻并且转移到具有25mL RPMI1640培养基的50ml管中。使用EasySep™人CD14阳性选择试剂盒II(干细胞公司(Stemcell),目录:17858)来分离B细胞。将PBMC悬浮液在250g下离心15分钟,并且弃去上清液并将细胞重悬于1.5mL EasySep™缓冲液中。向14mL (17×100mm) 聚苯乙烯圆底管中添加选择鸡尾酒(Selection Cocktail)样品。100μl/ml,每种样品150μl。将细胞从50ml管转移到14mL (17×100mm) 聚苯乙烯圆底管中、混合并且在室温下温育15分钟。在转移到样品之前混合磁性颗粒。将磁性颗粒转移到样品。50μl/ml,每种样品75μl。在室温下混合并温育10分钟。添加8.5ml EasySep™缓冲液,以使样品达到10mL。通过轻轻上下吸移2-3次进行混合。将管置于磁体中并且温育5分钟。拾起磁体,并且在一个连续运动中倒置磁体和管,倒掉上清液。收集上清液用于B细胞富集。重复上述洗涤步骤另外2次。将细胞重悬于5mL RPMI 1640中。计算细胞密度。

[0490] 将来自人PBMC的分离的CD14⁺细胞调整为 1×10^6 个细胞/毫升,并且向细胞培养基中添加GM-CSF和IL-4。将细胞在37℃、5%CO₂加湿的温育箱中温育3天。在第3天,通过将培养物上清液转移到离心管中并且然后以250x g离心5分钟来更换培养基。使用含有GM-CSF和IL-4的10ml新鲜培养基将细胞沉淀物悬浮于离心管中,并且然后在离心期间添加到烧瓶中,使得由此形成的细胞沉淀物将重悬于10ml新鲜培养基中。将重悬浮的细胞添加回同一孔或烧瓶,并且温育另外2天。在第5天,重复以上步骤用于培养基更换。将细胞进一步温育另一个另外2天。在第7天,可以观察到未成熟的树突细胞并且准备用于所期望的应用中。

[0491] 为了进行DC激活测定,将具有细胞的培养基从T75-烧瓶中取出,放入50ml管中并且在室温下以500x g离心5分钟。弃去上清液并且将细胞重悬于3mL RPMI1640 10%FBS培养基中。计算细胞密度并且将细胞密度调整为 1×10^6 /mL。向96孔板, 2.5×10^4 个细胞/孔添加0.05mL的细胞悬浮液。在细胞培养物上清液中24小时后(第3天)用HuIL-12-P70检测试剂盒(Cisbio,目录号:62HIL12PEH)和HuIL-8检测试剂盒(Cisbio,目录号:62HIL08PEH)检测IL-8和IL12 P70。还在与Fc γ R2B表达性CHO细胞共培养的情况下进行DC激活测定。

[0492] 如图5A-5D所示,所测试的CD40抗体IgG突变体在不同程度上刺激人CD40激活,如通过抗体温育后从DC培养物分泌IL8所证明的。DC激活的量级受其中所含有的Fc变体的影响,这是由于每种抗体同种型结构的铰链柔性以及与由DC培养物表达的Fc受体的相互作用。

[0493] 为了确定Fc-Fc γ RIIB交联对CD40激活的作用,还在与Fc γ R2B表达性CHO细胞共培养的情况下进行DC激活。在微环境中抗体分子与CD40和Fc γ RIIB同时结合将影响个体结合,这是由于亲和力效应导致抗体的CD40激动作用的改变。抗体显示出与所述抗体与Fc γ RIIB的结合活性相关的增加的活性,这与上文所述的报告基因测定中的观察结果一致。因此,抗体的Fc结构将影响具有相同可变结构域的抗体的总体激动剂活性。

[0494] 实例5. IgG突变体中的CD40抗体显示出与细胞CD40类似的结合

[0495] FACS用于评估示例性抗CD40抗体IgG变体的结合性质。使用胰蛋白酶-EDTA部分消化,随后在1000rpm下离心5分钟,收获CHO细胞过表达性人CD40或食蟹猴CD40。将细胞以 5×10^6 /ml重悬于冷PBS-BSA(2%)中并且等分为100微升/管。将嵌合的抗CD40抗体在PBS-BSA

中稀释三次(最终浓度为0.01、0.1、1和10 μ g/ml),并且向CHO-CD40细胞中添加50 μ l的每种浓度。将细胞溶液混合并且在4 $^{\circ}$ C下在黑暗中温育2小时。然后将细胞用PBS-BSA洗涤两次。以100微升/小瓶的浓度添加二级抗体缀合物(山羊F(ab')₂抗人IgG-Fc(PE),预吸附的(艾博抗公司(Abcam),#ab98596))并且将细胞混合并在4 $^{\circ}$ C下在黑暗中温育1小时。然后将细胞用PBS-BSA洗涤两次,随后固定在含2%PFA的PBS中,并且然后用FACScaliber进行FACS分析。如图6A-6B所示,这些抗体对CHO细胞表面上表达的人CD40表现出高结合活性。

[0496] 实例6. IgG突变体中的CD40抗体在体内动物模型中表现出差异抗肿瘤活性

[0497] 在小鼠同源肿瘤模型中体内测试具有各种Fc突变体的示例性抗CD40抗体,以确定Fc突变体如何可以影响这些抗体的功效和毒性。使用具有人CD40胞外结构域敲入的C57BL6小鼠来开发同源小鼠肿瘤模型。在第0天将鼠结肠癌MC38细胞皮下植入到纯合子人CD40敲入C57BL6小鼠中。当肿瘤大小为大约150 $\pm$ 50mm³(n=6)时,将小鼠分组。通过腹膜内注射施用CD40抗体,并且在4-6周的抗体处理期间测量肿瘤大小。每周2次通过口径测量肿瘤大小,并且使用0.5 $\times$ 长度 $\times$ 宽度²的公式计算为肿瘤体积。在对照组和抗体处理组的肿瘤大小之间评估抗肿瘤功效。

[0498] 如图7A所示,鼠IgG2aDANA(Fc无效)提供了由Fab'₂诱导的CD40激活驱动的参考功效。人G4m2、G1m2、G2m20和G2m40显示出优于或相当于mIgG2aDANA的功效。

[0499] 通过测量抗体处理之后的血清ALT水平,在小鼠模型中检查抗体诱导的肝毒性的可能性。人G2显示出非常大的ALT升高,其中其值超过测定的上限(>1000U/L)。包含G1m2、G2m20和G2m40的有效Fc突变体显示出较少或最小的ALT升高。

[0500] 作为实例,383-G2m20和-G2m40在不存在交联的情况下显示出较高的激动剂活性,并且显示出体内功效以及Fc γ R相互作用(G2m40在结合和DC激活测定两者中均是Fc γ R无效的)。进一步地,G2m20的残留Fc γ RIIB结合活性增强了功效。考虑到Fc变体G2m1和G2m43的体外活性概况与G2m20和G2m40的体外活性概况类似,预期其具有类似的功效但具有改进的毒性窗口。

[0501] 作为另一个实例,在不存在交联的情况下,383-G1m2显示出降低的激动剂活性。体内残留的Fc γ RIIB结合活性增强了这种IgG变体的体内激动剂活性,但对肝毒性影响最小。考虑到Fc变体G1mAA、G1 N279A、G4m20、G4m30和G4m46的体外活性概况与G1m2的体外活性概况类似,预期其具有类似的功效和毒性窗口。

[0502] 其它实施例

[0503] 本说明书中公开的所有特征可以以任何组合来组合。本说明书中公开的每个特征可以通过充当相同、等效或类似目的的替代性特征替代。因此,除非另有明确说明,否则所公开的每个特征仅仅是等效或类似特征的通用系列的实例。

[0504] 通过以上描述,本领域的技术人员可以很容易地确定本发明的实质特性,并且在不偏离本发明的精神和范围的情况下,可以对本发明进行各种改变和修改以使其适于各种用途和条件。因此,其它实施例也在权利要求范围内。

[0505] 等效物

[0506] 尽管本文已经描述和展示了若干个本发明实施例,但本领域的普通技术人员将容易想到用于执行功能和/或获得结果和/或本文所述的优点中的一个或多个优点的各种其它装置和/或结构,并且此类变异和/或修改中的每一个均被视为在本文所述的本发明实施

例的范围内。更一般地,本领域的技术人员将容易地理解,本文所述的所有参数、尺寸、材料和配置意味着示例性的,并且实际参数、尺寸、材料和/或配置将取决于使用本发明教导的一种或多种具体应用。仅使用常规实验,本领域的技术人员将认识到或能够确定本文所述的具体本发明实施例的许多等效物。因此,应理解,前述实施例仅以实例的方式呈现,并且在所附权利要求及其等效物的范围内,可以以不同于具体描述的和要求保护的方式来实践本发明实施例。本公开的本发明实施例涉及本文所述的每个单独的特征、系统、制品、材料、试剂盒和/或方法。另外,如果此类特征、系统、制品、材料、试剂盒和/或方法并不相互矛盾,则两个或更多个此类特征、系统、制品、材料、试剂盒和/或方法的任何组合包含在本公开的发明范围内。

[0507] 本文中定义和使用的所有定义都应当理解为对字典定义的控制、通过引用并入的文件中的定义和/或定义术语的普通含义。

[0508] 本文公开的所有参考文献、专利和专利申请相对于各自所引用的主题而并入本文,在一些情况下,其可能涵盖整个文件。

[0509] 除非清楚地相反地指出,否则如本文中在说明书和权利要求中使用的不定冠词“一个(a)”和“一种(an)”应理解为意指“至少一个”。

[0510] 如本文中在说明书和权利要求中所使用的,短语“和/或”应当理解为意指如此联合的要素中的“任一个或两个”,即要素在一些情况下结合地存在而在其它情况下分开存在。用“和/或”列出的多个要素应以相同的方式理解,即如此联合的要素中的“一个或多个”。除了通过“和/或”从句具体标识的要素之外,还可以任选地存在其它要素,而无论是与具体标识的那些要素相关还是不相关。因此,作为非限制性实例,当与开放式语言,如“包括”结合使用时,对“A和/或B”的引用在一个实施例中可以仅指代A(任选地包含除了B之外的要素);在另一个实施例中,仅指代B(任选地包含除了A之外的要素);在又一个实施例中,指代A和B两者(任选地包含其它要素);等。

[0511] 如本文中在说明书和权利要求中所使用的,“或”应被理解为具有与如上文定义的“和/或”相同的含义。例如,当将列表中的项目分开时,“或”或“和/或”应被解释为包含性的,即,包含多个要素或要素列表中的至少一个要素、但是还包含多于一个要素,以及任选地另外未列出的项。只有明确地指示相反的术语,如“……中的仅一个”或“……中的恰好一个”或者在权利要求中使用时“由……组成”将指代包含多个要素或要素列表中的恰好一个要素。通常,当之前有排他性术语,如“任一个”、“……之一”、“……中的仅一个”或“……中的恰好一个”时,如本文中所使用的术语“或”应当仅被解释为指示排他性替代方案(即“一个或另一个而非两者”)。当在权利要求中使用时,“基本上由……组成”应具有如在专利法领域中所使用的普通含义。

[0512] 如本文中在说明书和权利要求中所使用的,关于一个或多个要素的列表的短语“至少一个”应被理解为意指选自要素列表中的任何一个或多个要素的至少一个要素,但不必要包含要素列表内具体列出的每个要素中的至少一个并且不排除要素列表中的要素的任何组合。这个定义还允许可以任选地存在除了短语“至少一个”所指代的要素列表内具体标识的要素之外的要素,无论与具体标识的那些要素相关还是不相关。因此,作为非限制性实例,“A和B中的至少一个”(或等效地,“A或B中的至少一个”,或等效地“A和/或B中的至少一个”)在一个实施例中可以指代至少一个,任选地包含多于一个A,而不存在B(并且任选地

