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(54)发明名称

用于体内核酸表达的系统和方法

(57)摘要

本发明提供用于使一种或多种生物分子在受试者、人或非人哺乳动物中表达(例如,在治疗性水平下持续产生治疗作用所需的延长的时间段)的组合物、系统、试剂盒以及方法。在某些实施方案中,提供组合物、系统、试剂盒和方法,其包括:第一组合物,所述第一组合物包含聚阳离子结构(例如,空阳离子脂质体、阳离子胶束、阳离子乳液或阳离子聚合物);以及第二组合物,所述第二组合物包含编码一种或多种感兴趣的生物分子的表达载体(例如,不与脂质体或其他载剂缔合的非病毒表达载体)。

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1.包含地塞米松的组合物、第一组合物和第二组合物在制备用于在受试者中表达抗病毒单克隆抗体(mAb)或其抗原结合部分的药物中的用途，

a)其中所述第一组合物包含：

i)第一量的阳离子脂质体，其中所述阳离子脂质体包含阳离子脂质和地塞米松棕榈酸酯，并且

ii)中性脂质体，其中所述中性脂质体包含中性脂质和地塞米松棕榈酸酯，并且

其中所述第一组合物不含或基本上不含核酸分子；以及

b)其中所述第二组合物包含治疗有效量的编码所述mAb或其抗原结合部分的非病毒表达载体，其中所述mAb或其抗原结合部分特异性地结合至所述病毒，其中所述第二组合物不包含可检测的阳离子脂质。

2.根据权利要求1所述的用途，其中所述抗原结合部分是Fab、F(ab)2和/或scFv。

3.根据权利要求1所述的用途，其中所述mAb或其抗原结合部分包含所述mAb。

4.根据权利要求1所述的用途，其中所述非病毒表达载体中的每一个包括编码抗体重链和抗体轻链两者的质粒。

5.根据权利要求1至4中任一项所述的用途，其中所述抗病毒单克隆抗体是抗A型流感病毒抗体。

6.根据权利要求1至4中任一项所述的用途，其中将包含地塞米松的组合物、所述第一组合物和所述第二组合物配制用于顺序施用。

7.根据权利要求5所述的用途，其中将包含地塞米松的组合物、所述第一组合物和所述第二组合物配制用于顺序施用。

8.根据权利要求1至4中任一项所述的用途，其中将包含地塞米松的组合物配制用于在所述第一组合物和所述第二组合物之前施用。

9.根据权利要求5所述的用途，其中将包含地塞米松的组合物配制用于在所述第一组合物和所述第二组合物之前施用。

10.根据权利要求1至4中任一项所述的用途，其中将所述第一组合物配制用于在所述第二组合物之前施用。

11.根据权利要求5所述的用途，其中将所述第一组合物配制用于在所述第二组合物之前施用。

12.根据权利要求8所述的用途，其中将所述第一组合物配制用于在所述第二组合物之前施用。

13.根据权利要求10所述的用途，其中将所述第二组合物配制用于在施用所述第一组合物的约300分钟内施用。

14.根据权利要求11所述的用途，其中将所述第二组合物配制用于在施用所述第一组合物的约300分钟内施用。

15.根据权利要求12所述的用途，其中将所述第二组合物配制用于在施用所述第一组合物的约300分钟内施用。

16.根据权利要求13至15中任一项所述的用途，其中将所述第二组合物配制用于在施用在所述第一组合物后的约100分钟内施用。

17.根据权利要求16所述的用途，其中将所述第二组合物配制用于在施用在所述第一

组合物后的约10分钟内施用。

18.根据权利要求17所述的用途，其中将所述第二组合物配制用于在施用在所述第一组合物后的约5分钟内。

19.根据权利要求1至3中任一项所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

20.根据权利要求4所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

21.根据权利要求5所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

22.根据权利要求6所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

23.根据权利要求8所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

24.根据权利要求10所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

25.根据权利要求13至15中任一项所述的用途，其中所述非病毒表达载体是CpG减少的或其中所述非病毒表达载体不含CpG。

用于体内核酸表达的系统和方法

[0001] 本申请要求2017年3月23日提交的美国临时申请62/475,477的 优先权,所述申请以引用的方式整体并入本文。

技术领域

[0002] 本发明提供用于使一种或多种生物分子在受试者、人或非人哺乳 动物中表达(例如,在治疗性水平下持续产生治疗作用所需的延长的 时间段)的组合物、系统、试剂盒以及方法。在某些实施方案中,提 供组合物、系统、试剂盒和方法,其包括:第一组合物,所述第一组 合物包含聚阳离子结构(例如,空阳离子脂质体、阳离子胶束、阳离 子乳液或阳离子聚合物);以及第二组合物,所述第二组合物包含编 码一种或多种感兴趣的生物分子的表达载体(例如,不与脂质体或其 他载剂缔合的非病毒表达载体)。

背景技术

[0003] 最简单的非病毒基因递送系统使用裸表达载体DNA。将游离 DNA直接注射到某些组织(特别是肌肉)中已经显示产生高水平的基 因表达,并且这种方法的简单性已使得其在许多临床方案中采用。具 体地说,这种方法已经应用于癌症的基因疗法,其中DNA可直接注 射到肿瘤中,或者可注射到肌细胞中以便表达可充当癌症疫苗的肿瘤 抗原。

[0004] 尽管质粒DNA的直接注射已显示产生基因表达,但总体表达水 平远低于用病毒或脂质体载体。由于存在血清核酸酶,裸DNA通常 也被认为不适于全身施用。结果,质粒DNA的直接注射似乎仅限于 涉及直接注射容易地进入的组织如皮肤和肌细胞的一些应用。

发明内容

[0005] 本发明提供用于使一种或多种生物分子在受试者、人或非人哺乳 动物中表达(例如,在治疗性水平下持续产生治疗作用所需的延长的 时间段)的组合物、系统、试剂盒以及方法。在某些实施方案中,提 供组合物、系统、试剂盒和方法,其包括:第一组合物,所述第一组 合物包含聚阳离子结构(例如,空阳离子脂质体、阳离子胶束、阳离 子乳液或阳离子聚合物);以及第二组合物,所述第二组合物包含编 码一种或多种感兴趣的生物分子的表达载体(例如,不与脂质体或其 他载剂缔合的非病毒表达载体)。在一些实施方案中,所述组合物、 系统、试剂盒和方法可采用2016年9月16日提交的美国专利申请序 列号15/268,000中所述的组合物、系统、试剂盒和方法的一个或多个 组分,所述申请的公开内容以引用的方式整体并入本文。

[0006] 在一些实施方案中,本文提供组合物、试剂盒和/或系统,其包 括:a)第一组合物,所述第一组合物包含第一量的聚阳离子结构脂质 体,其中所述第一组合物不含或基本上不含核酸分子;以及b)第二组 合物,所述第二组合物包含表达载体(例如,表达感兴趣的生物分子 的一种或多种表达载体)(例如,治疗有效量的一种或多种表达载体)。 在一些实施方案中,所述组合物、试剂盒和/或系统具有以下特性中 的一种或多种或全部:i)第一量的所述聚阳离子结构与表达载体的比 例为5:1至25:1;ii)2.0%至6.0%或者2.0%至20%

(例如,2%..5%… 10%…15%..或20%)的第一组合物包含地塞米松棕榈酸酯和/或地塞米松;iii)第一组合物还包含中性脂质;以及iv)聚阳离子结构包含空 脂质体,其中存在于第一组合物中的空脂质体具有约20-85nm的z- 平均直径。

[0007] 在一些实施方案中,本文提供含水组合物,其包含以下或基本上 由以下组成:a)以介于500nM与500mM之间的浓度存在于所述组 合物中的聚阳离子结构;b)以介于所述组合物的1%-10%之间的浓度 存在于所述组合物中的地塞米松和/或地塞米松棕榈酸酯;以及c)生 理上可耐受的缓冲液,并且其中所述组合物不含或基本上不含核酸分 子。在一些实施方案中,所述聚阳离子结构是作为小单层囊泡存在的 阳离子脂质。在一些实施方案中,所述生理上可耐受的缓冲液选自由 以下组成的组:生理盐水缓冲液、5%在水中的右旋糖、乳酸化林格 氏缓冲液以及它们的任何组合。在一些实施方案中,所述聚阳离子结 构包含DOTAP。在一些实施方案中,所述聚阳离子结构以介于800 nM与1500nM之间或介于10mM与100mM之间的浓度存在于所述 组合物中。

[0008] 在一些实施方案中,本文提供含水组合物,其包含以下或基本上 由以下组成:a)以介于500nM与500mM之间的浓度存在于所述组 合物中的中性脂质;b)以介于所述组合物的1%-10%之间的浓度存在 于所述组合物中的地塞米松和/或地塞米松棕榈酸酯;以及c)生理上 可耐受的缓冲液,并且其中所述组合物不含或基本上不含核酸分子。 在一些实施方案中,所述中性脂质作为多层囊泡存在。在一些实施方 案中,所述生理上可耐受的缓冲液选自由以下组成的组:生理盐水缓 冲液、5%在水中的右旋糖、乳酸化林格氏缓冲液以及它们的任何组 合。在一些实施方案中,所述中性脂质包含DMPC。在一些实施方案 中,所述中性脂质以介于800nM与1500nM之间或介于10mM与 100mM之间的浓度存在于所述组合物中。

[0009] 在一些实施方案中,本文提供含水组合物,其包含以下或基本上 由以下组成:a)以介于500nM与500mM之间的浓度存在于所述组 合物中的聚阳离子结构;b)以介于500nM与500mM之间的浓度存 在于所述组合物中的中性脂质;以及c)生理上可耐受的缓冲液,并且其中所述组合物不含或基本上不含核酸分子。在一些实施方案中,所 述中性脂质作为多层囊泡存在。在一些实施方案中,组合物包含具有 (例如,挤压至)75-250nm(例如,100nm、150nm、200nm等)的平 均直径的中性脂质体。在一些实施方案中,所述聚阳离子结构是作为小单层囊泡存在的阳离子脂质。在一些实施方案中,所述聚阳离子结 构是作为多层囊泡存在的阳离子脂质。在一些实施方案中,组合物还 包含:d)地塞米松,其中所述地塞米松以一定浓度存在,使得它为所 述组合物的1%-10%。在一些实施方案中,组合物还包含:d)地塞米 松棕榈酸酯,其中所述地塞米松棕榈酸酯以一定浓度存在,使得它为 所述组合物的1%-10%。在一些实施方案中,所述中性脂质包含 DMPC。在一些实施方案中,所述中性脂质以介于800nM与1300nM 之间或介于10mM与100mM之间的浓度存在于所述组合物中。在 一些实施方案中,所述聚阳离子结构包含DOTAP。在一些实施方案 中,所述聚阳离子结构以介于800nM与1500nM之间或介于10mM 与100mM之间的浓度存在于所述组合物中。

[0010] 在一些实施方案中,本文提供组合物、试剂盒和/或系统,其包 括:a)第一组合物,所述第一组合物包含第一量的聚阳离子结构脂质 体,其中所述第一组合物不含或基本上不含核酸分子;以及b)第二组 合物,所述第二组合物包含治疗有效量的表达载体,其中所述表达载 体包含编码一种或多种生物分子(例如,治疗性生物分子)的环化合成 扩增的核

酸或微环DNA。在一些实施方案中，合成扩增的核酸通过 聚合酶链反应产生。在一些实施方案中，在载体的生产中不使用细胞 (例如，载体不在培养物中重组表达来产生)。在一些实施方案中，载 体由编码一种或多种生物分子的核酸以及操作性地连接到其的一种 或多种启动子和增强子组成。

[0011] 在一些实施方案中，一种或多种生物分子是治疗性生物分子。在 一些实施方案中，治疗性生物分子是抗体。在一些实施方案中，抗体 是广泛中和抗体。在一些实施方案中，广泛中和抗体特异性结合至病 原体或病原体组分。在一些实施方案中，病原体是病毒。在一些实施 方案中，抗体特异性结合至肿瘤抗原。在一些实施方案中，mAb或 其抗原结合部分特异性结合至细胞因子。

[0012] 在一些实施方案中，一种或多种抗体包含：第一抗体，其特异性 结合至第一靶分子；第二抗体，其特异性结合至第二不同靶分子；以 及在一些实施方案中第三抗体，其特异性结合至第三不同靶分子。

[0013] 在一些实施方案中，一种或多种生物分子包含CRISPR/Cas9组 分(例如，用于基因疗法、研究或诊断应用)。

[0014] 在一些实施方案中，一种或多种生物分子包含核酸(例如，治疗 性或诊断性核酸)。在一些实施方案中，核酸是反义寡核苷酸(参见例 如，7,592,440、7,919,472和9,045,754，其以引用的方式整体并入本 文)。在一些实施方案中，核酸是核酶。在一些实施方案中，核酸是 shRNA、miRNA、siRNA、piRNA、snoRNA、tsRNA或srRNA。

[0015] 在一些实施方案中，表达载体包含超增强子，其调控所述一种或 多种生物分子中的至少一种的表达。在一些实施方案中，表达载体编 码第一治疗性生物分子和第二治疗性生物分子，其中所述第一治疗性 生物分子和第二治疗性生物分子彼此表达不同的时间长度(例如，使 用不同的启动子和/或增强子表达或者在载体内在不同的表达盒中表 达)。在某些实施方案中，表达载体编码第一治疗性生物分子和第二 治疗性生物分子，其中所述第一治疗性生物分子和第二治疗性生物分 子是相同的(例如，单一载体具有两个表达盒，这两个表达盒都表达 相同或不同的治疗性生物分子)。在其他实施方案中，表达载体编码 第一治疗性生物分子、第二治疗性生物分子和第三治疗性生物分子， 其中所述第一治疗性生物分子、第二治疗性生物分子、第三治疗性生 物分子全部是相同的(例如，单一载体具有三个表达盒，这三个表达 盒全部表达相同或不同的治疗性生物分子)。

[0016] 在一些实施方案中，表达载体包含R6K复制起点。在一些实施 方案中，表达载体是不含CpG的或CpG减少的表达载体。在一些实 施方案中，表达载体不是不含CpG的或CpG减少的表达载体。

[0017] 本文还提供使用本文所述的组合物、试剂盒和/或系统的方法。例如，在一些实施方案中，本文提供使一种或多种治疗性生物分子在 受试者中表达的方法，其包括：a)将所述系统的第一组合物施用到受 试者中；以及b)将所述系统的第二组合物施用到所述受试者中。

[0018] 在一些实施方案中，本文提供使两种或更多种治疗性生物分子在 受试者中以不同的持续时间表达的方法，其包括：a)将系统的第一组 合物施用到受试者中；以及b)(例如，随后在300分钟内)将所述系统 的第二组合物施用到所述受试者中，其中载体在单独的盒中或在不同 启动子和/或增强子的控制下各自表达第一生物分子和第二生物分 子，使

得第一生物分子和第二生物分子在受试者中彼此表达不同的时 间长度。例如,由第一盒表达的第一分子在注射后存在至少7或21 或100天,而由第二盒表达的生物分子保持存在小于7天或14天。

[0019] 在一些实施方案中,方法的步骤b)从步骤a)之后的1至400分钟 (例如,1、2、3、4、5、6、7、8、9、10、12、15、20、30、40、50、 100、200、300、400分钟或其间的任何增量)开始。在一些实施方案 中,所述一种或多种生物分子在所述受试者中在所需(例如,治疗性) 水平下表达至少连续7天(例如,至少30天、至少1年或其间的任何 增量)。在某些实施方案中,第一治疗性生物分子在治疗性水平下表 达至少7天(例如,7…14…21…190…365天),并且第二治疗性 生物分子在第7天以与所述第二治疗性生物分子在第1天的初始表达 相比降低了至少50%(例如,至少50%…65%…75%…90%…或 99%降低)的水平表达。在具体实施方案中,第一治疗性生物分子在治 疗性水平下表达至少14天,并且第二治疗性生物分子在第14天以与 所述第二治疗性生物分子在第1天的初始表达相比降低了至少75% 的水平表达。在另外的实施方案中,第一治疗性生物分子包含CRISP 或单克隆抗体序列(或其片段,诸如F(ab)2),并且第二治疗性生物分 子包含Cas9蛋白。

