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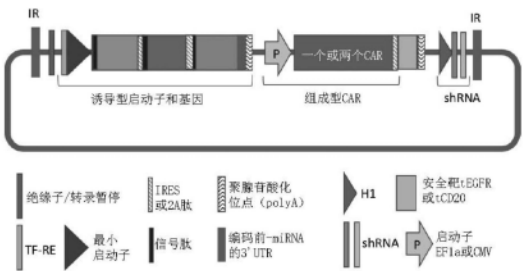
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(54) 发明名称

人工免疫监视嵌合抗原受体 (AI-CAR) 及其表达细胞

(57) 摘要

本申请提供了非病毒载体,其包含侧翼为两个转座子或病毒末端重复序列 (IR) 的人工免疫监视嵌合抗原受体 (AI-CAR) 表达盒,其中所述 AI-CAR 表达盒包含诱导型基因表达单元和 CAR 表达单元。



AI-CAR 基因表达盒的一般主题, 其在非病毒载体 (pPI) 中包含诱导型基因表达单元和 CAR 表达单元, 用于组成型表达一个或两个 CAR 以诱导宿主抗肿瘤应答的基因表达。

1. 一种嵌合抗原受体复合物,其包含:

第一蛋白,其包含通过第一接头与第一细胞间结构域连接的第一细胞外结构域,其中所述第一细胞外结构域包含对第一肿瘤表位具有亲和力的第一scFv,并且其中所述第一细胞间结构域包含JAK1结合结构域,和

第二蛋白,其包含通过第二接头与第二细胞间结构域连接的第二细胞外结构域,其中所述第二细胞外结构域包含对第二肿瘤表位具有亲和力的第二scFv,并且其中所述第二细胞间结构域包含JAK3结合结构域;

其中所述第一肿瘤表位在第一肿瘤抗原上,并且其中所述第二肿瘤表位在第二肿瘤抗原上,其中所述第一细胞内进一步包含连接至JAK1结合结构域的第一细胞毒性信号传导结构域,所述第二细胞内结构域还包含连接至JAK3结合结构域的第二细胞毒性信号传导结构域,所述第一细胞内结构域被配置为与所述第二细胞内结构域二聚化,其中所述嵌合抗原受体的氨基酸序列如SEQ ID NO:1 和SEQ ID NO:2所示。

2. 一种生物分子复合物,其包含权利要求1所述的嵌合抗原受体复合物,和

第一肿瘤抗原,和

第二肿瘤抗原。

人工免疫监视嵌合抗原受体 (AI-CAR) 及其表达细胞

[0001] 相关申请的交叉引用

[0002] 本申请要求于2019年2月21日提交的美国临时申请序列第62/808,815号,于2019年2月21日提交的美国临时申请序列第62/808,823号和根据35 U.S.C.119(e)于2019年2月21日提交的美国临时申请序列第62/808,833号的优先权,其全部公开内容通过引用并入本文。

技术领域

[0003] 本发明涉及一种用于改善嵌合抗原受体 (CAR) - T细胞或NK细胞的扩增、制造、存活和功效的技术。

背景技术

[0004] 除非在此另外指出,否则本部分中描述的材料不是本申请中的权利要求的现有技术,并且不通过包括在本部分中而被认为是现有技术。

[0005] 制造CAR细胞是费力的,并且可能由于需要人工抗原递呈细胞 (aAPC), TCR的抗体刺激和共刺激受体和/或多种细胞因子以在施用前扩增自体或异源CAR细胞而复杂化。例如,当电穿孔条件设定为高CAR表达百分比时,用CAR的DNA载体电穿孔T细胞、NK细胞、PBL或PBMC通常导致大部分细胞的细胞死亡。因此,在电穿孔之后,可以将细胞与经照射的aAPC、抗体和/或生长因子共培养,并且可以将CAR细胞群特异性地扩增多次以产生用于治疗用途的单剂量。目前,标准CAR载体 (CAR) 不表达通常在免疫抑制的肿瘤微环境中需要的能够诱导患者抗肿瘤免疫应答的基因。

[0006] 理想地,施用后CAR细胞的功效应该与具有未分化记忆表型的T细胞相关,所述未分化记忆表型的特征在于体内持续性和最大治疗潜力。为了选择性地扩增具有这种表型的CAR细胞和/或防止终末分化,已经利用了几种细胞因子,包括IL15、IL7和IL21。已知IL15和IL7对于产生和支持早期记忆T细胞是关键的,这是由于它们指导从幼稚前体产生人记忆干细胞的能力 (Cieri等人,2013;Boyman等人,2012;Gattinoni L等人,2011)。IL15和IL7可以用于使T细胞 (例如人CD8+记忆T细胞亚群) 响应于抗原或体内平衡细胞因子而去分化的工具 (Geginat 2003)。IL15是先天样T细胞免疫监视所必需的 (Dadi S等人,2016)。可溶性和转运的IL15/IL-15R α 能够维持IL-15活性并有助于CD8记忆T细胞的长期存活 (Sato等人,2007)。因此,具有未分化记忆表型的CART细胞表现出最大的体内持续性和治疗功效。

[0007] 然而,由于每种组分的安全性评估,不能共同施用用于制造和维持具有高治疗潜能的此类CAR细胞的所有组分。然而,将这些组分构建到具有组成型表达的CAR载体中可能不是可行的实践,因为随时间毒性的可能性高。或者,如果CAR细胞扩增和未分化记忆表型的信号传导途径处于单一分子 (例如靶肿瘤抗原) 的控制下,那么其将不仅使成本大大降低而且使护理点治疗成为可能。以这种方式,CAR信号传导可以足以支持CAR细胞的扩增而没有终末分化。

[0008] 从临床观点来看,多种因素导致治疗复发,包括CAR细胞持续性不足 (耗竭或宿主

抗-CAR)、靶抗原丧失、缺乏诱导宿主抗-肿瘤应答和/或不能有效地定位至淋巴瘤/实体瘤。几乎所有形式的CAR解决了通过靶向2种或更多种肿瘤抗原解决的肿瘤抗原损失。因此,非常需要通过在CAR载体/RNA中包含额外的基因而具有一种或多种CAR以及持久的宿主应答。

发明内容

[0009] 在一个方面,本申请提供嵌合抗原受体复合体。在一个实施方案中,所述嵌合抗原受体复合物包含第一蛋白,所述第一蛋白包含通过第一接头与第一细胞间结构域连接的第一细胞外结构域,其中所述第一细胞外结构域包含对第一肿瘤表位具有亲和力的第一scFv,并且其中所述第一细胞间结构域包含JAK1结合结构域,和第二蛋白,所述第二蛋白包含通过第二接头与第二细胞间结构域连接的第二细胞外结构域,其中所述第二细胞外结构域包含对第二肿瘤表位具有亲和力的第二scFv,并且其中所述第二细胞间结构域包含JAK3结合结构域。所述第一肿瘤表位在第一肿瘤抗原上。所述第二肿瘤表位在第二肿瘤抗原上。

[0010] 在一个实施方案中,第一细胞内结构域包含IL7R α (CD127)。在一个实施方案中,第一细胞内结构域包含IL15R β (CD122)、IL21R α (CD360)或其组合的细胞内结构域。在一个实施方案中,第一细胞内还包含连接至JAK1结合结构域的第一细胞毒性信号传导结构域。

[0011] 在一个实施方案中,第一细胞毒性信号传导结构域包含CD28、CD3 ζ 、CD137、OX40、CD27、ICOS或其组合。

[0012] 在一个实施方案中,第一scFv结构域或第二scFv结构域独立地对CD19或CD22具有亲和力。在一个实施方案中,第一scFv结构域对CD19具有亲和力。在一个实施方案中,第二scFv结构域对CD22具有亲和力。在一个实施方案中,第二细胞内结构域包含 γ (CD132)。

[0013] 在一个实施方案中,第二细胞内结构域进一步包含连接至JAK3结合结构域的第二细胞毒性信号传导结构域。在一个实施方案中,第二细胞毒性结构域包含CD28、CD3 ζ 、CD137、OX40、CD27、ICOS或其组合。在一个实施方案中,第二细胞内结构域包含串联 γ (CD132)、JAK3结合结构域、CD28和CD3 ζ 。在一个实施方案中,第一细胞内结构域被配置为与第二细胞内结构域二聚化。

[0014] 在一个实施方案中,第一和第二接头独立地包含CD8。在一个实施方案中,第一和第二接头独立地包含茎和跨膜结构域。

[0015] 在一个实施方案中,茎包含CD8、Fc铰链,Fc CH2-CH3,TCR α 、TCR β 、截短的IL7R α (CD127)、截短的IL15R β (CD122)、IL15R α (CD215)、截短的 γ (CD132)、截短的IL21R α (CD360)或其组合。

[0016] 在一个实施方案中,所述跨膜结构域包含CD8、CD28、CD3 ζ 、CD3 ϵ 、CD3 δ 、CD3 γ 、CD3 ζ 、TCR α 、TCR β 、IL15R β (CD122)、 γ (CD132)、IL7R α (CD127)、IL21R α (CD360)、IL15R α (CD215)或其组合。

[0017] 在一个实施方案中,肿瘤抗原包含CDH17、TROP2、CD19、CD22、CD37、BCMA、CD48、EGFR、HER2、EpCAM、CEACAM5、PSMA、GD2、GPC3或其组合。

[0018] 在另一方面,本申请提供开放阅读框(ORF)。在一个实施方案中,开放阅读框(ORF)依次包含CD19 scFv、茎跨膜区和IL7 α 内结构域。在一个实施方案中,开放阅读框(ORF)依次包含CD22 scFv、茎跨膜区、 γ 链内结构域、CD28内结构域和CD3 ζ 内结构域。在一个实施方案中,开放阅读框(ORF)依次包含PD-1scFv、CCL21和IL7。

[0019] 在另一方面,本申请提供生物分子复合物。在一个实施方案中,所述生物分子复合物包含第一蛋白,所述第一蛋白包含通过第一接头与第一细胞间结构域连接的第一细胞外结构域,其中所述第一细胞外结构域包含对第一肿瘤表位具有亲和力的第一scFv,并且其中所述第一细胞间结构域包含JAK1结合结构域,第二蛋白,所述第一蛋白包含通过第二接头与第二细胞间结构域连接的第二细胞外结构域,其中所述第二细胞外结构域包含对第二肿瘤表位具有亲和力的第二scFv,并且其中所述第二细胞间结构域包含JAK3结构域、第一肿瘤抗原和第二肿瘤抗原。所述第一肿瘤表位结合第一肿瘤抗原。所述第二肿瘤表位与所述肿瘤抗原结合。

[0020] 在一个实施方案中,第一细胞内结构域与第二细胞内结构域二聚化。在一个实施方案中,JAK1与JAK3二聚化。

[0021] 在另一方面,本申请提供非病毒DNA构建体。在一个实施方案中,所述非病毒DNA构建体依次包含从5'至3'的诱导型启动子,其随后是第一ORF,其中所述第一ORF包含抗PD-1scFv、CLL21和IL7,各自以单一肽引导并以核糖体跳跃肽结束,第二ORF包含至少一种组成型嵌合抗原受体,和第三启动子,其随后是至少一种RNA序列。

[0022] 在另一方面,本申请提供了嵌合抗原受体。在一个实施方案中,所述嵌合抗原受体依次包含细胞因子结构域、接头、截短的CD8结构域和信号传导内结构域。

[0023] 在一个实施方案中,细胞因子结构域包括IL7、IL12、IL21或其组合。在一个实施方案中,截短的CD8结构域包含铰链、跨膜结构域和胞质结构域的至少一部分。在一个实施方案中,胞质结构域包含CD28/CD170、CD3 ζ 或其组合。

[0024] 在一个实施方案中,嵌合抗原受体进一步包含在细胞因子结构域和截短的CD8结构域中间的肿瘤抗原结构域。

[0025] 在一个实施方案中,本申请提供生物分子复合物,其包含与肿瘤抗原结合的如其所公开的嵌合抗原受体。

[0026] 在另一方面,本申请提供了非病毒载体,其包含侧翼为两个转座子或病毒末端重复序列(IR)的人工免疫监视嵌合抗原受体(AI-CAR)表达盒,其中所述AI-CAR表达盒包含诱导型基因表达单元和CAR表达单元。

[0027] 在一个实施方案中,所述诱导型基因表达单元包含STAT、NFAT或NF- κ B诱导型启动子,通过IRES或自身切割核糖体跳跃肽连接的一个或多个基因的编码区,随后是第一polyA信号序列。在一个实施方案中,自身切割核糖体跳跃肽包含TA2。在一个实施方案中,诱导型基因表达单元包含用于表达至少两种不同细胞因子受体的基因。在一个实施方案中,诱导型基因表达单元包含用于表达抗原结合蛋白的基因。在一个实施方案中,诱导型基因表达单元包含用于表达抗-PD1 scFv的基因。在一个实施方案中,所述诱导型基因表达单元包含用于表达CCL21的基因。在一个实施方案中,诱导型基因表达单元包含用于表达IL7的基因。

[0028] 在一个实施方案中,CAR表达单元包含用于表达抗-CDH17 scFv,抗-TROP2 scFv,和CAR的基因。在一个实施方案中,CAR表达单元包含启动子、一个或两个CAR基因,随后是第二polyA信号序列。在一个实施方案中,CAR表达单元还包含用于表达安全开关的基因。在一个实施方案中,安全开关包含截短的EGFR(tEGFR)或截短的CD20。在一个实施方案中,AI-CAR表达盒被配置为表达shRNA,其中所述shRNA被配置为抑制所述内源TCR。

[0029] 在另一方面,本申请提供分离的核酸,其编码如其所公开的生物分子复合物、生物

分子、抗原和蛋白质。

[0030] 在另一方面,本申请提供表达载体,其包含如其所公开的分离的核酸。在一个实施方案中,表达载体包含如其所公开的ORF。在一个实施方案中,表达载体包含如其所公开的非病毒DNA构建体。所述表达载体可以是病毒的或非病毒的。该载体可以在细胞中表达。

[0031] 在进一步的实施方案中,本申请提供宿主细胞。在一个实施方案中,宿主细胞包含如其所公开的分离的核酸和/或表达载体。在一个实施方案中,宿主细胞包含如其所公开的非病毒DNA构建体。在一个实施方案中,宿主细胞包含如其所公开的非病毒载体。

[0032] 在另一个实施方案中,本申请提供哺乳动物细胞,其包含嵌合抗原受体复合物、生物分子复合物、生物分子、抗原和如其公开的蛋白质。在一个实施方案中,哺乳动物细胞包含如其所公开的嵌合抗原受体。在一个实施方案中,哺乳动物细胞包含如其所公开的生物分子复合物。

[0033] 在进一步的实施方案中,本申请提供CAR-T或CAR-NK细胞。在一个实施方案中,CAR-T或CAR-NK细胞表达如其所公开的嵌合抗原受体复合物。在一个实施方案中,CAR-T或CAR-NK细胞表达如其所公开的嵌合抗原受体。

[0034] 在另一个实施方案中,本申请提供用于治疗受试者中的肿瘤的方法,包括向受试者施用足够量的如其所公开的CAR-T或CAR-NK细胞。

[0035] 在另一方面,本申请提供药物组合物。在一个实施方案中,药物组合物包含治疗有效量的如其所公开的载体、非病毒载体、CAR-T或CAR-NK细胞、蛋白质、生物分子或生物分子复合物。在一个实施方案中,所述药物组合物还包含药学上可接受的媒介物。

