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(73)专利权人 科优基因公司
地址 美国马萨诸塞州
(72)发明人 李跃升 芮凌云 徐静
(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
专利代理师 李敏春 郑霞
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# 新型白介素-15(IL-15)融合蛋白及其用途

(57)摘要

本公开内容提供了用于治疗癌症和其他紊乱的新型且改进的IL-15融合蛋白。在各种实施方案中,本发明的融合蛋白具有两个功能结构域:IL-15/IL-15Rα Sushi结构域(在本文中也称为“IL-15/IL-15Rα Sushi复合物”)和抗体结构域,每个结构域可以采取不同的形式,并且被配置成使得IL-15融合到抗体结构域的C末端,并且与IL-15Rα Sushi共表达和非共价复合。重要的是,本发明的融合蛋白解决了迄今为止评价的IL-15治疗剂观察到的若干缺陷;具体而言,融合蛋白显示出延长的IL-15在体内的半衰期,并显示出与rIL-15或相关细胞因子治疗剂相比优化的临床前活性。

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1. 一种分离的白介素-15 (IL-15)融合蛋白复合物,包含:(1) IL-15变体多肽,所述IL-15变体多肽通过肽接头共价附接到Fc结构域;和(2) IL-15受体α (“IL-15Rα”)结构域,所述IL-15受体α (“IL-15Rα”)结构域与所述IL-15变体多肽非共价连接以形成Fc-IL-15/IL-15Rα融合蛋白,其中所述IL-15变体多肽由氨基酸残基位置V63、I68或Q108的一个或更多个氨基酸残基被另一氨基酸取代的SEQ ID NO: 2的氨基酸序列组成,其中所述氨基酸取代选自由以下组成的组:取代V63A、V63K、V63R、I68Q、I68G、I68H、Q108E和Q108K,或这些取代的任何组合,并且

其中所述IL-15Rα结构域是IL-15受体αSushi (“IL-15RαSushi”)结构域,所述IL-15受体αSushi (“IL-15RαSushi”)结构域由SEQ ID NO: 5中列出的氨基酸序列组成。

2. 根据权利要求1所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽连接到所述Fc结构域的C末端。

3. 根据权利要求1所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽连接到所述Fc结构域的N末端。

4. 根据权利要求1至3中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述Fc结构域是具有选自由以下所列的氨基酸序列组成的组的氨基酸序列的Fc结构域:SEQ ID NO:6、SEQ ID NO:7和SEQ ID NO:8,并且其中每个IL-15多肽通过肽接头共价附接到Fc结构域。

5. 根据权利要求1-3中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽包含在SEQ ID NO:2的氨基酸残基位置V63和I68处的两个氨基酸取代。

6. 根据权利要求4所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽包含在SEQ ID NO:2的氨基酸残基位置V63和I68处的两个氨基酸取代。

7. 根据权利要求1-3和6中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽选自具有SEQ ID NO: 72-81所列的氨基酸序列的多肽的组。

8. 根据权利要求4所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽选自具有SEQ ID NO: 72-81所列的氨基酸序列的多肽的组。

9. 根据权利要求5所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽选自具有SEQ ID NO: 72-81所列的氨基酸序列的多肽的组。

10. 根据权利要求1-3、6和8-9中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单体形式。

11. 根据权利要求4所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单体形式。

12. 根据权利要求5所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单体形式。

13. 根据权利要求7所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单体形式。

14. 一种分离的白介素-15 (IL-15)融合蛋白复合物,包含:(1) IL-15变体多肽,所述IL-15变体多肽通过肽接头共价附接到抗体(Ab)或抗体片段;和(2) IL-15受体α (“IL-15Rα”)结构域,所述IL-15受体α (“IL-15Rα”)结构域与所述IL-15变体多肽非共价连接以形成

Ab-IL-15/IL-15Rα融合蛋白复合物,

其中所述IL-15变体多肽与抗体的C末端连接,或

其中所述IL-15变体多肽与抗体的N末端连接;且

其中所述IL-15变体多肽由氨基酸残基位置V63、I68或Q108的一个或更多个氨基酸残基被另一氨基酸取代的SEQ ID NO: 2的氨基酸序列组成,其中所述氨基酸取代选自由以下组成的组:取代V63A、V63K、V63R、I68Q、I68G、I68H、Q108E和Q108K,或这些取代的任何组合,并且

其中所述抗体是拮抗性程序性死亡-1 (PD-1)抗体或抗体片段,并且

其中所述IL-15Rα结构域是IL-15受体αSushi (“IL-15RαSushi”)结构域,所述IL-15受体αSushi (“IL-15RαSushi”)结构域由SEQ ID NO: 5中列出的氨基酸序列组成。

15. 根据权利要求14所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述抗体是拮抗性PD-1抗体,所述拮抗性PD-1抗体由以下组成:SEQ ID NO:111和SEQ ID NO:112中所列的重链和轻链氨基酸序列;SEQ ID NO:113和SEQ ID NO:114中所列的重链和轻链氨基酸序列;SEQ ID NO:115和SEQ ID NO:116中所列的重链和轻链氨基酸序列;SEQ ID NO:117和SEQ ID NO:118中所列的重链和轻链氨基酸序列;以及SEQ ID NO:119和SEQ ID NO:120中所列的重链和轻链氨基酸序列。

16. 根据权利要求14至15中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽包含在SEQ ID NO:2的氨基酸残基位置V63和I68处的两个氨基酸取代。

17. 根据权利要求14至15中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽选自具有SEQ ID NO: 72-81所列的氨基酸序列的多肽的组。

18. 根据权利要求16所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述IL-15变体多肽选自具有SEQ ID NO: 72-81所列的氨基酸序列的多肽的组。

19. 根据权利要求14和18中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中融合蛋白复合物包含SEQ ID NO: 79、SEQ ID NO: 114、SEQ ID NO: 141和SEQ ID NO: 5。

20. 根据权利要求17所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中融合蛋白复合物包含SEQ ID NO: 79、SEQ ID NO: 114、SEQ ID NO: 141和SEQ ID NO: 5。

21. 根据权利要求14-15、18和20中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单聚体形式。

22. 根据权利要求16所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单聚体形式。

23. 根据权利要求17所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单聚体形式。

24. 根据权利要求19所述的分离的白介素-15 (IL-15)融合蛋白复合物,其中所述复合物是二聚体或单聚体形式。

25. 一种药物组合物,所述药物组合物包含与药学上可接受的载体混合的根据权利要求1至24中任一项所述的分离的白介素-15 (IL-15)融合蛋白复合物。

26.根据权利要求25所述的药物组合物在制备用于治疗受试者的癌症或癌症转移的药

物中的用途,其中所述癌症是结肠直肠癌。

27.根据权利要求26中任一项所述的用途,其中所述药物在使用时,还包括提供能够治疗癌症或癌症转移的第二疗法,提供对肿瘤细胞的增强的效应细胞杀伤。

# 新型白介素-15(IL-15)融合蛋白及其用途

[0001] 背景

[0002] 虽然癌症传统上通过化学疗法、放射疗法、靶向疗法和手术进行治疗,但癌症治疗的第五支柱免疫疗法在过去10年中出现,并彻底改变了对癌症的战争。免疫治疗药物的基准(benchmark)由T细胞检查点(CTLA-4和PD-1/PD-L1)抑制剂的开发建立。已经展示出,这些疗法有效地扩大和重新活化肿瘤特异性T细胞的库(pool),导致患有某些癌症的患者的高达50%的客观响应率。

[0003] 最近,细胞因子的四α-螺旋束家族的成员白介素-15(IL-15)已经成为用于治疗癌症的候选免疫调节剂。IL-15与其特异性受体IL-15Rα结合,IL-15Rα在抗原呈递树突细胞、单核细胞和巨噬细胞上表达,并反式活化响应细胞(包括T细胞和自然杀伤(NK)细胞)上的由IL-15Rβ和共有细胞因子受体γ链(γ$_c$)组成的异源二聚体受体复合物,以启动信号传导。IL-15显示出广泛的活性,并诱导T细胞、B细胞和自然杀伤(NK)细胞的分化和增殖。IL-15还增强$CD8^+$T细胞的溶细胞活性,并诱导持久的经历抗原的(antigen-experienced)$CD8^+$ $CD44^{hi}$记忆T细胞。IL-15刺激B细胞分化和免疫球蛋白合成,并诱导树突细胞成熟。IL-15不刺激免疫抑制性的调节性T细胞(Treg)。因此,假设提高IL-15活性可以增强固有免疫和适应性免疫并对抗肿瘤,使IL-15成为用于抗癌疗法的有前途的剂(Steel等人,Trends in Pharmacological Sciences,33(1):35-41,2012)。

[0004] 在对转移性恶性黑素瘤患者静脉内输注重组人类IL-15的首次人类I期临床试验中,据报道,IL-15可以安全地施用至转移性恶性肿瘤患者,并且IL-15的施用显著改变了血液中淋巴细胞亚群的体内稳态,NK细胞和γδ细胞受影响最大,其次是CD8记忆T细胞(Conlon等人,J Clin Oncol.,33(1),74-82)。

[0005] 尽管使用IL-15作为癌症免疫治疗剂来增强免疫应答取得了这些新进展,但IL-15作为治疗剂的有效使用仍然存在缺陷。例如,IL-15具有短的半衰期(<40分钟),导致1)生物可利用度低,妨碍其体内抗肿瘤作用,和2)需要施用高剂量以实现有治疗意义的暴露(therapeutic relevant exposure),这导致毒性。此外,据了解,IL-15在标准哺乳动物细胞系统中的表达水平差。

[0006] 对于提供高度有效且安全的用于治疗癌症的新型治疗剂仍存在迫切需求。

[0007] 发明的公开内容

[0008] 在一方面,本发明提供了用于治疗癌症的新型且改进的IL-15融合蛋白。在各种实施方案中,本发明的融合蛋白具有两个功能结构域:IL-15/IL-15受体α(IL-15Rα)组分(本文中也称为"IL-15/IL-15Rα复合物")和异源蛋白,其中每一个可以采取不同的形式。在各种实施方案中,融合蛋白被配置成使得IL-15融合到异源蛋白的C末端或异源蛋白的N末端,并且与IL-15Rα结构域共表达和非共价复合(参见图1B和图1C,其中异源蛋白是Fc结构域,以及图30A和图30B,其中异源蛋白是抗体)。

[0009] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,其中IL-15结构域包含如SEQ ID NO:2中列出的成熟的人类IL-15多肽(本文中也称为huIL-15或IL-15野生型(wt))的序列。在各种实施方案中,IL-15结构域将是IL-15变体(或突变体),该IL-

15变体(或突变体)包含源自如SEQ ID NO:2中列出的成熟的人类IL-15多肽序列的序列。本文使用天然氨基酸、天然氨基酸在成熟序列中的位置和变异氨基酸来指代IL-15的变体(或突变体)。例如,huIL-15“S58D”是指包含在SEQ ID NO:2的位置58处的S至D取代的人类IL-15。在各种实施方案中,IL-15变体作为IL-15超级激动剂(super-agonist)发挥作用,如通过例如,与天然IL-15多肽相比,对IL-15Rβ的结合活性增加和功能活性增加展示的。在各种实施方案中,IL-15变体作为IL-15拮抗剂发挥作用,如通过例如,与天然IL-15多肽相比,对IL-15Rβ有结合活性但功能活性降低或无功能活性展示的。在各种实施方案中,与天然IL-15多肽相比,IL-15变体对IL-15Rβγc受体的结合亲和力增加或结合活性降低。在各种实施方案中,与天然IL-15序列相比,IL-15变体的序列具有至少一个(即,1个、2个、3个、4个、5个、6个、7个、8个、9个、10个或更多个)氨基酸变化。氨基酸变化可以包括与IL-15Rβ和/或IL-15RγC相互作用的IL-15的结构域中的一个或更多个氨基酸取代、缺失或插入。在各种实施方案中,氨基酸变化是SEQ ID NO:2的位置30、31、32、58、62、63、67、68或108处的一个或更多个氨基酸取代。在各种实施方案中,氨基酸变化是成熟的人类IL-15序列的位置30处的D至T取代、位置31处的V至Y取代、位置32处的H至E取代、位置58处的S至D或H或R或Q或I或P取代、位置62处的T至D取代、位置63处的V至F或A或R或K取代、位置67处的I至V取代、位置68处的I至F或H或D或K或Q或G取代、或位置108处的Q至A或M或S或E或K取代,或这些取代的任何组合。在各种实施方案中,IL-15变体在SEQ ID NO:2的N末端处包含1个、或2个、或3个、或4个、5个或6个氨基酸缺失。在各种实施方案中,IL-15变体在SEQ ID NO:2的C末端处包含1个、或2个、或3个、或4个、或5个、或6个、或7个、或8个、或9个或10个氨基酸缺失。在各种实施方案中,IL-2变体包含SEQ ID NO:2的位置N95后的‘GS’(SEQ ID NO:12)、或‘GGSGG’(SEQ ID NO:153)或‘GSSGGSGGS’(SEQ ID NO:154)氨基酸插入。在各种实施方案中,IL-15变体包含氨基酸取代、缺失或插入的组合。在各种实施方案中,IL-15变体多肽包含SEQ ID NO:24-45、56-63和66-81中列出的序列。

[0010] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,其中IL-15Rα包含IL-15RαSushi结构域(SEQ ID NO:5)或IL-15Rα细胞外结构域(SEQ ID NO:4)或其任何功能结构域。在各种实施方案中,IL-15Rα结构域包含与SEQ ID NO:4中列出的序列至少90%同源的序列。在各种实施方案中,IL-15Rα结构域包含与SEQ ID NO:4中列出的序列至少95%同源的序列。在各种实施方案中,IL-15Rα结构域是IL-15RαSushi结构域,该IL-15RαSushi结构域包含与SEQ ID NO:5中列出的序列至少90%同源的序列。在各种实施方案中,IL-15RαSushi结构域包含与SEQ ID NO:5中列出的序列至少95%同源的序列。

[0011] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15RαSushi复合物和至少一种异源蛋白。

[0012] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,其中IL-15融合到异源蛋白的C末端或N末端。

[0013] 在各种实施方案中,本发明的IL-15融合蛋白包含呈二聚体或单体形式的IL-15/IL-15Rα-异源蛋白复合物。

[0014] 在各种实施方案中,异源蛋白是Fc结构域(或其功能片段)。在各种实施方案中,Fc结构域选自由以下组成的组:人类IgG1 Fc结构域、人类IgG2 Fc结构域、人类IgG3 Fc结构域、人类IgG4 Fc结构域、IgA Fc结构域、IgD Fc结构域、IgE Fc结构域、IgG Fc结构域和IgM

Fc结构域或它们的任何组合。在各种实施方案中,Fc结构域包含导致Fc结构域具有改变的补体结合特性或Fc受体结合特性的氨基酸变化。产生具有改变的补体结合特性或Fc受体结合特性的Fc结构域的氨基酸变化是本领域已知的。在各种实施方案中,用于制备二聚体IL-15/IL-15Rα复合物-Fc融合蛋白的Fc结构域序列是SEQ ID NO:6中列出的人类IgG1-Fc结构域序列。SEQ ID NO:6包含消除(ablate)Fcγ R和C1q结合的氨基酸取代。在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域序列是SEQ ID NO:7中列出的Knob-Fc结构域序列。SEQ ID NO:7包含消除Fcγ R和C1q结合的氨基酸取代。在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域序列是SEQ ID NO:8中列出的Hole-Fc结构域序列。SEQ ID NO:8包含消除Fcγ R和C1q结合的氨基酸取代。

[0015] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,并且异源蛋白是用于半衰期延长的全长非结合抗体,或者是用于靶向、多功能和半衰期延长的特异性抗体或片段。

[0016] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,并且异源蛋白是呈全长IgG或抗体片段形式的抗体(单特异性或双特异性),并提供与IL-15/IL-15RαSushi复合物的加性或协同作用。

[0017] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15Rα复合物,并且异源蛋白提供组织特异性靶向或肿瘤特异性靶向,以增加IL-15对肿瘤微环境的局部浓度和渗透,并增加肿瘤细胞杀伤效力和降低全身毒性。

[0018] 在各种实施方案中,异源蛋白是能够结合到肿瘤相关抗原(TAA)或组织特异性抗原或靶、细胞表面分子或细胞外基质蛋白、蛋白酶和任何翻译后修饰残基的抗体、或抗体片段、或配体或其变体、或受体或其变体。在各种实施方案中,抗体是抗成纤维细胞活化蛋白(FAP)抗体或抗体片段。在各种实施方案中,抗体是包含SEQ ID NO:109-110中列出的重链和轻链序列的人源化抗FAP抗体。在各种实施方案中,异源蛋白是针对免疫检查点调节剂的抗体或抗体片段。在各种实施方案中,抗体是拮抗性程序性死亡-1(PD-1)抗体或抗体片段。在各种实施方案中,抗体是包含SEQ ID NO:111-112中列出的重链和轻链氨基酸序列的拮抗性人源化PD-1抗体。在各种实施方案中,抗体是包含SEQ ID NO:113-114中列出的重链和轻链氨基酸序列的拮抗性人类PD-1抗体。在各种实施方案中,抗体是拮抗性程序性死亡配体-1(PD-L1)抗体或抗体片段。

[0019] 在各种实施方案中,异源蛋白通过多肽接头序列与IL-15/IL-15RαSushi复合物的IL-15多肽共价连接。在各种实施方案中,接头可以是相对地不含二级结构的在5个、10个、15个、20个、30个、40个或更多个氨基酸之间的人工序列。在各种实施方案中,接头G/S含量丰富(例如接头中至少约60%、70%、80%、90%或更多的氨基酸是G或S)。在各种实施方案中,接头选自SEQ ID NO:9-12、47和153-154中列出的序列的组。每个肽接头序列可以独立地选择。

[0020] 在另一方面,本公开内容提供了药物组合物,所述药物组合物包含与药学上可接受的载体混合的本发明的分离的IL-15融合蛋白。

[0021] 在另一方面,本公开内容提供了用于治疗受试者的癌症或癌症转移的方法,该方法包括向有相应需要的受试者施用治疗有效量的本发明的药物组合物。在一种实施方案

中,受试者是人类受试者。在各种实施方案中,癌症选自胰腺癌、胃癌、肝癌、乳腺癌、卵巢癌、结肠直肠癌、黑素瘤、白血病、骨髓增生异常综合征、肺癌、前列腺癌、脑癌、膀胱癌、头颈癌或横纹肌肉瘤。

[0022] 在另一方面,本公开内容提供了一种用于治疗受试者的癌症或癌症转移的方法,该方法包括施用与第二疗法组合的治疗有效量的本发明的药物组合物,所述第二疗法选自由以下组成的组:细胞毒性化学疗法、免疫疗法、小分子激酶抑制剂靶向疗法、手术、放射疗法、干细胞移植、细胞疗法包括CAR-T细胞、CAR-NK细胞、iPS诱导的NK细胞、iPS诱导的CAR-NK细胞、iPS诱导的T细胞、iPS诱导的CAR-T细胞或TCR-T细胞、以及疫苗诸如卡介苗(Bacille Calmette-Guerine,BCG)。在各种实施方案中,组合疗法可以包括向受试者施用治疗有效量的免疫疗法,所述免疫疗法包括但不限于,使用针对特定肿瘤抗原的消耗性抗体的治疗;使用抗体-药物缀合物的治疗;使用针对共刺激性或共抑制性分子(免疫检查点)(诸如CD276、CD272、CTLA-4、PD-1、PD-L1、CD40、SIRPα、CD47、OX-40、CD137、GITR、LAG3、ICOS、CD27、4-1BB、TIM-3、B7-H4、Siglec-7、Siglec-8、Siglec-9、Siglec-15和VISTA)的激动性抗体、拮抗性抗体或阻断性抗体的治疗;使用双特异性T细胞结合抗体(BiTE®)诸如博纳吐单抗(blinatumomab)的治疗;涉及施用生物响应调节剂(诸如IL-2、IL-7、IL-10、IL-12、IL-21、G-CSF、GM-CSF、IFN-α、IFN-β和IFN-γ)的治疗;使用治疗性疫苗诸如sipuleucel-T的治疗;使用树突细胞疫苗或肿瘤抗原肽疫苗的治疗;使用嵌合抗原受体(CAR)-T细胞的治疗;使用CAR-NK细胞的治疗;使用肿瘤浸润淋巴细胞(TIL)的治疗;使用过继转移的抗肿瘤T细胞(离体扩增的T细胞和/或TCR转基因T细胞)的治疗;使用TALL-104细胞的治疗;和使用免疫刺激剂诸如Toll样受体(TLR)剂(诸如TLR4、TLR7、TLR8、TLR9激动剂CpG和咪喹莫特)的治疗;以及使用疫苗诸如卡介苗(Bacille Calmette-Guerine,BCG)的治疗;其中组合疗法提供了增加的对肿瘤细胞的效应细胞杀伤,即,当被共施用时,IL-15/IL-15RαSushi-Fc融合蛋白和免疫疗法之间存在协同作用。

[0023] 在另一方面,本公开内容提供了一种在体外和体内扩增及更新NK细胞和T细胞以及与任何过继转移NK细胞和T细胞疗法或CAR-NK和CAR-T疗法组合以维持细胞存活和半衰期的方法。

[0024] 在另一方面,本公开内容提供了用于治疗受试者的病毒感染的方法,该方法包括向有相应需要的受试者施用治疗有效量的本发明的药物组合物。在一种实施方案中,受试者是人类受试者。

[0025] 在另一方面,本公开内容提供了IL-15融合蛋白用于制备用于治疗癌症的药物的用途。

[0026] 在另一方面,本公开内容提供了IL-15融合蛋白用于制备用于治疗病毒感染的药物的用途。

[0027] 在另一方面,本公开内容提供了分离的核酸分子,该分离的核酸分子包含编码本公开内容的IL-15融合蛋白的多核苷酸。在各种实施方案中,分离的核酸分子包含本文描述的多核苷酸,并且还包含编码本文描述的至少一种异源蛋白的多核苷酸。在各种实施方案中,核酸分子还包含编码本文描述的接头的多核苷酸。

[0028] 在另一方面,本公开内容提供了包含本文描述的核酸的载体。在各种实施方案中,载体是表达载体。在另一方面,本公开内容提供了包含本公开内容的核酸的分离的细胞。在

各种实施方案中,细胞是包含本公开内容的表达载体的宿主细胞。在另一方面,制备IL-15融合蛋白的方法通过在促进蛋白或多肽的表达的条件下培养宿主细胞来提供。

[0029] 附图简述

[0030] 图1描绘了本发明的IL-15/IL-15Rα-Fc融合蛋白的若干形式。(A)IL-15/IL-15Rα异源二聚体Fc融合形式。(B)单价IL-15/IL-15Rα(非共价)Fc融合形式。(C)二价IL-15/IL-15Rα(非共价)Fc融合形式;(D)单价IL-15(非共价)/IL-15RαFc融合蛋白形式。(E)二价IL-15(非共价)/IL-15RαFc融合蛋白形式。对于每种融合蛋白形式,IL-15/IL-15Rα复合物可以位于Fc结构域的C末端处或N末端处;并且IL-15Rα可以是IL-15RαSushi结构域或IL-15RαECD。

[0031] 图2描绘分别通过SDS-PAGE和SEC-HPLC确定的示例性IL-15/IL-15Rα(非共价)-Fc融合蛋白P-0217、P-0234和P-0313的A)纯度和B)单体百分比。所有三种融合蛋白都在C末端处包含IL-15/IL-15Rα复合物。P-0217是单价IL-15/IL-15Rα(非共价)Fc融合体,P-0234是P-0217的二聚体对应物,并且P-0313与P-0234共有相同的融合构型,但不同之处仅在于IL-15结构域中的S58D取代。

[0032] 图3描绘了若干不同构型的IL-15/IL-15Rα-Fc融合蛋白的SEC色谱图。除非另外说明,否则这些示例性融合蛋白都在C末端处包含IL-15/IL-15Rα复合物。P-0162是单体IL-15(单独)Fc融合蛋白。P-0197是单价IL-15/IL-15Rα(非共价)Fc融合体,其示意图在图1B中描绘。P-0153是单体IL-15/IL-15Rα融合体,具有异源二聚体Fc融合形式(图1A)。P-0167和P-0198分别是P-0162和P-0197的二聚体对应物。P-0234和P-0220及P-0223都是二价IL-15/IL-15Rα(非共价)Fc融合蛋白(图1C)。P-0220含有IL-15RαECD,P-0234含有IL-15RαSushi+结构域;P-0223不同于P-0234,P-0223的IL-15/IL-15Rα复合物附接到Fc的N末端。

[0033] 图4描绘了在ELISA测定中不同的IL-15/IL-15RαFc融合形式对与IL-15Rβ的结合活性的影响。展示了IL-15Rα增加了IL-15Fc融合蛋白的IL-15Rβ结合活性。P-0157是N末端二价IL-15(非共价)/IL-15RαSushi Fc融合蛋白;P-0153是C末端IL-15/IL-15RαSushi异源二聚体Fc融合蛋白;P-0162是C末端单价IL-15Fc融合蛋白且不具有复合的IL-15RαSushi。

[0034] 图5描绘了IL-15Rα对IL-15Fc融合蛋白的生物活性的影响。展示了IL-15Rα增强了IL-15Fc融合蛋白的生物活性。CD69阳性NK细胞(图5A)和CD8 T细胞(图5B)的诱导在基于离体人类PBMC FACS的测定中测量。P-0197是C末端单价IL-15/IL-15RαSushi(非共价)Fc融合蛋白;P-0162是与P-0197具有相同结构但不具有复合的IL-15RαSushi的融合蛋白。

[0035] 图6描绘了不同构型的IL-15/IL-15Rα复合对IL-15Fc融合蛋白的生物活性的影响。CD69阳性NK细胞(图6A)和CD8+T细胞(图6B)的诱导在基于离体人类PBMC FACS的测定中测量。P-0165是C末端单价IL-15(非共价)/IL-15RαFc融合蛋白;P-0197是C末端单价IL-15/IL-15Rα(非共价)Fc融合蛋白;P-0153是C末端IL-15/IL-15Rα异源二聚体Fc融合蛋白。

[0036] 图7描绘了接头对不同形式的IL-15/IL-15RαFc融合蛋白的生物活性的影响。CD69阳性NK细胞(图7A)和CD8 T细胞(图7B)的诱导在基于离体人类PBMC FACS的测定中测量。P-0165和P-0166分别是具有15个氨基酸的刚性接头和10个氨基酸的柔性接头的单价IL-15(非共价)/IL-15RαFc融合体。P-0197、P-0207和P-0217分别是具有15个氨基酸的刚性接头、10个氨基酸的柔性接头和15个氨基酸的柔性接头的单价IL-15/IL-15Rα(非共价)Fc融合蛋白。

[0037] 图8描绘了N末端融合或C末端融合对IL-15/IL-15RαFc融合蛋白的活性的影响。处理后,在基于离体人类PBMC FACS的测定中测量Ki67阳性CD8 T细胞的百分比。(A)P-0218和基准分别是C末端二价IL-15(非共价)/IL-15RαFc融合蛋白和N末端二价IL-15(非共价)/IL-15RαFc融合蛋白。(B)P-0234和P-0223分别是C末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白和N末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白。

[0038] 图9描绘了IL-15Rα完整ECD或IL-15RαSushi结构域对IL-15/IL-15RαFc融合蛋白的生物活性的影响。CD69阳性NK细胞的诱导在基于离体人类PBMC FACS的测定中测量。(A)P-0234和P-0220分别是具有IL-15RαSushi和IL-15Rα完整ECD的C末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白。(B)P-0223和P-0224分别是具有IL-15RαSushi和IL-15Rα完整ECD的N末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白。(C)P-0221和P-0222分别是具有IL-15RαSushi和IL-15Rα完整ECD的N末端单价IL-15/IL-15Rα(非共价)Fc融合蛋白。

[0039] 图10描绘了IL-15多肽中的S58D取代增强了IL-15融合蛋白在CD8+T细胞(A)、CD4+T细胞(B)和NK细胞(C)上诱导STAT5磷酸化的能力。P-0218和P-0314分别是包含IL-15野生型和S58D变体的二价IL-15(非共价)/IL-15RαFc融合蛋白。P-0234和P-0313分别是包含IL-15野生型和S58D变体的二价IL-15/IL-15Rα(非共价)Fc融合蛋白。

[0040] 图11描绘了含有IL-15 S58D变体的融合蛋白展示出增强的在CD8+T细胞(A)、CD4+T细胞(B)和NK细胞(C)上诱导Ki67表达的能力。P-0218和P-0314分别是包含IL-15野生型和S58D变体的二价IL-15(非共价)/IL-15RαFc融合蛋白。P-0234和P-0313分别是包含IL-15野生型和S58D变体的二价IL-15/IL-15Rα(非共价)Fc融合蛋白。

[0041] 图12描绘了在4天重复给药研究中,用rhIL-15、基准和P-0234处理的小鼠中IL-15的血清浓度。雌性Balb/C小鼠被每日腹膜内注射媒介物、rhIL-15(0.03mg/kg)、基准(0.1mg/kg和0.5mg/kg)或P-0234(0.1mg/kg和0.5mg/kg)。在第4天在最后一次注射后1小时收集终末血液(terminal blood),并使用ELISA测定测量血清IL-15水平。

[0042] 图13描绘了在4天重复给药研究期间,用rhIL-15、基准和P-0234处理的Balb/C小鼠的(A)体重和(B)从第0天起体重的变化%。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。***p<0.001,与第0天相比;#p<0.05,与PBS组相比。

[0043] 图14描绘了在4天重复给药研究中,IL-15化合物对Balb/C小鼠外周血中NK细胞增殖和扩增的影响。4次日剂量后,收集血液,通过FACS进行Ki67测量和NK细胞表型分析。(A)增殖标志物Ki67阳性NK细胞的百分比;(B)CD3阴性淋巴细胞群体中NK细胞的百分比。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,与媒介物组相比,#p<0.001并且##p<0.01,与等剂量的基准相比。

[0044] 图15描绘了在4天重复给药研究中,IL-15化合物对Balb/C小鼠的脾NK细胞的增殖、扩增和活化的影响。(A)增殖标志物Ki67阳性的脾NK细胞的百分比;(B)脾中的NK细胞总数;(C)CD69阳性脾NK细胞的百分比。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,**p<0.01,*p<0.05,与媒介物组相比。

[0045] 图16描绘了在Balb/C小鼠中单次腹膜内注射后P-0313和基准的血清浓度。在-24小时(给药前)以及给药后1小时、4小时、24小时、72小时、144小时和192小时,从用0.3mg/kg P-0313或基准处理的小鼠收集血液。(A)检测人类Fc-IL-15复合物的内部ELISA测定;(B)检测人类IL-15的商业ELISA测定。

[0046] 图17描绘了Balb/C小鼠在单次注射P-0313和基准后在8天的时间段内的体重。

[0047] 图18描绘了在Balb/C小鼠中单次注射后,IL-15/IL-15RαFc融合蛋白对NK细胞(A)和CD8+T细胞(B)的Ki67表达的剂量效应和时间依赖性效应。在-24小时(给药前)和1小时、4小时、24小时、72小时、144小时和192小时收集血液,以通过FACS分析进行淋巴细胞表型分析和Ki67测量。数据表示为平均值±SEM。通过双因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,**p<0.01,*p<0.05,在各自的时间点与PBS组相比。

[0048] 图19描绘了在Balb/C小鼠中单次注射后,IL-15/IL-15RαFc融合蛋白对外周血中NK细胞(A)和CD8+T细胞(B)的扩增的剂量效应和时间依赖性效应。在-24小时(给药前)和1小时、4小时、24小时、72小时、144小时和192小时收集血液,以通过FACS分析进行淋巴细胞表型分析。数据表示为平均值±SEM。通过双因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,***p<0.001,*p<0.05,在各自的时间点与PBS组相比。

[0049] 图20描绘了在小鼠CT26肺转移模型中P-0313和基准对肺转移的抑制。注射CT26细胞后1天开始给予媒介物、基准(0.3mg/kg)或P-0313(0.03mg/kg和0.1mg/kg)3×Q5D剂量。在第16天处死小鼠,对肺转移结节进行显微术计数。(A)在光学显微镜下获得的代表性的肺部照片,例示来自每个处理组的转移性结节。(B)所有动物的肺结节计数。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,*p<0.05,与PBS组相比。

[0050] 图21描绘了用P-0313或基准处理后CT26肺转移模型的免疫药效学谱分析(profiling)。在三次Q5D i.p.注射P-0313、基准或PBS后3天,通过流式细胞术确定CT26转移小鼠中每μl全血的循环A)NK细胞和B)CD8+T细胞的数目的增加。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,***p<0.001,**p<0.01,与PBS组相比。

[0051] 图22描绘了在CT26肺转移模型中,用P-0313或基准处理的小鼠中的脾重量。三次Q5D i.p.注射IL-15/IL-15RαFc融合蛋白后3天收集脾。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,与PBS组相比。

[0052] 图23描绘了对用P-0313或基准处理的CT26肺转移小鼠的肝毒性评估。在三次Q5D处理后三天收集肝。A)肝重量;B)血清ALT水平;和C)血清AST水平。血清中的ALT水平和AST水平使用商业ELISA试剂盒确定。数据表示为平均值±SEM。

[0053] 图24描绘了在皮下建立的CT26小鼠结肠直肠肿瘤模型中,P-0313的抗肿瘤功效。第0天皮下注射$1\times10^5$个CT26细胞。当平均肿瘤体积为~70$mm^3$(第11天)时,开始Q5D给予媒介物(PBS)或P-0313(0.1mg/kg或0.05mg/kg)的两次注射。(A)CT26 s.c.肿瘤的生长曲线。(B)体重从基线的变化。数据表示为平均值±SEM。通过双因素ANOVA检验、随后Tukey事后检验进行统计分析。**p<0.0001,与PBS组相比。

[0054] 图25描绘了接受(A)媒介物PBS、(B)0.05mg/kg P-0313或(C)0.01mg/kg P-0313的个体小鼠的皮下CT26肿瘤生长曲线。n=10只/组。

[0055] 图26描绘了在CT26鼠结直肠癌肿瘤模型中,用P-0313处理的小鼠中NK细胞和CD8 T细胞的增殖和扩增。在肿瘤植入后11天开始的两次Q5D处理后,在第19天通过流式细胞术确定NK细胞和CD8+T细胞的Ki67表达(A-B)和循环细胞数目(每μl全血)(C-D)的增加。数据表示为平均值±SEM;通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<

0.0001,*P<0.05,与PBS组相比。

[0056] 图27描绘了用P-0313处理的具有CT26结肠直肠肿瘤的小鼠中脾NK细胞和CD8 T细胞的免疫表型分析。在肿瘤植入后11天开始的两次Q5D处理后,在第21天通过流式细胞术确定脾NK细胞(A)和CD8+T细胞(B)的数目的增加。数据表示为平均值±SEM;通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。****p<0.0001,与PBS组相比。

[0057] 图28描绘了在未建立的CT26结肠直肠肿瘤模型中,P-0313的抗肿瘤功效。在皮下植入$1\times10^5$个CT26细胞后3天,对小鼠给予媒介物(PBS)或P-0313(0.1mg/kg,5次Q5D注射。(A)在第0天肿瘤细胞植入后,CT26s.c.肿瘤的生长曲线。(B)第25天的肿瘤重量。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。***p<0.001,*p<0.05,与PBS组相比。

[0058] 图29描绘了用P-0313处理的CT26荷瘤小鼠的脾重量和体重变化百分比。在CT26肿瘤细胞植入后三天,对小鼠给予媒介物(PBS)或P-0313(0.1mg/kg),5次Q5D注射。(A)第25天的脾重量。(B)在25天内体重的变化百分比。数据表示为平均值±SEM。通过单因素ANOVA检验、随后Tukey事后检验进行统计分析。**p<0.01,与PBS组相比。

[0059] 图30描绘了示例性的IL-15/IL-15Rα(非共价)抗体融合蛋白,其中IL-15/IL-15Rα复合物融合到以下的C末端:A)二价形式的同源二聚体重链,B)单价形式的异源二聚体重链和C)轻链。

[0060] 图31描绘了在A)S58、B)V63、C)I68或D)Q108位置处的不同IL-15单个氨基酸取代对该细胞因子诱导CD8+T细胞上Ki67表达的活性的影响。除了P-0764和P-0793(图31D)之外,所有示例性IL-15变体融合蛋白均为二价IL-15/IL-15Rα(非共价)Fc融合形式,P-0764和P-0793为单价IL-15/IL-15Rα(非共价)Fc融合形式。P-0313,一种充分表征的二价IL-15S58D/IL-15Rα(非共价)Fc融合蛋白,被包括在内作为对照。

[0061] 图32描绘了在新鲜的人类PBMC中用IL-15变体融合蛋白处理后,CD8+T细胞上Ki67表达的剂量依赖性诱导。P-0866、P-0867和P-0868均为二价IL-15/IL-15Rα(非共价)Fc融合形式,并且分别在IL-15的N末端处包含1个、2个和3个氨基酸缺失。P-0234为相同形式,包含野生型IL-15。

[0062] 图33描绘了通过在新鲜的人类PBMC中分析CD8+T细胞上Ki67表达的剂量依赖性诱导,对各种携带组合突变的IL-15融合蛋白的活性评估。A)P-0773、P-0772和P-0768包含对它们各自的携带单个氨基酸变化的等效物P-0358(I68H)、P-0736(I68Q)和P-0737(I68G)的一个另外的V63A取代。P-0771含有单个V63A突变。所有示例性IL-15变体融合蛋白均为二价IL-15/IL-15Rα(非共价)Fc融合形式。B)P-0886和P-0888为二价IL-15/IL-15Rα(非共价)抗体融合蛋白。P-0886在IL-15N末端处包含2个氨基酸缺失,而P-0888含有一个另外的V63A单个氨基酸取代。P-0313和P-0234为高效的二价IL-15/IL-15Rα(非共价)Fc融合蛋白,并被包括在内作为对照。

[0063] 图34描绘了在新鲜的人类PBMC中用各种IL-15变体融合蛋白处理后,A)CD8+T细胞和B)NK细胞上Ki67表达的剂量依赖性诱导。与高效的对照P-0313相比,所有测试化合物都展示出不同水平的活性减弱。

[0064] 图35描绘了在新鲜的人类PBMC中用IL-15变体融合蛋白处理后,CD8+T细胞上Ki67表达的剂量依赖性诱导。A)P-0773为二价IL-15/IL-15Rα(非共价)Fc融合形式,而P-0870为

P-0773的抗体融合对应物,包含相同的氨基酸取代V63A/I68H,以减弱IL-15的效力。B)P-0867为二价IL-15/IL-15Rα(非共价)Fc融合形式,在IL-15的N末端处包含2个氨基酸缺失,而P-0886为P-0867的抗体融合对应物。

[0065] 用于进行本公开内容的方式

[0066] 本公开内容提供了用于治疗癌症和其他紊乱的新型且改进的IL-15融合蛋白。在各种实施方案中,本发明的融合蛋白具有两个功能结构域:IL-15/IL-15RαSushi结构域(在本文中也称为"IL-15/IL-15RαSushi复合物")和Fc结构域,每个结构域可以采取不同的形式,并且被配置成使得IL-15融合到Fc结构域的C末端或N末端,并且与IL-15Rα、IL-15RαSushi或IL-15RαECD或其任何功能片段共表达和非共价复合(参见图1)。在各种实施方案中,本发明的融合蛋白具有两个功能结构域:IL-15/IL-15RαSushi结构域和抗体或抗体片段,它们中的每一个可以采取不同的形式,并且被配置成使得IL-15融合到抗体重链或轻链的C末端或N末端,并且与IL-15Rα、IL-15RαSushi或IL-15RαECD或其任何功能片段共表达和非共价复合(在图30中例示)。

[0067] 本公开内容提供了具有氨基酸取代、缺失、插入的IL-15变体,并用作IL-15超级激动剂、激动剂或拮抗剂,以用于治疗癌症和其他紊乱。

[0068] 本发明人理解,为了延长IL-15或IL-15融合蛋白的循环半衰期和/或增加IL-15或IL-15融合蛋白的生物活性,非常合意的是将IL-15共价连接到人类Fc或抗体/抗体片段的N末端或C末端处,以增强IL-15对其信号传导受体的呈递,并防止IL-15从融合蛋白解离。本发明人还认为,非常合意的是产生包含非共价结合到IL-15的IL-15Rα结构域的融合蛋白复合物,以更自然地将IL-15呈递给IL-15信号传导受体。使用本文描述的形式和策略,本发明人展示了,可以实现蛋白表达增加、免疫原性潜在降低和保护IL-15免于降解。在本文描述的各种实施方案中,优选将IL-15-IL-15Rα复合物置于C末端处,以实现增强的生物活性和可开发性。

[0069] 本公开内容因此提供了具有一个或更多个氨基酸取代、缺失或插入的IL-15变体,并且其用作IL-15拮抗剂,具有最佳减弱的效力,以便防止途径过度活化并降低不需要的靶吸收(target sink),以减轻系统毒性并改进药代动力学。

[0070] 定义

[0071] 术语"多肽"、"肽"和"蛋白"在本文中可互换使用,以指氨基酸残基的聚合物。在各种实施方案中,"肽"、"多肽"和"蛋白"是其α碳通过肽键连接的氨基酸链。因此链的一个末尾(氨基末端)处的末端氨基酸具有游离氨基基团,而链的另一个末尾(羧基末端)处的末端氨基酸具有游离羧基基团。如本文使用的,术语"氨基末端"(缩写为N末端)是指在肽的氨基末端处的氨基酸上的游离α-氨基基团,或指在肽中的任何其他位置处的氨基酸的α-氨基基团(参与肽键时的氨基基团)。类似地,术语"羧基末端"是指肽的羧基末端上的游离羧基基团,或肽中任何其他位置处的氨基酸的羧基基团。肽还包括基本上任何多氨基酸,包括但不限于肽模拟物(peptide mimetic),诸如通过醚键而非酰胺键连接的氨基酸。

[0072] 本公开内容的多肽包括已经以任何方式和出于任何原因被修饰的多肽,例如,以:(1)降低对蛋白水解的敏感性,(2)降低对氧化的敏感性,(3)改变形成蛋白复合物的结合亲和力,(4)改变结合亲和力,和(5)赋予或改变其他物理化学特性或功能特性。例如,单氨基酸取代或多氨基酸取代(例如,保守氨基酸取代)可以在天然存在的序列中进行(例如,在形

成分子间接触的结构域以外的多肽部分中)。“保守氨基酸取代”是指多肽中的氨基酸被功能上相似的氨基酸取代。以下六组各自包含互相为保守取代的氨基酸:

[0073] 1)丙氨酸(A)、丝氨酸(S)和苏氨酸(T)

[0074] 2)天冬氨酸(D)和谷氨酸(E)

[0075] 3)天冬酰胺(N)和谷氨酰胺(Q)

[0076] 4)精氨酸(R)和赖氨酸(K)

[0077] 5)异亮氨酸(I)、亮氨酸(L)、甲硫氨酸(M)和缬氨酸(V)

[0078] 6)苯丙氨酸(F)、酪氨酸(Y)和色氨酸(W)

[0079] “非保守氨基酸取代”是指这些类别之一的成员取代为来自另一类别的成员。在进行这样的改变时,根据各种实施方案,可以考虑氨基酸的亲水指数(hydropathic index)。基于氨基酸的疏水性和电荷特征,每种氨基酸已经被指定了亲水指数。它们是:异亮氨酸(+4.5);缬氨酸(+4.2);亮氨酸(+3.8);苯丙氨酸(+2.8);半胱氨酸/胱氨酸(+2.5);甲硫氨酸(+1.9);丙氨酸(+1.8);甘氨酸(-0.4);苏氨酸(-0.7);丝氨酸(-0.8);色氨酸(-0.9);酪氨酸(-1.3);脯氨酸(-1.6);组氨酸(-3.2);谷氨酸(-3.5);谷氨酰胺(-3.5);天冬氨酸(-3.5);天冬酰胺(-3.5);赖氨酸(-3.9)和精氨酸(-4.5)。

[0080] 本领域理解亲水氨基酸指数在赋予蛋白相互作用的生物功能中的重要性(参见例如,Kyte等人,1982,J.Mol.Biol.157:105-131)。已知,某些氨基酸可以被具有相似亲水指数或评分的其他氨基酸取代,并且仍保持相似的生物活性。在基于亲水指数进行改变时,在各种实施方案中,包括了其亲水指数在±2内的氨基酸的取代。在各种实施方案中,包括在±1内的那些,并且在各种实施方案中,包括在±0.5内的那些。

[0081] 本领域还理解,可以基于亲水性有效地进行相似氨基酸的取代,特别是当从而产生的生物功能蛋白或肽被意图用于在免疫学实施方案中使用时,如本文所公开的。在各种实施方案中,蛋白的最大局部平均亲水性(如由其相邻氨基酸的亲水性决定的)与其免疫原性和抗原性,即,与蛋白的生物学特性相关。

[0082] 以下亲水性值(hydrophilicity values)被指定至这些氨基酸残基:精氨酸(+3.0);赖氨酸(+3.0);天冬氨酸(+3.0.+-.1);谷氨酸(+3.0.+-.1);丝氨酸(+0.3);天冬酰胺(+0.2);谷氨酰胺(+0.2);甘氨酸(0);苏氨酸(-0.4);脯氨酸(-0.5.+-.1);丙氨酸(-0.5);组氨酸(-0.5);半胱氨酸(-1.0);甲硫氨酸(-1.3);缬氨酸(-1.5);亮氨酸(-1.8);异亮氨酸(-1.8);酪氨酸(-2.3);苯丙氨酸(-2.5)和色氨酸(-3.4)。在基于相似亲水性值进行改变时,在各种实施方案中,包括其亲水性值在±2内的氨基酸的取代,在各种实施方案中,包括在±1内的那些,并且在各种实施方案中,包括在±0.5内的那些。

[0083] 示例性的氨基酸取代在表1中列出。

[0084] 表1

[0085]

| 原始残基 | 示例性取代 | 优选的取代 |
|---|---|---|
| Ala | Val, Leu, Ile | Val |
| Arg | Lys, Gln, Asn | Lys |
| Asn | Gln | |
| Asp | Glu | |
| Cys | Ser, Ala | Ser |
| Gln | Asn | Asn |
| Glu | Asp | Asp |
| Gly | Pro, Ala | Ala |
| His | Asn, Gln, Lys, Arg | Arg |
| Ile | Leu, Val, Met, Ala, Phe, 正亮氨酸 | Leu |
| Leu | 正亮氨酸, Ile, Val, Met, Ala, Phe | Ile |
| Lys | Arg, 1,4 二氨基丁酸, Gln, Asn | Arg |
| Met | Leu, Phe, Ile | Leu |
| Phe | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro | Ala | Gly |
| Ser | Thr, Ala, Cys | Thr |
| Thr | Ser | |
| Trp | Tyr, Phe | Tyr |
| Tyr | Trp, Phe, Thr, Ser | Phe |
| Val | Ile, Met, Leu, Phe, Ala, 正亮氨酸 | Leu |

[0086]

[0087] 技术人员将能够使用公知技术确定如本文列出的合适的多肽变体。在各种实施方案中,本领域技术人员可以通过靶向被认为对于活性不重要的区域来鉴定分子中可以被改变而不破坏活性的适合区域。在其他实施方案中,技术人员可以鉴定在相似多肽间保守的分子的残基和部分。在另外的实施方案中,即使可能对生物活性或对结构重要的区域也可以经历保守氨基酸取代,而不破坏生物活性或不会不利地影响多肽结构。

[0088] 此外,本领域技术人员可以回顾鉴定相似多肽中对活性或结构重要的残基的结构-功能研究。鉴于这样的比较,技术人员可以预测对应于相似多肽中对活性或结构重要的氨基酸残基的多肽中的氨基酸残基的重要性。本领域技术人员可以选择对这样预测的重要氨基酸残基进行化学上相似的氨基酸取代。