[0020] 在一些实施方案中(例如,为了增加所需生物分子的表达水平), 所述方法还包括步骤c):重复步骤a)和b)一次或多次。

[0021] 在一些实施方案中,生物分子是治疗性生物分子。可选择任何合 适的或所需的治疗性生物分子。在一些实施方案中,一种或多种治疗 性生物分子包含抗PCSK9单克隆抗体,其在足以减少LDL(例如, 在人受试者中)的水平下表达。在一些实施方案中,一种或多种治疗 性生物分子表达抗A型流感干细胞抗原单克隆抗体(例如,针对广泛 范围的A型流感株广泛地免疫的单克隆抗体)。在一些实施方案中, 一种或多种治疗性生物分子表达抗CD20和抗CD47单克隆抗体的组 合。在一些实施方案中,一种或多种治疗性生物分子表达抗PD-1单 克隆抗体、一种或多种自身肿瘤新抗原以及任选地一种或多种免疫调 节细胞因子。

[0022] 在一些实施方案中,本发明提供用于使一种或多种蛋白质和/或 生物活性核酸分子在受试者中表达(例如,在治疗性水平下持续在宿 主中产生治疗作用所需的延长的时间段)的组合物、系统、试剂盒以 及方法。在某些实施方案中,提供系统和试剂盒,其包括:第一组合 物,所述第一组合物包含第一量的聚阳离子结构(例如,空阳离子脂 质体、空阳离子胶束或空阳离子乳液);以及第二组合物,所述第二 组合物包含治疗有效量的一种或多种表达载体(例如,不与脂质体缔 合的非病毒表达载体)(例如,不含CpG的或CpG减少的表达载体), 其中所述表达载体包含第一核酸序列,所述第一核酸序列编码:i)第 一治疗性蛋白(或非治疗性蛋白,诸如标记物蛋白),和/或ii)第一生物 活性核酸分子。在某些实施方案中,所述表达载体包含编码第二、第 三和/或第四治疗性或非治疗性蛋白和/或第二、第三或第四生物活性 核酸分子的第二、第三或第四核酸序列。在一些实施方案中,所述第一核酸序列进一步编码第二、第三、第四、第五和/或第六治疗性蛋 白和/或第二、第三、第四、第五和/或第六生物活性核酸分子。在其 他实施方案中,将此类第一组合物和第二组合物依序(例如,全身性 地)施用至受试者,使得所述一种或多种治疗性蛋白和/或生物活性核 酸分子在所述受试者中表达(例如,在治疗性水平下(例如,持续至少 5天或至少50天,或至少100...200....或至少400天),使得一种或多 种疾病或病状得到治疗或者一种或多种生理性状得到改变;在预防性 水平下(例如,持续至少5天或至少50天,或至少

100...200....或至 少400天)，使得一种或多种疾病、病状和/或感染得到预防)。

[0023] 在一些实施方案中，本文提供使第一治疗性蛋白和/或生物活性 核酸分子在受试者(例如，人或非人哺乳动物)中表达的方法，其包括：a)向受试者施用(例如，全身性地)第一组合物，其中所述第一组合物 包含第一量的聚阳离子结构(例如，空阳离子脂质体、空阳离子胶束 或空阳离子乳液)，并且其中所述第一组合物不含或基本上不含核酸 分子(例如，核酸在组合物中是不可检测的或几乎不可检测的)；以及 b)向所述受试者施用(例如，全身性地，血管内地等)第二组合物(例如， 在施用第一组合物后的约2…10…50…100…200…300…400分 钟内开始)，其中所述第二组合物包含一定量的表达载体(例如，不与 脂质体或任何其他载剂缔合的非病毒表达载体)，其中所述表达载体 是不含CpG的或CpG减少的表达载体，其中所述表达载体中的每种 包含一种或多种编码以下的核酸序列：i)第一、第二、第三、第四、 第五和/或第六治疗性蛋白或非治疗性蛋白；和/或ii)第一、第二、第三、第四、第五和/或第六生物活性核酸分子。在某些实施方案中， 作为施用所述第一组合物和施用所述第二组合物的结果，所述第一治 疗性或非治疗性蛋白和/或所述生物活性核酸分子在所述受试者中表 达(例如，在针对疾病或病状的治疗性水平下，持续至少5…50…100…300天…400天或更长时间，或者在足以改变生理或疾病性状 的有效水平下)。在某些实施方案中，存在于所述第一组合物中的聚 阳离子结构(例如，空脂质体)具有约20-85nm(例如20…25…30… 40…45…50…55…60…65…70…75…80…85nm)的z-平均 直径。在某些实施方案中，所述聚阳离子结构是具有约72-76nm的 z-平均直径的空脂质体，并且是小单层囊泡。

[0024] 在一些实施方案中，本文提供使第一治疗性或非治疗性蛋白和/ 或生物活性核酸分子在受试者中表达的方法，其包括：a)向受试者施 用第一组合物，其中所述受试者具有疾病或病状的至少一种症状，或 至少具有待改变的生理性状，其中所述第一组合物包含第一量的聚阳 离子结构(例如，空阳离子脂质体、空阳离子胶束或空阳离子乳液)， 并且其中所述第一组合物不含或基本上不含核酸分子；以及b)在施用 所述第一组合物后的约100分钟或约200…或400分钟内向所述受试 者施用(或开始向所述受试者施用)第二组合物，其中所述第二组合物 包含治疗有效量的表达载体(例如，其中所述表达载体是不含CpG的 或CpG减少的表达载体)，其中所述表达载体各自包含第一核酸序列， 所述第一核酸序列编码：i)第一治疗性或非治疗性蛋白，和/或ii)第一 生物活性核酸分子；c)向所述受试者施用地塞米松棕榈酸酯和/或中性 脂质，所述地塞米松棕榈酸酯和/或中性脂质在所述第一组合物和/或 第二组合物中，或存在于第三组合物(例如，在施用所述第一组合物 或第二组合物后的100或200…或400分钟内施用)中。在一些实施 方案中，作为施用所述第一组合物、施用所述第二组合物和施用地塞 米松棕榈酸酯和/或中性脂质的结果，所述第一治疗性蛋白和/或生物 活性核酸分子在所述受试者中在针对所述疾病或病状的治疗性水平 下或在足以改变所述生理或疾病性状的有效水平下表达。

[0025] 在某些实施方案中，地塞米松棕榈酸酯是在所述第一组合物中， 并且其中2.0％至20.0％(例如，2.0％…2.5％…3.0％…10％… 15％…或20％)的所述第一组合物包含地塞米松棕榈酸酯。在某些实 施方案中，地塞米松棕榈酸酯以所述第三组合物形式施用，所述第三 组合物在施用所述第一组合物和/或第二组合物之前施用，或在所述 第一组合物和/或第二组合物之后施用，但在所述第一组合物和/或第 二组合物施用后的100…400分

钟内施用。在某些实施方案中，所述 方法还包括d)向所述受试者施用地塞米松，所述地塞米松在所述第一 组合物和/或第二组合物和/或第三组合物中，或存在于第四组合物(例如，在施用所述第一或第二组合物或第三组合物后的100或300分钟 内开始，如在所述施用中的任一者之前或在其他施用之后)中。在某 些实施方案中，存在于所述第一组合物中的聚阳离子结构(例如，空 脂质体)具有约20-85nm(例如20…25…30…40…45…50… 55…60…65…70…75…80…85nm)的z-平均直径。在某些实施 方案中，所述聚阳离子结构是具有约72-76nm的z-平均直径的空脂 质体，并且是小单层囊泡。

[0026] 在一些实施方案中，A)所述比例是10:1至18:1；B)2.0％至20.0％ 的所述第一组合物包含地塞米松或地塞米松棕榈酸酯；和/或C)所述 表达载体中的每种各自仅包含单个表达盒(即，每种载体中不存在其 他表达盒)，其中所述表达盒包含编码第一治疗性蛋白的第一核酸序 列和编码第二治疗性蛋白的第二核酸序列，并且其中所述表达盒编码 在所述第一核酸序列与所述第二核酸序列之间的自裂解肽序列(或其 他裂解序列)。在某些实施方案中，自裂解肽包含F2A、P2A、T2A 或E2A。在一些实施方案中，在自裂解肽的上游包括弗林蛋白酶识别 位点和/或(S)GSG接头以增强裂解效率。在具体实施方案中，所述第 一治疗性蛋白包含单克隆抗体轻链，并且所述第二治疗性蛋白包含所 述单克隆抗体的重链(例如，当在受试者中表达时所述轻链和重链组 合以形成单克隆抗体片段(例如，Fab)或单克隆抗体)。在某些实施方 案中，所述聚阳离子结构包含空脂质体。在具体实施方案中，存在于 所述第一组合物中的空脂质体具有约50-85nm的平均直径。在某些 实施方案中，所述方法还包括施用药剂或另外的调控表达载体，所述 药剂或另外的调控表达载体在所述第一组合物和/或第二组合物中或 存在于第三组合物中，其中与不向所述受试者施用所述药物剂时相比 (例如对于仅需要表达特定有限时间量的治疗剂来说)，所述药剂增加 或减少在治疗或有效水平下的表达和/或在所述治疗或有效水平下的 表达的时间长度。在具体实施方案中，所述药剂选自秋水仙碱、地塞 米松、地塞米松棕榈酸酯、中性脂质、丙戊酸、茶碱、西地那非、氨 来呫诺、氯喹、SAHA以及L-精氨酸+西地那非。

[0027] 在一些实施方案中，所述表达载体各自还包含调控核酸序列，其 中所述调控核酸序列减少在不存在所述调控核酸序列的情况下将发 生的第一核酸序列的表达的持续时间。在其他实施方案中，所述调控 核酸序列选自由以下组成的组：启动子、增强子、编码第二蛋白质的 第二核酸序列和/或第二生物活性核酸分子。在另外的实施方案中， 所述第一组合物中的第一量的聚阳离子结构包含至少第一种和第二 种不同类型的阳离子脂质体的混合物，与在所述方法中采用仅所述第 一种或仅所述第二种类型的阳离子脂质体时第一治疗性蛋白和/或第 一生物活性核酸分子的表达相比，所述混合物降低这种表达。在具体实施方案中，所述治疗性蛋白在高于1ug/ml(例如，1.1-1.5ug/ml) 的水平下表达，并且其中所述治疗性蛋白在所述受试者中在所述水平 下表达至少连续7天(例如，至少7…21…50…100…或400天)。

[0028] 在某些实施方案中，本文提供使第一治疗性蛋白和/或生物活性 核酸分子在受试者中表达的方法，其包括：a)向受试者施用(例如，全 身性地)第一组合物，其中所述受试者具有疾病或病状的至少一种症 状，具有感染一种或多种传染性疾病的风险，或具有待改变的至少一 种生理性状(例如，造血干细胞的水平)，其中所述第一组合物包含第 一量的聚阳离子结构(例如，空阳离子脂质体、空阳离子胶束或空阳 离子乳液)，并且其中所述第一

组合物不含或基本上不含核酸分子；以及b)在施用所述第一组合物后的约2…10…25…100…200或 400分钟内开始(或完成)向所述受试者施用(例如,全身性地)第二组合 物,其中所述第二组合物包含治疗有效量的表达载体(例如,质粒)， 其中所述表达载体是不含CpG的或CpG减少的表达载体(例如,所述 表达载体的核酸序列已被改变为含有比通常存在于所述载体中的序 列的野生型型式中更少的CpG二核苷酸),或者是含有CpG的载体(例如,采用野生型C-CSF,其含有多个CpG二核苷酸),其中所述表达 载体各自包含一个或多个核酸序列,其编码:i)第一治疗性蛋白(或第 一和第二治疗性蛋白,或第一、第二和第三治疗性蛋白等),和/或ii) 第一生物活性核酸分子(或第一和第二或更多生物活性核酸分子),并 且其中,作为施用所述第一组合物和施用所述第二组合物的结果,并 且其中,作为施用所述第一组合物和第二组合物的结果,所述一种或 多种治疗性蛋白和/或所述一种或多种生物活性核酸分子在所述受试 者中在针对所述疾病或病状的治疗性水平下或在足以改变所述生理 或疾病性状的有效水平下表达。

[0029] 在某些实施方案中,在第二组合物中所述表达载体不与聚阳离子 结构(例如,空阳离子脂质体、空阳离子胶束或空阳离子乳液))或其他 分子缔合(并且在所述第二组合物中不存在可检测的聚阳离子结构)。在其他实施方案中,所述表达载体是裸非病毒表达载体(例如,质粒)。在某些实施方案中,所述表达载体是病毒表达载体(例如,腺相关病 毒载体或腺病毒载体或合成mRNA、miRNA、核酶或shRNA核酸载 体)。在具体实施方案中,所述第一组合物和/或第二组合物全身、局 部、经皮、皮内、口服、肌内、静脉内、到胃肠道、膀胱中或通过肺 吸入或通过鞘内或心室内途径施用。

[0030] 在某些实施方案中,所述一种或多种治疗性蛋白和/或一种或多 种生物活性核酸分子在所述受试者中在治疗或有效水平下表达连续 至少5…20…63…100…200…300天…1年或更长。在一些实 施方案中,所述方法还包括:c)在自施用所述第一组合物和第二组合物起的至少5…20…63…100…200…300天…或1年后测试所述 受试者(例如,身体成像或扫描)或来自所述受试者的样品(例如,血液、 血清、血浆、组织、尿液等),以及确定所述一种或多种治疗性蛋白 和/或一种或多种生物活性核酸分子在所述受试者中在所述治疗性或 有效水平下表达(例如,由于第一组合物和第二组合物的单次治疗， 治疗水平在受试者中得以维持在所述受试者中产生治疗性和/或预防 性作用所需的时间段)。在另外的实施方案中,所述方法还包括:d) 生成指示所述治疗性蛋白和/或生物活性核酸分子在所述受试者中在 所述治疗性或有效水平下表达(例如,持续一定量的时间)的书面和/ 或电子报告。在其他实施方案中,将所述报告从进行所述测试的实验 室发送至治疗临床医生或从业者和/或患者。

[0031] 在一些实施方案中,所述治疗性蛋白和/或生物活性核酸分子在 至少50pg/ml…100…500…1000…1500…4000…8000… 9500…1,000,000pg/ml(1ug/ml)…1.5ug/ml或更高的水平下表达， 并且其中测定来自所述受试者的血液、血清或血浆样品(或其他生物 样品)以确定在施用所述第一组合物和第二组合物后达到治疗性或有 效水平,持续至少5…7…10…25…45…63…150…300天或更 长时间。在其他实施方案中,所述一种或多种治疗性蛋白在至少50 pg/ml或至少100pg/ml或至少500、1,000,000pg/ml(1ug/ml)…1.5 ug/ml或更高的水平下表达,并且其中所述治疗性蛋白在所述受试者 中在所述水平下表达连续至少5…7…10…25…45…63…150… 300…350天。在某些实施方案中,在施用所述第一组

合物和第二组 合物后至少48小时后,所述治疗性蛋白和/或生物活性核酸分子在所 述受试者中表达(例如,在治疗水平下)而无临床上显著的升高的毒性 (例如,如通过ALT(丙氨酸转氨酶)和/或AST(天冬氨酸转氨酶)所测 量)。