附图说明

[0036] 结合附图,根据以下描述和所附权利要求书,本公开的前述和其他特征将变得更加完全清楚。应理解,这些附图仅描绘了根据本公开安排的若干实施方案并且因此不应被认为是对其范围的限制,将通过使用附图以额外的特性和细节来描述本公开,其中:

[0037] 图1描述了在非病毒载体(pPI)中包含诱导型基因表达单元和CAR表达单元的AI-CAR基因表达盒,用于组成型表达一个或两个CAR以诱导用于宿主抗肿瘤应答的基因表达;

[0038] 图2显示了AI-CAR的一般概念;

[0039] 图3描绘了编码组成型表达的双重CAR的AI-CAR表达载体,该双重CAR在非病毒载体(pPI)中在诱导型启动子下靶向CDH17和TROP2以及抗PD1 scFv、CCL21和IL17基因盒,用于CAR诱导的宿主抗肿瘤应答;AI-CAR表达载体编码组成型表达的双重CAR,该双重CAR在非病毒载体(pPI)中在诱导型启动子下靶向CDH17和TROP2以及抗PD1 scFv、CCL21和IL17基因盒,用于CAR诱导的宿主抗肿瘤应答;

[0040] 图4显示了整合的pPI抗-CDH17 AI-CAR载体基因的肿瘤抗原诱导;整合的pPI-抗-CDH17-AI-CAR载体基因的肿瘤抗原诱导。(A)通过响应于不同浓度的CDH17的T细胞(Jurkat)中的GFP水平来测量整合的pPI-抗-CDH17-AI-CAR载体的表达;(B)在结肠癌细胞中用重组CDH17诱导(SW480);和(C)pPI-抗-CDH17-AI-CAR整合的T细胞对表达CDH17的SW480细胞的细胞毒性;

[0041] 图5显示了pPI-抗-CDH17-TROP2 AI-CAR的表达和结合特异性;并且

[0042] 图6描述了支持AI-CAR增殖和持续性的iPro变体。支持AI-CAR增殖和持续性的

iPro变体。(A) iPro7表达的示例; (B) CD25⁺ T细胞群增殖的诱导; 以及 (C) 增加T细胞存活。

具体实施方式

[0043] 在下面的详细描述中,参考了形成其一部分的附图。在附图中,类似的符号通常标识类似的部件,除非上下文另外指示。在详细描述、附图和权利要求中描述的说明性实施方案并不意味着是限制性的。可以利用其他实施方案,并且可以进行其他改变,而不偏离在此呈现的主题的精神或范围。将容易理解的是,如在此一般描述的以及在附图中示出的本公开的这些方面可以被安排、替代、组合、分离,以及设计成多种不同的配置,在此明确地考虑了所有这些配置。

[0044] 在下面的详细描述中,参考了形成其一部分的附图。在附图中,类似的符号通常标识类似的部件,除非上下文另外指示。在详细描述、附图和权利要求中描述的说明性实施方案并不意味着是限制性的。可以利用其他实施方案,并且可以进行其他改变,而不偏离在此呈现的主题的精神或范围。将容易理解的是,如在此一般描述的以及在附图中示出的本公开的这些方面可以被安排、替代、组合、分离,以及设计成多种不同的配置,在此明确地考虑了所有这些配置。

[0045] 本公开尤其提供分离的抗体、制备此类抗体的方法、由此类抗体或抗原结合片段组成的双特异性或多特异性分子、抗体-药物缀合物和/或免疫缀合物、含有所述抗体、双特异性或多特异性分子、抗体-药物缀合物和/或免疫缀合物的药物组合物、制备所述分子和组合物的方法,以及使用本文公开的分子和组合物治疗癌症的方法。

[0046] 术语“抗体”以最广泛的含义使用,并且具体涵盖单一单克隆抗体(包括激动剂抗体和拮抗剂抗体),具有多表位特异性的抗体组合物以及抗体片段(例如Fab、F(ab')₂和Fv),只要它们表现出所需的生物学活性即可。在一些实施方案中,抗体可以是单克隆抗体、多克隆抗体、嵌合抗体、单链抗体、双特异性抗体或双有效抗体、模拟抗体、人抗体和人源化抗体及其活性片段。与已知抗原结合的分子的活性片段的实例包括Fab、F(ab')₂、scFv和Fv片段,包括Fab免疫球蛋白表达文库的产物和任何上述抗体和片段的表位结合片段。在一些实施方案中,抗体可包括免疫球蛋白分子和免疫球蛋白分子的免疫活性部分,即含有免疫特异性结合抗原的结合位点的分子。免疫球蛋白可以是任何类型(IgG、IgM、IgD、IgE、IgA和IgY)或类(IgG1、IgG2、IgG3、IgG4、IgA1和IgA2)或免疫球蛋白分子的亚类。在一个实施方案中,抗体可以是全抗体和衍生自全抗体的任何抗原结合片段。典型的抗体是指通常包含两条重(H)链和两条轻(L)链的异四聚体蛋白。每条重链由重链可变结构域(缩写为VH)和重链恒定结构域组成。每条轻链由轻链可变结构域(缩写为VL)和轻链恒定结构域组成。VH和VL区可以进一步细分为高变互补决定区(CDR)的结构域和更保守的称为构架区(FR)的区域。每个可变结构域(VH或VL)通常由三个CDR和四个FR组成,按以下顺序排列:从氨基末端到羧基末端的FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。在轻链和重链的可变结构域内有与抗原相互作用的结合区。

[0047] 如本文所用,术语“单克隆抗体”是指从基本上均质的抗体群获得的抗体,即,包含所述群的各个抗体是相同的,除了可能以少量存在的可能的天然存在的突变。单克隆抗体是高度特异性的,针对单一抗原位点。此外,与通常包括针对不同决定簇(表位)的不同抗体的常规(多克隆)抗体制剂相反,每种单克隆抗体针对抗原上的单一决定簇。除了它们的特

异性,单克隆抗体是有利的,因为它们是通过杂交瘤培养物合成的,没有被其它免疫球蛋白污染。修饰语“单克隆”表示抗体的特性是从基本上均质的抗体群获得的,并且不应被解释为需要通过任何特定方法产生抗体。例如,根据本公开使用的单克隆抗体可以通过Kohler& Milstein, *Nature*, 256:495 (1975) 首次描述的杂交瘤方法制备,或者可以通过重组DNA方法制备(参见,例如美国专利第4,816,567号)。

[0048] 单克隆抗体可以包括“嵌合”抗体(免疫球蛋白),其中重链和/或轻链的一部分与衍生自特定物种或属于特定抗体类或亚类的抗体中的相应序列相同或同源,而链的剩余部分与衍生自另一物种或属于另一抗体类或亚类的抗体以及此类抗体的片段中的相应序列相同或同源,只要它们表现出所需的生物学活性(美国专利第4,816,567号;和Morrison等人, *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 [1984])。

[0049] 单克隆抗体可以使用各种方法产生,包括小鼠杂交瘤或噬菌体展示(参见 Siegel, *Transfus. Clin. Biol.* 9:15-22 (2002) 综述) 或直接从原代B细胞的抗体的分子克隆(参见Tiller, *New Biotechnol.* 28:453-7 (2011))。在本公开内容中,通过用人PD-L1蛋白和在细胞表面瞬时表达人PD-L1的细胞免疫兔子产生抗体。已知兔子产生高亲和力、多样性和特异性的抗体(Weber等人, *Exp. Mol. Med.* 49:e305)。将来自免疫动物的B细胞体外培养并筛选抗PD-L1抗体的产生。使用重组DNA技术分离抗体可变基因,并重组表达所得抗体,并进一步筛选期望的特征,例如抑制PD-L1与PD-1结合的能力,与非灵长类PD-L1结合的能力和增强人T细胞活化的能力。这种抗体发现的一般方法类似于Seeber等人, *PLoS One* 9:e86184 (2014) 描述的方法。

[0050] 术语“抗原或表位结合部分或片段”是指能够结合抗原(在这种情况下是CD19)的抗体片段。这些片段可以具有抗原结合功能和完整抗体的其它功能。结合片段的实例包括但不限于单链Fv片段(scFv)或Fab片段,所述单链Fv片段(scFv)由通过合成接头连接在单一多肽链中的抗体的单臂的VL和VH结构域组成,所述Fab片段是由VL、恒定轻链(CL)、VH和恒定重链1(CH1)结构域组成的单价片段。抗体片段可以是甚至更小的亚片段,并且可以由与单个CDR结构域一样小的结构域,特别是来自VL和/或VH结构域的CDR3区组成(例如参见Beiboer等人, *J. Mol. Biol.* 296:833-49 (2000)) 使用本领域技术人员已知的常规方法产生抗体片段。可以使用与完整抗体使用的相同技术筛选抗体片段的效用。

[0051] “抗原-或表位-结合片段”可以通过许多本领域已知的技术衍生自本公开的抗体。例如,纯化的单克隆抗体可以用酶例如胃蛋白酶切割,并进行HPLC凝胶过滤。然后通过膜过滤等收集并浓缩含有Fab片段的合适部分。关于分离抗体的活性片段的一般技术的进一步描述,参见例如Khaw, B. A. 等人, *J. Nucl. Med.* 23:1011-1019 (1982); Rousseaux等人, *Methods Enzymology*, 121:663-69, Academic Press, 1986。

[0052] 抗体的木瓜蛋白酶消化产生两个相同的抗原结合片段,称为“Fab”片段,每个片段具有单个抗原结合位点,和残余的“Fc”片段,其名称反映了其容易结晶的能力。胃蛋白酶处理产生具有两个抗原结合位点并且仍然能够交联抗原的F(ab')₂片段。

[0053] Fab片段可以含有轻链的恒定结构域和重链的第一恒定结构域(CH1)。Fab'片段与Fab片段的不同在于在重链CH1结构域的羧基端添加了几个残基,包括来自抗体铰链区的一个或多个半胱氨酸。Fab'-SH在本文中是指其中恒定结构域的半胱氨酸残基带有游离巯基的Fab'。F(ab')₂抗体片段最初作为Fab'片段对产生,Fab'片段之间具有铰链半胱氨酸。其

它抗体片段的化学偶联也是已知的。

[0054] “Fv”是含有完整抗原识别和结合位点的最小抗体片段。该区域由一个重链和一个轻链可变结构域以紧密的、非共价缔合的二聚体组成。在这种配置中,每个可变结构域的三个CDR相互作用以在VH-VL二聚体的表面上限定抗原结合位点。6个CDR共同赋予抗体抗原结合特异性。然而,即使是单个可变结构域(或者仅包含三个对抗原特异的CDR的Fv的一半)也具有识别和结合抗原的能力,尽管亲和力低于整个结合位点。

[0055] 来自任何脊椎动物物种的抗体(免疫球蛋白)的“轻链”可基于其恒定结构域的氨基酸序列而分配至称为 κ 和 λ 的两种明显不同类型中的一种。

[0056] 根据免疫球蛋白重链恒定结构域的氨基酸序列,免疫球蛋白可分为不同的类别。有五种主要类型的免疫球蛋白:IgA、IgD、IgE、IgG和IgM,并且这些中的一些可以进一步分为亚类(同种型),例如,IgG-1、IgG-2、IgG-3和IgG-4;IgA-1和IgA-2。对应于不同免疫球蛋白类别的重链恒定结构域分别称为 α 、 δ 、 ϵ 、 γ 和 μ 。不同类别免疫球蛋白的亚单位结构和三维配置是熟知的。

[0057] “人源化抗体”是指一类工程抗体,其CDR衍生自非人供体免疫球蛋白,分子的其余免疫球蛋白衍生部分衍生自一种(或多种)人免疫球蛋白。此外,可改变构架支持残基以保持结合亲和力。获得“人源化抗体”的方法是本领域技术人员熟知的。(参见,例如,Queen等人,Proc.Natl Acad Sci USA,86:10029-10032(1989),Hodgson等人,Bio/Technology,9:421(1991))。

[0058] 如本文所用,术语“多肽”、“肽”和“蛋白质”可互换并且定义为意指由通过肽键连接的氨基酸组成的生物分子。

[0059] 如在此使用的术语“一个”、“一种”和“该”被定义为意指“一个或多个”并且包括复数,除非上下文不适当。

[0060] “分离的”是指不含其天然存在的至少一些组分的生物分子。“分离的”当用于描述本文公开的各种多肽时,意指已经从其表达的细胞或细胞培养物鉴定和分离和/或回收的多肽。通常,分离的多肽将通过至少一个纯化步骤制备。“分离的抗体”是指基本上不含具有不同抗原结合特异性的其它抗体的抗体。

[0061] “重组”意指使用重组核酸技术在外源宿主细胞中产生抗体。

[0062] 术语“抗原”是指可以在生物体,特别是动物,更特别是哺乳动物(包括人)中诱导免疫应答的实体或其片段。该术语包括免疫原及其负责抗原性或抗原决定簇的区域。

[0063] 此外,如本文所用,术语“免疫原性的”是指引起或增强针对免疫原性剂的抗体、T-细胞或其它反应性免疫细胞的产生并且有助于人或动物中的免疫应答的物质。当个体针对所施用的本公开的免疫原性组合物产生足够的抗体、T-细胞和其它反应性免疫细胞以减轻或缓解待治疗的病症时,发生免疫应答。

[0064] “特异性结合”或“特异性结合至”或“特异性于”特定抗原或表位是指可测量地不同于非特异性相互作用的结合。特异性结合可以例如通过测定分子与对照分子的结合的结合来测量,所述对照分子通常是不具有结合活性的类似结构的分子。例如,特异性结合可以通过与类似于靶的对照分子竞争来测定。

[0065] 例如,对特定抗原或表位的特异性结合可以由对抗原或表位具有至少约 10^{-4} M、至少约 10^{-5} M、至少约 10^{-6} M、至少约 10^{-7} M、至少约 10^{-8} M、至少约 10^{-9} M、或者至少约 10^{-10} M、至少约

10^{-11} M、至少约 10^{-12} M或更大KD的抗体来显示,其中KD指特定抗体-抗原相互作用的解离速率。通常,特异性结合抗原的抗体对于对照分子将具有相对于抗原或表位为20-、50-、100-、500-、1000-、5,000-、10,000-或更多倍的KD。

[0066] 此外,例如,通过对于抗原或表位具有相对于对照为该表位的至少20-、50-、100-、500-、1000-、5,000-、10,000-或更多倍的KA或Ka的抗体,可以表现出对于特定抗原或表位的特异性结合,其中KA或Ka是指特定抗体-抗原相互作用的结合速率。

[0067] 通过序列同一性确定两个序列之间的“同源性”。如果待比较的两个序列长度不同,则序列同一性优选是指与较长序列的核苷酸残基相同的较短序列的核苷酸残基的百分比。可以使用计算机程序常规地确定序列同一性。在给定序列与本公开的上述序列之间的比较中出现的偏差可以由例如添加、缺失、取代、插入或重组引起。

[0068] 通过参考以下对本文包括的具体实施方案和实施例的详细描述,可以更容易地理解本公开。尽管已参考本公开的某些实施方案的特定细节描述了本公开,但并不希望这些细节应视为对本公开的范围的限制。