包含除了B之外的要素);在另一个实施例中指代至少一个、任选地包含多于一个B,而不存在A(并且任选地包含除了A之外的要素);在又另一个实施例中指代至少一个、任选地包含多于一个A,以及至少一个、任选地包含多于一个B(并且任选地包含其它要素);等。

[0513] 还应该理解,除非明确相反地指出,否则在本文要求保护的包含多于一个步骤或动作的任何方法中,方法的步骤或动作的顺序不一定限于叙述方法的步骤或动作的顺序。

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[3841]	Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr		
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[3913]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
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[3915]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
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[4027]	Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
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[4106]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met		
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[4108]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
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[4503]	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val
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[4523]	Glu	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu

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[4554]	Gly	Trp	Ile	Asn	Pro	Asp	Ser	Gly	Gly	Thr	Asn	Tyr	Ala	Gln	Lys	Phe
[4555]					50					55					60	
[4556]	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
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[4568]	Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val		
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[4570]	His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser		
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[4572]	Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys		
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[4574]	Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val		
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[4576]	Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val		
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[4578]	Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile		
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[4580]	Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp		
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[4582]	Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His		
[4583]	275	280	285
[4584]	Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg		
[4585]	290	295	300
[4586]	Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys		
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[4588]	Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu		
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[4590]	Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr		
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[4592]	Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu		
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[4594]	Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp		
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[4596]	Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile		
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[4598]	Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln		
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[4619]	Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
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[4623]	Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
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[4629]	Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr
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[4631]	Thr Gly Ser Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
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[4633]	Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
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[4635]	His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
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[4637]	Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys
[4638]	195 200 205
[4639]	Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu
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[4643]	Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
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[4645]	Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
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[4647]	Val Ala Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
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[4649]	Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
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[4651]	Tyr Ala Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
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[4653]	Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
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[4657]	Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
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[4659]	Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
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[4662]	385 390 395 400
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[4667]	Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
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[4690]	Ala	Arg	Asp	Gln	Pro	Leu	Gly	Tyr	Cys	Thr	Asn	Gly	Val	Cys	Ser	Tyr
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[4693]			115					120					125			
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[4700]	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser
[4701]				180					185					190		
[4702]	Ser	Val	Thr	Val	Thr	Ser	Ser	Thr	Trp	Pro	Ser	Gln	Ser	Ile	Thr	Cys
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[4705]		210					215					220				
[4706]	Pro	Arg	Gly	Pro	Thr	Ile	Lys	Pro	Cys	Pro	Pro	Cys	Lys	Cys	Pro	Ala
[4707]	225					230				235					240	
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[4709]				245					250					255		
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[4711]			260					265					270			
[4712]	Val	Asp	Val	Ser	Glu	Asp	Asp	Pro	Asp	Val	Gln	Ile	Ser	Trp	Phe	Val
[4713]			275					280					285			
[4714]	Asn	Asn	Val	Glu	Val	His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu	Asp
[4715]		290					295					300				
[4716]	Tyr	Asn	Ser	Thr	Leu	Arg	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His	Gln
[4717]	305					310				315				320		
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[4721]		340		345		350
[4722]	Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr					
[4723]		355		360		365
[4724]	Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu					
[4725]		370		375		380
[4726]	Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr					
[4727]	385		390		395	400
[4728]	Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr					
[4729]		405		410		415
[4730]	Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr					
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[4732]	Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys					
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[4734]	Ser Phe Ser Arg Thr Pro Gly Lys					
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[4747]	Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu					
[4748]		35		40		45
[4749]	Val Thr Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys					
[4750]		50		55		60
[4751]	Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys					
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[4753]	Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu					
[4754]		85		90		95
[4755]	Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys					
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[4759]	Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser		
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[4761]	Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys		
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[4763]	Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln		
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[4765]	Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly		
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[4767]	Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln		
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[4769]	Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn		
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[4771]	His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
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[4784]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
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[4786]	Val Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr		
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[4788]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
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[4790]	Gln Phe Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His		
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[4792]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
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[4794]	Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln		
[4795]	115	120	125
[4796]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met		

[4797]	130	135	140
[4798]	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[4799]	145	150	155 160
[4800]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
[4801]	165	170	175
[4802]	Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu		
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[4804]	Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val		
[4805]	195	200	205
[4806]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
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[4817]	Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys		
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[4819]	Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro		
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[4821]	Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys		
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[4823]	Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp		
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[4825]	Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu		
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[4827]	Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu		
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[4829]	His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn		
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[4831]	Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly		
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[4833]	Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu		
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[4835]	Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr		

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[4837]	Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn			
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[4839]	Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe			
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[4841]	Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn			
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[4925]	20 25 30
[4926]	Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
[4927]	35 40 45
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[5150]	Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
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[5175]	Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
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[5179]	Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
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[5181]	Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
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[5183]	Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
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[5253]	Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
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[5257]	Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[5258]	165 170 175
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[5261]	Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
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[5731]	His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
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[5737]	Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
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[5757]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
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[5762]	420 425 430
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[5784]	Met	Glu	Leu	Asn	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
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[5820]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
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[5822]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
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[5926]	His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
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[5928]	Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
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[5942]	Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
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[5992]				180					185					190		
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[5996]		210					215				220					
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[6009]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala		
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[6767]	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro
[6768]	145					150					155					160
[6769]	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val
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[6771]	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser
[6772]				180					185					190		
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[6778]	225					230					235					240
[6779]	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
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[6782]				260					265					270		
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[6784]			275					280					285			
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[6786]	290	295	300
[6787]	Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln		
[6788]	305	310	315
[6789]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala		
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[6791]	Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro		
[6792]	340	345	350
[6793]	Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr		
[6794]	355	360	365
[6795]	Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser		
[6796]	370	375	380
[6797]	Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr		
[6798]	385	390	395
[6799]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr		
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[6801]	Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe		
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[6803]	Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys		
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[6805]	Ser Leu Ser Leu Ser Pro Gly Lys		
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[6893]	Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
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[7014]				260						265					270	
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[7016]			275						280					285		
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[7030]	385	390	395	400
[7031]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr			
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[7034]		420	425	430
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[7046]	Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys			
[7047]	1	5	10	15
[7048]	Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu			
[7049]		20	25	30
[7050]	Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu			
[7051]		35	40	45
[7052]	Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro			
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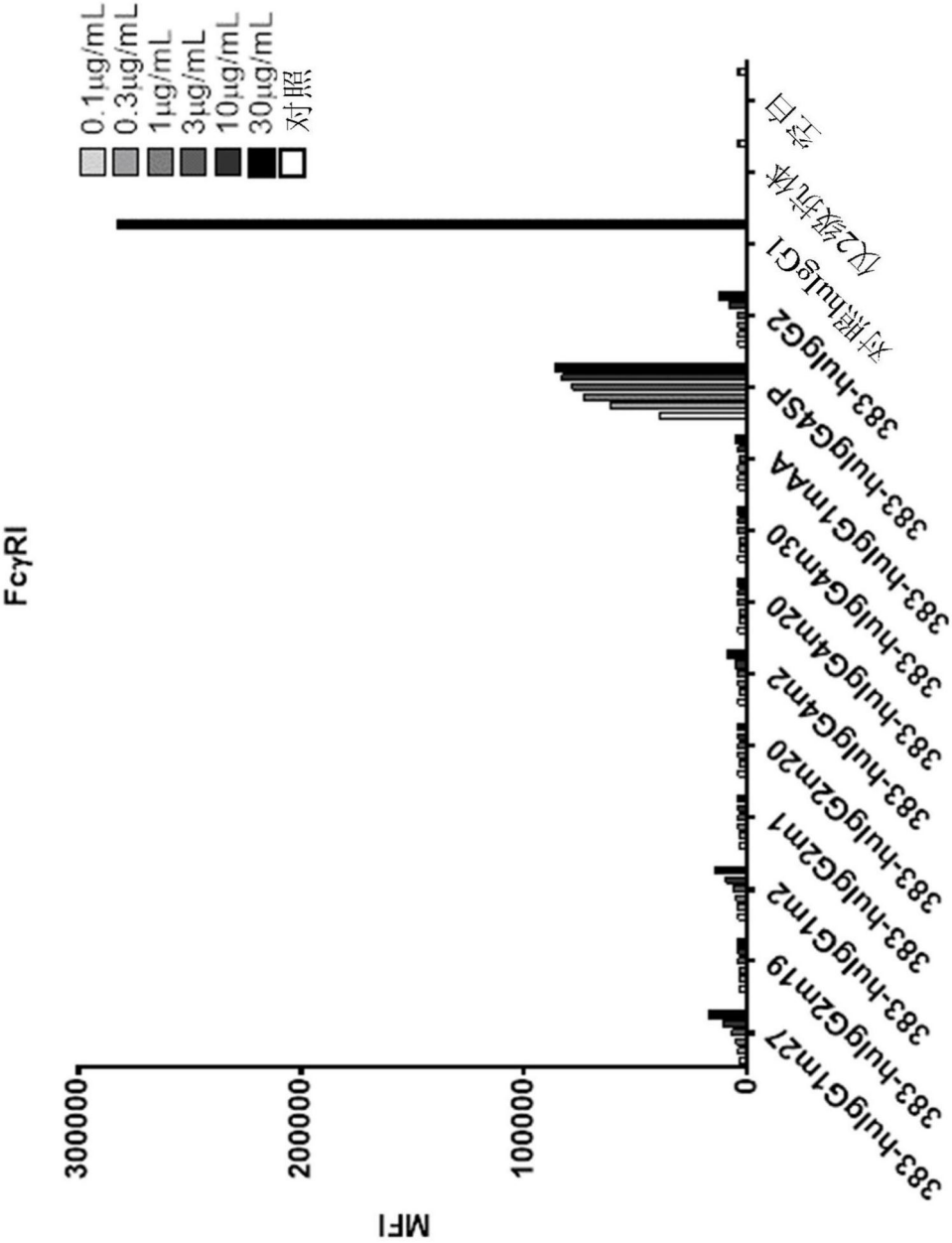