[0032] 在某些实施方案中,所述治疗性蛋白是人G-CSF(例如,如由SEQ ID NO:1编码,或与SEQ ID NO:1具有至少98%同一性的序列)并且 在受试者中在至少100pg/ml的治疗性水平下(如在血液、血清或血浆 样品中所测量)表达,其中所述治疗性蛋白在所述受试者中表达至少7 天,并且其中所述疾病、病状或生理性状选自由以下组成的组:由化 学疗法引起的中性粒细胞减少症、干细胞供体或受体的血液中造血干 细胞的水平不升高、心脏变性、脑缺血、肌萎缩性侧索硬化、嗜中性 粒细胞缺乏病以及辐射暴露。在具体实施方案中,所述G-CSF表达 至少5或6或7天但不超过约10天(例如,使用药物、启动子/增强子 组合、在核酸载体内的另外表达盒或另外表达的蛋白质以将产生限制 至约10天,以避免由表达超过约10天引起的任何毒性嗜中性粒细胞 相关的副作用)。在其他实施方案中,所述治疗性蛋白是利妥昔单抗 或类似的抗CD20抗体或抗体片段。在一些实施方案中,所述治疗性 蛋白是人因子IX或类似的蛋白质。

[0033] 在具体实施方案中,所述一种或多种治疗性蛋白和/或一种或多 种生物活性核酸分子在所述治疗水平下在受试者中表达足够量的时 间以减少或消除至少一种症状(或所有症状)而所述受试者不必接受向 所述受试者提供所述一种或多种治疗性蛋白和/或一种或多种生物活 性核酸分子的任何其他治疗。在其他实施方案中,在足够时间期间, 所述受试者不接受任何其他特定治疗(例如,没有向所述受试者提供 一种或多种治疗性蛋白或生物活性核酸分子的其他特定的治疗性治 疗)。在某些实施方案中,所述受试者具有一种或多种疾病的多种症 状,并且其中所述足够量的时间是使得所述一种或多种疾病和/或所述一种或多种病状的多种症状的全部或基本上全部在所述受试者中 减轻或消除(例如,永久性地或持续至少20天…50天…200天… 1年或更长时间)。在其他实施方案中,在足够的时间期间,所述受试 者不接受任何其他疾病特异性治疗。

[0034] 在一些实施方案中,所述聚阳离子结构(例如,空阳离子脂质体、空阳离子胶束或空阳离子乳液)的第一量是约0.01-70、30-50或20-60 微摩尔/1千克的受试者(例如,0.01…1…10…20…40…或60微 摩尔/千克)。在其他实施方案中,所述第一量的聚阳离子结构(例如, 空阳离子脂质)与所述治疗有效量的表达载体的比例是0.5:1至25:1 纳摩尔的聚阳离子结构(例如,空阳离子脂质)与1μg的表达载体(例 如,0.5:1…1:1…4:1…8:1…12:1…17:1…21:1…或25:1)。在某 些实施方案中,所述第一量的聚阳离子结构(例如,空阳离子脂质)与 所述治疗有效量的表达载体的比例是7:1至13:1纳摩尔的聚阳离子结 构(例如,空阳离子脂质)与1μg的表达载体。在具体实施方案中,所 述表达载体的治疗有效量是0.001-8.0毫克的表达载体/1千克的受试 者(例如,0.001…0.1…3.0…4.5…5.7…7.1…8.0毫克/千克)。在 一些实施方案中,表达载体的治疗有效量是0.001至1μg/1千克的受 试者(例如,0.001…0.01…0.1…1μg/千克的受试者)。在某些实施 方案中,所述表达载体的治疗有效量是约0.01-4.0毫克的表达载体/1 千克的受试者。

[0035] 在一些实施方案中,所述第一核酸序列编码第一、或第一和第二、或第一、第二和第三治疗性蛋白。在另外的实施方案中,所述第一核 酸序列编码所述一种或多种生物活性核酸分子。在其他实施方案中, 所述受试者是人。在另外的实施方案中,所述表达载体是不

含CpG 的表达载体。在其他实施方案中，所述表达载体是CpG减少的表达 载体。在其他实施方案中，所述治疗性蛋白是人蛋白质或动物蛋白质。

[0036] 在一些实施方案中，所述聚阳离子结构不含有胆固醇(例如，不 含胆固醇的空阳离子胶束或脂质体)。在某些实施方案中，所述阳离 子脂质体各自包含至少60％DOTAP和/或DPTAP(例如，60％… 75％…85％…95％…98％…100％DOTAP和/或DPTAP)。在其他 实施方案中，全部或基本上全部的阳离子脂质体是多层囊泡。在其他 实施方案中，全部或基本上全部的阳离子脂质体是单层囊泡。在其他 实施方案中，所述阳离子脂质体各自包含至少99％DOTAP或99％ DPTAP。在其他实施方案中，所述空阳离子脂质体各自包含DOTAP 和胆固醇。在另外的实施方案中，所述阳离子脂质体各自包含约三分 之一的胆固醇和约三分之二的DOTAP和/或DPTAP。在其他实施方 案中，所述第一核酸序列编码人G-CSF(例如，如在SEQ ID NO:1中 所示)。

[0037] 在某些实施方案中，所述生物活性核酸分子包含选自以下的序 列：shRNA序列、miRNA序列、反义序列、核酶和/或CRISPR单一 引导RNA序列(sgRNA)。在其他实施方案中，所述CRISPR sgRNA 包含：i)Cas9核酸酶募集序列(tracRNA)，和ii)与sgRNA靶位点杂交 的靶特异性序列(crRNA)。在具体实施方案中，所述生物活性核酸分 子靶向人p65(亦称NF-κ-B p65或RELA)。一种或多种RNA序列的 任何所需组合可在载体中编码或与感兴趣的非RNA编码的分子组 合。例如，在一些实施方案中，在载体中包括多个表达盒(例如，2、3、4个等)，每个表达不同的感兴趣的分子。在一些实施方案中，感 兴趣的分子包括载体中含有的多个单一CRISPR/Cas9引导盒。

[0038] 在其他实施方案中，所述表达载体中的每种还包含第二核酸序 列，所述第二核酸序列编码：i)第二治疗性蛋白，和/或ii)第二生物活 性核酸分子。在一些实施方案中，所述表达载体中的每种还包含第三 核酸序列，所述第三核酸序列编码：i)第三和/或第四治疗性蛋白，和 /或ii)第三和/或第四生物活性核酸分子。在其他实施方案中，所述表 达载体中的每种还包含与第一核酸序列缔合的第一启动子和与第二 核酸序列缔合的第二启动子，并且其中所述第一启动子和第二启动子 相同或不同。在其他实施方案中，所述第一核酸序列的治疗性或有效 表达水平和/或所述治疗性或有效表达水平的持续时间与在所述第二 核酸不存在和/或不从所述表达载体表达时的所述表达水平和持续时 间相比降低。在其他实施方案中，所述第一核酸序列在治疗性水平下 表达至少5天，但少于21天(例如，5…7…13…16…20…以及 21天)。在某些实施方案中，所述第一核酸序列编码治疗性蛋白，并 且其中所述治疗性蛋白包含人G-CSF。

[0039] 在其他实施方案中，当所述表达载体中的每种包含与所述第一核 酸序列缔合的第一启动子和第一增强子时，所述表达载体提供在治疗 性或有效水平下持续第一时间长度和/或在第一表达水平下的表达，并且其中当不同于所述第一启动子的第二启动子置换所述表达载体 上的第一启动子和/或不同于所述第二增强子的第二增强子置换所述 表达载体上的第一增强子时，所述第一时间长度和/或表达水平发生 改变。在其他实施方案中，在治疗性或有效水平下持续第一时间长度 的表达是持续至少10…15…45…100…200…300天，并且其中 用第二启动子和/或第二增强子置换使在所述治疗性或有效水平下的 表达减少至少于10…15…45…100…200天的第二时间长度。在 其他实施方案中，所述表达载体中的每种包含第一启动子和第一增强 子，并且其中所述第一启动子和所述第一增强子

引起在治疗性水平下 持续至少5天但少于21…15…或10天的表达。在具体实施方案中，所述第一核酸序列编码治疗性蛋白，并且其中所述治疗性蛋白包含人 G-CSF。

[0040] 在一些实施方案中，所述方法还包括施用一种或多种药物剂，所 述一种或多种药物剂在所述第一组合物和/或第二组合物中或存在于 第三组合物中，其中与不向受试者施用所述一种或多种药物剂时相 比，所述一种或多种药物剂增加或减少第一核酸的表达(例如，在治 疗性或有效水平下，和/或在所述治疗性或有效水平下的表达的时间 长度)。在具体实施方案中，所述药物剂增加受试者中第一核酸的表 达水平，并且其中所述药物选自秋水仙碱、免疫抑制剂、地塞米松、 地塞米松棕榈酸酯、西地那非或L-精氨酸+西地那非。在某些实施方 案中，所述药物(例如，地塞米松或地塞米松棕榈酸酯)以聚阳离子结 构(例如，空阳离子脂质组合物)的2.0％与20.0％之间，诸如以2.0％… 2.5％…3.5％..4.5％…6.0％…15％…或20％)存在。在其他实施方案 中，在施用聚阳离子结构和载体组合物之前或之后，向受试者施用所 述药物(例如，地塞米松或地塞米松棕榈酸酯)。在某些实施方案中， 存在于所述第一组合物中的聚阳离子结构(例如，空脂质体)具有约 20-85nm(例如20…25…30…40…45…50…55…60…65… 70…75…80…85nm)的z-平均直径。在某些实施方案中，所述聚 阳离子结构是具有约72-76nm的z-平均直径的空脂质体，并且是小 单层囊泡。在一些实施方案中，除将此类药剂并入第一组合物中之外， 在所述第一组合物和/或第二组合物的给药之前，向受试者提供药物 剂(例如，地塞米松)。

[0041] 在其他实施方案中，与未向受试者施用所述药物剂时相比，当向 所述受试者施用所述药物剂时，治疗性蛋白以至少两倍高(或至少3 或4或5倍高)的水平表达。在具体实施方案中，所述药物剂降低第 一核酸序列的表达水平，并且其中所述药物剂是L-精氨酸。在其他 实施方案中，与未向受试者施用所述药物剂时相比，当向所述受试者 施用所述药物剂时，治疗性蛋白以至少两倍低(或至少三倍或四倍低) 的水平表达。在一些实施方案中，所述药物剂包含抗炎剂。在另外的 实施方案中，所述药物剂选自由以下组成的组：氨来呫诺、氯喹、丙 戊酸、茶碱、DHA、前列腺素以及SAHA。

[0042] 在其他实施方案中，所述表达载体不含可操作的基质附着区 (MAR)序列。在某些实施方案中，所述表达载体不含可操作的EBNA-1 和/或EBV病毒序列。在某些实施方案中，就在所述施用所述第一组 合物和第二组合物之前，受试者的血压未改变(例如，无物理转染助 剂应用于所述受试者以尝试增加第一核酸序列的表达)。在某些实施 方案中，表达载体包含以下中的至少一种：R6K复制起点(例如，位 于载体中的基因的3'或5'UTR)、hr3增强子、BV3信号序列、Syn21 序列、Δ-p10序列或MITD(MHC I类输送信号(MHC class I trafficking signal))序列。

[0043] 在具体实施方案中，所述治疗性水平和/或有效水平是至少150… 100…500…1000…1500…5000…1,000,000pg/ml(1ug/ml)… 1.5ug/ml或更高，并且其中来自受试者的血液、血清或血浆样品(或 其他生物样品)在施用所述第一组合物和第二组合物后至少7… 10…25…45…63…150…300…400天或更长时间被确定为在所 述治疗性水平和/或有效水平下。在具体实施方案中，将来自受试者 的样品用ELISA测定法或通过质谱法进行测试以确定表达水平。

[0044] 在一些实施方案中，所述方法还包括向所述受试者施用治疗有效 量的中性脂质体，其中所述中性脂质体存在于所述第一组合物和/或 第二组合物中，和/或在第三组合物

中施用,并且其中所述治疗有效 量的中性脂质体在施用所述第二组合物之前施用至受试者。在某些实 施方案中,所述中性脂质体至少包含选自以下的材料:phospholipon 90H、氢化大豆PC、硬脂酸以及棕榈酸。在其他实施方案中,所述 治疗有效量的中性脂质体存在于第一组合物中或存在于施用至受试 者的第三组合物中。在其他实施方案中,所述中性脂质体是多层囊泡 或被挤压至0.2或0.1um。在具体实施方案中,施用治疗有效量的中 性脂质体引起受试者中第一治疗性蛋白和/或生物活性核酸分子与不 向所述受试者施用中性脂质体时发生的相比至少3…4…25… 100…350…或600倍高的表达。在某些实施方案中,施用至受试者 的空阳离子脂质体与中性脂质体的比例在约2:1与1:5之间(例如, 2:1…1:1…2:5…1:5)。

[0045] 在一些实施方案中,本文提供使第一治疗性蛋白和/或生物活性 核酸分子在受试者中表达的方法,其包括:a)向受试者施用第一组合 物,其中所述第一组合物包含抗炎剂;以及b)在施用所述第一组合物 的约2分钟…20分钟…1小时…24小时…5天…7天…9天 或更长时间内向所述受试者施用或开始施用第二组合物,其中所述第 二组合物包含治疗有效量的聚合复合物,其中每种聚合复合物包含表 达载体和聚乙烯亚胺,其中所述表达载体是不含CpG的或CpG减少 的表达载体,其中每种表达载体包含第一核酸序列,所述第一核酸序 列编码:i)第一治疗性蛋白(和/或第一蛋白质和第二蛋白质),和/或ii) 第一(和/或第一和第二)生物活性核酸分子,并且其中作为施用所述第 一组合物和施用所述第二组合物的结果,所述第一治疗性蛋白和/或 生物活性核酸分子在所述受试者中表达。在其他实施方案中,所述受 试者具有疾病或病状的至少一种症状,或具有至少一种期望被改变的 生理性状,并且其中所述第一治疗性蛋白和/或生物活性核酸分子在 针对所述疾病、病状或待改变的生理性状的治疗性水平下表达。在一 些实施方案中,所述抗炎剂选自由以下组成的组:氨来呫诺、氯喹和 辛二酰苯胺异羟肟酸(suberanilohydroxamic acid)(SAHA)。

[0046] 在一些实施方案中,所述表达载体包含质粒或其他非病毒载体。在其他某些实施方案中,步骤b)中的施用通过全身性地施用第二组合 物来完成。

[0047] 在一些实施方案中,本文提供系统或试剂盒,其包括:a)第一组 合物,所述第一组合物包含第一量的聚阳离子结构(例如,空阳离子 脂质体、空阳离子胶束或空阳离子乳液),其中所述第一组合物不含 或基本上不含核酸分子;以及b)第二组合物,所述第二组合物包含治 疗有效量的表达载体(例如,非病毒且不与脂质体或其他载剂分子缔 合),其中所述表达载体是不含CpG的或CpG减少的表达载体,其中 所述表达载体中的每种包含第一核酸序列,所述第一核酸序列编码: i)第一治疗性蛋白或非治疗性蛋白,和/或ii)第一生物活性核酸分子。在其他实施方案中,所述表达载体是裸非病毒表达载体(例如,质粒)。在某些实施方案中,以下情况中的至少一种适用:i)其中第一量的聚 阳离子结构(例如,空阳离子脂质体)与治疗有效量的表达载体的比例 是2:1至25:1或5:1至25:1;ii)其中2.0%至20.0%的第一组合物包含 地塞米松棕榈酸酯;iii)其中所述第一组合物还包含中性脂质,并且 iv)其中所述聚阳离子结构包含空脂质体,并且其中存在于所述第一组 合物中的空脂质体具有约20-85nm(例如,20…25…30…40… 45…50…55…60…65…70…75…80…85nm)的z-平均直径。在某些实施方案中,所述载体是病毒载体(例如,AAV或腺病毒载体)。在具体实施方案中,所述治疗性蛋白是人G-CSF(例如,如SEQ ID NO:1中所示)或含有多个CpG二核苷酸的野生型人G-CSF。