[0069] 在先前的公开中,通过细胞因子信号传导途径解决CAR耗竭以驱动扩增而没有末端分化。本文所公开的组合物和使用方法涉及用于人工免疫监测嵌合抗原受体的AI-CAR载体。该AI-CAR技术的进步旨在替代标准CAR制造并实现有效的“组合”和护理点治疗。虽然其它CAR技术可能需要可溶性细胞因子生长因子的表达和/或持续活性的多次给药以产生完全且持久的应答,但AI-CAR载体掺入了这些活性并能够在不存在增殖的组成型活性驱动物或持久抗肿瘤应答的多次CAR给药的情况下产生有效且持续的CAR细胞。

[0070] 第二,在保持与标准CAR相同功能的同时,AI-CAR信号传导增加了制造CAR细胞的效率。AI-CAR在体外和体内可能仅需要一种靶抗原以获得完全增殖和细胞毒活性。在本文中,由于标准CAR-T细胞的扩增通常需要使用生长因子和aAPC的组合来制造,所以AI-CAR可以显著降低制造成本。

[0071] 第三,在体内肿瘤细胞的AI-CAR接合后,可以诱导由整合的AI-CAR载体编码的几种抗肿瘤基因的表达。这些内源基因的表达可以使患者产生更广泛地靶向不同肿瘤抗原例如新抗原的抗肿瘤应答。例如,STAT5报告系统用于在人T细胞中诱导STAT5响应性基因(Kanai等人,2014;Zeng等人,2016;Bednorz等人,2011;以及Fang等人,2008)。该特征是独特的,因为标准CAR构建体通常不能诱导基因表达。与这些辅助因子一起,AI-CAR将成为为癌症护理点治疗提供实用、经济和有效解决方案的平台技术。许多形式的癌症可以存在于免疫抑制的肿瘤环境中。AI-CAR将是高度合乎需要的,因为AI-CAR载体经设计以表达额外的抗癌基因,所述抗癌基因可降低肿瘤免疫抑制并激活患者的抗肿瘤免疫应答。AI-CAR的独特特征之一是其在肿瘤位点调节相关抗肿瘤基因的表达的能力,而不是使它们组成型表达,这可能是有毒的。另一特征是AI-CAR经设计以在施用时具有单剂量,接着具有其长期活性和较大功效。具有这些有利特征,AI-CAR对于市场上未得到满足的挑战是更好的解决方案,其预示治疗大多数(如果不是所有)类型的癌症的功效。

[0072] 关于用于治疗血液癌症的CAR疗法,靶包括CD19和CD22、CD20、CD9、CD38,其可通过使用非病毒DNA载体或RNA-CAR(瞬时)的双重双特异性AI-CAR靶向。以这种方式,AI-CAR可用作移植或更持续性的瞬时治疗桥。此外,AI-CAR可用作诱导针对新抗原的宿主抗肿瘤免疫应答的定点护理治疗。

[0073] 此外,对于某些实体瘤,可以应用编码AI-CAR组合治疗的RNA。对于其他治疗失败的侵袭性肿瘤,由于RNA的高电穿孔效率,现成的RNA CAR可以有效且快速地制造。由RNA AI-CAR瞬时表达的多种抗肿瘤机制,如诱导的AI-CAR载体基因,应当能够实现更有效和更安全的抗肿瘤活性并潜在地诱导患者免疫应答。多剂量RNA AI-CAR可作用在用某些持续性AI-CAR细胞治疗之前测定功效的桥梁。

[0074] 实施例

[0075] 实施例1.用于持续和联合治疗的AI-CAR载体的构建

[0076] AI-CAR细胞的目的是通过在静止状态下持续、长期的免疫监视直至被肿瘤细胞刺激来提高癌症免疫治疗的功效。肿瘤刺激后,诱导型AI-CAR基因能够进行涉及抗肿瘤活性的其它机制的局部安全且更有效的“组合”治疗。对于更高频率的完全和持久应答,预期刺激患者的抗肿瘤应答。

[0077] 通常,AI-CAR构建体由非病毒载体(pPI)如基于转座子的整合系统中的AI-CAR表达盒组成(Ivics和Izsvák,2010;Z Cooper等人,US9,629,877;Uckert等人,US20190071484A1)。如图1所示,AI-CAR载体包含诱导型基因表达单元和CAR表达单元,即侧翼为转座子末端反向重复(IR)的AI-CAR表达盒。可以用STAT、NFAT或NF- κ B诱导型启动子,通过IRES或自身切割核糖体跳跃肽如P2A或T2A(例如SEQ ID 18-21)连接的一个或多个基因的编码区,以及随后的polyA信号序列构建AI-CAR表达盒。这之后可以是用于组成型表达一个或两个CAR的另一个启动子,其之后是另一个polyA信号。AI-CAR链对的实例参见SEQ ID 1和2、3和4、5和6、7和8、9和10。两个编码区可以位于两个转座子或用于整合的病毒末端重复序列(IR)之间。或者,AI-CAR构建体的编码区可使用锌指、TALEN或CRISPR/Cas9核酸酶整合在特定基因组位点(Eyquem2017)。

[0078] 如图2所示,T细胞表面上一个或两个CAR的组成型表达在肿瘤处与肿瘤相关抗原结合。所述AI-CAR诱导型基因的表达,实现抗肿瘤活性的安全且多重机制和宿主抗肿瘤应答的有效刺激。理想地,这些基因的表达将在AI-CAR与肿瘤抗原或肿瘤微环境(TME)内的抗原接合后被诱导。为了延伸这些基因的库,可以从第二载体表达第二AI-CAR链。

[0079] AI-CAR非病毒载体的组成至少有一些灵活性,例如piggyBac、Tol2和Sleeping Beauty(Ivics和Izsvák,2010)。另外,AI-CAR可表达安全开关,例如截短的EGFR(tEGFR),其可被FDA批准的抗体西妥昔单抗靶向用于消除。或者,安全靶可以是截短的CD20,其可被利妥昔单抗靶向用于CAR细胞消除。AI-CAR载体可表达shRNA,所述shRNA例如抑制内源TCR以使得能够产生通用AI-CAR细胞。

[0080] 作为诱导型启动子的替代,AI-CAR可包括弱启动子,例如经修饰的PGK启动子,以安全表达其它抗肿瘤活性机制。

[0081] 实施例2.单和双重AI-CAR设计

[0082] 设计单或双重AI-CAR以通过细胞因子受体途径发信号以获得更大的CAR细胞持续性并诱导载体编码的基因以获得额外的抗肿瘤机制和增强的功效。此外,简单接合AI-CAR可促进有效的AI-CAR扩增,并且可用于制造以简化给药前的体外扩增。

[0083] 用IL12、IL7、IL21或IL15细胞因子受体结构域构建双重AI-CAR以使载体基因能够持续和诱导以用于额外的抗肿瘤机制。如表2所列,细胞因子内结构域融合至一个或多个TCR或TCR共刺激胞质区(也称为共刺激结构域),例如CD3 ζ 、CD28、CD137、CD27、OX40和ICOS。

例如,可以用由融合至茎和跨膜结构域以及IL12 β 1链的细胞内(内)结构域和CD3 ζ 的片段的肿瘤抗原特异性scFv组成的一种CAR构建双重AIL-CAR。第二CAR可由融合至茎和跨膜结构域的肿瘤抗原特异性scFv、共同 β 2链内结构域的片段和CD137共刺激内结构域组成。

[0084] AI-CAR可通过转录因子如STAT4诱导基因表达。IL12 β 1链具有Ty2k结合位点,而 β 2链具有JAK2结合位点。两条链的结合可以通过与邻近靶抗原或与相同肿瘤靶抗原的两个不同但邻近的表位结合来稳定。当CAR与肿瘤抗原结合时,Ty2k和JAK2将磷酸化 β 链并最终磷酸化STAT4,然后STAT4二聚化并转位至细胞核。然后STAT4可以与启动子转录因子(TF)应答元件结合并促进基因表达的诱导。可以将可通过STAT4调节的启动子和下游基因掺入到CAR转座子或病毒载体中。一旦整合,这些基因可以在CAR细胞接合肿瘤或TME抗原之后被诱导。STAT4诱导的内源基因也支持CAR细胞持续性(DeRenzo 2019)。

[0085] 大多数双重AI-CAR组分是独立的功能单元,即抗肿瘤scFv、茎、跨膜结构域和内结构域,以及IL15、IL7和IL21链、CD3 ζ 和共刺激蛋白的不同片段,并且为了许多具体目的而进行替换。如表1和表2中所示的实例,可存在用于制造特定AI-CAR的许多组合。

[0086] 可以构建单特异性AI-CAR,使得CAR细胞持续性由CAR载体内编码的诱导型基因支持。AI-CAR可由靶向肿瘤或TME相关抗原的scFv、茎、跨膜结构域和共刺激CD137和CD3 ζ 内结构域组成。在接合具有肿瘤抗原活性的NFAT后,将产生结合至整合CAR载体内的应答元件的NFAT,所述应答元件诱导支持持续性的一种或多种基因(例如IL15、IL12和IL7)的表达以及抗肿瘤活性的其它机制。

[0087] 表2显示了编码具有持续性活性或抗肿瘤活性的蛋白质或miRNA的额外基因,例如抗免疫检查点抑制剂(ICI)、OX40激动剂、TLR激动剂、细胞因子、双特异性抗体、iPro、趋化因子和趋化因子受体,其可以被置于诱导型启动子的控制下。或者,编码这些蛋白(例如SEQ ID18-20)的mRNA可用AI-CAR载体共转染以瞬时表达。或者,编码CAR和这些蛋白的mRNA可用作瞬时、安全治疗的AI-CAR(SEQ ID 11-17)。瞬时表达这些基因的若干剂量的AI-CAR可足以降低肿瘤微环境中的免疫抑制并激活患者的抗肿瘤免疫应答。

[0088] 实施例3. 编码双特异性抗-CDH17和抗-TROP2 CAR的AI-CAR和用于持续性和增强的抗肿瘤应答的诱导型基因

[0089] 如图3所示,可以用NFAT诱导型启动子,由核糖体跳跃肽如T2A连接的一个或多个基因如抗PD-1、CCL21和IL7的编码区以及其后的polyA信号序列构建AI-CAR载体。这之后可以是靶向具有CD137和CD3 ζ 内结构域的CDH17和TROP2的单一双特异性CAR的启动子,之后是T2A、信号肽、tEGFR和polyA信号。两个编码区可以位于转座子或病毒末端重复序列(IR)之间用于整合。或者,可使用TALEN或CRISPR/Cas9(Eyquem2017)将AI-CAR表达盒整合在特定基因组位点处。

[0090] 实施例4. 肿瘤靶抗原的AI-CAR基因诱导

[0091] 重组和细胞肿瘤靶抗原用于在整合到T细胞系中后诱导AI-CAR载体基因。将在NFAT诱导型启动子控制下表达GFP的pPI-抗-CDH17-AI-CAR构建体电穿孔入Jurkat T细胞系。将该pBac转座子构建体与转座酶表达载体共同电穿孔以进行AI-CAR载体整合。将具有整合的pPI抗-CDH17 AI-CAR载体的T细胞系(Jurkat)在用0、1.25、2.5、5、10或20 μ g/ml CDH17-Fc包被的微量滴定孔中孵育(37 $^{\circ}$ C, 5%CO₂)2小时或14小时。pPI抗-CDH17 AI-CAR载体含有受NFAT诱导型启动子调节的GFP。在14小时时,通过流式细胞荧光测定法测定GFP表

达水平。GFP表达的水平相对于免疫培养物处理14小时时最大诱导的水平(抗-CD3、CD28和CD2;干细胞)。仅暴露2小时的CDH17,通过流式细胞术检测到低水平的GFP,如图4A所示。14小时后,相对于免疫培养物,CDH17暴露后GFP以浓度依赖性方式增加至70%。在未刺激的细胞中存在可接受水平的GFP。通过用0、1.25、5、10或20 μ g CDH17 RNA(每 10^7 细胞)电穿孔,在SW480细胞中以不同水平表达CDH17。通过标准流式细胞荧光测定法测定CDH17的表达,如图4B所示。将整合有pPI抗CDH17 AI-CAR载体的Jurkat系与表达不同水平CDH17的单层SW480一起温育2或14小时。在14小时时,通过流式细胞荧光测定法测定GFP表达水平。GFP表达水平相对于免疫培养14小时的最大诱导水平。如图4C所示,将AI-CAR暴露于表达Sw480的CDH17 2或14小时后,检测到相似水平的GFP诱导(50-80%)。因此,表达靶抗原的肿瘤细胞似乎有效地诱导AI-CAR载体基因表达。因此,该AI-CAR构建体可用于在肿瘤位点表达具有抗肿瘤活性的蛋白以安全和增强肿瘤杀伤。

[0092] 实施例5. 双重AI-CAR的表达

[0093] 显示了双链双重AI-CAR的表达和结合活性。在CHO细胞中表达双重AI-CAR,一个具有IL15 β 和CD28内结构域,另一个具有IL15 γ 和CD3 ζ 内结构域(SEQ ID 1和2)。并且如图5所示,通过用生物素化的蛋白质-L(对于scFv)染色测定单个链,pSh3C15b28和pSh3A4C15g3,或两个链的表达。也通过流式细胞术测定与肿瘤抗原,CDH17-Fc或TROP2-Fc的结合。使用抗生蛋白链菌素-藻红蛋白(对于蛋白质-L)和抗人IgG-Alexa647(对于CDH17和TROP2)测定表达和肿瘤抗原结合。这些结果表明可以容易地实现双重CAR的转染、表达和配体结合功能。

[0094] 实施例6. 支持AI-CAR增殖和持续性的iPro设计和表达

[0095] 可在单一AI-CAR中诱导增殖诱导剂(iPro)以支持增殖和持续性。iPro可以用N-末端细胞因子或结合TME抗原的scFv,随后是接头、茎、跨膜结构域和具有JAK家族和STAT结合位点的内结构域来构建,如图6A所示。在N-末端结构域与细胞因子受体或肿瘤抗原接合后,iPro可通过STAT发信号以诱导T或NK细胞蛋白的表达,所述T或NK细胞蛋白支持naïve和Tcm茎表型的存活和维持。具有N-末端细胞因子结构域,例如IL7、IL15或IL12。iPro可以支持双向由内向外和由外向内刺激,除了AI-CAR细胞外,其还激活患者T细胞和NK细胞。除了增强体内AI-CAR活性,iPro的表达可促进AI-CAR的内含子扩增以用于制造。

[0096] 通过流式细胞术在24小时而不是48小时检测到通过电穿孔其体外转录的mRNA在PBMC中瞬时表达的具有N-末端IL7的iPro(iPro7;SEQ ID 19)(图6B,左图)。在第2天,通过流式细胞术证明IL2受体CD25的诱导表达(图6C,中间图)。在没有进一步刺激的情况下,T细胞计数在10天内保持稳定,而模拟对照T细胞计数显著减少(图6D,右图)。这些结果表明,可设计AI-CAR诱导基因(例如iPro)的变体以支持AI-CAR增殖和持续性。

[0097] 参考文献

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[0102] 表

[0103] 表1列出了AI-CAR组合物的实例。可使用编码不同功能性片段的不同基因的片段来构建AI-CAR,所述功能性片段包括抗肿瘤相关抗原 (TAA) scFv、茎、跨膜结构域和内结构域。不同种类的内结构域可以例如在信号传导细胞因子受体增殖和存活应答或肿瘤细胞毒性应答中起作用。细胞因子受体,CD3 ζ 和共刺激内结构域可以以各种串联排列融合。