[0089] 本领域技术人员还可以分析相似多肽中与该结构相关的三维结构和氨基酸序列。鉴于这样的信息,本领域技术人员可以预测多肽的氨基酸残基在其三维结构方面的排列。在各种实施方案中,本领域技术人员可以选择不对预测在多肽表面上的氨基酸残基进行根

本改变(radical changes),因为此类残基可能参与与其他分子的重要相互作用。此外,本领域技术人员可以产生在每个期望的氨基酸残基处包含单个氨基酸取代的测试变体。然后可以使用本领域技术人员已知的活性测定来筛选变体。这些变体可以用于收集关于合适变体的信息。例如,如果人们发现,特定氨基酸残基的改变导致破坏的、不期望地减少的或不合适的活性,则可以避免具有这样的改变的变体。换句话说,基于从这样的常规实验收集的信息,本领域技术人员可以容易地确定应避免在该处单独的或与其他突变组合的进一步取代的氨基酸。

[0090] 如本文使用的术语“多肽片段”和“截短的多肽”是指与对应的全长蛋白相比具有氨基末端缺失和/或羧基末端缺失的多肽。在某些实施方案中,片段的长度可以是例如,至少5个、至少10个、至少25个、至少50个、至少100个、至少150个、至少200个、至少250个、至少300个、至少350个、至少400个、至少450个、至少500个、至少600个、至少700个、至少800个、至少900个或至少1000个氨基酸。在某些实施方案中,片段的长度还可以是例如,最多1000个、最多900个、最多800个、最多700个、最多600个、最多500个、最多450个、最多400个、最多350个、最多300个、最多250个、最多200个、最多150个、最多100个、最多50个、最多25个、最多10个或最多5个氨基酸。片段还可以在其任一个或两个末端处包含一个或更多个另外的氨基酸,例如,来自不同的天然存在的蛋白的氨基酸的序列(例如,Fc或亮氨酸拉链结构域)或人工氨基酸序列(例如,人工接头序列)。

[0091] 如本文使用的术语“多肽变体”、“杂合多肽(hybrid polypeptide)”和“多肽突变体”是指包含这样的氨基酸序列的多肽,其中相对于另一个多肽序列,一个或更多个氨基酸残基被插入到该氨基酸序列中、从该氨基酸序列中缺失和/或被取代到该氨基酸序列中。在某些实施方案中,待被插入、缺失或取代的氨基酸残基的数目可以是例如,至少1个、至少2个、至少3个、至少4个、至少5个、至少10个、至少25个、至少50个、至少75个、至少100个、至少125个、至少150个、至少175个、至少200个、至少225个、至少250个、至少275个、至少300个、至少350个、至少400个、至少450个或至少500个氨基酸的长度。本公开内容的杂合体包括融合蛋白。

[0092] 多肽的“衍生物”是已经被化学修饰的多肽,所述化学修饰例如,缀合至另一个化学部分(诸如例如,聚乙二醇、白蛋白(例如,人类血清白蛋白))、磷酸化和糖基化。

[0093] 术语“%序列同一性”与术语“%同一性”在本文中可互换使用并且指当使用序列比对程序比对时,在两个或更多个肽序列之间的氨基酸序列同一性的水平或在两个或更多个核苷酸序列之间的核苷酸序列同一性的水平。例如,如本文使用的,通过定义的算法确定的80%同一性与80%序列同一性意指相同的意思,并且意指给定序列与另一长度的另一序列至少80%相同。在某些实施方案中,%同一性选自例如,与给定序列至少60%、至少65%、至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或至少99%或更大的序列同一性。在某些实施方案中,%同一性在例如约60%至约70%、约70%至约80%、约80%至约85%、约85%至约90%、约90%至约95%或约95%至约99%的范围内。

[0094] 术语“%序列同源性”与术语“%同源性”在本文中可互换使用并且指当使用序列比对程序比对时,在两个或更多个肽序列之间的氨基酸序列同源性的水平或在两个或更多个核苷酸序列之间的核苷酸序列同源性的水平。例如,如本文使用的,通过定义的算法确定的80%同源性与80%序列同源性意指相同的意思,并且因此给定序列的同源物具有相对于

给定序列的长度大于80％的序列同源性。在某些实施方案中，％同源性选自例如，与给定序列至少60％、至少65％、至少70％、至少75％、至少80％、至少85％、至少90％、至少95％或至少99％或更大的序列同源性。在某些实施方案中，％同源性在例如约60％至约70％、约70％至约80％、约80％至约85％、约85％至约90％、约90％至约95％或约95％至约99％的范围内。

[0095] 可以用于确定两个序列之间的同一性的示例性计算机程序包括但不限于在互联网在NCBI的网站上公开地可得的一套BLAST程序，例如BLASTN、BLASTX和TBLASTX、BLASTP和TBLASTN。另参见Altschul等人，J.Mol.Biol.215:403-10,1990(特别参考公布的默认设置，即参数w＝4、t＝17)和Altschul等人，Nucleic Acids Res.,25:3389-3402,1997。当相对于GenBank蛋白序列和其他公开数据库中的氨基酸序列评价给定氨基酸序列时，通常使用BLASTP程序进行序列检索。BLASTX程序优选用于针对在GenBank蛋白序列和其他公开数据库中的氨基酸序列检索在所有阅读框中已经被翻译的核酸序列。使用开放空位(gap)罚分为11.0和延伸空位罚分为1.0的默认参数并且使用BLOSUM-62矩阵运行BLASTP和BLASTX两者。参见同上。

[0096] 除了计算序列同一性百分比以外，BLAST算法还进行两个序列之间的相似性的统计分析(参见例如，Karlin&Altschul，Proc.Nat'l.Acad.Sci.USA,90:5873-5787,1993)。由BLAST算法提供的相似性的一个量度是最小总概率(P(N))，所述最小总概率提供在两个核苷酸序列或氨基酸序列之间的匹配偶然发生的概率的指示。例如，如果在测试核酸与参考核酸的比较中，最小总概率为例如小于约0.1、小于约0.01或小于约0.001，则该核酸被认为与参考序列相似。

[0097] 如本文使用的术语“异源”是指非天然的或在自然界不存在的组合或状态，所述组合或状态例如可以通过用源自另一来源的组分或状态替换现有的天然组分或状态来实现。类似地，在蛋白天然地表达的生物体之外的生物体中表达该蛋白构成异源表达系统和异源蛋白。

[0098] 如本文使用的术语“抗体”是指包含一个或更多个多肽并且具有对肿瘤抗原的特异性或对在病理状态过表达的分子的特异性的蛋白，所述多肽基本上或部分地由免疫球蛋白基因或免疫球蛋白基因的片段编码。公认的免疫球蛋白基因包括κ、λ、α、γ、δ、ε和μ恒定区基因，以及这些基因的亚型和大量免疫球蛋白可变区基因。轻链(LC)被分类为κ或λ。重链(HC)被分类为γ、μ、α、δ或ε，其继而分别地定义免疫球蛋白类别IgG、IgM、IgA、IgD和IgE。典型的免疫球蛋白(例如，抗体)结构单元包含四聚体。每个四聚体包含相同的两对多肽链，每一对具有一条“轻链”(约25kD)和一条“重链”(约50-70kD)。每条链的N末端定义主要负责抗原识别的约100个至110个或更多个氨基酸的可变区。

[0099] 如本文使用的术语“Fc区”定义免疫球蛋白重链的C末端区域，其可通过木瓜蛋白酶消化完整抗体生成。Fc区可以是天然序列Fc区或变体Fc区。免疫球蛋白的Fc区通常包含两个恒定结构域，$C_{H2}$结构域和$C_{H3}$结构域，并且任选地包含$C_{H4}$结构域。抗体的Fc部分介导若干重要的效应子功能，例如细胞因子诱导、ADCC、吞噬作用、补体依赖性细胞毒性(CDC)以及抗体和抗原-抗体复合物的半衰期/清除率(例如，新生FcR(FcRn)在内体(endosome)中的酸性pH与IgG的Fc区结合并保护IgG免受降解，从而对IgG的长血清半衰期作出贡献)。替换Fc部分中的氨基酸残基以改变抗体效应子功能是本领域已知的(参见例如，Winter等人，美国

专利第5,648,260号和第5,624,821号)。示例性Fc氨基酸取代以消除与Fc γ R和C1q的结合,但保留FcRn结合,包括L234A/L235A/G237A突变和L234A/L235A/P329G突变。

[0100] “多核苷酸”是指包含核苷酸单元的聚合物。多核苷酸包括天然存在的核酸,诸如脱氧核糖核酸(“DNA”)和核糖核酸(“RNA”)以及核酸类似物。核酸类似物包括包含以下的那些:非天然存在的碱基,以天然存在的磷酸二酯键以外的连接与其他核苷酸衔接(engage)的核苷酸,或包含通过除了磷酸二酯键以外的连接来附接的碱基的核苷酸。因此,核苷酸类似物包括例如并且不限于,硫代磷酸酯、二硫代磷酸酯、磷酸三酯(phosphorotriester)、氨基磷酸酯(phosphoramidate)、硼烷磷酸酯(boranophosphate)、甲基膦酸酯、手性甲基膦酸酯、2-O-甲基核糖核苷酸、肽核酸(PNA)等。这样的多核苷酸可以例如使用自动化的DNA合成仪来合成。术语“核酸”通常是指大的多核苷酸。术语“寡核苷酸”通常是指短的多核苷酸,通常不大于约50个核苷酸。将理解的是,当核苷酸序列由DNA序列(即,A、T、G、C)表示时,这还包括其中“U”代替“T”的RNA序列(即,A、U、G、C)。

[0101] 本文使用常规符号描述多核苷酸序列:单链多核苷酸序列的左手末端为5'-末端;双链多核苷酸序列的左手方向被称作5'-方向。向新生RNA转录物5'至3'添加核苷酸的方向被称作转录方向。具有与mRNA相同的序列的DNA链被称作“编码链”;在具有与从该DNA转录的mRNA相同的序列的DNA链上并且位于RNA转录物的5'-末端的5'的序列被称作“上游序列”;在具有与RNA相同的序列的DNA链上并且在编码RNA转录物的3'-末端的3'的序列被称作“下游序列”。

[0102] “互补的”是指两个多核苷酸的相互作用表面的拓扑相容性或匹配在一起。因此,这两个分子可以被描述为互补的,并且更进一步地,接触表面特征是彼此互补的。如果第一多核苷酸的核苷酸序列与第二多核苷酸的多核苷酸结合配偶体的核苷酸序列基本上相同,或者如果第一多核苷酸可以与第二多核苷酸在严格杂交条件下杂交,则第一多核苷酸与第二多核苷酸是互补的。

[0103] “载体”是可以被用于将与其连接的另一核酸引入到细胞中的多核苷酸。一种类型的载体是“质粒”,其是指可以将另外的核酸区段连接到其中的线性或环状双链DNA分子。另一种类型的载体是病毒载体(例如,复制缺陷型逆转录病毒、腺病毒和腺相关病毒),其中另外的DNA区段可以被引入到病毒基因组中。某些载体能够在引入了它们的宿主细胞中自主复制(例如,包含细菌复制起点的细菌载体和附加型哺乳动物载体(episomal mammalian vector))。其他载体(例如,非附加型哺乳动物载体)在引入到宿主细胞中后被整合到宿主细胞的基因组中,并且从而与宿主基因组一起复制。“表达载体”是可以指导选择的多核苷酸的表达的一种类型的载体。

[0104] “调控序列”是影响与其可操作地连接的核酸的表达(例如,表达的水平、时机或位置)的核酸。调控序列可以例如直接对被调控的核酸发挥其作用,或通过一种或更多种其他分子(例如,与调控序列和/或核酸结合的多肽)的作用发挥其作用。调控序列的实例包括启动子、增强子和其他表达控制元件(例如多腺苷酸化信号)。调控序列的另外的实例描述于例如Goeddel,1990,Gene Expression Technology:Methods in Enzymology 185,Academic Press,San Diego;Calif.和Baron等人,1995,Nucleic Acids Res.23:3605-06中。如果调控序列影响核苷酸序列的表达(例如,表达的水平、时机或位置),则核苷酸序列与调控序列“可操作地连接”。

[0105] “宿主细胞”是可以被用于表达本公开内容的多核苷酸的细胞。宿主细胞可以是原核生物,例如大肠杆菌(E.coli),或者宿主细胞可以是真核生物,例如单细胞真核生物(例如,酵母或其他真菌)、植物细胞(例如,烟草或番茄植物细胞)、动物细胞(例如,人类细胞、猴细胞、仓鼠细胞、大鼠细胞、小鼠细胞或昆虫细胞)或杂交瘤。通常,宿主细胞是可以用编码多肽的核酸转化或转染的培养的细胞,所述核酸然后可以在宿主细胞中被表达。措辞“重组宿主细胞”可以被用于表示已经用待表达的核酸转化或转染的宿主细胞。宿主细胞还可以是包含核酸但不以期望的水平表达该核酸的细胞,除非调控序列被引入到宿主细胞中,使得调控序列变成与该核酸可操作地连接。应理解,术语宿主细胞不仅指特定的受试者细胞,而且还指这样的细胞的后代或潜在后代。因为某些修饰可以由于例如突变或环境影响而在随后世代中发生,这样的后代实际上可能与亲本细胞不相同,但仍然被包括在如本文使用的该术语的范围内。

[0106] 术语“分离的分子”(其中分子是例如多肽或多核苷酸)是这样的分子:该分子凭借其起源或衍生的来源(1)不与在其天然状态中伴随其的、天然地缔合的组分缔合,(2)基本上不含来自相同物种的其他分子,(3)由来自不同物种的细胞表达,或(4)不存在于自然界中。因此,化学合成的或在与其天然起源的细胞不同的细胞系统中表达的分子将是与其天然缔合的组分“分离”的。也可以通过使用本领域熟知的纯化技术分离使分子基本上不含天然缔合的组分。分子纯度或均一性可以通过本领域熟知的许多手段来测定。例如,多肽样品的纯度可以使用本领域熟知的技术使用聚丙烯酰胺凝胶电泳和对凝胶染色以使多肽可视化来测定。为了某些目的,可以通过使用HPLC或本领域熟知的用于纯化的其他手段来提供更高的分辨率。

[0107] 当样品的至少约60%至75%表现为单一种类的多肽时,蛋白或多肽是“基本上纯的”、“基本上均一的”或“基本上纯化的”。多肽或蛋白可以是单体的或多聚体的。基本上纯的多肽或蛋白将通常包含约50%、60%、70%、80%或90%W/W的蛋白样品,更通常约95%并且优选地将超过99%纯。蛋白纯度或均一性可以通过本领域熟知的许多手段来指示,所述手段诸如蛋白样品的聚丙烯酰胺凝胶电泳,随后用本领域熟知的染色剂对凝胶进行染色后使单个多肽条带可视化。为了某些目的,可以通过使用HPLC或本领域熟知的用于纯化的其他手段来提供更高的分辨率。

[0108] “接头”是指共价地或通过离子键、范德华力或氢键连接两个其他分子的分子,例如在5’末端处与一个互补序列杂交并且在3’末端处与另一个互补序列杂交从而连接两个非互补序列的核酸分子。“可裂解的接头”是指可以被降解或以其他方式切断以使通过该可裂解的接头连接的两个组分分开的接头。可裂解的接头通常被酶,通常是肽酶、蛋白酶、核酸酶、脂肪酶等裂解。可裂解的接头还可以通过环境因素,诸如例如温度、pH、盐浓度等的改变来裂解。

[0109] 如本文使用的术语“标记”或“标记的”是指在抗体中掺入另一种分子。在一种实施方案中,标记物是可检测的标志物,例如掺入放射性标记的氨基酸或附接至可以通过标记的亲和素检测的生物素基部分的多肽(例如,包含荧光标志物的链霉亲和素或可以通过光学方法或量热法检测的酶活性)。在另一种实施方案中,标记物或标志物可以是治疗性的,例如药物缀合物或毒素。标记多肽和糖蛋白的各种方法是本领域中已知的并且可以被使用。用于多肽的标记物的实例包括但不限于以下:放射性同位素或放射性核素(例如$^{3}H$、$^{14}C$

、$^{15}N$、$^{35}S$、$^{90}Y$、$^{99}Tc$、$^{111}In$、$^{125}I$、$^{131}I$);荧光标记物(例如FITC、罗丹明、镧系元素荧光团);酶标记物(例如辣根过氧化物酶、β-半乳糖苷酶、萤光素酶、碱性磷酸酶);化学发光标志物;生物素基基团;由第二报告物识别的预定的多肽表位(例如亮氨酸拉链配对序列、第二抗体的结合位点、金属结合结构域、表位标签);磁性剂(magnetic agent),诸如钆螯合物;毒素诸如百日咳毒素、紫杉醇、细胞松弛素B、短杆菌肽D、溴化乙锭、吐根碱、丝裂霉素、依托泊苷、替尼泊苷、长春新碱、长春花碱、秋水仙碱、多柔比星、柔红霉素、二羟基蒽二酮(dihydroxy anthracin dione)、米托蒽醌、光神霉素、放线菌素D、1-去氢睾酮、糖皮质激素、普鲁卡因、丁卡因、利多卡因、普萘洛尔(propranolol)和嘌呤霉素及其类似物或同系物。在一些实施方案中,标记物通过各种长度的间隔臂(spacer arm)附接,以降低潜在的空间位阻。

[0110] 术语"免疫疗法"是指包括但不限于以下的癌症治疗:使用针对特定肿瘤抗原的消耗性抗体的治疗;使用抗体-药物缀合物的治疗;使用针对共刺激性或共抑制性分子(免疫检查点)(诸如CD276、CD272、CTLA-4、PD-1、PD-L1、CD40、SIRPα、CD47、OX-40、CD137、GITR、LAG3、ICOS、CD27、4-1BB、TIM-3、B7-H4、Siglec-7、Siglec-8、Siglec-9、Siglec-15和VISTA)的激动性抗体、拮抗性抗体或阻断性抗体的治疗;使用双特异性T细胞结合抗体(BiTE®)诸如博纳吐单抗(blinatumomab)的治疗;涉及施用生物响应调节剂(诸如IL-2、IL-12、IL-15、IL-21、GM-CSF、IFN-α、IFN-β和IFN-γ)的治疗;使用治疗性疫苗诸如sipuleucel-T的治疗;使用树突细胞疫苗或肿瘤抗原肽疫苗的治疗;使用嵌合抗原受体(CAR)-T细胞的治疗;使用CAR-NK细胞的治疗;使用肿瘤浸润淋巴细胞(TIL)的治疗;使用过继转移的抗肿瘤T细胞(离体扩增的和/或TCR转基因的)的治疗;使用TALL-104细胞的治疗;和使用免疫刺激剂(诸如Toll样受体(TLR)激动剂CpG和咪喹莫特)的治疗,以及使用疫苗诸如BCG的治疗,而组合疗法提供了增加的对肿瘤细胞的效应细胞杀伤,即,当被共施用时,IL-15构建体和免疫疗法之间存在协同作用。

[0111] 如本文使用的术语"有效量"或"治疗有效量"是指足以治疗特定紊乱、状况或疾病,诸如改善、缓和、减轻和/或延迟其一种或更多种症状的化合物或组合物的量。述及NHL和其他癌症或其他不需要的细胞增殖,有效量包括足以实现以下的量:(i)降低癌细胞的数目;(ii)降低肿瘤尺寸;(iii)在一定程度抑制、延缓、减缓并且优选地停止癌细胞浸润到外周器官中;(iv)抑制(即,在一定程度减缓并且优选地停止)肿瘤转移;(v)抑制肿瘤生长;(vi)预防或延迟肿瘤的发生和/或复发;和/或(vii)在一定程度减轻一种或更多种与癌症相关的症状。有效量可以以一次或更多次施用来施用。

[0112] 术语"患者"、"个体"和"受试者"可以互换地使用,并且指哺乳动物,优选人类或非人类灵长类动物,但也指家养哺乳动物(例如犬科动物或猫科动物)、实验室哺乳动物(例如小鼠、大鼠、兔、仓鼠、豚鼠)和农业哺乳动物(例如马科动物、牛科动物、猪、绵羊(ovine))。在各种实施方案中,患者可以是在医院、精神病护理机构如门诊或其他临床环境中的医师或其他卫生工作者的护理下的人类(例如,成年男性、成年女性、青少年男性、青少年女性、男性儿童、女性儿童)。在各种实施方案中,患者可以是免疫功能低下的患者或免疫系统减弱的患者,包括但不限于患有原发性免疫缺陷、AIDS的患者;服用某些免疫抑制药物的癌症患者和移植患者;以及患有影响免疫系统的遗传性疾病(例如,先天性无丙种球蛋白血症、先天性IgA缺乏症)的患者。在各种实施方案中,患者患有免疫原性癌症,包括但不限于膀胱癌、肺癌、黑素瘤和报道具有高突变率的其他癌症(Lawrence等人,Nature,499(7457):214-

218,2013)。

[0113] “药物组合物”是指适于在哺乳动物中药物使用的组合物。药物组合物包含药理学有效量的活性剂和药学上可接受的载体。“药理学有效量”是指有效产生预期药理学结果的剂的量。“药学上可接受的载体”是指任何标准的药物载体、媒介物、缓冲剂和赋形剂,诸如磷酸盐缓冲盐水溶液、5%右旋糖的水性溶液,和乳液,诸如油/水乳液或水/油乳液,和各种类型的润湿剂和/或佐剂。合适的药学载体和制剂在Remington's Pharmaceutical Sciences,第21版2005,Mack Publishing Co,Easton中描述。“药学上可接受的盐”是可以被配制成用于药学用途的化合物的盐,包括例如金属盐(钠、钾、镁、钙等)和氨的盐或有机胺的盐。

[0114] 措辞“施用”或“引起施用(cause to be administered)”是指由医学专业人员(例如医师)或控制患者的医疗护理的人员采取的控制和/或允许向患者施用所讨论的剂/化合物的行动。引起施用可以包括诊断和/或确定合适的治疗方案,和/或为患者开特定的剂/化合物的处方。这样的开处方可以包括例如起草处方形式、注释医疗记录等。当本文中描述施用时也设想了“引起施用”。

[0115] “耐受性或难治性癌症”是指不响应于先前的抗癌疗法的肿瘤细胞或癌症,所述先前的抗癌疗法包括例如化学疗法、手术、放射疗法、干细胞移植和免疫疗法。肿瘤细胞可以在治疗的开始时是耐受性或难治性的,或者它们可以在治疗期间变成耐受性或难治性的。难治性肿瘤细胞包括在治疗的开始时不响应的肿瘤,或最初持续短的时间段响应治疗但不能响应治疗的肿瘤。难治性肿瘤细胞还包括响应于使用抗癌疗法的治疗但不能响应于随后几轮疗法的肿瘤。为了本发明的目的,难治性肿瘤细胞还包括通过使用抗癌疗法的治疗表现出被抑制但在治疗停止后长达5年,有时长达10年或更长时间而复发的肿瘤。抗癌疗法可以使用单独的化学治疗剂、单独的放射、单独的靶向疗法、单独的手术或其组合。为了便于描述而非限制,应理解,难治性肿瘤细胞与耐受性肿瘤是可互换的。

[0116] 术语“治疗(treat)”、“治疗(treating)”和“治疗(treatment)”是指减轻或消除生物学紊乱和/或其至少一个伴随症状的方法。如本文使用的,“减轻”疾病、紊乱或状况意指降低疾病、紊乱或状况的症状的严重性和/或发生频率。另外,本文中述及“治疗”包括述及治愈性、缓解性和预防性治疗。

[0117] 应理解,本文描述的本公开内容的方面和实施方案包括“由这些方面和实施方案组成”和/或“主要由这些方面和实施方案组成”。

[0118] 本文中述及“约”值或参数包括(并且描述)针对该值或参数本身的变化。例如,述及“约X”的描述包括对“X”的描述。

[0119] 除非上下文另外明确规定,否则如本文和所附的权利要求中使用的单数形式“一”、“或”和“该”包括复数指代物。应理解,本文描述的本公开内容的方面和变化形式包括“由这些方面和变化形式组成”和/或“主要由这些方面和变化形式组成”。

[0120] IL-15/IL-15RαSushi复合物

[0121] 白介素-15(IL-15)是一种细胞因子,由两个独立的研究组根据其在中和性抗IL-2抗体的存在下刺激IL-2依赖性CTLL-2T细胞系增殖的能力鉴定出(Steel等人,Trends in Pharmacological Sciences,33(1):35-41,2012)。IL-15和白介素-2(IL-2)在体外具有相似的生物学特性,与它们的共有受体(R)信号传导组分(IL-2/15Rβγ$_c$)一致。然而,IL-15与

IL-2的特异性是由独特的私有的α链受体提供的,这些α链受体使IL-15Rαβγ和IL-2Rαβγ异源三聚体高亲和力受体复合物完整,并且从而允许取决于所表达的配体和高亲和力受体的不同的响应性。令人感兴趣地,IL-15转录物和IL-15Rα转录物两者具有比IL-2/IL-2Rα广泛得多的组织分布。此外,多于一种复杂的转录后调控机制严格控制IL-15表达。因此,基于复杂的调控以及IL-15和IL-15Rα表达的不同模式,这种受体/配体对的关键的体内功能可能不同于IL-2和IL-2Rα的体内功能。迄今为止,检查IL-15的生物学的研究已经鉴定出若干关键的非冗余作用,诸如IL-15在自然杀伤(NK)细胞、NK-T细胞和肠上皮内淋巴细胞的发育过程中的重要性和功能。IL-15在自身免疫过程(诸如类风湿性关节炎)和恶性肿瘤(诸如成人T细胞白血病)期间的作用,表明IL-15的失调可能导致对宿主的有害影响(Fehniger等人,Blood,97:14-32,2001)。

[0122] 如本文使用的,术语"天然IL-15"和"天然白介素-15"在蛋白或多肽的上下文中是指任何天然存在的哺乳动物白介素-15氨基酸序列,包括未成熟形式或前体形式和成熟形式。各个物种的天然哺乳动物白介素-15的氨基酸序列的GenBank登录号的非限制性实例包括NP_000576(人类,未成熟形式)、CAA62616(人类,未成熟形式)、NP_001009207(家猫(Felis catus),未成熟形式)、AAB94536(大鼠属(rattus),未成熟形式)、AAB41697(大鼠属,未成熟形式)、NP_032383(小家鼠(Mus musculus),未成熟形式)、AAR19080(犬)、AAB60398(猕猴(macaca mulatta),未成熟形式)、AAI00964(人类,未成熟形式)、AAH23698(小家鼠,未成熟形式)和AAH18149(人类)。在本发明的各种实施方案中,天然IL-15是天然存在的哺乳动物IL-15的未成熟或前体形式。在其他实施方案中,天然IL-15是天然存在的哺乳动物IL-15的成熟形式。在各种实施方案中,天然IL-15是天然存在的人类IL-15的前体形式。在各种实施方案中,天然IL-15是天然存在的人类IL-15的成熟形式。在各种实施方案中,天然IL-15蛋白/多肽是分离或纯化的。在各种实施方案中,IL-15结构域源自SEQ ID NO:1中列出的人类IL-15前体序列的氨基酸序列:

[0123] MRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFSAGLPKTEANWVNVISDLKKIED LIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSS NGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 1)

[0124] IL-15受体是一种I型细胞因子受体,由与IL-2受体共有的beta(β)和gamma(γ)亚基以及以高亲和力结合IL-15的alpha(α)亚基组成。全长人类IL-15Rα是一种具有多个N-连接或O-连接的糖基化位点的1型跨膜蛋白,包含32个AA的信号肽、173个AA的细胞外结构域、21个AA的跨膜结构域和37个AA的细胞质尾(Anderson等人,J.Biol Chem,270:29862-29869,1995)。先前已经展示了,对应于IL-15Rα完整细胞外结构域的IL-15Rα链的天然可溶性形式起高亲和力IL-15拮抗剂的作用。然而,与该发现形成鲜明对比的是,已展示,具有对IL-15的大部分结合亲和力的IL-15Rα的重组可溶性sushi结构域,通过IL-15Rβ/γ异源二聚体增强其结合和生物效应(增殖和防止凋亡),起有效的IL-15激动剂的作用,而sushi结构域不影响IL-15结合和IL-15Rα/β/γ三部分膜受体的功能。这些结果表明,如果是天然产生的,这样的可溶性sushi结构域可能参与IL-15的反式呈递机制(Mortier等人,J.Biol Chem,281(3):1612-1619,2006)。

[0125] 如本文使用的,术语"天然IL-15Rα"和"天然白介素-15受体α"在蛋白或多肽的上下文中是指任何天然存在的哺乳动物白介素-15受体α("IL-15Rα")氨基酸序列,包括未成

熟形式或前体形式和成熟形式以及天然存在的同种型。各种天然哺乳动物IL-15Rα的氨基酸序列的GenBank登录号的非限制性实例包括NP_002180(人类)、ABK41438(猕猴)、NP_032384(小家鼠)、Q60819(小家鼠)、Q13261(人类)。在各种实施方案中,天然IL-15Rα是天然存在的哺乳动物IL-15Rα多肽的未成熟形式。在各种实施方案中,天然IL-15Rα是天然存在的哺乳动物IL-15Rα多肽的成熟形式。在各种实施方案中,天然IL-15Rα是天然存在的哺乳动物IL-15Rα多肽的形式。在各种实施方案中,天然IL-15Rα是天然存在的哺乳动物IL-15Rα多肽的全长形式。在各种实施方案中,天然IL-15Rα是天然存在的人类IL-15Rα多肽的未成熟形式。在各种实施方案中,天然IL-15Rα是天然存在的人类IL-15Rα多肽的成熟形式。在各种实施方案中,天然IL-15Rα是天然存在的人类IL-15Rα多肽的形式。在各种实施方案中,天然IL-15Rα是天然存在的人类IL-15Rα多肽的全长形式。在各种实施方案中,天然IL-15Rα蛋白或多肽是分离或纯化的。在各种实施方案中,IL-15Rα结构域源自SEQ ID NO:3中列出的人类IL-15Rα序列的氨基酸序列:

[0126] MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVEHADIWVKSYSLYSRERYIC NSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTP QPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSHGTPS QTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSRQTPP LASVEMEAMEALPVTWGTSSRDEDLENCSHHL (SEQ ID NO: 3)

[0127] 在各种实施方案中,天然IL-15Rα是天然存在的人类IL-15Rα多肽的完整的细胞外形式。在各种实施方案中,天然IL-15Rα蛋白或多肽是分离或纯化的。在各种实施方案中,IL-15Rα细胞外结构域源自SEQ ID NO:4中列出的人类IL-15Rα序列的氨基酸序列:

[0128] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTP SLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVP GSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQGHSDTT (SEQ ID NO: 4)

[0129] 在各种实施方案中,本发明的IL-15融合蛋白包含IL-15/IL-15RαSushi复合物,其中IL-15结构域包含SEQ ID NO:2中列出的成熟的人类IL-15多肽的氨基酸序列:

[0130] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 2)

[0131] 并且其中IL-15RαSushi结构域包含SEQ ID NO:5中列出的成熟的人类IL-15Rα多肽的氨基酸序列:

[0132] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTP SLKCIRDPALVHQRPAPP (SEQ ID NO: 5)

[0133] 在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是IL-15变体(或突变体),其包含源自SEQ ID NO:2中列出的成熟的人类IL-15多肽序列的序列。本文使用天然氨基酸、天然氨基酸在成熟序列中的位置和变异氨基酸来指代IL-15的变体(或突变体)。例如,“huIL-15S58D”是指包含在SEQ ID NO:2的位置58处的S至D取代的人类IL-15。在各种实施方案中,IL-15变体结合IL-15Rα多肽,并且起IL-15激动剂或拮抗剂的作用。在各种实施方案中,具有激动剂活性的IL-15变体具有超级激动剂活性。在各种实施方案中,IL-15变体可以起IL-15激动剂或拮抗剂的作用,与其与IL-15Rα的缔合无关。IL-15激动剂通过与野生型IL-15相比生物活性相当或增加来例示。IL-15拮抗剂通过与野生型IL-15相比生

物活性降低或通过抑制IL-15介导的响应的能力来例示。在各种实施方案中,IL-15变体以增加或减少的活性与IL-15Rβγ$_C$受体结合。在各种实施方案中,与天然IL-15序列相比,IL-15变体的序列具有至少一个氨基酸变化,例如取代或缺失;这样的变化导致IL-15激动剂或拮抗剂活性。在各种实施方案中,氨基酸取代/缺失位于与IL-15Rβ和/或γ$_C$相互作用的IL-15的结构域中。在各种实施方案中,氨基酸取代/缺失不影响与IL-15Rα多肽的结合或产生IL-15变体的能力。基于已知的IL-15结构、IL-15与同源分子诸如具有已知结构的IL-2的比较,通过本文提供的合理或随机诱变和功能测定或其他经验方法,可以鉴定产生IL-15变体的合适的氨基酸取代/缺失。此外,合适的氨基酸取代可以是保守或非保守的改变和另外氨基酸的插入。在各种实施方案中,本发明的IL-15变体在SEQ ID NO:2中列出的成熟的人类IL-15序列的位置30、31、32、62、63、67、68或108处包含一个或多于一个氨基酸取代。在各种实施方案中,D30T、V31Y、H32E、S58R、S58Q、T62D、V63A、V63R、V63K、I68H、I68F、I68D、I68K、I68Q、I68G、Q108A、Q108S、Q108E、Q108K或Q108M取代或取代组合导致具有拮抗剂活性的IL-15变体,而S58D取代导致具有激动剂活性的IL-15变体。

[0134] 在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有从位置111-114缺失的人类IL-15变体多肽(SEQ ID NO:39)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有从位置109-114缺失的人类IL-15变体多肽(SEQ ID NO:40)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有从位置108-114缺失的人类IL-15变体多肽(SEQ ID NO:41)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有从位置105-114缺失的人类IL-15变体多肽(SEQ ID NO:42)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是在N末端处具有一个、或两个、或三个、或四个、或五个或六个氨基酸缺失的人类IL-15变体多肽(SEQ ID NO:56-61)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有氨基酸取代和缺失的组合的人类IL-15变体多肽,由SEQ ID NO:62和63表示。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有位置N95后的'GS'(SEQ ID NO:12)插入的人类IL-15变体多肽(SEQ ID NO:43)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有位置N95后的'GGSGG'(SEQ ID NO:153)插入的人类IL-15变体多肽(SEQ ID NO:44)。在各种实施方案中,IL-15/IL-15RαSushi复合物的IL-15结构域将是具有位置N95后的'GSSGGSGGS'(SEQ ID NO:154)插入的人类IL-15变体多肽(SEQ ID NO:45)。

[0135] Fc结构域

[0136] IgG类的免疫球蛋白是人类血液中最丰富的蛋白之一。它们的循环半衰期可长达21天。已经报道了将IgG的Fc区与另一种蛋白(诸如各种细胞因子和受体)的结构域组合的融合蛋白(参见例如,Capon等人,Nature,337:525-531,1989;Chamow等人,Trends Biotechnol.,14:52-60,1996);美国专利第5,116,964号和第5,541,087号)。原型融合蛋白是通过IgG Fc的铰链区中的半胱氨酸残基连接的同源二聚体蛋白,产生类似于IgG分子、没有重链可变区和CH1结构域以及轻链的分子。包含Fc结构域的融合蛋白的二聚体性质在提供与其他分子的更高级相互作用(即二价或双特异性结合)方面可能是有利的。由于结构同源性,Fc融合蛋白表现出与具有相似同种型的人类IgG相当的体内药代动力学谱。

[0137] 术语"Fc"是指包含完整抗体的非抗原结合片段的序列的分子或序列,无论是单体形式还是多聚体形式。天然Fc的原始免疫球蛋白来源优选地为人类来源,并且可以是任何

免疫球蛋白。天然Fc由单体多肽组成,单体多肽可以通过共价(即二硫键)和非共价缔合连接成二聚体或多聚体形式。天然Fc分子的单体亚基之间的分子间二硫键的数目取决于类别(例如IgG、IgA、IgE)或亚类(例如IgG1、IgG2、IgG3、IgA1、IgGA2)而在从1至4的范围内。天然Fc的一种实例是由木瓜蛋白酶消化IgG产生的二硫键合的二聚体(参见Ellison等人(1982),Nucleic Acids Res.10:4071-9)。如本文使用的术语“天然Fc”是单体、二聚体和多聚体形式的总称。Fc结构域包含蛋白A、蛋白G、各种Fc受体和补体蛋白的结合位点。

[0138] 在各种实施方案中,术语“Fc变体”是指从天然Fc修饰、但仍然包含补救受体FcRn的结合位点的分子或序列。国际申请WO 97/34631(1997年9月25日公布)和WO 96/32478描述了示例性的Fc变体以及与补救受体的相互作用,并特此通过引用并入。此外,天然Fc包含可被去除的位点,因为它们提供本发明的融合分子不需要的结构特征或生物活性。因此,在各种实施方案中,术语“Fc变体”包括缺乏一个或更多个天然Fc位点或残基的分子或序列,所述天然Fc位点或残基影响或参与(1)二硫键形成,(2)与所选宿主细胞的不相容性,(3)在所选宿主细胞中表达时的N末端或C末端异质性,(4)糖基化,(5)与补体的相互作用,(6)与补救受体以外的Fc受体的结合,或(7)抗体依赖性细胞毒性(ADCC)。

[0139] 术语“Fc结构域”包括如上文定义的天然Fc和Fc变体分子和序列。如同Fc变体和天然Fc,术语“Fc结构域”包括单体或多聚体形式的分子,无论是从完整抗体消化的还是通过重组基因表达或通过其他方式产生的。在各种实施方案中,Fc结构域中的每个Fc结构域单体包含CH2抗体恒定结构域中的氨基酸取代,以降低Fc结构域和Fcγ受体之间的相互作用或结合。在各种实施方案中,Fc结构域的每个亚基包含三个氨基酸取代,这三个氨基酸取代降低与活化性Fc受体的结合和/或效应子功能,其中所述氨基酸取代是L234A、L235A和G237A(SEQ ID NO:6)。

[0140] 在各种实施方案中,Fc结构域中的两个Fc结构域单体中的每一个包含促进两个单体异源二聚体化的氨基酸取代。在各种其他实施方案中,Fc结构域单体的异源二聚体化可以通过在两个Fc结构域单体中引入不同但相容的取代诸如“knob-into-hole”残基对来促进。“knob-into-hole”技术也公开于美国专利公布第8,216,805号中。在又另一种实施方案中,一个Fc结构域单体包含knob突变T366W,并且另一个Fc结构域单体包含hole突变T366S、L358A和Y407V。在各种实施方案中,引入形成稳定化的二硫桥的两个Cys残基(S354C在“knob”侧,并且Y349C在“hole”侧)(SEQ ID NO:7和8)。

[0141] 在一方面,本发明的IL-15融合蛋白包含IL-15/IL-15RαSushi复合物和至少一种与IL-15/IL-15RαSushi复合物附接的异源蛋白,所述异源蛋白直接或通过肽接头序列与IL-15/IL-15RαSushi复合物附接以形成IL-15融合蛋白。如本文使用的术语“融合蛋白”是指具有经由重组DNA技术附接的异源多肽的蛋白。在各种实施方案中,异源蛋白是Fc结构域(或其功能片段),并且所得的融合蛋白是IL-15/IL-15RαSushi复合物-Fc融合蛋白。在各种实施方案中,IL-15/IL-15RαSushi复合物与至少一种赋予融合分子延长的半衰期的多肽融合。这样的多肽包括结合新生Fcγ/受体的IgG Fc或其他多肽、人类血清白蛋白或结合具有延长的血清半衰期的蛋白的多肽,包括IgG、非IgG免疫球蛋白、蛋白和非蛋白剂,其由于存在结合FcRn的IgG恒定结构域或其部分而具有增加的体内半衰期,具有增加恒定结构域或片段对FcRn的亲和力的一个或更多个氨基酸修饰。这样的具有增加的半衰期的蛋白和分子具有这样的优点,即在这种分子的治疗、预防或诊断用途中需要更少的量和/或更少的给药

频率(参见例如,美国专利第7,658,921号)。在各种实施方案中,Fc结构域选自由以下组成的组:人类IgG1 Fc结构域、人类IgG2 Fc结构域、人类IgG3 Fc结构域、人类IgG4 Fc结构域、IgAFc结构域、IgD Fc结构域、IgE Fc结构域、IgG Fc结构域和IgM Fc结构域或它们的任何组合。在各种实施方案中,Fc结构域包含导致Fc结构域具有改变的补体结合特性或Fc受体结合特性的氨基酸变化。产生具有改变的补体结合特性或Fc受体结合特性的Fc结构域的氨基酸变化是本领域已知的。

[0142] 在各种实施方案中,Fc结构域可以被突变以进一步延长体内半衰期。在各种实施方案中,Fc结构域的每个亚基包含增强与人类FcRn的结合的三个氨基酸取代,其中所述氨基酸取代是M252Y、S254T和T256E(SEQ ID NO:105),公开于美国专利公布第7,658,921号中。在各种实施方案中,Fc结构域的每个亚基包含增强与人类FcRn的结合的一个氨基酸取代,其中所述氨基酸取代是N434A(SEQ ID NO:106),公开于美国专利公布第7,371,826号中。在各种实施方案中,Fc结构域的每个亚基包含增强与人类FcRn的结合的一个氨基酸取代,其中所述氨基酸取代是M428L和N434S,公开于美国专利公布第8,546,543号中。在各种实施方案中,半衰期延长突变可以与降低/消除与活化性Fc受体的结合并因此减少/消除效应子功能的氨基酸取代组合。

[0143] 在各种实施方案中,用于制备二聚体IL-15/IL-15Rα复合物-Fc融合蛋白的Fc结构域序列是具有降低/消除的效应子功能并且具有SEQ ID NO:6中列出的氨基酸序列的IgG1-Fc结构域。

[0144] 在各种实施方案中,用于制备二聚体IL-15/IL-15Rα复合物-Fc融合蛋白的Fc结构域是具有降低/消除的效应子功能和延长的半衰期并且具有SEQ ID NO:105中列出的氨基酸序列的IgG1-Fc结构域。

[0145] 在各种实施方案中,用于制备二聚体IL-15/IL-15Rα复合物-Fc融合蛋白的Fc结构域是具有降低/消除的效应子功能和延长的半衰期并且具有SEQ ID NO:106中列出的氨基酸序列的IgG1-Fc结构域。

[0146] 在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域序列是具有降低/消除的效应子功能并且具有SEQ ID NO:7中列出的序列的Knob-Fc结构域。

[0147] 在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域序列是具有降低/消除的效应子功能并且具有SEQ ID NO:8中列出的序列的Hole-Fc结构域。

[0148] 在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域是具有降低/消除的效应子功能和延长的半衰期并且具有SEQ ID NO:107中列出的氨基酸序列的Knob-Fc结构域。

[0149] 在各种实施方案中,用于制备单价IL-15/IL-15Rα复合物-Fc融合蛋白的异源二聚体Fc结构域是具有降低/消除的效应子功能和延长的半衰期并且具有SEQ ID NO:108中列出的氨基酸序列的Hole-Fc结构域。

[0150] 肿瘤相关抗原抗体和蛋白/肽结合物

[0151] 在各种实施方案中,异源蛋白可以包括能够结合到病变细胞或病变组织上的肿瘤相关抗原(TAA)的抗体、抗体片段、或蛋白或肽。TAA可以是针对其需要免疫应答的任何分

子、大分子、分子组合等。TAA可以是包含多于一个多肽亚基的蛋白。例如,蛋白可以为二聚体、三聚体或更高级多聚体。在各种实施方案中,蛋白的两个或更多个亚基可以以共价键诸如例如二硫键连接。在各种实施方案中,蛋白的亚基可以以非共价相互作用保持在一起。因此,TAA可以是技术人员希望针对其诱导免疫应答的任何肽、多肽、蛋白、核酸、脂质、碳水化合物或有机小分子或其任何组合。在各种实施方案中,TAA为包含以下的肽:约5个、约6个、约7个、约8个、约9个、约10个、约11个、约12个、约13个、约14个、约15个、约16个、约17个、约18个、约19个、约20个、约25个、约30个、约35个、约40个、约45个、约50个、约55个、约60个、约65个、约70个、约75个、约80个、约85个、约90个、约95个、约100个、约150个、约200个、约250个、约300个、约400个、约500个、约600个、约700个、约800个、约900个或约1000个氨基酸。在各种实施方案中,肽、多肽或蛋白是通常通过注射向受试者施用的分子。在各种实施方案中,在施用后,肿瘤特异性抗体或结合蛋白用作靶向部分,以将融合分子引导至病变部位,诸如癌症部位,在该部位,活性结构域可以与其在病变细胞或病变组织上的同源受体相互作用。

[0152] 任何前述标志物都可以用作本发明的构建体的疾病相关靶或TAA靶。在各种实施方案中,设想用于本公开内容的构建体和方法的一种或更多种疾病相关靶或其变体、或TAA、TAA变体或TAA突变体选自或源自表2中提供的列表。

[0153] 表2

[0154] 肿瘤相关抗原的列表

[0155]

| 肿瘤相关抗原 | RefSeq (蛋白) |
|---|---|
| Her2/neu | NP_001005862 |
| Her3 | NP_001005915 |
| Her4 | NP_001036064 |
| EGF | NP_001171601 |
| EGFR | NP_005219 |
| CD2 | NP_001758 |
| CD3 | NM_000732 |
| CD5 | NP_055022 |
| CD7 | NP_006128 |
| CD13 | NP_001141 |
| CD19 | NP_001171569 |
| CD20 | NP_068769 |
| CD21 | NP_001006659 |
| CD22 | NP_001762 |
| CD23 | NP_001193948 |
| CD30 | NP_001234 |
| CD33 | NP_001234.3 |
| CD34 | NP_001020280 |
| CD38 | NP_001766 |
| CD40 | NP_001241 |
| CD46 | NP_002380 |
| CD55 | NP_000565 |
| CD59 | NP_000602 |
| CD69 | NP_001772 |
| CD70 | NM_001252 |
| CD71 | NP_001121620 |
| CD80 | NP_005182 |
| CD97 | NP_001020331 |
| CD117 | NP_000213 |
| CD127 | NP_002176 |
| CD134 | NP_003318 |
| CD137 | NP_001552 |
| CD138 | NP_001006947 |
| CD146 | NP_006491 |
| CD147 | NP_001719 |
| CD152 | NP_001032720 |

[0156]

| | |
|---|---|
| CD154 | NP_000065 |
| CD195 | NP_000570 |
| CD200 | NP_001004196 |
| CD212 | NP_001276952 |
| CD223 | NP_002277 |
| CD253 | NP_001177871 |
| CD272 | NP_001078826 |
| CD274 (PD-L1) | NP_001254635 |
| CD276 | NP_001019907 |
| CD278 | NP_036224 |
| CD279 (PD-1) | NP_005009 |
| CD309 (VEGFR2) | NP_002244 |
| DR6 | NP_055267 |
| Kv1.3 | NP_002223 |
| 5E10 | NP_006279 |
| MUC1 | NP_001018016 |
| uPA | NP_002649 |
| SLAMF7 (CD319) | NP_001269517 |
| MAGE 3 | NP_005353 |
| MUC 16 (CA-125) | NP_078966 |
| KLK3 | NP_001025218 |
| K-ras | NP_004976 |
| 间皮素 | NP_001170826 |
| p53 | NP_000537 |
| 存活蛋白 | NP_001012270 |
| G250 (肾细胞癌抗原) | GenBank CAB82444.1 |
| PSMA | NP_001014986 |
| HLA-DR | NP_001020330 |
| 1D10 | NP_114143 |
| I型胶原 | NP_000079 |
| II型胶原 | NP_000080 |
| 纤连蛋白 | XP_005246463 |
| 生腱蛋白 | NP_002151 |
| 基质金属蛋白酶-2 (MMP-2) | NP_001121363 |
| 基质金属蛋白酶-9 (MMP-9) | NP_004985 |
| 基质金属蛋白酶-14 (MMP-14) | NP_004986 |
| 成纤维细胞活化蛋白 (FAP) | NM_004460.3 |
| Siglec-8 | NP_055257 |
| Siglec-9 | NP_001185487 |