[0048] 在具体实施方案中,所述聚阳离子结构(例如,空阳离子脂质体) 的第一量是在0.1至7.0毫摩尔(例如,0.1…5.0…7.0毫摩尔)或1.5 与5.0毫摩尔之间(例如,用于施用至人受试者的合适量)。在其他实 施方案中,所述第一量的聚阳离子结构(例如,空阳离子脂质体)与所 述治疗有效量的表达载体的比例是0.5:1至25:1纳摩尔的空阳离子脂 质与1μg的表达载体(例如,0.5:1…1:1…5:1…10:1…15:1… 25:1)。在一些实施方案中,所述第一量的聚阳离子结构(例如,空阳 离子脂质)与所述治疗有效量的表达载体的比例是7:1至13:1纳摩尔 的聚阳离子结构与1μg的表达载体(例如,7:1…10:1…或13:1)。在 其他实施方案中,所述表达载体的治疗有效量在0.1与800毫克之间 (例如,用于施用至人受试者的合适量,诸如当载体是质粒时)。在某 些实施方案中,所述量是1…25…400…或800毫克的用于人施用 的表达载体。

[0049] 在其他实施方案中,所述第一核酸序列编码第一治疗性蛋白。在 另外的实施方案中,所述第一核酸序列编码所述生物活性核酸分子。 在具体实施方案中,所述表达载体是不含CpG的表达载体。在其他 实施方案中,所述表达载体是CpG减少的表达载体。在其他实施方 案中,所述第一治疗性蛋白是人蛋白质。在其他实施方案中,所述第 一核酸序列编码治疗性蛋白,并且其中所述治疗性蛋白包含人 G-CSF、利妥昔单抗、单克隆抗体或单克隆抗体片段(例如,Fab)或人 因子IX。

[0050] 在某些实施方案中,所述空阳离子脂质体、胶束或乳液各自包含 至少60%DOTAP和/或DPTAP(例如,60%…75%…85%…95%…98%…100%DOTAP和/或DPTAP),并且可不含胆固醇(例如,组合 物中无可检测的胆固醇)。在其他实施方案中,全部或基本上全部的空阳离子脂质体、胶束或乳液是多层囊泡。在其他实施方案中,全部 或基本上全部的空阳离子脂质体、胶束或乳液是单层、多层或寡层囊 泡。在其他实施方案中,所述空阳离子脂质体、胶束或乳液各自包含 至少99%DOTAP或至少99%DPTAP,并且可不含胆固醇。在其他 实施方案中,所述空阳离子脂质体各自包含DOTAP和/或DPTAP和 胆固醇。在另外的实施方案中,所述空阳离子脂质体、胶束或乳液各 自包含约三分之一的胆固醇和约三分之二的DOTAP和/或DPTAP。

[0051] 在某些实施方案中,所述第一生物活性核酸分子包含选自以下的 序列:siRNA或shRNA序列、miRNA序列、反义序列、CRISPR多 聚化单一引导序列以及CRISPR单一引导RNA序列(sgRNA)。在其 他实施方案中,所述CRISPR sgRNA包含:i)Cas9核酸酶募集序列(tracRNA),和ii)与sgRNA靶位点杂交的靶特异性序列(crRNA)。

[0052] 在其他实施方案中,所述表达载体中的每种还包含第二核酸序 列,所述第二核酸序列编码:i)第二治疗性蛋白,和/或ii)第二生物活 性核酸分子。在其他实施方案中,所述表达载体中的每种还包含与第 一核酸序列缔合的第一启动子和与第二核酸序列缔合的第二启动子, 并且其中所述第一启动子和第二启动子相同或不同。

[0053] 在一些实施方案中,所述试剂盒和系统还包括第一容器和第二容 器,并且其中第一组合物存在于所述第一容器中,且第二组合物存在 于所述第二容器中。在其他实施方案中,试剂盒和系统还包括包装部 件(例如,纸板盒、塑料袋等),其中所述第一容器和所述第二容器在 所述包装部件内部。

[0054] 在某些实施方案中,所述试剂盒和系统还包括一种或多种药物 剂,其中所述一种或多种药物剂存在于第一组合物和/或第二组合物 中或存在于第三组合物中。在另外的实

施方案中,所述药物剂选自秋 水仙碱、免疫抑制剂、地塞米松、西地那非、L-精氨酸或L-精氨酸+ 西地那非。在其他实施方案中,所述药物剂包含抗炎剂。在其他实施 方案中,所述药物剂选自由以下组成的组:氨来呫诺、丙戊酸、茶碱、 氯喹以及SAHA。

[0055] 在具体实施方案中,所述表达载体不含可操作的基质附着区 (MAR)序列。在另外的实施方案中,所述表达载体不含可操作的 EBNA-1和/或EBV病毒序列。

[0056] 在某些实施方案中,所述试剂盒和系统还包括治疗有效量的中性 脂质体,其中所述中性脂质体存在于第一组合物和/或第二组合物中 或存在于第三组合物中。在另外的实施方案中,所述治疗有效量的中 性脂质体存在于第一组合物中。在其他实施方案中,所述中性脂质体 是多层或寡层或单层囊泡。在其他实施方案中,空阳离子脂质体或胶 束与中性脂质体的比例在约2:1与1:5之间(例如,2:1…1:1…3:5… 1:5)。

[0057] 在一些实施方案中,本文提供用于组合用于治疗适于用第一治疗 性蛋白和/或生物活性核酸分子的体内表达治疗的疾病的第一组合物 和第二单独的组合物,其中所述第一组合物包含第一量的聚阳离子结 构(例如,空阳离子脂质体、空阳离子胶束或空阳离子乳液),其中所 述第一组合物不含或基本上不含核酸分子;以及b)包含治疗有效量的 表达载体的第二组合物,其中所述表达载体是不含CpG的或CpG减 少的表达载体,其中所述表达载体中的每种包含第一核酸序列,所述 第一核酸序列编码:i)第一治疗性蛋白,和/或ii)第一生物活性核酸分 子。

[0058] 在某些实施方案中,本文提供使第一治疗性蛋白和/或生物活性 核酸分子在受试者中表达的方法,其包括:a)向受试者施用第一组合 物,其中所述第一组合物包含第一量的聚阳离子结构(例如,空阳离 子脂质体、空阳离子胶束或空阳离子乳液),并且其中所述第一组合 物不含或基本上不含核酸分子;以及b)在施用所述第一组合物后的约 100分钟或200分钟内向所述受试者施用第二组合物,其中所述第二 组合物包含治疗有效量的非病毒表达载体,其中所述表达载体是不含 CpG的或CpG减少的表达载体,其中所述表达载体各自包含第一核 酸序列,所述第一核酸序列编码:i)第一治疗性蛋白,和/或ii)第一生 物活性核酸分子,并且其中作为施用所述第一组合物和施用约所述第 二组合物的结果,所述第一治疗性蛋白和/或所述生物活性核酸分子 在所述受试者中在高于(例如,至少150…300…575…1000… 1500…2000…5000…或1,000,000pg/ml)的水平下表达(例如,如在 来自所述受试者的血清样品中所测量(例如,在自所述第一施用和第 二施用起的7…25…50天后)。

[0059] 在某些实施方案中,本文提供方法,其包括:向受试者施用组合 物,所述组合物包含治疗有效量的不含CpG或CpG减少的非病毒表 达载体或含有CpG的载体并且包含第一核酸序列,所述第一核酸序 列编码:i)第一治疗性蛋白,和/或ii)第一生物活性核酸分子,并且其 中作为施用所述第一组合物和第二组合物的结果,所述第一治疗性蛋 白和/或所述生物活性核酸分子在所述受试者中在高于100pg/ml(例 如,至少150..400...1200…2000…5000…或超过1,000,000pg/ml) 的水平下表达(例如,如在来自所述受试者的血清样品中所测量(例如, 在自所述第一施用和第二施用起的7…25…50天后)。

[0060] 在某些实施方案中,所述聚阳离子结构包含空阳离子脂质体、胶 束或乳液。在其他实施方案中,所述聚阳离子结构包含以下中的一种 或多种(单独地或与聚阳离子结构组合):直链或支链聚乙烯亚胺、树 枝状聚合物(例如,基于乙二胺、聚赖氨酸、聚精氨酸和硫

酸鱼精蛋 白的第四代聚酰胺-胺型(pamaam)树枝状聚合物)、聚赖氨酸以及硫酸 鱼精蛋白。在某些实施方案中,所述聚阳离子结构作为阳离子乳液提 供。在具体实施方案中,所述乳液中的表面活性剂选自:氯化十六烷 基吡啶、十六烷基三甲基溴化铵等。在其他实施方案中,所述乳液还 包含中性组分,诸如吐温、斯盘和甘油三酯。在具体实施方案中,所 述乳液包含阳离子脂质,例如像DOTAP、DPTAP、DOTMA或DDAB。 在一些实施方案中,所述乳液是自乳化乳液或微乳液(SEDDS、 SMEDDS)。

[0061] 在一些实施方案中,本文提供使第一蛋白质和第二蛋白质和/或 第一生物活性核酸分子和第二生物活性核酸分子在受试者中表达的 方法,其包括:a)向受试者施用第一组合物,其中所述受试者具有疾 病或病状的至少一种症状,或至少具有待改变的生理性状,其中所述 第一组合物包含第一量的聚阳离子结构,并且其中所述第一组合物不 含或基本上不含核酸分子;以及b)在施用所述第一组合物后的约100 分钟内向所述受试者施用第二组合物,其中所述第二组合物包含治疗 有效量的表达载体,其中所述表达载体是非病毒的且是不含CpG的 或CpG减少的表达载体,其中所述表达载体各自包含:i)第一表达盒, 所述第一表达盒编码:A)第一蛋白质,和/或B)第一生物活性核酸分 子;以及ii)第二表达盒,所述第二表达盒编码:A)第二蛋白质和/或 B)第二生物活性核酸分子。在某些实施方案中,作为施用所述第一组 合物和施用所述第二组合物的结果,所述第一蛋白质和第二蛋白质和/或所述第一生物活性核酸分子和第二生物活性核酸分子在所述受试 者中在针对所述疾病或病状的治疗性水平下或在足以改变所述生理 或疾病性状的有效水平下表达。

[0062] 在具体实施方案中,所述第一蛋白质包含单克隆抗体轻链,并且 所述第二蛋白质包含所述单克隆抗体的重链。在其他实施方案中,所 述第一表达盒和第二表达盒均包含调控元件。在另外的实施方案中, 所述调控元件在所述第一表达盒和第二表达盒中是相同的或不同的。

[0063] 在一些实施方案中,本文提供在使单克隆抗体(mAb)、Fab、F(ab)2 和/或scFv受试者中表达的方法,其包括:a)向受试者施用第一组合 物,其中所述受试者具有疾病或病症的至少一种症状,或至少具有待 改变的生理性状,其中所述第一组合物包含第一量的聚阳离子结构, 并且其中所述第一组合物不含或基本上不含核酸分子;以及b)在施用 所述第一组合物后的约300分钟内向所述受试者施用第二组合物,其 中所述第二组合物包含治疗有效量的表达载体,所述表达载体编码 mAb、Fab、F(ab)2和/或scFv,并且其中作为施用所述第一组合物和 施用所述第二组合物的结果,所述第一治疗性蛋白在所述受试者中在 针对所述疾病或病状的治疗性水平下或在足以改变所述生理或疾病 性状的有效水平下表达。

[0064] 在某些实施方案中,所述第一量的聚阳离子结构与所述治疗有效 量的表达载体的比例是5:1至25:1。在其他实施方案中,表达载体是 不含CpG的或CpG减少的表达载体。在其他实施方案中,所述表达 载体含有多个CpG基序,并且/或者不是不含CpG的或CpG减少的表达载体。在另外的实施方案中,mAb、Fab、F(ab)2和/或scFv在所 述受试者中在治疗性水平下表达持续至少连续7天而没有任何其他 施用。在其他实施方案中,所述至少连续7天是至少连续190天而没 有任何其他施用。

[0065] 在一些实施方案中,所述F(ab)2选自由以下组成的组:F(ab')2 阿非莫单抗(Afelimomab)、培阿赛珠单抗(Alacizumab pegol)、阿托度 单抗(Dorlimomab aritox)、厄

利珠单抗(Erlizumab)和伊戈伏单抗 (Igovomab)。在另外的实施方案中,Fab选自由以下组成的组:阿昔 单抗(Abciximab)、麻安莫单抗(Anatumomab mafenatox)、泊西他珠单 抗(Citatuzumab bogatox)、他那可单抗(Nacolomab tafenatox)、他那莫 单抗(Naptumomab estafenatox)、巯诺莫单抗(Nofetumomab merpentan)、雷珠单抗(Ranibizumab)、托珠单抗(Tadocizumab)、阿替 莫单抗(Telimomab aritox)、阿西莫单抗(Arcitumomab)、贝妥莫单抗 (Bectumomab)、比西单抗(Biciromab)、赛妥珠单抗(Certolizumab pegol) 和硫索单抗(Sulesomab)。在某些实施方案中,scFv选自由以下组成 的组:依芬古单抗(Efungumab)、莫奥珠单抗(Oportuzumab monatox) 和培克珠单抗(Pexelizumab)。

[0066] 在具体实施方案中,mAb选自由以下组成的组:3F8、8H9、阿 巴伏单抗(Abagovomab)、阿吐珠单抗(Abituzumab)、阿布鲁单抗 (Abrilumab)、阿克托单抗(Actoxumab)、阿达木单抗(Adalimumab)、 阿德木单抗(Adecatumumab)、阿杜单抗(Aducanumab)、阿非西维单抗 (Afasevikumab)、奥法木单抗(Afutuzumab)、阿仑珠单抗(Alemtuzumab)、阿利库单抗(Alirocumab)、喷替酸阿妥莫单抗 (Altumomab pentetate)、阿麦妥昔单抗(Amatuximab)、雷星-阿奈妥单 抗(Anetumab ravtansine)、阿尼富路单抗(Anifrolumab)、安芦珠单抗 (Anrukinzumab)、阿珀利珠单抗(Apolizumab)、阿伐苏单抗(Ascrinvacumab)、阿瑟利珠单抗(Aselizumab)、阿特利珠单抗 (Atezolizumab)、阿替努单抗(Atinumab)、阿特立单抗(Atlizumab)、阿 托木单抗(Atorolimumab)、阿维鲁单抗(Avelumab)、巴匹奈珠单抗 (Bapineuzumab)、巴司利昔单抗(Basiliximab)、巴韦妥昔单抗(Bavituximab)、贝戈洛单抗(Begelomab)、贝利木单抗(Belimumab)、 本雷利珠单抗(Benralizumab)、柏替利木单抗(Bertilimumab)、贝西来 索单抗(Besilesomab)、贝伐赛珠单抗(Bevacizumab)、贝洛托舒单抗 (Bezlotoxumab)、比玛卢单抗(Bimagrumab)、比美吉珠单抗 (Bimekizumab)、莫-比伐珠单抗(Bivatuzumab mertansine)、比勒斯单 抗(Bleselumab)、布隆妥维单抗(Blontuvetmab)、布洛索珠单抗 (Blosozumab)、伯考赛珠单抗(Bococizumab)、布雷库单抗 (Brazikumab)、维汀-布仑妥昔单抗(Brentuximab vedotin)、布瑞吉努单 抗(Briakinumab)、布洛鲁单抗(Brodalumab)、布洛赛珠单抗(Brolucizumab)、布隆妥珠单抗(Brontictuzumab)、布洛舒单抗 (Burosumab)、卡比利珠单抗(Cabiralizumab)、卡那吉努单抗 (Canakinumab)、莫星-坎妥珠单抗(Cantuzumab mertansine)、雷星-坎 妥珠单抗(Cantuzumab ravtansine)、卡普赛珠单抗(Caplacizumab)、卡 罗单抗喷地肽(Capromab pendetide)、卡鲁单抗(Carlumab)、卡罗妥昔 单抗(Carotuximab)、cBR96-阿霉素免疫缀合物、西利珠单抗 (Cedelizumab)、克果图珠单抗(Cergutuzumab amunaleukin)、西妥昔单 抗(Cetuximab)、Ch.14.18、西舒妥木单抗(Cixutumumab)、克拉吉珠单 抗(Clazakizumab)、克立昔单抗(Clenoliximab)、泰坦-克利妥珠单抗(Clivatuzumab tetraxetan)、考曲妥珠单抗(Codrituzumab)、雷星-考妥 昔单抗(Coltuximab ravtansine)、考那妥木单抗(Conatumumab)、康赛 珠单抗(Concizumab)、CR6261、克瑞奈珠单抗(Crenezumab)、克罗特 度单抗(Crotedumab)、达塞妥珠单抗(Dacetuzumab)、达克利珠单抗 (Daclizumab)、达洛妥珠单抗(Dalotuzumab)、培戈-达匹利珠单抗 (Dapirolizumab pegol)、达雷妥木单抗(Daratumumab)、德屈库单抗(Dectrekumab)、登赛珠单抗(Demcizumab)、地宁图珠单抗 (Denintuzumab mafodotin)、迪诺舒单抗(Denosumab)、玛汀-迪妥昔珠 单抗(Depatuxizumab mafodotin)、德尔罗妥单抗