[0104]	功能结构域	靶或贡献者
	抗-肿瘤相关抗原	CDH17, TROP2, CD19, CD20, CD22, CD37, BCMA, CD48, EGFR, HER2, EpCAM, CEACAM5, PSMA, GD2, GPC3, FAPa, Claudin18.2
[0105]	茎	CD8、Fc 铰链、Fc CH2-CH3、TCR α 、TCR β 、截短的 IL7R α (CD127) 截短的 IL15R β (CD122)、IL15R α (CD215)、截短的 γ (CD132) 截短的 IL21R α (CD360)
	跨膜	CD8、CD28、CD3 ζ 、CD3 ϵ 、CD3 δ 、CD3 γ 、CD3 ζ 、TCR α 、TCR β 、IL15R β (CD122)、 γ (CD132)、IL7R α (CD127)、IL21R α (CD360)、IL15R α (CD215)、IL12R β 1、(CD212)、IL12R β 2
	细胞因子受体信号传导内结构域	IL15R β (CD122) 或截短的 β 、 γ (CD132) 或截短的 γ 、IL7R α (CD127)或截短的 CD127、IL15R α (CD215)或截短的 α 、IL21R α (CD360) 或截短的 CD360、IL12R β 1 (CD212)、IL12R β 2
	CD3 ζ 和共刺激信号传到内结构域	无, CD3 ζ ,CD28, CD137, OX40, CD27, ICOS

[0106] 表2列出了可掺入AI-CAR载体中的诱导型基因的实例。可选择这些基因以增强CAR定位至肿瘤(例如淋巴瘤),逆转肿瘤免疫抑制和刺激宿主免疫应答或用于直接抗肿瘤细胞活性。可将所述基因置于STAT5诱导型启动子的下游以避免长期组成型表达可能发生的任何毒性。或者,某些趋化因子和趋化因子受体基因和细胞因子,例如IL7可以位于弱启动子的下游。低水平的表达可以避免毒性。

[0107]	诱导基因	诱导功能
	OX40L (CD134L/CD252) 激动剂	树突细胞活化和成熟。活化和延长T _{eff} 存活时间的抑制T _{reg} 活性
	TLR 激动剂	树突细胞 (cDC/mDC) 例如肽或 scFv TLR4 激动剂 TLR4 的活化和成熟增加 MHC 1 类
	T 或 NK 细胞共刺激膜蛋白激动剂	对 CD137、ICOS、CD40、GITR、A3 腺苷受体、TNFR、NTB-A、NKP80、CD48、NKG2 特异性的激动剂 scFv
	细胞因子、iPro	IL-12、IL7、IL15、IL18、IL21、IFN γ iPro
	趋化因子和趋化因子受体	CCL5、CCL21、CXCL10、CCL19、XCL1、CXCL12、CXCL8、CXCL9、CXCL14、CLCL9；CCR2b、CCR3、CCR8、CCR9。CAR 和宿主 T 细胞、NK 细胞和树突细胞的募集。
	检查点抑制剂拮抗剂	例如，基于抗体的 CTLA4、PD-1、PD-L1/L2、TIGIT、TIM3、LAG3 的拮抗剂。逆转肿瘤免疫抑制
[0108]	多特异性抗体	抗肿瘤活性的其它机制 例如：双特异性抗体靶向 CDH17 和 CD3/NKG2D 或 TROP2 和 CD3/NKG2D/TRAILR2
	miRNA	AICD 降低，CAR 细胞细胞毒活性增加；抑制 ICI、miR-191、miR-19b、miR-20b、miR-138、miR-155、miR-181a-Sp、miR-19、iR-466a-3p

[0109] 序列表

[0110] SEQ ID NO:1

[0111] TROP2特异性AI-CAR (pSh3A4C15g3)

[0112] MEFGLSWVFLVALLRGVQCQVQLVQSGAEVKKPGASVKVSCKASGYTFTDFYMNWVRQAPGQGLEWMGR
VNPSNGDTNYNQKFKGRVTSTRDTSISTAYMELSRRLSDDTAVYYCARERIYYGISWYFDVWDTGTTVTVSSGGGGS
GGGSGGGGSDIQMTQSPSSLSASVGDRVITICRASGNIHNYLAWYQQKPGKAPKLLLYNAKTLAEGVPSRFSGSGS
GTDYTLTISSLQPEDFATYYCHHYYSTPPTFGQGTKLEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDAVVISVGSMLIIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVSKGLAESLQPDYSE
RLCLVSEIPPKGALGEGPGASPCNQHSPYWAPPCYTLKPETRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPP
R

[0113] SEQ ID NO:2

[0114] CDH17特异性AI-CAR (pSh3C15b28)

[0115] MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSDYYMYWVRQAPGKGLEWVA
SISFDGTYTYTYTDRVKGRFTISRDNKNTLYLQMNLSRAEDTAVYYCARDPAWFPYWGQGLTVTVSAGGGGSGGG
GSGGGGSGDIVMTQTPLSLSVTPGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVDPDRFS
GSGSGTDFTLKISRVEAEDVGYYCFQGSHVPLTFGAGTKLELKGAPTTTPAPRPPTPAPTIASQPLSLRPEACRP
AAGGAVHTRGLDFAADIPWLGHLLVGLSGAFGFIILVYLLINCRNTGPWLKKVLKNTDPDSKFFSGLSSEHGGDV
QKWLSSFPSSSFSPGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLSCTFTNQGYFFFHLPDALEIE
ACQVYFRSKRSRGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS P

[0116] SEQ ID NO:3

[0117] h2FM19AIg3z (CD19特异性AI-CAR-g3z)

[0118] MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSQTLSTCTVSGVSLPDYGVSWIRQHPGKGLEWIGV
IWGSETTYNSALKSRVTISVDTSKNQFSLKSSVTAADTAVYYCARHYGGSYAMDYWGQGLTVTVSSGGGGSGG
GGSGGGGSDIQTQSPSSLSASVGDRVTITCRASQDISKYNWYQQKPGGAPKLLIYHTSRLHSGVPSRFSGSGSGT
DFTFTISSLQQEDIATYYCQQGNTLPYTFGGGKTKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGAVH
TRGLDFAADAVVISVGSMLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVSKGLAESLPDYSERL
CLVSEIPPKGKGGALGEGPGASPCNQHSPLYWAPPCTYLPETRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK
RRGRDPEMGGKPKRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKGDGLYQGLSTATKDTYDALHMQUALPPR

[0119] SEQ ID NO:4

[0120] hAT38AIa7 (CD38特异性, AI-CAR-a7)

[0121] MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSQTLSTCTVSGFTFTSYGVHWVRQPPGRGLEWIGV
MWRGGSTDYNAAFMSRVTMLVDTSKNQFSLRLSSVTAADTAVYYCAKSMITTFVMDSWGQGLTVTVSSGGGGSGGG
GSGGGGSDIQTQSPSSLSASVGDRVTITCKASEDIYNRLTWYQQKPGKAPKLLISGATSLETGVPSRFSGSGSGTD
FTFTISSLPEDIATYYCQQYWSNPYTFGQGTKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGAVHT
RGLDFAADPILLTISILSFFSVALLVILACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSNPESFLDCQI
HRVDDIARDEVEGFLQDTPFPQQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNVSACDAPILSSS
RSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPPFSLQSGILTLNPVAQQQPILTSLSGNQEEAYVTMSSFYQNQ

[0122] SEQ ID NO:5

[0123] h81AIaI7 (CD81特异性, AI-CAR-a7)

[0124] MKHLWFFLLLVAAPRWVLSQVQLVQSGAEVKKPGASVKVSCKASGYTFSSWMNWVRQAPGQRLEWMG
RIYSGDGDAIYNGKFKGRVTITADTSASTAYMELSSLRSEDTAVYYCAREGKTGDLRLSWGQGLTVTVSSGGGGG
GGGGSGGGGSDIVMTQSPDSLAVSLGERATINCRASKSVSTSIYSYMHWYQQKPGQPPKLLIYYASYLESVPDRF
SGSGSGTDFTLTISSLQAEDVAVYYCEHSREFPFTFGQGTKLEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASR
PAAGGAVHTRGLDFAADPILLTISILSFFSVALLVILACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSN
NPESFLDCQIHRVDDIARDEVEGFLQDTPFPQQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNV
SACDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPPFSLQSGILTLNPVAQQQPILTSLSGNQEEAYV
TMSSFYQNQSEQ ID NO:6

[0125] hRF22AIgC7 (CD22特异性, AI-CAR-gC7)

[0126] MKHLWFFLLLVAAPRWVLSQVQLVESGGGLVQPGGSLRLSCAASGFAFSIYDMSWVRQAPGKGLEWVSY
ISSGGGTYYPDYTKGRFTISRDNKNSLYLQMNLSRAEDTAVYYCARHSGYGSYGVLFAYWGQGLTVTVSSGGGGG
GGGGSGGGGSDIQTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSILHSGVPSRFSGSGS

GTDFTFITSSSLQQEDIATYYCQQGNTLPWTFGGGKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGA
VHTRGLDFAADIPWLGHLVLVGLSGAFGFIILVYLLINCRNTGPWLKKVLKCNTPDPSKFFSLSSEHGQDVQKWLSS
PFPSSSFSPGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLSCTFNQGYFFFHLPDALEIEACQVYFR
SKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSP

[0127] SEQ ID NO:7

[0128] h2FM19b1AI3z (CD19特异性AI-CAR-IL12b1 CD137-CD3z)

[0129] MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSQTLSTCTVSGVSLPDYGVSWIRQHPGKGLEWIGV
IWGSETTYNSALKSRVTISVDTSKNQFSLKSSVTAADTAVYYCARHYYYGGSYAMDYWGQGLTVTVSSGGGGSGG
GGSGGGGSDIQTQSPSSLSASVGDRVTITCRASQDISKYLNWYQQKPGGAPKLLIYHSTRLSHSGVPSRFSGSGSGT
DFTFTISSSLQQEDIATYYCQQGNTLPYTFGGGKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGAVH
TRGLDFAADWLIFASLGSFLSILLVGVGLGYNLAARHLCPPLPTPCASSAIEFPGGKETWQWINPVDFQEEASL
QEALVVEMSWDKGERTEPLEKTELPEGAPELALDTELSLEDGDRCKAKMKRGRKKLLYIFKQPFMRPVQTTQEEDGC
SCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRRGRDPEMGGKPQRRKNPQEGLYNEL
QKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

[0130] SEQ ID NO:8

[0131] hAT38bAI2 (CD38特异性, AI-CAR-IL12b2)

[0132] MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSQTLSTCTVSGFTFTSYGVHWVRQPPGRGLEWIGV
MWRGGSTDYNAAFMSRVTMLVDTSKNQFSLRLSSVTAADTAVYYCAKSMITTFVMDSWGQGLTVTVSSGGGGSGGG
GSGGGGSDIQTQSPSSLSASVGDRVTITCKASEDIYNRLTWYQQKPGKAPKLLISGATSLETGVPSRFSGSGSGTD
FTFTISSLPEDIATYYCQQYWSNPYTFGQGTKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGAVHT
RGLDFAADWMAFVAPSICIAIIMVGIFSTHYFQQKVFLLAALRPQWCSREIPDPANSTCAKKYPIAEKTQLPLDR
LLIDWPTPEDPEPLVISEVLHQVTPVFRHPPCSNWPQREKGIQGHQASEKMMHSASSPPPPRALQAESRQLVDLYK
VLESRGSDPKPENPACPWTVLPAGDLPTHGGLPSNIDDLPSHEAPLADSLEELEPQHISLSVFPSSSLHPLTFSCG
DKLTLDQLKMRCDSLML

[0133] SEQ ID NO:9

[0134] h5AIg137.3z (CDH17特异性AI-CAR γ /CD137/CD3z)

[0135] MEFGLSWVFLVALLRGVQCQVQLVQSGAEVKKPGASVKVSCKVSAYAFSSSWMNWVRQAPGKGLEWMGR
IYPRDGDNTYNGKFKGRVTMTADTSTDYAMELSSLRSEDTAVYYCAREGDGYYWYFDVWGQGTITVTVSSGGGGSGG
GGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSIRNYLHWYQQKPGAPRLLIYYASQSIGIPARFSGSGSGT
DFTLTISSLETEDFAMYYCQHSNSWPLTFGQGTKLEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEASRPAAGGAVH
TRGLDFAADAVVISVGSMLIIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVSKGLAESLQPDYSERL
CLVSEIPPKGALGEGPGASPCNQHSPLYWAPPCTYLPETKRGKRLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEE
GGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAY
SEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

[0136] SEQ ID NO:10

[0137] h10AIa7 (CDH17特异性a7)

[0138] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPDYTKDRFTISRDNKNTLYLQMNSLRRAEDTAVYYCSSYTNLGAYWGQGLTVTVSAGGGGSGGGSGG
GGGSDIQTQSPSSLSASVGDRVTITCRASQDISGYLNLWYQQKPGGAIKRLIYTTSTLDSGVPKRFSGSGSGTDFTL

TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTTAPRPPTPAPTIASQPLSLRPEASRPAAGGAVHTRG
LDFAADPILLTISILSFFSVALLVILACVLWKKRIKPIVWPSPLDHKKTLEHLCKKPRKNLNVSNPESFLDCQIHR
VDDIQARDEVEGFLQDTPPQQLEESEKQRLGGDVQSPNCPSDDVVITPESFGRDSSLTCLAGNVSACDAPILSSRS
LDCRESGKNGPHVYQDLLLLSLGTTNSTLPPFSLQSGILTLNPVAGGQPIILSLGSNQEEAYVTMSSFYQNQ

[0139] RNA AI-CAR的实例

[0140] SEQ ID NO:11

[0141] h10C7-P2A-IL18 (CDH17 CAR-IL18)

[0142] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶TLTVSAGGGGSGGGGSG
GGGSDIQMTQSPSSLSASVGD⁷RVTITCRASQDISGYLN⁸WLQQKPGGA⁹IKRLIYTTSTLD¹⁰SGVPKR¹¹FSGSGSGTDFTL
TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVL¹²DKRRGRDPEMGGK¹³QRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCYFGK
LESKLSVIRNLNDQVLFIDQGNRPLFEDMTSDCDRNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKII
SFKEMNPPDNIKDTKSDIIFQ¹⁴RSVPGHDNKM¹⁵QFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQ¹⁶NED

[0143] SEQ ID NO:12

[0144] h10C7-P2A-INF γ (CDH17 CAR-INF γ)

[0145] -MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWV
AVIDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶TLTVSAGGGGSGGGG
SGGGGSDIQMTQSPSSLSASVGD⁷RVTITCRASQDISGYLN⁸WLQQKPGGA⁹IKRLIYTTSTLD¹⁰SGVPKR¹¹FSGSGSGTD
FTLT¹²TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR
GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF
SRSADAPAYQQGQNQLYNELNLGRREEYDVL¹³DKRRGRDPEMGGK¹⁴QRRKNPQEGLYNELQKDKMAEAYSEIGMKGER
RRGKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMKHLWFFLLLVAAPRWLSQD
PYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMN
KFFNSNKKKRDDFEKL¹⁵TNYSVTDLNVQRKAIHEL¹⁶IQVMAELSPA¹⁷AKTGKRKRSQMLFRGRRASQ