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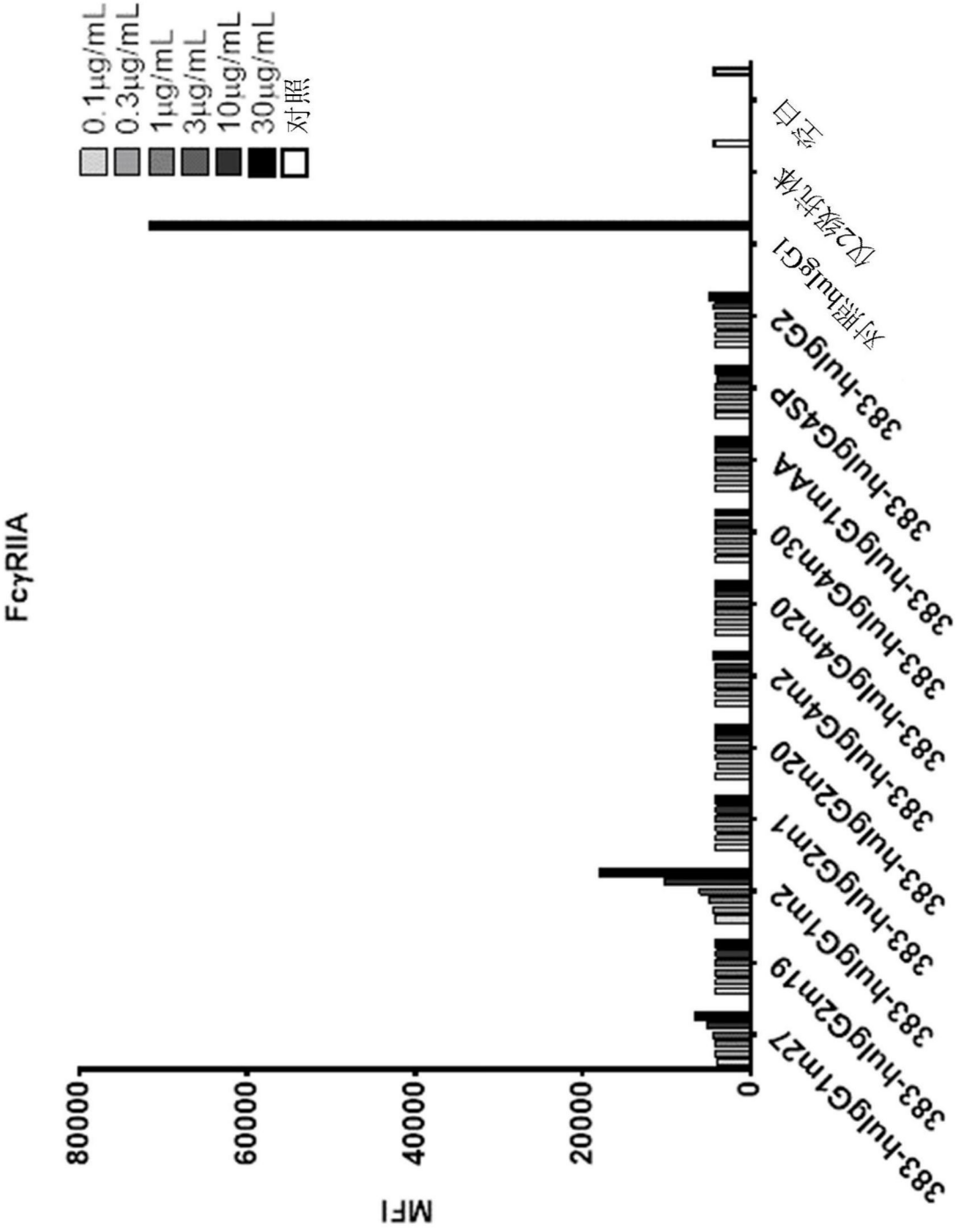


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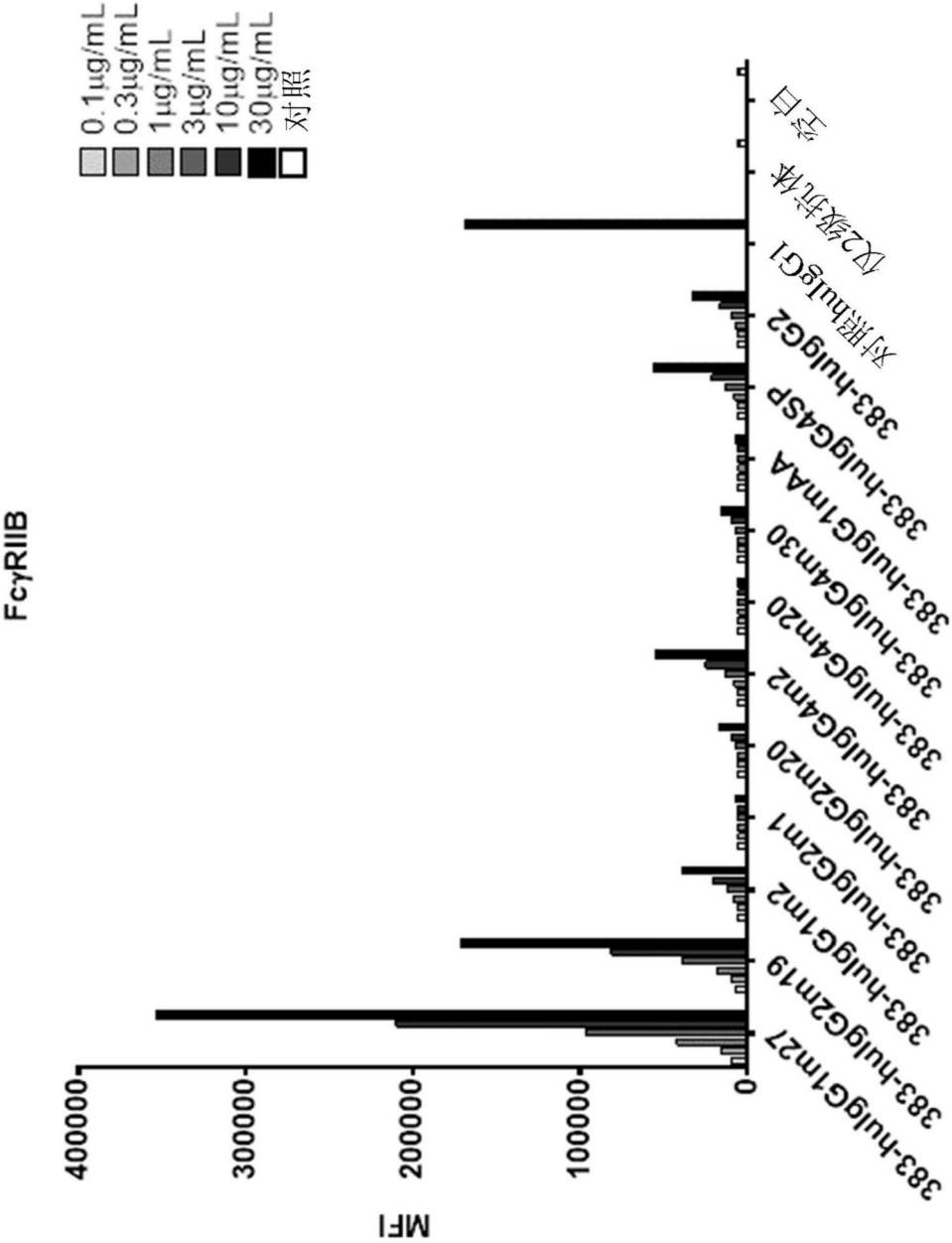


图1C

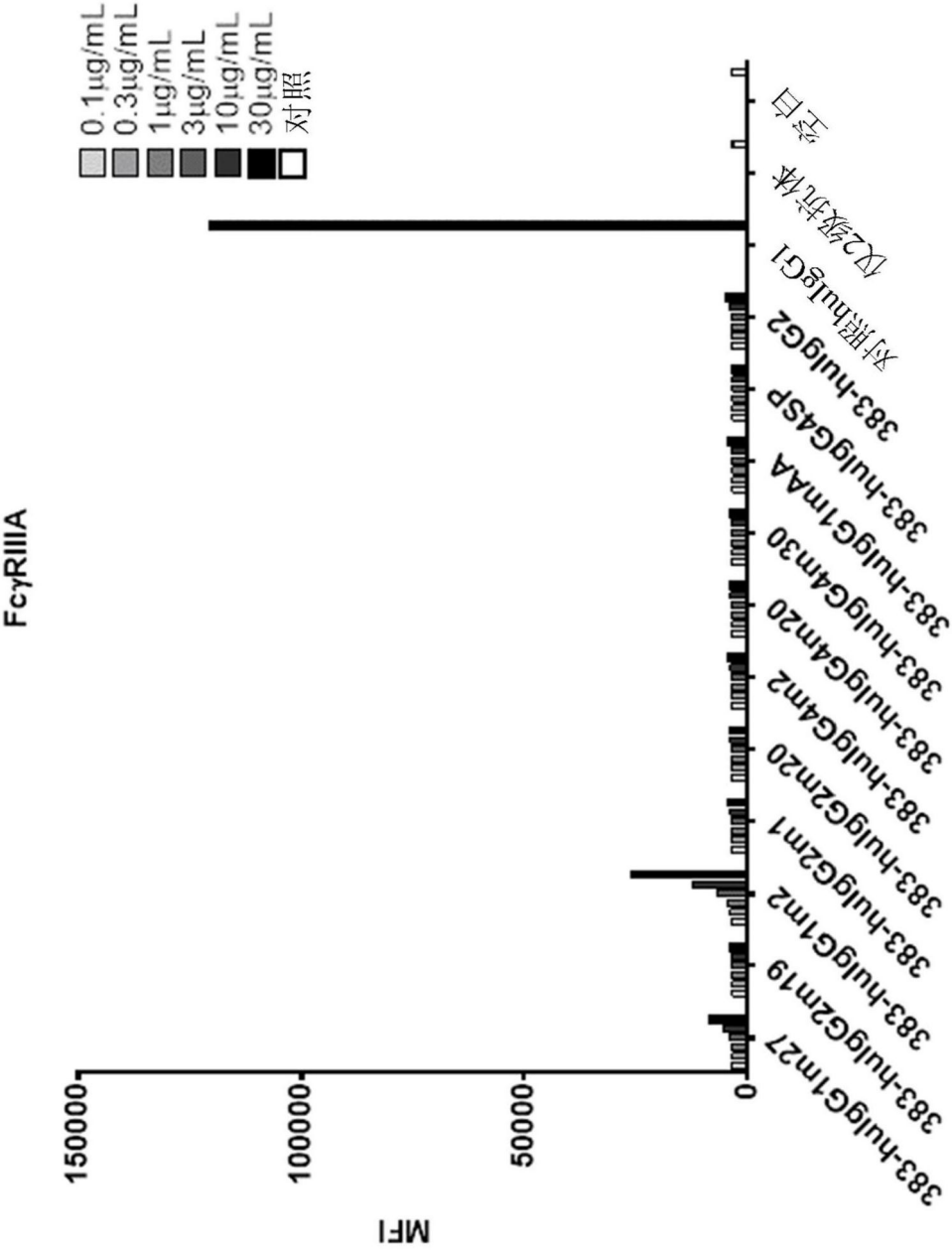


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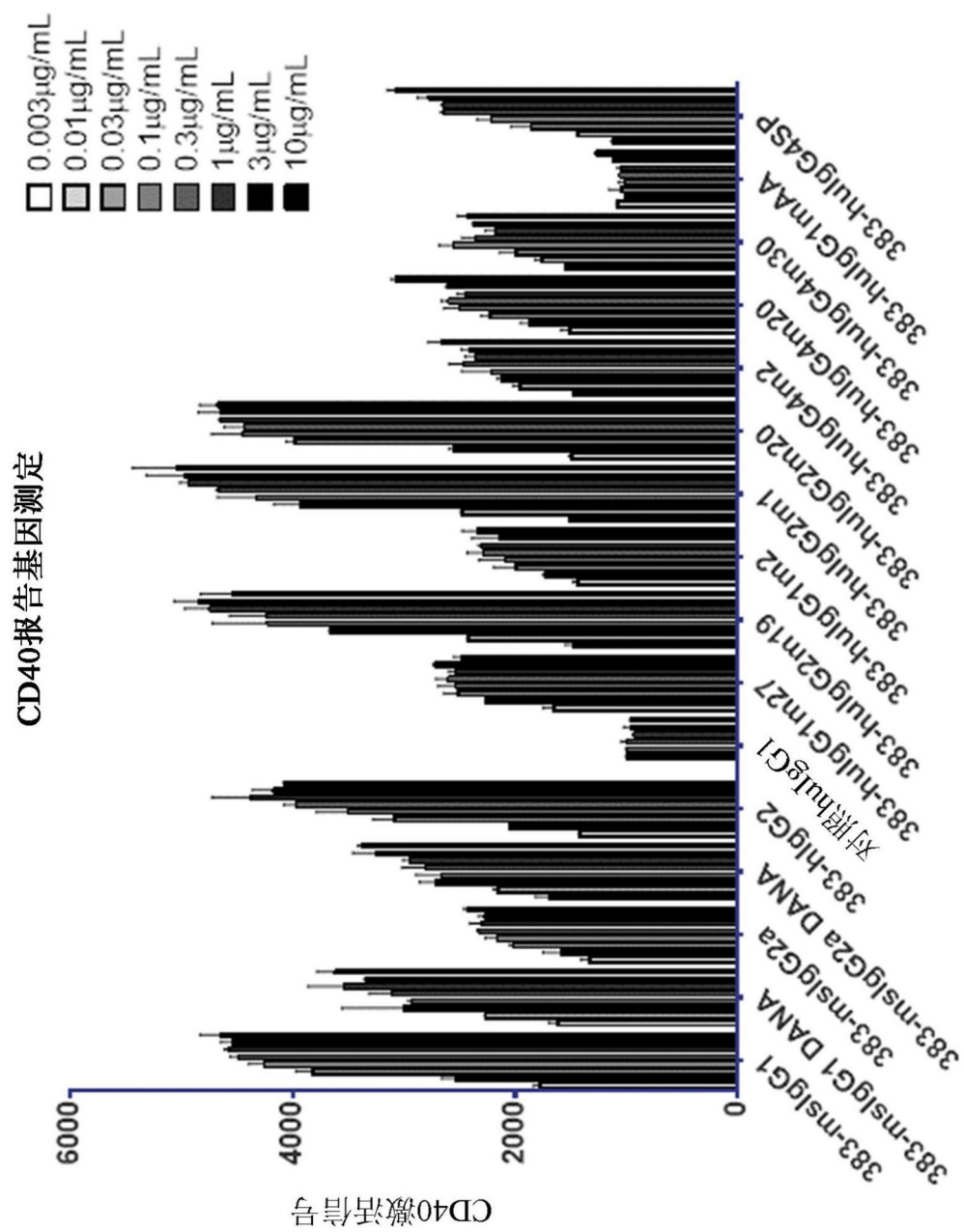