[0157]

| | |
|---|---|
| Siglec-15 | NP_998767 |
| 豆荚蛋白(legumain) | NP_001008530 |
| 酪氨酸酶 | NP_000363 |
| 黑色素-A (Melan-A，MART I) | NP_005502 |
| SSX-2 | NP_003138 |
| MAGE-1 | NP_004979 |
| NY-ESO-1 (CTAG1) | NP_001318 |
| PRAME | NP_006106 |
| PSA | NP_001639 |
| C35 | NP_115715 |
| SSX-4 | NP_783856 |
| gp100 (Pmel17) | NP_008859 |
| TTF1 | NP_003308 |
| 乳腺球蛋白 | NP_002402 |
| Brst2 | NP_002643 |
| 间皮素，同种型1 | NP_005814 |
| 间皮素，同种型2 | NP_037536 |
| PSCA | NP_005663 |
| SYCP-1 | NP_003167 |
| PLK1 | NP_005321 |
| VEGF-A | NP_001020537.2 |
| 甲胎蛋白(AFP) | NP_001125 |

[0158] 肿瘤相关抗原的另外的实例包括TRP-1、TRP-2、MAG-1、MAGE-3、BAGE、GAGE-1、GAGE-2、p15(58)、CEA、RAGE、NY-BSO(LAGE)、SCP-1、Hom/Mel-40、H-Ras、BCR-ABL、E2A-PRL、H4-RET、IGH-IGK、MYL-RAR、人类乳头瘤病毒(HPV)抗原E6和E7、TSP-180、MAGE-4、MAGE-5、MAGE-6、p185erbB2、p180erbB-3、c-met nm-23H1、PSA、TAG-72-4、CA19-9、CA 72-4、CAM 17.1、Numa、K-ras、β-联蛋白、CDK4、Muni-1、p16、TAGE、PSCA、CT7、端粒酶、43-9F、5T4、791Tgp72、β-HCG、BCA225、BTAA、CA 15-3(CA 27.29\BCAA)、CA 195、CA 242、CA-50、CAM43、CD68\KF1、CO-029、FGF-5、G250、Ga733(EpCAM)、HTgp-175、M344、MA-50、MG7-Ag、MOV18、NB/70K、NY-CO-1、RCAS1、SDCCAG16、TA-90(Mac-2结合蛋白\亲环蛋白C-相关蛋白)、TAAL6、TAG72、TLP和TPS。

[0159] 免疫检查点调节剂

[0160] 已经报道了在各种免疫细胞上表达的许多免疫检查点蛋白抗原，包括例如，CD152(由活化的CD8+T细胞、CD4+T细胞和调节性T细胞表达)、CD279(在肿瘤浸润性淋巴细胞上表达，由活化的T细胞(CD4和CD8两者)、调节性T细胞、活化的B细胞、活化的NK细胞、无变应性T细胞、单核细胞、树突细胞表达)、CD274(在T细胞、B细胞、树突细胞、巨噬细胞、血管内皮细胞、胰岛细胞上表达)和CD223(由活化的T细胞、调节性T细胞、无变应性T细胞、NK细胞、NKT细胞和浆细胞样树突细胞表达)(参见，例如，Pardoll，D.，Nature Reviews Cancer，12:252-264，2012)。结合被确定为免疫检查点蛋白的抗原的抗体是本领域技术人员已知的。例如，本领域已经描述了各种抗CD276抗体(参见，例如，美国专利公布第20120294796号

(Johnson等人)及其中引用的参考文献);本领域已经描述了各种抗CD272抗体(参见,例如,美国专利公布第20140017255号(Mataraza等人)及其中引用的参考文献);本领域已经描述了各种抗CD152/CTLA-4抗体(参见,例如,美国专利公布第20130136749号(Korman等人)及其中引用的参考文献);本领域已经描述了各种抗LAG-3/CD223抗体(参见,例如,美国专利公布第20110150892号(Thudium等人)及其中引用的参考文献);本领域已经描述了各种抗CD279/PD-1抗体(参见例如,美国专利第7,488,802号(Collins等人)及其中引用的参考文献);本领域已经描述了各种抗CD274/PD-L1抗体(参见例如,美国专利公布第20130122014号(Korman等人)及其中引用的参考文献);本领域已经描述了各种抗TIM-3抗体(参见,例如,美国专利公布第20140044728号(Takayanagi等人)及其中引用的参考文献);并且本领域已经描述了各种抗B7-H4抗体(参见,例如,美国专利公布第20110085970号(Terrett等人)及其中引用的参考文献)。这些参考文献中的每一篇关于其中教导的特定抗体和序列通过引用以其整体特此并入。

[0161] 在各种实施方案中,异源蛋白可以包括表现出与存在于免疫细胞表面的免疫检查点蛋白抗原结合的抗体、抗体片段、或蛋白或肽。在各种实施方案中,免疫检查点蛋白抗原选自由以下组成但不限于以下的组:CD276、CD272、CD152、CD223、CD279(PD-1)、CD274(PD-L1)、CD40、SIRPα、CD47、OX-40、GITR、ICOS、CD27、4-1BB、TIM-3、B7-H4、Siglec-7、Siglec-8、Siglec-9、Siglec-15和VISTA。

[0162] 在各种实施方案中,抗体是包含SEQ ID NO:109-110中列出的重链和轻链序列的人源化抗FAP抗体。在各种实施方案中,抗体是拮抗性程序性死亡-1(PD-1)抗体或抗体片段。在各种实施方案中,抗体是包含SEQ ID NO:111-112中列出的重链和轻链氨基酸序列的拮抗性人源化PD-1抗体。在各种实施方案中,抗体是包含SEQ ID NO:113-114中列出的重链和轻链氨基酸序列的拮抗性人类PD-1抗体。在各种实施方案中,抗体是拮抗性程序性死亡配体-1(PD-L1)抗体或抗体片段。

[0163] 接头

[0164] 在各种实施方案中,异源蛋白(例如Fc结构域或抗体/抗体片段)通过多肽接头序列与IL-15/IL-15RαSushi(或其功能片段)复合物的IL-15多肽共价地连接。在各种实施方案中,接头可以是相对地不含二级结构的在5个、10个、15个、20个、30个、40个或更多个氨基酸之间的人工序列。在各种实施方案中,接头G/S含量丰富(例如接头中至少约60%、70%、80%、90%或更多的氨基酸是G或S)。在各种实施方案中,接头选自SEQ ID NO:9-12、SEQ ID NO:47和SEQ ID NO:153-154中列出的序列的组。每个肽接头序列可以独立地选择。

[0165] 新型IL-15/IL-15RαSushi复合物融合蛋白的实例

[0166] 在各种实施方案中,本发明的示例性IL-15/IL-15RαSushi异源二聚体Fc融合蛋白在表3A中以融合蛋白ID号和融合蛋白链1和链2 SEQ ID NO列出。

[0167] 表3A

[0168] 示例性IL-15/IL-15RαSushi异源二聚体Fc融合蛋白

[0169]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | |
|---|---|---|
| | 链1 | 链2 |
| P-0153 | 13 | 14 |
| P-0156 | 15 | 16 |
| P-0155 | 17 | 18 |

[0170] 在各种实施方案中,本发明的示例性单价IL-15/IL-15RαSushi(非共价)Fc融合蛋白在表3B中以融合蛋白ID号和融合蛋白链1、链2和链3 SEQ ID NO列出。

[0171] 表3B

[0172] 示例性单价IL-15/IL-15RαSushi(非共价)Fc融合蛋白

[0173]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | | |
|---|---|---|---|
| | 链1 | 链2 | 链3 |
| P-0197 | 13 | 5 | 7 |
| P-0201 | 15 | 5 | 7 |
| P-0207 | 18 | 5 | 7 |
| P-0217 | 54 | 5 | 7 |
| P-0219 | 54 | 4 | 7 |
| P-0221 | 19 | 5 | 7 |
| P-0222 | 19 | 4 | 7 |

[0174] 在各种实施方案中,本发明的示例性二价IL-15/IL-15RαSushi(非共价)Fc融合蛋白在表3C中以融合蛋白ID号和融合蛋白链1、链2和链3 SEQ ID NO列出。

[0175] 表3C

[0176] 示例性二价IL-15/IL-15RαSushi(非共价)Fc融合蛋白

[0177]

| 融合蛋白 ID | 融合蛋白 SEQ ID NO: | | |
|---|---|---|---|
| | 链 1 | 链 2 | 链 3 |
| P-0198 | 13 | 5 | 55 |
| P-0234 | 20 | 5 | × |
| P-0223 | 21 | 5 | × |

[0178] 在各种实施方案中,本发明的示例性二价IL-15/IL-15RαECD(非共价)Fc融合蛋白在表3D中以融合蛋白ID号和融合蛋白链1和链2 SEQ ID NO列出。

[0179] 表3D

[0180] 示例性二价IL-15/IL-15RαECD(非共价)Fc融合蛋白

[0181]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | |
|---|---|---|
| | 链1 | 链2 |
| P-0220 | 20 | 4 |
| P-0224 | 21 | 4 |

[0182] 在各种实施方案中,本发明的示例性单价IL-15(非共价)/IL-15RαSushi Fc融合蛋白在表3E中以融合蛋白ID号和融合蛋白链1、链2和链3 SEQ ID NO列出。

[0183] 表3E

[0184] 示例性单价IL-15(非共价)/IL-15RαSushi Fc融合蛋白

[0185]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | | |
|---|---|---|---|
| | 链1 | 链2 | 链3 |
| P-0165 | 2 | 14 | 8 |
| P-0166 | 2 | 22 | 8 |

[0186] 在各种实施方案中,本发明的二价IL-15(非共价)/IL-15RαSushi Fc融合蛋白(下文中也称为"P-0218")包含具有SEQ ID NO:2中列出的氨基酸序列的链1(IL-15)、具有SEQ ID NO:23中列出的氨基酸序列的链2(Fc-接头-IL-15Rα-Sushi+)。

[0187] 在各种实施方案中,IL-15/IL-15RαSushi复合物将包含IL-15变体,所述IL-15变体具有选自由以下中列出的序列组成的组的氨基酸序列:SEQ ID NO:24、SEQ ID NO:25、SEQ ID NO:26、SEQ ID NO:27、SEQ ID NO:28、SEQ ID NO:29、SEQ ID NO:30、SEQ ID NO:31、SEQ ID NO:32、SEQ ID NO:33、SEQ ID NO:34、SEQ ID NO:35、SEQ ID NO:36、SEQ ID NO:37、SEQ ID NO:38、SEQ ID NO:39、SEQ ID NO:40、SEQ ID NO:41、SEQ ID NO:42、SEQ ID NO:43、SEQ ID NO:44、SEQ ID NO:45、SEQ ID NO:56、SEQ ID NO:57、SEQ ID NO:58、SEQ ID NO:59、SEQ ID NO:60、SEQ ID NO:61、SEQ ID NO:62、SEQ ID NO:63、SEQ ID NO:66、SEQ ID NO:67、SEQ ID NO:68、SEQ ID NO:69、SEQ ID NO:70、SEQ ID NO:71、SEQ ID NO:72、SEQ ID NO:73、SEQ ID NO:74、SEQ ID NO:75、SEQ ID NO:76、SEQ ID NO:77、SEQ ID NO:78、SEQ ID NO:79、SEQ ID NO:80和SEQ ID NO:81。

[0188] 在各种实施方案中,在IL-15中包含S58D突变并且为本发明的图1中图示的各种形式的示例性IL-15/IL-15RαSushi Fc融合蛋白在表3F中以融合蛋白ID号和融合蛋白链1、链2和链3 SEQ ID NO列出。

[0189] 表3F

[0190] 在IL-15中包含S58D突变的示例性IL-15/IL-15RαFc融合蛋白

[0191]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | | |
|---|---|---|---|
| | 链1 | 链2 | 链3 |
| P-0313 | 46 | 5 | × |
| P-0314 | 23 | 24 | × |
| P-0666 | 48 | 5 | 7 |
| P-0667 | 49 | 5 | 7 |
| P-0668 | 50 | 5 | × |
| P-0669 | 24 | 22 | 8 |
| P-0670 | 24 | 51 | 8 |
| P-0671 | 24 | 52 | × |

[0192] 在各种实施方案中,包含两个或更多个异源二聚体链的另外的IL-15变体/IL-15Rα复合物-FC融合蛋白在表3G中列出:

[0193] 表3G

[0194] 另外的IL-15变体/IL-15Rα复合物-Fc融合蛋白

[0195]

| 融合蛋白 ID | 融合蛋白 SEQ ID NO: | | |
|---|---|---|---|
| | 链 1 | 链 2 | 链 3 |
| P-0739 | 82 | 5 | × |
| P-0740 | 83 | 5 | × |
| P-0741 | 84 | 5 | × |
| P-0742 | 85 | 5 | × |
| P-0743 | 86 | 5 | × |
| P-0744 | 87 | 5 | × |
| P-0771 | 88 | 5 | × |
| P-0184 | 26 | 14 | 8 |
| P-0769 | 89 | 5 | × |
| P-0770 | 90 | 5 | × |
| P-0356 | 91 | 5 | × |
| P-0357 | 92 | 5 | × |
| P-0358 | 93 | 5 | × |
| P-0738 | 94 | 5 | × |
| P-0736 | 95 | 5 | × |
| P-0737 | 96 | 5 | × |
| P-0764 | 97 | 7 | 5 |
| P-0793 | 98 | 7 | 5 |
| P-0805 | 99 | 8 | 5 |

[0196]

| | | | |
|---|---|---|---|
| P-0797 | 100 | 8 | 5 |
| P-0796 | 101 | 8 | 5 |
| P-0773 | 102 | 5 | × |
| P-0772 | 103 | 5 | × |
| P-0768 | 104 | 5 | × |
| P-0866 | 149 | 5 | × |
| P-0867 | 150 | 5 | × |
| P-0868 | 151 | 5 | × |
| P-0822 | 152 | 5 | × |

[0197] 在各种实施方案中,在IL-15/IL-15Rα抗体融合蛋白中使用具有减弱效力的IL-15变体可以有助于在IL-15和靶向抗体之间建立化学计量平衡,以实现最佳剂量,在该剂量抗体可以实现足够的靶位占据,同时IL-15部分不会引起途径的过度活化,从而使外周活化最小化、减轻抗原吸收并促进经由抗体臂的肿瘤靶向。

[0198] 在各种实施方案中,包含两个或更多个异源二聚体链的示例性IL-15变体/IL-15Rα复合物-PD-1拮抗剂抗体融合蛋白在表3H中列出:

[0199] 表3H

[0200] 示例性IL-15变体/IL-15Rα复合物-PD-1拮抗剂抗体融合蛋白

[0201]

| 融合蛋白ID | 融合蛋白SEQ ID NO: | | | |
|---|---|---|---|---|
| | 链1 | 链2 | 链3 | 链4 |
| P-0820 | 138 | 114 | 5 | x |
| P-0801 | 139 | 144 | 114 | 5 |
| P-0821 | 140 | 144 | 114 | 5 |
| P-0870 | 141 | 114 | 5 | x |
| P-0856 | 142 | 144 | 114 | 5 |
| P-0857 | 143 | 144 | 114 | 5 |
| P-0858 | 145 | 114 | 5 | x |
| P-0886 | 146 | 114 | 5 | x |
| P-0887 | 147 | 114 | 5 | x |
| P-0888 | 148 | 114 | 5 | x |

[0202] 多核苷酸

[0203] 在另一方面,本公开内容提供了分离的核酸分子,该分离的核酸分子包含编码以下的多核苷酸:本公开内容的IL-15、IL-15变体、IL-15Rα、IL-15Rα变体、Fc、Fc变体、IL-15-Fc融合蛋白、IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-Fc融合蛋白、靶向TAA或免疫检查点调节剂的抗体、抗体片段、IL-15-抗体融合蛋白、IL-15/IL-15RαSushi-抗体融合蛋白。主题核酸可以是单链的或双链的。这样的核酸可以是DNA或RNA分子。DNA包括例如cDNA、基因组DNA、合成的DNA、通过PCR扩增的DNA及其组合。编码IL-15/IL-15RαSushi复合物的基因组DNA获取自基因组文库,该基因组文库对许多物种是可得的。合成的DNA从化学合成重叠的寡核苷酸片段然后组装片段以重构编码区和侧翼序列的部分或全部而可获得。可以从指导mRNA的高水平合成的原核表达载体,诸如使用T7启动子和RNA聚合酶的载体获得RNA。cDNA获取自从分离自表达IL-15的各种组织的mRNA制备的文库。本公开内容的DNA分子包括全长基因以及多核苷酸及其片段。全长基因还可以包含编码N末端信号序列的序列。这样的核酸可以例如在用于制备新型IL-15/IL-15RαSushi融合蛋白的方法中使用。

[0204] 在各种实施方案中,分离的核酸分子包含本文描述的多核苷酸,并且还包含编码本文描述的至少一种异源蛋白的多核苷酸。在各种实施方案中,核酸分子还包含编码本文描述的接头或铰链接头的多核苷酸。

[0205] 在各种实施方案中,本公开内容的重组核酸可以可操作地连接至表达构建体中的一种或更多种调控核苷酸序列。调控序列是本领域所认知的并且被选择以指导IL-15/IL-15RαSushi融合蛋白的表达。相应地,术语调控序列包括启动子、增强子和其他表达控制元件。在Goeddel;Gene Expression Technology:Methods in Enzymology,Academic Press,San Diego,Calif.(1990)中描述了示例性的调控序列。通常,所述一种或更多种调控核苷酸序列可以包括但不限于启动子序列、前导或信号序列、核糖体结合位点、转录起始和终止序列、翻译起始和终止序列、以及增强子或激活序列。本公开内容设想了本领域已知的组成型或诱导型启动子。启动子可以是天然存在的启动子或者组合多于一个启动子的元件的杂合启动子。表达构建体可以存在于细胞中的附加体诸如质粒上,或者表达构建体可以插入染色体中。在各种实施方案中,表达载体包含选择性标志物基因以允许选择转化的宿主细

胞。选择性标志物基因是本领域熟知的并且将随着使用的宿主细胞变化。

[0206] 在本公开内容的另一方面,主题核酸在表达载体中提供,所述表达载体包含编码IL-15/IL-15RαSushi复合物并可操作地连接至至少一个调控序列的核苷酸序列。术语“表达载体”是指用于从多核苷酸序列表达多肽的质粒、噬菌体、病毒或载体。适于在宿主细胞中表达的载体是容易地可得的并利用标准重组DNA技术将核酸分子插入到载体中。这样的载体可以包括各种各样的表达控制序列,当被可操作地连接至DNA序列时,所述表达控制序列控制该DNA序列的表达,并可以在这些载体中使用以表达编码IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白的DNA序列。这样的有用的表达控制序列包括,例如,SV40的早期启动子和晚期启动子、tet启动子、腺病毒或巨细胞病毒介导的早期启动子、RSV启动子、lac系统、trp系统、TAC或TRC系统、其表达由T7 RNA聚合酶指导的T7启动子、λ噬菌体的主要操纵子和启动子区域、fd外壳蛋白的控制区域、3-磷酸甘油酸激酶或其他糖酵解酶的启动子、酸性磷酸酶例如PhoS的启动子、酵母a-交配因子的启动子、杆状病毒系统的多角体启动子和已知控制原核细胞或真核细胞或它们的病毒的基因表达的其他序列,及其各种组合。应理解,表达载体的设计可能取决于诸如待转化的宿主细胞的选择和/或期望表达的蛋白的类型的因素。此外,还应考虑载体的拷贝数、控制该拷贝数的能力、以及载体编码的任何其他蛋白诸如抗生素标志物的表达。

[0207] 本公开内容的重组核酸可以通过将克隆的基因或其一部分连接到适于在原核细胞、真核细胞(酵母、鸟类、昆虫或哺乳动物)或两者中表达的载体中来产生。用于产生重组IL-15/IL-15RαSushi复合物的表达载体包括质粒和其他载体。例如,合适的载体包括以下类型的质粒:用于在原核细胞诸如大肠杆菌中表达的pBR322衍生的质粒、pEMBL衍生的质粒、pEX衍生的质粒、pBTac衍生的质粒和pUC衍生的质粒。

[0208] 一些哺乳动物表达载体包含利于载体在细菌中增殖的原核序列以及在真核细胞中表达的一种或更多种真核转录单元两者。pcDNAI/amp、pcDNAI/neo、pRc/CMV、pSV2gpt、pSV2neo、pSV2-dhfr、pTk2、pRSVneo、pMSG、pSVT7、pko-neo和pHyg衍生的载体为适于转染真核细胞的哺乳动物表达载体的实例。这些载体中的一些被来自细菌质粒诸如pBR322的序列修饰,以利于在原核细胞和真核细胞两者中复制和药物抗性选择。可选地,病毒诸如牛乳头瘤病毒的衍生物(BPV-1)或Epstein-Barr病毒的衍生物(pHEBo、pREP衍生的和p205)可以用于蛋白在真核细胞中的瞬时表达。其他病毒(包括逆转录病毒)表达系统的实例可见于下文基因疗法递送系统的描述中。在质粒的制备方面和宿主生物体的转化方面所采用的各种方法是本领域熟知的。对于适于原核细胞和真核细胞两者的其他表达系统以及一般的重组程序,参见Sambrook、Fritsch和Maniatis的Molecular Cloning A Laboratory Manual,第2版(Cold Spring Harbor Laboratory Press,1989)第16和17章。在一些情形下,可能期望通过使用杆状病毒表达系统来表达重组多肽。此类杆状病毒表达系统的实例包括pVL衍生的载体(诸如pVL1392、pVL1393和pVL941)、pAcUW衍生的载体(诸如pAcUW1)以及pBlueBac衍生的载体(诸如含有B-gal的pBlueBac III)。

[0209] 在各种实施方案中,载体将被设计成用于在CHO细胞中产生主题IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白,诸如Pcmv-Script载体(Stratagene,La Jolla,Calif.)、pcDNA4载体(Invitrogen,Carlsbad,Calif.)和pCI-neo载体(Promega,Madison,Wis.)。将明显的是,主题基因构建体可以被用于引起主题IL-15/

IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白在增殖于培养基中的细胞中表达,例如以产生用于纯化的蛋白,包括融合蛋白或变体蛋白。

[0210] 本公开内容还涉及用重组基因转染的宿主细胞,所述重组基因包含编码一种或更多种主题IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白的氨基酸序列的核苷酸序列。宿主细胞可以是原核细胞或真核细胞。例如,本公开内容的IL-15/IL-15RαSushi复合物可以在细菌细胞诸如大肠杆菌、昆虫细胞(例如,使用杆状病毒表达系统)、酵母或哺乳动物细胞中表达。其他合适的宿主细胞是本领域技术人员已知的。

[0211] 相应地,本公开内容还涉及产生主题IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白的方法。例如,可以在允许发生IL-15/IL-15RαSushi复合物的表达的适当条件下培养用编码IL-15/IL-15RαSushi复合物的表达载体转染的宿主细胞。IL-15/IL-15RαSushi复合物可以从含有IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白的细胞分泌和从含有IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白的细胞和培养基的混合物分离。可选地,IL-15/IL-15RαSushi复合物可以保留在细胞质中或保留在膜级分中,并收获、裂解细胞和分离蛋白。细胞培养物包括宿主细胞、培养基和其他副产物。用于细胞培养的合适培养基是本领域熟知的。

[0212] 本公开内容的多肽和蛋白可以根据本领域技术人员熟知的蛋白纯化技术来纯化。这些技术在一个层面上涉及蛋白质级分和非蛋白质级分的粗分级。将肽或多肽与其他蛋白分离后,可以利用色谱技术和电泳技术进一步纯化感兴趣的肽或多肽,以实现部分或完全纯化(或纯化至均一)。如本文使用的术语“分离的多肽”或“纯化的多肽”意图指可与其他组分分离的组合物,其中多肽被纯化至相对于其天然可获得状态的任何程度。因此纯化的多肽还指脱离其可能天然存在的环境的多肽。通常,“纯化的”将指已经经历分级以去除各种其他组分的多肽组合物,并且多肽该组合物基本上保留了其表达的生物活性。当使用术语“基本上纯化的”时,该指定将指这样的肽或多肽组合物,其中多肽或肽形成组合物的大部分组分,诸如构成组合物中的蛋白的约50%、约60%、约70%、约80%、约85%或约90%或更多。

[0213] 适用于纯化的各种技术将是本领域技术人员熟知的。这些技术包括,例如,用硫酸铵、PEG、抗体(免疫沉淀)等沉淀或通过热变性沉淀,然后离心;色谱,诸如亲和色谱(蛋白A柱)、离子交换色谱、凝胶过滤色谱、反相色谱、羟磷灰石色谱、疏水相互作用色谱;等电聚焦;凝胶电泳;以及这些技术的组合。如本领域一般已知的,认为进行各种纯化步骤的顺序可以改变,或者某些步骤可以省略,并且仍得到用于制备基本上纯化的多肽的合适方法。

[0214] 药物组合物

[0215] 在另一方面,本公开内容提供了药物组合物,该药物组合物包含与药学上可接受的载体混合的IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白。这样的药学上可接受的载体是本领域普通技术人员所熟知并理解的,并且已被广泛描述(参见例如,Remington’s Pharmaceutical Sciences,第18版,A.R.Gennaro编著,Mack Publishing Company,1990)。可以包括药学上可接受的载体以用于改变、保持或维持,例如,pH、摩尔渗透压浓度、黏度、澄清度、颜色、等渗性、气味、无菌性、稳定性、溶解或释放速率、组合物的吸收或渗透的目的。这样的药物组合物可以影响多肽的物理状态、稳定性、体内释放速率以及体内清除速率。合适的药学上可接受的载体包括但不限于,氨基酸(诸如甘

氨酸、谷氨酰胺、天冬酰胺、精氨酸或赖氨酸);抗菌剂;抗氧化剂(诸如抗坏血酸、亚硫酸钠或亚硫酸氢钠);缓冲剂(诸如硼酸盐、碳酸氢盐、Tris-HCl、柠檬酸盐、磷酸盐、其他有机酸);填充剂(bulking agents)(诸如甘露醇或甘氨酸);螯合剂(诸如乙二胺四乙酸(EDTA));复合剂(complexing agent)(诸如咖啡因、聚乙烯吡咯烷酮、β-环糊精或羟丙基-β-环糊精);填料;单糖;二糖和其他碳水化合物(诸如葡萄糖、甘露糖或糊精);蛋白(诸如血清白蛋白、明胶或免疫球蛋白);着色剂;调味剂和稀释剂;乳化剂;亲水性聚合物(诸如聚乙烯吡咯烷酮);低分子量多肽;盐形成抗衡离子(诸如钠);防腐剂(诸如苯扎氯铵、苯甲酸、水杨酸、硫柳汞、苯乙醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、氯己定、山梨酸或过氧化氢);溶剂(诸如甘油、丙二醇或聚乙二醇);糖醇(诸如甘露醇或山梨醇);悬浮剂;表面活性剂或润湿剂(诸如普朗尼克、PEG、山梨醇酐酯(sorbitan esters)、聚山梨醇酯诸如聚山梨醇酯20、聚山梨醇酯80、曲拉通(triton)、氨丁三醇、卵磷脂、胆固醇、tyloxapal);稳定性增强剂(蔗糖或山梨醇);张度增强剂(诸如碱金属卤化物(优选氯化钠或氯化钾)、甘露醇和山梨醇);递送媒介物;稀释剂;赋形剂和/或药物佐剂(pharmaceutical adjuvants)。

[0216] 药物组合物中的主要媒介物或载体实质上可以是水性的或非水性的。例如,合适的媒介物或载体可以是可能补充有用于肠胃外施用的组合物中常见的其他材料的注射用水、生理盐水溶液或人工脑脊液。中性缓冲盐水或与血清白蛋白混合的盐水是另外的示例性媒介物。其他的示例性药物组合物包含约pH 7.0-8.5的Tris缓冲液或约pH 4.0-5.5的乙酸盐缓冲液,其还可以包含山梨醇或山梨醇的合适替代物。在本公开内容的一种实施方案中,可以通过将选择的具有期望程度的纯度的组合物与任选的制剂用剂(formulation agent)(Remington's Pharmaceutical Sciences,同上)混合来制备组合物以便以冻干的块状物或水性溶液形式储存。另外,可以使用合适的赋形剂诸如蔗糖将治疗组合物配制为冻干物。最佳的药物组合物将取决于例如意图的施用途径、递送形式和期望的剂量由本领域普通技术人员确定。

[0217] 当设想肠胃外施用时,治疗性药物组合物可以呈在药学上可接受的媒介物中包含期望的IL-15/IL-15RαSushi复合物的无致热原、肠胃外可接受的水性溶液的形式。用于肠胃外注射的特别合适的媒介物是无菌蒸馏水,其中多肽被配制为合适储存的无菌、等渗溶液。在各种实施方案中,适于可注射施用的药物制剂可以在水性溶液,优选地在生理上相容的缓冲液诸如Hanks溶液、Ringer溶液或生理缓冲盐水中配制。水性注射悬浮液可以包含增加悬浮液黏度的物质,诸如羧甲基纤维素钠、山梨醇或右旋糖酐。此外,活性化合物的悬浮液可以被制备为合适的油性注射悬浮液。任选地,悬浮液还可以包含合适的稳定剂或增加化合物的溶解度并允许制备高度浓缩的溶液的剂。

[0218] 在各种实施方案中,可以使用胶体分散系统将治疗性药物组合物配制为用于靶向递送。胶体分散系统包括大分子复合体、纳米胶囊、微球、珠、和基于脂质的系统,基于脂质的系统包括水包油乳液、胶束、混合的胶束和脂质体。在脂质体产生中有用的脂质的实例包括磷脂酰化合物,诸如磷脂酰甘油、磷脂酰胆碱、磷酯酰丝氨酸、磷脂酰乙醇胺、鞘脂、脑苷脂和神经节苷脂。示例性磷脂包括卵磷脂、二棕榈酰磷脂酰胆碱和二硬脂酰磷脂酰胆碱。脂质体的靶向还可以基于例如器官特异性、细胞特异性和细胞器特异性并且是本领域已知的。

[0219] 在各种实施方案中,设想了药物组合物的口服施用。以该形式施用的药物组合物

可以使用或不使用固体剂型诸如片剂和胶囊的复合中通常使用的那些载体配制。在用于口服施用的固体剂型(胶囊、片剂、丸剂、糖衣丸、粉末、颗粒等)中,本公开内容的一种或更多种治疗化合物可以与一种或更多种药学上可接受的载体诸如柠檬酸钠或磷酸氢钙(dicalcium phosphate)和/或以下中的任一种混合:(1)填料或增量剂(extender),诸如淀粉、乳糖、蔗糖、葡萄糖、甘露醇和/或硅酸;(2)粘合剂,诸如例如羧甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和/或阿拉伯树胶;(3)保湿剂,诸如甘油;(4)崩解剂,诸如琼脂-琼脂、碳酸钙、马铃薯或木薯淀粉、藻酸、某些硅酸盐和碳酸钠;(5)溶液阻滞剂,诸如石蜡;(6)吸收加速剂,诸如季铵化合物;(7)润湿剂,诸如例如鲸蜡醇和单硬脂酸甘油酯;(8)吸收剂,诸如高岭土和膨润土;(9)润滑剂,诸如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠及其混合物;以及(10)着色剂。在胶囊、片剂和丸剂的情况下,药物组合物还可以包含缓冲剂。相似类型的固体组合物还可以用作使用诸如乳糖(lactose)或乳糖(milk sugar)以及高分子量聚乙二醇等的赋形剂软填充和硬填充的明胶胶囊中的填料。用于口服施用的液体剂型包括药学上可接受的乳液、微乳液、溶液、悬浮液、糖浆剂和酏剂。除了活性成分之外,液体剂型可以包含本领域中常用的惰性稀释剂,诸如水或其他的溶剂、增溶剂和乳化剂诸如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苄醇、苯甲酸苄酯、丙二醇、1,3-丁二醇、油(特别地,棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油和芝麻油)、甘油、四氢糠醇、聚乙二醇和脱水山梨醇的脂肪酸酯及其混合物。除惰性稀释剂之外,口服组合物还可以包含辅料(adjuvants),诸如润湿剂、乳化剂和悬浮剂、增甜剂、调味剂、着色剂、增香剂和防腐剂。

[0220] 在各种实施方案中,设想了将药物组合物表面施用(topical administration)至皮肤或施用至黏膜。表面制剂还可以包含已知作为皮肤或角质层渗透增强剂有效的各种各样的剂中的一种或更多种。这些剂的实例是2-吡咯烷酮、N-甲基-2-吡咯烷酮、二甲基乙酰胺、二甲基甲酰胺、丙二醇、甲醇或异丙醇、二甲基亚砜和氮酮。还可以包含另外的剂以使制剂在化妆品上可接受。这些剂的实例是脂肪、蜡、油、染料、芳香剂、防腐剂、稳定剂和表面活性剂。还可以包含角质软化剂(keratolytic agent),诸如本领域已知的那些角质软化剂。实例是水杨酸和硫磺。用于表面或经皮施用的剂型包括粉末、喷雾剂、软膏剂(ointments)、糊剂、霜剂(creams)、洗剂、凝胶、溶液、贴剂和吸入剂。可以在无菌条件下将活性化合物与药学上可接受的载体以及与可能需要的任何防腐剂、缓冲剂或喷射剂混合。除了本公开内容的主题化合物(例如,IL-15/IL-15RαSushi-Fc融合蛋白)之外,软膏剂、糊剂、霜剂和凝胶可以包含赋形剂,诸如动物和植物脂肪、油、蜡、石蜡、淀粉、黄芪胶、纤维素衍生物、聚乙二醇、硅酮、膨润土、硅酸、滑石和氧化锌或其混合物。

[0221] 本文中设想的用于使用的另外的药物组合物包括在持续递送或控制递送的制剂中包含多肽的制剂。在各种实施方案中,药物组合物可以被配制成纳米颗粒、作为缓释水凝胶或掺入溶瘤病毒中。这样的纳米颗粒方法包括,例如,包封在包含作为药物载体的具有疏水主链和亲水支链的聚合物的纳米颗粒中,包封在微米颗粒中,以乳剂插入到脂质体中,以及与其他分子缀合。纳米颗粒的实例包括用壳聚糖和卡波姆包衣的粘膜粘附性(mucoadhesive)纳米颗粒(Takeuchi等人,Adv.Drug Deliv.Rev.47(1):39-54,2001)以及包含带电荷的组合聚酯、聚(2-磺丁基-乙烯醇)和聚(D,L-乳酸-共-羟基乙酸)的纳米颗粒(Jung等人,Eur.J.Pharm.Biopharm.50(1):147-160,2000)。基于白蛋白的纳米颗粒组合物已被开发为用于递送疏水性药物诸如紫杉烷的药物递送系统。参见,例如,美国专利第5,

916,596号、第6,506,405号、第6,749,868号、第6,537,579号、第7,820,788号和第7,923,536号。Abraxane®(白蛋白稳定的紫杉醇纳米颗粒制剂)于2005年在美国获得批准,并随后在其他多个国家获得批准,用于治疗转移性乳腺癌。

[0222] 用于配制各种其他持续递送或控制递送工具诸如脂质体运载体、生物可侵蚀的微粒或多孔珠和贮库型注射剂的技术也是本领域技术人员已知的。

[0223] 待被治疗上使用的药物组合物的有效量将取决于例如治疗背景和治疗目标。本领域技术人员将理解,用于治疗的适当剂量水平将因此部分地取决于所递送的分子、多肽所用于的适应症、施用途径、以及患者的尺寸(体重、体表或器官尺寸)和状况(年龄和总体健康)而变化。相应地,临床医师可以调整剂量并改变施用途径以获得最佳治疗效果。典型的剂量可以取决于上文提及的因素而在从约0.0001mg/kg至最多约100mg/kg或更多的范围内。多肽组合物可以优选地注射或皮下或静脉内施用。长效药物组合物可以取决于特定制剂的半衰期和清除速率每三天至每四天一次、每周一次、每两周一次或每月一次施用。给药频率将取决于使用的制剂中的多肽的药代动力学参数。通常,施用组合物直至达到实现期望的效果的剂量。因此组合物可以作为单剂量或作为随时间的多剂量(以相同或不同的浓度/剂量)或作为持续的输注施用。常规地进行适当剂量的进一步改进。适当的剂量可以通过使用适当的剂量-响应数据来确定。

[0224] 药物组合物的施用途径根据已知方法,例如口服;通过静脉内、腹膜内、瘤内、脑内(实质内)、脑室内、肌内、眼内、动脉内、门静脉内、病灶内途径,髓内、鞘内、囊泡内、心室内、经皮、皮下或腹膜内注射;以及鼻内、肠内、表面、舌下、尿道、阴道或直肠方式;通过持续释放系统或通过植入装置。当期望时,组合物可以通过团注(bolus)注射施用,或通过输注持续施用,或通过植入装置施用。可选地或另外地,组合物可以经由期望的分子已经吸附或包封至其上的膜、海绵状物或另一种适当的材料的植入局部施用。当使用植入装置时,可以将该装置植入到任何合适的组织或器官中,并且期望的分子的递送可以经由扩散施用、缓释团注或持续施用。

[0225] 治疗用途

[0226] 本公开内容提供了治疗受试者的癌细胞的方法,包括向所述受试者施用药学上可接受的载体中的治疗有效量(作为单一疗法或在组合疗法方案中)的本公开内容的IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白,其中此类施用抑制癌细胞的生长和/或增殖。特别地,本公开内容的IL-15/IL-15RαSushi-Fc融合蛋白在治疗以癌症为特征的紊乱中是有用的。此类紊乱包括但不限于实体瘤,诸如乳腺癌、呼吸道癌、脑癌、生殖器官的癌症、消化道的癌症、尿道的癌症、眼癌、肝癌、皮肤癌、头颈癌、甲状腺癌、甲状旁腺癌以及它们的远端转移,淋巴瘤,肉瘤,多发性骨髓瘤和白血病。乳腺癌的实例包括但不限于侵袭性导管癌、侵袭性小叶癌、原位导管癌和原位小叶癌。呼吸道的癌症的实例包括但不限于小细胞肺癌和非小细胞肺癌,以及支气管腺瘤和胸膜肺母细胞瘤(pleuropulmonary blastoma)。脑癌的实例包括但不限于脑干和下丘脑胶质瘤、小脑和大脑星形细胞瘤、神经母细胞瘤、髓母细胞瘤、室管膜瘤以及神经外胚层和松果体肿瘤。男性/雄性生殖器官的肿瘤包括但不限于前列腺癌和睾丸癌。女性/雌性生殖器官的肿瘤包括但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫的肉瘤。消化道的肿瘤包括但不限于肛门癌、结肠癌、结肠直肠癌、食管癌、胆囊癌、胃癌、肝癌、乳腺癌、胰腺癌、直肠

癌、小肠癌和唾液腺癌。尿道的肿瘤包括但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌和尿道癌。眼癌包括但不限于眼内黑素瘤和视网膜母细胞瘤。肝癌的实例包括但不限于肝细胞癌(具有或不具有纤维板层变体的肝细胞癌)、胆管癌(肝内胆管癌)和混合性肝细胞胆管癌。皮肤癌包括但不限于鳞状细胞癌、卡波济氏肉瘤(Kaposi's sarcoma)、恶性黑素瘤、梅克尔细胞癌(Merkel cell skin cancer)和非黑素瘤皮肤癌。头颈癌包括但不限于鼻咽癌以及唇和口腔癌。淋巴瘤包括但不限于AIDS相关淋巴瘤、非霍奇金淋巴瘤、皮肤T细胞淋巴瘤、霍奇金病和中枢神经系统淋巴瘤。肉瘤包括但不限于软组织肉瘤、骨肉瘤、恶性纤维组织细胞瘤、淋巴肉瘤和横纹肌肉瘤。白血病包括但不限于急性髓性白血病、急性淋巴母细胞白血病、慢性淋巴细胞白血病、慢性髓细胞性白血病和毛细胞白血病。在某些实施方案中,癌症将是具有TGF-β家族成员(诸如激活蛋白A、肌生成抑制蛋白、TGF-β和GDF15)的高表达的癌症,例如胰腺癌、胃癌、卵巢癌、结肠直肠癌、黑素瘤白血病、肺癌、前列腺癌、脑癌、膀胱癌和头颈癌。

[0227] 本公开内容提供了一种通过作为辅助手段增强现有癌症治疗剂的治疗效果来治疗难治性或耐药性液体肿瘤或实体瘤的方法。

[0228] 本公开内容还提供了治疗受试者的病毒感染(包括甲型肝炎、乙型肝炎、丙型肝炎、HIV感染中的AIDS、人类乳头瘤病毒(HPV)感染、生殖器疣等)的方法,包括向有需要的人类患者施用药学上可接受的载体中的本公开内容的IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白,其中这样的施用抑制病毒的生长和/或复制。

[0229] "治疗有效量"或"治疗有效剂量"是指将使被治疗的紊乱的一种或更多种症状缓解至一定程度的被施用的治疗剂的量。

[0230] 治疗有效剂量可以通过确定$IC_{50}$从细胞培养物测定初始地评估。然后,可以在动物模型中配制剂量以实现包括如在细胞培养物中确定的$IC_{50}$的循环血浆浓度范围。此类信息可以被用于更精确地确定在人类中有用的剂量。血浆中的水平可以例如通过HPLC测量。确切的组合物、施用途径和剂量可以由个体医师鉴于受试者的状况来选择。

[0231] 可以调整剂量方案以提供最佳的期望的响应(例如,治疗响应或预防响应)。例如,可以施用单次团注,可以随时间施用若干分次剂量(多个或重复或维持)并且剂量可以根据治疗情境的迫切需要所指示的按比例减少或增加。为了便于施用和剂量的一致性,配制呈剂量单位形式的肠胃外组合物是特别有益的。如本文使用的剂量单位形式是指适合作为用于待治疗的哺乳动物受试者的单一剂量的物理分散的单位;每一个单位包含与需要的药物载体一起的被计算产生期望的治疗作用的预定的量的活性化合物。本公开内容的剂量单位形式的规格将主要由抗体的独特特征和待实现的特定治疗作用或预防作用决定。

[0232] 因此,技术人员将理解,基于本文提供的公开内容,根据治疗领域熟知的方法调整剂量和给药方案。即,最大可耐受剂量可以被容易地确定,并且向受试者提供可检测的治疗益处的有效量也可以被确定,向受试者提供可检测的治疗益处而施用每种剂的时间要求同样可以被确定。因此,尽管在本文中例举了某些剂量和施用方案,这些实例绝非限制在实践本公开内容时可以向受试者提供的剂量和施用方案。

[0233] 应注意,剂量值可以随着待减轻的状况的类型和严重性而变化,并且可以包括单个剂量或多于一个剂量。还应理解,对于任何特定受试者,应根据个体需要和施用组合物或监督组合物的施用的人士的专业判断随时间调整具体剂量方案,并且本文列出的剂量范围

仅是示例性的并且不意图限制所要求保护的组合物的范围或实践。另外,本公开内容的组合物的剂量方案可以基于多个因素,包括疾病的类型、受试者的年龄、体重、性别、医学状况、状况的严重性、施用途径和使用的特定抗体。因此,剂量方案可以广泛变化,但可以使用标准方法常规地确定。例如,剂量可以基于药代动力学或药效学参数调整,所述参数可以包括临床作用诸如毒性作用和/或实验值。因此,本公开内容包括如技术人员确定的受试者内的剂量递增(intra-subject dose-escalation)。确定适当的剂量和方案是相关技术领域熟知的并且将被理解为一旦提供本文所公开的教导,则由技术人员掌握。

[0234] 对于本公开内容的IL-15/IL-15RαSushi融合蛋白的治疗有效量或预防有效量的示例性的、非限制性的每天给药范围可以为0.0001至100mg/kg体重、0.0001至90mg/kg体重、0.0001至80mg/kg体重、0.0001至70mg/kg体重、0.0001至60mg/kg体重、0.0001至50mg/kg体重、0.0001至40mg/kg体重、0.0001至30mg/kg体重、0.0001至20mg/kg体重、0.0001至10mg/kg体重、0.0001至5mg/kg体重、0.0001至4mg/kg体重、0.0001至3mg/kg体重、0.0001至2mg/kg体重、0.0001至1mg/kg体重、0.0010至50mg/kg体重、0.0010至40mg/kg体重、0.0010至30mg/kg体重、0.0010至20mg/kg体重、0.0010至10mg/kg体重、0.0010至5mg/kg体重、0.0010至4mg/kg体重、0.0010至3mg/kg体重、0.0010至2mg/kg体重、0.0010至1mg/kg体重、0.01至50mg/kg体重、0.01至40mg/kg体重、0.01至30mg/kg体重、0.01至20mg/kg体重、0.01至10mg/kg体重、0.01至5mg/kg体重、0.01至4mg/kg体重、0.01至3mg/kg体重、0.01至2mg/kg体重、0.01至1mg/kg体重、0.1至50mg/kg体重、0.1至40mg/kg体重、0.1至30mg/kg体重、0.1至20mg/kg体重、0.1至10mg/kg体重、0.1至5mg/kg体重、0.1至4mg/kg体重、0.1至3mg/kg体重、0.1至2mg/kg体重、或0.1mg/kg体重、1至50mg/kg体重、1至40mg/kg体重、1至30mg/kg体重、1至20mg/kg体重、1至10mg/kg体重、1至5mg/kg体重、1至4mg/kg体重、1至3mg/kg体重、1至2mg/kg体重或1至1mg/kg体重。应注意,剂量值可以随着待被缓解的状况的类型和严重性变化。还应理解,对于任何特定受试者,应根据个体需要和施用组合物或监督组合物的施用的人士的专业判断随时间调整具体剂量方案,并且本文列出的剂量范围仅是示例性的并且不意图限制所要求保护的组合物的范围或实践。

[0235] 本公开内容的药物组合物的毒性和治疗指数可以在细胞培养物或实验动物中通过标准制药学程序确定,例如,确定$LD_{50}$(对群体的50%致死的剂量)和$ED_{50}$(对群体的50%治疗有效的剂量)。毒性剂量和治疗有效剂量之间的剂量比是治疗指数,并且治疗指数可以表示为比率$LD_{50}/ED_{50}$。表现出大治疗指数的组合物通常是优选的。

[0236] IL-15/IL-15RαSushi融合蛋白药物组合物的施用的给药频率取决于疗法的性质和被治疗的特定疾病。受试者可以以规律间隔治疗,诸如每周一次或每月一次,直到实现期望的治疗结果。示例性给药频率包括但不限于:无间断地每周一次或两次;每隔一周地一周一次或两次;每2周一次;每3周一次;无间断地每周一次,持续2周,然后每月一次;无间断地每周一次,持续3周,然后每月一次;每两个月一次;每3个月一次;每4个月一次;每5个月一次;或每6个月一次或每年一次。

[0237] 组合疗法

[0238] 如本文使用的,提及本公开内容的IL-15/IL-15RαSushi融合蛋白和一种或更多种其他治疗剂时,术语“共施用(co-administration)”、“共施用(co-administered)”和“与...组合(in combination with)”意图意指,并且的确是指并且包括以下:本公开内容