[0146] SEQ ID NO:13

[0147] h10C7-P2A-IL18-pro-CCL21 (CDH17 CAR-IL18-proCCL21)

[0148] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶TLTVSAGGGGSGGGGSG
GGGSDIQMTQSPSSLSASVGD⁷RVTITCRASQDISGYLN⁸WLQQKPGGA⁹IKRLIYTTSTLD¹⁰SGVPKR¹¹FSGSGSGTDFTL
TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVL¹²DKRRGRDPEMGGK¹³QRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCYFGK
LESKLSVIRNLNDQVLFIDQGNRPLFEDMTSDCDRNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKII
SFKEMNPPDNIKDTKSDIIFQ¹⁴RSVPGHDNKM¹⁵QFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQ¹⁶NEDP
AGGGTKTESSSRSDGGAQDCCLKYSQRKIPAKVVR¹⁷SYRKQEP¹⁸SLGCSIPA¹⁹ILFLPRKRSQAELCADPKELWVQQLMQ

HLDKTPSPQKPAQGCRCRASKTGKKGKSGCKRTERSQTPKGP

[0149] SEQ ID NO:14

[0150] h10C7-P2A-h8C7-P2A-IL18 (CDH17 CAR-TROP2CAR-IL18)

[0151] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶GLTVTSAGGGGSGGGGSG
GGGSDI⁷QMTQSPSSLSASV⁸GDRVTITCRASQ⁹DISGYLN¹⁰WLQQK¹¹PGGA¹²IKRLI¹³YTTSTL¹⁴D¹⁵SGVPK¹⁶RFSGSGSGTDFTL
TISSLQ¹⁷SEDFATYYCL¹⁸QYASSP¹⁹FTFGGGTK²⁰VEIKGAP²¹TTTPAPRPPTPAPT²²IASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVL²³DKRRGRDPEMGGK²⁴PQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCEVQL
VESGGGLVQPGGSLRLSCAASGFTFSTYTMSWVRQTPAKGLVWVSTINS²⁵DGYNIYSDSMKGRFTISRDN²⁶AKYTLYL
QMN²⁷SLRAEDTAMYYCARCSYYSYDYFDYWGQ²⁸GLTVTVSSGGGGSGGGGSGGGGSDI²⁹QMTQSPSSLSASV³⁰GDRVTITC
RASENIDNYLAWYQQKQKGV³¹PKLLIYAATNLADGMPSRFSGSGSGTDFTLT³²ISSLQ³³PEDVATYYCQHYYSNQLTFGQ
GTKLEIKGAP³⁴TTTPAPRPPTPAPT³⁵IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYD
VL³⁶DKRRGRDPEMGGK³⁷PQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL
PPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCYFGKLESKLSVIRNLNDQVLFIDQGNRPLFE
DMTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFQRSVPG
HDNKMQFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQ³⁸NED

[0152] SEQ ID NO:15

[0153] h10C7-P2A-h3U1 (CDH17 CAR-双特异性抗体抗-CDH17xCD3)

[0154] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶GLTVTSAGGGGSGGGGSG
GGGSDI⁷QMTQSPSSLSASV⁸GDRVTITCRASQ⁹DISGYLN¹⁰WLQQK¹¹PGGA¹²IKRLI¹³YTTSTL¹⁴D¹⁵SGVPK¹⁶RFSGSGSGTDFTL
TISSLQ¹⁷SEDFATYYCL¹⁸QYASSP¹⁹FTFGGGTK²⁰VEIKGAP²¹TTTPAPRPPTPAPT²²IASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVL²³DKRRGRDPEMGGK²⁴PQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCQVQL
VESGGGVVQPG²⁵RSRLSCAASGFTFSDYYMYWVRQAPGKGLEWVASISFDGTYTYTDRVKG²⁶RFTISRDN²⁷SKNTLYL
QMN²⁸SLRAEDTAVYYCARD²⁹PAWFPYWGQ³⁰GLTVTVSAGGGGSGGGGSGGGGSGDIVMTQTPLSLSVTPGQPASISCRS
SQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVS³¹NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLT
FGAGTKLELKPAGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYSTGYTMNWVRQAPGKGLEWVALINPYKGVST
YNQKFKDRFTISVDKSKNTAYLQMN³²SLRAEDTAVYYCARSGYYGDSWDYFDVWGQ³³GLTVTVSSGGGGSGGGGSGGGG
SDI³⁴QMTQSPSSLSASV³⁵GDRVTITCRASQ³⁶DIRNYLNWYQQKPGKAPKLLIYYTSRLES³⁷GVPSRFSGSGSGTDYTLTIS
SLQPEDFATYYCQQGNTLPWTFGQGTKVEIK

[0155] SEQ ID NO:16

[0156] h10C7-P2A-h3U1-pro-IL18 (CDH17 CAR-双特异性抗体抗-CDH17xCD3-pro-IL18)

[0157] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKGLEWVAV
IDSNGGSTYYPD¹TVKDRFTISRDN²SKNTLYLQMN³SLRAEDTAVYYC⁴SSYTNL⁵GAYWGQ⁶GLTVTSAGGGGSGGGGSG

GGGSDIQMTQSPSSLSASVGDRVITITCRASQDISGYLNWLQQKPGGAIKRLIYTTSTLD SGVPKRFSGSGSGTDFTL
TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCQVQL
VESGGGVVQPGRSLRLSCAASGFTFSDYYMYWVRQAPGKGLEWVASISFDGTYTYTDRVKGRFTISRDN SKNTLYL
QMNSLRAEDTAVYYCARDPAWFPYWGQGLVTVSAGGGGSGGGGSGGGGSGDIVMTQTPLSLSVTPGQPASISCRS
SQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLT
FGAGTKLELKPAGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYSTGYTMNWVRQAPGKGLEWVALINPYKGVST
YNQKFKDRFTISVDKSKNTAYLQMNSLRAEDTAVYYCARSGYYGDSWYFDVWGQGLVTVSSGGGGSGGGGSGGGG
SDIQMTQSPSSLSASVGDRVITITCRASQDIRNYLNWYQQKPGKAPKLLIYTSRLESGVPSRFSGSGSGTDYTLTIS
SLQPEDFATYYCQQGNTLPWTFGQGTKVEIKPAGGGTKTESSSRGYFGKLESKLSVIRNLNDQVLFIDQGNRPLFED
MTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIIISFKEMNPPDNIKDTKSDIIFFQRSVP GH
DNKMQFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNE D

[0158] SEQ ID NO:17

[0159] h10C7-P2A-h3U1-pro-IL18-pro-XCL1 (CDH17 CAR-双特异性抗体抗-CDH17xCD3-
proIL18-proXCL1)

[0160] MEFGLSWVFLVALLRGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQTPGKLEWVAV
IDSNGGSTYYPD TVKDRFTISRDN SKNTLYLQMNSLRAEDTAVYYCSSYTNLGAYWGQGLVTVSAGGGGSGGGGSG
GGGSDIQMTQSPSSLSASVGDRVITITCRASQDISGYLNWLQQKPGGAIKRLIYTTSTLD SGVPKRFSGSGSGTDFTL
TISSLQSEDFATYYCLQYASSPFTFGGGTKVEIKGAPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL
DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSR
SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRASGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCQVQL
VESGGGVVQPGRSLRLSCAASGFTFSDYYMYWVRQAPGKGLEWVASISFDGTYTYTDRVKGRFTISRDN SKNTLYL
QMNSLRAEDTAVYYCARDPAWFPYWGQGLVTVSAGGGGSGGGGSGGGGSGDIVMTQTPLSLSVTPGQPASISCRS
SQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLT
FGAGTKLELKPAGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYSTGYTMNWVRQAPGKGLEWVALINPYKGVST
YNQKFKDRFTISVDKSKNTAYLQMNSLRAEDTAVYYCARSGYYGDSWYFDVWGQGLVTVSSGGGGSGGGGSGGGG
SDIQMTQSPSSLSASVGDRVITITCRASQDIRNYLNWYQQKPGKAPKLLIYTSRLESGVPSRFSGSGSGTDYTLTIS
SLQPEDFATYYCQQGNTLPWTFGQGTKVEIKPAGGGTKTESSSRGYFGKLESKLSVIRNLNDQVLFIDQGNRPLFED
MTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIIISFKEMNPPDNIKDTKSDIIFFQRSVP GH
DNKMQFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNE DSGGGTKTESSSRGVGSEVSDKRTC VSLTT
QRLPVSRIKTYTITEGSLRAVIFITKRGLKVCA

[0161] DPQATWVRDVVRSM DRKS NTRNNMIQTKPTGTQQSTNTAVTLTG

[0162] AI-CAR诱导型基因组合的实例

[0163] SEQ ID NO:18

[0164] h3U1-P2A-IL18 (双特异性抗体抗-CDH17xCD3-IL18)

[0165] MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSDYYMYWVRQAPGKGLEWVAS

ISFDGTYTYTDRVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRPAWFPYWGQGLVTVSAGGGGSGGGGS
GGGGSGDIVMTQTPLSLSVTPGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVS NRFSGVPDRFSGSG
SGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGAGTKLELKPAGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYS
FTGYTMNWVRQAPGKGLEWVALINPYKGVSTYNQKFKDRFTISVDKSKNTAYLQMNSLRAEDTAVYYCARS GYYGDS
DWYFDVWGQGLVTVSSGGGGSGGGSGGGGSDI QMTQSPSSLSASVGDRVITITCRASQDIRNYLNWYQQKPGKAPK
LLIYYTSRLES GVP SRFSGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPWTFGGGTKVEIKASGSGATNFSLLKQA
GDVEENPGPMEFGLSWVFLVALLRGVQCYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFII
SMYKDSQPRGMAVTISVKCEKISTLSCENKII SFKEMNPPDN IKDTKSDI IFFQRSVP GHDNKMQFESSSYEGYFLA
CEKERDLFKLILKKEDELGDRSIMFTVQNE D

[0166] SEQ ID NO:19

[0167] iPro7 (具有n-末端IL7的iPro)

[0168] MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKD GKQYESVLMVSI DQLLDSMKEIGSNCLNNEFNFFKR
HICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGT TILLNCTGQVKGRKPAALGEAQPTKSLEENKSLKE
QKKLNDLCFLKRLLEIKTCWNKILMGTKEHGGGSGGGSGAPT TTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKKPAGRNTGPWLKKVLKCNTPDP SKFFS QLSSEHG G DVQK WLS
SPFPSSSFSPGGLAPEISPLEVLERDKVTQLLLNTDAYLSLQELQGQDP

[0169] SEQ ID NO:20

[0170] iPro7-P2A-h3U1-P2A-IL18 (iProIL7-双特异性抗体抗-CDH17xCD3-IL18)

[0171] MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKD GKQYESVLMVSI DQLLDSMKEIGSNCLNNEFNFFKR
HICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGT TILLNCTGQVKGRKPAALGEAQPTKSLEENKSLKE
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GNRPLFEDMTDSDCRDNAPRTIFII SMYKDSQPRGMAVTISVKCEKISTLSCENKII SFKEMNPPDN IKDTKSDI IFF
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[0173] iPro7-P2A-h3U1-P2A-IL18-pro-CCL21 (iProIL7-双特异性抗体抗-CDH17xCD3-IL18-proCCL21)

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FGAGTKLELKPAGSGATNFSLLKQAGDVEENPGPMEFGLSWVFLVALLRGVQCYFGKLESKLSVIRNLNDQVLFIDQ
GNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIF
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[0266]	Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe	
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[0268]	Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr	
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[0270]	Cys Gln Gln Tyr Trp Ser Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys	
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[0276]	Ala Ser Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp		
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[0278]	Phe Ala Ala Asp Pro Ile Leu Leu Thr Ile Ser Ile Leu Ser Phe Phe		
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[0286]	Pro Glu Ser Phe Leu Asp Cys Gln Ile His Arg Val Asp Asp Ile Gln		
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[0333]	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly	Glu	Arg	Ala	Thr	Ile	Asn	
[0334]	165				170				175								
[0335]	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser	Ile	Tyr	Ser	Tyr	Met	His	
[0336]	180				185				190								
[0337]	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Tyr	
[0338]	195				200				205								
[0339]	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	
[0340]	210				215				220								
[0341]	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	
[0342]	225				230				235				240				
[0343]	Val	Ala	Val	Tyr	Tyr	Cys	Glu	His	Ser	Arg	Glu	Phe	Pro	Phe	Thr	Phe	
[0344]	245				250				255								
[0345]	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Gly	Ala	Pro	Thr	Thr	Thr	Pro	
[0346]	260				265				270								
[0347]	Ala	Pro	Arg	Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	
[0348]	275				280				285								
[0349]	Ser	Leu	Arg	Pro	Glu	Ala	Ser	Arg	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	
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[0353]	Ile Leu Ser Phe Phe Ser Val Ala Leu Leu Val Ile Leu Ala Cys Val
[0354]	325 330 335
[0355]	Leu Trp Lys Lys Arg Ile Lys Pro Ile Val Trp Pro Ser Leu Pro Asp
[0356]	340 345 350
[0357]	His Lys Lys Thr Leu Glu His Leu Cys Lys Lys Pro Arg Lys Asn Leu
[0358]	355 360 365
[0359]	Asn Val Ser Phe Asn Pro Glu Ser Phe Leu Asp Cys Gln Ile His Arg
[0360]	370 375 380
[0361]	Val Asp Asp Ile Gln Ala Arg Asp Glu Val Glu Gly Phe Leu Gln Asp
[0362]	385 390 395 400
[0363]	Thr Phe Pro Gln Gln Leu Glu Glu Ser Glu Lys Gln Arg Leu Gly Gly
[0364]	405 410 415
[0365]	Asp Val Gln Ser Pro Asn Cys Pro Ser Glu Asp Val Val Ile Thr Pro
[0366]	420 425 430
[0367]	Glu Ser Phe Gly Arg Asp Ser Ser Leu Thr Cys Leu Ala Gly Asn Val
[0368]	435 440 445
[0369]	Ser Ala Cys Asp Ala Pro Ile Leu Ser Ser Ser Arg Ser Leu Asp Cys
[0370]	450 455 460
[0371]	Arg Glu Ser Gly Lys Asn Gly Pro His Val Tyr Gln Asp Leu Leu Leu
[0372]	465 470 475 480
[0373]	Ser Leu Gly Thr Thr Asn Ser Thr Leu Pro Pro Pro Phe Ser Leu Gln
[0374]	485 490 495
[0375]	Ser Gly Ile Leu Thr Leu Asn Pro Val Ala Gln Gly Gln Pro Ile Leu
[0376]	500 505 510
[0377]	Thr Ser Leu Gly Ser Asn Gln Glu Glu Ala Tyr Val Thr Met Ser Ser
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[0379]	Phe Tyr Gln Asn Gln
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[0393]				35					40					45		
[0394]	Ser	Ile	Tyr	Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu
[0395]				50					55					60		
[0396]	Glu	Trp	Val	Ser	Tyr	Ile	Ser	Ser	Gly	Gly	Gly	Thr	Thr	Tyr	Tyr	Pro
[0397]				65					70					75		80
[0398]	Asp	Thr	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn
[0399]					85					90					95	
[0400]	Ser	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val
[0401]					100					105					110	
[0402]	Tyr	Tyr	Cys	Ala	Arg	His	Ser	Gly	Tyr	Gly	Ser	Ser	Tyr	Gly	Val	Leu
[0403]					115					120					125	
[0404]	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Gly	Gly	Gly
[0405]					130					135					140	
[0406]	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Gln	Met
[0407]															155	160
[0408]	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr
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[0413]					195					200					205	
[0414]	Ile	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly
[0415]															220	
[0416]	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Gln	Glu	Asp	Ile	Ala
[0417]																240
[0418]	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Trp	Thr	Phe	Gly	Gly
[0419]																255
[0420]	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Ala	Pro	Thr	Thr	Thr	Pro	Ala	Pro
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[0422]	Arg	Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu
[0423]																285
[0424]	Arg	Pro	Glu	Ala	Ser	Arg	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	Thr	Arg
[0425]																300
[0426]	Gly	Leu	Asp	Phe	Ala	Ala	Asp	Ile	Pro	Trp	Leu	Gly	His	Leu	Leu	Val
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[0428]	Gly	Leu	Ser	Gly	Ala	Phe	Gly	Phe	Ile	Ile	Leu	Val	Tyr	Leu	Leu	Ile