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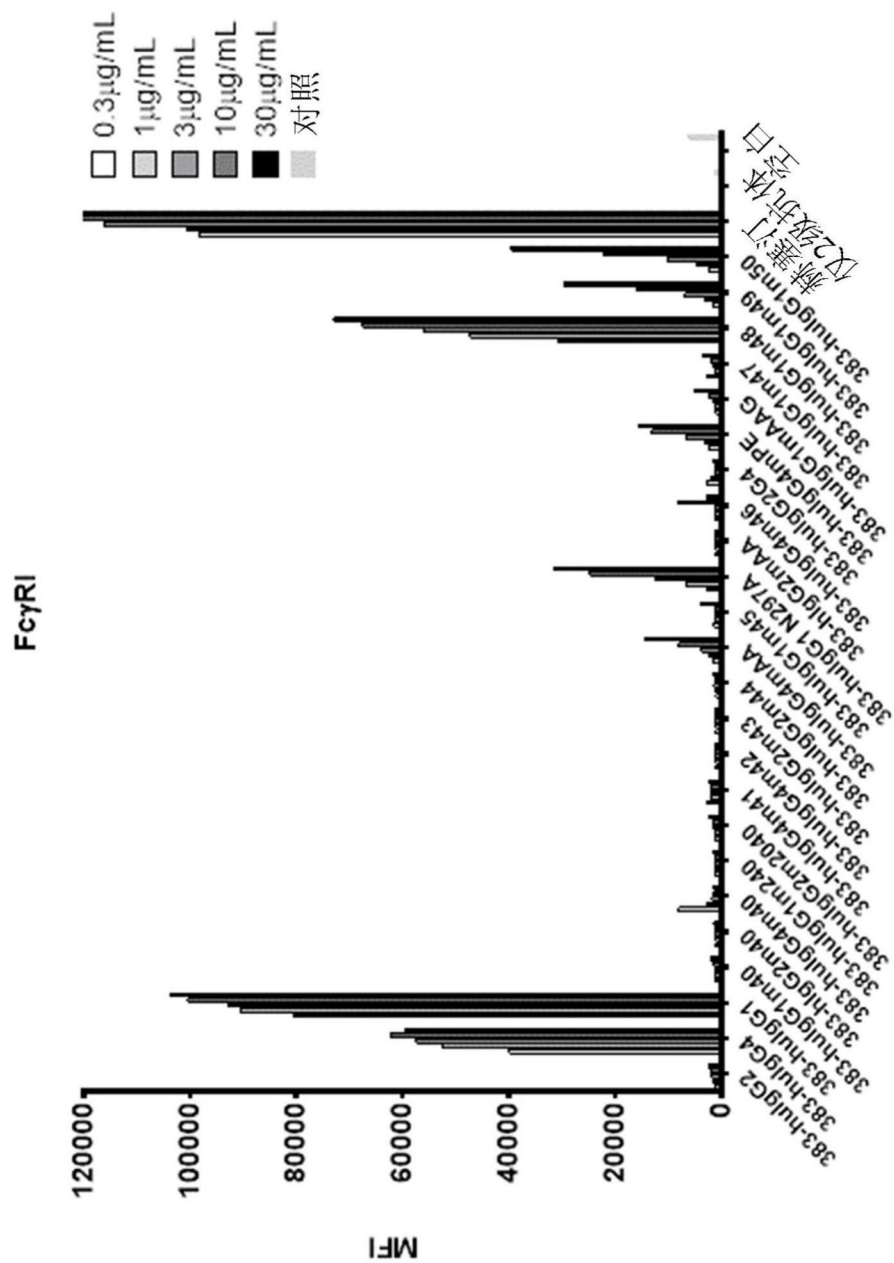