的IL-15/IL-15RαSushi融合蛋白和一种或更多种治疗剂的此类组合同时施用至需要治疗的受试者,其中这样的组分被一起配制成单一剂型,所述单一剂型在基本上相同的时间将所述组分释放至所述受试者;本公开内容的IL-15/IL-15RαSushi融合蛋白和一种或更多种治疗剂的此类组合基本上同时施用至需要治疗的受试者,其中这样的组分彼此分开配制成单独的剂型,所述单独的剂型在基本上相同的时间被所述受试者服用,届时所述组分基本上在相同的时间释放至所述受试者;本公开内容的IL-15/IL-15RαSushi融合蛋白和一种或更多种治疗剂的此类组合顺序施用至需要治疗的受试者,其中这样的组分彼此分开配制成单独的剂型,所述单独的剂型被所述受试者在连续的时间服用,每次施用之间具有显著的时间间隔,届时所述组分在基本上不同的时间释放至所述受试者;以及,本公开内容的IL-15/IL-15RαSushi融合蛋白和一种或更多种治疗剂的此类组合顺序施用至需要治疗的受试者,其中这样的组分一起配制成单一剂型,所述单一剂型以受控方式释放所述组分,届时所述组分在相同和/或不同的时间同时、连续和/或重叠地释放至所述受试者,其中每个部分可以通过相同或不同的途径施用。

[0239] 在另一方面,本公开内容提供了一种用于治疗受试者的癌症或癌症转移的方法,该方法包括施用与第二疗法组合的治疗有效量的本发明的药物组合物,所述第二疗法包括但不限于免疫疗法、细胞毒性化学疗法、小分子激酶抑制剂靶向疗法、手术、放射疗法和干细胞移植。例如,这样的方法可以被用于预防性癌症预防、预防手术后癌症复发和转移,以及作为其他常规癌症疗法的辅助手段。本公开内容认识到,常规癌症疗法(例如,化学疗法、放射疗法、光疗法、免疫疗法和手术)的有效性可以通过本文描述的组合方法的使用来增强。

[0240] 大量的常规化合物已经被证明具有抗赘生物活性。这些化合物已经被用作化学疗法中的药剂以缩小实体瘤,预防转移和进一步生长,或减少白血病或骨髓恶性肿瘤中的恶性T细胞的数目。尽管化学疗法在治疗各种类型的恶性肿瘤中是有效的,但许多抗赘生物化合物诱导不期望的副作用。已经显示出,当将两种或更多种不同的治疗组合时,治疗可以协同地工作,并且允许降低每种治疗的剂量,从而降低每种化合物在较高的剂量产生的有害副作用。在其他情况下,对于治疗是难治性的恶性肿瘤可以响应于两种或更多种不同治疗的组合疗法。

[0241] 在各种实施方案中,第二抗癌剂,诸如化学治疗剂将被施用至患者。示例性化学治疗剂的列表包括但不限于,柔红霉素、更生霉素(dactinomycin)、多柔比星、博莱霉素、丝裂霉素、氮芥、苯丁酸氮芥、美法仑、环磷酰胺、6-巯基嘌呤、6-硫鸟嘌呤、苯达莫司汀、阿糖胞苷(CA)、5-氟尿嘧啶(5-FU)、氟尿苷(5-FUdR)、氨甲蝶呤(MTX)、秋水仙碱、长春新碱、长春花碱、依托泊苷、替尼泊苷、顺铂、卡铂、奥沙利铂、喷司他丁、克拉屈滨、阿糖胞苷、吉西他滨、普拉曲沙、米托蒽醌、己烯雌酚(DES)、氟达拉滨(fluradabine)、异环磷酰胺、羟基脲紫杉烷(hydroxyureataxanes)(诸如紫杉醇和多西他赛(doxetaxel))和/或蒽环类抗生素,以及剂的组合,诸如但不限于DA-EPOCH、CHOP、CVP或FOLFOX。在各种实施方案中,这样的化疗剂的剂量包括但不限于约10mg/$m^2$、20mg/$m^2$、30mg/$m^2$、40mg/$m^2$、50mg/$m^2$、60mg/$m^2$、75mg/$m^2$、80mg/$m^2$、90mg/$m^2$、100mg/$m^2$、120mg/$m^2$、150mg/$m^2$、175mg/$m^2$、200mg/$m^2$、210mg/$m^2$、220mg/$m^2$、230mg/$m^2$、240mg/$m^2$、250mg/$m^2$、260mg/$m^2$和300mg/$m^2$中的任一种。

[0242] 在各种实施方案中,本公开内容的组合治疗方法还可以包括向受试者施用治疗有

效量的免疫疗法,所述免疫疗法包括但不限于,使用针对特定肿瘤抗原的消耗性抗体的治疗;使用抗体-药物缀合物的治疗;使用针对共刺激性或共抑制性分子(免疫检查点)(诸如CD276、CD272、CTLA-4、PD-1、PD-L1、CD40、SIRPα、CD47、OX-40、CD137、GITR、LAG3、ICOS、CD27、4-1BB、TIM-3、B7-H4、Siglec 7、Siglec 8、Siglec 9、Siglec 15和VISTA)的激动性抗体、拮抗性抗体或阻断性抗体的治疗;使用双特异性T细胞结合抗体(BiTE®)诸如博纳吐单抗(blinatumomab)的治疗;涉及施用生物响应调节剂(诸如IL-2、IL-7、IL-12、IL-21、GM-CSF、IFN-α、IFN-β和IFN-γ)的治疗;使用治疗性疫苗诸如sipuleucel-T的治疗;使用树突细胞疫苗或肿瘤抗原肽疫苗的治疗;使用NK细胞的治疗;使用TCR-T细胞的治疗;使用嵌合抗原受体(CAR)-T细胞的治疗;使用CAR-NK细胞的治疗;使用iPS诱导的NK细胞、iPS诱导的TCR-T细胞、iPS诱导的CAR-T细胞或iPS诱导的CAR-NK细胞的治疗;使用树突细胞的治疗;使用肿瘤浸润淋巴细胞(TIL)的治疗;使用过继转移的抗肿瘤T细胞(离体扩增的和/或TCR转基因的)的治疗;使用疫苗诸如卡介苗(BCG)的治疗;使用TALL-104细胞的治疗;和使用免疫刺激剂(诸如Toll样受体(TLR)激动剂CpG和咪喹莫特)的治疗;其中组合疗法提供了增加的对肿瘤细胞的效应细胞杀伤,即,当被共施用时,IL-15/IL-15RαSushi-Fc融合蛋白和免疫疗法之间存在协同作用。

[0243] 在各种实施方案中,组合疗法包括同时施用在同一药物组合物中或在单独的药物组合物中的IL-15/IL-15RαSushi-Fc融合蛋白或IL-15/IL-15RαSushi-抗体融合蛋白和第二剂组合物。在各种实施方案中,顺序地施用IL-15/IL-15RαSushi融合蛋白组合物和第二剂组合物,即,在施用第二剂组合物之前或之后施用IL-15/IL-15RαSushi融合蛋白组合物。

[0244] 在各种实施方案中,IL-15/IL-15RαSushi融合蛋白组合物和第二剂组合物的施用是同时的,即,IL-15/IL-15RαSushi融合蛋白组合物和第二剂组合物的施用时间段彼此重叠。在各种实施方案中,IL-15/IL-15RαSushi融合蛋白组合物和第二剂组合物的施用是非同时的。例如,在各种实施方案中,终止IL-15/IL-15RαSushi融合蛋白组合物的施用,然后施用第二剂组合物。在各种实施方案中,终止施用第二剂组合物,然后施用IL-15/IL-15RαSushi融合蛋白组合物。

[0245] 提供以下实施例以更充分地说明本公开内容,但不应解释为限制本公开内容的范围。

[0246] 实施例1

[0247] IL-15/IL-15RαSushi-Fc融合蛋白的构建、表达和纯化

[0248] 对所有基因进行密码子优化以便在哺乳动物细胞中表达,合成这些基因并亚克隆到接受者哺乳动物表达载体(GenScript)中。蛋白表达由CMV启动子驱动,并且合成的SV40聚腺苷酸(polyA)信号序列存在于CDS的3'端。在构建体的N末端处工程化有前导序列,以确保合适的信号传导和加工以便分泌。

[0249] 融合蛋白通过使用聚乙烯亚胺(PEI,25,000MW线性,Polysciences)用哺乳动物表达载体共转染悬浮生长的HEK293-F细胞来产生。如果有两种或更多种表达载体,则载体用1:1的比转染。对于转染,将HEK293细胞在无血清FreeStyle™ 293表达培养基(ThermoFisher)中培养。对于在1000ml摇瓶(最大工作体积330mL)中的产生,将HEK293细胞以$0.8\times10^6$个细胞/ml的密度接种,24小时后进行转染。将总量为330μg DNA的表达载体与16.7ml Opti-mem培养基(ThermoFisher)混合。在添加稀释于16.7ml Opti-mem培养基中的

0.33mg PEI后,将混合物涡旋15秒,并随后在室温孵育10min。然后将DNA/PEI溶液添加至细胞,并在37℃在具有8%的$CO_2$气氛的培养箱中孵育。在第4天,将丁酸钠(Millipore Sigma)以2mg/L的终浓度添加至细胞培养物,以帮助维持蛋白表达。培养6天后,收集上清液用于通过以2200rpm离心20min进行纯化。将溶液进行无菌过滤(0.22μm过滤器,Corning)。

[0250] 可选地,在ExpiCHO细胞(ThermoFisher)中按照制造商的说明书产生构建体。

[0251] 使用蛋白A亲和色谱从细胞培养物上清液纯化所分泌的蛋白。将细胞培养物上清液加载到用5倍柱体积(CV)的磷酸盐缓冲盐水pH 7.2(ThermoFisher)平衡过的HiTrap MabSelect SuRe 5ml柱(GE Healthcare)上。通过用5CV的PBS pH 7.2洗涤来去除未结合的蛋白,并用25mM柠檬酸钠、25mM氯化钠,pH 3.2洗脱目标蛋白。蛋白溶液通过添加3%的1M Tris pH 10.2来中和。使用Amicon®Ultra-15 Ultracel 10K(Merck Millipore)浓缩目标蛋白,并将缓冲液交换为PBS,pH 7.2。

[0252] 在还原剂存在和不存在的情况下,通过SDS-PAGE和用考马斯亮蓝(Coomassie)(Imperial™ protein stain,ThermoFisher)染色来分析所纯化的分子的纯度和分子量。根据制造商的说明书使用NuPAGE®预制凝胶系统(4%-12%Bis-Tris,ThermoFisher)。分子的聚集体含量在Agilent 1200高效液相色谱(HPLC)系统上进行分析。在25℃,使用150mM磷酸钠pH 7.0作为流动相,将样品注射到AdvanceBio尺寸排阻柱(300Å,4.6x150mm,2.7μm,LC柱,Agilent)上。

[0253] 纯化的蛋白样品的蛋白浓度通过使用Nanodrop分光光度计(ThermoFisher)测量280nm处的吸光度除以基于氨基酸序列计算的摩尔消光系数来确定。根据制造商的说明书,使用Endosafe nexgen-PTS(Charles River)测量纯化的蛋白样品的内毒素水平。

[0254] 作为展示分离的IL-15/IL-15RαFc融合构建体的蛋白谱(profile)的实例,对P-0217、P-0234和P-0313的SDS-PAGE分析在图2A中示出。P-0217、P-0234和P-0313都是在C末端处包含IL-15/IL-15Rα复合物的IL-15/IL-15Rα(非共价)-Fc融合蛋白。P-0217是单价的IL-15/IL-15Rα(非共价)Fc融合体,P-0234是P-0217的二聚体对应物,并且P-0313与P-0234共有相同的融合构型,但不同之处仅在于IL-15结构域中的S58D取代。

[0255] 对于单价Fc融合体和二价Fc融合体两者,计算分子量为8.6kDa的IL-15RαSushi+结构域均与融合到Fc结构域的IL-15或IL-15变体非共价地缔合,并且在变性条件下解离并作为清晰条带迁移至预期位置(图2A)。凝胶上IL-15Rα-sushi+条带的存在证实了细胞培养生长期间IL-15和IL-15Rα之间的非共价缔合;在低pH洗脱条件下的蛋白A纯化过程中,这样的缔合得以维持。

[0256] 图2B中的尺寸排阻色谱图表明两种融合形式的低聚集倾向,因为在没有进一步精制的初始的蛋白A捕获步骤之后,所有三种融合蛋白仅存在1%-2%的聚集。尖锐的主峰进一步表明在天然缓冲条件下IL-15和IL-15Rα的紧密但非共价的缔合。

[0257] 此外,在相同载体和培养条件下,融合蛋白的表达水平与仅含Fc的蛋白的表达水平相当(相差2倍以内)。高产量和低聚集倾向展示了单价和二价IL-15/IL-15Rα(非共价)Fc融合蛋白的有利的可开发性谱。此外,以P-0313示例的IL-15中的氨基酸取代未影响融合蛋白的表达谱;P-0313显示出与其野生型对应物P-0234几乎相同的纯度和聚集倾向(图2)。

[0258] 实施例2

[0259] 对不同融合蛋白形式的集中于纯度的可开发性评估突出了正确复合的IL-15Rα结构域在增强融合蛋白可开发性谱方面的作用

[0260] 对蛋白A纯化样品的SEC分析被用于评估不同融合形式对蛋白聚集倾向和纯度的影响。本发明人观察到,虽然由于细胞生长差异,不同批次之间的蛋白表达水平可能不同,但蛋白聚集倾向和纯度表现为与特定蛋白相关的固有特性,批次之间差异很小,如图3F和图3H针对P-0234所示。

[0261] 首先,基于5种分子评价了IL-15Rα的复合对IL-15-Fc融合蛋白的蛋白纯度的影响。P-0162是C末端单体IL-15(单独)Fc融合蛋白,包含Hole-Fc-接头1-IL-15链(SEQ ID NO:13)和空的Knob-Fc链(SEQ ID NO:7)。P-0197是C末端单价IL-15/IL-15Rα(非共价)Fc融合体,其示意图在图1B中描绘。P-0197与P-0162的不同之处在于存在与IL-15非共价复合的游离的IL-15RαSushi+结构域。P-0153是C末端单体IL-15/IL-15Rα融合体,具有异源二聚体Fc融合形式,其卡通图在图1A中示出。P-0167(SEQ ID NO:13和55)和P-0198分别是P-0162和P-0197的二聚体对应物。在图3A-图3E中说明了5种分子的尺寸排阻图。

[0262] 如在图3A中观察到的,无IL-15Rα的IL-15-Fc单体融合体具有84.5%的单体含量,并且大多数杂质具有较低的分子量。相比之下,P-0197含有98.6%的单体含量(图3B),并且纯度的这种显著改进明显是由游离的IL-15RαSushi+结构域促进的。在二聚体形式中,进一步突出了游离的IL-15RαSushi+结构域对IL-15-Fc融合蛋白的蛋白质量的影响,其分别用图3D和图3E中的P-0167和P-0198的SEC色谱图描绘。P-0167包含一个宽且不规则的峰,主峰两侧具有肩部。更值得注意的是,P-0167在活化新鲜的人类PBMC的NK细胞和T细胞方面显示出显著受损的离体活性,这可能是由于蛋白的折叠不正确。然而,包含二聚体形式的非共价结合的IL-15RαSushi+结构域的P-0198展示出具有90.5%单体含量的尖锐主峰(图3E)。有点令人感兴趣的是,当IL-15RαSushi+结构域不是游离的,而是如P-0153中的共价融合到匹配的异源二聚体Fc时,IL-15RαSushi+结构域与IL-15-Fc的复合并没有产生蛋白纯度的任何提高;相反,蛋白样品含有>25%的二聚体和更高分子量的可溶性聚集体(图3C)。IL-15和IL-15Rα两者与Fc结构域的融合可能会产生空间限制,阻止它们以生理方式相互作用。综上所述,IL-15RαSushi+结构域可以显著改进IL-15-Fc融合蛋白的纯度和生物物理特性,但前提是IL-15Rα结构域能够以有利且不受限的方式与IL-15缔合。

[0263] 其次,IL-15RαECD(SEQ ID NO:4)对比IL-15RαSushi+(SEQ ID NO:5)对IL-15/IL-15Rα-Fc融合蛋白的可开发性的影响通过比较P-0234和P-0220来评价。两种构建体都是C末端Fc融合体,共有相同的如图1C中描绘的构型,在P-0234中具有IL-15RαSushi+结构域,并且在P-0220中具有IL-15RαECD。它们的SEC色谱图分别在图3F和图3G中示出。包含IL-15RαECD结构域的蛋白P-0220不仅具有的纯度低于其包含IL-15RαSushi+的对应物P-0234(88.5%对比100%),而且在同一批次细胞中以低2.5倍的水平表达。简而言之,明显的是,在构建更可开发的IL-15/IL-15Rα融合蛋白方面,IL-15RαSushi+结构域是比IL-15RαECD更优选的配偶体。

[0264] 此外,还评价了融合末端对IL-15/IL-15Rα-Fc融合蛋白的可开发性的影响。P-0234和P-0223是二聚体IL-15/IL-15Rα(非共价)Fc融合蛋白,IL-15/IL-15RαSushi复合物分别连接到Fc的C末端和N末端。它们的SEC色谱图(图3H和图3I)显示出相当细微的纯度差异(98.5%对比93.9%)。然而,纯化的P-0223始终含有较高分子量物质的宽峰和含有较低

分子杂质的小而可察觉的峰,这在P-0234中实质上不存在。尽管差异小,但具有C末端融合的P-0234具有无可争议的更佳的SEC纯度谱,并且考虑到两种分子以相当的水平表达,从可开发性的角度来看,P-0234是优选的形式。

[0265] 综上所述,将IL-15Rα亚基与IL-15-Fc融合体复合可以显著提高表达、纯度,并减少聚集;并且这样的改进需要IL-15Rα与IL-15以最小的空间限制正确缔合。并且基于生产率和纯度评估两者,IL-15RαECD的截短和功能形式IL-15RαSushi+表现为优于全长ECD。此外,将IL-15/IL-15Rα复合物置于Fc的C末端比N末端融合更有利于获得高纯度。因此,以P-0234示例的二聚体IL-15/IL-15Rα(非共价)C末端Fc融合形式整合了所有优选的组分并且代表了优越的形式。

[0266] 实施例3

[0267] IL-15Rα的非共价缔合增强IL-15/IL-15RαFc融合蛋白的受体结合和生物活性

[0268] IL-15以高亲和力结合其特异性受体IL-15Rα,并且两者都在抗原呈递细胞上表达。IL-15Rα与IL-15的缔合将IL-15反式呈递至响应性淋巴细胞(包括NK细胞、T细胞和B细胞)上由IL-15Rβ和$\gamma_C$组成的异源二聚体受体复合物。配体-三聚体受体复合物(IL-15-IL-15Rαβγ)的形成启动细胞内信号级联,导致下游生物效应。IL-15受体生物学的复杂性使得难以应对设计最佳IL-15融合蛋白以实现构象有效的配体-三聚体受体信号传导复合物的挑战。

[0269] 我们假设,IL-15与人类IgG的Fc部分的N末端或C末端处共价连接,将比IL-15与IL-15RαFc融合蛋白非共价缔合更有利于体内半衰期延长。我们还假设,IL-15Rα结构域是IL-15Fc融合蛋白增强其与中等亲和力IL-2Rβγ受体的相互作用并促进高亲和力配体-三聚体受体信号传导复合物的形成所需要的。此外,我们认为,IL-15Rα结构域与IL-15Fc融合蛋白的非共价缔合保留了IL-15和IL-15Rα的天然缔合并且是IL-15反式呈递的最佳构象。此外,我们假设,由于IL-15和IL-15Rα结构域之间极高的结合亲和力,产生这样的融合蛋白复合物是可行的。

[0270] 构建了不同构型的包含IL-15/IL-15Rα结构域复合物的IL-15Fc融合蛋白的不同形式。通过测量CD69在人类CD8细胞和NK细胞上的表达,确定了融合蛋白与IL-15Rβ亚基的结合活性,并分析了它们刺激淋巴细胞活化的生物活性。融合蛋白的示例性结构图在图1中示出。

[0271] 用ELISA测定测试了结合活性。简而言之,在4℃将Nunc Maxisorp(ThermoFisher)板用碳酸氢盐缓冲液pH 9.4(ThermoFisher)中的huIL-15Rβ-6His以1μg/孔(100μl/孔)包被过夜。用PBS/0.05%吐温20洗涤3次后,在室温将板用SuperBlock(300μl/孔)孵育2hrs以阻断非特异性结合。洗涤后,将IL-15化合物(每种用封闭缓冲液3倍系列稀释)添加到板中(100μl/孔),并在室温孵育1hr。洗涤后,通过与在封闭缓冲液(ThermoFisher)中以1:5000稀释的缀合有辣根过氧化物酶(HRP)的山羊抗人类IgG Fc二抗(100μl/孔)一起在室温孵育1hr来检测Fc融合体。洗涤后,添加TMB底物(ThermoFisher)(100ul/孔)。将板密封并在室温在黑暗中孵育5-20min。通过添加2N硫酸(Ricca Chemical)(50uL/孔)停止反应,并在450-590nm处读取吸光度。

[0272] 生物活性通过测量人类NK细胞和CD8 T细胞上CD69表达的诱导来确定。CD69是淋巴细胞活化过程中被早期诱导的细胞表面糖蛋白。建立了离体人类外周血单核细胞(PBMC)

测定,以分析IL-15处理后表达CD69的NK细胞或CD8 T细胞的数目/百分比。具体地,通过Ficoll-Hypaque离心法从购自Blood Oklahoma Institute的血沉棕黄层分离人类PBMC。将纯化的人类PBMC用每种IL-15测试化合物的系列稀释液处理,并在37℃孵育48小时。通过300xg离心收集细胞并重悬于FACS缓冲液中。通过添加人类TruStain FcX(1:50稀释)封闭Fc受体后,用抗人类CD56-FITC抗体、抗人类CD69-PE抗体和抗人类CD8-APC抗体(1:50稀释)对细胞进行染色。在室温与抗体一起孵育30分钟后,收集细胞并洗涤,重悬于FACS缓冲液中,并准备进行流式细胞术分析。确定CD56+NK细胞和CD8+T细胞上的CD69表达,并且数据表示为门控的群体中CD69阳性细胞的%。

[0273] P-0157是N末端二价IL-15(非共价)/IL-15RαSushi Fc融合蛋白;P-0153是C末端IL-15/IL-15RαSushi异源二聚体Fc融合蛋白;P-0162是C末端单价Fc-IL-15融合蛋白且不具有复合的IL-15RαSushi。ELISA结合测定表明,与不具有复合的IL-15Rα的融合蛋白(P-0162)相比,IL-15RαSushi结构域的掺入显著增加了IL-15Fc融合蛋白(P-0157和P0153)与IL-15Rβ的结合强度(图4),表明IL-15Rα在促进融合蛋白与受体相互作用中的重要作用。此外,与IL-15非共价结合到IL-15RαFc融合蛋白(P-0157)相比,当IL-15和IL-15Rα两者都以异源二聚体形式共价缀合到Fc(P-0153)时受体结合活性降低(图4),表明构象受限的融合形式会对受体结合活性产生负面影响。

[0274] 与结合能力一致,与不具有IL-15Rα的融合蛋白相比,IL-15Rα的掺入也增加了IL-15融合蛋白的生物活性。P-0197是C末端单价IL-15/IL-15Rα(非共价)Fc融合蛋白,并且P-0162与P-0197共有相同的结构但不包含IL-15RαSushi。与P-0162相比,P-0197在诱导CD69阳性NK细胞(图5A)和CD8 T细胞(图5B)方面分别展示出10倍和6倍的增加的效力,这归因于IL-15Rα的包含。

[0275] 最后,对三种C末端单价IL-15/IL-15RαFc融合蛋白的生物活性进行了比较。P-0165是Fc融合蛋白,具有与Fc结构域融合的IL-15Rα和非共价结合的IL-15;P-0197是反向布置的,具有与Fc结构域融合的IL-15和非共价结合的IL-15Rα;P-0153具有IL-15和IL-15Rα两者都与Fc结构域融合的异源二聚体结构。如图6中示出的,在诱导CD69阳性NK细胞(图6A)和CD8 T细胞(图6B)方面,与具有共价且异源二聚体地融合到Fc的IL-15/IL-15Rα两者的融合蛋白相比,与IL-15或IL-15Rα非共价复合的融合蛋白展示出更好的效力。数据表明,IL-15和IL-15Rα之间的构象上最佳的缔合对于IL-15融合蛋白结合其受体并发挥其生物活性至关重要。增加的构象限制,例如异源二聚体Fc融合形式,对生物活性产生负面影响。

[0276] 实施例4

[0277] 接头对IL-15/IL-15RαFc融合蛋白的活性的影响

[0278] 选择合适的接头来连接蛋白结构域在融合蛋白工程化中是至关重要的。肽接头不仅提供融合蛋白结构域之间的空间距离并允许它们独立折叠,而且直接影响融合蛋白的结构稳定性和功能特性。在此,我们检查了接头的柔性和长度对IL-15/IL-15RαFc融合蛋白的生物活性的影响。

[0279] 如先前描述的,生物活性通过在基于离体人类PBMC FACS的测定中测量人类NK细胞和CD8 T细胞上CD69表达的诱导来确定。P-0165和P-0166分别是具有15个氨基酸的刚性接头和10个氨基酸的柔性接头的单价IL-15(非共价)/IL-15RαFc融合体。P-0197、P-0207和P-0217均为单价IL-15/IL-15Rα(非共价)Fc融合蛋白。P-0197包含刚性接头,P-0207包含10

个氨基酸的富含GS的柔性接头,并且P-0217具有15个氨基酸的柔性接头。结果(图7A和图7B)表明,连接Fc和IL-15(P-0165和P-0166)或连接Fc和IL-15Rα(P-0197、P-0207和P-0217)的肽接头的刚性或长度不影响所测试的融合蛋白的生物活性。

[0280] 实施例5

[0281] 化合价对IL-15/IL-15Rα融合蛋白的活性的影响

[0282] 用于治疗用途的Fc融合蛋白大多是同源二聚体的,因为IgG1 Fc由于铰链区中形成的二硫键而天然地同源二聚体化。二聚体蛋白在亲合力、稳定性、数量、尺寸和功能方面具有优势。然而,Fc工程化可以产生单体Fc融合蛋白。该改变可以影响生物活性、药代动力学、副作用,或减少二聚体蛋白的尺寸以便组织渗透。为了评价化合价对IL-15/IL-15RαFc融合蛋白的生物活性的影响,构建了具有不同的IL-15/IL-15RαFc融合体构型的单体和同源二聚体形式,并测试了其生物活性。

[0283] 如先前描述的,生物活性通过在基于离体人类PBMC FACS的测定中测量人类NK细胞和CD8 T细胞上CD69表达的诱导来确定。结果表明,跨所有测试的融合形式,IL-15/IL-15RαFc融合蛋白的同源二聚体形式与各自的单体对应物相比显示出生物活性约2倍的增强(表4),表明二聚体化合价可以提供功能上的优势。

[0284] 表4

[0285] IL-15/IL-15RαSushi复合物化合价对IL-15/IL-15Rα融合蛋白的生物活性的影响

[0286]

| 蛋白 ID | 描述 | 活化 $EC_{50}$ (pM) | |
|---|---|---|---|
| | | $CD8^+$ T 细胞 | $CD56^+$ NK |
| P-0166 | IL-15 (非共价)/IL-15Rα Fc 单体、C 末端 | 17.4 | 5.9 |
| P-0218 | P-0166 的二聚体对应物 | 10 | 3.1 |
| P-0217 | IL-15/IL-15Rα (非共价) Fc 单体、C 末端 | 139 | 28.3 |
| P-0234 | P-0217 的二聚体对应物 | 45.8 | 4.1 |
| P-0197 | IL-15/IL-15Rα (非共价) Fc 单体、C 末端、刚性接头 | 498 | X |
| P-0198 | P-0197 的二聚体对应物 | 293 | X |
| P-0221 | IL-15/IL-15Rα (非共价) Fc 单体、N 末端 | 50.3 | 12.5 |
| P-0223 | P-0221 的二聚体对应物 | 47.2 | 9.1 |

[0287] 实施例6

[0288] N末端Fc融合或C末端Fc融合对IL-15的生物活性的影响

[0289] Fc融合蛋白可以通过将IL-15/IL-15Rα复合物放置(通过间隔接头连接)在Fc的N末端或C末端来构建。最佳支架由融合蛋白是否正确折叠和表达以及生物活性是否被保留来决定。IL-15/IL-15RαFc融合蛋白通过将IL-15/IL-15Rα复合物附接(通过接头隔开)到Fc的N末端或C末端来产生。IL-15/IL-15Rα复合物在C末端融合和N末端融合的情况下也有不同的构型。P-0218是C末端二价IL-15(非共价)/IL-15RαFc融合蛋白,并且基准是P-0218的N

末端对应物(在IL-15中另外含有N72D取代)。P-0234是C末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白,并且P-0223是P-0234的N末端对应物。

[0290] 融合蛋白的生物活性通过测量IL-15化合物处理后NK细胞和CD8 T细胞的细胞核中的Ki67表达来确定。IL-15是一种有效的淋巴细胞生长因子,刺激NK细胞、T细胞和B细胞的增殖和分化。Ki67是一种在细胞周期的所有活跃期(G1、S、G2和M)被诱导,但在静止期(G0)不被诱导的核蛋白,并且因此是细胞增殖的标志物。

[0291] 建立了离体人类PBMC测定。简而言之,将纯化的人类PBMC用IL-15测试化合物的系列稀释液处理,并在37℃孵育5天。在第5天,用FACS缓冲液(1%FBS/PBS)洗涤细胞一次,并首先用Fc封闭剂和表面标志物抗体(包括抗人类CD56-FITC、抗人类CD8-APC和抗人类CD4-Percp-cy5.5(1:50稀释))染色。在30分钟的孵育和洗涤后,用200μl/孔的1×Foxp3固定及透化工作溶液将细胞沉淀充分重悬,并在室温在黑暗中孵育30分钟。离心后,向每个孔添加200μl的1×透化缓冲液进行另一次洗涤。用抗人类Ki67-PE(1:10稀释)将细胞沉淀重悬于透化缓冲液中。在室温孵育30分钟后,收集细胞并洗涤,重悬于FACS缓冲液中,并准备进行流式细胞术分析。数据表示为门控的群体中Ki67阳性细胞的%。

[0292] 如图8中示出的,与N末端Fc融合体对应物(基准和P-0223)相比,C末端Fc融合体(P-0218和P-0234)始终展示出更强的对Ki67阳性CD8 T细胞或CD8 T细胞增殖的诱导(图8A和图8B)。数据表明,Fc的C末端是连接IL-15/IL-15Rα复合物的优选位点,并允许生物活性的保持。

[0293] 实施例7

[0294] 受体-α结构域选择对IL-15/IL-15RαFc融合蛋白的活性的影响

[0295] IL-15与IL-15Rα的细胞外结构域(ECD)结合,并且该结合主要由一种称为Sushi结构域的保守蛋白结合基序引起。对于融合蛋白的构建,短的和截短形式的IL-15Rα可能是期望的,以减小尺寸和结构复杂性。为了确保结合特异性和亲和力,将赋予对IL-15的结合的ECD结构域的全部或一部分(具有额外12AA的Sushi结构域)构建到融合蛋白中,并确定功能活性。

[0296] P-0234和P-0220是C末端二聚体IL-15/IL-15Rα(非共价)融合蛋白,其中IL-15Rα分别是sushi和完整ECD。P-0223和P-0224是N末端二聚体IL-15/IL-15Rα(非共价)Fc融合蛋白,其中IL-15Rα分别是sushi和完整ECD。P-0221和P-0222是N末端单价IL-15/IL-15Rα(非共价)Fc融合蛋白,其中IL-15Rα分别是sushi和完整ECD。结果表明,在诱导CD69阳性NK细胞方面,与IL-15RαSushi结构域非共价复合的融合蛋白比与IL-15Rα完整ECD复合的融合蛋白更有效,无论融合形式为N末端还是C末端、二聚体还是单体(图9)。数据表明,IL-15RαSushi结构域比完整ECD更适于构建IL-15/IL-15RαFc融合蛋白,并为IL-15与信号传导受体相互作用赋予最佳构象。

[0297] 实施例8

[0298] IL-15突变体和该变体融合蛋白与IL-15Rβ的结合活性

[0299] 在探寻IL-15激动剂、超级激动剂或拮抗剂时,将缺失、插入或点突变引入人类IL-15肽序列中IL-15与受体β或γ之间的接触界面处。将变体引入到不同形式的IL-15/IL-15RαFc融合蛋白中,并通过如先前描述的酶联免疫吸附测定(ELISA)对与IL-15Rβ的结合活性进行定量。

[0300] 表5示出了C末端IL-15变体/IL-15Rα异源二聚体Fc融合蛋白的IL-15Rβ结合活性。IL-15变体具有引入到人类IL-15肽中的氨基酸缺失、插入或点突变。与全长野生型IL-15融合蛋白相比,从IL-15的C末端截短3个氨基酸保留了融合蛋白与IL-15Rβ的结合活性,而从IL-15的C末端进一步截短6个或9个氨基酸导致融合蛋白的结合活性逐渐降低。在N95后插入不同长度的GS均导致融合蛋白的IL-15Rβ结合活性降低。

[0301] 表6示出了单体IL-15变体(非共价)/IL-15RαFc融合蛋白的IL-15Rβ结合活性,其中人类IL-15结构域在位置58、62、63、67或68处含有单个氨基酸取代。包含IL-15(I67V)变体的Fc融合蛋白P-0185展示出与野生型融合蛋白相似的与IL-15Rβ的结合活性。P-0182是一种融合蛋白,包含在位置58处具有从丝氨酸到天冬氨酸的氨基酸取代(S58D)的IL-15变体,与野生型融合蛋白相比,P-0182展示出与IL-15Rβ的结合能力的4倍增强。在IL-15的位置62、63和68处的取代导致融合蛋白的IL-15Rβ结合活性的不同程度的降低。

[0302] 表7示出了二聚体IL-15变体/IL-15Rα(非共价)Fc融合蛋白的IL-15Rβ结合活性,其中人类IL-15在位置58或68位处包含单个氨基酸取代或在N95后包含氨基酸插入。类似地,如在P-0182(表4)中观察到的,包含相同的具有S58D的IL-15变体的P-0313与其相应的野生型融合蛋白P-0234相比,展示出与IL-15Rβ的结合能力的2倍增强。数据加强了这样的观点,即IL-15肽中的S58D取代可以将IL-15调节为归因于增强的受体结合活性的超级激动剂。

[0303] 总之,创建了IL-15变体Fc融合蛋白,并鉴定其具有不同的IL-15Rβ结合活性。一些IL-15变体显示出比其野生型对应物降低的与IL-15Rβ结合的能力(表5-表7)。一些变体,诸如P-0173和P-0185,保留了与野生型相似的与IL-15Rβ的结合活性(表5)。人类IL-15结构域中位置58处的丝氨酸被取代为天冬氨酸的单点突变提供了融合蛋白(P-0182和P-0313)与IL-15Rβ的增强的结合活性(表6和表7)。

[0304] 表5

[0305] IL-15变体/IL-15Rα异源二聚体Fc蛋白的IL-15Rβ结合活性

[0306]

| 蛋白 ID | IL-15/IL-15α 异源二聚体 Fc 融合形式 | ELISA 结合 | |
|---|---|---|---|
| | | $EC_{50}$ (nM) | 变化倍数 |
| P-0153 | IL-15 野生型 | 0.65 | 1 |
| P-0173 | IL-15d1 (111-114 缺失) | 0.66 | 1 |
| P-0174 | IL-15d2 (108-114 缺失) | 4.54 | 7 |
| P-0175 | IL-15d3 (105-114 缺失) | 23.1 | 36 |
| P-0176 | IL-15i1 (N95 后插入 GS) | 10.2 | 16 |
| P-0177 | IL-15i2 (N95 后插入 GGSGG) | 38.0 | 59 |
| P-0178 | IL-15i3 (N95 后插入 GSSGGSGGS) | 23.1 | 36 |

[0307] 表6

[0308] 单体IL-15变体(非共价)/IL-15RαFc融合蛋白的IL-15Rβ结合活性

[0309]

| 蛋白 ID | 单价 IL-15 (非共价)/ IL-15Rα Fc 融合形式 | ELISA 结合 $EC_{50}$ (nM) | 变化倍数 |
|---|---|---|---|
| P-0165 | IL-15 野生型 | 1.24 | 1 |
| P-0182 | IL-15 S58D | 0.31 | 0.25 |
| P-0183 | IL-15 T62D | 6.29 | 5 |
| P-0184 | IL-15 V63F | 15.6 | 13 |
| P-0185 | IL-15 I67V | 1.96 | 1.6 |
| P-0186 | IL-15 I68F | 106 | 86 |

[0310] 表7

[0311] 二聚体IL-15变体/IL-15Rα(非共价)Fc融合蛋白的IL-15Rβ结合活性

| 蛋白 ID | 二价 IL-15/IL-15Rα (非共价) Fc 融合形式 | ELISA 结合 $EC_{50}$ (nM) | 变化倍数 |
|---|---|---|---|
| P-0234 | IL-15 野生型 | 0.83 | 1 |
| P-0313 | IL-15-(S58D) | 0.36 | 0.43 |
| P-0361 | IL-15i1 (N95 后插入'GS') | 7.66 | 9 |

[0312] 实施例9

[0313] IL-15 S58D变体/IL-15RαFc融合蛋白的T细胞活化活性

[0314] 对IL-15变体/IL-15Rα复合物的Fc融合蛋白刺激淋巴细胞活化的功能活性进行了评价。如先前描述的,建立了离体人类PBMC测定,以分析表达淋巴细胞活化标志物CD69的CD8 T细胞的数目/百分比。

[0315] P-0234是C末端二聚体IL-15/IL-15RαSushi(非共价)Fc融合蛋白,通过优选构型的组合(包括IL-15与Fc的共价连接、C末端融合、二聚化合价和非共价IL-15RαSushi复合)进行了优化。P-0313是P-0234的S58D对应物。P-0313与P-0234共有相同的融合构型,但不同之处仅在于IL-15多肽中的S58D取代。先前与野生型对应物P-0234相比,P-0313展示出增加的IL-15Rβ结合活性(表7)。与增强的对IL-15Rβ的结合活性一致,含有S58D突变的变体P-0313也展示出增加的诱导CD69阳性T细胞的效力(对于P-0313和P-0234分别为7pM与12pM),证实P-0313显示出超级激动剂活性。

[0316] 实施例10

[0317] IL-15 S58D/IL-15RαFc融合蛋白的信号传导活性

[0318] IL-15 S58D变体展示出增加的与IL-15Rβ的结合活性和增强的刺激CD69阳性淋巴细胞的能力。目前的研究检查了IL-15 S58D/IL-15Rα融合蛋白刺激NK细胞和T细胞中的信号转导及转录激活因子5(signal transducer and activator of transcription 5)的细胞内磷酸化(pSTAT5)的信号传导活性。

[0319] 在IL-15化合物处理后的离体人类PBMC测定中,通过细胞内FACS分析来确定STAT5磷酸化。简而言之,将纯化的人类PBMC用IL-15测试化合物的系列稀释液处理,并在37℃孵育15分钟。在处理结束时,用FACS缓冲液(1%FBS/PBS)洗涤细胞一次,并在37℃在150μl/孔的预热的Cytofix固定缓冲液中孵育15分钟。再次洗涤经固定的细胞,并在4℃重悬于150μl/孔的预冷却Perm缓冲液II中30分钟。通过添加人类TruStain FcX(1:50稀释)封闭Fc受体后,用抗人类CD56-FITC、抗人类pSTAT5-PE、抗人类CD8-APC和抗人类CD4-Percp-cy5.5(1:50稀释)对细胞进行染色。在室温与抗体一起孵育45分钟后,收集细胞并洗涤,重悬于FACS

缓冲液中,并准备进行流式细胞术分析。数据表示为门控的群体中pSTAT5阳性细胞的%。

[0320] S58D突变被引入到两种形式的Fc融合蛋白中:二价IL-15(非共价)/IL-15RαFc融合体和二价IL-15/IL-15Rα(非共价)Fc融合体。P-0218和P-0314分别是包含野生型IL-15和S58D变体IL-15的C末端二聚体IL-15(非共价)/IL-15RαFc融合蛋白。P-0234和P-0313分别是包含野生型IL-15和S58D变体IL-15的C末端二聚体IL-15/IL-15Rα(非共价)Fc融合蛋白。在CD8 T细胞(图10A)、CD4 T细胞(图10B)以及NK细胞(图10C)中,无论融合构型如何,IL-15(S58D)变体融合蛋白(P-0314和P-0313)与其各自的野生型融合蛋白(P-0218和P-0234)相比展示出刺激STAT5磷酸化的能力的约2倍增加。数据证实,IL-1使5肽中的S58D取代导致各种IL-15/IL-15Rα融合蛋白的超级激动剂活性。

[0321] 实施例11

[0322] IL-15 S58D/IL-15-RαFc融合蛋白的细胞增殖活性

[0323] 在观察到与IL-15Rβ结合、刺激STAT5磷酸化和诱导CD69表达的能力增加后,通过测量NK细胞和CD8 T细胞中的Ki67表达,测试了IL-15S58D变体Fc融合蛋白与野生型融合蛋白相比刺激细胞增殖的能力。人类PBMC用递增剂量的IL-15融合分子处理,并且Ki67表达通过对CD56+NK细胞群体和CD8+T细胞群体进行门控的细胞内FACS分析来确定,如先前描述的。

[0324] 类似于(图10)中示出的对STAT5磷酸化观察到的,在CD8+T细胞(图11A)和CD4+T细胞(图11B)以及CD56+NK细胞(图11C)中,与野生型相比,IL-15 S58D变体的融合蛋白还展示出刺激Ki67表达的能力的2倍增加。这些数据加强了,在IL-15结构域中引入S58D突变提供了一系列生物活性(包括受体结合、细胞内信号传导、细胞表面标志物的活化和细胞增殖)的增强。

[0325] 实施例12

[0326] 小鼠中与rhIL-15和基准进行比较的P-0234的4天重复给药研究

[0327] IL-15/IL-15RαFc融合蛋白在体外和离体情况下展示出强的结合IL-15Rβ、诱导细胞内信号级联以及刺激NK和CD8 T淋巴细胞的增殖的能力。在此,我们检查了各种IL-15化合物在小鼠中的血清暴露以及对小鼠的NK细胞增殖和扩增的影响。测试的蛋白包括重组的人类天然IL-15(rhIL-15)、P-0234(C末端二价IL-15/IL-15Rα(非共价)Fc融合蛋白)和基准化合物(在IL-15中包含N72D突变的N末端二价IL-15(非共价)/IL-15RαFc融合蛋白)。

[0328] 7周龄的雌性Balb/c小鼠从Charles River实验室接收,并且在机构内适应至少7天,然后进行研究。对小鼠给予每日i.p.注射等摩尔剂量的IL-15化合物,持续4天。处理包括媒介物、0.03mg/kg rhIL-15(40pmol/kg)、0.1mg/kg和0.5mg/kg基准(40pmol/kg和200pmol/kg)、以及0.1mg/kg和0.5mg/kg P-0234(40pmol/kg和200pmol/kg)。每组有5只小鼠。处理前和处理期间每日记录体重。最后一次注射后1小时处死小鼠,并通过心脏穿刺收集终末血液。

[0329] 收集肝素化的全血和脾进行NK细胞表型分析和Ki67细胞内染色。在裂解红细胞并用纯化的抗小鼠CD16/CD32(1:50稀释)封闭Fc受体后,对单细胞悬浮液中的单核血细胞和脾细胞的NK细胞表面标志物染色(包括抗小鼠CD3-FITC和抗小鼠CD49b-APC(1:50稀释)),在室温在黑暗中持续30分钟。对于细胞内Ki67染色,用200ul/孔的1×Foxp3固定/透化工作溶液将细胞沉淀充分重悬,并在室温在黑暗中孵育30分钟。用200ul的1×透化缓冲液洗涤

细胞,并用纯化的抗小鼠CD16/CD32(1:50稀释)封闭Fc受体。然后针对NK细胞群体用Ki67-PE以及抗小鼠CD3-FITC和抗小鼠CD49b-APC对细胞进行染色(1:50稀释)。孵育30分钟后,收集细胞并洗涤,重悬于FACS缓冲液中,并准备进行流式细胞术分析。通过GraphPad prism软件中的单因素ANOVA和Tukey事后多重比较进行统计分析。

[0330] 图12示出了最后一次注射IL-15化合物后1小时IL-15的血清浓度。按照制造商的说明书(R&D systems;Cat#DY247),通过检测IL-15的商业ELISA试剂盒测量IL-15。以等摩尔剂量给予的化合物的4次每日给药后,IL-15的累积血清浓度在用P-0234处理的小鼠中最高,在用基准处理的小鼠中居中,并且在用rhIL-15处理的小鼠中最低(图12)。将以0.1mg/kg和0.5mg/kg施用的基准和P-0234进行比较,P-0234始终展示出为基准6倍高和4倍高的血清浓度。IL-15的平均血清浓度为:rhIL-15(0.03mg/kg给药)为3.2±0.6(ng/ml),基准化合物(分别给药0.1mg/kg和0.5mg/kg)为13±8和121±36(ng/ml),并且P-0234(分别给药0.1mg/kg和0.5mg/kg)为72±14和443±57(ng/ml)。更高的血清暴露表明,与基准和rhIL-15相比,P-0234可以显示出更长的体内半衰期和血清保留。

[0331] 虽然处理组之间总体重没有差异,但用较高剂量的基准处理的小鼠在处理的4天内体重减轻了近6%(图13A和图13B)。与在第0天的基线值和媒介物组相比,影响是统计学上显著的,表明用基准化合物而不是P-0234观察到潜在的剂量限制毒性。

[0332] 所有测试的IL-15化合物都使外周血中Ki67阳性NK细胞的百分比增加(图14A),表明了增强的NK细胞增殖。然而,在CD3阴性外周血淋巴细胞中NK细胞数目百分比的显著增加仅在以两种测试剂量水平的P-0234处理的小鼠中观察到(图14B)。虽然在用rhIL-15和较低剂量的基准处理的小鼠中也观察到NK细胞百分比的增加,但影响未达到统计学显著性(图14B)。令人感兴趣地,在用较高剂量的基准处理的小鼠中观察到外周血中NK细胞数目的下降(图14B)。这样的反向的药效学剂量-响应提示了与观察到的该组体重减轻一致的毒性。

[0333] 还在淋巴器官脾中检查了IL-15化合物对淋巴细胞增殖和扩增的影响。与在外周血中观察到的相似,与媒介物相比,所有IL-15化合物都使脾Ki67阳性NK细胞增加(图15A)。只有低剂量的基准和P-0234使脾中NK细胞的总数显著增加(图15B)。同样,观察到基准对脾NK细胞扩增的反向剂量-响应(图15B),并且这与终止后4天测量的脾NK细胞上高且持久的CD69表达相关(图15C)。数据表明,基准化合物可能过度刺激NK细胞,并导致细胞消耗。对于与IL-15RαFc融合蛋白非共价结合的IL-15,IL-15可能从基准化合物的融合复合物解离,并导致淋巴细胞过度刺激、细胞消耗、毒性和体重减轻。

[0334] 实施例13

[0335] 在小鼠中单次注射后IL-15/IL-15RαFc融合蛋白的药代动力学和药效学效应

[0336] 在Balb/C小鼠中单次注射后,对P-0313(C末端二价IL-15 S58D IL-15Rα(非共价)Fc融合蛋白)进行了剂量-响应研究。监测了随时间推移对外周血淋巴细胞增殖和扩增的影响。此外,单次注射后,将P-0313的药代动力学和药效学(PK/PD)与基准(N末端二价IL-15(非共价)/IL-15RαFc融合蛋白,在IL-15中包含N72D突变)的PK/PD进行比较。

[0337] 7周龄的雌性Balb/c小鼠从Charles River实验室接收,并且在机构内适应至少7天,然后进行研究。在时间0向小鼠经由腹膜内(i.p.)注射施用媒介物、基准(0.3mg/kg)或P-0313(0.01mg/kg、0.03mg/kg、0.1mg/kg和0.3mg/kg)。在-24hr(给药前)以及注射后1小时、4小时、24小时、72小时、120小时和192小时抽取血液。处理前和处理期间每日记录体重。