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[0432]	Thr	Pro	Asp	Pro	Ser	Lys	Phe	Phe	Ser	Gln	Leu	Ser	Ser	Glu	His	Gly
[0433]					355					360					365	
[0434]	Gly	Asp	Val	Gln	Lys	Trp	Leu	Ser	Ser	Pro	Phe	Pro	Ser	Ser	Ser	Phe
[0435]					370					375					380	
[0436]	Ser	Pro	Gly	Gly	Leu	Ala	Pro	Glu	Ile	Ser	Pro	Leu	Glu	Val	Leu	Glu
[0437]	385					390					395					400
[0438]	Arg	Asp	Lys	Val	Thr	Gln	Leu	Leu	Leu	Gln	Gln	Asp	Lys	Val	Pro	Glu
[0439]					405					410					415	
[0440]	Pro	Ala	Ser	Leu	Ser	Ser	Asn	His	Ser	Leu	Thr	Ser	Cys	Phe	Thr	Asn
[0441]					420					425					430	
[0442]	Gln	Gly	Tyr	Phe	Phe	Phe	His	Leu	Pro	Asp	Ala	Leu	Glu	Ile	Glu	Ala
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[0444]	Cys	Gln	Val	Tyr	Phe	Arg	Ser	Lys	Arg	Ser	Arg	Gly	Gly	His	Ser	Asp
[0445]					450					455					460	
[0446]	Tyr	Met	Asn	Met	Thr	Pro	Arg	Arg	Pro	Gly	Pro	Thr	Arg	Lys	His	Tyr
[0447]	465					470					475					480
[0448]	Gln	Pro	Tyr	Ala	Pro	Pro	Arg	Asp	Phe	Ala	Ala	Tyr	Arg	Ser	Pro	
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[0461]	Pro	Ser	Gln	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu
[0462]					35					40					45	
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[0464]					50					55					60	
[0465]	Glu	Trp	Ile	Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Asn	Ser
[0466]	65					70					75					80
[0467]	Ala	Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Glu

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[0469]	Phe	Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr		
[0470]					100					105					110			
[0471]	Tyr	Cys	Ala	Arg	His	Tyr	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr		
[0472]					115					120					125			
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[0475]	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Gln	Met	Thr	Gln		
[0476]					145					150					155			
[0477]	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr		
[0478]					165					170					175			
[0479]	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln		
[0480]					180					185					190			
[0481]	Lys	Pro	Gly	Gly	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu		
[0482]					195					200					205			
[0483]	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp		
[0484]					210					215					220			
[0485]	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Gln	Glu	Asp	Ile	Ala	Thr	Tyr		
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[0491]	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro		
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[0495]	Asp	Phe	Ala	Ala	Asp	Trp	Leu	Ile	Phe	Phe	Ala	Ser	Leu	Gly	Ser	Phe		
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[0497]	Leu	Ser	Ile	Leu	Leu	Val	Gly	Val	Leu	Gly	Tyr	Leu	Gly	Leu	Asn	Arg		
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[0501]	Ala	Ile	Glu	Phe	Pro	Gly	Gly	Lys	Glu	Thr	Trp	Gln	Trp	Ile	Asn	Pro		
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[0504]					370					375					380			
[0505]	Met	Ser	Trp	Asp	Lys	Gly	Glu	Arg	Thr	Glu	Pro	Leu	Glu	Lys	Thr	Glu		
[0506]					385					390					395			
																400		

[0507]	Leu Pro Glu Gly Ala Pro Glu Leu Ala Leu Asp Thr Glu Leu Ser Leu		
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[0509]	Glu Asp Gly Asp Arg Cys Lys Ala Lys Met Lys Arg Gly Arg Lys Lys		
[0510]		420	425 430
[0511]	Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr		
[0512]		435	440 445
[0513]	Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly		
[0514]		450	455 460
[0515]	Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala		
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[0517]	Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg		
[0518]		485	490 495
[0519]	Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu		
[0520]		500	505 510
[0521]	Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr		
[0522]		515	520 525
[0523]	Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly		
[0524]		530	535 540
[0525]	Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln		
[0526]	545	550	555 560
[0527]	Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln		
[0528]		565	570 575
[0529]	Ala Leu Pro Pro Arg		
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[0540]	Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg		
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[0542]	Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe		
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[0544]	Thr Ser Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Arg Gly Leu		
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[0546]	Glu Trp Ile Gly Val Met Trp Arg Gly Gly Ser Thr Asp Tyr Asn Ala
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[0548]	Ala Phe Met Ser Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln
[0549]	85 90 95
[0550]	Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
[0551]	100 105 110
[0552]	Tyr Cys Ala Lys Ser Met Ile Thr Thr Gly Phe Val Met Asp Ser Trp
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[0554]	Gly Gln Gly Ser Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
[0555]	130 135 140
[0556]	Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser
[0557]	145 150 155 160
[0558]	Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
[0559]	165 170 175
[0560]	Lys Ala Ser Glu Asp Ile Tyr Asn Arg Leu Thr Trp Tyr Gln Gln Lys
[0561]	180 185 190
[0562]	Pro Gly Lys Ala Pro Lys Leu Leu Ile Ser Gly Ala Thr Ser Leu Glu
[0563]	195 200 205
[0564]	Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
[0565]	210 215 220
[0566]	Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr
[0567]	225 230 235 240
[0568]	Cys Gln Gln Tyr Trp Ser Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys
[0569]	245 250 255
[0570]	Val Glu Ile Lys Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
[0571]	260 265 270
[0572]	Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
[0573]	275 280 285
[0574]	Ala Ser Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
[0575]	290 295 300
[0576]	Phe Ala Ala Asp Trp Met Ala Phe Val Ala Pro Ser Ile Cys Ile Ala
[0577]	305 310 315 320
[0578]	Ile Ile Met Val Gly Ile Phe Ser Thr His Tyr Phe Gln Gln Lys Val
[0579]	325 330 335
[0580]	Phe Val Leu Leu Ala Ala Leu Arg Pro Gln Trp Cys Ser Arg Glu Ile
[0581]	340 345 350
[0582]	Pro Asp Pro Ala Asn Ser Thr Cys Ala Lys Lys Tyr Pro Ile Ala Glu
[0583]	355 360 365
[0584]	Glu Lys Thr Gln Leu Pro Leu Asp Arg Leu Leu Ile Asp Trp Pro Thr

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[0586]	Pro Glu Asp Pro Glu Pro Leu Val Ile Ser Glu Val Leu His Gln Val		
[0587]	385	390	395 400
[0588]	Thr Pro Val Phe Arg His Pro Pro Cys Ser Asn Trp Pro Gln Arg Glu		
[0589]	405	410	415
[0590]	Lys Gly Ile Gln Gly His Gln Ala Ser Glu Lys Asp Met Met His Ser		
[0591]	420	425	430
[0592]	Ala Ser Ser Pro Pro Pro Pro Arg Ala Leu Gln Ala Glu Ser Arg Gln		
[0593]	435	440	445
[0594]	Leu Val Asp Leu Tyr Lys Val Leu Glu Ser Arg Gly Ser Asp Pro Lys		
[0595]	450	455	460
[0596]	Pro Glu Asn Pro Ala Cys Pro Trp Thr Val Leu Pro Ala Gly Asp Leu		
[0597]	465	470	475 480
[0598]	Pro Thr His Asp Gly Tyr Leu Pro Ser Asn Ile Asp Asp Leu Pro Ser		
[0599]	485	490	495
[0600]	His Glu Ala Pro Leu Ala Asp Ser Leu Glu Glu Leu Glu Pro Gln His		
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[0602]	Ile Ser Leu Ser Val Phe Pro Ser Ser Ser Leu His Pro Leu Thr Phe		
[0603]	515	520	525
[0604]	Ser Cys Gly Asp Lys Leu Thr Leu Asp Gln Leu Lys Met Arg Cys Asp		
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[0606]	Ser Leu Met Leu		
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[0617]	Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys		
[0618]	20 25 30		
[0619]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Val Ser Ala Tyr Ala Phe		
[0620]	35 40 45		
[0621]	Ser Ser Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu		
[0622]	50 55 60		
[0623]	Glu Trp Met Gly Arg Ile Tyr Pro Arg Asp Gly Asp Thr Asn Tyr Asn		

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[0625]	Gly Lys Phe Lys Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Asp			
[0626]		85	90	95
[0627]	Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val			
[0628]		100	105	110
[0629]	Tyr Tyr Cys Ala Arg Glu Gly Asp Gly Tyr Tyr Trp Tyr Phe Asp Val			
[0630]		115	120	125
[0631]	Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser			
[0632]		130	135	140
[0633]	Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln			
[0634]	145	150	155	160
[0635]	Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser			
[0636]		165	170	175
[0637]	Cys Arg Ala Ser Gln Ser Ile Arg Asn Tyr Leu His Trp Tyr Gln Gln			
[0638]		180	185	190
[0639]	Lys Pro Gly Glu Ala Pro Arg Leu Leu Ile Tyr Tyr Ala Ser Gln Ser			
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[0641]	Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp			
[0642]		210	215	220
[0643]	Phe Thr Leu Thr Ile Ser Ser Leu Glu Thr Glu Asp Phe Ala Met Tyr			
[0644]	225	230	235	240
[0645]	Tyr Cys Gln His Ser Asn Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr			
[0646]		245	250	255
[0647]	Lys Leu Glu Ile Lys Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro			
[0648]		260	265	270
[0649]	Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro			
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[0651]	Glu Ala Ser Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu			
[0652]		290	295	300
[0653]	Asp Phe Ala Ala Asp Ala Val Val Ile Ser Val Gly Ser Met Gly Leu			
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[0655]	Ile Ile Ser Leu Leu Cys Val Tyr Phe Trp Leu Glu Arg Thr Met Pro			
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[0657]	Arg Ile Pro Thr Leu Lys Asn Leu Glu Asp Leu Val Thr Glu Tyr His			
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[0659]	Gly Asn Phe Ser Ala Trp Ser Gly Val Ser Lys Gly Leu Ala Glu Ser			
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[0661]	Leu Gln Pro Asp Tyr Ser Glu Arg Leu Cys Leu Val Ser Glu Ile Pro			
[0662]		370	375	380

[0663]	Pro Lys Gly Gly Ala Leu Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn
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[0665]	Gln His Ser Pro Tyr Trp Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu
[0666]	405 410 415
[0667]	Thr Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
[0668]	420 425 430
[0669]	Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
[0670]	435 440 445
[0671]	Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
[0672]	450 455 460
[0673]	Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
[0674]	465 470 475 480
[0675]	Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
[0676]	485 490 495
[0677]	Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys
[0678]	500 505 510
[0679]	Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
[0680]	515 520 525
[0681]	Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
[0682]	530 535 540
[0683]	Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
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[0685]	Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
[0686]	565 570
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[0700]	Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu
[0701]	50 55 60

[0702]	Glu Trp Val Ala Val Ile Asp Ser Asn Gly Gly Ser Thr Tyr Tyr Pro
[0703]	65 70 75 80
[0704]	Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
[0705]	85 90 95
[0706]	Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
[0707]	100 105 110
[0708]	Tyr Tyr Cys Ser Ser Tyr Thr Asn Leu Gly Ala Tyr Trp Gly Gln Gly
[0709]	115 120 125
[0710]	Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
[0711]	130 135 140
[0712]	Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
[0713]	145 150 155 160
[0714]	Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
[0715]	165 170 175
[0716]	Gln Asp Ile Ser Gly Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gly
[0717]	180 185 190
[0718]	Ala Ile Lys Arg Leu Ile Tyr Thr Thr Ser Thr Leu Asp Ser Gly Val
[0719]	195 200 205
[0720]	Pro Lys Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
[0721]	210 215 220
[0722]	Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
[0723]	225 230 235 240
[0724]	Tyr Ala Ser Ser Pro Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
[0725]	245 250 255
[0726]	Lys Gly Ala Pro Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
[0727]	260 265 270
[0728]	Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Ser
[0729]	275 280 285
[0730]	Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
[0731]	290 295 300
[0732]	Ala Asp Pro Ile Leu Leu Thr Ile Ser Ile Leu Ser Phe Phe Ser Val
[0733]	305 310 315 320
[0734]	Ala Leu Leu Val Ile Leu Ala Cys Val Leu Trp Lys Lys Arg Ile Lys
[0735]	325 330 335
[0736]	Pro Ile Val Trp Pro Ser Leu Pro Asp His Lys Lys Thr Leu Glu His
[0737]	340 345 350
[0738]	Leu Cys Lys Lys Pro Arg Lys Asn Leu Asn Val Ser Phe Asn Pro Glu
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[0740]	Ser Phe Leu Asp Cys Gln Ile His Arg Val Asp Asp Ile Gln Ala Arg