生物素(Derlotuximab biotin)、地莫单抗(Detumomab)、地努妥昔单抗(Dinutuximab)、地利 伏单抗(Diridavumab)、多玛洛珠单抗(Domagrozumab)、卓齐妥单抗 (Drozitumab)、杜利图单抗(Duligotumab)、度匹鲁单抗(Dupilumab)、 度伐鲁单抗(Durvalumab)、度司妥单抗(Dusigitumab)、依洛美昔单抗 (Ecromeximab)、依库利珠单抗(Eculizumab)、埃巴单抗(Edobacomab)、 依曲考罗单抗(Edrecolomab)、依法利珠单抗(Efalizumab)、埃迪鲁单 抗(Eldelumab)、依更妥单抗(Elgemtumab)、依洛妥珠单抗 (Elotuzumab)、艾西莫单抗(Elsilimomab)、依米妥珠单抗 (Emactuzumab)、依玛妥珠单抗(Emibetuzumab)、依米赛珠单抗 (Emicizumab)、依那妥珠单抗(Enavatuzumab)、维汀-恩弗妥单抗 (Enfortumab vedotin)、培戈赖莫单抗(Enlimomab pegol)、依诺妥珠单 抗(Enoblituzumab)、依诺吉珠单抗(Enokizumab)、依诺苏单抗 (Enoticumab)、恩司妥昔单抗(Ensituximab)、西坦-依匹妥莫单抗 (Epitumomab cituxetan)和依普妥珠单抗(Epratuzumab)。

[0067] 在一些实施方案中,mAb选自由以下组成的组:厄瑞努单抗 (Erenumab)、依他赛珠单抗(Etaracizumab)、依卓利珠单抗 (Etrolizumab)、依维苏单抗(Evinacumab)、依沃苏单抗(Evolocumab)、 埃比韦卢单抗(Exbivirumab)、法索单抗(Fanolesomab)、法拉莫单抗(Faralimomab)、法乐妥珠单抗(Farletuzumab)、法司努单抗 (Fasinumab)、非维珠单抗(Felvizumab)、菲扎吉努单抗(Fezakinumab)、 菲巴珠单抗(Fibatuzumab)、菲拉妥珠单抗(Ficlatuzumab)、菲吉妥木单 抗(Figitumumab)、非利伏单抗(Firivumab)、夫兰妥单抗(Flanvotumab)、 夫来库单抗(Fletikumab)、芳托利珠单抗(Fontolizumab)、弗雷鲁单抗(Foralumab)、弗雷韦卢单抗(Foravirumab)、夫瑞利木单抗 (Fresolimumab)、伏雷努单抗(Fulranumab)、伏妥昔单抗(Futuximab)、 伽奈珠单抗(Galcanezumab)、加利昔单抗(Galiximab)、加尼妥单抗 (Ganitumab)、冈特奈卢单抗(Gantenerumab)、加威利莫单抗(Gavilimomab)、奥-吉妥珠单抗(Gemtuzumab ozogamicin)、格沃吉珠 单抗(Gevokizumab)、吉仑妥昔单抗(Girentuximab)、维汀-格仑妥木单 抗(Glembatumumab vedotin)、戈利木单抗(Golimumab)、戈利昔单抗 (Gomiliximab)、谷瑟库单抗(Guselkumab)、艾巴利珠单抗(Ibalizumab)、 替坦-艾瑞妥莫单抗(Ibritumomab tiuxetan)、艾卢苏单抗(Icrucumab)、 艾达赛珠单抗(Idarucizumab)、IMAB362、伊玛鲁单抗(Imalumab)、英 赛罗单抗(Imciromab)、英加妥珠单抗(Imgatuzumab)、英拉苏单抗(Inclacumab)、雷星-英达妥昔单抗(Indatuximab ravtansine)、维汀-英度 妥单抗(Indusatumab vedotin)、英比利珠单抗(Inebilizumab)、英夫利西 单抗(Infliximab)、艾诺利莫单抗(Inolimomab)、奥星-艾诺妥珠单抗 (Inotuzumab ozogamicin)、英特妥木单抗(Intetumumab)、艾匹利木单 抗(Ipilimumab)、艾雷妥木单抗(Iratumumab)、艾萨妥昔单抗(Isatuximab)、艾托利珠单抗(Itolizumab)、艾塞吉珠单抗(Ixekizumab)、 克立昔单抗(Keliximab)、拉贝珠单抗(Labetuzumab)、兰帕利珠单抗 (Lampalizumab)、拉那鲁单抗(Lanadelumab)、兰洛珠单抗 (Landogrozumab)、恩星-拉妥昔单抗(Laprituximab emtansine)、乐瑞吉 珠单抗(Lebrikizumab)、乐玛来索单抗(Lemalesomab)、棱德里珠单抗(Lendalizumab)、仑兹鲁单抗(Lenzilumab)、乐迪利木单抗 (Lerdelimumab)、乐萨妥木单抗(Lexatumumab)、利比韦卢单抗 (Libivirumab)、维汀-利法妥珠单抗(Lifastuzumab vedotin)、利格利珠 单抗(Ligelizumab)、沙泰坦-利洛托单抗(Lilotomab satetraxetan)、林妥 珠单抗(Lintuzumab)、利瑞鲁单抗(Lirilumab)、洛迪赛珠单抗

(Lodelcizumab)、洛吉维单抗(Lokivetmab)、莫星-洛沃妥珠单抗(Lorvotuzumab mertansine)、鲁卡妥木单抗(Lucatumumab)、培戈-鲁利 珠单抗(Lulizumab pegol)、鲁昔单抗(Lumiliximab)、鲁妥珠单抗 (Lumretuzumab)、MABp1、玛帕妥木单抗(Mapatumumab)、玛格妥昔 单抗(Margetuximab)、马妥珠单抗(Matuzumab)、玛弗利木单抗(Mavrilimumab)、美珀利珠单抗(Mepolizumab)、美特利木单抗 (Metelimumab)、米拉妥珠单抗(Milatuzumab)、明瑞妥莫单抗 (Minretumomab)、索星-米妥昔单抗(Mirvetuximab soravtansine)、米妥 莫单抗(Mitumomab)、莫加利珠单抗(Mogamulizumab)、莫那利珠单抗(Monalizumab)、莫罗木单抗(Morolimumab)、莫他韦珠单抗 (Motavizumab)、帕舒托-莫塞妥莫单抗(Moxetumomab pasudotox)、莫 罗单抗-CD3(Muromonab-CD3)、那米鲁单抗(Namilumab)、恩星-那妥 昔单抗(Naratuximab emtansine)、那呐妥单抗(Narnatumab)、那他利珠 单抗(Natalizumab)、那赛昔珠单抗(Navicixizumab)、那韦伏单抗 (Navivumab)、奈巴库单抗(Nebacumab)、奈西妥木单抗(Necitumumab)、 奈莫利珠单抗(Nemolizumab)、奈瑞利莫单抗(Nerelimomab)、奈伐苏 单抗(Nesvacumab)、尼莫妥珠单抗(Nimotuzumab)、尼沃鲁单抗 (Nivolumab)、奥托萨昔单抗(Obiltoxaximab)、奥比妥珠单抗 (Obinutuzumab)、奥卡妥珠单抗(Ocaratuzumab)、奥瑞利珠单抗 (Ocrelizumab)、奥度莫单抗(Odulimomab)、奥法妥木单抗 (Ofatumumab)、奥拉妥单抗(Olaratumab)、奥洛吉珠单抗(Olokizumab)、 奥玛利珠单抗(Omalizumab)、奥那妥珠单抗(Onartuzumab)、昂妥昔珠 单抗(Ontuxizumab)、奥匹努单抗(Opicinumab)、奥瑞戈沃单抗 (Oregovomab)、奥替苏单抗(Orticumab)、奥特昔珠单抗(Otelixizumab)、 奥乐妥珠单抗(Otlertuzumab)、奥塞鲁单抗(Oxelumab)、奥扎奈珠单抗 (Ozanezumab)、奥佐利珠单抗(Ozoralizumab)、帕吉昔单抗 (Pagibaximab)、帕利韦珠单抗(Palivizumab)、潘瑞鲁单抗 (Pamrevlumab)、帕尼妥木单抗(Panitumumab)、帕尼库单抗 (Pankomab)、帕诺巴库单抗(Panobacumab)、帕萨妥珠单抗 (Parsatuzumab)、帕考利珠单抗(Pascolizumab)和帕妥昔珠单抗 (Pasotuxizumab)。

[0068] 在某些实施方案中,mAb选自由以下组成的组:帕特利珠单抗 (Pateclizumab)、帕曲妥单抗(Patritumab)、兰洛利珠单抗 (Pembrolizumab)、珀雷吉珠单抗(Perakizumab)、珀妥珠单抗 (Pertuzumab)、匹地利珠单抗(Pidilizumab)、维汀-匹那妥珠单抗(Pinatuzumab vedotin)、阿巴伏单抗(Pintumomab)、普拉鲁单抗 (Placulumab)、洛扎利珠单抗(Plozalizumab)、泊加丽珠单抗 (Pogalizumab)、维汀-珀拉妥珠单抗(Polatuzumab vedotin)、珀奈珠单 抗(Ponezumab)、帕博利珠单抗(Prezalizumab)、普立昔单抗(Priliximab)、瑞托萨昔单抗(Pritoxaximab)、普瑞妥木单抗 (Pritumumab)、奎利珠单抗(Quilizumab)、雷考妥莫单抗 (Racotumomab)、雷曲妥单抗(Radretumab)、雷非韦卢单抗(Rafivirumab)、雷泮赛珠单抗(Ralpancizumab)、雷姆赛卢单抗 (Ramucirumab)、雷昔巴库单抗(Raxibacumab)、瑞法奈珠单抗 (Refanezumab)、瑞加韦单抗(Regavirumab)、瑞司利珠单抗 (Reslizumab)、瑞洛妥木单抗(Rilotumumab)、利努苏单抗(Rinucumab)、 利散吉珠单抗(Risankizumab)、瑞妥昔单抗(Rituximab)、培戈-利伐巴 珠单抗(Rivabazumab pegol)、洛巴妥木单抗(Robatumumab)、洛来度 单抗(Roledumab)、洛莫索珠单抗(Romosozumab)、隆他利珠单抗 (Rontalizumab)、特司林-洛伐妥珠单抗(Rovalpituzumab tesirine)、洛维利珠单抗(Rovelizumab)、卢普利珠单抗(Ruplizumab)、戈维替康-沙西 妥珠单抗(Sacituzumab govitecan)、萨玛利珠单抗(Samalizumab)、沙培 利单抗(Sapelizumab)、萨

瑞鲁单抗(Sarilumab)、喷地肽沙妥莫单抗 (Satumomab pendetide)、瑟库吉努单抗(Secukinumab)、瑟瑞妥单抗 (Seribantumab)、瑟托萨昔单抗(Setoxaximab)、SGN-CD19A、SGN-CD33A、西罗珠单抗(Sibrotuzumab)、司法利木单抗 (Sifalimumab)、司妥昔单抗(Siltuximab)、辛妥珠单抗(Simtuzumab)、 西普利珠单抗(Siplizumab)、司卢库单抗(Sirukumab)、维汀-索非妥珠 单抗(Sofituzumab vedotin)、索拉奈珠单抗(Solanezumab)、松妥珠单抗 (Sontuzumab)、司达鲁单抗(Stamulumab)、苏韦珠单抗(Suvizumab)、 他巴鲁单抗(Tabalumab)、替他珠单抗(Tacatuzumab tetraxetan)、他利 珠单抗(Talizumab)、坦妥维单抗(Tamtuvetmab)、他奈珠单抗 (Tanezumab)、帕他普莫单抗(Taplitumomab paptox)、他瑞妥单抗 (Tarextumab)、特非巴珠单抗(Tefibazumab)、特那妥莫单抗 (Tenatumomab)、特奈利昔单抗(Teneliximab)、特普利珠单抗 (Teplizumab)、特普妥木单抗(Teprotumumab)、特度鲁单抗 (Tesidolumab)、特托罗单抗(Tetulomab)、特折鲁单抗(Tezepelumab)、 替西木单抗(Ticilimumab)、替加妥珠单抗(Tigatuzumab)、替曲吉珠单 抗(Tildrakizumab)、替莫鲁单抗(Timolumab)、维汀-替索妥单抗 (Tisotumab vedotin)、托西利珠单抗(Tocilizumab)、托雷利珠单抗 (Toralizumab)、托萨托舒单抗(Tosatoxumab)、托维妥单抗(Tovetumab)、 曲洛吉努单抗(Tralokinumab)、曲妥珠单抗(Trastuzumab)、曲妥珠单 抗-美坦新偶联物(Trastuzumab emtansine)、曲加利珠单抗(Tregalizumab)、曲美利木单抗(Tremelimumab)、曲戈卢单抗 (Trevogrumab)、塞莫白介素-2-妥考妥珠单抗(Tucotuzumab celmoleukin)、乌利妥昔单抗(Ublituximab)、乌洛鲁单抗(Ulocuplumab)、 乌瑞鲁单抗(Urelumab)、厄托萨珠单抗(Urtoxazumab)、优特吉努单抗(Ustekinumab)、乌托鲁单抗(Utomilumab)、他立林-伐达妥昔单抗 (Vadastuximab talirine)、维汀-万多妥珠单抗(Vandortuzumab vedotin)、 万替妥单抗(Vantictumab)、伐努赛珠单抗(Vanucizumab)、伐帕利昔单 抗(Vapaliximab)、伐立鲁单抗(Varlilumab)、伐特利珠单抗 (Vatelizumab)、维多利珠单抗(Vedolizumab)、维妥珠单抗 (Veltuzumab)、维帕利莫单抗(Vepalimomab)、维森苏单抗 (Vesencumab)、威司利珠单抗(Visilizumab)、沃巴利珠单抗 (Vobarilizumab)、沃洛赛昔单抗(Volociximab)、玛汀-沃瑟妥珠单抗(Vorsetuzumab mafodotin)、伏妥莫单抗(Votumumab)、珍妥珠单抗 (Xentuzumab)、扎鲁妥木单抗(Zalutumumab)、扎诺利木单抗 (Zanolimumab)、扎妥昔单抗(Zatuximab)、齐拉木单抗(Ziralimumab) 和阿托-佐利莫单抗(Zolimomab aritox)。