图3A

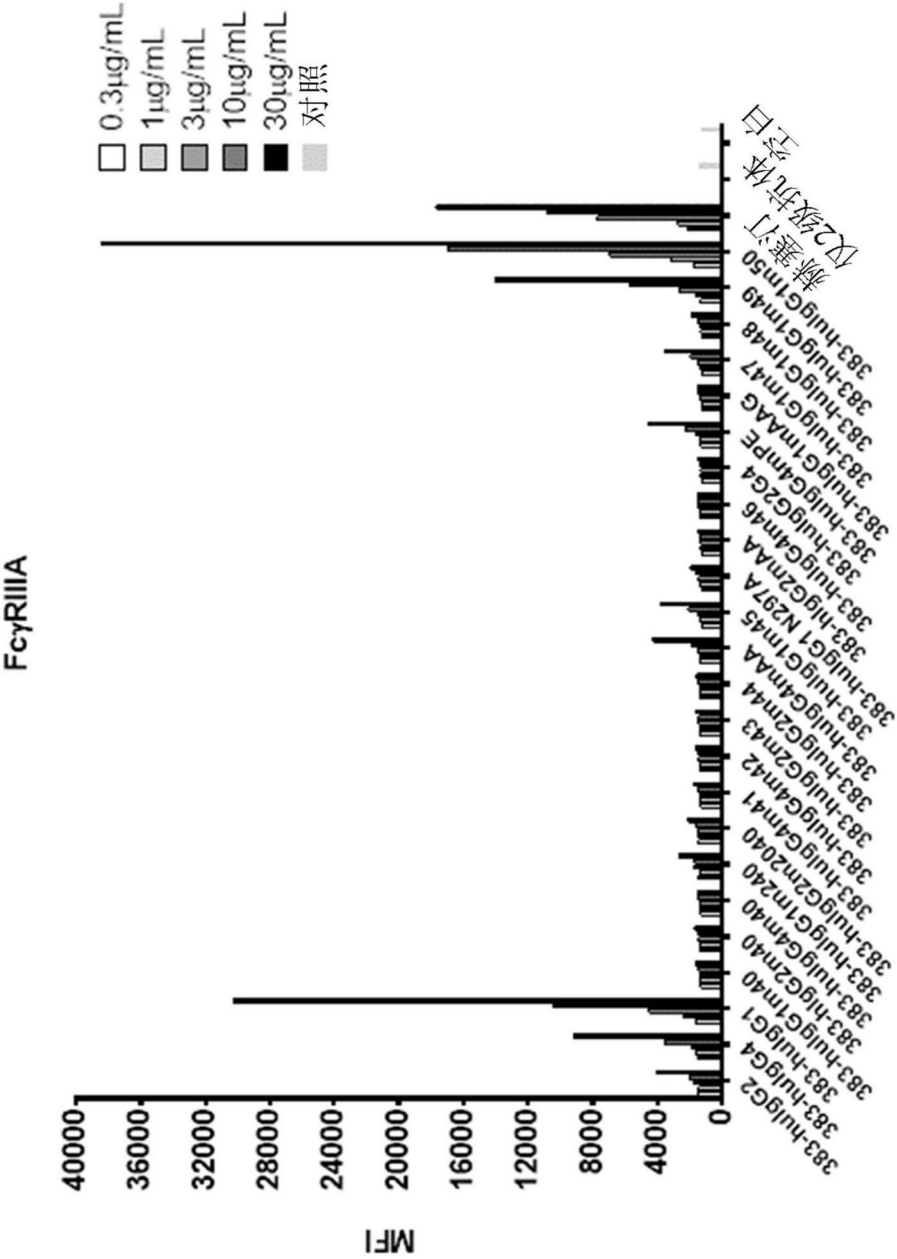


图3D

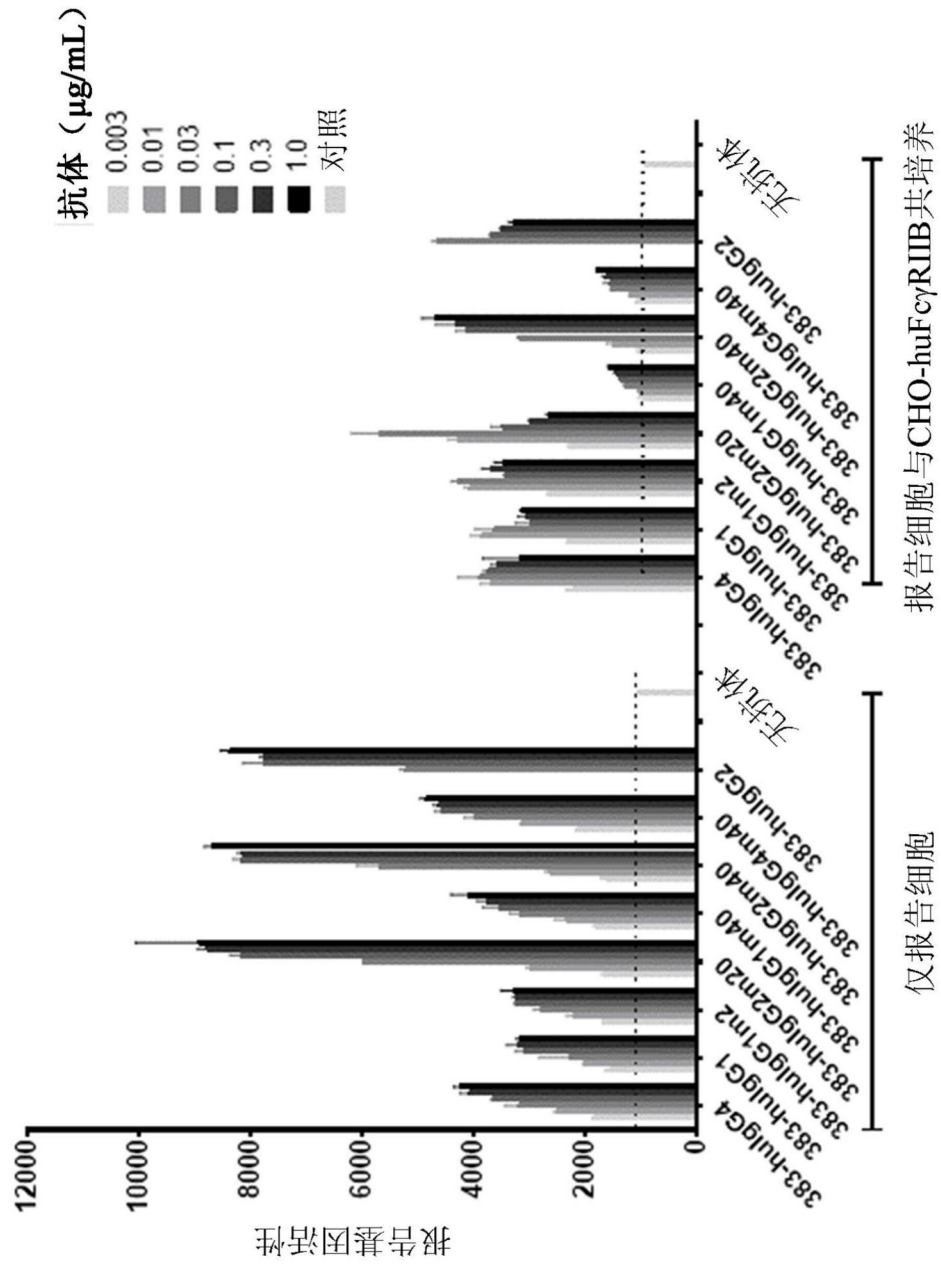


图4A

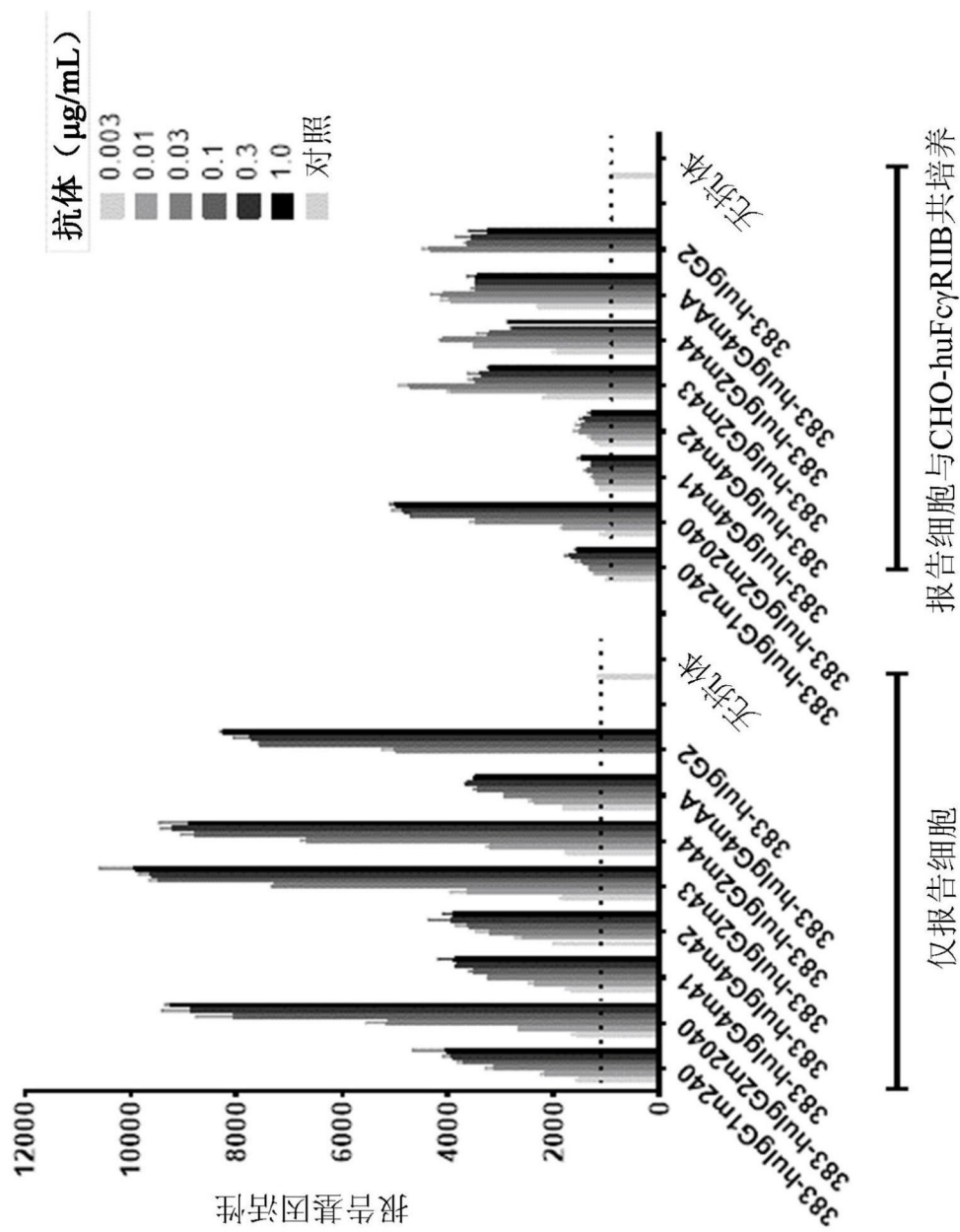


图4B

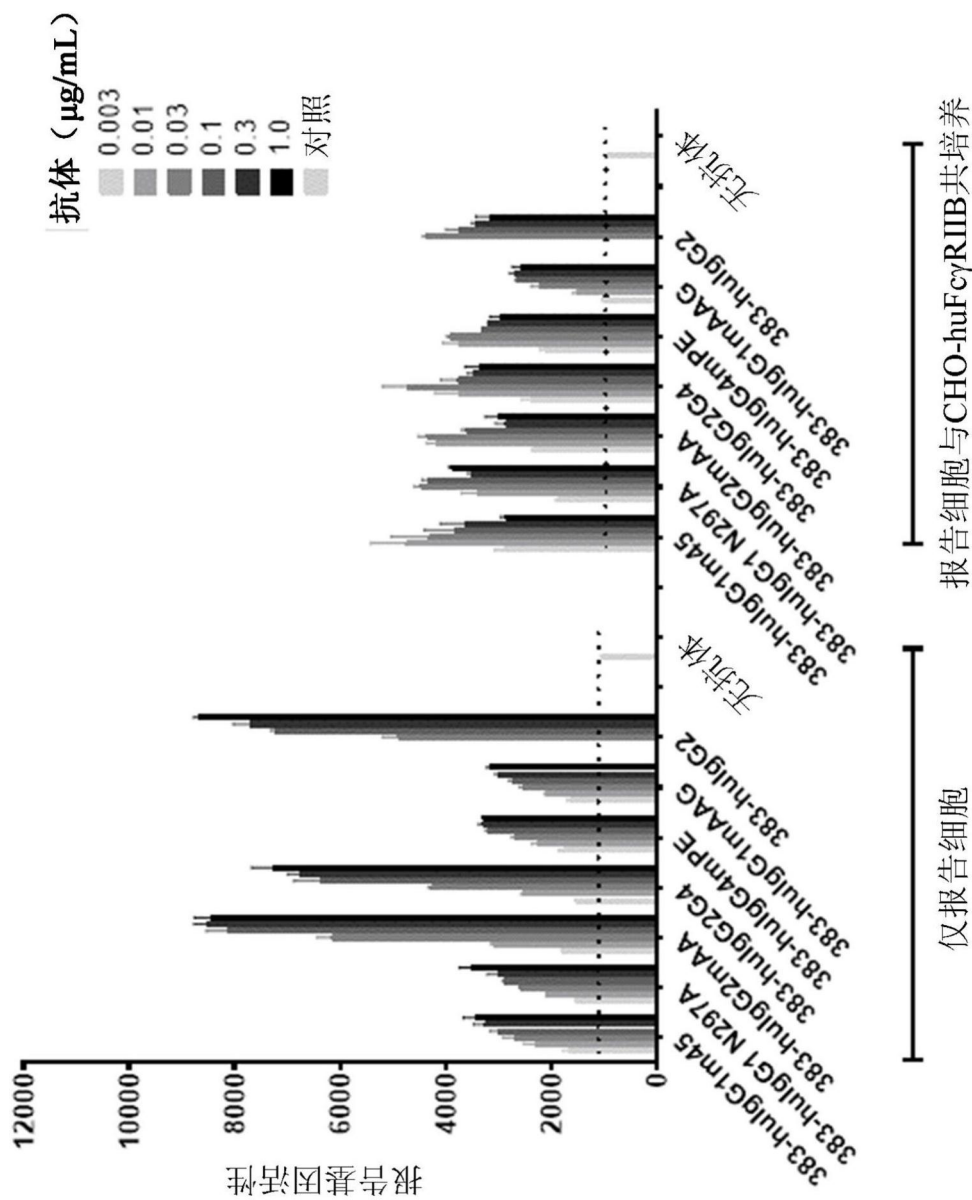


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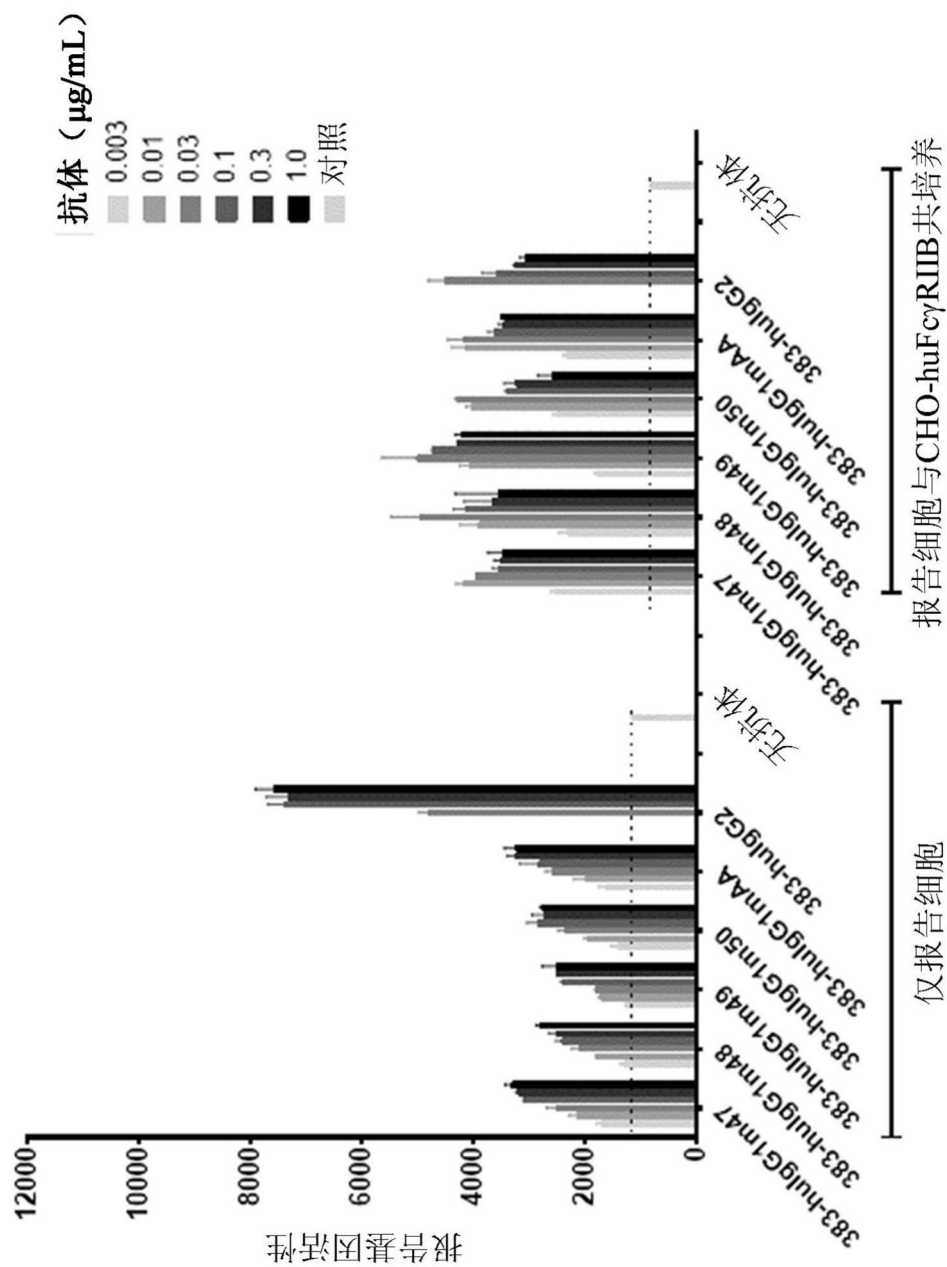