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[0746]	Pro Ser Glu Asp Val Val Ile Thr Pro Glu Ser Phe Gly Arg Asp Ser		
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[0750]	Leu Ser Ser Ser Arg Ser Leu Asp Cys Arg Glu Ser Gly Lys Asn Gly		
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[0754]	Thr Leu Pro Pro Pro Phe Ser Leu Gln Ser Gly Ile Leu Thr Leu Asn		480
[0755]	485	490	495
[0756]	Pro Val Ala Gln Gly Gln Pro Ile Leu Thr Ser Leu Gly Ser Asn Gln		
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[0773]	Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu		
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[0775]	Glu Trp Val Ala Val Ile Asp Ser Asn Gly Gly Ser Thr Tyr Tyr Pro		
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[0777]	Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn		80
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[0789]	Gln	Asp	Ile	Ser	Gly	Tyr	Leu	Asn	Trp	Leu	Gln	Gln	Lys	Pro	Gly	Gly												
[0790]	180							185							190													
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[0793]	Pro	Lys	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr												
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[0800]	260							265							270													
[0801]	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro	Glu	Ala	Cys	Arg												
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[0803]	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	Thr	Arg	Gly	Leu	Asp	Phe	Ala	Cys												
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[0805]	Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala	Gly	Thr	Cys	Gly	Val	Leu	Leu												
[0806]	305							310							315							320						
[0807]	Leu	Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys	Lys	Arg	Gly	Arg	Lys	Lys	Leu												
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[0809]	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met	Arg	Pro	Val	Gln	Thr	Thr	Gln												
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[0811]	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Pro	Glu	Glu	Glu	Glu	Gly	Gly												
[0812]	355							360							365													
[0813]	Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg	Ser	Ala	Asp	Ala	Pro	Ala	Tyr												
[0814]	370							375							380													
[0815]	Gln	Gln	Gly	Gln	Asn	Gln	Leu	Tyr	Asn	Glu	Leu	Asn	Leu	Gly	Arg	Arg												
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[0821]	Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
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[0823]	Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
[0824]	450 455 460
[0825]	Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
[0826]	465 470 475 480
[0827]	Leu Pro Pro Arg Ala Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu
[0828]	485 490 495
[0829]	Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Glu Phe Gly
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[0831]	Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly Val Gln Cys Tyr
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[0833]	Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn Asp
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[0835]	Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp Met
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[0839]	Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile Ser
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[0845]	Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys Met
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[0847]	Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu Lys
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[0849]	Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly
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[0868]	Glu	Trp	Val	Ala	Val	Ile	Asp	Ser	Asn	Gly	Gly	Ser	Thr	Tyr	Tyr	Pro
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[0870]	Asp	Thr	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn
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[0872]	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val
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[0874]	Tyr	Tyr	Cys	Ser	Ser	Tyr	Thr	Asn	Leu	Gly	Ala	Tyr	Trp	Gly	Gln	Gly
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[0900]	Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu		
[0901]	325	330	335
[0902]	Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln		
[0903]	340	345	350
[0904]	Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly		
[0905]	355	360	365
[0906]	Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr		
[0907]	370	375	380
[0908]	Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg		
[0909]	385	390	395
[0910]	Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met		
[0911]	405	410	415
[0912]	Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn		
[0913]	420	425	430
[0914]	Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met		
[0915]	435	440	445
[0916]	Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly		
[0917]	450	455	460
[0918]	Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala		
[0919]	465	470	475
[0920]	Leu Pro Pro Arg Ala Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu		
[0921]	485	490	495
[0922]	Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Lys His Leu		
[0923]	500	505	510
[0924]	Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln		
[0925]	515	520	525
[0926]	Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys Tyr Phe Asn Ala		
[0927]	530	535	540
[0928]	Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe Leu Gly Ile Leu		
[0929]	545	550	555
[0930]	Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met Gln Ser Gln Ile		
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[0932]	Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys Asp Asp Gln Ser		
[0933]	580	585	590
[0934]	Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met Asn Val Lys Phe		
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[0936]	Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu Lys Leu Thr Asn
[0937]	610 615 620
[0938]	Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala Ile His Glu Leu
[0939]	625 630 635 640
[0940]	Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys Thr Gly Lys Arg
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[0955]	Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
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[0957]	Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu
[0958]	50 55 60
[0959]	Glu Trp Val Ala Val Ile Asp Ser Asn Gly Gly Ser Thr Tyr Tyr Pro
[0960]	65 70 75 80
[0961]	Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
[0962]	85 90 95
[0963]	Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
[0964]	100 105 110
[0965]	Tyr Tyr Cys Ser Ser Tyr Thr Asn Leu Gly Ala Tyr Trp Gly Gln Gly
[0966]	115 120 125
[0967]	Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
[0968]	130 135 140
[0969]	Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
[0970]	145 150 155 160
[0971]	Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
[0972]	165 170 175
[0973]	Gln Asp Ile Ser Gly Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gly
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[0980]	225						230					235				240
[0981]	Tyr	Ala	Ser	Ser	Pro	Phe	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile
[0982]					245					250					255	
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[0984]				260					265					270		
[0985]	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro	Glu	Ala	Cys	Arg
[0986]			275					280					285			
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[0992]				325						330					335	
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[1002]				405						410					415	
[1003]	Gly	Gly	Lys	Pro	Gln	Arg	Arg	Lys	Asn	Pro	Gln	Glu	Gly	Leu	Tyr	Asn
[1004]				420					425					430		
[1005]	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu	Ala	Tyr	Ser	Glu	Ile	Gly	Met
[1006]			435					440					445			
[1007]	Lys	Gly	Glu	Arg	Arg	Arg	Gly	Lys	Gly	His	Asp	Gly	Leu	Tyr	Gln	Gly
[1008]		450						455				460				
[1009]	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp	Ala	Leu	His	Met	Gln	Ala
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[1011]	Leu	Pro	Pro	Arg	Ala	Ser	Gly	Ser	Gly	Ala	Thr	Asn	Phe	Ser	Leu	Leu
[1012]				485						490					495	
[1013]	Lys	Gln	Ala	Gly	Asp	Val	Glu	Glu	Asn	Pro	Gly	Pro	Met	Glu	Phe	Gly

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[1017]	Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn Asp		
[1018]	530	535	540
[1019]	Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp Met		
[1020]	545	550	555
[1021]	Thr Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile Ile		
[1022]	565	570	575
[1023]	Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile Ser		
[1024]	580	585	590
[1025]	Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile Ile		
[1026]	595	600	605
[1027]	Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys Ser		
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[1029]	Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys Met		
[1030]	625	630	635
[1031]	Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu Lys		
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[1033]	Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly		
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[1035]	Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp Pro Ala Gly Gly		
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[1037]	Gly Thr Lys Thr Glu Ser Ser Ser Arg Ser Asp Gly Gly Ala Gln Asp		
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[1039]	Cys Cys Leu Lys Tyr Ser Gln Arg Lys Ile Pro Ala Lys Val Val Arg		
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[1041]	Ser Tyr Arg Lys Gln Glu Pro Ser Leu Gly Cys Ser Ile Pro Ala Ile		
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[1043]	Leu Phe Leu Pro Arg Lys Arg Ser Gln Ala Glu Leu Cys Ala Asp Pro		
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[1047]	Ser Pro Gln Lys Pro Ala Gln Gly Cys Arg Lys Asp Arg Gly Ala Ser		
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[1436]	Cys	Phe	Gln	Gly	Ser	His	Val	Pro	Leu	Thr	Phe	Gly	Ala	Gly	Thr	Lys
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[1507]	Glu Trp Val Ala Val Ile Asp Ser Asn Gly Gly Ser Thr Tyr Tyr Pro		
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[1509]	Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn		
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[1511]	Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val		
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[1513]	Tyr Tyr Cys Ser Ser Tyr Thr Asn Leu Gly Ala Tyr Trp Gly Gln Gly		
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[1515]	Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly		
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[1517]	Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser		
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[1519]	Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser		
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[1521]	Gln Asp Ile Ser Gly Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gly
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[1523]	Ala Ile Lys Arg Leu Ile Tyr Thr Thr Ser Thr Leu Asp Ser Gly Val
[1524]	195 200 205
[1525]	Pro Lys Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
[1526]	210 215 220
[1527]	Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
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[1529]	Tyr Ala Ser Ser Pro Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
[1530]	245 250 255
[1531]	Lys Gly Ala Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
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[1533]	Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
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[1535]	Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
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[1537]	Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
[1538]	305 310 315 320
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[1740]	Phe	Gly	Lys	Leu	Glu	Ser	Lys	Leu	Ser	Val	Ile	Arg	Asn	Leu	Asn	Asp
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[1773]	Leu Asp Ser Met Lys Glu Ile Gly Ser Asn Cys Leu Asn Asn Glu Phe		
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[1781]	Ile Leu Leu Asn Cys Thr Gly Gln Val Lys Gly Arg Lys Pro Ala Ala		
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[1783]	Leu Gly Glu Ala Gln Pro Thr Lys Ser Leu Glu Glu Asn Lys Ser Leu		
[1784]	130	135	140
[1785]	Lys Glu Gln Lys Lys Leu Asn Asp Leu Cys Phe Leu Lys Arg Leu Leu		
[1786]	145	150	155
[1787]	Gln Glu Ile Lys Thr Cys Trp Asn Lys Ile Leu Met Gly Thr Lys Glu		
[1788]	165	170	175
[1789]	His Gly Gly Gly Ser Gly Gly Gly Ser Gly Ala Pro Thr Thr Thr Pro		
[1790]	180	185	190
[1791]	Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu		
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[1794]	210	215	220
[1795]	Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu		
[1796]	225	230	235
[1797]	Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr		
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[1803]	Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro		
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[1805]	Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu		
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[1833]	115	120	125
[1834]	Leu Gly Glu Ala Gln Pro Thr Lys Ser Leu Glu Glu Asn Lys Ser Leu		
[1835]	130	135	140
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[1841]	180	185	190
[1842]	Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu		
[1843]	195	200	205
[1844]	Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His		
[1845]	210	215	220
[1846]	Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu		
[1847]	225	230	235
[1848]	Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr		
[1849]	245	250	255
[1850]	Cys Lys Lys Pro Ala Gly Arg Asn Thr Gly Pro Trp Leu Lys Lys Val		
[1851]	260	265	270
[1852]	Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser		
[1853]	275	280	285
[1854]	Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro		
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[1862]	Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu		
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[1864]	Glu Asn Pro Gly Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val		
[1865]	370	375	380
[1866]	Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe		
[1867]	385	390	395
[1868]	Thr Phe Ser Asp Tyr Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Lys		
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[1870]	Gly Leu Glu Trp Val Ala Ser Ile Ser Phe Asp Gly Thr Tyr Thr Tyr		
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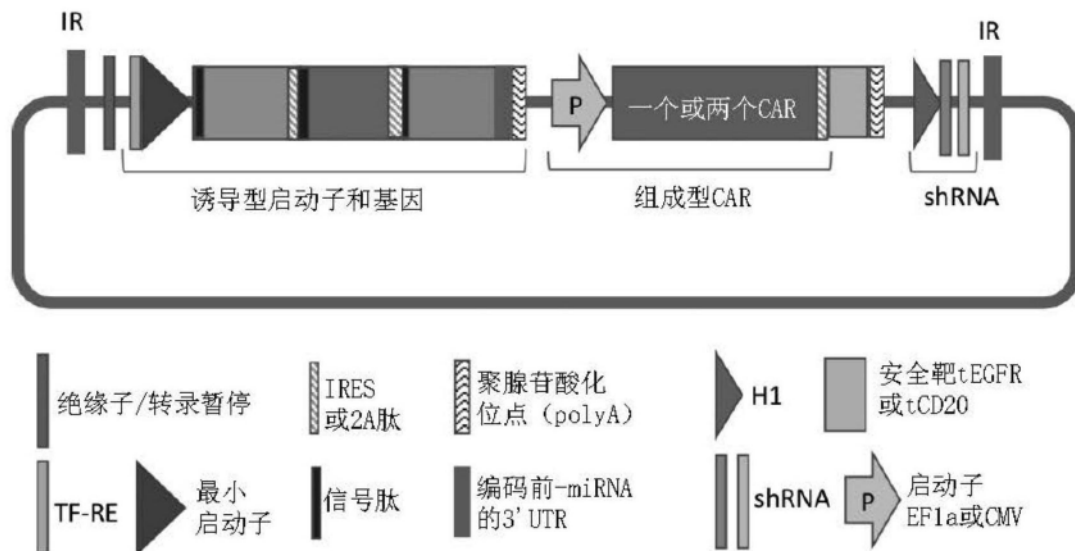
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[1876]	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Pro	Ala	Trp	Phe	Pro	Tyr	Trp
[1877]	465						470				475					480
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[1880]	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Asp	Ile	Val	Met	Thr	Gln
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[1895]		610					615					620				
[1896]	Thr	Asn	Phe	Ser	Leu	Leu	Lys	Gln	Ala	Gly	Asp	Val	Glu	Glu	Asn	Pro
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[1905]		690					695				700					
[1906]	Arg	Thr	Ile	Phe	Ile	Ile	Ser	Met	Tyr	Lys	Asp	Ser	Gln	Pro	Arg	Gly
[1907]	705					710				715						720
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[1940]	Thr Gly Asp Phe Asp Leu His Leu Leu Lys Val Ser Glu Gly Thr Thr		
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[1942]	Ile Leu Leu Asn Cys Thr Gly Gln Val Lys Gly Arg Lys Pro Ala Ala		
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[1945]	130	135	140
[1946]	Lys Glu Gln Lys Lys Leu Asn Asp Leu Cys Phe Leu Lys Arg Leu Leu		
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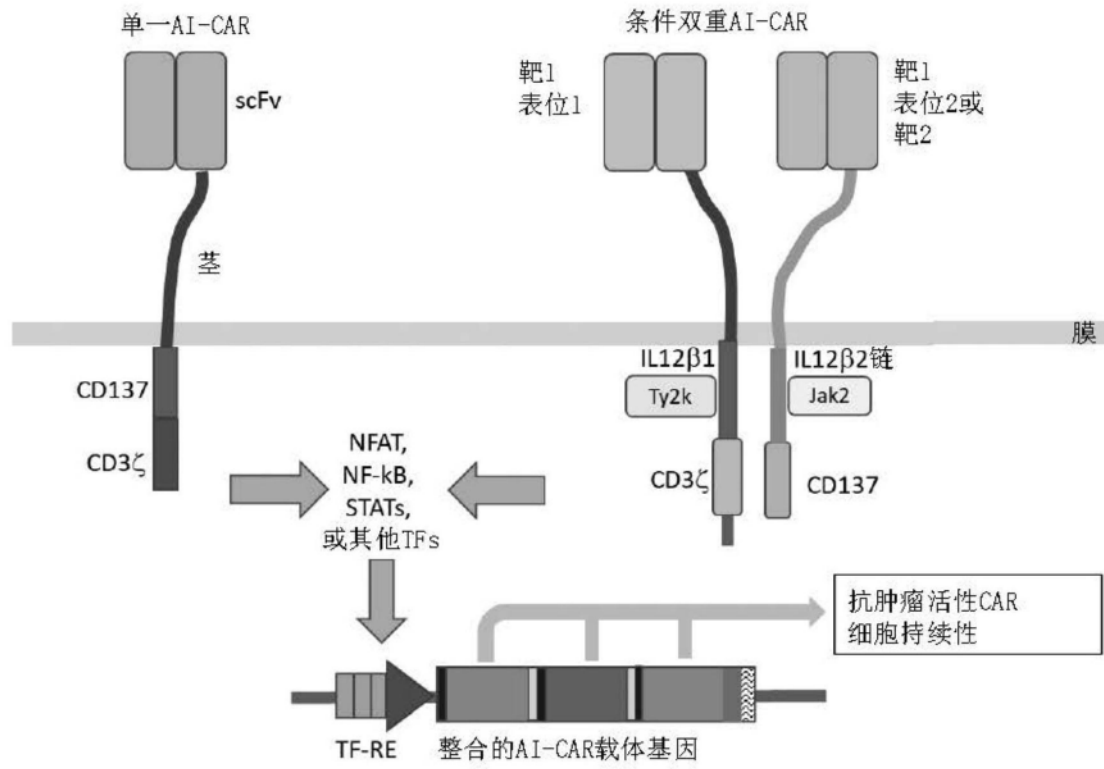
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[2003]					595					600					605		
[2004]	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Pro	Ala	Gly	Ser	Gly	Ala	
[2005]					610					615					620		
[2006]	Thr	Asn	Phe	Ser	Leu	Leu	Lys	Gln	Ala	Gly	Asp	Val	Glu	Glu	Asn	Pro	
[2007]					625					630					635		640
[2008]	Gly	Pro	Met	Glu	Phe	Gly	Leu	Ser	Trp	Val	Phe	Leu	Val	Ala	Leu	Leu	
[2009]					645					650					655		
[2010]	Arg	Gly	Val	Gln	Cys	Tyr	Phe	Gly	Lys	Leu	Glu	Ser	Lys	Leu	Ser	Val	
[2011]					660					665					670		
[2012]	Ile	Arg	Asn	Leu	Asn	Asp	Gln	Val	Leu	Phe	Ile	Asp	Gln	Gly	Asn	Arg	
[2013]					675					680					685		
[2014]	Pro	Leu	Phe	Glu	Asp	Met	Thr	Asp	Ser	Asp	Cys	Arg	Asp	Asn	Ala	Pro	
[2015]					690					695					700		
[2016]	Arg	Thr	Ile	Phe	Ile	Ile	Ser	Met	Tyr	Lys	Asp	Ser	Gln	Pro	Arg	Gly	
[2017]					705					710					715		720
[2018]	Met	Ala	Val	Thr	Ile	Ser	Val	Lys	Cys	Glu	Lys	Ile	Ser	Thr	Leu	Ser	
[2019]					725					730					735		
[2020]	Cys	Glu	Asn	Lys	Ile	Ile	Ser	Phe	Lys	Glu	Met	Asn	Pro	Pro	Asp	Asn	
[2021]					740					745					750		
[2022]	Ile	Lys	Asp	Thr	Lys	Ser	Asp	Ile	Ile	Phe	Phe	Gln	Arg	Ser	Val	Pro	
[2023]					755					760					765		
[2024]	Gly	His	Asp	Asn	Lys	Met	Gln	Phe	Glu	Ser	Ser	Ser	Tyr	Glu	Gly	Tyr	
[2025]					770					775					780		
[2026]	Phe	Leu	Ala	Cys	Glu	Lys	Glu	Arg	Asp	Leu	Phe	Lys	Leu	Ile	Leu	Lys	
[2027]					785					790					795		800