[0069] 在具体实施方案中,所述疾病或病状包括病毒或细菌感染。在其 他实施方案中,所述疾病或病状包括心血管疾病或动脉粥样硬化。在 其他实施方案中,所述疾病或病状包括自身免疫疾病。在某些实施方 案中,所述疾病或病状包括癌症(例如,肺癌、卵巢癌、皮肤癌、淋 巴瘤、脑癌、前列腺癌、胰腺癌、乳腺癌、甲状腺癌、结肠癌等)。在其他实施方案中,所述方法还包括以下情况中的至少一种:i)其中 2.0%至20%的第一组合物包含地塞米松棕榈酸酯;ii)其中所述第一组 合物还包含中性脂质;并且iii)其中聚阳离子结构包含空脂质体,并 且其中存在于所述第一组合物中的空脂质体具有约20-85nm的z-平 均直径。

[0070] 在一些实施方案中,本文提供系统和试剂盒,其包括:第一组合 物,所述第一组合物包含第一量的聚阳离子结构脂质体,其中所述第 一组合物不含或基本上不含核酸分子;以及b)第二组合物,所述第二 组合物包含治疗有效量的表达载体,其中所述表达载体包含编码单克 隆抗体(mAb)、Fab、F(ab)2和/或scFv的核酸序列。在其他实施方案 中,单克隆抗

体(mAb)、Fab、F(ab)2和/或scFv选自以上以及以下表 3中列举的那些。

[0071] 在某些实施方案中,以下情况中的至少一种适用:i)其中第一量 的聚阳离子结构与治疗有效量的表达载体的比例是5:1至25:1;ii)其 中2.0%至20%的第一组合物包含地塞米松棕榈酸酯;iii)其中所述第 一组合物还包含中性脂质;并且iv)其中所述聚阳离子结构包含空脂 质体,并且其中存在于所述第一组合物中的空脂质体具有约20-85nm 的z-平均直径。

[0072] 在一些实施方案中,所述中性脂质包括1,2-二肉豆蔻酰基-SN-甘 油基-3-磷酰胆碱(DMPC;二肉豆蔻酰基磷脂酰胆碱)。在其他实施方 案中,所述中性脂质选自:二硬脂酰基磷脂酰胆碱(DSPC)、二棕榈酰 基磷脂酰胆碱(DPPC)、棕榈酰基油酰基磷脂酰胆碱(POPC)、棕榈酰 基硬脂酰基磷脂酰胆碱(PSPC)、卵黄磷脂酰胆碱(EPC)、氢化或非氢 化的大豆磷脂酰胆碱(HSPC)或向日葵磷脂酰胆碱。

附图说明

[0073] 图1,h-GCSF的不含CpG的修饰的核酸序列(SEQ ID NO:1)和 h-GCSF的氨基酸序列(SEQ ID NO:2)。在SEQ ID NO:1中以下划线示 出CpG二核苷酸已被消除的位置。这些序列是可与本文的方法、组 合物、系统和试剂盒一起使用的修饰的h-GCSF的实例。

[0074] 图2A示出单一IV顺序注射离子脂质体,接着注射编码利妥昔 单抗的双盒或单表达盒质粒DNA载体产生长期治疗性血清水平的利 妥昔单抗蛋白。

[0075] 图2B示出,如实施例1中所述,162天并且随后176天前(参见 图2A)顺序注射阳离子脂质体,接着注射双盒抗CD20 DNA表达载体 的小鼠的血清裂解CD20阳性Raji人B淋巴瘤细胞,与高浓度的重 组利妥昔单抗单克隆抗体蛋白的效率一样。

[0076] 图3示出通过在小鼠中进行顺序IV阳离子脂质体注射,接着IV 注射含有DNA载体的双盒或单盒2A在小鼠中产生的血清抗CD20 水平。

[0077] 图4示出在单一IV注射双盒抗CD20 DNA载体之后24小时, 将超增强子元件并入DNA表达载体中增加小鼠中的血清抗CD20 mAb水平。

[0078] 图5示出质粒715.1 2a(P2A)(SEQ ID NO:3),其编码通过2A自 裂解肽分离的抗CD20 mAb重链和轻链cDNA。

[0079] 图6示出质粒718.1(SEQ ID NO:4),其为分别编码抗CD20 mAb 重链和轻链cDNA的双表达盒质粒载体。

[0080] 图7示出质粒902.8(P2A)(SEQ ID NO:5),其编码通过2A自裂 解肽分离的抗CD20 mAb重链和轻链cDNA。

[0081] 图8示出质粒p113.2(SEQ ID NO:6),其与p718.1相同,但在第 二编码盒的上游包括单一超增强子。

[0082] 图9示出在小鼠中进行IV注射之后分别8天和1天的小鼠 NFkB-p65蛋白的抗p65 CRISPR/Cas9和抗p65核酶介导的敲低。

[0083] 图10示出IV注射之后13天小鼠NFkB-p65蛋白的抗p65 CRISPR 介导的敲低。

[0084] 图11示出在小鼠中进行IV注射之后分别13天和1天的小鼠 NFkB-p65蛋白的抗p65 CRISPR和抗p65反义介导的敲低。

[0085] 图12示出在小鼠中进行IV注射之后1天的小鼠NFkB-p65蛋白 的抗p65 shRNA介导

的敲低。

[0086] 图13示出核酶抗p65质粒(SEQ ID NO:7)。

[0087] 图14示出CRISPR1抗p65质粒(SEQ ID NO:8)。

[0088] 图15示出CRISPR2抗p65质粒(SEQ ID NO:9)。

[0089] 图16示出CRISPR抗p65质粒(SEQ ID NO:10)。

[0090] 图17A至图17B示出描述所实施的实验的实施例3的结果,其 证明单一IV顺序注射阳离子脂质体,接着注射编码人G-CSF基因的 质粒DNA载体在接下来的至少582天在小鼠中产生上述治疗性人 G-CSF血清蛋白水平(图17A)以及高于正常ANC水平(蓝线)的升高的 绝对嗜中性粒细胞计数(ANC)(图17B)。

[0091] 图18示出在顺序IV注射DOTAP阳离子脂质体,接着注射编码 HG-CSF的质粒DNA之后大鼠血清中的嗜中性粒细胞升高。

[0092] 图19示出抗p65反义质粒的质粒序列(SEQ ID NO:11)。

[0093] 图20示出抗小鼠NFkB-p65 shRNA载体p65 shB的质粒序列(图20,SEQ ID NO:12)。

[0094] 图21示出顺序IV注射1050纳摩尔的DOTAP阳离子脂质体, 接着注射70ug的HG-CSF质粒或不同形式的PCR生成的HG-CSF 表达盒DNA之后24小时的大鼠血清中人G-CSF的水平。

[0095] 图22示出在初始注射之后接下来至少302天的小鼠中小鼠血清 或血浆中的人G-CSF的水平(左轴)和全血中以每微升数千计的绝对 嗜中性粒细胞计数(ANC)(右轴)。

[0096] 图23示出在一次顺序注射阳离子脂质体,接着注射具有或没有 R6K复制起点的PCR生成的DNA之后106天的小鼠血清中的人 G-CSF水平。

[0097] 图24示出顺序注射具有或没有中性脂质或地塞米松棕榈酸酯的 阳离子脂质体,接着注射质粒DNA的小鼠中人G-CSF和对应的绝对 嗜中性粒细胞计数(ANC,右轴)水平。

[0098] 图25示出实施例6的结果,其示出使用第二增强子增加顺序IV 注射之后1天和8天的小鼠中的人G-CSF表达。

[0099] 图26示出质粒sv40-mCMVEF1的核酸序列(SEQ ID NO:13)。

[0100] 图27示出质粒mCMV-mCMVEF1的核酸序列(SEQ ID NO:14)。

[0101] 图28示出质粒mCMV-hCMVEF1的核酸序列(SEQ ID NO:15)。

[0102] 图29示出质粒mCMVEF1的核酸序列(SEQ ID NO:16)。

[0103] 图30示出顺序IV注射脂质体,接着注射质粒DNA(图中的前三 个组含有超增强子元件)之后24小时的人G-CSF的小鼠血清水平。

[0104] 图31示出质粒hr3-mCMVEF1#2的核酸序列(SEQ ID NO:17)。

[0105] 图32示出质粒hr3-mcmvEF1#5的核酸序列(SEQ ID NO:18)。

[0106] 图33示出质粒hr3-mcmvEF1#18的核酸序列(SEQ ID NO:19)。

[0107] 图34示出顺序IV注射脂质体和各种不同的FIX DNA表达质粒 之后24小时的人因子IX的血浆浓度。

[0108] 图35示出FIX质粒的核酸序列(SEQ ID NO:20)。

[0109] 图36示出FIX R6K1的核酸序列(SEQ ID NO:21)。

[0110] 图37示出FIX R6K2的核酸序列(SEQ ID NO:22)。

[0111] 图38示出FIX超增强子的核酸序列(SEQ ID NO:23)。

[0112] 图39示出FIX RNA-out的核酸序列(SEQ ID NO:24)。

[0113] 图40示出在小鼠中进行顺序IV注射之后40天的小鼠NFkB-p65 蛋白的抗p65 CRISPR/Cas9介导的敲低。

[0114] 图41A至图41B示出来自对一次顺序IV注射CRISPR/Cas9抗 NFkB p65质粒DNA载体的小鼠进行的实验的免疫组织化学染色的 切片。图41A示出林格氏处理的对照,并且图41B示出CRISPR/Cas9 抗NFkB p65处理的小鼠组织。

[0115] 图42A至图42D示出单一顺序IV注射阳离子脂质体,然后注射 HG-CSF DNA表达载体之后582天的对照和处理小鼠的骨髓的IHC 结果。图42A(20x)和图42B(60x),对照骨髓,示出各种不同的细胞 类型混合物包围正常股骨髓腔的骨小梁,其中深色染色的红系细胞特 别明显。图42C(20x)和图42D(60x),经处理的骨髓,示出单调的几 乎实心片的浅色染色的细胞替代股骨骨髓浅色染色的髓样细胞(多形 核白细胞)中的骨小梁元素,其中椭圆形、凹陷椭圆形、带和片段化 形式替代股骨骨髓内的其他细胞类型。

[0116] 图43A至图43D示出单一顺序IV注射阳离子脂质体,然后注射 HG-CSF DNA表达载体之后582天的对照和处理小鼠的脾脏组织的IHC结果。图43A(20x)和图43B(60x),对照脾脏,示出显示各种不 同细胞群体的正常脾脏的白(淋巴)髓的红色/深色部分。图43C(20x)和图43D(60x),经处理的脾脏,示出浅色染色的髓样细胞(多形核白 细胞),其中椭圆形、凹陷椭圆形、带和片段化形式替代大多数其他 细胞类型。

[0117] 图44A至图44D示出最后顺序IV注射阳离子脂质体,然后注射 HG-CSF DNA之后168天的对照和处理大鼠的骨髓组织的IHC结果。图44A(20x)和图42B(60x),对照骨髓,示出股骨骨髓中的各种不同 的细胞类型,其中圆形的深色染色的红细胞谱系特别明显。图44C(20x)和图44D(60x),经处理的骨髓,示出股骨骨髓中的浅色染色的 髓样细胞(多形核白细胞),其中椭圆形、凹陷椭圆形、带和片段化形 式占优势。仍然有少量深色染色的红细胞谱系细胞的簇。

[0118] 图45A至图45B。图45A,来自与图44相同的实验,示出40x 下的对照大鼠椎体,而图45B示出40x下的HGCSF大鼠椎体。

[0119] 图46示出质粒DNARx-31H4-2A的核酸序列(SEQ ID NO:25), 其编码通过2A自裂解肽分离的抗PCSK9 mAb重链和轻链cDNA。

[0120] 图47示出质粒DNARx-31H4的核酸序列(SEQ ID NO:26),其为 编码不同型式的抗PCSK9 mAb重链和轻链cDNA的双表达盒质粒载 体。

[0121] 图48示出质粒DNARx-21B12(P2A)的核酸序列(SEQ ID NO:27),其编码通过2A自裂解肽分离的抗PCSK9 mAb重链和轻链 cDNA。

[0122] 图49示出质粒DNARx-21B12的核酸序列(SEQ ID NO:28),其为 编码不同型式的抗PCSK9 mAb重链和轻链cDNA的双表达盒质粒载 体。

[0123] 图50示出质粒DNARx-CD47-2A(P2A)的核酸序列(SEQ ID NO:29),其编码通过2A自裂解肽分离的抗CD47 mAb重链和轻链 cDNA。

[0124] 图51示出质粒DNARx-CD47的核酸序列(SEQ ID NO:30),其为 分别编码抗CD47 mAb重链和轻链cDNA的双表达盒质粒载体。

[0125] 图52示出质粒DNARx-D8-2A的核酸序列(SEQ ID NO:31)。

[0126] 图53示出质粒DNARx-F10-2A的核酸序列(SEQ ID NO:32)。

[0127] 图54示出质粒DNARx-A66-2A(P2A)的核酸序列(SEQ ID NO:33)。

[0128] 图55示出质粒DNARx-D8的核酸序列(SEQ ID NO:34)。

[0129] 图56示出质粒DNARx-F10的核酸序列(SEQ ID NO:35)。

[0130] 图57示出质粒DNARx-A66的核酸序列(SEQ ID NO:36)。

[0131] 图58示出质粒DNARx-HA-MITD的核酸序列(SEQ ID NO:37)。

[0132] 图59示出质粒DNARx-SEC-部分HA-MITD的核酸序列(SEQ ID NO:38)。

[0133] 图60示出质粒DNARx-D8-2A-HA-MITD的核酸序列(SEQ ID NO:39)。

[0134] 图61示出质粒DNARx-F10-2A-HA-MITD的核酸序列(SEQ ID NO:40)。

[0135] 图62示出质粒DNARx-A66-2A-HA-MITD的核酸序列(SEQ ID NO:41)。

[0136] 图63示出质粒DNARx-D8-2A-SEC-部分-HA-MITD的核酸序列 (SEQ ID NO:42)。

[0137] 图64示出质粒DNARx-F10-2A-SEC-部分-HA-MITD的核酸序列 (SEQ ID NO:43)。

[0138] 图65示出质粒DNARx-A66-2A SEC-部分-MITD的核酸序列 (SEQ ID NO:44)。

[0139] 图66示出质粒011215#7的核酸序列(SEQ ID NO:45)。

[0140] 图67示出质粒011315#2的核酸序列(SEQ ID NO:46)。

[0141] 图68示出质粒122014#235的核酸序列(SEQ ID NO:47)。

[0142] 图69示出质粒DNARx-PD1-2A(P2A)的核酸序列(SEQ ID NO:48)。

[0143] 图70示出质粒DNARx-SEC-OVA-MITD的核酸序列(SEQ ID NO:49)。

[0144] 图71示出质粒DNARx-SEC-gp70-MITD的核酸序列(SEQ ID NO:50)。

[0145] 图72示出质粒DNARx-PD1-2A OVA的核酸序列(SEQ ID NO:51)。

[0146] 图73示出质粒DNARx-PD1-2A gp70的核酸序列(SEQ ID NO:52)。

[0147] 图74示出质粒DNARx CD20-2A Cas9的核酸序列(SEQ ID NO:53)。

[0148] 图75示出质粒DNARx CD20-2A HG-CSF的核酸序列(SEQ ID NO:54)。

[0149] 图76示出质粒p65 shA2的核酸序列(SEQ ID NO:55)。

[0150] 图77示出示出质粒PECAM sh对照的核酸序列是SEQ ID NO:56,图77。

[0151] 图78示出IV注射之后10天小鼠NFkB-p65蛋白的抗p65 CRISPR 介导的敲低。

[0152] 图79示出质粒EF1/U6 RelA1(020117#5)的核酸序列(SEQ ID NO:57)。

[0153] 图80示出质粒EF1/U6 RelA4(020117#8)的核酸序列(SEQ ID NO:58)。

[0154] 图81示出质粒hu1/EF1/U6 RelA1(021417#3)的核酸序列(SEQ ID NO:59)。

[0155] 图82示出实施例18的结果,其描述包含中性脂质(DMPC)和阳 离子脂质体如何增加小鼠中的血清抗CD20单克隆抗体水平。

[0156] 图83示出来自实施例19的结果,其描述采用地塞米松棕榈酸酯 和中性脂质体进一步增加体内基因表达。

[0157] 图84示出来自实施例20的结果,其描述在载体中包含Syn 21 和/或Δ-p10序列如何增加基因表达。

[0158] 图85示出表达抗CD20抗体并包含Syn 21和Δ-p10序列的载体 构建体的核酸序列(SEQ ID NO:82)。

[0159] 图86A至图86B示出实施例21的结果,其示出当在质粒中包含 hr3超增强子时,GCSF表达增加(图86A)并且利妥昔单抗抗CD20 表达增加(图86b)。