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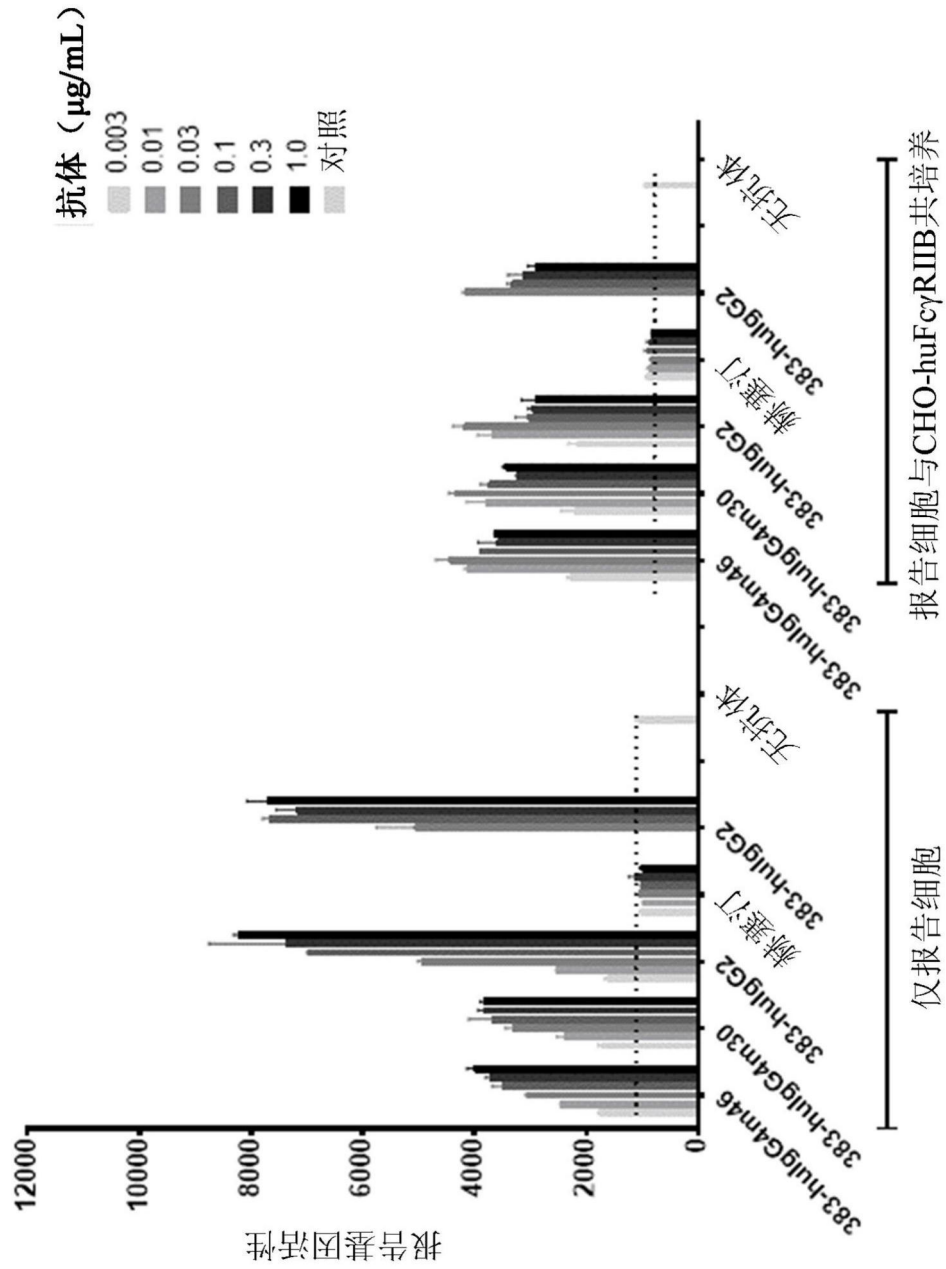


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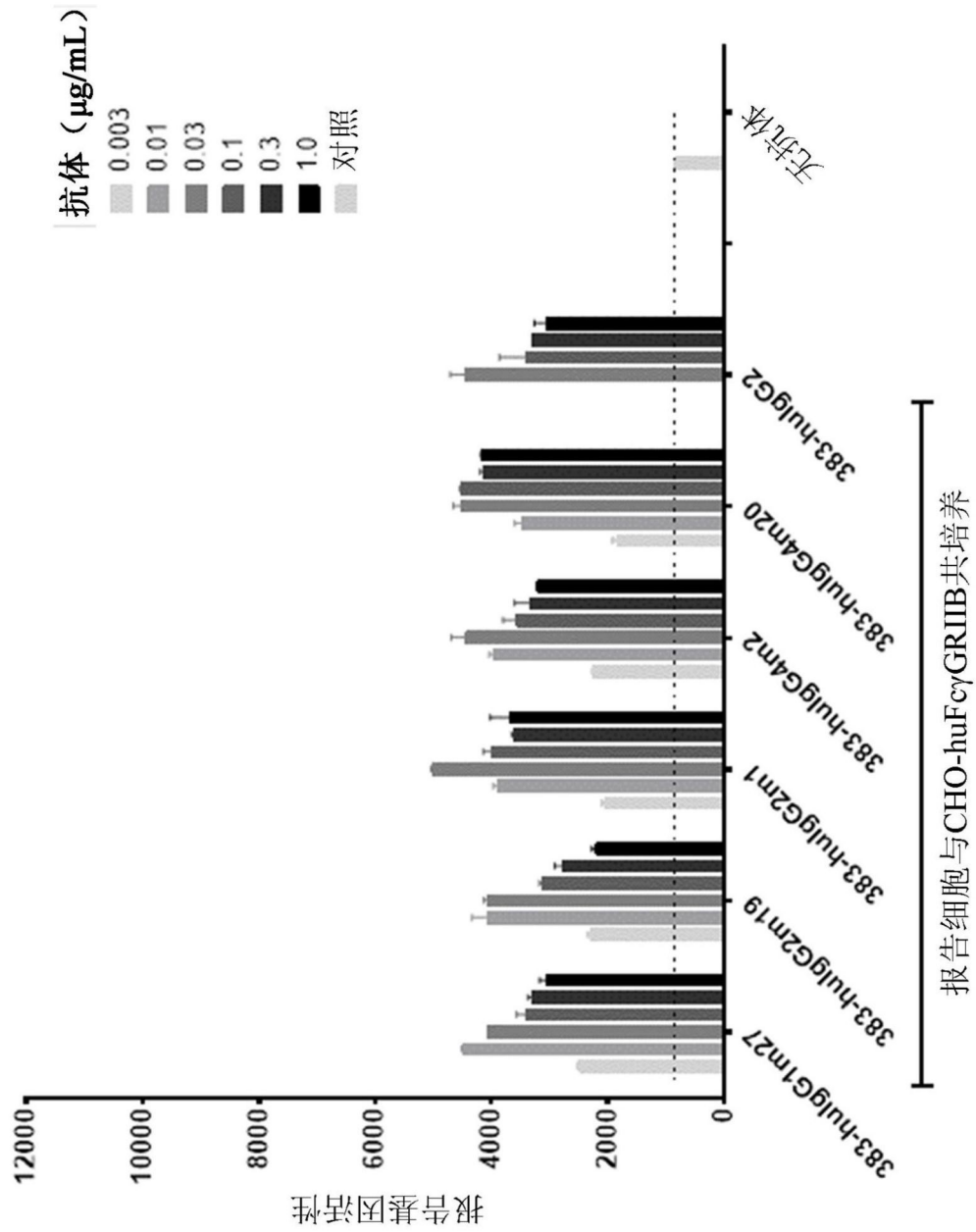


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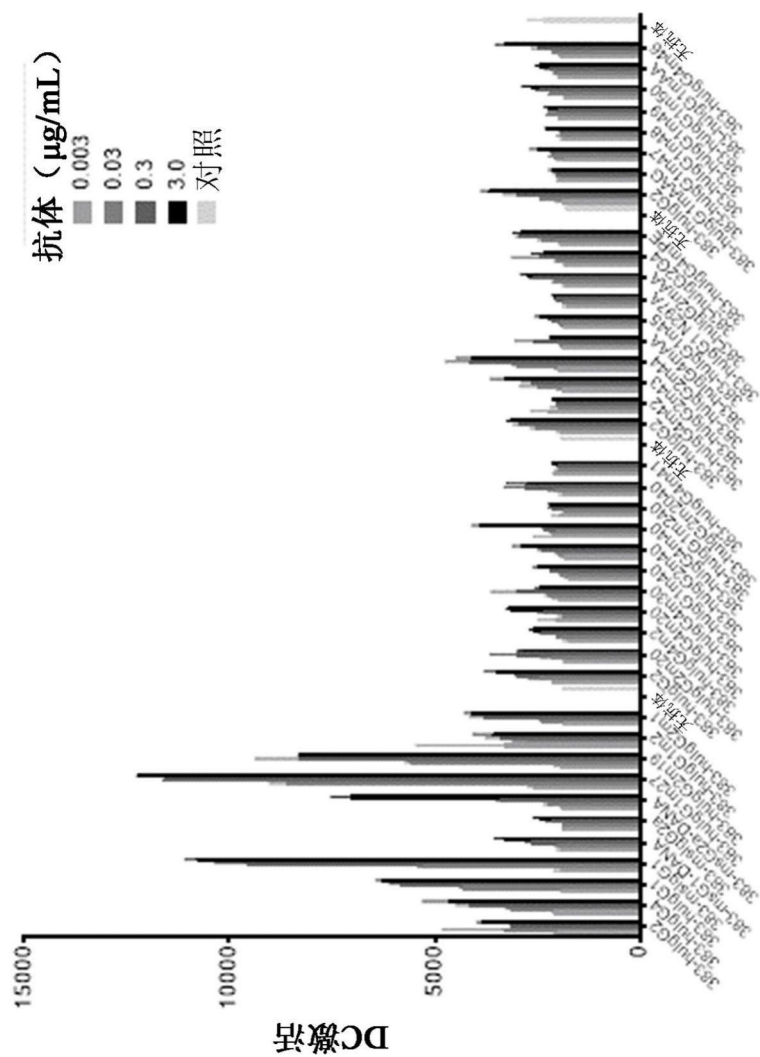