每组包括5只小鼠。

[0338] 肝素处理的全血被用于免疫表型分析,并记录体积。使用BD pharm裂解缓冲液裂解红细胞后,通过台盼蓝死细胞排除法对存活的单核血细胞总数进行计数,并进行Ki67细胞内染色。用200μl/孔的1×Foxp3固定/透化工作溶液将细胞沉淀充分重悬,并在室温在黑暗中孵育30分钟。离心后,向每个孔添加200μl的1×透化缓冲液进行另一次洗涤。用纯化的抗小鼠CD16/CD32(1:50稀释)封闭Fc受体后,用抗小鼠CD3-FITC、Ki67-PE、抗小鼠CD49b-APC和抗小鼠CD8-Percpy5.5(1:50稀释)对细胞进行染色。孵育30分钟后,收集细胞并洗涤,重悬于FACS缓冲液中,并通过流式细胞术进行分析。通过GraphPad prism软件中的单因素ANOVA单因素ANOVA和Tukey多重比较进行统计分析。

[0339] 使用两种不同的ELISA测定来测量化合物的血清浓度。开发了一种内部ELISA测定来测量IL-15和Fc复合物,而商业ELISA测定仅测量IL-15(捕获抗体和检测抗体两者均与人类IL-15反应)。对于内部ELISA测定,在4℃用抗IL-15抗体(R&D systems MAB647)包被maxisorp板过夜。将板用SuperBlock封闭。将不同稀释度的标准品和样品施加至板,并在室温孵育1小时。用抗人类IgG Fc-HRP检测活性化合物并且信号使用Ultra TMB底物溶液显影。值使用来自非线性回归曲线拟合的GraphPad Prism插值来计算。

[0340] 两种化合物在最初24小时的血清中均可检测到,具有相当的血清浓度。在i.p.施用后4小时观察到峰值浓度。在72小时,只有P-0313保持可被测量到,而基准在所有三只小鼠中均变为检测不到(图16A-图16B)。使用两种不同的ELISA测定获得了类似的结果,证实P-0313具有优于基准的药代动力学谱。该结果证实了先前实施例12中示出的观察结果,即P-0234(IL-15/IL-15Rα(非共价)Fc融合蛋白)也展示出高于基准的血清暴露。这些数据有力地支持了,在IL-15体内半衰期的延长方面,IL-15/IL-15Rα(非共价)Fc融合构型优于IL-15(非共价)/IL-15RαFc融合蛋白的构型。

[0341] 在任何处理组中均未观察到体重的显著变化(图17)。

[0342] 在用P-0313处理的小鼠中,在NK细胞和CD8 T细胞中观察到Ki67表达的剂量依赖性增加(图18A和图18B)。效应在72小时达到峰值,并且对于基准持续到120小时,并且对于P-0313进一步延长到192小时(图18A),表明P-0313比基准的作用更久。此外,P-0313在剂量为基准的剂量的3-10倍低时显示出类似的Ki67诱导,表明P-0313比基准更有效(图18A和图18B)。在10倍低的剂量,与CD8 T细胞相比,观察到NK细胞的显著响应,表明NK细胞比CD8 T细胞对P-0313处理更敏感。

[0343] 与观察到的细胞增殖标志物Ki67的增加一致,在P-0313处理组中观察到血液中NK细胞和CD8+T细胞的剂量依赖性扩增(图19A和图19B)。在72小时观察到细胞扩增,并在120小时达到峰值。P-0313在0.01mg/kg、0.03mg/kg、0.1mg/kg和0.3mg/kg剂量分别使NK细胞从基线增加4倍、15倍、50倍和163倍(图19A),并且在0.1mg/kg和0.3mg/kg剂量还使CD8 T细胞从基线增加10倍和50倍(图19B)。相比之下,0.3mg/kg剂量的基准仅使外周NK细胞扩增28倍,并使CD8 T细胞扩增12倍(图19A和图19B)。

[0344] 总之,对于NK细胞和CD8 T细胞增殖和扩增,P-0313展示出优于基准化合物的药代动力学和药效学。

[0345] 实施例14

[0346] IL-15/IL-15RαFc融合蛋白对抑制小鼠结肠癌肺转移的作用

[0347] 为了研究IL-15/IL-15Rα-Fc融合蛋白在肿瘤模型中的抗转移功效和免疫应答,将$1\times10^5$个小鼠结肠癌细胞CT26-WT(ATCC CRL-2638)静脉内注射到雌性Balb/C小鼠(10-12周龄)中。第二天,每五天(细胞移植后第1天、第6天、第11天)通过静脉内(i.v.)注射给予0.03mg/kg或0.1mg/kg的P-0313或0.3mg/kg的基准化合物。媒介物(PBS)被包括作为阴性对照,并且每组包含8只小鼠。在第15天,收集血液样品进行淋巴细胞表型分析和肝酶测量。在第16天,将所有小鼠处死进行组织收获。将肺用15%印度墨汁膨胀,并在Fekete溶液(10%甲醛、5%冰乙酸和60%乙醇)中脱色。在光学显微镜下对整个肺的肺部肿瘤结节进行计数,并且通过处理组和媒介物对照之间肿瘤结节的不同数目来表示抗转移作用。

[0348] 为了研究免疫应答,在第15天在肝素处理过的管中收集小鼠外周血,并记录每只小鼠用于测定的血液体积。通过BD pharm裂解缓冲液裂解红细胞后,通过台盼蓝死细胞排除法对存活的单核血细胞总数进行计数,并如先前描述的用于细胞内染色以进行免疫细胞表型分析和Ki67增殖分析。在细胞固定、透化和抗体染色后,收集细胞并洗涤,重悬于FACS缓冲液中,并通过流式细胞术进行分析。

[0349] 图20A示出了来自每组的肺的代表性照片,以说明肺结节。对肺转移病灶进行显微术计数和定量(图20B)。如图20中示出的,以0.3mg/kg给予的基准分子抑制了肺转移,肺结节计数减少84%,证实活化IL-15途径有效地阻止了肺转移的形成和生长。引人注目的是,以3倍低的剂量(0.1mg/kg)施用IL-15/IL-15Rα-Fc复合物P-0313导致对肺转移发展的完全抑制,在所有8只处理的小鼠中观察到零个结节(图20A和图20B)。在抑制肺转移的形成和生长方面P-0313优于基准,这与先前展示的增强的药代动力学和药效学作用一致(实施例12和实施例13)。与基准(其包含通过IL-15RαSushi结构域与Fc链非共价连接的IL-15)相比,P-0313(其IL-15部分与Fc结构域共价连接)展示出IL-15血清半衰期的显著提高(实施例13)。以0.03mg/kg给药的P-0313也降低了肺转移,抑制效果为~35%(图20A和图20B)。该观察结果进一步突出了P-0313在比基准低得多的剂量是有效的,并且突出了IL-15/IL-15Rα-Fc复合物的生物分布和生物可利用度对其体内抗癌作用的重要性。

[0350] 在三次重复的Q5D给药后,在P-0313处理的小鼠中,外周血中NK细胞和CD8+T细胞两者的扩增保持显著升高(图21A和图21B),这与该处理组的脾重量的显著增加相关(图22)。相比之下,对用0.3mg/kg基准处理的组,仅观察到CD8+T细胞非常轻微的扩增;与对照组相比,未观察到循环NK细胞数目的增加(图21A和图21B)。然而,在基准处理组中,脾重量显著增加(图22)。数据表明,在重复给药后,扩增的淋巴细胞可能会迁移到淋巴组织进行储存,或者也可能发生细胞消耗。由于所有三个处理组都显示出抗肿瘤作用,因此数据表明,CD8+T细胞或NK细胞可能是参与抗肿瘤作用的效应亚群。然而,在用0.1mg/kg的P-0313处理的组中观察到的肺转移的完全根除表明,利用NK细胞和CD8+T细胞两者的作用诱导了对肿瘤生长的最强抑制。

[0351] 测量了肝重量以及丙氨酸氨基转移酶(ALT)和天冬氨酸氨基转移酶(AST)的血清浓度,以评估与处理相关的肝毒性。如图23A-图23C中描绘的,与媒介物组相比,任何处理组的肝重量、ALT水平或AST水平都没有增加。数据表明,IL-15/IL-15RαFc融合蛋白的强抗肿瘤作用未伴有肝毒性。

[0352] 实施例15

[0353] IL-15/IL-15RαFc融合蛋白对小鼠中已建立的CT26实体瘤生长的影响

[0354] 为了进一步研究IL-15/IL-15RαFc融合蛋白在已建立的肿瘤模型中的抗肿瘤功效和免疫应答,在雌性Balb/C小鼠(10-12周龄)的右肋腹皮下注射$1\times10^5$个CT26细胞。在第11天,当平均肿瘤体积为~70$mm^3$时,小鼠被随机分为三组(n=10只/组),并在随机分组的同一天接受腹膜内注射媒介物(PBS)或P-0313(0.1mg/kg或0.05mg/kg)。在第16天进行各自测试剂的一次另外的腹膜内注射(总共2剂)。使用卡尺每周测量肿瘤三次,并且肿瘤体积计算如下:体积=0.5x(宽度)$^2$x(长度)。为了研究免疫应答,在第19天在肝素处理过的管中收集非终末外周血。在第21天,将所有小鼠处死进行组织收获。

[0355] 如图24A中示出的,PBS处理的小鼠迅速发展了大的皮下肿瘤。用0.1mg/kg或0.05mg/kg的P-0313处理小鼠,在延迟肿瘤生长方面大致相等(图24A)。对所有三个处理组绘制了每只个体小鼠的肿瘤生长曲线(图25A-图25C)。明显的是,小鼠对P-0313的处理响应良好,并且显示出延迟且同步的肿瘤生长抑制,特别是在两个测试剂量组的初始阶段(图25A-图25C)。在肿瘤接种后的第21天,与PBS处理的小鼠中的平均肿瘤体积为820$mm^3$相比,用两种剂量的P-0313处理的小鼠中的平均肿瘤体积为410$mm^3$(图25A**P<0.01;单因素ANOVA和Tukey事后检验)。值得注意的是,起初,P-0313在较高剂量(0.1mg/kg)显示出比较低剂量组更大的肿瘤负荷降低,但差异随着处理进行逐渐减小。

[0356] 在21天的研究过程中,P-0313处理的小鼠展示出与PBS处理的小鼠相似的体重增加(图24B),表明在两个测试剂量,P-0313被良好地耐受,并且未伴有显著的毒性。

[0357] 接下来,我们检查了P-0313对外周血和脾中的CD8 T细胞和NK细胞群体的影响。向荷瘤小鼠施用P-0313诱导了强烈的NK细胞和CD8 T细胞增殖(图26A和图26B)以及NK细胞和CD8 T细胞的剂量依赖性扩增(图26C和图26D),在非荷瘤小鼠中观察到类似程度的免疫细胞应答(实施例13)。在这两种淋巴细胞群体中,在NK细胞中观察到较高的变化倍数(对于0.1mg/kg给药组为~100倍,并且对于0.05mg/kg给药组为~38倍)。CD8+T细胞在0.1mg/kg剂量时扩增~5.4倍,并且对于0.05mg/kg给药组扩增~2.7倍。

[0358] P-0313还增强了脾中NK细胞和CD8+T细胞两者的扩增,这和外周血中一样(图27A和图27B),但脾中的变化幅度/倍数不太明显。在NK细胞中观察到较高的变化倍数(对于0.1mg/kg给药组为~10倍,并且对于0.05mg/kg给药组为~8倍)。CD8+T细胞在0.1mg/kg剂量时扩增~2.7倍,并且对于0.05mg/kg给药组仅轻微扩增。

[0359] 综上所述,这些数据展示,P-0313处理能够显著延迟和抑制实体瘤生长,并且这种抗肿瘤作用与荷瘤小鼠中细胞毒性NK细胞和CD8 T细胞的增殖和扩增相关,这与IL-15的总体免疫调节特性一致。由于P-0313含有缺乏效应子功能的Fc区,因此P-0313在体内的抗肿瘤活性不是由于直接杀伤肿瘤细胞,而是由于细胞毒性CD8+T细胞和NK细胞的稳健活化导致针对肿瘤细胞的有效免疫应答。

[0360] 实施例16

[0361] IL-15/IL-15RαFc融合蛋白对Balb/C小鼠中未建立的CT26实体瘤生长的影响

[0362] 在未建立的CT26肿瘤模型中进行了类似的研究,以证实P-0313的抗肿瘤功效。在用$1\times10^5$个CT26细胞进行肿瘤细胞皮下植入后3天,小鼠每5天接受媒介物(PBS)或P-0313(0.1mg/kg)的腹膜内注射,共5次注射。在第25天处死(terminate)小鼠,并且每周测量肿瘤2至3次。

[0363] 与在已建立的CT26肿瘤模型中观察到的(实施例15)相似,P-0313展示出对肿瘤生

长的显著抑制(图28A)和实体瘤质量的显著减少(图28B)。对于5次重复剂量,用P-0313处理的小鼠显示出脾重量中度增加(图29A),并且体重增加没有显著减少(图29B),表明P-0313被良好地耐受。

[0364] 总体上,这些数据还展示出,P-0313是一种有效的针对实体瘤和液体肿瘤以及肿瘤细胞转移的免疫治疗剂,具有良好耐受的安全性谱。

[0365] 实施例17

[0366] IL-15拮抗剂变体/IL-15RαFc融合蛋白的构建

[0367] 如实施例8和相关的表5-表7所公开的,在ELISA测定中,显著数量的包含氨基酸取代、插入和缺失的IL-15变体导致与IL-15Rβ的结合降低。在本实施例中,将另外的破坏IL-15Rβγ的取代引入IL-15/IL-15RαFc融合蛋白形式的IL-15部分中,旨在实现最佳的减弱效力。本发明人推断较低的效力可以防止途径过度活化,并降低不需要的靶吸收;并且因此,具有减弱的活性的IL-15变体/IL-15RαFc融合蛋白可以导致潜在地降低的毒性和改进的药代动力学。

[0368] 与IL-15Rβ的界面处的三个IL-15残基S58、V63和I68和一个γC相互作用残基Q108被靶向进行诱变,旨在减弱效力。此外,还类似地构建了在N末端处具有不同长度的氨基酸缺失的IL-15变体。

[0369] 氨基酸取代和缺失及其对应的IL-15变体/IL-15RαFc融合蛋白在表8中列出。

[0370] 表8

[0371] 示例性IL-15拮抗剂变体/IL-15RαFc融合蛋白。

[0372] (全都具有二价IL-15/IL-15Rα(非共价)Fc融合形式,除非另外说明)

[0373]

| IL-15氨基酸取代/缺失 | IL-15变体 SEQ ID NO: | 融合蛋白ID |
|---|---|---|
| S58G | 66 | P-0739 |
| S58H | 67 | P-0740 |
| S58R | 68 | P-0741 |
| S58Q | 69 | P-0742 |
| S58I | 70 | P-0743 |
| S58P | 71 | P-0744 |
| V63A | 72 | P-0771 |
| V63F | 26 | P-0184[1] |
| V63K | 73 | P-0769 |
| V63R | 74 | P-0770 |
| I68F | 26 | P-0356 |
| I68D | 30 | P-0357 |
| I68H | 31 | P-0358 |
| I68K | 29 | P-0738 |
| I68Q | 75 | P-0736 |

[0374]

| | | |
|---|---|---|
| I68G | 76 | P-0737 |
| Q108S | 34 | P-0764[2] |
| Q108A | 32 | P-0793[2] |
| Q108M | 33 | P-0805[2] |
| Q108E | 77 | P-0797 |
| Q108K | 78 | P-0796[2] |
| 1-aa N末端缺失 | 56 | P-0866 |
| 2-aa N末端缺失 | 57 | P-0867 |
| 3-aa N末端缺失 | 58 | P-0868 |
| 4-aa N末端缺失 | 59 | P-0822 |

[0375] [1]单价IL-15(非共价)/IL-15RαFc融合形式

[0376] [2]单价IL-15/IL-15Rα(非共价)Fc融合形式

[0377] 实施例18

[0378] IL-15拮抗剂变体/IL-15Rα抗体融合蛋白的构建

[0379] 制备和评估了各种IL-15拮抗剂变体/IL-15RαSushi抗体融合蛋白。本领域应理解,重组抗体-细胞因子融合蛋白(免疫细胞因子)的使用可以通过将细胞因子靶向病变部位来增强细胞因子的治疗指数。除了肿瘤靶向抗体,绕开肿瘤微环境中的免疫抑制效应的免疫检查点阻断性抗体或增强现有应答的免疫刺激性抗体的使用也可以用于构建抗体-细胞因子融合蛋白。免疫检查点阻断性抗体-细胞因子融合蛋白预期进一步增强免疫系统对抗肿瘤的活性。本发明人提出,使用具有减弱活性的IL-15变体可能有助于在细胞因子和抗体臂之间建立化学计量平衡。此外,细胞因子活性减弱预期使外周活化最小化、减轻抗原吸收并促进经由抗体臂的肿瘤靶向。

[0380] 按照这一概念,构建了各种IL-15/IL-15RαSushi-抗体融合蛋白。用于制备融合蛋白的示例性抗体包括各种PD-1拮抗剂抗体(具有SEQ ID NO:111-120中列出的序列);PD-L1阻断性抗体(SEQ ID NO:121-122);抗CTLA4抗体(SEQ ID NO:123-124);CD40激动性抗体(SEQ ID NO:125-126);针对纤连蛋白的外结构域的L19抗体(SEQ ID NO:127-128);针对CD20的利妥昔单抗(SEQ ID NO:129-130);针对Her-2的抗体曲妥珠单抗(SEQ ID NO:131-132);针对EGFR的西妥昔单抗(SEQ ID NO:133-134);用于肿瘤靶向和保留的抗FAP抗体(SEQ ID NO:109-110)。

[0381] 为了制备IL-15/IL-15RαSushi-抗体融合蛋白,将上文列出的抗体的重链的CH1-CH2-CH3(基于EU编号的抗体残基118-447)结构域替换为SEQ ID NO:135中列出的IgG1序列,该IgG1序列包含L234A、L235A、G237A突变,以消除与Fc γR和C1q的结合,但保留FcRn结合或PK。IL-15变体肽经由具有表6中列出的序列的肽接头融合到Fc结构域的C末端。可选地,为了表达单价IL-15变体,上文列出的抗体的重链的CH1-CH2-CH3结构域被SEQ ID NO:136-137中列出的异源二聚体链替换。IL-15变体肽经由肽接头融合到使用knob-into-hole技术工程化的含有knob的异源二聚体重链的C末端。半衰期延长突变,例如N434A,可以被进一步引入同源二聚体或异源二聚体Fc链中。生成二价IL-15/IL-15RαSushi-抗体融合蛋白的又另一种方法是将IL-15变体肽经由肽接头融合到轻链的C末端。在所有情况中,IL-15Rα与IL-15部分共表达和非共价复合。示例性的IL-15变体/IL-15RαSushi-PD-1拮抗剂抗体融

合蛋白在表9中列出,并且其卡通图在图30中图示出。

[0382] 表9

[0383] 示例性IL-15拮抗剂变体/IL-15Rα-PD-1拮抗剂抗体融合蛋白

[0384]

| IL-15 氨基酸取代/缺失 | 抗体融合 SEQ ID NO: | IL-15/IL-15Rα 化合价 | 蛋白 ID |
|---|---|---|---|
| Q108S | 138 + 114 + 5 | 二聚体 | P-0820 |
| Q108S | 139 + 144 + 114 + 5 | 单体 | P-0801 |
| Q108A | 140 + 144 + 114 + 5 | 单体 | P-0821 |
| I68G | 142 + 144 + 114 + 5 | 单体 | P-0856 |
| V63A/I68G | 143 + 144 + 114 + 5 | 单体 | P-0857 |
| V63A/I68G | 145 + 114 + 5 | 二聚体 | P-0858 |
| V63A/I68H | 141 + 114 + 5 | 二聚体 | P-0870 |
| 2-aa N 末端缺失 | 146 + 114 + 5 | 二聚体 | P-0886 |
| 4-aa N 末端缺失 | 147 + 114 + 5 | 二聚体 | P-0887 |
| 2-aa N 末端缺失+ V63A | 148 + 114 + 5 | 二聚体 | P-0888 |

[0385] 按照实施例1中详述的相同程序进行基因合成、表达载体构建、以及蛋白产生、纯化和表征。所有IL-15变体/IL-15Rα-PD-1拮抗剂抗体融合蛋白以与亲本抗体相当的合适的产率表达,具有低聚集倾向(数据未示出)。

[0386] 实施例19

[0387] IL-15变体/IL-15Rα融合蛋白展示出离体功能活性的不同水平的效力调节

[0388] 通过测量CD8 T细胞的Ki67表达,筛选示例性的IL-15变体/IL-15RαFc融合蛋白(单体或二聚体)刺激细胞增殖的能力。人类PBMC用递增剂量的IL-15融合分子处理,并且Ki67表达通过对CD8+T细胞群体进行门控的细胞内FACS分析来确定,如先前描述的。P-0313,具有增强的结合和功能活性的包含S58D取代的二价IL-15/IL-15RαSushi(非共价)Fc融合体,用作阳性对照,因为其已经被充分表征。

[0389] 如图31A图示的,用各种尺寸、溶解度和电离特性的氨基酸替换IL-15残基S58仅稍许调节刺激CD8 T细胞增殖的效力。表10A总结了示例性变体刺激CD8 T细胞增殖的$EC_{50}$值。与P-0313相比,所有变体显示出略微降低的效力;降低范围从1.7倍到7倍。

[0390] 表10A

[0391] S58处的氨基酸变化对CD8 T细胞增殖效力的影响

[0392]

| 蛋白ID | 取代 | EC50 (pM) | 对比P-0313的变化倍数 |
|---|---|---|---|
| P-0313 | S58D | 20 | 1 |
| P-0739 | S58G | 41.5 | 2.1 |
| P-0740 | S58H | 63.3 | 3.2 |
| P-0741 | S58R | 95.8 | 4.8 |
| P-0742 | S58Q | 139 | 7 |
| P-0743 | S58I | 78.6 | 3.9 |
| P-0744 | S58P | 34.3 | 1.7 |

[0393] 同样地,包含位置V63处的取代的示例性的IL-15变体/IL-15RαFc融合体仅导致CD8 T细胞增殖的中度减弱,如图31B图示的。与P-0313相比,变体刺激CD8 T细胞增殖的$EC_{50}$值和降低倍数总结在表10B中。

[0394] 表10B

[0395] V63处的氨基酸变化对CD8 T细胞增殖效力的影响

[0396]

| 蛋白ID | 取代 | EC50 (pM) | 对比P-0313的变化倍数 |
|---|---|---|---|
| P-0313 | S58D | 32 | 1 |
| P-0739 | V63K | 359.8 | 11.3 |
| P-0740 | V63R | 184.4 | 5.8 |
| P-0741 | V63A | 131.7 | 4.2 |

[0397] 与残基S58和V63形成对比,位置I68处的氨基酸(其与多于一个IL-15Rβ残基形成范德华相互作用)取代产生了在增殖CD8 T细胞中具有广泛效力谱的变体,$EC_{50}$在从0.4nM至~300nM的范围,700倍差异的程度。与P-0313相比,活性减弱的水平在从10倍跨至~7000倍。数据在图31C中图示出,并总结在表10C中。

[0398] 表10C

[0399] I68处的氨基酸变化对CD8 T细胞增殖效力的影响

[0400]

| 蛋白ID | 取代 | EC50 (pM) | 对比P-0313的变化倍数 |
|---|---|---|---|
| P-0313 | S58D | 44 | 1 |
| P-0358 | I68H | 419 | 9.5 |
| P-0356 | I68F | 1251 | 29 |
| P-0736 | I68Q | 4473 | 102 |
| P-0737 | I68G | 14466 | 330 |
| P-0738 | I68K | 24842 | 564 |
| P-0357 | I68D | ~296000 | ~6727 |

[0401] 又另一个被靶向用于减弱IL-15功能活性的残基是Q108,一个与γC中多于一个残基相互作用的关键的热点残基。分别携带Q108S和Q108A突变的两种示例性的IL-15 Q108变体/IL-15RαFc融合蛋白P-0763和P-0793均显示出CD8 T细胞增殖的显著降低(>1000倍)(图31D和表10D)。

[0402] 表10D

[0403] Q108处的氨基酸变化对CD8 T细胞增殖效力的影响

[0404]

| 蛋白ID | 取代 | EC50 (pM) | 对比P-0313的变化倍数 |
|---|---|---|---|
| P-0313 | S58D | 32 | 1 |
| P-0764 | Q108S | 62051 | 1956 |
| P-0793 | Q108A | 68817 | 2169 |

[0405] 除了取代与IL-15Rβ和/或γc受体亚基的界面处的IL-15残基以实现期望的活性减弱之外,N末端缺失提供了另一条途径来实现相同的目标。IL-15的N末端是α螺旋的一部分,其含有与IL-15Rβ和γc相互作用的重要残基,例如Asp8和Lys10。在人类PBMC测定中测定了分别在IL-15N末端处包含1个、2个、3个和4个氨基酸缺失的二价IL-15变体/IL-15Rα(非共价)Fc融合蛋白P-0866、P-0867、P-0868和P-822。如图32图示出的,当与P-0866的野生型IL-15对应物P-0234相比时,1个氨基酸缺失并不影响P-0866刺激CD8 T细胞增殖的效力。相比之下,P-0867的2个氨基酸缺失导致约100倍的效力降低($EC_{50}$为24.8nM,对比P-0234的289pM)。P-0868缺失中的一个另外的氨基酸缺失并没有进一步降低功能。然而,一个额外的氨基酸缺失或总共四个氨基酸缺失基本上消除了融合蛋白P-0822的生物活性。

[0406] 此外,破坏IL-15Rβ和/或γc相互作用的IL-15氨基酸取代的组合被认为导致不同水平的效力减弱。构建了掺入表8中描述的V63A和I68处的一个优选突变(包括I68H、I68Q和I68G)的示例性组合突变体,并且评估了其对人类PBMC中的CD8 T细胞增殖。破坏IL-15Rβ的取代的组合导致CD8 T细胞增殖效力的递增减弱(表11)。与P-0313相比,由于V63A取代导致效力降低4.2倍,并且分别在I68H、I68Q和I68G的突变情况下,V63A一致地导致CD8 T细胞增殖效力的2.1倍、4.3倍和3.8倍的减弱。数据也在图33A中图示出。同样地,在N末端氨基酸缺失的情况下增加V63A氨基酸取代也导致CD8 T细胞增殖效力的3倍减弱,这由P-0886和P-0888示例并在图33B中图示出。这两种化合物都是在IL-15的N末端处包含两个氨基酸缺失的IL-15变体/IL-15RαPD-1抗体融合蛋白。P-0888含有一个另外的V63A突变。

[0407] 表11

[0408] 破坏IL-15Rβ的氨基酸取代的示例性组合对CD8 T细胞增殖效力的影响

[0409]

| 取代 | SEQ ID NO: | 融合蛋白ID | EC50 (pM) | 对比P-0313的变化倍数 | V63A的影响(变化倍数) |
|---|---|---|---|---|---|
| S58D | 24 | P-0313 | 31.7 | 1 | N/A |
| V63A | 72 | P-0771 | 132 | 4.2 | 4.2 |
| I68H | 31 | P-0358 | 683 | 21.5 | N/A |
| V63A/I68H | 79 | P-0773 | 1418 | 45 | 2.1 |
| I68Q | 75 | P-0736 | 3614 | 114 | N/A |
| V63A/I68Q | 80 | P-0772 | 15379 | 485 | 4.3 |
| I68G | 76 | P-0737 | 12783 | 403 | N/A |
| V63A/I68G | 81 | P-0768 | 48015 | 1513 | 3.8 |

[0410] 如技术人员可以理解的,通过组合表8中描述的优选突变,例如V63K/Q108M、I68H/Q108K,可以获得具有不同水平的效力减弱的另外的突变体。任何另外的组合突变体都符合本发明的精神和范围。

[0411] 通过如先前描述测量Ki67表达进一步测试了具有从3.6nM至69nM范围的CD8 T细

胞Ki67 $EC_{50}$的代表性的IL-15变体/IL-15RαSushi Fc融合蛋白P-0736、P-0772、P-0737、P-0768、P-0793和P-0764刺激NK细胞增殖的能力。数据在图34A和图34B中图示出,并且$EC_{50}$值总结在表12中。

[0412] 表12

[0413] 代表性IL-15变体/IL-15RαSushi融合蛋白的CD8 T细胞和NK细胞增殖效力

[0414]

| 蛋白ID | 取代 | CD8 T 细胞 | | NK 细胞 | |
|---|---|---|---|---|---|
| | | EC50 (pM) | 对比P-0313的变化倍数 | EC50 (pM) | 对比P-0313的变化倍数 |
| P-0313 | S58D | 31.7 | 1 | 13 | 1 |
| P-0736 | I68Q | 3614 | 114 | 416 | 32 |
| P-0772 | V63A/I68Q | 15379 | 485 | 1110 | 85 |
| P-0737 | I68G | 12783 | 403 | 2064 | 159 |
| P-0768 | V63A/I68G | 48015 | 1515 | 5852 | 450 |
| P-0793 | Q108A | 68817 | 2171 | 4125 | 317 |
| P-0764 | Q108S | 62051 | 1957 | 9746 | 750 |

[0415] 类似地,如在CD8 T细胞中观察到的,代表性IL-15变体/IL-15RαSushi Fc融合蛋白在刺激NK细胞增殖方面也展示出宽的效力范围,$EC_{50}$范围从0.42nm至9.7nM。与P-0313相比,每种分子的效力明显减弱;对CD8 T细胞的效力降低水平从100倍跨至2000倍,并且对NK细胞范围从30倍至750倍。虽然每种分子在增殖CD8 T细胞方面遵循相似的效力排序,但所有化合物都对NK细胞更好响应。

[0416] 最后,在图35中清楚地图示出,IL-15/IL-15Rα复合物无论是Fc融合形式还是抗体融合形式,都展示出相同的生物活性。图35A中的P-0773和P-0870两者均包含V63A/I68H氨基酸取代,并且分别为IL-15/IL-15RαFc融合体和抗体融合体。图35B中的P-0867和P-0886是在IL-15的N末端处包含2个氨基酸缺失的类似的对。

[0417] 总之并且重要的是,将破坏IL-15Rβγc的氨基酸取代或缺失单独地或组合地引入IL-15部分中导致IL-15变体具有广泛的刺激细胞毒性淋巴细胞(以CD8 T细胞和NK细胞为代表)的效力谱。不同突变或突变组合在Fc融合蛋白和抗体融合蛋白中的活性减弱水平相同。

[0418] 本文公开的和要求保护的所有物品和方法鉴于本公开内容均可被制备和执行而无需过度实验。尽管已根据优选的实施方案描述本公开内容的物品和方法,但对于本领域技术人员将明显的是,变化形式可被应用到所述物品和方法而不偏离本公开内容的精神和范围。对于本领域技术人员明显的是,所有这样的变化和等效物,无论是现存的或以后开发的,都被认为是在由所附权利要求限定的本公开内容的精神和范围之内。说明书中提及的所有专利、专利申请和出版物指示本公开内容所属领域的普通技术人员的水平。为了所有目的,所有专利、专利申请和出版物通过引用以其整体并入本文,并且其程度如同每个单独出版物单独地且具体地被指示为了任何和所有目的通过引用以其整体并入本文。本文例证地表述的本公开内容可在本文未具体地公开的任何一个或更多个要素不存在的条件下被合适地实践。因此,应理解,尽管本公开内容已通过优选的实施方案和任选的特征被具体地

公开,但是本领域技术人员可寻求本文公开的概念的改变和变化形式,并且认为此类改变和变化形式在由所附的权利要求限定的本公开内容的范围内。

[0419] 序列表

[0420] 所附序列表中列出的氨基酸序列使用氨基酸的标准字母缩写示出,如37 C.F.R.1.822中规定的。

[0421] SEQ ID NO:1是人类IL-15前体氨基酸序列。

[0422] SEQ ID NO:2是人类IL-15成熟形式氨基酸序列。

[0423] SEQ ID NO:3是人类IL-15R氨基酸序列。

[0424] SEQ ID NO:4是人类IL-15Rα细胞外结构域氨基酸序列。

[0425] SEQ ID NO:5是人类IL-15Rαsushi结构域+氨基酸序列。

[0426] SEQ ID NO:6是人类IgG1-Fc氨基酸序列。

[0427] SEQ ID NO:7是Knob-Fc氨基酸序列。

[0428] SEQ ID NO:8是Hole-Fc氨基酸序列。

[0429] SEQ ID NO:9-12是各种肽接头的氨基酸序列。

[0430] SEQ ID NO:13是Hole-Fc-接头1-IL-15链的氨基酸序列。

[0431] SEQ ID NO:14是Knob-Fc-接头1-IL-15Rα-Sushi+链的氨基酸序列。

[0432] SEQ ID NO:15是IL-15-接头4-Hole-Fc链的氨基酸序列。

[0433] SEQ ID NO:16是IL-15Rα-Sushi+-接头4-Knob-Fc链的氨基酸序列。

[0434] SEQ ID NO:17是Knob-Fc-接头2-IL-15Rα-Sushi+链的氨基酸序列。

[0435] SEQ ID NO:18是Hole-Fc-接头2-IL-15链的氨基酸序列。

[0436] SEQ ID NO:19是IL-15-接头3-Hole-Fc链的氨基酸序列。

[0437] SEQ ID NO:20是Fc-接头3-IL-15链的氨基酸序列。

[0438] SEQ ID NO:21是IL-15-接头3-Fc链的氨基酸序列。

[0439] SEQ ID NO:22是Knob-Fc-接头2-IL-15Rα-Sushi+链的氨基酸序列。

[0440] SEQ ID NO:23是Fc-接头2-IL-15Rα-Sushi+链的氨基酸序列。

[0441] SEQ ID NO:24-45是各种IL-15变体多肽的氨基酸序列。

[0442] SEQ ID NO:46是Fc-接头3-IL-15 S58D链的氨基酸序列。

[0443] SEQ ID NO:47是肽接头的氨基酸序列。

[0444] SEQ ID NO:48是Hole-Fc-接头3-IL-15-S58D链的氨基酸序列。

[0445] SEQ ID NO:49是IL-15-S58D-接头3-Hole-Fc链的氨基酸序列。

[0446] SEQ ID NO:50是IL-15-S58D-接头3-Fc链的氨基酸序列。

[0447] SEQ ID NO:51是IL-15Rα-Sushi-接头2-Knob-Fc链的氨基酸序列。

[0448] SEQ ID NO:52是IL-15Rα-Sushi-接头2-Fc链的氨基酸序列。

[0449] SEQ ID NO:53是Hole-Fc-接头1-IL-15-S58D链的氨基酸序列。

[0450] SEQ ID NO:54是Hole-Fc-接头3-IL-15链的氨基酸序列。

[0451] SEQ ID NO:55是Knob-Fc-接头1-IL-15链的氨基酸序列。

[0452] SEQ ID NO:56-63是包含N末端缺失的各种IL-15变体多肽的氨基酸序列。

[0453] SEQ ID NO:64和65是基准的两个多肽链的氨基酸序列。

[0454] SEQ ID NO:66-81是各种IL-15变体多肽的氨基酸序列。

[0455] SEQ ID NO:82-104是各种IL-15变体Fc融合构建体的氨基酸序列。

[0456] SEQ ID NO:105-106是具有降低/消除的效应子功能和延长的半衰期的人类IgG1-Fc氨基酸序列。

[0457] SEQ ID NO:107是具有延长的半衰期的Knob-Fc氨基酸序列。

[0458] SEQ ID NO:108是具有延长的半衰期的Hole-Fc氨基酸序列。

[0459] SEQ ID NO:109-110是人源化抗FAP抗体的重链和轻链的氨基酸序列。

[0460] SEQ ID NO:111-112是人源化PD-1拮抗剂抗体的重链和轻链的氨基酸序列。

[0461] SEQ ID NO:113-114是人类PD-1拮抗剂抗体的重链和轻链的氨基酸序列。

[0462] SEQ ID NO:115-116是PD-1拮抗剂抗体的重链和轻链的氨基酸序列。

[0463] SEQ ID NO:117-118是PD-1拮抗剂抗体的重链和轻链的氨基酸序列。

[0464] SEQ ID NO:119-120是PD-1拮抗剂抗体的重链和轻链的氨基酸序列。

[0465] SEQ ID NO:121-122是PD-L1拮抗剂抗体的重链和轻链的氨基酸序列。

[0466] SEQ ID NO:123-124是CTLA-4拮抗剂抗体的重链和轻链的氨基酸序列。

[0467] SEQ ID NO:125-126是CD40激动剂抗体的重链和轻链的氨基酸序列。

[0468] SEQ ID NO:127-128是抗纤连蛋白抗体的重链和轻链的氨基酸序列。

[0469] SEQ ID NO:129-130是CD20拮抗剂抗体的重链和轻链的氨基酸序列。

[0470] SEQ ID NO:131-132是Her-2/neu拮抗剂抗体的重链和轻链的氨基酸序列。

[0471] SEQ ID NO:133-134是EGFR拮抗剂抗体的重链和轻链的氨基酸序列。

[0472] SEQ ID NO:135是具有降低/消除的Fc效应子功能的人类IgG1CH1CH2CH3结构域序列的氨基酸序列。

[0473] SEQ ID NO:136是具有降低/消除的Fc效应子功能的人类IgG1CH1CH2CH3结构域knob链序列的氨基酸序列。

[0474] SEQ ID NO:137是具有降低/消除的Fc效应子功能的人类IgG1CH1CH2CH3结构域hole链序列的氨基酸序列。

[0475] SEQ ID NO:138-148是各种示例性的IL-15/IL-15RαSushi-抗体融合蛋白的氨基酸序列。

[0476] SEQ ID NO:149-152是各种IL-15缺失变体Fc融合构建体的氨基酸序列。

[0477] SEQ ID NO:153-154是各种肽接头的氨基酸序列。

[0478] 序列表

[0479] 人类IL-15前体序列

[0480] MRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:1)

[0481] 人类IL-15成熟形式序列

[0482] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:2)

[0483] 人类IL-15Rα序列

[0484] MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTA

AIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLSA VSLLACYLKSRQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHL(SEQ ID NO:3)

[0485] 人类IL-15Rα,细胞外结构域

[0486] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPA LVHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSHGT PSQTTAKNWELTASASHQPPGVYPQGHSDTT(SEQ ID NO:4)

[0487] 人类IL-15Rα,sushi结构域+

[0488] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPA LVHQRPAPP(SEQ ID NO:5)

[0489] 具有降低的效应子功能的人类IgG1-Fc

[0490] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG(SEQ ID NO:6)

[0491] Knob-Fc

[0492] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG(SEQ ID NO:7)

[0493] Hole-Fc

[0494] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG(SEQ ID NO:8)

[0495] 肽接头序列

[0496] EPKSSDKTHTSPPSP(SEQ ID NO:9)

[0497] 肽接头序列

[0498] GGGGSGGGGS(SEQ ID NO:10)

[0499] 肽接头序列

[0500] GGGGSGGGGSGGGGS(SEQ ID NO:11)

[0501] 肽接头序列

[0502] GSGS(SEQ ID NO:12)

[0503] Hole-Fc-接头1-IL-15链

[0504] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGEPKSSDKTHTSPPSPNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:13)

[0505] Knob-Fc-IL-接头1-IL-15Rα-Sushi+链

[0506] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGEPKSSDKTHTSPPSPITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAH WTTPSLKCIRDPALVHQRPAPP(SEQ ID NO:14)

[0507] IL-15-接头4-Hole-Fc链

[0508] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGCPPCPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL VSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:15)

[0509] IL-15Rα-Sushi+-接头4-Knob-Fc链

[0510] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPA LVHQRPAPPGCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG(SEQ ID NO:16)

[0511] Knob-Fc-接头2-IL-15Rα-+链

[0512] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPP(SEQ ID NO:17)

[0513] Hole-Fc-接头2-IL-15链

[0514] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:18)

[0515] IL-15-接头3-Hole-Fc链

[0516] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSGGGGSGGGGSCPPCPAPEAAGAPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:19)

[0517] Fc-接头3-IL-15链

[0518] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS

LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:20)

[0519] IL-15-接头3-Fc链

[0520] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSGGGGSGGGGSCPPCPAPEAAGAPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:21)

[0521] Knob-Fc-接头2-IL-15Rα-Sushi+链

[0522] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPP(SEQ ID NO:22)

[0523] Fc-接头2-IL-15Rα-Sushi+链

[0524] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPS LKCIRDPALVHQRPAPP(SEQ ID NO:23)

[0525] 人类IL-15 S58D变体多肽

[0526] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDADIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:24)

[0527] 人类IL-15 T62D变体多肽

[0528] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDDVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:25)

[0529] 人类IL-15 V63F变体多肽

[0530] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTFENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:26)

[0531] 人类IL-15 I67V变体多肽

[0532] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLVI LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:27)

[0533] 人类IL-15 I68F变体多肽

[0534] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIF LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:28)

[0535] 人类IL-15 I68K变体多肽

[0536] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIK LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:29)

[0537] 人类IL-15 I68D变体多肽

[0538] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLID LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:30)

[0539] 人类IL-15 I68H变体多肽

[0540] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIH LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:31)

[0541] 人类IL-15 Q108A变体多肽

[0542] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVAMFINTS(SEQ ID NO:32)

[0543] 人类IL-15 Q108M变体多肽

[0544] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVMMFINTS(SEQ ID NO:33)

[0545] 人类IL-15 Q108S变体多肽

[0546] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:34)

[0547] 人类IL-15 Q108S/D30T变体多肽

[0548] NWVNVISDLKKIEDLIQSMHIDATLYTESTVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:35)

[0549] 人类IL-15 Q108S/V31Y变体多肽

[0550] NWVNVISDLKKIEDLIQSMHIDATLYTESDYHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:36)

[0551] 人类IL-15 Q108S/H32E变体多肽

[0552] NWVNVISDLKKIEDLIQSMHIDATLYTESDVEPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:37)

[0553] 人类IL-15 Q108S/D30T/V31Y/H32E变体多肽

[0554] NWVNVISDLKKIEDLIQSMHIDATLYTESTYEPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:38)

[0555] 缺失111-114的人类IL-15变体多肽

[0556] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMF(SEQ ID NO:39)

[0557] 缺失109-114的人类IL-15变体多肽

[0558] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ(SEQ ID NO:40)

[0559] 缺失108-114的人类IL-15变体多肽

[0560] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIV(SEQ ID NO:41)

[0561] 缺失105-114的人类IL-15变体多肽

[0562] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV(SEQ ID NO:42)

[0563] N95后插入‘GS’的人类IL-15变体多肽

[0564] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNGSIKEFLQSFVHIVQMFINTS(SEQ ID NO:43)

[0565] N95后插入'GGSGG'的人类IL-15变体多肽

[0566] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNGGSGGIKEFLQSFVHIVQMFINTS(SEQ ID NO:44)

[0567] N95后插入'GSSGGSGGS'的人类IL-15变体多肽

[0568] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNGSSGSSGGSIKEFLQSFVHIVQMFINTS(SEQ ID NO:45)

[0569] Fc-接头3-IL-15 S58D链

[0570] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DADIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:46)

[0571] 肽接头序列

[0572] GGGGSGGGG(SEQ ID NO:47)

[0573] Hole-Fc-接头3-IL-15 S58D链

[0574] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DADIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:48)

[0575] IL-15 S58D-接头3-Hole-Fc链

[0576] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDADIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSGGGGSGGGGSCPPCPAPEAAGAPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:49)

[0577] IL-15 S58D-接头3-Fc链

[0578] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDADIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTSGGGGSGGGGSGGGGSCPPCPAPEAAGAPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:50)

[0579] IL-15Rα-Sushi-接头2-Knob-Fc链

[0580] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPA LVHQRPAPPGGGGSGGGGSCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEM TKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN

HYTQKSLSLSPG(SEQ ID NO:51)

[0581] IL-15Rα-Sushi-接头2-Fc链

[0582] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPGGGGSGGGGSCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:52)

[0583] Hole-Fc-接头1-IL-15-S58D链

[0584] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPKSSDKTHTSPPSPNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDADIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:53)

[0585] Hole-Fc-接头3-IL-15链

[0586] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:54)

[0587] Knob-Fc-接头1-IL-15链

[0588] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPKSSDKTHTSPPSPNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:55)

[0589] 在N末端处具有1个氨基酸缺失的人类IL-15变体

[0590] WVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:56)

[0591] 在N末端处具有2个氨基酸缺失的人类IL-15变体

[0592] VNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:57)

[0593] 在N末端处具有3个氨基酸缺失的人类IL-15变体

[0594] NVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:58)

[0595] 在N末端处具有4个氨基酸缺失的人类IL-15变体

[0596] VISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:59)

[0597] 在N末端处具有5个氨基酸缺失的人类IL-15变体

[0598] ISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNS

LSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:60)

[0599] 在N末端处具有6个氨基酸缺失的人类IL-15变体

[0600] SDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:61)

[0601] 在N末端处具有2个氨基酸缺失的人类IL-15 V63A变体

[0602] VNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:62)

[0603] 在N末端处具有2个氨基酸缺失的人类IL-15 I68H变体

[0604] VNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIHLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:63)

[0605] 基准链1

[0606] ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIREPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:64)

[0607] 基准链2

[0608] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANDSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:65)

[0609] 人类IL-15 S58G变体多肽

[0610] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAGIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:66)

[0611] 人类IL-15 S58H变体多肽

[0612] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAHIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:67)

[0613] 人类IL-15 S58R变体多肽

[0614] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDARIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:68)

[0615] 人类IL-15 S58Q变体多肽

[0616] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAQIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:69)

[0617] 人类IL-15 S58I变体多肽

[0618] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAIIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:70)

[0619] 人类IL-15 S58P变体多肽

[0620] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAPIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:71)

[0621] 人类IL-15 V63A变体多肽

[0622] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAENLII

LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:72)

[0623] 人类IL-15 V63K变体多肽

[0624] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTKENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:73)

[0625] 人类IL-15 V63R变体多肽

[0626] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTRENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:74)

[0627] 人类IL-15 I68Q变体多肽

[0628] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIQ LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:75)

[0629] 人类IL-15 I68G变体多肽

[0630] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIG LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:76)

[0631] 人类IL-15 Q108E变体多肽

[0632] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS(SEQ ID NO:77)

[0633] 人类IL-15 Q108K变体多肽

[0634] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVKMFINTS(SEQ ID NO:78)

[0635] 人类IL-15 V63A/I68H变体多肽

[0636] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAENLIH LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:79)

[0637] 人类IL-15 V63A/I68Q变体多肽

[0638] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAENLIQ LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:80)

[0639] 人类IL-15 V63A/I68G变体多肽

[0640] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAENLIG LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:81)

[0641] Fc-接头3-IL-15 S58G链

[0642] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DAGIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:82)

[0643] Fc-接头3-IL-15 S58H链

[0644] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG

DAHIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:83)

[0645] Fc-接头3-IL-15 S58R链

[0646] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DARIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:84)

[0647] Fc-接头3-IL-15 S58Q链

[0648] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DAQIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:85)

[0649] Fc-接头3-IL-15 S58I链

[0650] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DAIIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:86)

[0651] Fc-接头3-IL-15 S58P链

[0652] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DAPIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:87)

[0653] Fc-接头3-IL-15 V63A链

[0654] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTAENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:88)

[0655] Fc-接头3-IL-15 V63K链

[0656] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTKENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:89)

[0657] Fc-接头3-IL-15 V63R链

[0658] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK

TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTRENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:90)

[0659] Fc-接头3-IL-15 I68F链

[0660] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIFLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:91)

[0661] Fc-接头3-IL-15 I68D链

[0662] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIDLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:92)

[0663] Fc-接头3-IL-15 I68H链

[0664] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIHLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:93)