[0160] 图87A至图87B示出来自实施例22的结果,其描述将R6K复 制起点定位在因子IX基因的3'或5'UTR中增加在75ug水平(图87A) 和60ug水平(图87B)两者下的表达水平。

[0161] 图88A示出来自实施例23的结果，其示出在284天内在不同时 间点处的长期利妥昔单抗表达水平，从而显示长期表达。

[0162] 图88B示出来自实施例23的结果，其示出抗CD20小鼠血清能 够在与利妥昔单抗蛋白相当的水平下诱导人肿瘤细胞裂解。

[0163] 图89示出来自实施例24的结果，其示出在小鼠中表达至少92 天的治疗性抗IL-5mAb(2B6)血清水平。

[0164] 图90示出在实施例24中所使用的双盒单质粒DNA载体的核酸 序列，其编码抗人白介素-5mAb(美泊利单抗(Mepoluzimab)；2B6) 重链和轻链cDNA。

[0165] 图91A示出来自实施例25的结果，其示出完全中和的抗流感抗体 (5J8)在小鼠中表达至少85天。

[0166] 图91B示出来自实施例25的结果，其示出表达的抗流感抗体有 效地中和Ca109流行性流感株，持续>92天。

[0167] 图92示出在实施例25中所使用的双盒单质粒DNA载体的核酸 序列(SEQ ID NO:84)，其编码抗流感抗体(5J8)重链和轻链cDNA。

[0168] 图93示出实施例26的结果，其示出抗IL-5mAb以及hG-CSF 在小鼠中的表达水平在治疗性水平下持续至少66天。

[0169] 图94示出在实施例26中所使用的三盒单质粒DNA载体的核酸 序列(SEQ ID NO:85)，其编码抗人白介素-5mAb(美泊利单抗；2B6) 重链和轻链cDNA和人G-CSF cDNA。

[0170] 图95示出来自实施例27的结果，其示出hG-CSF表达的双盒 cDNA在小鼠中提供比单盒hG-CSF表达更高的血清水平。

[0171] 图96示出来自实施例28的结果，其示出表达抗人IL-5重链和 轻链的双盒载体产生比编码抗人IL-5的单盒DNA载体更高的抗人IL-5血清mAb水平。

[0172] 图97示出来自实施例29的结果，其示出表达抗5J8 mAb的双盒 载体在体内产生比编码抗5J8的单盒DNA载体更高的抗5J8血清 mAb水平。

[0173] 图98示出来自实施例30的结果，其示出双盒单质粒如何在体内 表达不同的mAb，并且共同注射的两个单盒质粒如何在体内表达不 同的mAb。

[0174] 图99A至图99B。图99A示出来自实施例31的结果，其示出在 43天内抗人IL-5mAb的血清表达水平，并且图99B示出在43天内 抗A型流感mAb的血清表达水平。

[0175] 图100示出来自实施例32的结果，其示出利妥昔单抗(抗CD20)、抗IL5 mAb和抗流感mAb均从单一载体(左侧)以及通过共同注射三 个单独载体(右侧)的同时表达。

[0176] 图101示出实施例33的结果，其示出表达抗PCSK9 mAb的单 质粒载体降低小鼠中的LDL水平。

[0177] 图102示出实施例34的结果，其示出表达抗PCSK9 mAb的小 鼠中的长期LDL水平降低。

[0178] 图103示出实施例35的结果，其示出表达抗PCSK9 mAb的小 鼠随时间推移具有与表达对照抗CD20抗体的对照小鼠相比更低的 LDL水平。

[0179] 图104示出实施例36的结果，其示出抗流感FI6 mAb表达约25 天，抗流感5J8 mAb和抗IL4 mAB表达超过100天，并且利妥昔单 抗表达超过275天。

[0180] 图105示出来自实施例37的结果，其示出来自所测试的全部四 个质粒剂量的良好

表达水平。

[0181] 图106示出实施例38的结果，其示出通过使用BV3信号序列增 强5J8 mAb的表达。

[0182] 图107A至图107D示出来自实施例39的结果。图107A示出对 照小鼠肺组织，并且图107B示出针对p53染色的人p53注射小鼠肺 组织，显示p53基因在小鼠肺中广泛地表达。图107C和图107D示 出染色的小鼠组织，其示出p53注射的小鼠中占优势的血管内皮细胞 人p53表达。

[0183] 图108示出在实施例39中所使用的质粒DNA载体的核酸序列 (SEQ ID NO:86)，其编码人p53。

[0184] 图109示出作为SUV、0.1μm挤出或MLV注射DOTAP脂质体 各自有效地在小鼠中表达hG-CSF。给予每组三只小鼠顺序IV注射。 第一注射含有800纳摩尔或1000纳摩尔的阳离子脂质体。阳离子脂 质体是以下三种大小中的一种:MLV、SUV或.1微米挤出。第一注 射两分钟之后接着编码hG-CSF的质粒载体的第二注射，以100ug 或120ug注射。

[0185] 图110示出作为0.2μm挤出或MLV共同注射DMPC或卵黄PC 中性脂质体各自有效地在小鼠中表达hG-CSF。给予每组三只小鼠顺 序IV注射。第一注射含有800纳摩尔的DOTAP SUV阳离子脂质体 以及500纳摩尔中性脂质体。中性脂质体为卵黄PC或DMPC，并且 为MLV或.2微米挤出。第一注射两分钟之后接着编码hG-CSF DNA 的90ug质粒载体。

[0186] 定义

[0187] 如本文所用，短语“CpG减少的”是指核酸序列或表达载体具有的 CpG二核苷酸比该序列或载体的野生型型式中存在的CpG二核苷酸 少。“不含CpG”是指主题核酸序列或载体不具有任何CpG二核苷酸。 含有CpG二核苷酸(例如，人G-CSF的野生型型式)的初始序列可通 过改变核酸序列而进行修饰以除去CpG二核苷酸。此类CpG二核苷 酸可不仅在编码序列中、而且在非编码序列中合适地减少或消除，所 述非编码序列包括例如5’和3’非翻译区(UTR)、启动子、增强子、 polyA、ITR、内含子以及存在于核酸分子或载体中的任何其他序列。

[0188] 如本文所用，“空脂质体”是指不含核酸分子但可含有其他生物活 性分子的脂质体(例如，仅由脂质分子本身或仅由脂质分子和小分子 药物组成的脂质体)。

[0189] 如本文所用，“空阳离子胶束”是指不含核酸分子但可含有其他生 物活性分子的阳离子胶束(例如，仅由脂质和表面活性剂分子本身组 成或仅由脂质和表面活性剂分子以及小分子药物组成的胶束)。

[0190] 如本文所用，“空阳离子乳液”是指不含核酸分子但可含有其他生 物活性分子的阳离子乳液或微乳液。

具体实施方式

[0191] 本发明提供用于使一种或多种生物分子在受试者、人或非人哺乳 动物中表达(例如，在治疗性水平下持续产生治疗作用所需的延长的 时间段)的组合物、系统、试剂盒以及方法。在某些实施方案中，提 供组合物、系统、试剂盒和方法，其包括:第一组合物，所述第一组 合物包含聚阳离子结构(例如，空阳离子脂质体、阳离子胶束、阳离 子乳液或阳离子聚合物);以及第二组合物，所述第二组合物包含编 码一种或多种感兴趣的生物分子的表达载体(例如，不与脂质体或其 他载剂缔合的非病毒表达载体)。

[0192] 本公开提供方法、系统和组合物，其使得能够通过单次注射(例 如，静脉内注射)阳离子脂质体并在之后不久接着注射(例如，静脉内 注射)编码治疗性蛋白的载体来产生比蛋白质的治疗性血清水平高许 多倍(例如，高2-20倍)的循环蛋白水平，持续延长的时间段，诸如190天或超过500天。因此，本文提供的方法实现全身性非病毒基因 递送的成功治疗性应用。

[0193] 此外，本文提供的系统、方法和组合物提供能够更精确地控制递 送基因在治疗水平下的表达的持续时间的通用(例如，非病毒)基因递 送和表达平台。这种控制递送基因的表达的持续时间的能力解决了基 因疗法领域内的需求，即控制蛋白质在治疗性水平下表达的持续时间 的能力。具体地说，现在存在广泛和扩展范围的FDA批准的重组分 泌型人蛋白质疗法。不同的批准的蛋白质疗法必须在治疗性水平下存 在持续非常不同的持续时间，以便有效且安全地治疗患者。不同蛋白 质疗法的推荐治疗持续时间从不到两周(HG-CSF)到患者的一生(因子 IX)变化。例如，对于每个三周化疗周期的仅前10天每天给予重组人G-CSF蛋白Neupogen。在每个每日Neupogen剂量之后大约14小时， 血清HG-CSF水平恢复至基线。使用这种10天治疗方案，因为其嗜 中性粒细胞增加作用仅在化疗诱导的嗜中性粒细胞减少症的这一大 约10天时期期间指示。从第11天到第21天的G-CSF升高通常不是 有益的，因为患者自身的嗜中性粒细胞产生能力恢复。给予Neupogen 超过第10天可引起有毒的嗜中性粒细胞相关副作用。相比之下，抗 TNF抗体常规施用数月或数年，并且因子IX置换持续患者的一生。 因此，不同的蛋白质必须在治疗性水平下产生持续不同的持续时间， 从不到两周到患者的一生。因此，能够控制其在患者中产生的在治疗 性水平下的基因表达的持续时间的基因治疗方法实现治疗终点，同时 避免了广泛范围的现在FDA批准的人治疗性蛋白的有毒副作用。本 文提供了可用于提供这种控制的各种技术。

[0194] 在某些实施方案中，本公开采用不含载体DNA的聚阳离子结构 (例如，空阳离子脂质体、空阳离子胶束或空阳离子乳液)，所述聚阳 离子结构在载体施用之前施用至受试者。在某些实施方案中，所述聚 阳离子结构是阳离子脂质和/或作为乳液提供。本公开不限于所采用 的阳离子脂质，在一些实施方案中，其可由以下中的一种或多种构成：DDAB，二甲基双十八烷基溴化铵;DPTAP(1,2-二棕榈酰基3-三甲 基铵丙烷);DHA;前列腺素，N-[1-(2,3-二油酰基氧基)丙基]-N,N,N-- 三甲基铵甲基硫酸酯;1,2-二酰基-3-二甲基铵-丙烷，(包括但不限于 二油酰基(DOTAP)、二肉豆蔻酰基、二棕榈酰基、二硬脂酰基);1,2- 二酰基-3-二甲基铵-丙烷，(包括但不限于二油酰基、二肉豆蔻酰基、 二棕榈酰基、二硬脂酰基);DOTMA，N-[1-[2,3-双(油酰基氧基)]丙 基]-N,N,N-三甲基氯化铵;DOGS，双十八烷基酰胺甘氨酰精胺;DC- 胆固醇，3.β.-[N-(N',N'-二甲基氨基乙烷)氨基甲酰基]胆固醇;DOSPA， 2,3-二油酰基氧基-N-(2(精胺甲酰胺基)-乙基)-N,N-二甲基-1-丙铵三氟 乙酸酯;1,2-二酰基-sn-甘油基-3-乙基磷酸胆碱(包括但不限于二油酰 基(DOEPC)、二月桂酰基、二肉豆蔻酰基、二棕榈酰基、二硬脂酰基、 棕榈酰基-油酰基);β-丙氨酰基胆固醇;CTAB，十六烷基三甲基溴化 铵;diC14-脒，N-叔丁基-N'-十四烷基-3-十四烷基氨基丙脒;14Dea2， O,O'-二十四烷酰基-N-(三甲基铵基乙酰基)二乙醇胺氯化物; DOSPER，1,3-二油酰基氧基-2-(6-羧基-精胺基)-丙基酰胺;N,N,N',N'- 四甲基-N,N'-双(2-羟乙基)-2,3-二油酰基氧基-1,4-丁烷二铵碘化物; 1-[2-酰氧基)乙基]2-烷基(烯基)-3-(2-羟乙基-)咪唑啉鎓氯化物衍生物 如1-[2-(9(Z)-十八碳烯酰基氧基)乙基]-2-(8(Z)-十七碳烯基-

3-(2-羟乙 基)咪唑啉鎓氯化物(DOTIM),1-[2-(十六烷酰基氧基)乙基]-2-十五烷 基-3-(2-羟乙基)咪唑啉鎓氯化物(DPTIM);1-[2-十四烷酰基氧基)乙 基]-2-十三烷基-3-(2-羟乙基)咪唑啉鎓氯化物(DMTIM)(例如,如 Solodin等人(1995)Biochem.43:13537-13544中所描述,以引用的方式 并入本文);在季胺上含有羟烷基部分的2,3-二烷基氧基丙基季铵化合 物衍生物,如1,2-二油酰基-3-二甲基-羟乙基溴化铵(DORI);1,2-二油 烯基氧基丙基-3-二甲基-羟乙基溴化铵(DORIE);1,2-二油烯基氧基丙 基-3-二甲基-羟基丙基溴化铵(DORIE-HP),1,2-二油烯基氧基丙基-3- 二甲基-羟基丁基溴化铵(DORIE-HB);1,2-二油烯基氧基丙基-3-二甲 基-羟基戊基溴化铵(DORIE-HPe);1,2-二肉豆蔻基氧基丙基-3-二甲基 -羟乙基溴化铵(DMRIE);1,2-二棕榈基氧基丙基-3-二甲基-羟乙基溴 化铵(DPRIE);1,2-二硬脂基氧基丙基-3-二甲基-羟乙基溴化铵(DSRIE) (例如,如Felgner等人(1994)J.Biol.Chem.269:2550-2561中所描述, 以引用的方式整体并入本文)许多上述脂质可从例如Avanti Polar Lipids,Inc.;Sigma Chemical Co.;Molecular Probes,Inc.;Northern Lipids,Inc.;Roche Molecular Biochemicals;以及Promega Corp获得。

[0195] 在某些实施方案中,所述方法、组合物、系统和试剂盒所采用的 中性脂质包括二酰基甘油基磷酸胆碱,其中酰基链的长度通常为至少 12个碳(例如,长度为12…14…20…24…或更多个碳),并且可含 有一个或多个顺式或反式双键。所述化合物的实例包括但不限于二硬 脂酰基磷脂酰胆碱(DSPC)、二肉豆蔻酰基磷脂酰胆碱(DMPC)、二棕 榈酰基磷脂酰胆碱(DPPC)、棕榈酰基油酰基磷脂酰胆碱(POPC)、棕 榈酰基硬脂酰基磷脂酰胆碱(PSPC)、卵黄磷脂酰胆碱(EPC)、氢化或 非氢化的大豆磷脂酰胆碱(HSPC)或向日葵磷脂酰胆碱。