图5A

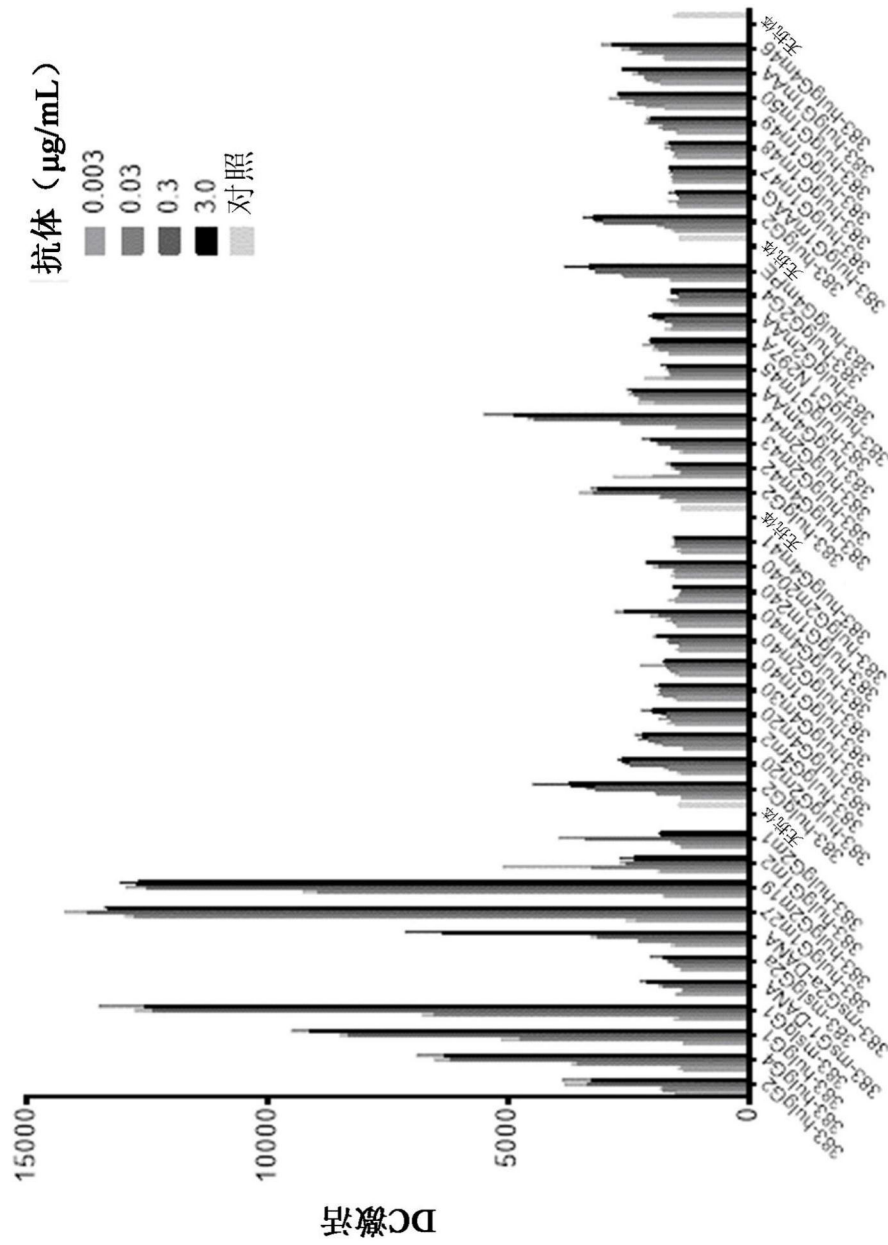


图5B

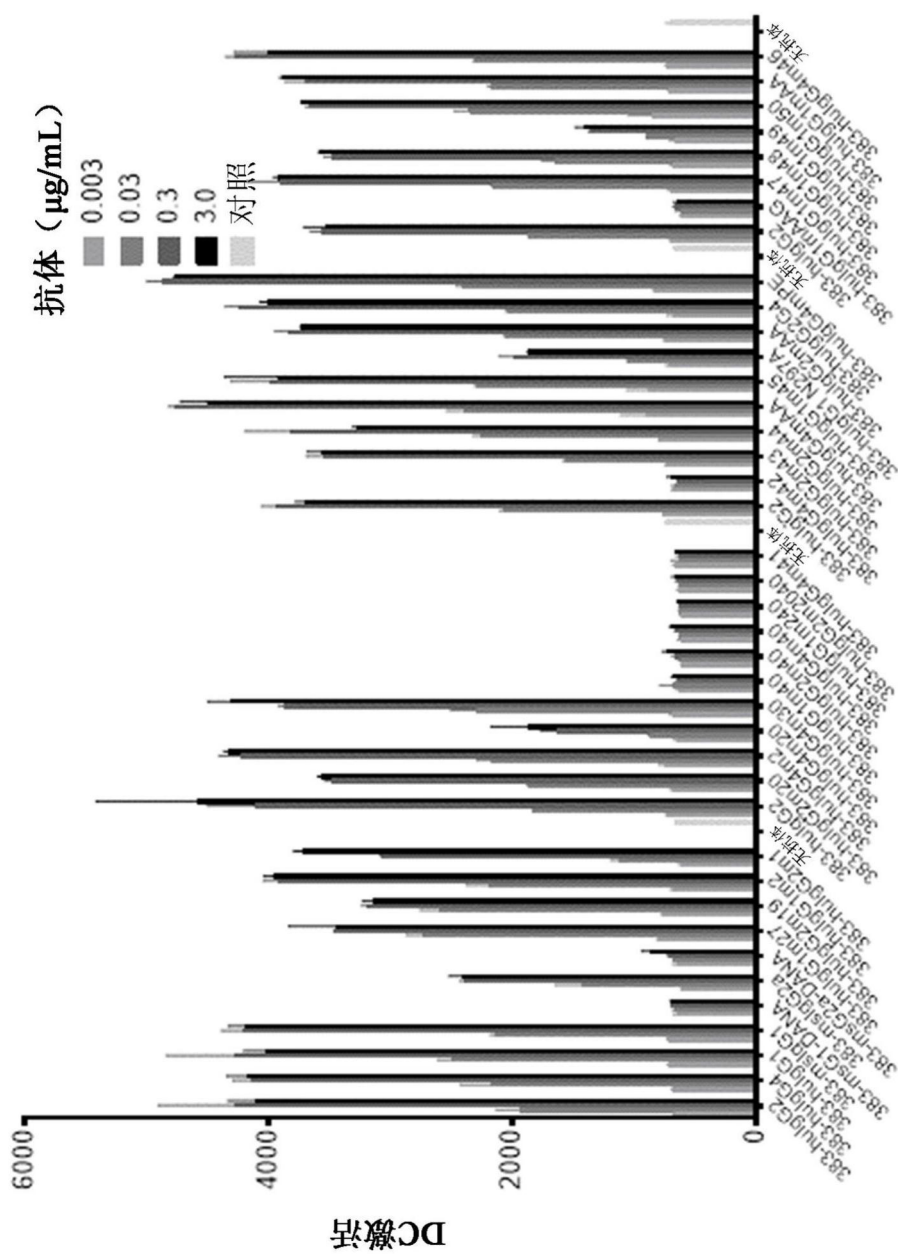


图5C

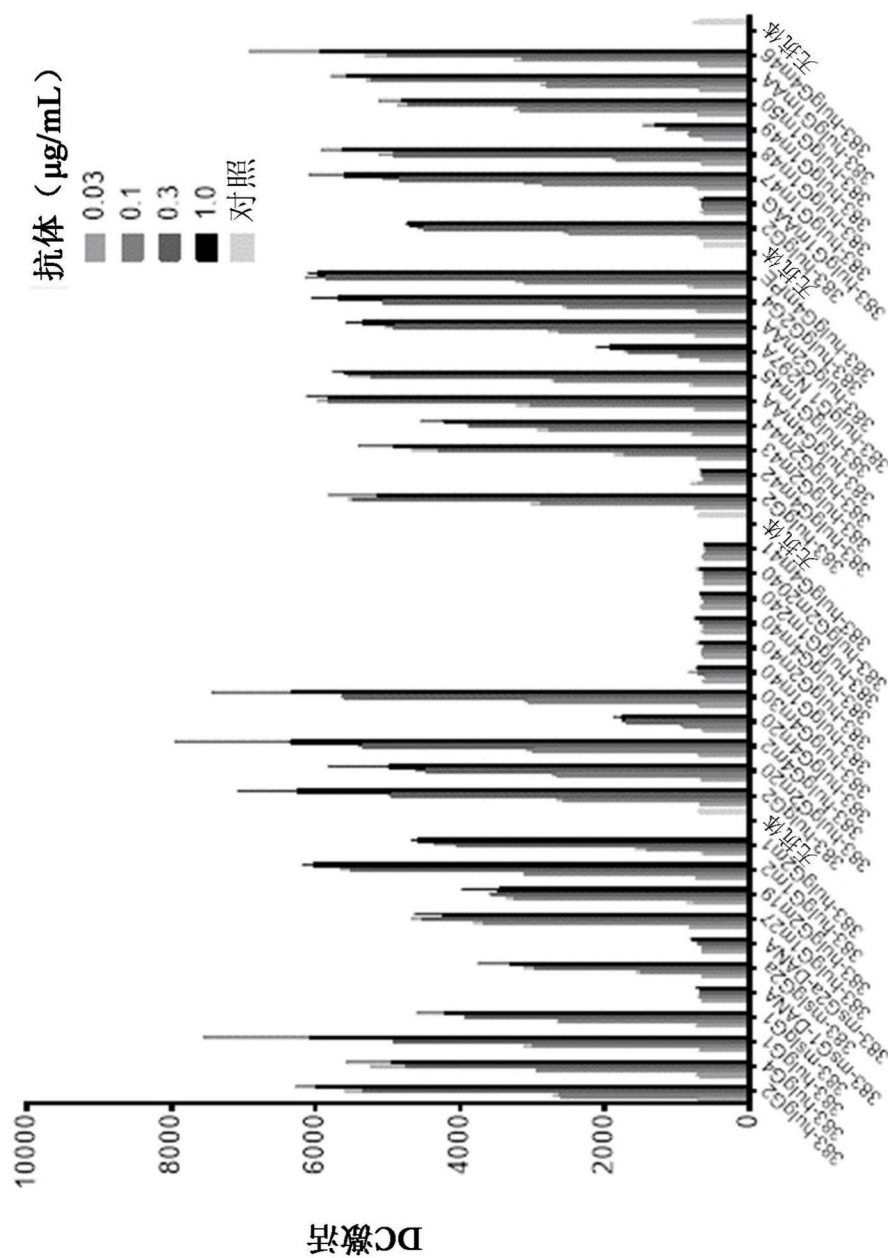


图5D