[0665] Fc-接头3-IL-15 I68K链

[0666] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIKLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:94)

[0667] Fc-接头3-IL-15 I68Q链

[0668] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIQLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:95)

[0669] Fc-接头3-IL-15 I68G链

[0670] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG

DASIHDTVENLIGLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:96)

[0671] Hole Fc-接头1-IL-15 Q108S链

[0672] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS
LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGEPKSSDKTHTSPPSPNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:97)

[0673] Hole Fc-接头1-IL-15 Q108A链

[0674] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS
LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGEPKSSDKTHTSPPSPNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVAMFINTS(SEQ ID NO:98)

[0675] Knob Fc-接头3-IL-15 Q108M链

[0676] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVMMFINTS(SEQ ID NO:99)

[0677] Knob Fc-接头3-IL-15 Q108E链

[0678] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS(SEQ ID NO:100)

[0679] Knob Fc-接头3-IL-15 Q108K链

[0680] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVKMFINTS(SEQ ID NO:101)

[0681] Fc-接头3-IL-15 V63A/I68H链

[0682] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTAENLIHLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:102)

[0683] Fc-接头3-IL-15 V63A/I68Q链

[0684] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK

TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTAENLIQLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:103)

[0685] Fc-接头3-IL-15 V63A/I68G链

[0686] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGGGGGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG
DASIHDTAENLIGLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:104)

[0687] 具有降低/消除的效应子功能和延长的半衰期的人类IgG1-Fc

[0688] DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPG(SEQ ID NO:105)

[0689] 具有降低/消除的效应子功能和延长的体内半衰期的人类IgG1-Fc

[0690] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHAHYTQKS
LSLSPG(SEQ ID NO:106)

[0691] 具有延长的体内半衰期的Knob-Fc

[0692] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHAHYTQKS
LSLSPG(SEQ ID NO:107)

[0693] 具有延长的体内半衰期的Hole-Fc

[0694] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVS
LSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHAHYTQKS
LSLSPG(SEQ ID NO:108)

[0695] 人源化抗FAP抗体重链

[0696] QVQLVQSGAEVKKPGASVKVSCKASGYTFTENIIHWVRQAPGQGLEWMGWFHPGSGSIKYAQKFQGRV
TMTADKSTSTVYMELSSLRSEDTAVYYCARHGGTGRGAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO:109)

[0697] 人源化抗FAP抗体κ轻链

[0698] DIQMTQSPSSLSASVGDRVTITCRASRSISTSAYSYMHWYQQKPGKAPKLLIYLASNLESGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQHSRELPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:110)

[0699] 人类PD-1拮抗剂抗体重链

[0700] EVQLVQSGAEVKKPGASVKVSCKASGYRFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRV TMTTDTSTNTAYMELRSLRSDDTAVYYCARDADYSSGSGYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:111)

[0701] 人类PD-1拮抗剂抗体Lλ

[0702] SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPGQAPVMVIYKDTERPSGIPERFSGSSSGT KVTLTISGVQAEDEADYYCQSADNSITYRVFGGGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS(SEQ ID NO:112)

[0703] 人源化PD-1拮抗剂抗体-HC

[0704] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:113)

[0705] 人源化PD-1拮抗剂抗体-Lκ

[0706] DIVMTQSPLSLPVTPGEPASITCKASQDVETVVAWYLQKPGQSPRLLIYWASTRHTGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCQQYSRYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:114)

[0707] 人源化PD-1拮抗剂抗体-HC

[0708] QGQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWMGVIESETGGTAYNQKFKGRA KITADKSTSTAYMELSSLRSEDTAVYYCTREGITTVATTYYWYFDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLGK(SEQ ID NO:115)

[0709] 人源化PD-1拮抗剂抗体-Lκ

[0710] DVVMTQSPLSLPVTLGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:116)

[0711] 人源化PD-1拮抗剂抗体-HC

[0712] QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:117)

[0713] 人源化PD-1拮抗剂抗体-Lκ

[0714] EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:118)

[0715] 人类PD-1拮抗剂抗体-HC

[0716] QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:119)

[0717] 人类PD-1拮抗剂抗体-Lκ

[0718] EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:120)

[0719] 人源化PD-L1拮抗剂抗体-HC

[0720] EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:121)

[0721] 人源化PD-L1拮抗剂抗体-Lκ

[0722] DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:122)

[0723] 人类CTLA-4拮抗剂抗体-HC

[0724] QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:123)

[0725] 人类CTLA-4拮抗剂抗体-Lκ

[0726] EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:124)

[0727] 人类CD40激动剂抗体-HC

[0728] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV DKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK(SEQ ID NO:125)

[0729] 人类CD40激动剂抗体-Lκ

[0730] DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:126)

[0731] 人源化抗纤连蛋白抗体-HC

[0732] EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWVRQAPGKGLEWVSSISGSSGTTYYADSVKGRF TISRDSKNTLYLQMNSLRAEDTAVYYCAKPFPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:127)

[0733] 人源化抗纤连蛋白抗体-Lκ

[0734] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYYASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQTGRIPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:128)

[0735] 嵌合抗CD20抗体-HC

[0736] QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:129)

[0737] 嵌合抗CD20抗体-Lκ

[0738] QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:130)

[0739] 人源化抗Her2抗体-HC

[0740] EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:131)

[0741] 人源化抗Her2抗体-Lκ

[0742] DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:132)

[0743] 嵌合抗EGFR抗体-HC

[0744] QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:133)

[0745] 嵌合抗EGFR抗体-Lκ

[0746] DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSG TDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:134)

[0747] 具有降低/消除的效应子功能的人类IgG1 CH1-CH2-CH3结构域

[0748] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:135)

[0749] 具有降低/消除的效应子功能knob链的人类IgG1 CH1-CH2-CH3结构域

[0750] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:136)

[0751] 具有降低/消除的效应子功能Hole链的人类IgG1 CH1-CH2-CH3结构域

[0752] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG(SEQ ID NO:137)

[0753] PD-1拮抗剂抗体-HC-IL-15 Q108S链

[0754] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:138)

[0755] PD-1拮抗剂抗体-HC-IL-15 Q108S knob链

[0756] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV

ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVSMFINTS(SEQ ID NO:139)

[0757] PD-1拮抗剂抗体-HC-IL-15 Q108A knob链

[0758] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV
ENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVAMFINTS(SEQ ID NO:140)

[0759] PD-1拮抗剂抗体HC-IL-15 V63A/I68H链

[0760] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTA
ENLIHLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:141)

[0761] PD-1拮抗剂抗体-HC-IL-15 I68G knob链

[0762] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTV
ENLIGLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:142)

[0763] PD-1拮抗剂抗体-HC-IL-15 V63A/I68G knob链

[0764] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLWCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTA
ENLIGLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:143)

[0765] PD-1拮抗剂抗体-HC hole链

[0766] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF

TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLSCAVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO:144)

[0767] PD-1拮抗剂抗体-HC-IL-15 V63A/I68G链

[0768] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTA
ENLIGLANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:145)

[0769] PD-1拮抗剂抗体-HC-IL-15N末端2-aa缺失链

[0770] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN
LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:146)

[0771] PD-1拮抗剂抗体-HC-IL-15N末端4-aa缺失链

[0772] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSGGGGSGGGGSVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLI
ILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:147)

[0773] PD-1拮抗剂抗体-HC-IL-15 V63A和N末端2-aa缺失链

[0774] EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVATISGGGSYTYYPDSVKGRF
TISRDNAKNSLYLQMNSLRAEDTAVYYCASPDSSGVAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF

YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTAEN LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:148)

[0775] Fc-接头3-IL-15N末端1-aa缺失链

[0776] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGD ASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:149)

[0777] Fc-接头3-IL-15N末端2-aa缺失链

[0778] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:150)

[0779] Fc-接头3-IL-15N末端3-aa缺失链

[0780] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDAS IHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:151)

[0781] Fc-接头3-IL-15N末端4-aa缺失链

[0782] DKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGGGSVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASI HDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS(SEQ ID NO:152)

[0783] 肽接头序列

[0784] GGSGG(SEQ ID NO:153)

[0785] 肽接头序列

[0786] GSSGGSGGS(SEQ ID NO:154)。

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[0025] 100 105 110

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[0028] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0029] 130 135 140

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[0042] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

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[0044] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

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[0046] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[0047] 65 70 75 80

[0048] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0049] 85 90 95

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[0051] 100 105 110

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[0071] 100 105 110

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[0073] 115 120 125

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[0128] Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
[0129] 35 40 45
[0130] Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
[0131] 50 55 60
[0132] Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro
[0133] 65 70 75
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[0151] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
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[0165] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

[0166] 195 200 205

[0167] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

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[0181] 20 25 30

[0182] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

[0183] 35 40 45

[0184] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

[0185] 50 55 60

[0186] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

[0187] 65 70 75 80

[0188] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

[0189] 85 90 95

[0190] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

[0191] 100 105 110

[0192] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

[0193] 115 120 125

[0194] Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

[0195] 130 135 140

[0196] Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

[0197] 145 150 155 160

[0198] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

[0199] 165 170 175

[0200] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

[0201] 180 185 190

[0202] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

[0203] 195 200 205

[0204] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

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[0206] Pro Gly

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[0222] 50 55 60

[0223] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

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[0225] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

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[0227] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

[0228] 100 105 110

[0229] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

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[0234] 145 150 155 160

[0235] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

[0236] 165 170 175

[0237] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val

[0238] 180 185 190

[0239] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

[0240] 195 200 205

[0241] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

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[0243] Pro Gly

[0244] 225

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[0254] <210> 10

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[0289] 1 5 10 15

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[0291] 20 25 30

[0292] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

[0293] 35 40 45

[0294] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

[0295] 50 55 60

[0296] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

[0297] 65 70 75 80

[0298] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

[0299] 85 90 95

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[0789] 50 55 60

[0790] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

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[0794] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

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[0806] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

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[0808] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

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[0831] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0832] 20 25 30

[0833] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0834] 35 40 45

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[0836] 50 55 60

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[0838] 65 70 75 80

[0839] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0840] 85 90 95

[0841] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0842] 100 105 110

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[0853] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0854] 20 25 30

[0855] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0856] 35 40 45

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[0858] 50 55 60

[0859] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[0860] 65 70 75 80

[0861] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0862] 85 90 95

[0863] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0864] 100 105 110

[0865] Thr Ser

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[0875] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0876] 20 25 30

[0877] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0878] 35 40 45

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[0880] 50 55 60

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[0882] 65 70 75 80

[0883] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0884] 85 90 95

[0885] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0886] 100 105 110

[0887] Thr Ser

[0888] <210> 27

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[0902] 50 55 60
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[0904] 65 70 75 80
[0905] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[0906] 85 90 95
[0907] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[0908] 100 105 110
[0909] Thr Ser
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[0918] 1 5 10 15
[0919] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[0920] 20 25 30
[0921] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[0922] 35 40 45
[0923] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[0924] 50 55 60
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[0926] 65 70 75 80
[0927] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[0928] 85 90 95
[0929] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[0930] 100 105 110
[0931] Thr Ser
[0932] <210> 29
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[0937] <223> 人类IL-15 I68K变体多肽

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[0940] 1 5 10 15

[0941] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0942] 20 25 30

[0943] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0944] 35 40 45

[0945] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[0946] 50 55 60

[0947] Asn Leu Ile Lys Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[0948] 65 70 75 80

[0949] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0950] 85 90 95

[0951] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0952] 100 105 110

[0953] Thr Ser

[0954] <210> 30

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[0962] 1 5 10 15

[0963] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0964] 20 25 30

[0965] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0966] 35 40 45

[0967] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[0968] 50 55 60

[0969] Asn Leu Ile Asp Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[0970] 65 70 75 80

[0971] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0972] 85 90 95

[0973] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0974] 100 105 110

[0975] Thr Ser

[0976] <210> 31

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[0981] <223> 人类IL-15 I68H变体多肽

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[0984] 1 5 10 15

[0985] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[0986] 20 25 30

[0987] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[0988] 35 40 45

[0989] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[0990] 50 55 60

[0991] Asn Leu Ile His Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[0992] 65 70 75 80

[0993] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[0994] 85 90 95

[0995] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[0996] 100 105 110

[0997] Thr Ser

[0998] <210> 32

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[1007] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[1008] 20 25 30

[1009] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1010] 35 40 45

[1011] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1012] 50 55 60

[1013] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1014] 65 70 75 80
[1015] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1016] 85 90 95
[1017] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ala Met Phe Ile Asn
[1018] 100 105 110
[1019] Thr Ser
[1020] <210> 33
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[1030] 20 25 30
[1031] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1032] 35 40 45
[1033] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1034] 50 55 60
[1035] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1036] 65 70 75 80
[1037] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1038] 85 90 95
[1039] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Met Met Phe Ile Asn
[1040] 100 105 110
[1041] Thr Ser
[1042] <210> 34
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[1051] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[1052] 20 25 30

[1053] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1054] 35 40 45
[1055] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1056] 50 55 60
[1057] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1058] 65 70 75 80
[1059] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1060] 85 90 95
[1061] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ser Met Phe Ile Asn
[1062] 100 105 110
[1063] Thr Ser
[1064] <210> 35
[1065] <211> 114
[1066] <212> PRT
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[1069] <223> 人类IL-15 Q108S/D30T变体多肽
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[1072] 1 5 10 15
[1073] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Thr Val His
[1074] 20 25 30
[1075] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1076] 35 40 45
[1077] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1078] 50 55 60
[1079] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1080] 65 70 75 80
[1081] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1082] 85 90 95
[1083] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ser Met Phe Ile Asn
[1084] 100 105 110
[1085] Thr Ser
[1086] <210> 36
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[1095] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Tyr His

[1096] 20 25 30

[1097] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1098] 35 40 45

[1099] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1100] 50 55 60

[1101] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1102] 65 70 75 80

[1103] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[1104] 85 90 95

[1105] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ser Met Phe Ile Asn

[1106] 100 105 110

[1107] Thr Ser

[1108] <210> 37

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[1116] 1 5 10 15

[1117] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val Glu

[1118] 20 25 30

[1119] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1120] 35 40 45

[1121] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1122] 50 55 60

[1123] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1124] 65 70 75 80

[1125] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[1126] 85 90 95

[1127] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ser Met Phe Ile Asn

[1128] 100 105 110

[1129] Thr Ser

[1130] <210> 38

[1131] <211> 114
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[1135] <223> 人类IL-15 Q108S/D30T/V31Y/H32E变体多肽
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[1138] 1 5 10 15
[1139] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Thr Tyr Glu
[1140] 20 25 30
[1141] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1142] 35 40 45
[1143] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1144] 50 55 60
[1145] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1146] 65 70 75 80
[1147] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1148] 85 90 95
[1149] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Ser Met Phe Ile Asn
[1150] 100 105 110
[1151] Thr Ser
[1152] <210> 39
[1153] <211> 110
[1154] <212> PRT
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[1160] 1 5 10 15
[1161] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[1162] 20 25 30
[1163] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1164] 35 40 45
[1165] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1166] 50 55 60
[1167] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1168] 65 70 75 80
[1169] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[1170] 85 90 95

[1171] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe

[1172] 100 105 110

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[1175] <212> PRT

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[1181] 1 5 10 15

[1182] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[1183] 20 25 30

[1184] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1185] 35 40 45

[1186] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1187] 50 55 60

[1188] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1189] 65 70 75 80

[1190] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[1191] 85 90 95

[1192] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln

[1193] 100 105

[1194] <210> 41

[1195] <211> 107

[1196] <212> PRT

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[1198] <220>

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[1202] 1 5 10 15

[1203] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[1204] 20 25 30

[1205] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1206] 35 40 45

[1207] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1208] 50 55 60

[1209] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1210] 65 70 75 80
[1211] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1212] 85 90 95
[1213] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val
[1214] 100 105
[1215] <210> 42
[1216] <211> 104
[1217] <212> PRT
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[1220] <223> 人类IL-15缺失105-114变体多肽
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[1225] 20 25 30
[1226] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[1227] 35 40 45
[1228] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[1229] 50 55 60
[1230] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[1231] 65 70 75 80
[1232] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[1233] 85 90 95
[1234] Lys Glu Phe Leu Gln Ser Phe Val
[1235] 100
[1236] <210> 43
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[1245] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[1246] 20 25 30
[1247] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1248] 35 40 45

[1249] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1250] 50 55 60

[1251] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1252] 65 70 75 80

[1253] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Gly

[1254] 85 90 95

[1255] Ser Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe

[1256] 100 105 110

[1257] Ile Asn Thr Ser

[1258] 115

[1259] <210> 44

[1260] <211> 119

[1261] <212> PRT

[1262] <213> 人工(Artificial)

[1263] <220>

[1264] <223> N95后插入'GGSGG'的人类IL-15变体多肽

[1265] <400> 44

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[1267] 1 5 10 15

[1268] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[1269] 20 25 30

[1270] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[1271] 35 40 45

[1272] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[1273] 50 55 60

[1274] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[1275] 65 70 75 80

[1276] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Gly

[1277] 85 90 95

[1278] Gly Ser Gly Gly Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val

[1279] 100 105 110

[1280] Gln Met Phe Ile Asn Thr Ser

[1281] 115

[1282] <210> 45

[1283] <211> 123

[1284] <212> PRT

[1285] <213> 人工(Artificial)

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[1533] Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn

[1534] 35 40 45

[1535] Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile

[1536] 50 55 60

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[1538] 65 70 75 80

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[1599] 180 185 190
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[1714] Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
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[1716] Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
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[1777] <212> PRT
[1778] <213> 人工(Artificial)
[1779] <220>
[1780] <223> 在N末端处具有1个氨基酸缺失的人类IL-15变体
[1781] <400> 56
[1782] Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
[1783] 1 5 10 15
[1784] Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
[1785] 20 25 30
[1786] Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
[1787] 35 40 45
[1788] Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn
[1789] 50 55 60
[1790] Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
[1791] 65 70 75 80
[1792] Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
[1793] 85 90 95

[1794] Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
[1795] 100 105 110
[1796] Ser
[1797] <210> 57
[1798] <211> 112
[1799] <212> PRT
[1800] <213> 人工(Artificial)
[1801] <220>
[1802] <223> 在N末端处具有2个氨基酸缺失的人类IL-15变体
[1803] <400> 57
[1804] Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
[1805] 1 5 10 15
[1806] Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
[1807] 20 25 30
[1808] Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
[1809] 35 40 45
[1810] Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
[1811] 50 55 60
[1812] Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
[1813] 65 70 75 80
[1814] Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
[1815] 85 90 95
[1816] Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
[1817] 100 105 110
[1818] <210> 58
[1819] <211> 111
[1820] <212> PRT
[1821] <213> 人工(Artificial)
[1822] <220>
[1823] <223> 在N末端处具有3个氨基酸缺失的人类IL-15变体
[1824] <400> 58
[1825] Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met
[1826] 1 5 10 15
[1827] His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys
[1828] 20 25 30
[1829] Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser
[1830] 35 40 45
[1831] Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile
[1832] 50 55 60

[1833] Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser
[1834] 65 70 75 80
[1835] Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe
[1836] 85 90 95
[1837] Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
[1838] 100 105 110
[1839] <210> 59
[1840] <211> 110
[1841] <212> PRT
[1842] <213> 人工(Artificial)
[1843] <220>
[1844] <223> 在N末端处具有4个氨基酸缺失的人类IL-15变体
[1845] <400> 59
[1846] Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His
[1847] 1 5 10 15
[1848] Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys
[1849] 20 25 30
[1850] Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu
[1851] 35 40 45
[1852] Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile
[1853] 50 55 60
[1854] Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly
[1855] 65 70 75 80
[1856] Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu
[1857] 85 90 95
[1858] Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
[1859] 100 105 110
[1860] <210> 60
[1861] <211> 109
[1862] <212> PRT
[1863] <213> 人工(Artificial)
[1864] <220>
[1865] <223> 在N末端处具有5个氨基酸缺失的人类IL-15变体
[1866] <400> 60
[1867] Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile
[1868] 1 5 10 15
[1869] Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
[1870] 20 25 30
[1871] Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu

[1872] 35 40 45

[1873] Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu

[1874] 50 55 60

[1875] Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys

[1876] 65 70 75 80

[1877] Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln

[1878] 85 90 95

[1879] Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser

[1880] 100 105

[1881] <210> 61

[1882] <211> 108

[1883] <212> PRT

[1884] <213> 人工(Artificial)

[1885] <220>

[1886] <223> 在N末端处具有6个氨基酸缺失的人类IL-15变体

[1887] <400> 61

[1888] Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp

[1889] 1 5 10 15

[1890] Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr

[1891] 20 25 30

[1892] Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser

[1893] 35 40 45

[1894] Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala

[1895] 50 55 60

[1896] Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys

[1897] 65 70 75 80

[1898] Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser

[1899] 85 90 95

[1900] Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser

[1901] 100 105

[1902] <210> 62

[1903] <211> 112

[1904] <212> PRT

[1905] <213> 人工(Artificial)

[1906] <220>

[1907] <223> 在N末端处具有2个氨基酸缺失的人类IL-15 V63A变体

[1908] <400> 62

[1909] Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser

[1910] 1 5 10 15

[1911] Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
[1912] 20 25 30
[1913] Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
[1914] 35 40 45
[1915] Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Ala Glu Asn Leu
[1916] 50 55 60
[1917] Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
[1918] 65 70 75 80
[1919] Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
[1920] 85 90 95
[1921] Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
[1922] 100 105 110
[1923] <210> 63
[1924] <211> 112
[1925] <212> PRT
[1926] <213> 人工(Artificial)
[1927] <220>
[1928] <223> 在N末端处具有2个氨基酸缺失的人类IL-15 I68H变体
[1929] <400> 63
[1930] Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
[1931] 1 5 10 15
[1932] Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
[1933] 20 25 30
[1934] Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
[1935] 35 40 45
[1936] Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
[1937] 50 55 60
[1938] Ile His Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
[1939] 65 70 75 80
[1940] Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
[1941] 85 90 95
[1942] Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
[1943] 100 105 110
[1944] <210> 64
[1945] <211> 296
[1946] <212> PRT
[1947] <213> 人工(Artificial)
[1948] <220>
[1949] <223> 基准链 1

[1950] <400> 64

[1951] Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
[1952] 1 5 10 15
[1953] Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
[1954] 20 25 30
[1955] Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
[1956] 35 40 45
[1957] Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
[1958] 50 55 60
[1959] Arg Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
[1960] 65 70 75 80
[1961] Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1962] 85 90 95
[1963] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1964] 100 105 110
[1965] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1966] 115 120 125
[1967] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1968] 130 135 140
[1969] Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1970] 145 150 155 160
[1971] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1972] 165 170 175
[1973] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[1974] 180 185 190
[1975] Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
[1976] 195 200 205
[1977] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
[1978] 210 215 220
[1979] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
[1980] 225 230 235 240
[1981] Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[1982] 245 250 255
[1983] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[1984] 260 265 270
[1985] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
[1986] 275 280 285
[1987] Lys Ser Leu Ser Leu Ser Pro Gly
[1988] 290 295

[1989] <210> 65
[1990] <211> 114
[1991] <212> PRT
[1992] <213> 人工(Artificial)
[1993] <220>
[1994] <223> 基准链 2
[1995] <400> 65
[1996] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[1997] 1 5 10 15
[1998] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[1999] 20 25 30
[2000] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2001] 35 40 45
[2002] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[2003] 50 55 60
[2004] Asn Leu Ile Ile Leu Ala Asn Asp Ser Leu Ser Ser Asn Gly Asn Val
[2005] 65 70 75 80
[2006] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2007] 85 90 95
[2008] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2009] 100 105 110
[2010] Thr Ser
[2011] <210> 66
[2012] <211> 114
[2013] <212> PRT
[2014] <213> 人工(Artificial)
[2015] <220>
[2016] <223> 人类IL-15 S58G变体多肽
[2017] <400> 66
[2018] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2019] 1 5 10 15
[2020] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2021] 20 25 30
[2022] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2023] 35 40 45
[2024] Val Ile Ser Leu Glu Ser Gly Asp Ala Gly Ile His Asp Thr Val Glu
[2025] 50 55 60
[2026] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2027] 65 70 75 80

[2028] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2029] 85 90 95
[2030] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2031] 100 105 110
[2032] Thr Ser
[2033] <210> 67
[2034] <211> 114
[2035] <212> PRT
[2036] <213> 人工(Artificial)
[2037] <220>
[2038] <223> 人类IL-15 S58H变体多肽
[2039] <400> 67
[2040] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2041] 1 5 10 15
[2042] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2043] 20 25 30
[2044] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2045] 35 40 45
[2046] Val Ile Ser Leu Glu Ser Gly Asp Ala His Ile His Asp Thr Val Glu
[2047] 50 55 60
[2048] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2049] 65 70 75 80
[2050] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2051] 85 90 95
[2052] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2053] 100 105 110
[2054] Thr Ser
[2055] <210> 68
[2056] <211> 114
[2057] <212> PRT
[2058] <213> 人工(Artificial)
[2059] <220>
[2060] <223> 人类IL-15 S58R变体多肽
[2061] <400> 68
[2062] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2063] 1 5 10 15
[2064] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2065] 20 25 30
[2066] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[2067] 35 40 45

[2068] Val Ile Ser Leu Glu Ser Gly Asp Ala Arg Ile His Asp Thr Val Glu

[2069] 50 55 60

[2070] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[2071] 65 70 75 80

[2072] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[2073] 85 90 95

[2074] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[2075] 100 105 110

[2076] Thr Ser

[2077] <210> 69

[2078] <211> 114

[2079] <212> PRT

[2080] <213> 人工(Artificial)

[2081] <220>

[2082] <223> 人类IL-15 S58Q变体多肽

[2083] <400> 69

[2084] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile

[2085] 1 5 10 15

[2086] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[2087] 20 25 30

[2088] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[2089] 35 40 45

[2090] Val Ile Ser Leu Glu Ser Gly Asp Ala Gln Ile His Asp Thr Val Glu

[2091] 50 55 60

[2092] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[2093] 65 70 75 80

[2094] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[2095] 85 90 95

[2096] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[2097] 100 105 110

[2098] Thr Ser

[2099] <210> 70

[2100] <211> 114

[2101] <212> PRT

[2102] <213> 人工(Artificial)

[2103] <220>

[2104] <223> 人类IL-15 S58I变体多肽

[2105] <400> 70

[2106] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2107] 1 5 10 15
[2108] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2109] 20 25 30
[2110] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2111] 35 40 45
[2112] Val Ile Ser Leu Glu Ser Gly Asp Ala Ile Ile His Asp Thr Val Glu
[2113] 50 55 60
[2114] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2115] 65 70 75 80
[2116] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2117] 85 90 95
[2118] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2119] 100 105 110
[2120] Thr Ser
[2121] <210> 71
[2122] <211> 114
[2123] <212> PRT
[2124] <213> 人工(Artificial)
[2125] <220>
[2126] <223> 人类IL-15 S58P变体多肽
[2127] <400> 71
[2128] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2129] 1 5 10 15
[2130] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2131] 20 25 30
[2132] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2133] 35 40 45
[2134] Val Ile Ser Leu Glu Ser Gly Asp Ala Pro Ile His Asp Thr Val Glu
[2135] 50 55 60
[2136] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2137] 65 70 75 80
[2138] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2139] 85 90 95
[2140] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2141] 100 105 110
[2142] Thr Ser
[2143] <210> 72
[2144] <211> 114

[2145] <212> PRT
[2146] <213> 人工(Artificial)
[2147] <220>
[2148] <223> 人类IL-15 V63A变体多肽
[2149] <400> 72
[2150] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2151] 1 5 10 15
[2152] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2153] 20 25 30
[2154] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2155] 35 40 45
[2156] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Ala Glu
[2157] 50 55 60
[2158] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2159] 65 70 75 80
[2160] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2161] 85 90 95
[2162] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2163] 100 105 110
[2164] Thr Ser
[2165] <210> 73
[2166] <211> 114
[2167] <212> PRT
[2168] <213> 人工(Artificial)
[2169] <220>
[2170] <223> 人类IL-15 V63K变体多肽
[2171] <400> 73
[2172] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2173] 1 5 10 15
[2174] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2175] 20 25 30
[2176] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2177] 35 40 45
[2178] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Lys Glu
[2179] 50 55 60
[2180] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2181] 65 70 75 80
[2182] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2183] 85 90 95

[2184] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2185] 100 105 110
[2186] Thr Ser
[2187] <210> 74
[2188] <211> 114
[2189] <212> PRT
[2190] <213> 人工(Artificial)
[2191] <220>
[2192] <223> 人类IL-15 V63R变体多肽
[2193] <400> 74
[2194] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2195] 1 5 10 15
[2196] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2197] 20 25 30
[2198] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2199] 35 40 45
[2200] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Arg Glu
[2201] 50 55 60
[2202] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2203] 65 70 75 80
[2204] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2205] 85 90 95
[2206] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
[2207] 100 105 110
[2208] Thr Ser
[2209] <210> 75
[2210] <211> 114
[2211] <212> PRT
[2212] <213> 人工(Artificial)
[2213] <220>
[2214] <223> 人类IL-15 I68Q变体多肽
[2215] <400> 75
[2216] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
[2217] 1 5 10 15
[2218] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2219] 20 25 30
[2220] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2221] 35 40 45
[2222] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[2223] 50 55 60

[2224] Asn Leu Ile Gln Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[2225] 65 70 75 80

[2226] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[2227] 85 90 95

[2228] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[2229] 100 105 110

[2230] Thr Ser

[2231] <210> 76

[2232] <211> 114

[2233] <212> PRT

[2234] <213> 人工(Artificial)

[2235] <220>

[2236] <223> 人类IL-15 I68G变体多肽

[2237] <400> 76

[2238] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile

[2239] 1 5 10 15

[2240] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His

[2241] 20 25 30

[2242] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln

[2243] 35 40 45

[2244] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

[2245] 50 55 60

[2246] Asn Leu Ile Gly Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

[2247] 65 70 75 80

[2248] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile

[2249] 85 90 95

[2250] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn

[2251] 100 105 110

[2252] Thr Ser

[2253] <210> 77

[2254] <211> 114

[2255] <212> PRT

[2256] <213> 人工(Artificial)

[2257] <220>

[2258] <223> 人类IL-15 Q108E变体多肽

[2259] <400> 77

[2260] Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile

[2261] 1 5 10 15

[2262] Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
[2263] 20 25 30
[2264] Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
[2265] 35 40 45
[2266] Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
[2267] 50 55 60
[2268] Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
[2269] 65 70 75 80
[2270] Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
[2271] 85 90 95
[2272] Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Glu Met Phe Ile Asn
[2273] 100 105 110
[2274] Thr Ser
[2275] <210> 78
[2276] <211> 114
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[2589] 50 55 60

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[2672] 290 295 300

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[2753] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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[2774] 260 265 270
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[2827] 260 265 270
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[2914] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
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[2925] 195 200 205
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[2986] 260 265 270

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[3225] 50 55 60
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[3382] 35 40 45
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[3410] 260 265 270
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[3435] 35 40 45
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[3438] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
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[3442] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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[3674] 85 90 95
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[3676] 100 105 110
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[3730] <210> 109
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[4242] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
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[4245] 115 120 125
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[4248] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
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[4251] 165 170 175

[4252] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys

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[4254] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp

[4255] 195 200 205

[4256] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala

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[4276] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

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[4281] 405 410 415

[4282] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys

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[4298] 35 40 45

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[4300] 50 55 60

[4301] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

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[4304] 85 90 95

[4305] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

[4306] 100 105 110

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[4308] 115 120 125

[4309] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

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[4312] 145 150 155 160

[4313] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

[4314] 165 170 175

[4315] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

[4316] 180 185 190

[4317] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

[4318] 195 200 205

[4319] Phe Asn Arg Gly Glu Cys

[4320] 210

[4321] <210> 121

[4322] <211> 448

[4323] <212> PRT

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[4326] <223> 人源化PD-L1拮抗剂抗体-HC

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[4333] 35 40 45
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[4335] 50 55 60
[4336] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[4337] 65 70 75 80
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[4372] Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
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[4374] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
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[4379] 405 410 415
[4380] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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[4412] 165 170 175
[4413] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4414] 180 185 190
[4415] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4416] 195 200 205
[4417] Phe Asn Arg Gly Glu Cys
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[4433] 50 55 60
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[4493] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

[4494] 35 40 45

[4495] Ile Tyr Gly Ala Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser

[4496] 50 55 60

[4497] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

[4498] 65 70 75 80

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[4507] Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

[4508] 145 150 155 160

[4509] Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

[4510] 165 170 175

[4511] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

[4512] 180 185 190

[4513] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys

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[4515] Ser Phe Asn Arg Gly Glu Cys

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[4528] Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
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[4530] Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
[4531] 50 55 60
[4532] Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
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[4534] Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
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[4538] Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
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[4540] Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
[4541] 130 135 140
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[4544] Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
[4545] 165 170 175
[4546] His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
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[4557] 260 265 270
[4558] His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
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[4596] 50 55 60
[4597] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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[4635] 85 90 95
[4636] Lys Pro Phe Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[4637] 100 105 110
[4638] Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[4639] 115 120 125
[4640] Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val

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[4645] 165 170 175

[4646] Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly

[4647] 180 185 190

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[4649] 195 200 205

[4650] Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys

[4651] 210 215 220

[4652] Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu

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[4654] Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu

[4655] 245 250 255

[4656] Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys

[4657] 260 265 270

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[4659] 275 280 285

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[4674] Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln

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[4711] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
[4712] 195 200 205
[4713] Ser Phe Asn Arg Gly Glu Cys
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[4715] <210> 129
[4716] <211> 451
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[6157] Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
[6158] 260 265 270
[6159] Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
[6160] 275 280 285
[6161] Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu

[6162] 290 295 300

[6163] Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu

[6164] 305 310 315 320

[6165] Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu

[6166] 325 330 335

[6167] Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser

[6168] 340 345 350

[6169] <210> 152

[6170] <211> 351

[6171] <212> PRT

[6172] <213> 人工(Artificial)

[6173] <220>

[6174] <223> Fc-接头3-IL-15 N末端4-aa缺失链

[6175] <400> 152

[6176] Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly

[6177] 1 5 10 15

[6178] Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

[6179] 20 25 30

[6180] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

[6181] 35 40 45

[6182] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

[6183] 50 55 60

[6184] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

[6185] 65 70 75 80

[6186] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

[6187] 85 90 95

[6188] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

[6189] 100 105 110

[6190] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

[6191] 115 120 125

[6192] Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser

[6193] 130 135 140

[6194] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

[6195] 145 150 155 160

[6196] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

[6197] 165 170 175

[6198] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

[6199] 180 185 190

[6200] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

[6201] 195 200 205

[6202] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

[6203] 210 215 220

[6204] Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

[6205] 225 230 235 240

[6206] Ser Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met

[6207] 245 250 255

[6208] His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys

[6209] 260 265 270

[6210] Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser

[6211] 275 280 285

[6212] Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile

[6213] 290 295 300

[6214] Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser

[6215] 305 310 315 320

[6216] Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe

[6217] 325 330 335

[6218] Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser

[6219] 340 345 350

[6220] <210> 153

[6221] <211> 5

[6222] <212> PRT

[6223] <213> 人工(Artificial)

[6224] <220>

[6225] <223> 肽接头序列

[6226] <400> 153

[6227] Gly Gly Ser Gly Gly

[6228] 1 5

[6229] <210> 154

[6230] <211> 9

[6231] <212> PRT

[6232] <213> 人工(Artificial)

[6233] <220>

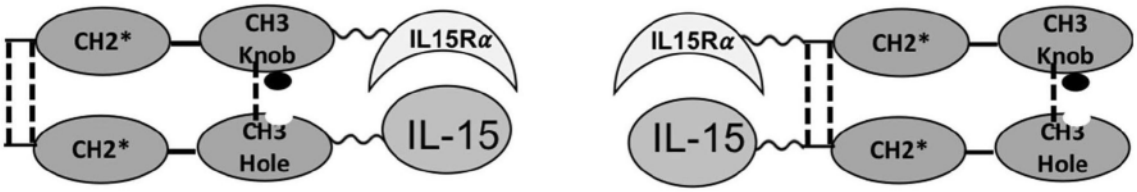
[6234] <223> 肽接头序列

[6235] <400> 154

[6236] Gly Ser Ser Gly Gly Ser Gly Gly Ser

[6237] 1 5

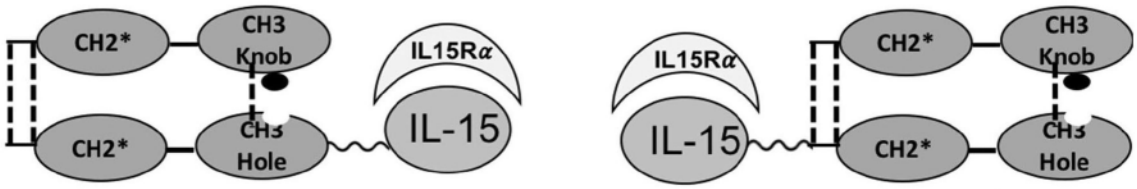
IL-15/IL-15RA异源二聚体FC融合形式




IL-15/IL-15RA在FC的C末端处　　IL-15/IL-15RA在FC的N末端处

图1A

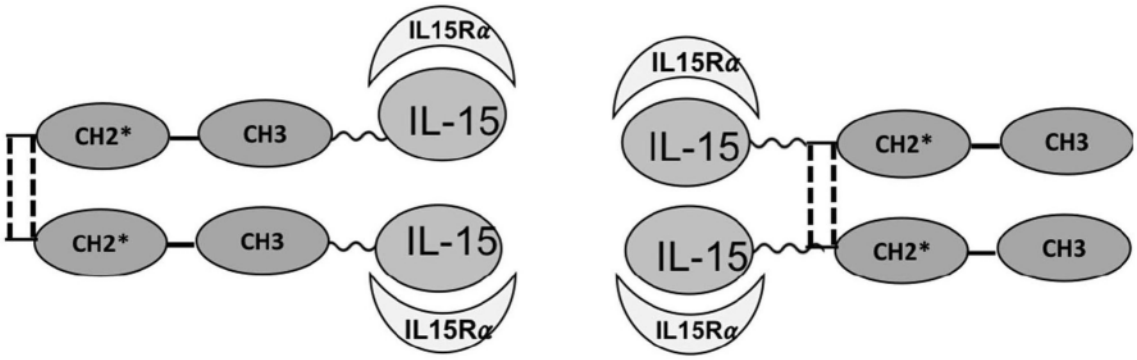
单价IL-15/IL-15RA (非共价) FC融合形式




IL-15/IL-15RA在FC的C末端处　　IL-15/IL-15RA在FC的N末端处

图1B

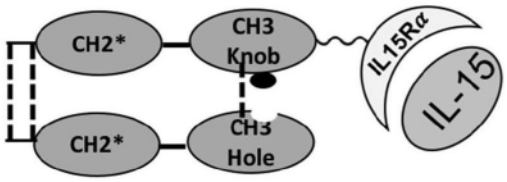
二价IL-15/IL-15RA (非共价) FC融合形式



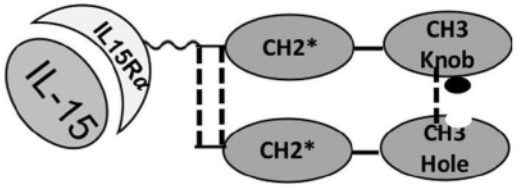

IL-15/IL-15RA在FC的C末端处　　IL-15/IL-15RA在FC的N末端处

图1C

单价IL-15 (非共价)/IL-15RA FC融合形式



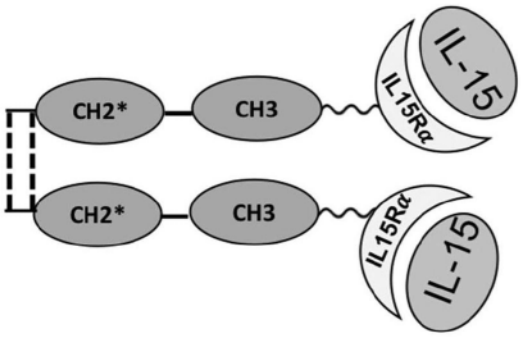

IL-15/IL-15RA在FC的C末端处



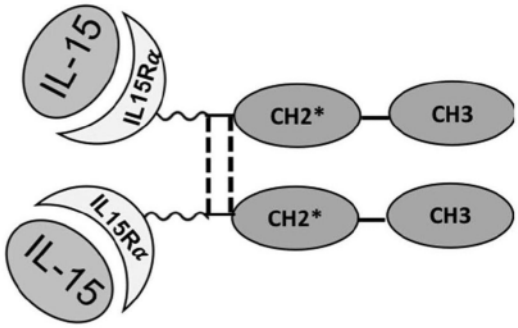

IL-15/IL-15RA在FC的N末端处

图1D

二价IL-15 (非共价)/IL-15RA FC融合形式




IL-15/IL-15RA在FC的C末端处




IL-15/IL-15RA在FC的N末端处

图1E

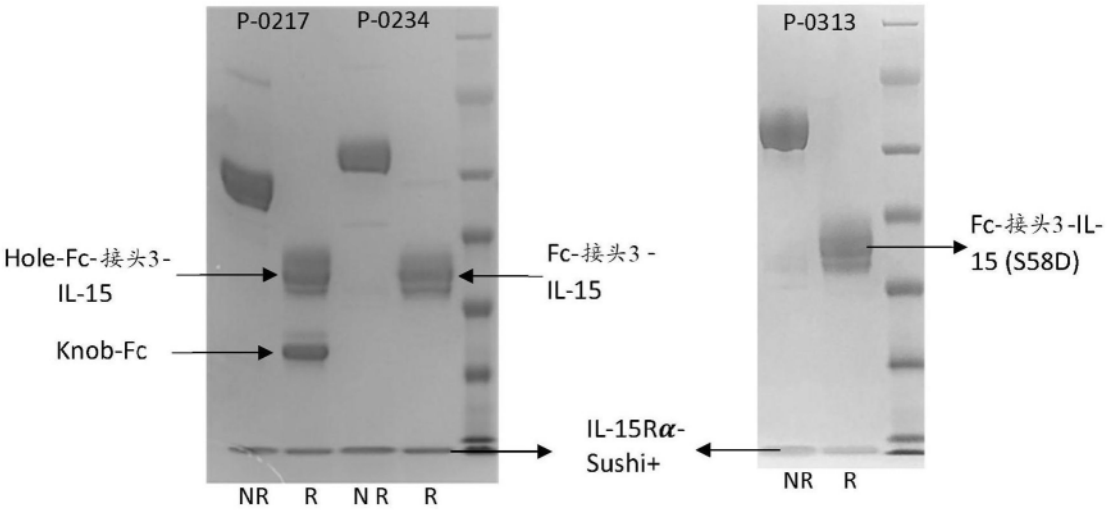

P-0217
P-0234
P-0313
Hole-Fc-接头3-IL-15
Knob-Fc
Fc-接头3-IL-15
IL-15Rα-Sushi+
Fc-接头3-IL-15 (S58D)
NR R N R R
NR R

图2A

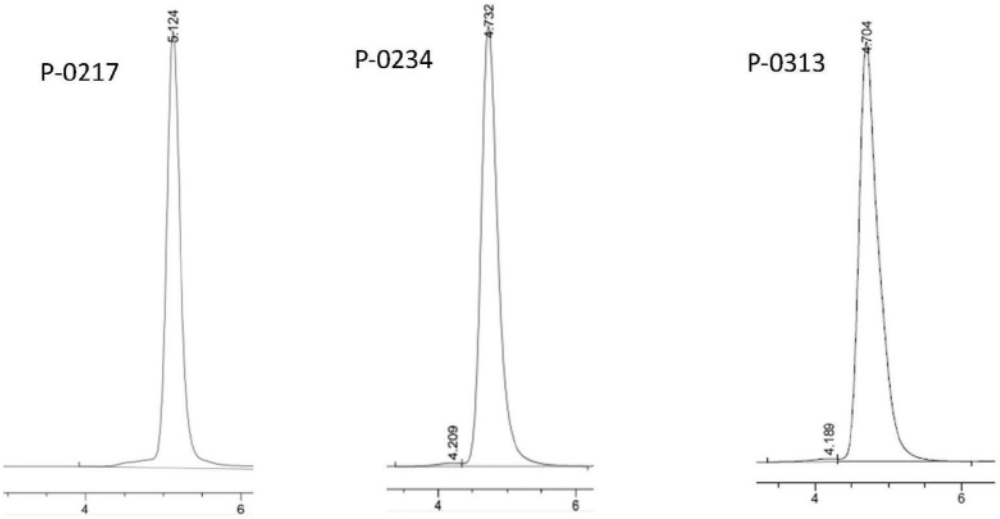

P-0217
5.124
4
6
P-0234
4.732
4.209
4
6
P-0313
4.704
4.189
4
6

图2B

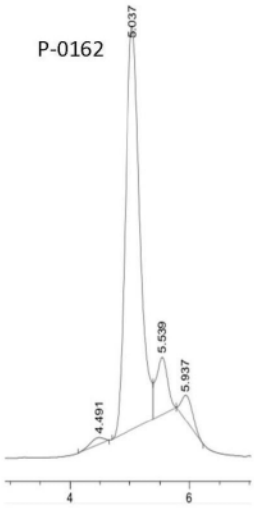



图3A

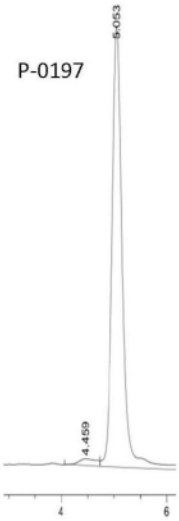



图3B




图3C

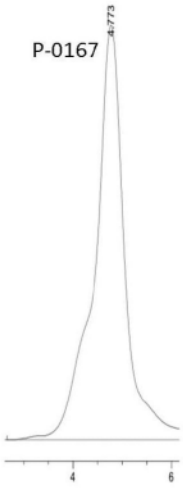



图3D




图3E

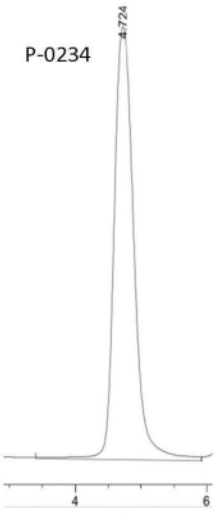



图3F

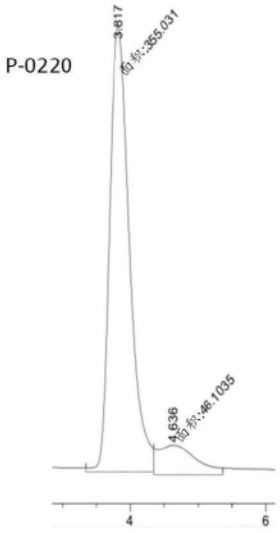



图3G

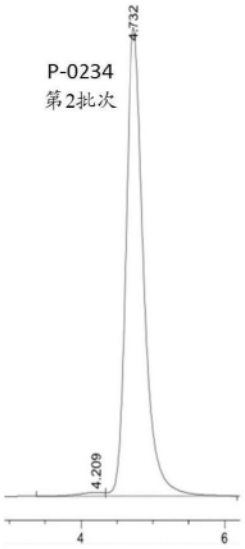



图3H

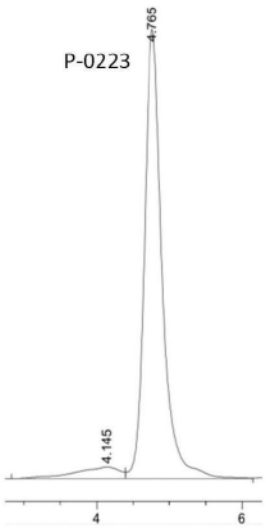



图3I

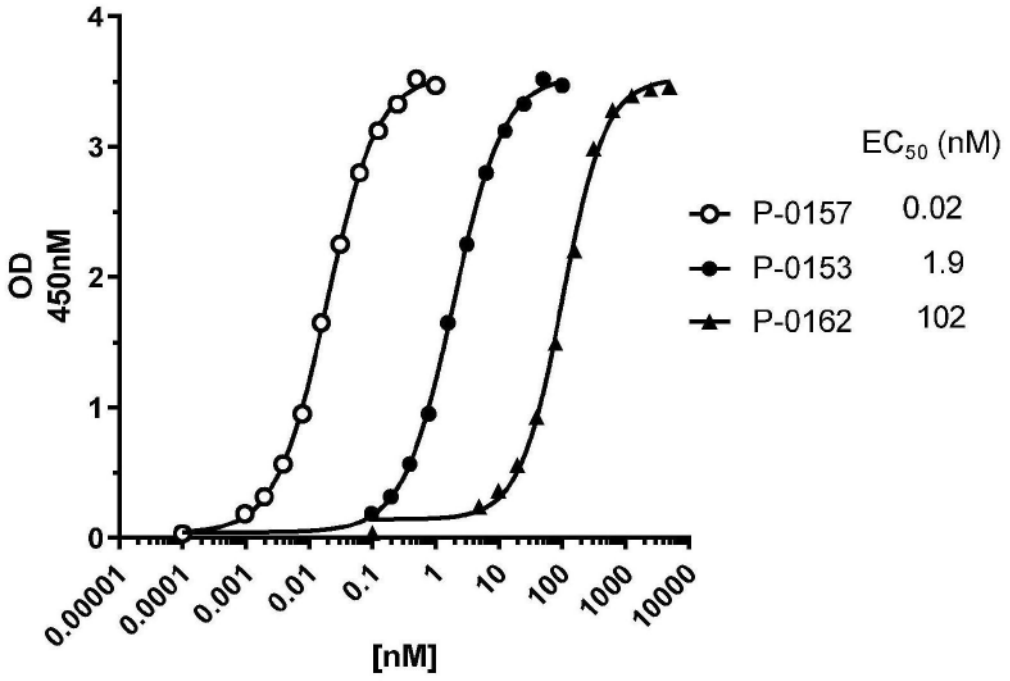

OD 450nM
4
3
2
1
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
[nM]
EC50 (nM)
P-0157 0.02
P-0153 1.9
P-0162 102