[2028]	Lys	Glu	Asp	Glu	Leu	Gly	Asp	Arg	Ser	Ile	Met	Phe	Thr	Val	Gln	Asn
[2029]					805				810						815	
[2030]	Glu	Asp	Gly	Gly	Gly	Thr	Lys	Thr	Glu	Ser	Ser	Ser	Arg	Ser	Asp	Gly
[2031]					820				825						830	
[2032]	Gly	Ala	Gln	Asp	Cys	Cys	Leu	Lys	Tyr	Ser	Gln	Arg	Lys	Ile	Pro	Ala
[2033]					835				840						845	
[2034]	Lys	Val	Val	Arg	Ser	Tyr	Arg	Lys	Gln	Glu	Pro	Ser	Leu	Gly	Cys	Ser
[2035]					850				855						860	
[2036]	Ile	Pro	Ala	Ile	Leu	Phe	Leu	Pro	Arg	Lys	Arg	Ser	Gln	Ala	Glu	Leu
[2037]	865						870				875					880
[2038]	Cys	Ala	Asp	Pro	Lys	Glu	Leu	Trp	Val	Gln	Gln	Leu	Met	Gln	His	Leu
[2039]					885					890						895
[2040]	Asp	Lys	Thr	Pro	Ser	Pro	Gln	Lys	Pro	Ala	Gln	Gly	Cys	Arg	Lys	Asp
[2041]					900					905					910	
[2042]	Arg	Gly	Ala	Ser	Lys	Thr	Gly	Lys	Lys	Gly	Lys	Gly	Ser	Lys	Gly	Cys
[2043]					915					920					925	
[2044]	Lys	Arg	Thr	Glu	Arg	Ser	Gln	Thr	Pro	Lys	Gly	Pro				
[2045]					930					935					940	



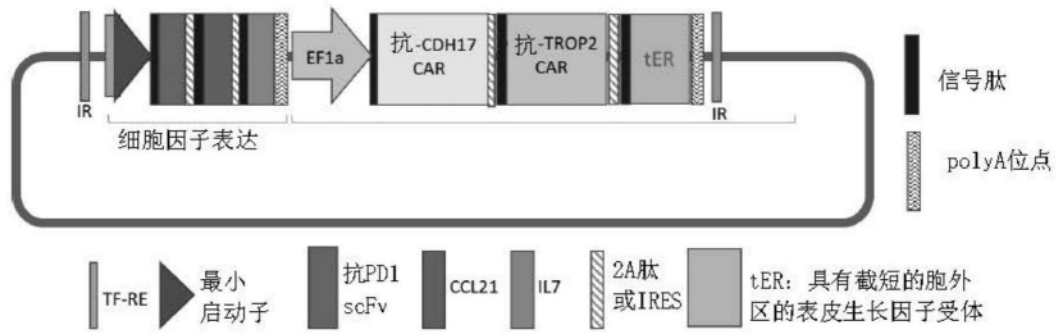
AI-CAR 基因表达盒的一般主题，其在非病毒载体（pPI）中包含诱导型基因表达单元和 CAR 表达单元，用于组成型表达一个或两个 CAR 以诱导宿主抗肿瘤应答的基因表达。

图1



AI-CAR 的一般概念。

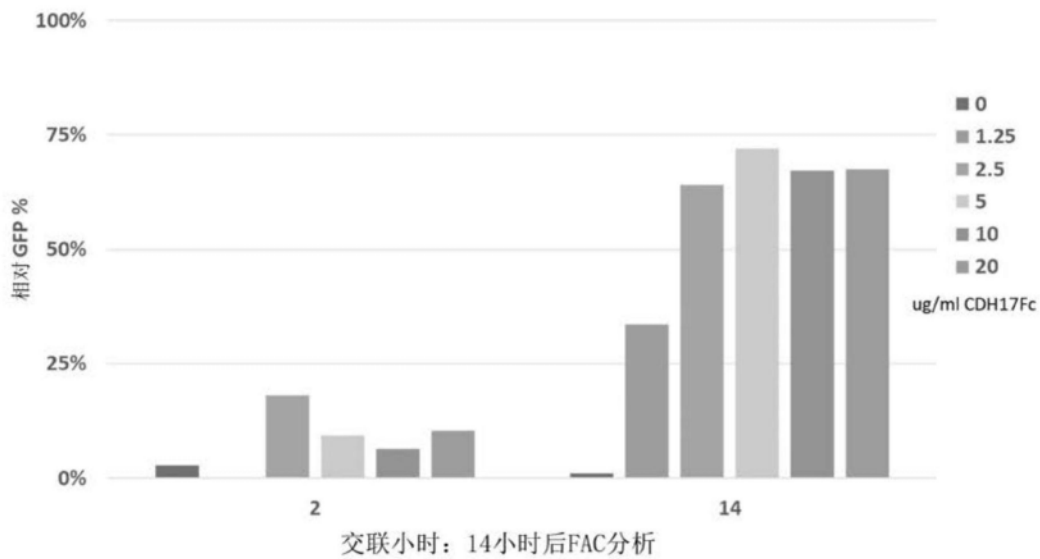
图2



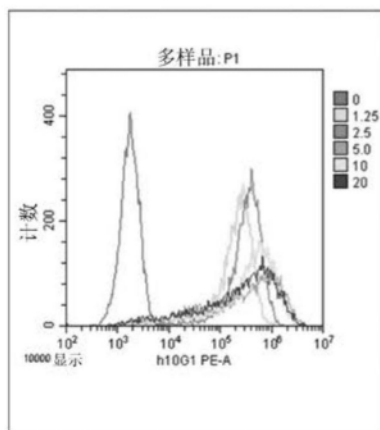
AI-CAR 表达载体编码组成型表达的双重 CAR，该双重 CAR 在非病毒载体（pPI）中在诱导型启动子下靶向 CDH17 和 TROP2 以及抗 PD1 scFv、CCL21 和 IL17 基因盒，用于 CAR 诱导的宿主抗肿瘤应答。

图3

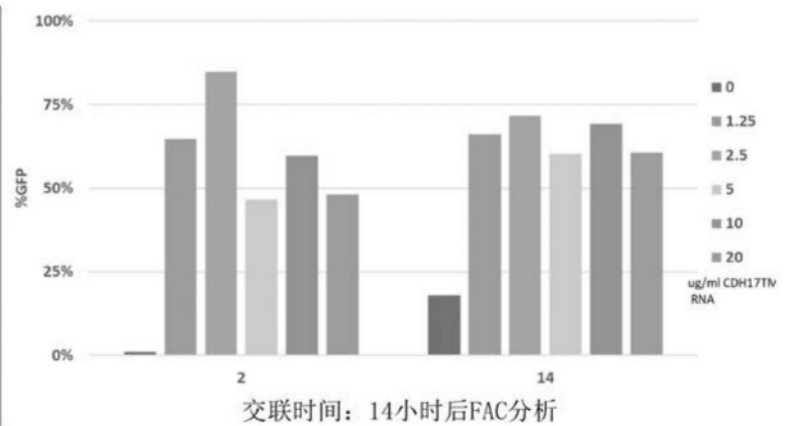
A.



B.

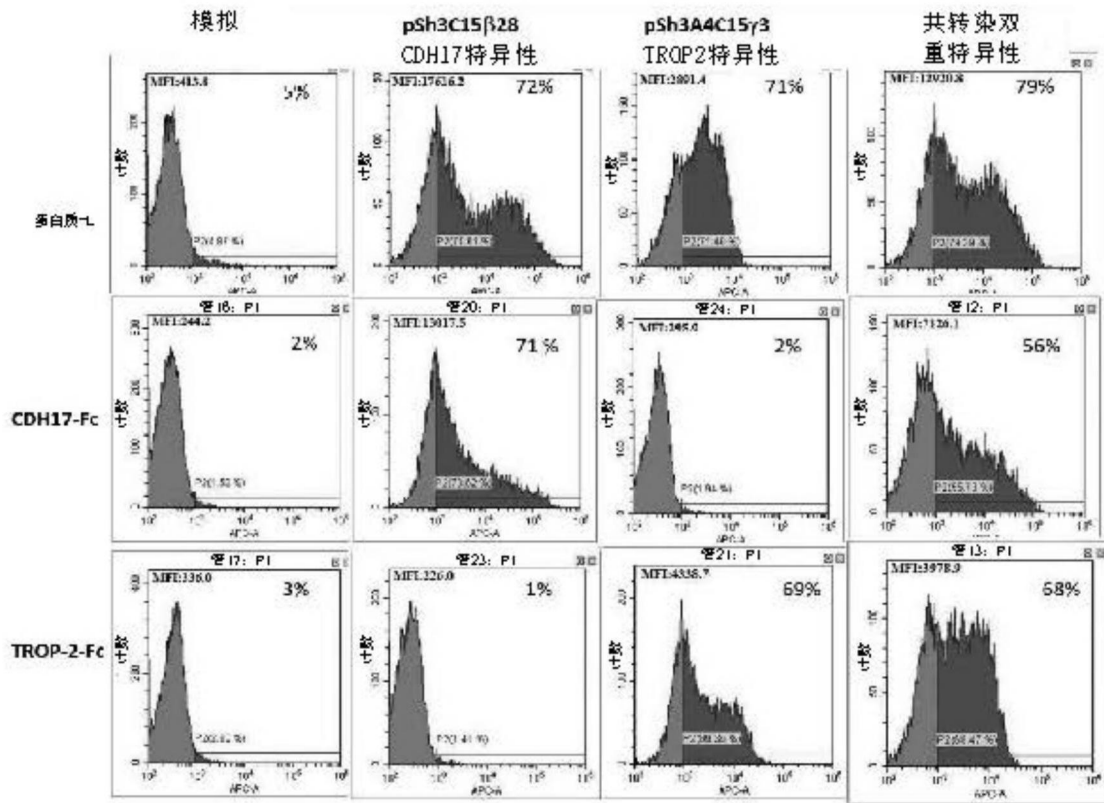


C.



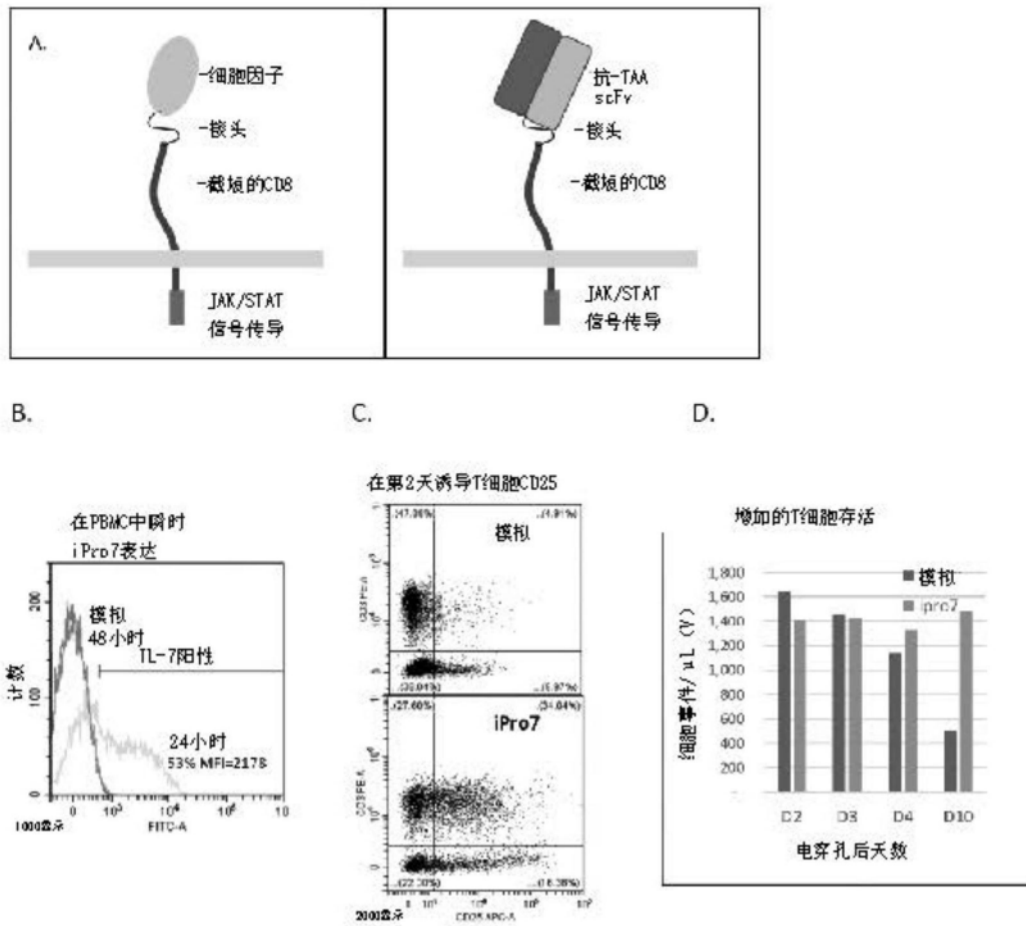
整合的 pPI-抗-CDH17-AI-CAR 载体基因的肿瘤抗原诱导。(A) 通过响应于不同浓度的 CDH17 的 T 细胞 (Jurkat) 中的 GFP 水平来测量整合的 pPI-抗-CDH17-AI-CAR 载体的表达；(B) 在结肠癌细胞中用重组 CDH17 诱导 (SW480)；和 (C) pPI-抗-CDH17-AI-CAR 整合的 T 细胞对表达 CDH17 的 SW480 细胞的细胞毒性。

图4



pPI-抗-CDH17-TROP2 AI-CAR 的表达和结合特异性

图5



支持 AI-CAR 增殖和持续性的 iPro 变体。(A) iPro7 表达的示例；(B) CD25 T 细胞群增殖的诱导；以及 (C) 增加 T 细胞存活。

图6