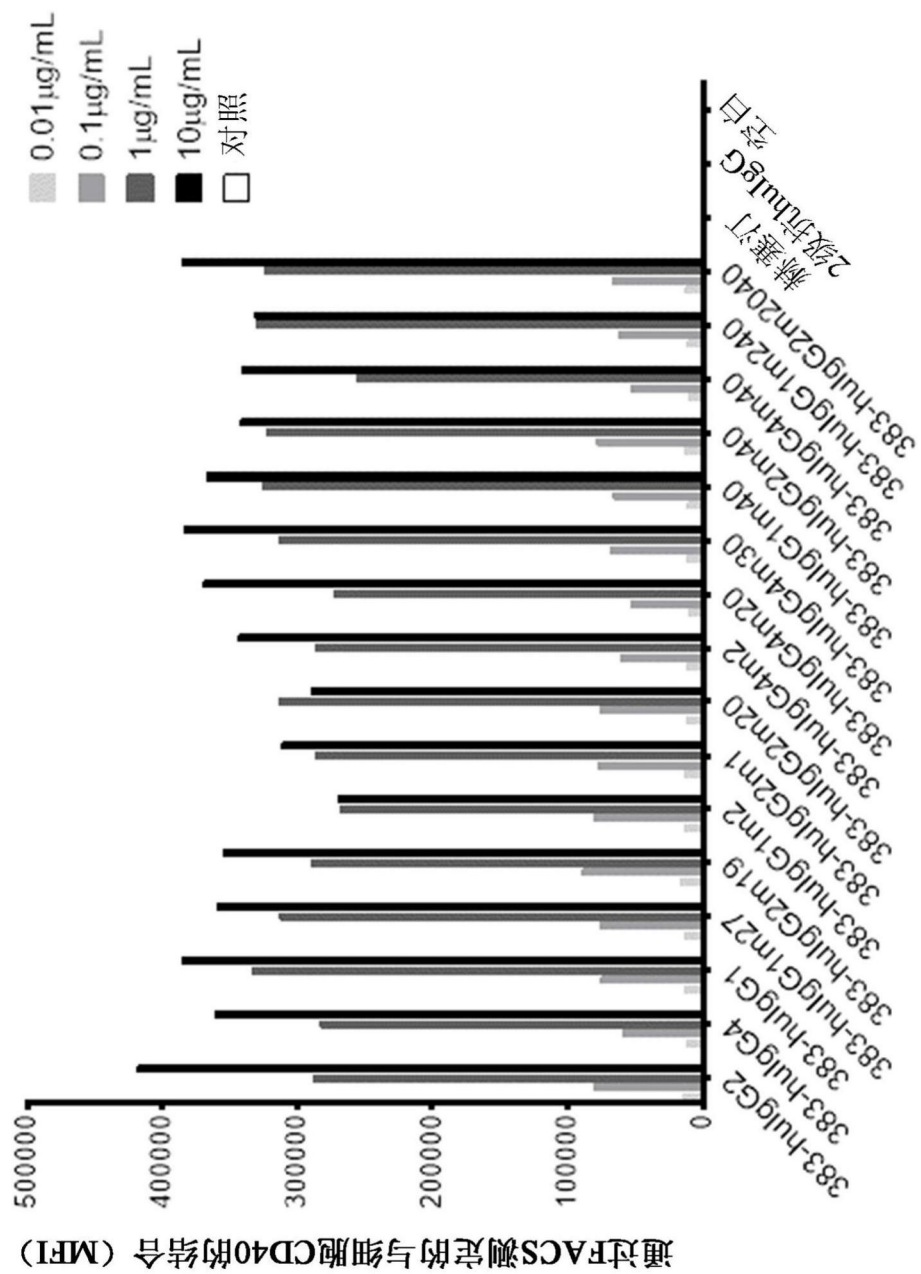


图6A

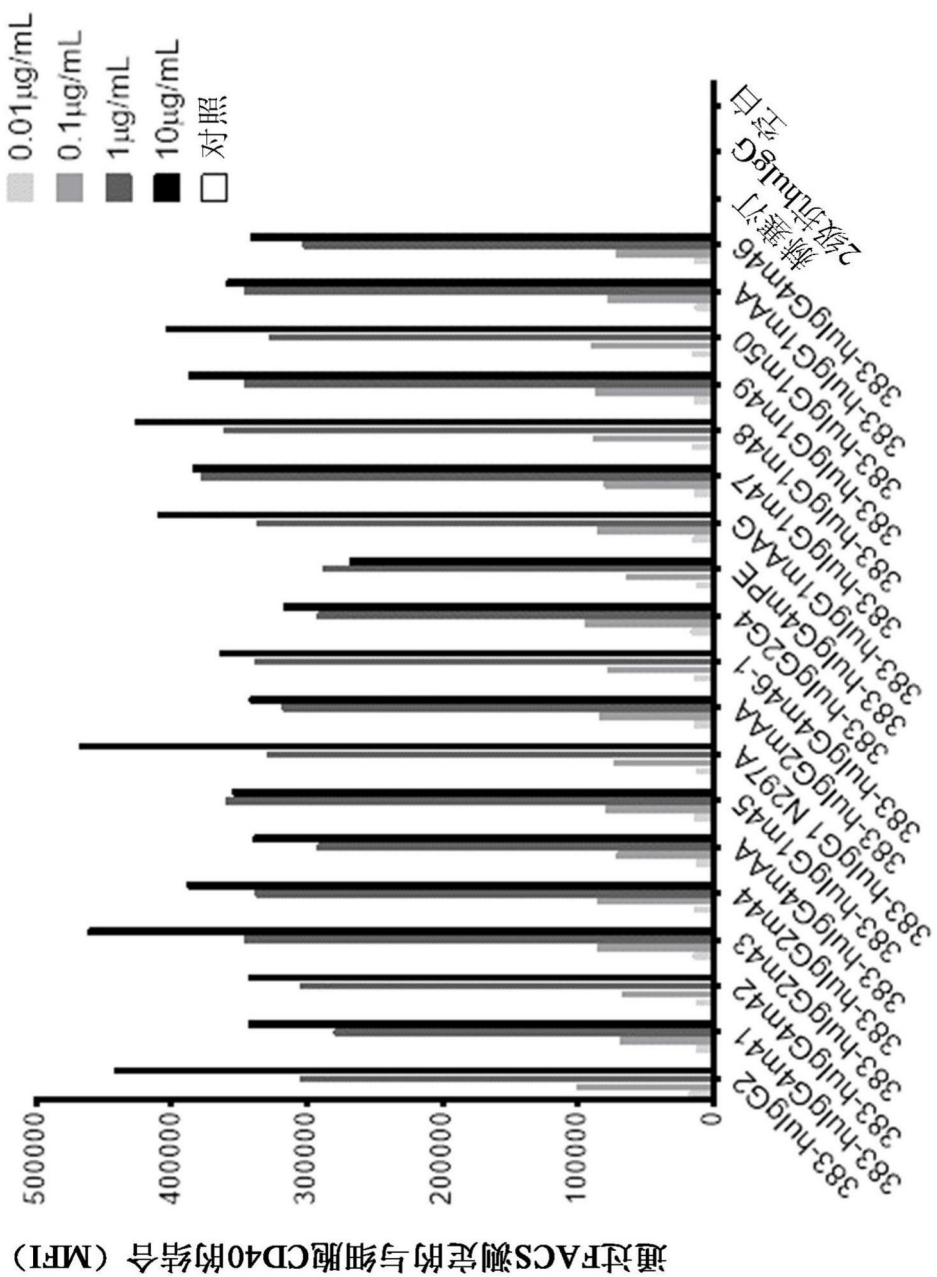


图6B

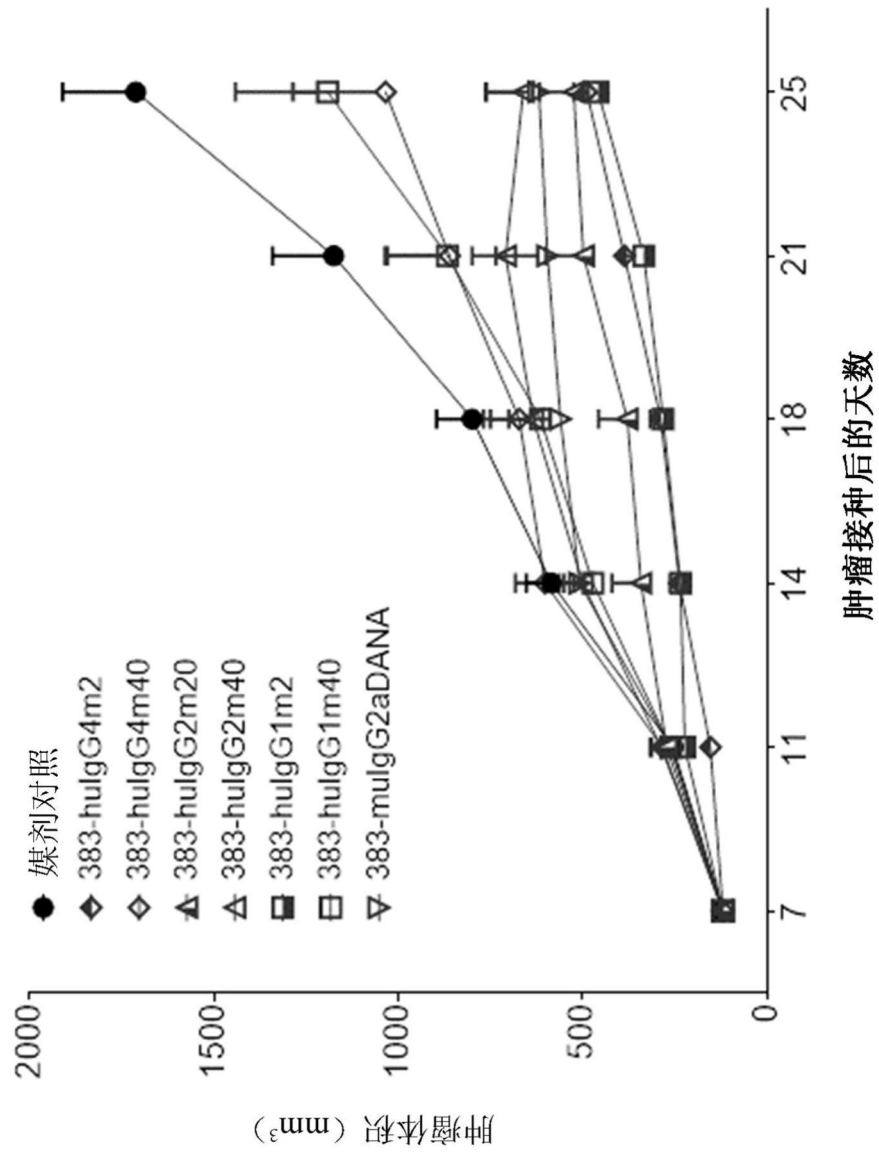


图7A

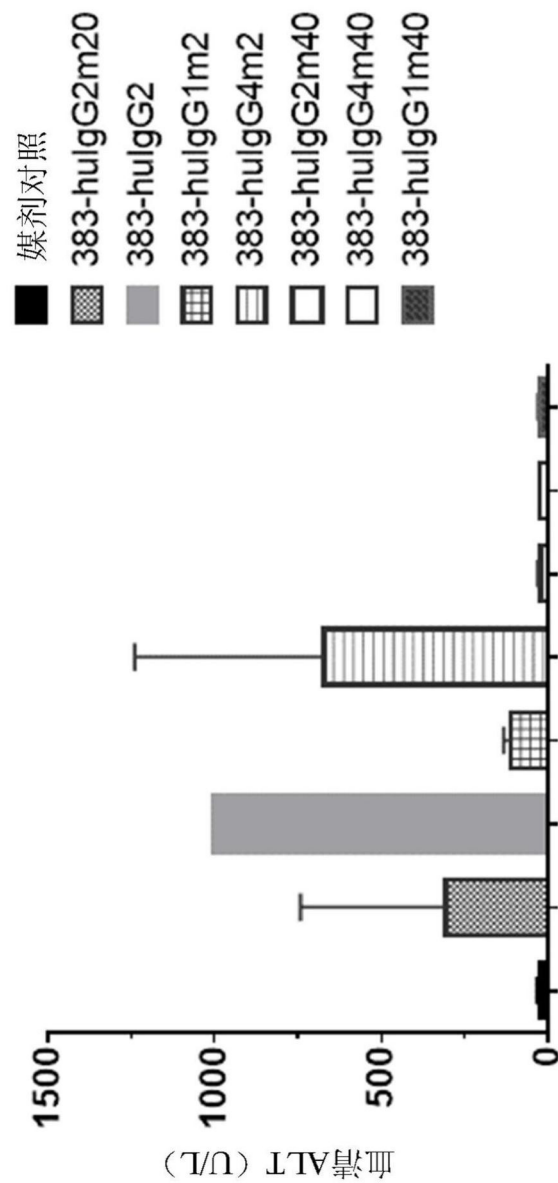


图7B