图4

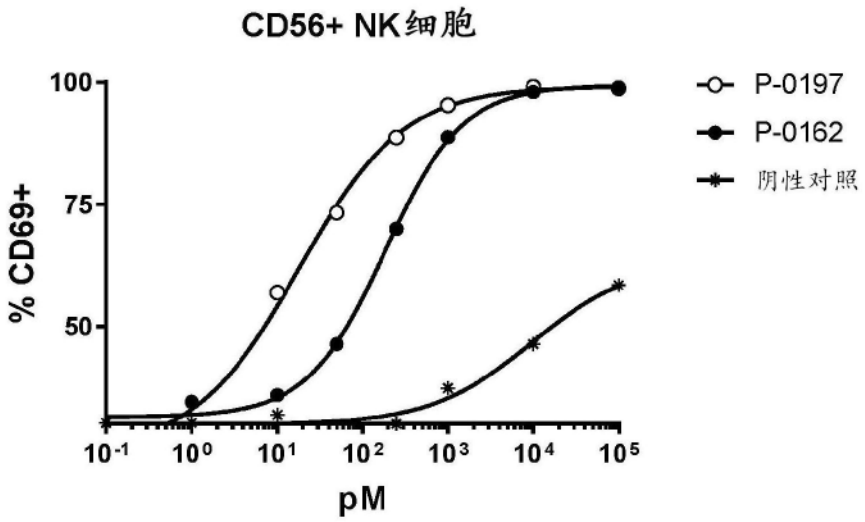

CD56+ NK细胞
% CD69+
100
75
50
10-1
100
101
102
103
104
105
pM
P-0197
P-0162
阴性对照

图5A

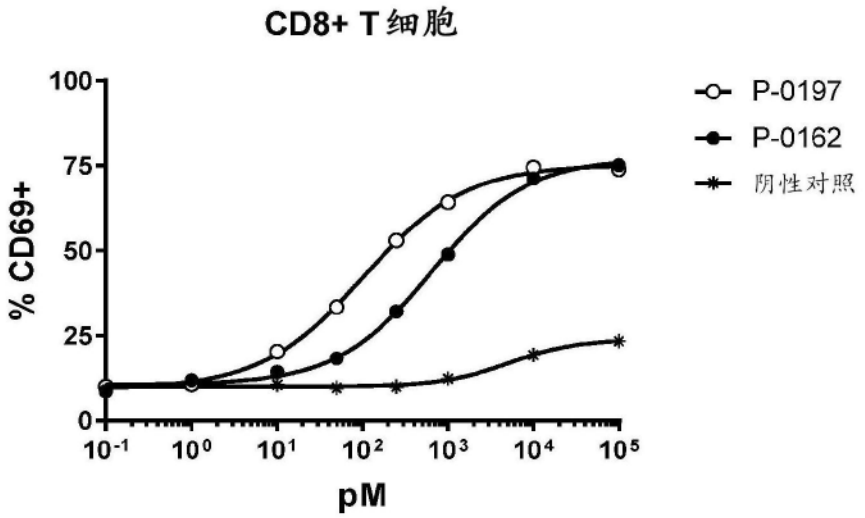

CD8+ T细胞
% CD69+
100
75
50
25
0
10-1
100
101
102
103
104
105
pM
P-0197
P-0162
阴性对照

图5B

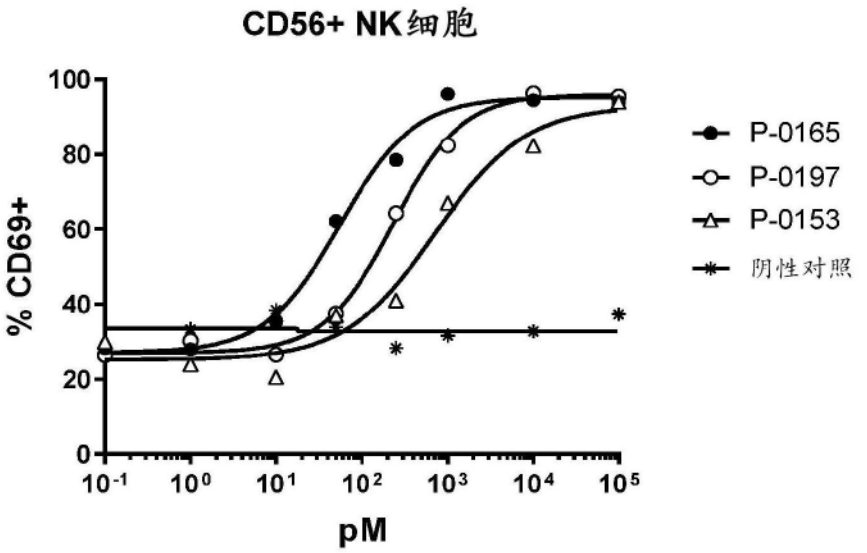

CD56+ NK细胞
% CD69+
100
80
60
40
20
0
10-1
100
101
102
103
104
105
pM
P-0165
P-0197
P-0153
阴性对照

图6A

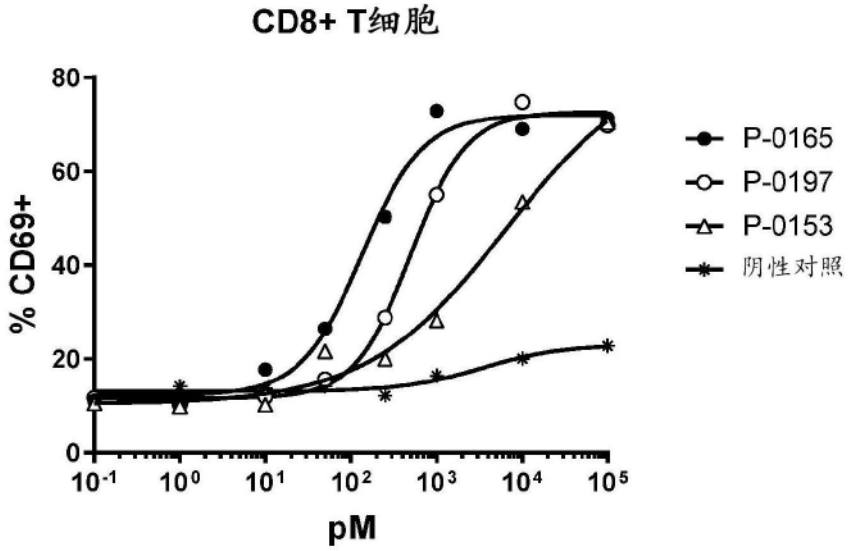

CD8+ T细胞
% CD69+
80
60
40
20
0
10-1
100
101
102
103
104
105
pM
P-0165
P-0197
P-0153
阴性对照

图6B

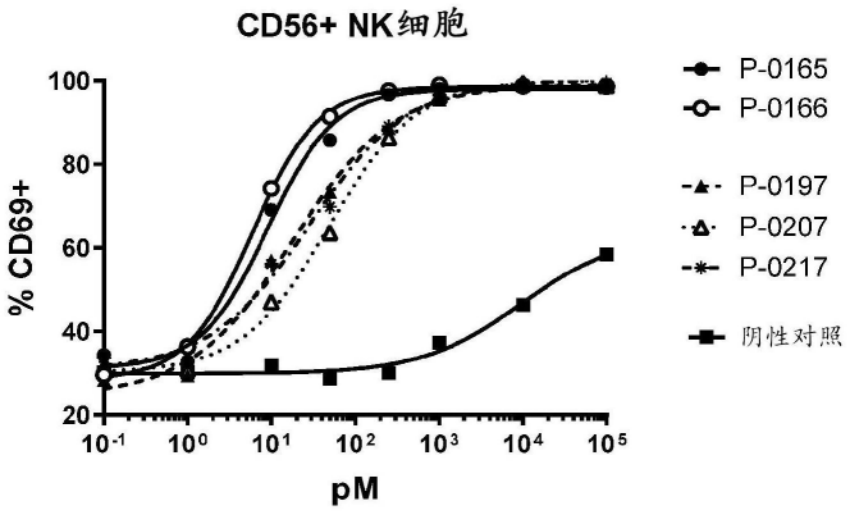

CD56+ NK细胞
% CD69+
100
80
60
40
20
10-1
100
101
102
103
104
105
pM
P-0165
P-0166
P-0197
P-0207
P-0217
阴性对照

图7A

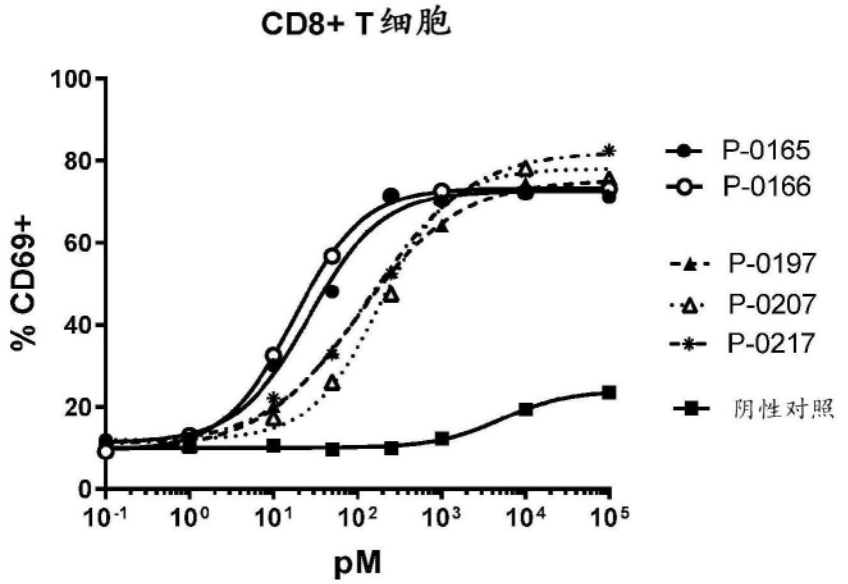

CD8+ T细胞
% CD69+
100
80
60
40
20
0
10-1
100
101
102
103
104
105
pM
P-0165
P-0166
P-0197
P-0207
P-0217
阴性对照

图7B

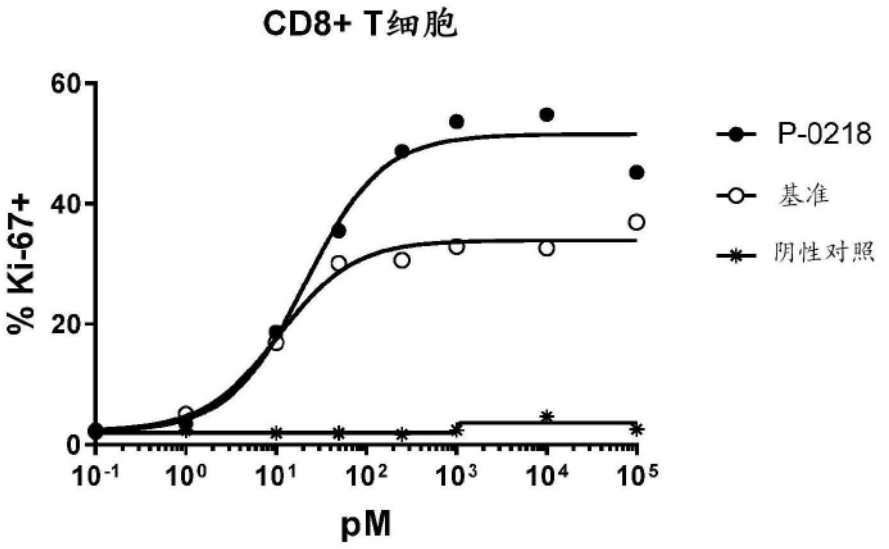

CD8+ T细胞
% Ki-67+
60
40
20
0
10-1
100
101
102
103
104
105
pM
P-0218
基准
阴性对照

图8A

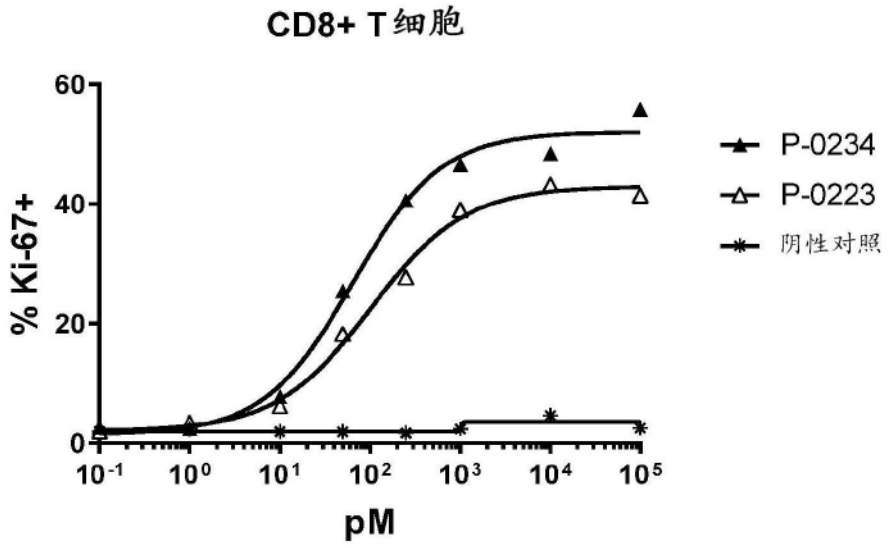

CD8+ T细胞
% Ki-67+
60
40
20
0
10-1
100
101
102
103
104
105
pM
P-0234
P-0223
阴性对照

图8B

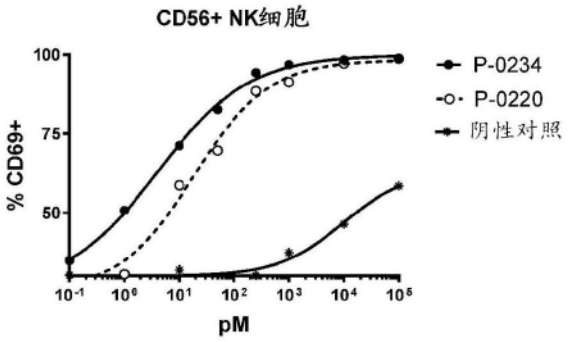

CD56+ NK细胞
% CD69+
100
75
50
pM
P-0234
P-0220
阴性对照

图9A

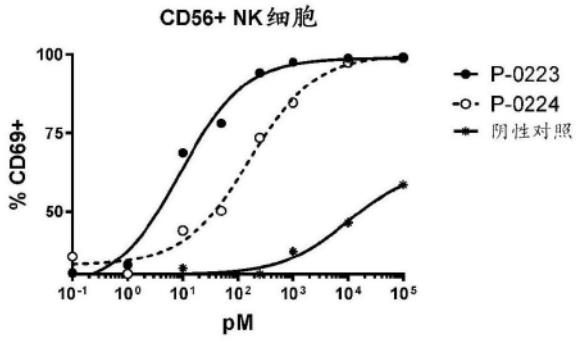

CD56+ NK细胞
% CD69+
100
75
50
pM
P-0223
P-0224
阴性对照

图9B

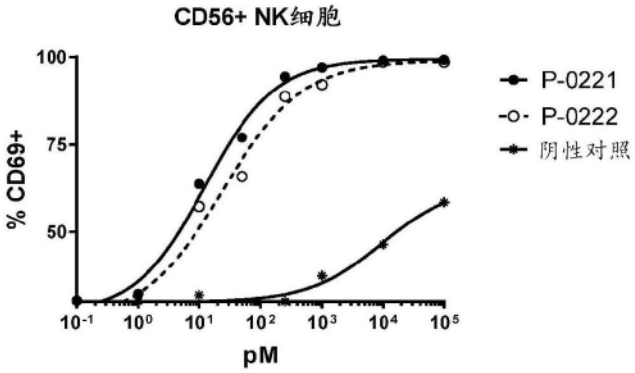

CD56+ NK细胞
% CD69+
100
75
50
pM
P-0221
P-0222
阴性对照

图9C

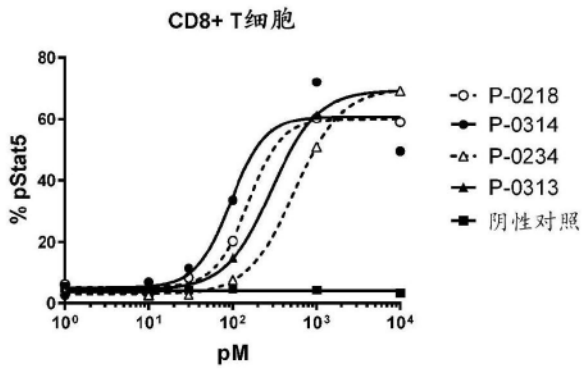



图10A

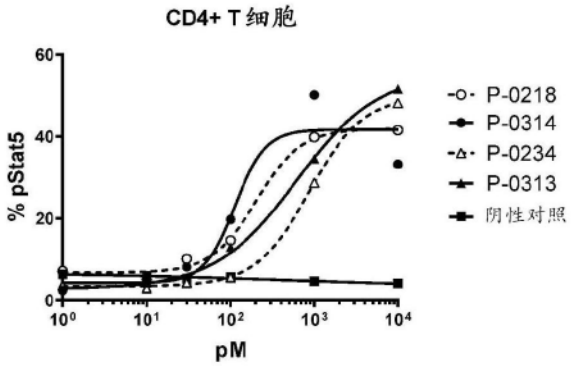



图10B

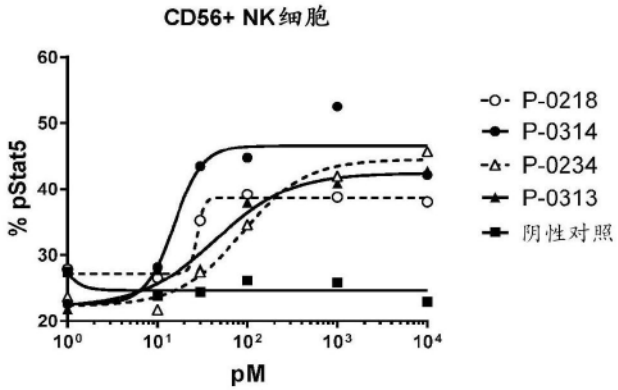



图10C

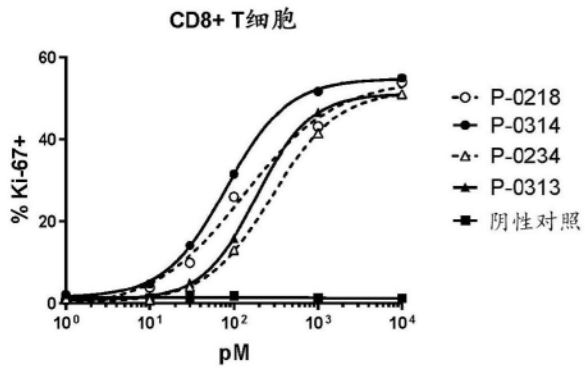



图11A

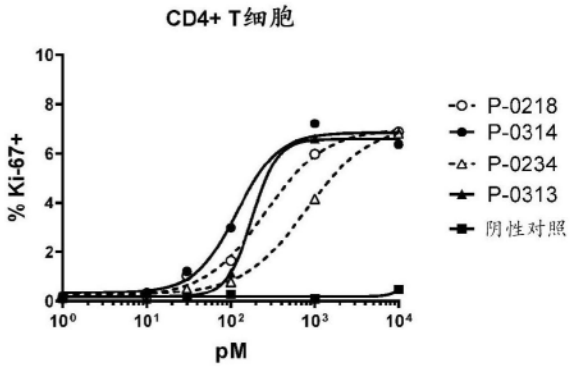



图11B

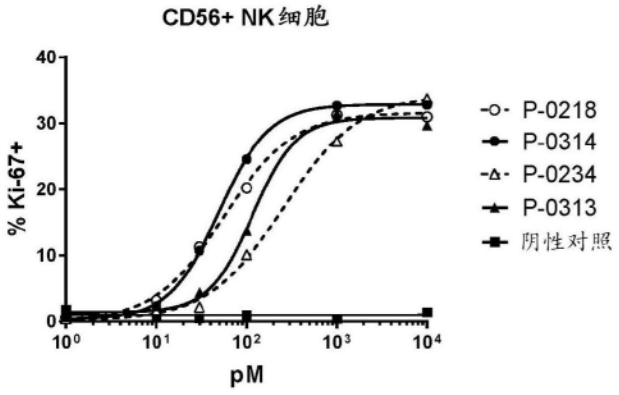



图11C

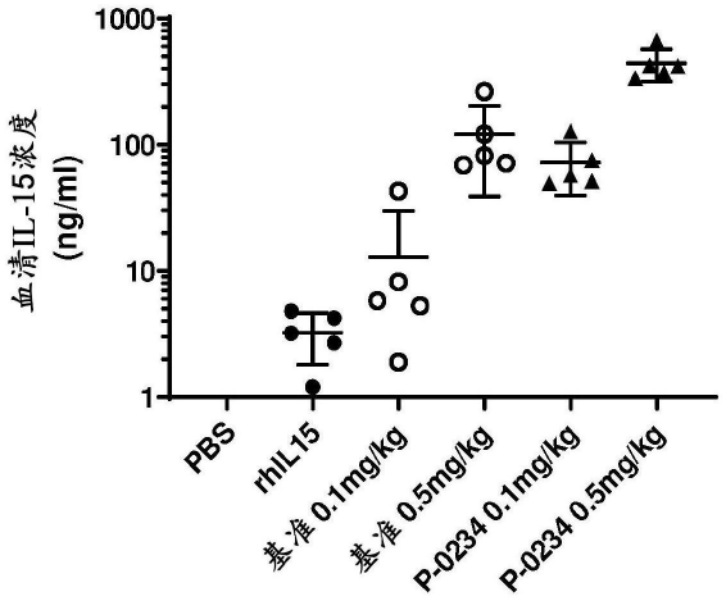

血清IL-15浓度
(ng/ml)
1000
100
10
1
PBS
rhIL15
基准 0.1mg/kg
基准 0.5mg/kg
P-0234 0.1mg/kg
P-0234 0.5mg/kg

图12

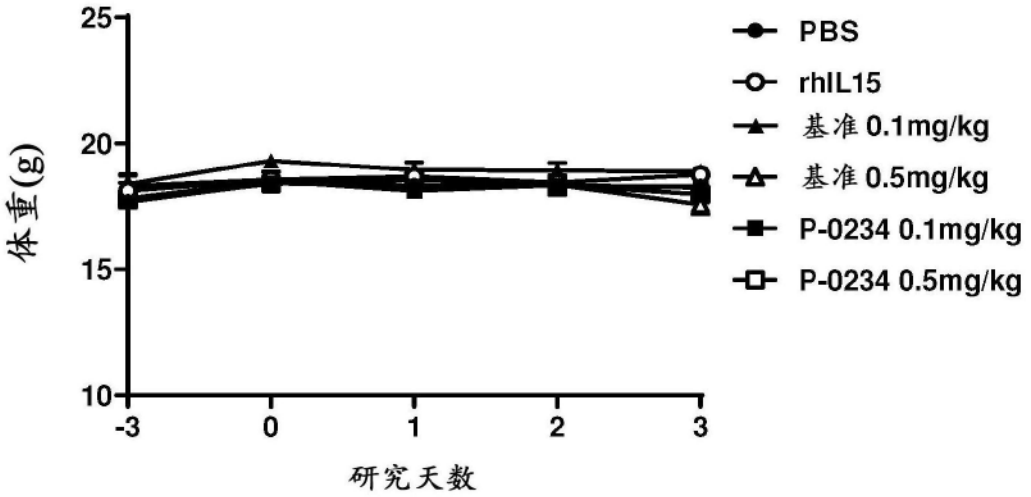

25
20
15
10
体重(g)
-3
0
1
2
3
研究天数
PBS
rhIL15
基准 0.1mg/kg
基准 0.5mg/kg
P-0234 0.1mg/kg
P-0234 0.5mg/kg

图13A

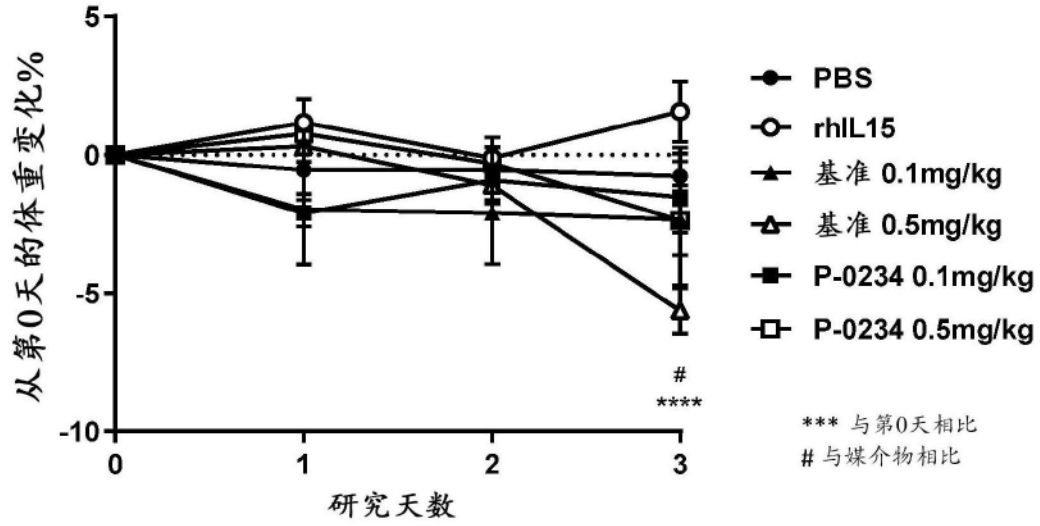

5
0
-5
-10
从第0天的体重变化%
0
1
2
3
研究天数
#
****
PBS
rhIL15
基准 0.1mg/kg
基准 0.5mg/kg
P-0234 0.1mg/kg
P-0234 0.5mg/kg
*** 与第0天相比
# 与媒介物相比

图13B

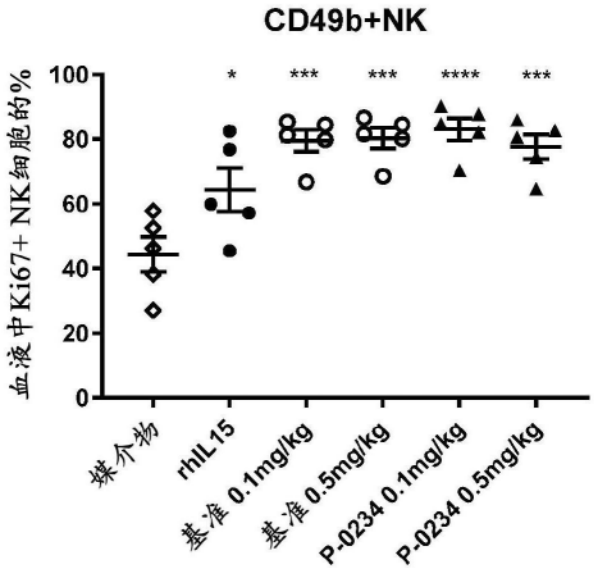

CD49b+NK
血液中Ki67+ NK细胞的%
100
80
60
40
20
0
*
***
***
****
***
媒介物
rhIL15
基准 0.1mg/kg
基准 0.5mg/kg
P-0234 0.1mg/kg
P-0234 0.5mg/kg

图14A

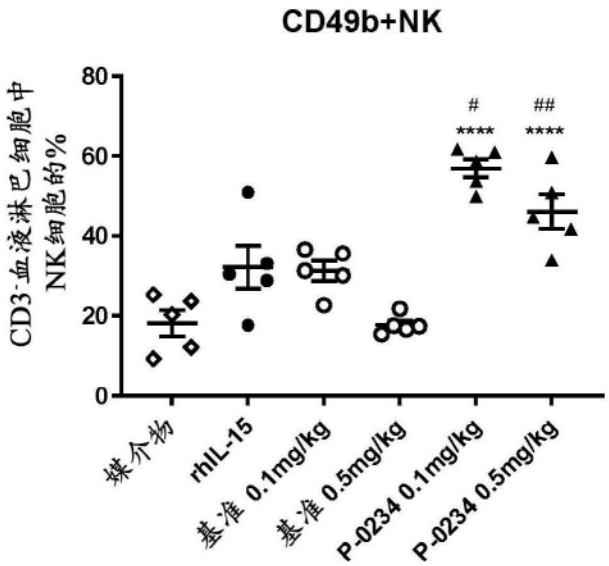

CD49b+NK
CD3-血液淋巴细胞中
NK细胞的%
80
60
40
20
0
#
##
****
****
媒介物
rhIL-15
基准 0.1mg/kg
基准 0.5mg/kg
P-0234 0.1mg/kg
P-0234 0.5mg/kg

图14B

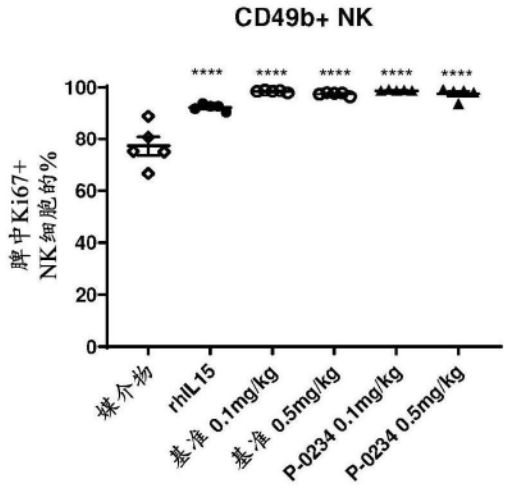



图15A

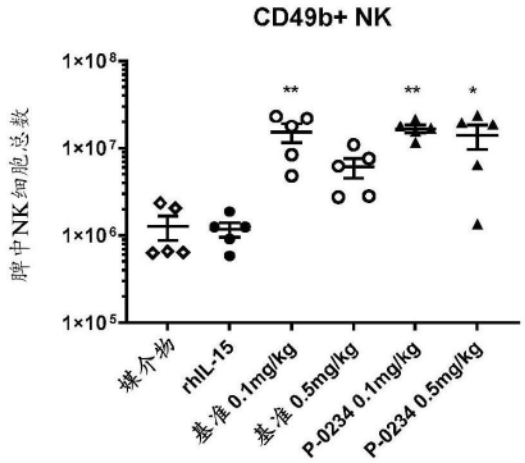



图15B

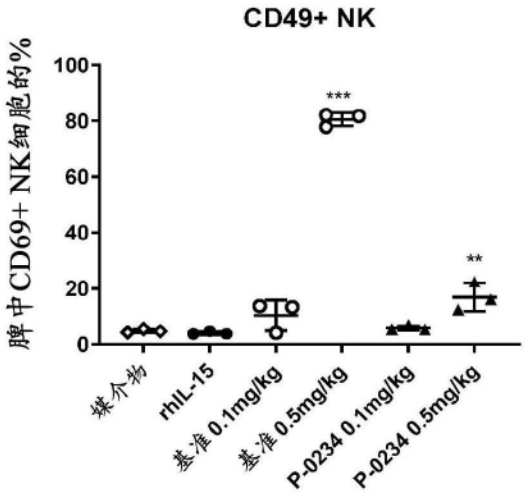



图15C

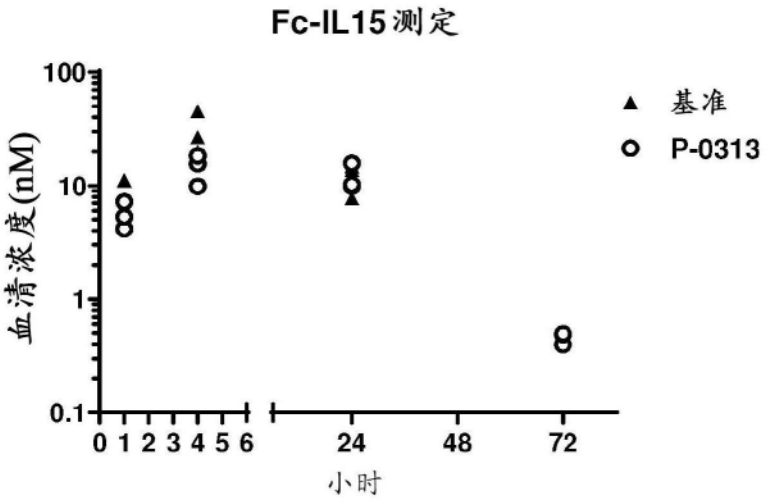

Fc-IL15测定
血清浓度(nM)
100
10
1
0.1
0 1 2 3 4 5 6
24
48
72
小时
基准
P-0313

图16A

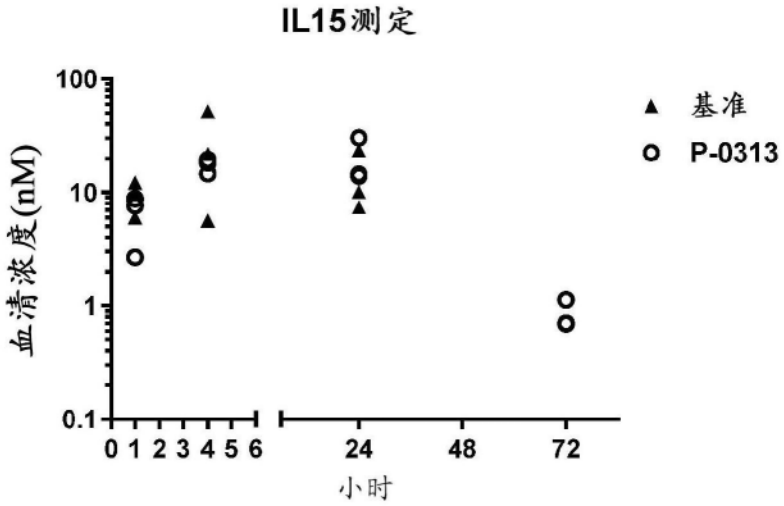

IL15测定
血清浓度(nM)
100
10
1
0.1
0 1 2 3 4 5 6
24
48
72
小时
基准
P-0313

图16B

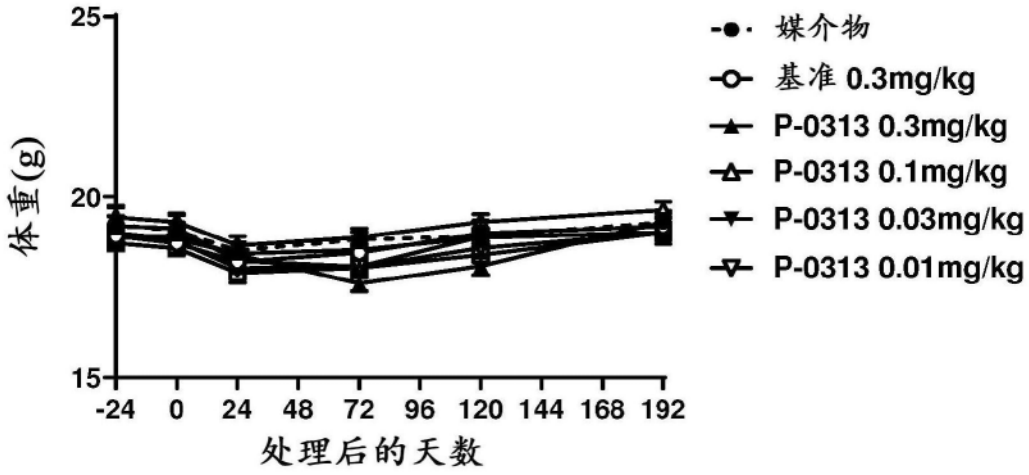

25
20
15
体重(g)
-24
0
24
48
72
96
120
144
168
192
处理后的天数
媒介物
基准 0.3mg/kg
P-0313 0.3mg/kg
P-0313 0.1mg/kg
P-0313 0.03mg/kg
P-0313 0.01mg/kg

图17

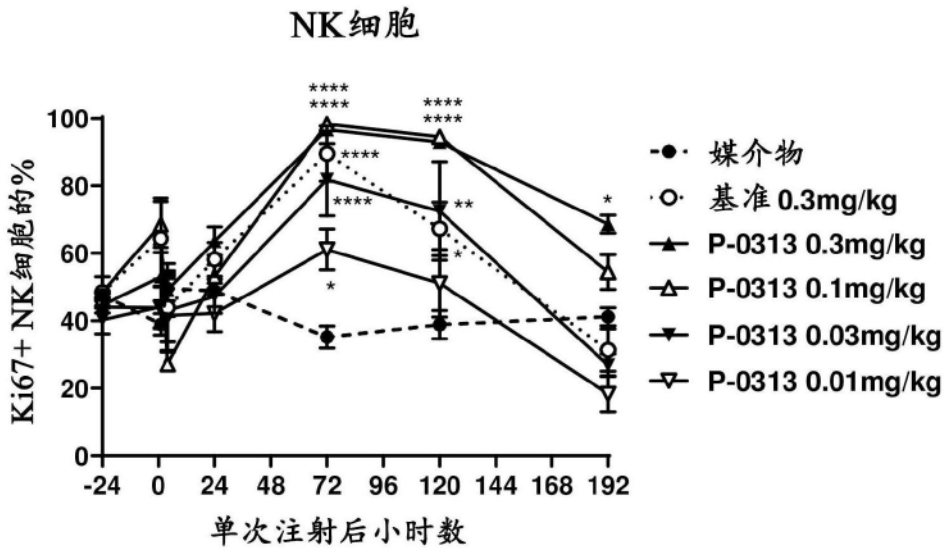

NK细胞
Ki67+ NK细胞的%
100
80
60
40
20
0
-24
0
24
48
72
96
120
144
168
192
单次注射后小时数
媒介物
基准 0.3mg/kg
P-0313 0.3mg/kg
P-0313 0.1mg/kg
P-0313 0.03mg/kg
P-0313 0.01mg/kg

图18A

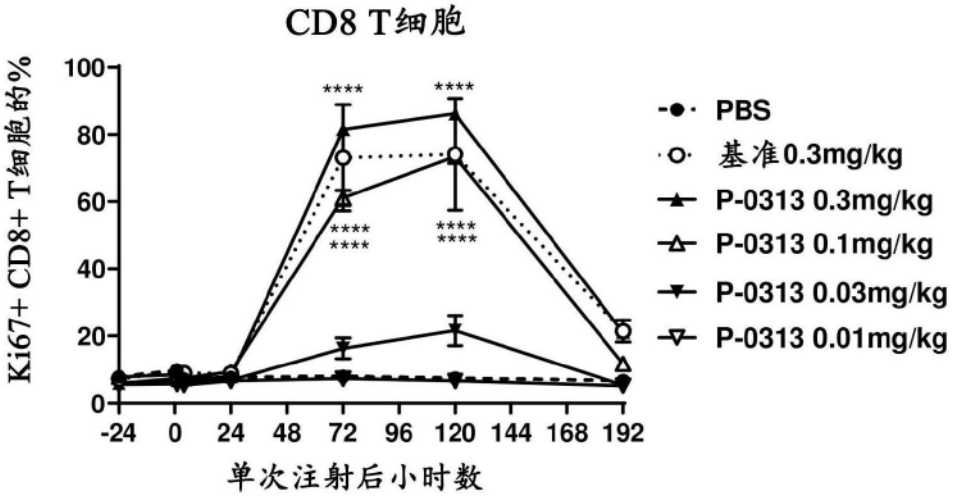

CD8 T细胞
Ki67+ CD8+ T细胞的%
100
80
60
40
20
0
-24
0
24
48
72
96
120
144
168
192
单次注射后小时数
PBS
基准0.3mg/kg
P-0313 0.3mg/kg
P-0313 0.1mg/kg
P-0313 0.03mg/kg
P-0313 0.01mg/kg

图18B

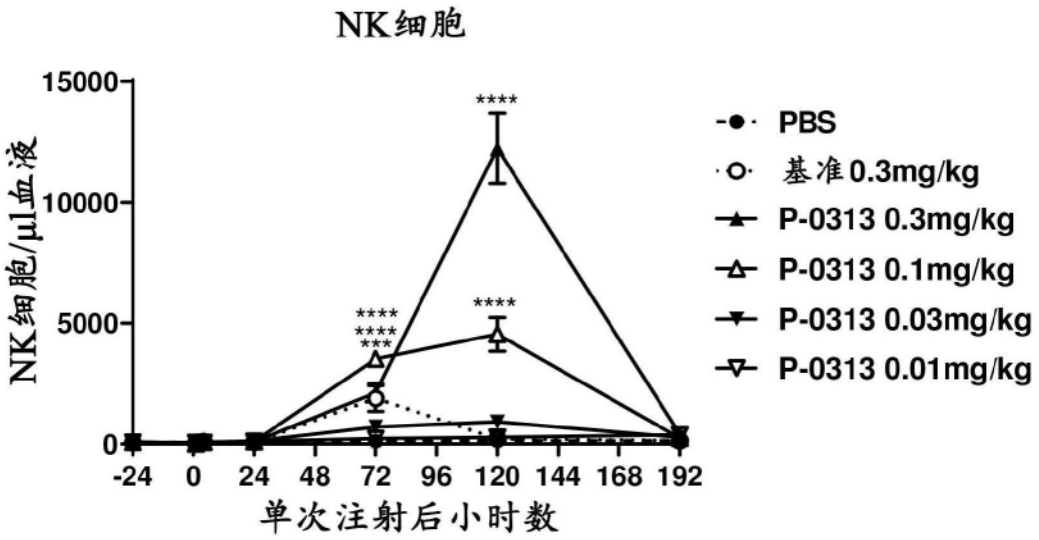

NK细胞
15000
10000
5000
0
NK细胞/μl血液
****
****
****
****
***
-24 0 24 48 72 96 120 144 168 192
单次注射后小时数
PBS
基准0.3mg/kg
P-0313 0.3mg/kg
P-0313 0.1mg/kg
P-0313 0.03mg/kg
P-0313 0.01mg/kg

图19A

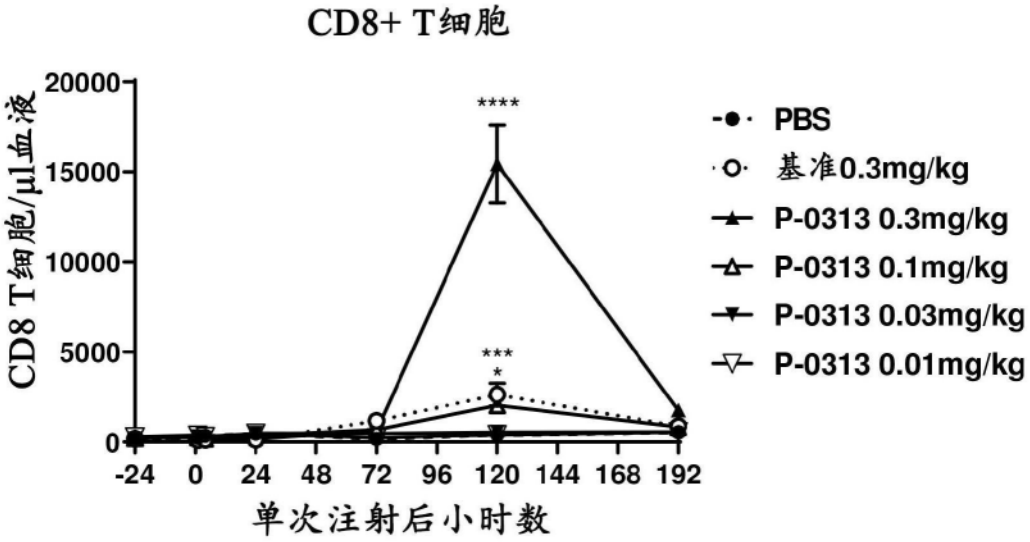

CD8+ T细胞
20000
15000
10000
5000
0
CD8 T细胞/μl血液
****
***
*
-24 0 24 48 72 96 120 144 168 192
单次注射后小时数
PBS
基准0.3mg/kg
P-0313 0.3mg/kg
P-0313 0.1mg/kg
P-0313 0.03mg/kg
P-0313 0.01mg/kg

图19B

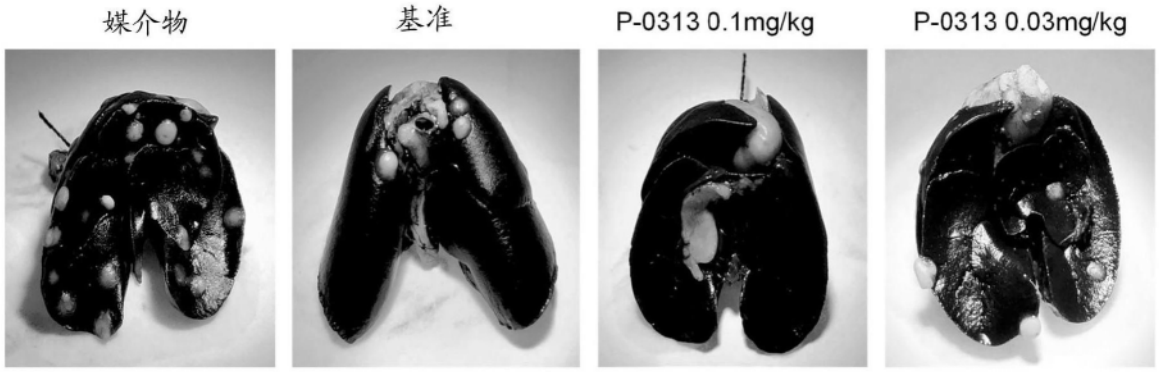

媒介物
基准
P-0313 0.1mg/kg
P-0313 0.03mg/kg

图20A

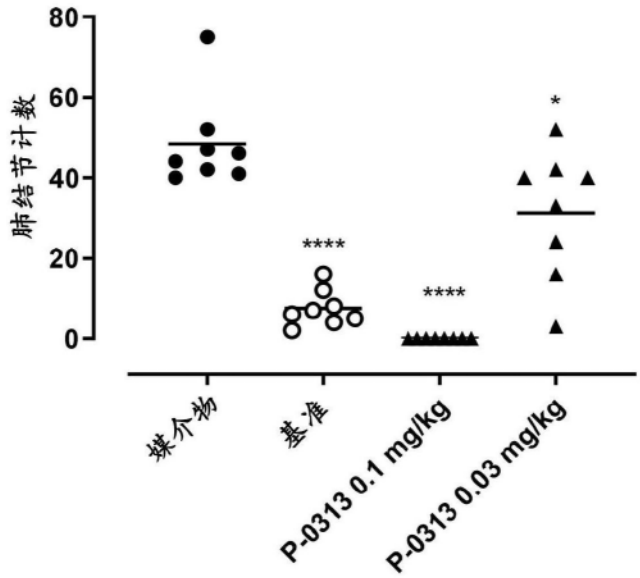

肺结节计数
80
60
40
20
0
****
****
*
媒介物
基准
P-0313 0.1 mg/kg
P-0313 0.03 mg/kg

图20B

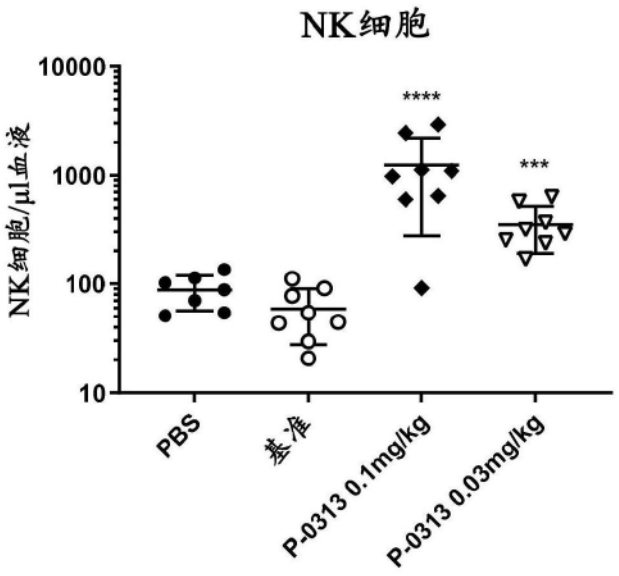

NK细胞
NK细胞/μl血液
10000
1000
100
10
****
***
PBS
基准
P-0313 0.1mg/kg
P-0313 0.03mg/kg

图21A

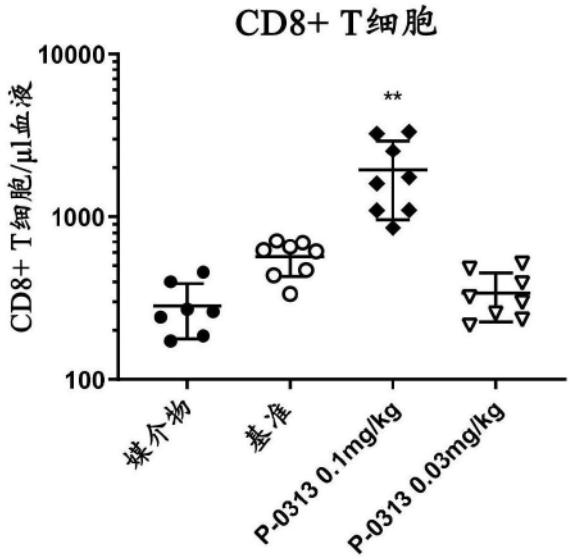

CD8+ T细胞
CD8+ T细胞/μl血液
10000
1000
100
**
媒介物
基准
P-0313 0.1mg/kg
P-0313 0.03mg/kg

图21B

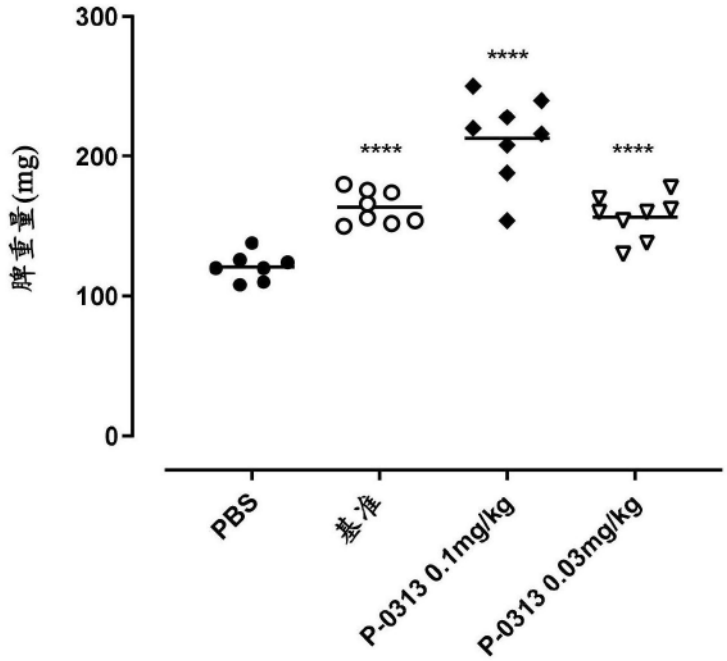



图22

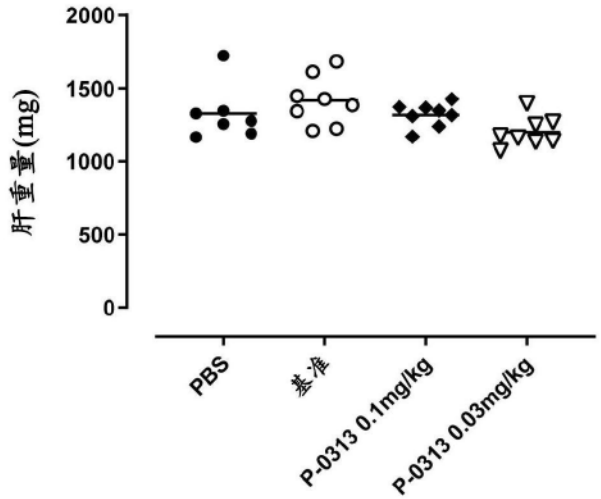



图23A

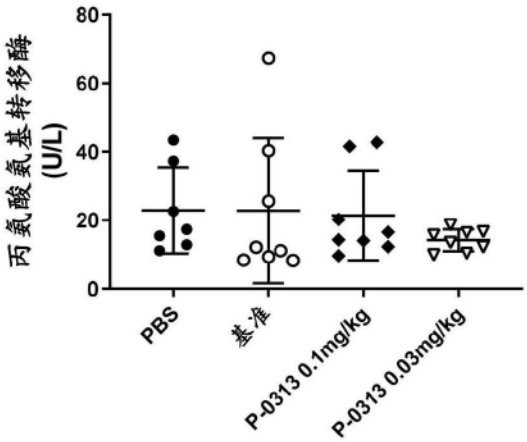



图23B

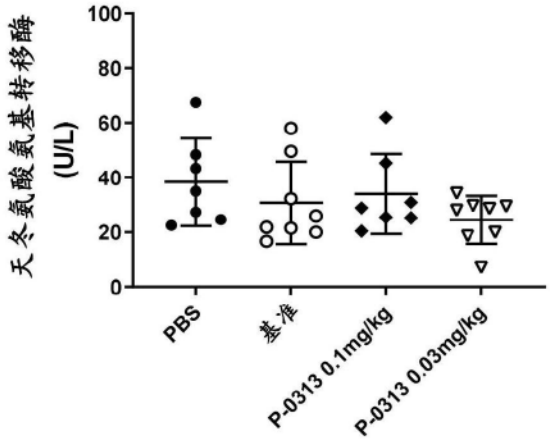



图23C

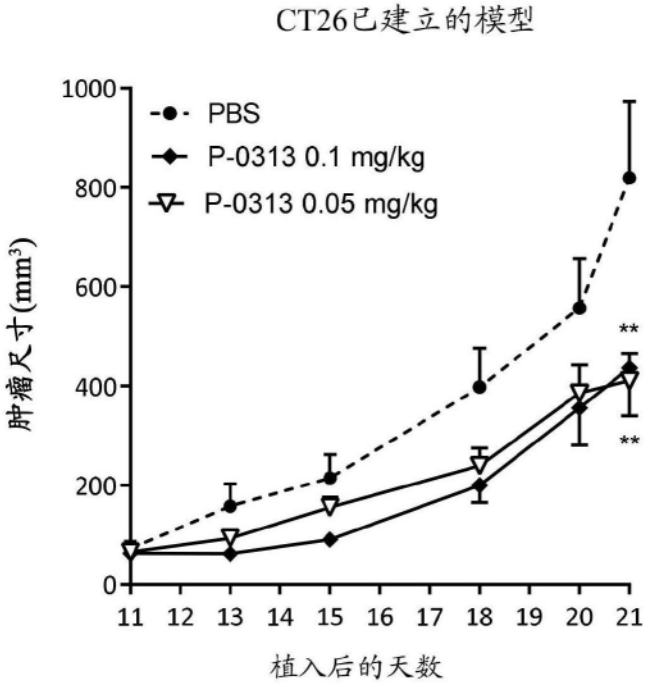

CT26已建立的模型
PBS
P-0313 0.1 mg/kg
P-0313 0.05 mg/kg
肿瘤尺寸(mm³)
1000
800
600
400
200
0
11 12 13 14 15 16 17 18 19 20 21
植入后的天数
**
**

图24A

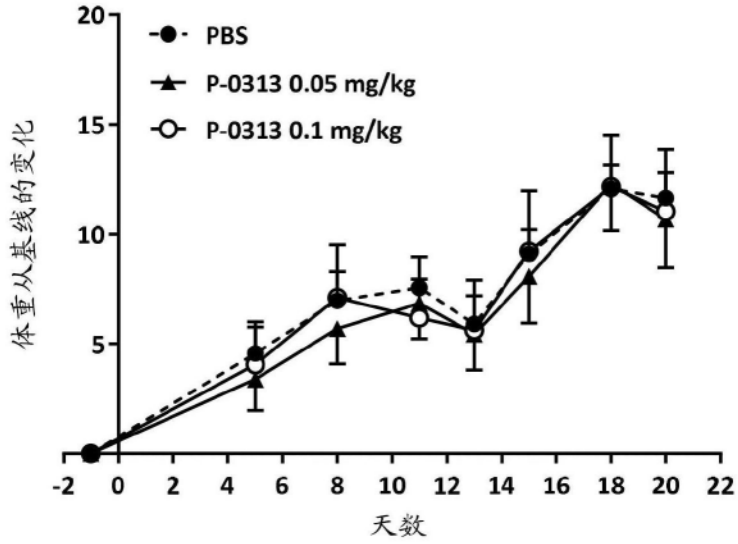

PBS
P-0313 0.05 mg/kg
P-0313 0.1 mg/kg
体重从基线的变化
20
15
10
5
-2 0 2 4 6 8 10 12 14 16 18 20 22
天数

图24B

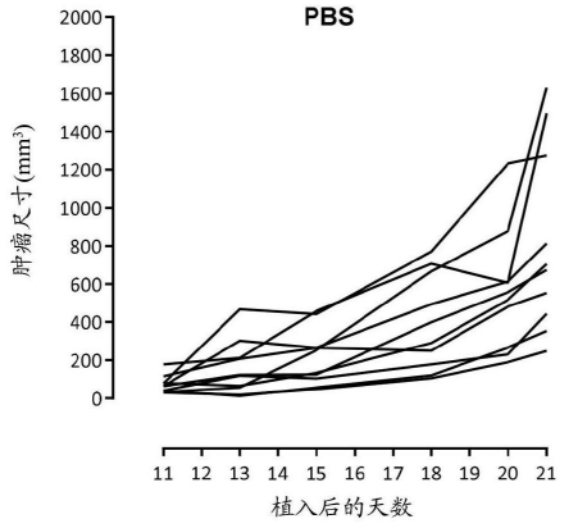



图25A

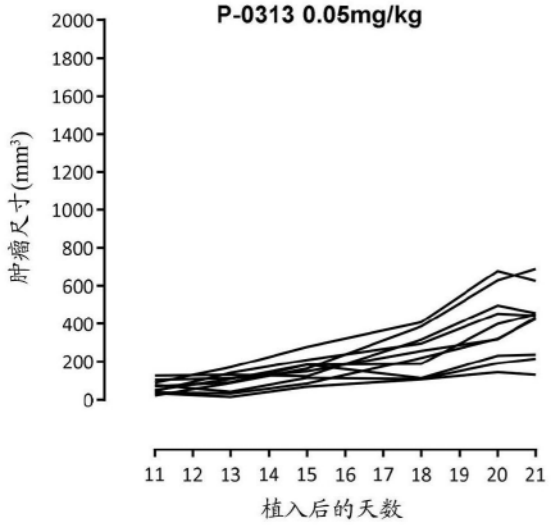



图25B

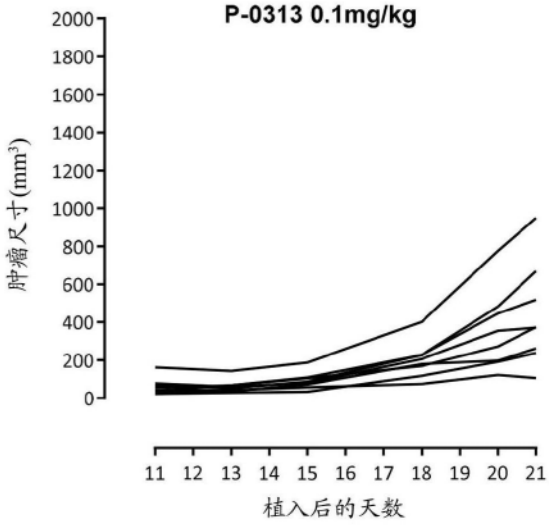



图25C

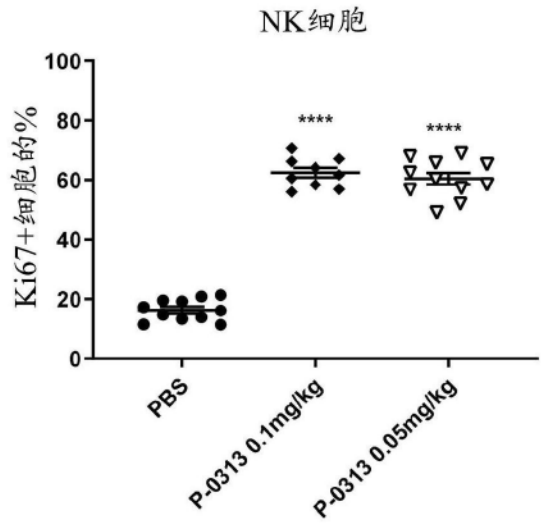



图26A

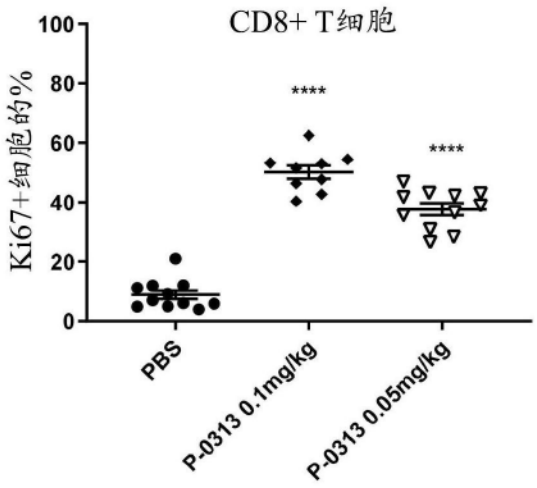



图26B

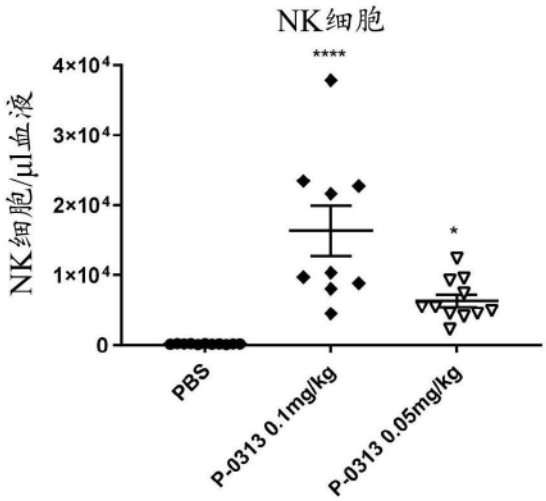



图26C

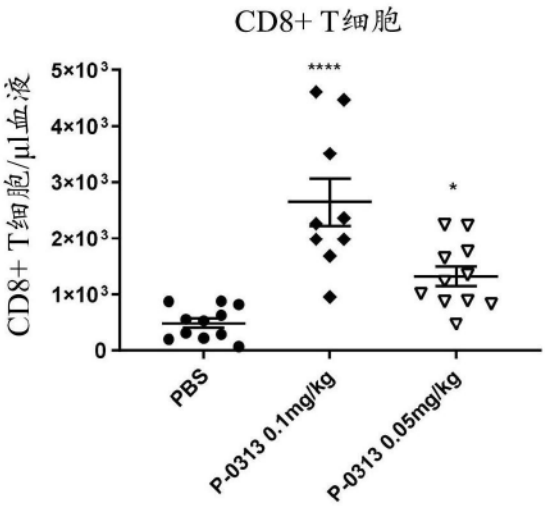



图26D

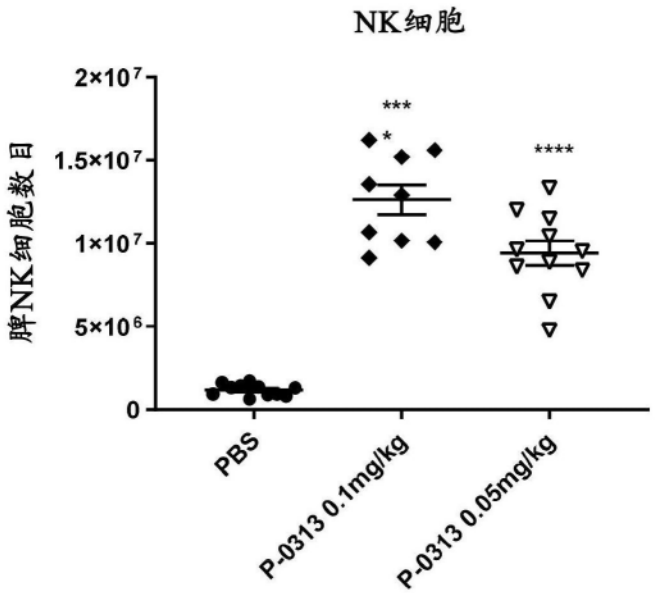

NK细胞
脾NK细胞数目
2×10^7
1.5×10^7
1×10^7
5×10^6
0
***
*
****
PBS
P-0313 0.1mg/kg
P-0313 0.05mg/kg

图27A

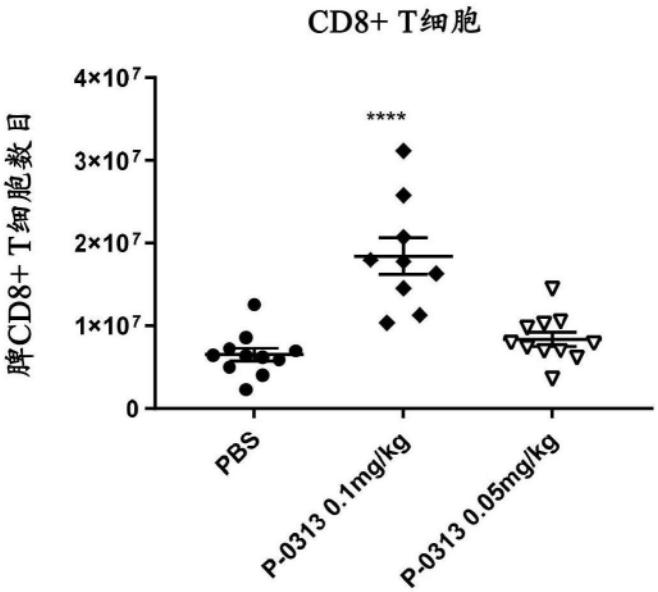

CD8+ T细胞
脾CD8+ T细胞数目
4×10^7
3×10^7
2×10^7
1×10^7
0
****
PBS
P-0313 0.1mg/kg
P-0313 0.05mg/kg

图27B

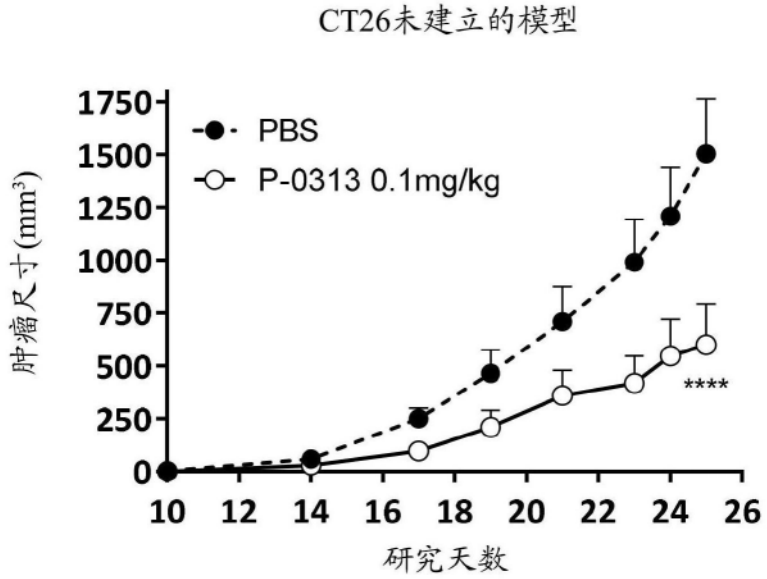

CT26未建立的模型
1750
1500
1250
1000
750
500
250
0
PBS
P-0313 0.1mg/kg
肿瘤尺寸(mm³)
****
10 12 14 16 18 20 22 24 26
研究天数

图28A

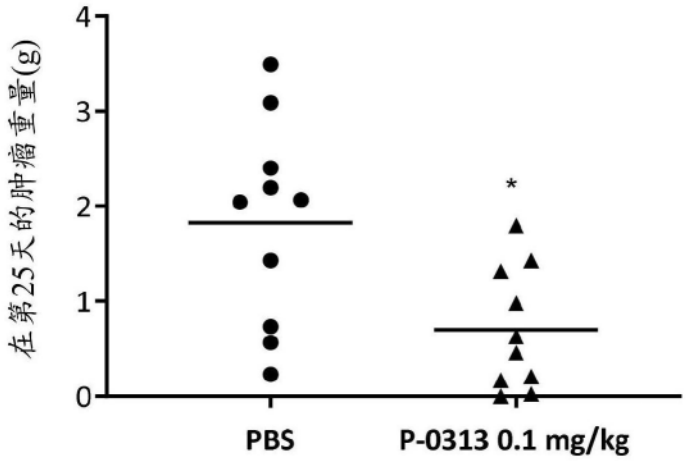

4
3
2
1
0
在第25天的肿瘤重量(g)
*
PBS
P-0313 0.1 mg/kg

图28B

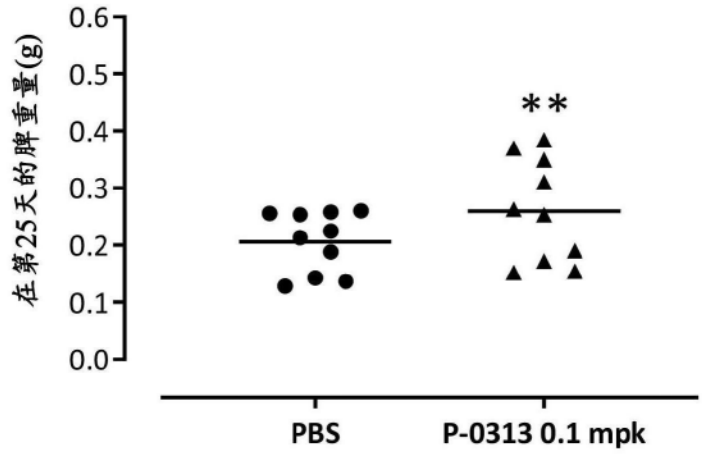

在第25天的脾重量(g)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
**
PBS
P-0313 0.1 mpk

图29A

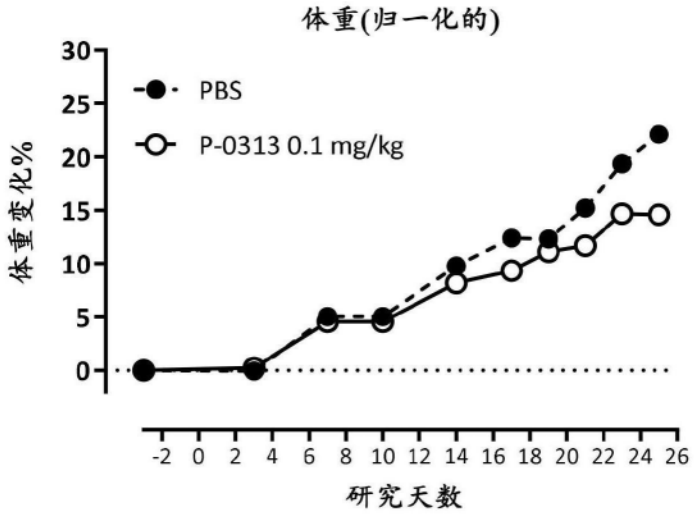

体重(归一化的)
体重变化%
30
25
20
15
10
5
0
PBS
P-0313 0.1 mg/kg
-2 0 2 4 6 8 10 12 14 16 18 20 22 24 26
研究天数

图29B

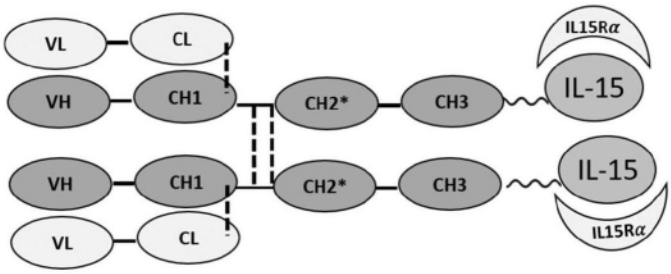



图30A

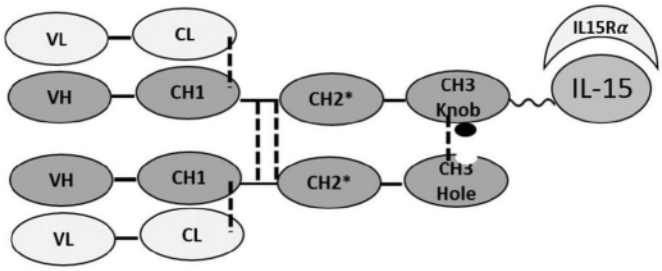



图30B

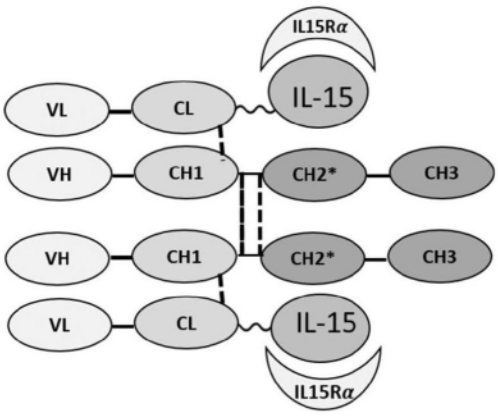



图30C

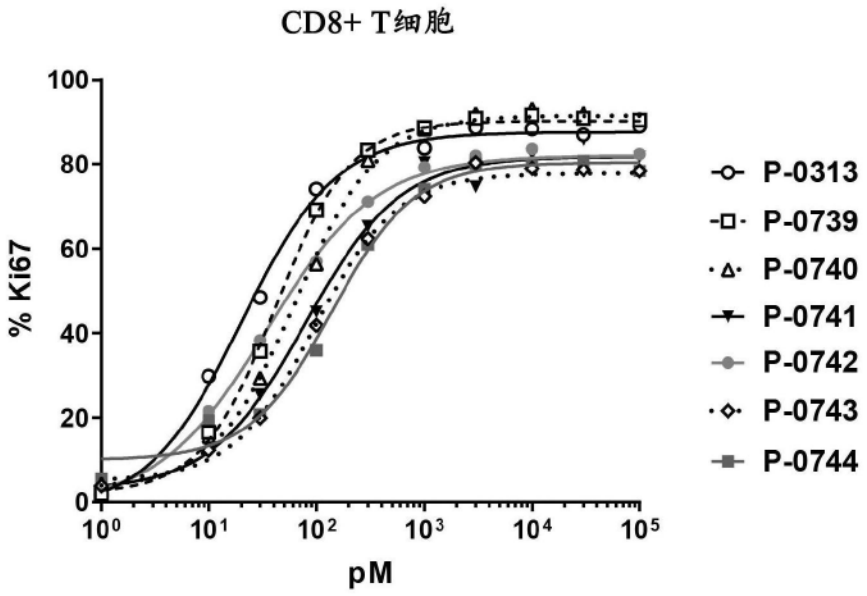

CD8+ T细胞
% Ki67
pM
P-0313
P-0739
P-0740
P-0741
P-0742
P-0743
P-0744

图31A

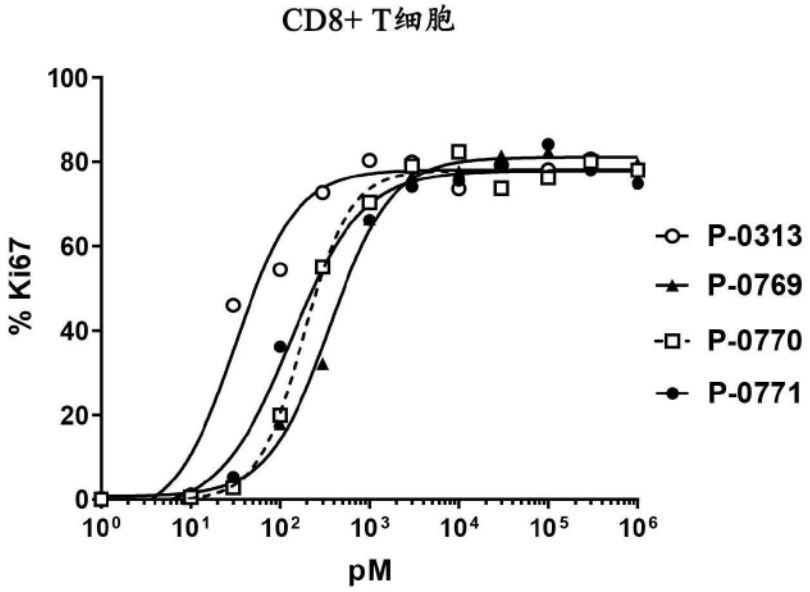

CD8+ T细胞
% Ki67
pM
P-0313
P-0769
P-0770
P-0771

图31B

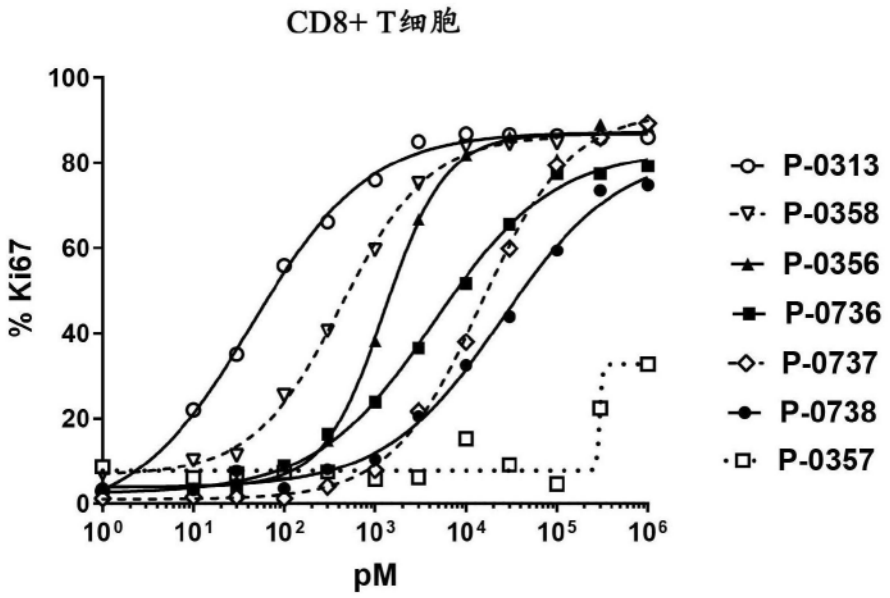

CD8+ T细胞
% Ki67
pM
P-0313
P-0358
P-0356
P-0736
P-0737
P-0738
P-0357

图31C

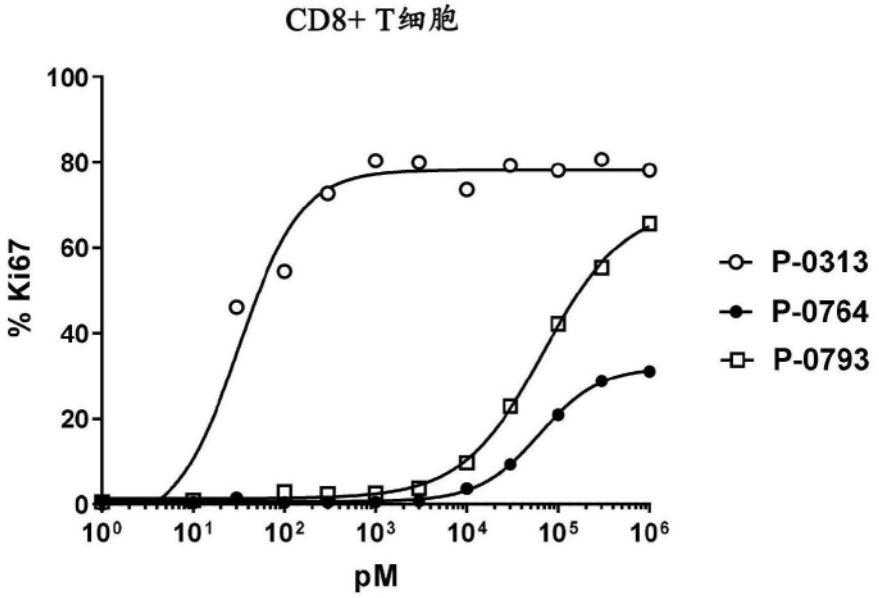

CD8+ T细胞
% Ki67
pM
P-0313
P-0764
P-0793

图31D

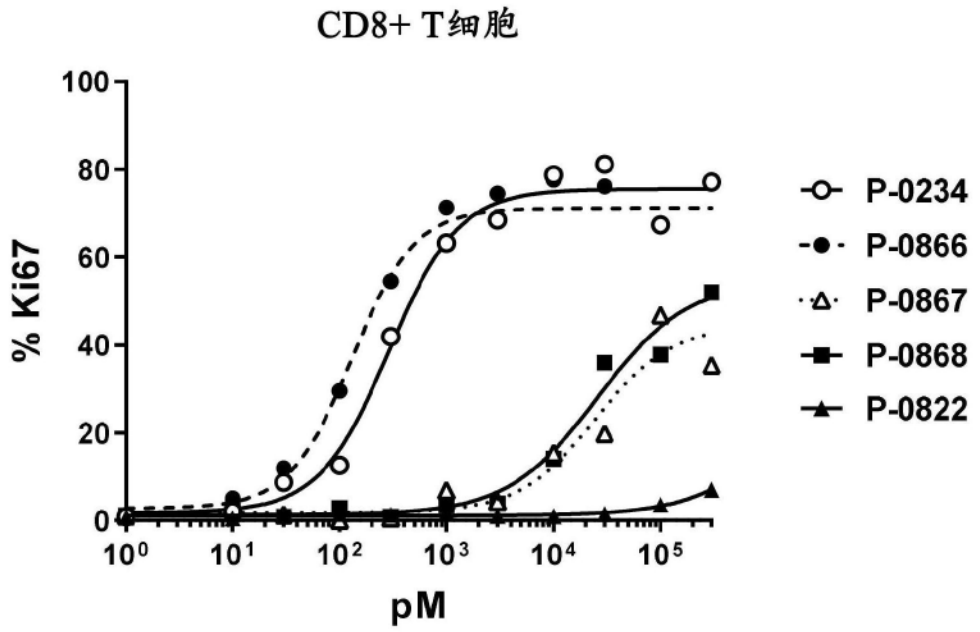

CD8+ T细胞
100
80
60
40
20
0
% Ki67
10⁰
10¹
10²
10³
10⁴
10⁵
pM
P-0234
P-0866
P-0867
P-0868
P-0822

图32

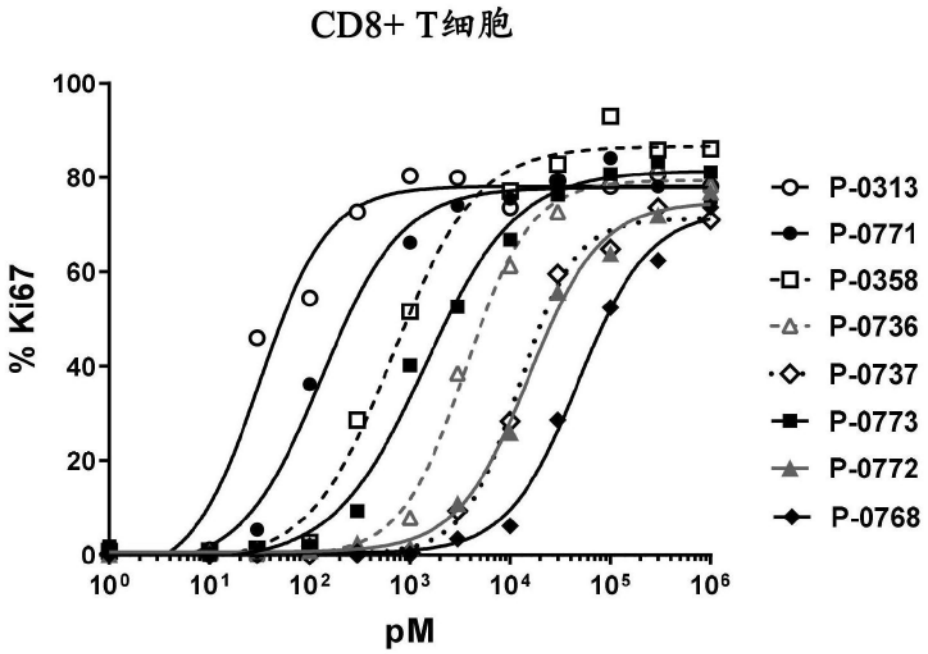

CD8+ T细胞
% Ki67
pM
P-0313
P-0771
P-0358
P-0736
P-0737
P-0773
P-0772
P-0768

图33A

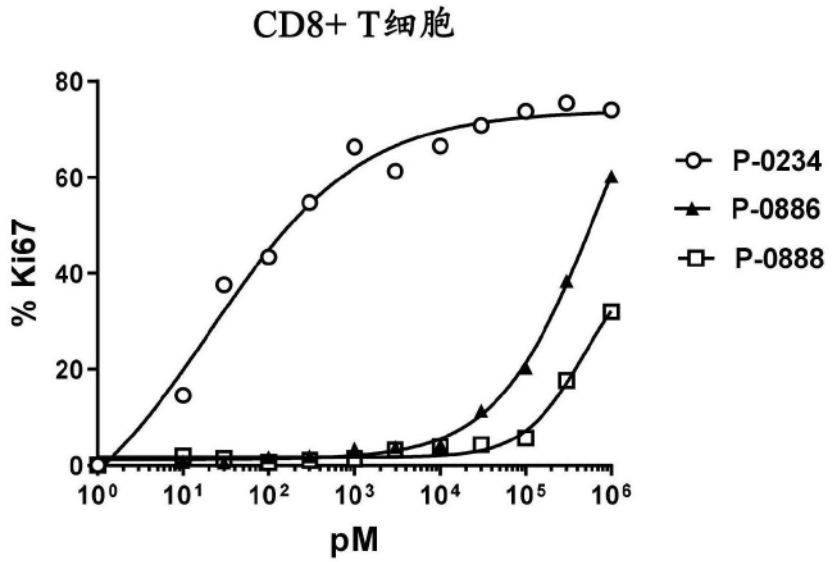

CD8+ T细胞
% Ki67
pM
P-0234
P-0886
P-0888

图33B

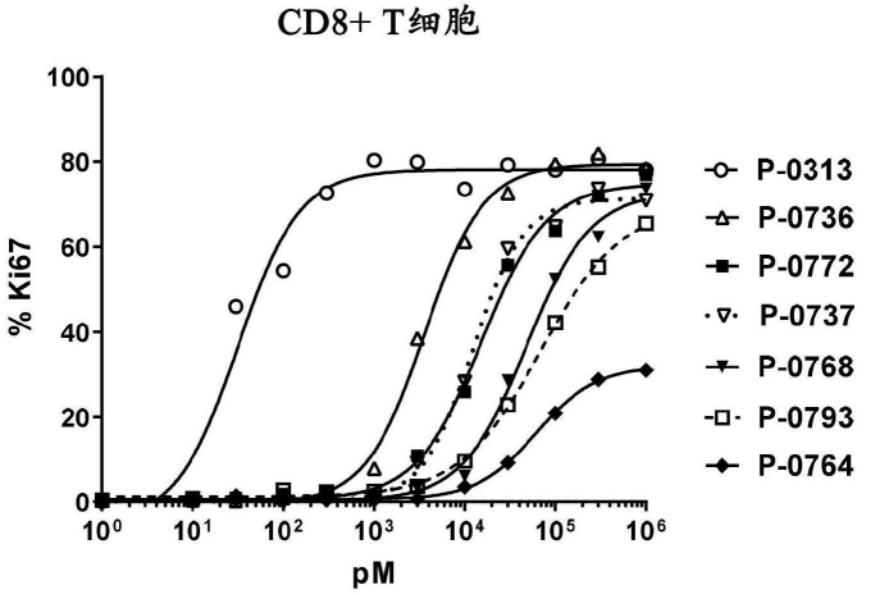

CD8+ T细胞
% Ki67
pM
P-0313
P-0736
P-0772
P-0737
P-0768
P-0793
P-0764

图34A

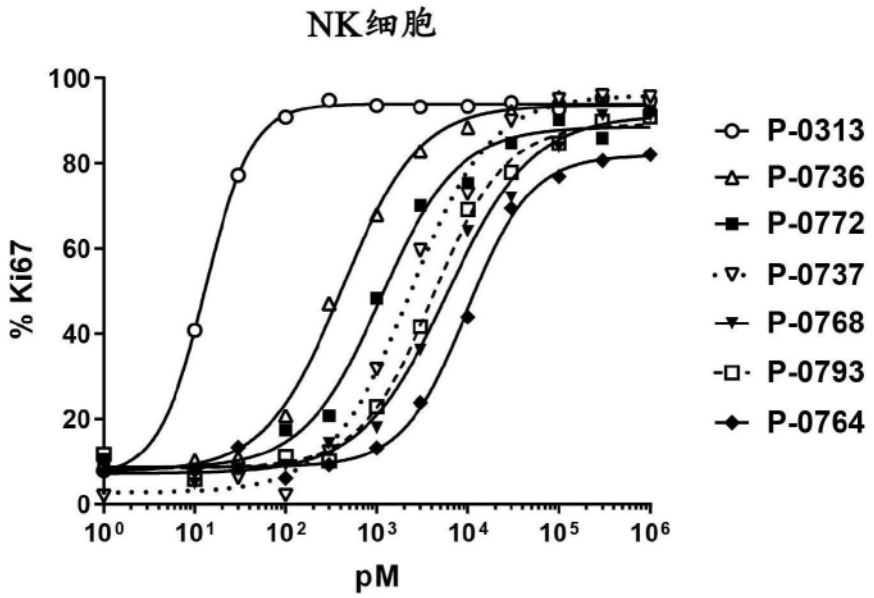

NK细胞
% Ki67
pM
P-0313
P-0736
P-0772
P-0737
P-0768
P-0793
P-0764

图34B

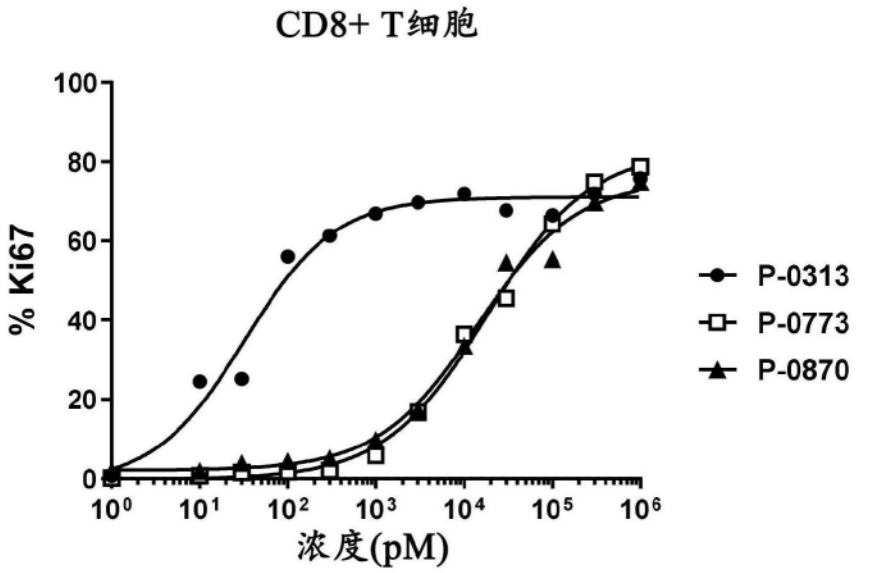

CD8+ T细胞
% Ki67
100
80
60
40
20
0
$10^0$ $10^1$ $10^2$ $10^3$ $10^4$ $10^5$ $10^6$
浓度(pM)
P-0313
P-0773
P-0870

图35A

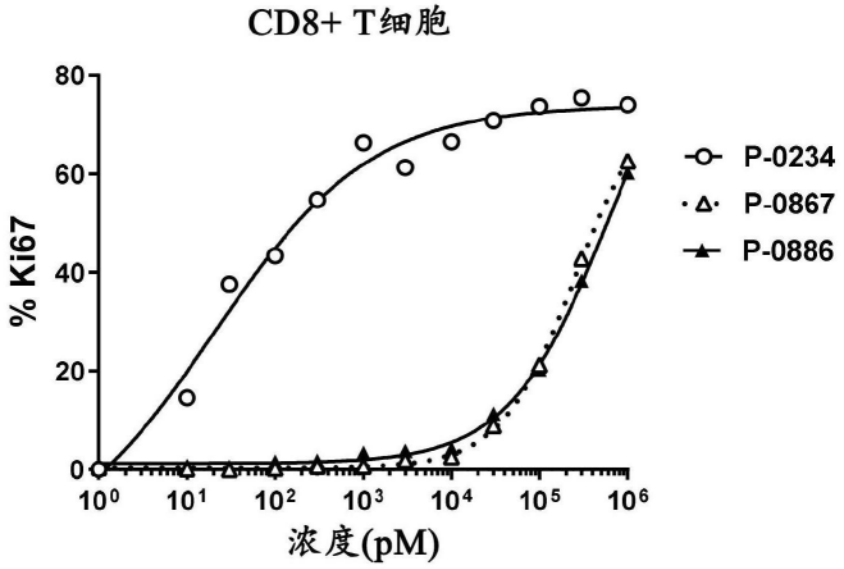

CD8+ T细胞
% Ki67
80
60
40
20
0
$10^0$ $10^1$ $10^2$ $10^3$ $10^4$ $10^5$ $10^6$
浓度(pM)
P-0234
P-0867
P-0886

图35B