[0196] 在某些实施方案中,中性脂质包含例如高达70mol二酰基甘油 基磷脂酰乙醇胺/100mol磷脂(例如,10/100mol…25/100mol… 50/100…70/100mol)。在一些实施方案中,二酰基甘油基磷脂酰乙 醇胺具有长度通常为至少12个碳(例如,长度为12…14…20… 24…或更多个碳),并且可含有一个或多个顺式或反式双键的酰基链。此类化合物的实例包括但不限于二硬脂酰基磷脂酰乙醇胺(DSPE)、二 肉豆蔻酰基磷脂酰乙醇胺(DMPE)、二棕榈酰基磷脂酰乙醇胺(DPPE)、 棕榈酰基油酰基磷脂酰乙醇胺(POPE)、卵黄磷脂酰乙醇胺(EPE)以及 反磷脂酰化磷脂酰乙醇胺(t-EPE),其可使用磷脂酶D由各种天然或 半合成的磷脂酰胆碱生成。

[0197] 在某些实施方案中,本公开使用CpG减少的或不含CpG的表达 载体。含有CpG二核苷酸(例如,人G-CSF的野生型型式)的初始序 列可通过改变核酸序列而进行修饰以除去CpG二核苷酸。图1示出 人G-CSF的不含CpG的型式,其具有已被改变以除去加下划线的 CpG的序列。此类CpG二核苷酸可不仅在编码序列中、而且在非编 码序列中合适地减少或消除,所述非编码序列包括例如5'和3'非翻译 区(UTR)、启动子、增强子、polyA、ITR、内含子以及存在于核酸分 子或载体中的任何其他序列。CpG二核苷酸可位于所选氨基酸的密码 子三联体内。存有五种氨基酸(丝氨酸、脯氨酸、苏氨酸、丙氨酸和 精氨酸),所述氨基酸具有一个或多个含有CpG二核苷酸的密码子三 联体。所有五种这些氨基酸具有不含CpG二核苷酸的可改变以避免 CpG、但仍然编码如以下表1中所示的相同氨基酸的替代密码子。因 此,在选定氨基酸的密码子三联体内分配的CpG二核苷酸可改变为 缺少CpG二核苷酸的相同氨基酸的密码子三联体。

[0198] 表1

[0199]

	DNA密码子	DNA密码子
氨基酸	含有CpG	缺乏CpG
丝氨酸(Ser或S)	TCG	TCT,TCC,TCA,
		AGT,AGC
脯氨酸(Pro或P)	CCG	CCT,CCC,CCA,
苏氨酸(Thr或T)	ACG	ACA,ACT,ACC
丙氨酸(Ala或A)	GCG	GCT,GCC,GCA
精氨酸(Arg或R)	CGT,CGC,	AGA,AGG
	CGA,CGG	

[0200] 另外,在编码区内,应考虑三联体之间的界面。例如,如果氨基 酸三联体在C-核苷酸中结束,C-核苷酸然后接着是仅以G-核苷酸(例 如,缬氨酸、甘氨酸、谷氨酸、丙氨酸、天冬氨酸)开始的氨基酸三 联体,则第一个氨基酸三联体的三联体被改变为不以C-核苷酸结束 的三联体。用于制备不含CpG的序列的方法例如在美国专利 7,244,609中示出,其以引用的方式并入本文。由INVIVOGEN提供 的商业服务也可用于产生不含CpG(或CpG减少)的核酸序列/载体(质 粒)。由ThermoScientific提供的商业服务产生不含CpG的核苷酸。

[0201] 以下表2中提供了可用于本文所述的载体中的示例性启动子和 增强子。此类启动子和本领域中已知的其他启动子可单独使用或与本 领域中已知的增强子中的任一种或多种增强子一起使用。另外,当从 同一载体表达多种蛋白质或生物活性核酸分子(例如2、3、4或更多 种)时,相同或不同的启动子可与主题核酸序列结合使用。

[0202] 表2

[0203]

启动子	增强子
CMV	人 CMV
EF1α	小鼠 CMV
铁蛋白(重/轻)链	SV40
GRP94	Ubc
U1	AP1
UbC	hr3
β 肌动蛋白	IE2
PGK1	IE6
GRP78	E2-RS
CAG	MEF2
SV40	C/EBP
TRE	HNF-1

[0204] 本公开不受所表达的治疗性蛋白的类型限制。在某些实施方案 中,所述治疗性蛋白包含抗体或抗体片段(例如,F(ab)或F(ab')2)。在 其他实施方案中,所述治疗性蛋白选自由以下组成的组:抗炎蛋白、凝血蛋白、抗癌蛋白、抗败血症蛋白等。可在本文所述的方法、系统 和组合物的情况下表达的治疗性蛋白的实例包括治疗性单克隆抗体 (mAb)、Fab、F(ab)2和scFv,其在以下表3中示出。

[0205] 表3

[0206]

抗体名称	商标名	类型	来源	靶	用途
3F8		mab	小鼠	GD2 神经节苷脂	神经母细胞瘤
8H9		mab	小鼠	B7-H3	神经母细胞瘤、肉瘤、转移性脑癌
阿巴伏单抗		mab	小鼠	CA-125 (模拟)	卵巢癌
阿昔单抗	ReoPro	Fab	嵌合	CD41 (整联蛋白 α-IIb)	血小板凝聚抑制剂
阿吐珠单抗		mab	人源化	CD51	癌症
阿布鲁单抗		mab	人	整联蛋白 α4β7	炎性肠病、溃疡性结肠炎、克罗恩氏病
阿克托单抗		mab	人	艰难梭菌	艰难梭菌性结肠炎

[0207]

阿达木单抗	Humira	mab	人	TNF-α	类风湿性关节炎、克罗恩氏病、斑块性银屑病、银屑病关节炎、强直性脊柱炎、幼年特发性关节炎、新生儿溶血病
阿德木单抗		mab	人	EpCAM	前列腺癌和乳腺癌
阿杜单抗		mab	人	β-淀粉样蛋白	阿尔茨海默氏病
阿非西维单抗		mab	人	IL17A 和 IL17F	---
阿非莫单抗		$F(ab')_2$	小鼠	TNF-α	败血症
奥法木单抗		mab	人源化	CD20	淋巴瘤
培阿赛珠单抗		$F(ab')_2$	人源化	VEGFR2	癌症
ALD518		---	人源化	IL-6	类风湿性关节炎
阿仑珠单抗	Lemtrada，Campath	mab	人源化	CD52	多发性硬化症
阿利库单抗		mab	人	PCSK9	高胆固醇血症
喷替酸阿妥莫单抗	Hybri-ceaker	mab	小鼠	CEA	结肠直肠癌(诊断)
阿麦妥昔单抗		mab	嵌合	间皮素	癌症
麻安莫单抗		Fab	小鼠	TAG-72	非小细胞肺癌
雷星-阿奈妥单抗		mab	人	MSLN	癌症
阿尼富路单抗		mab	人	干扰素α/β受体	系统性红斑狼疮
安芦珠单抗(=IMA-638)		mab	人源化	IL-13	哮喘
阿珀利珠单抗		mab	人源化	HLA-DR ---	血液学癌症
阿西莫单抗	CEA-Scan	Fab'	小鼠	CEA	胃肠道癌(诊断)
阿伐苏单抗		mab	人	激活素受体样激酶 1	癌症
阿瑟利珠单抗		mab	人源化	L-选择素(CD62L)	严重创伤患者
阿特利珠单抗		mab	人源化	CD274	癌症
阿替努单抗		mab	人	RTN4	---
阿特立单抗(=托西利珠单	Actemra，RoActemr	mab	人源化	IL-6 受体	类风湿性关节炎

[0208]

抗)	a				
阿托木单抗		mab	人	恒河猴因子	新生儿溶血病[来源请求]
阿维鲁单抗		mab	人	CD274	---
巴匹奈珠单抗		mab	人源化	β淀粉样蛋白	阿尔茨海默氏病
巴司利昔单抗	Simulect	mab	嵌合	CD25 (IL-2受体的α链)	预防器官移植排斥
巴韦妥昔单抗		mab	嵌合	磷脂酰丝氨酸	癌症，病毒感染
贝妥莫单抗	LymphoScan	Fab'	小鼠	CD22	非霍奇金淋巴瘤(检测)
贝戈洛单抗		mab	小鼠	DPP4	---
贝利木单抗	Benlysta，LymphoStat-B	mab	人	BAFF	非霍奇金淋巴瘤等
本雷利珠单抗		mab	人源化	CD125	哮喘
柏替利木单抗		mab	人	CCL11 (嗜酸性粒细胞趋化因子-1)	严重过敏性病症
贝西来索单抗	Scintimun	mab	小鼠	CEA 相关抗原	炎性病灶和转移瘤(检测)
贝伐赛珠单抗	安维汀	mab	人源化	VEGF-A	转移性癌症，早产儿视网膜病变
贝洛托舒单抗		mab	人	艰难梭菌	艰难梭菌性结肠炎
比西单抗	FibriScint	Fab'	小鼠	纤维蛋白 II，β链	血栓栓塞(诊断)
比玛卢单抗		mab	人	ACVR2B	肌肉抑制素抑制剂
比美吉珠单抗		mab	人源化	IL 17A 和 IL 17F	---
莫-比伐珠单抗		mab	人源化	CD44 v6	鳞状细胞癌
比勒斯单抗		mab	人	CD40	---
布利妥莫单抗		BiTE	小鼠	CD19	前 B ALL (CD19+)
布隆妥维单抗	Blontress	mab	兽医	CD20	---
布洛索珠单抗		mab	人源化	SOST	骨质疏松症
伯考赛珠单抗		mab	人源化	神经细胞凋亡调节蛋白酶 1	血脂异常
布雷库单抗		mab	人	IL23	克罗恩氏病

[0209]

维汀-布仑妥昔单抗		mab	嵌合	CD30 (TNFRSF8)	血液学癌症
布瑞吉努单抗		mab	人	IL-12，IL-23	银屑病、类风湿性关节炎、炎性肠病、多发性硬化症
布洛鲁单抗		mab	人	IL-17	炎性疾病
布洛赛珠单抗		mab	人源化	VEGFA	湿性老年性黄斑变性
布隆妥珠单抗		mab	人源化	Notch 1	癌症
布洛舒单抗		mab	人	FGF 23	X 连锁低磷酸盐血症
卡比利珠单抗		mab	人源化	CSF1R	---
卡那吉努单抗	Ilaris	mab	人	IL-1---	类风湿性关节炎
莫星-坎妥珠单抗		mab	人源化	粘蛋白 CanAg	结肠直肠癌等
雷星-坎妥珠单抗		mab	人源化	MUC1	癌症
卡普赛珠单抗		mab	人源化	VWF	血栓性血小板减少性紫癜，血栓形成
卡罗单抗喷地肽	Prostascint	mab	小鼠	前列腺癌细胞	前列腺癌(检测)
卡鲁单抗		mab	人	MCP-1	肿瘤学/免疫适应症
卡罗妥昔单抗		mab	嵌合	内皮糖蛋白	---
卡妥玛索单抗	Removab	3功能抗体	大鼠/小鼠杂种	EpCAM，CD3	卵巢癌、恶性腹水、胃癌
cBR96-阿霉素免疫缀合物		mab	人源化	Lewis-Y抗原	癌症
西利珠单抗		mab	人源化	CD4	预防器官移植排斥，治疗自身免疫疾病
克果图珠单抗		mab	人源化	IL2	---
赛妥珠单抗	Cimzia	Fab'	人源化	TNF-α	克罗恩氏病、类风湿性关节炎、可考虑中轴型脊柱炎、银屑病关节炎
西妥昔单抗	Erbitux	mab	嵌合	EGFR	转移性结肠直肠癌和头颈癌
Ch.14.18		mab	嵌合	GD2 神经节苷脂	神经母细胞瘤

[0210]

泊西他珠单抗		Fab	人源化	EpCAM	卵巢癌和其他实体瘤
西舒妥木单抗		mab	人	IGF-1 受体(CD221)	实体瘤
克拉吉珠单抗		mab	人源化	穴兔	类风湿性关节炎
克立昔单抗		mab	嵌合	CD4	类风湿性关节炎
泰坦-克利妥珠单抗	hPAM4-Cide	mab	人源化	MUC1	胰腺癌
考曲妥珠单抗		mab	人源化	蛋白多糖3	癌症
雷星-考妥昔单抗		mab	嵌合	CD19	癌症
考那妥木单抗		mab	人	TRAIL-R2	癌症
康赛珠单抗		mab	人源化	TFPI	出血
CR6261		mab	人	A性流感血凝素	传染性疾病/A型流感
克瑞奈珠单抗		mab	人源化	1-40-β-淀粉样蛋白	阿尔茨海默氏病
克罗特度单抗		mab	人	GCGR	糖尿病
达塞妥珠单抗		mab	人源化	CD40	血液学癌症
达克利珠单抗	Zenapax	mab	人源化	CD25 (IL-2受体的α链)	预防器官移植排斥
达洛妥珠单抗		mab	人源化	IGF-1 受体(CD221)	癌症等
培戈-达匹利珠单抗		mab	人源化	CD154 (CD40L)	---
达雷妥木单抗		mab	人	CD38 (环腺苷二磷酸核糖水解酶)	癌症
德屈库单抗		mab	人	IL-13	---
登赛珠单抗		mab	人源化	DLL4	癌症
地宁图珠单抗		mab	人源化	CD19	癌症
迪诺舒单抗	Prolia	mab	人	RANKL	骨质疏松症,骨转移癌等
玛汀-迪妥昔珠单抗		mab	嵌合/人源化	EGFR	癌症
德尔罗妥单抗生物素		mab	嵌合	组蛋白复合物	复发性多形性胶质母细胞瘤
地莫单抗		mab	小鼠	B-淋巴瘤细胞	淋巴瘤
地努妥昔单抗		mab	嵌合	GD2 神经节苷脂	神经母细胞瘤
地利伏单抗		mab	人	血凝素	A型流感

[0211]

多玛洛珠单抗		mab	人源化	GDF-8	杜氏肌营养不良
阿托度单抗		$F(ab')_2$	小鼠	---	---
卓齐妥单抗		mab	人	DR5	癌症等
杜利图单抗		mab	人	ERBB3 (HER3)	睾丸癌
度匹鲁单抗		mab	人	IL4	特应性疾病
度伐鲁单抗		mab	人	CD274	癌症
度司妥单抗		mab	人	ILGF2	癌症
依洛美昔单抗		mab	嵌合	GD3 神经节苷脂	恶性黑素瘤
依库利珠单抗	Soliris	mab	人源化	C5	阵发性夜间血红蛋白尿，非典型 HUS
埃巴单抗		mab	小鼠	内毒素	由革兰氏阴性细菌引起的败血症
依曲考罗单抗	Panorex	mab	小鼠	EpCAM	结肠直肠癌
依法利珠单抗	Raptiva	mab	人源化	LFA-1 (CD11a)	银屑病(阻断T-细胞迁移)
依芬古单抗	Mycograb	scFv	人	Hsp90	侵袭性念珠菌感染
埃迪鲁单抗		mab	人	干扰素 γ 诱导的蛋白	克罗恩氏病，溃疡性结肠炎
依更妥单抗		mab	人	ERBB3 (HER3)	癌症
依洛妥珠单抗		mab	人源化	SLAMF7	多发性骨髓瘤
艾西莫单抗		mab	小鼠	IL-6	---
依米妥珠单抗		mab	人源化	CSF1R	癌症
依玛妥珠单抗		mab	人源化	HHGFR	癌症
依米赛珠单抗		mab	人源化	活化的 F9、F10	A 型血友病
依那妥珠单抗		mab	人源化	TWEAK 受体	癌症等
维汀-恩弗妥单抗		mab	人	AGS-22M6	表达结合素-4的癌症
培戈赖莫单抗		mab	小鼠	ICAM-1 (CD54)	---
依诺妥珠单抗		mab	人源化	CD276	癌症
依诺吉珠单抗		mab	人源化	IL9	哮喘
依诺苏单抗		mab	人	DLL4	---
恩司妥昔单抗		mab	嵌合	5AC	癌症
西坦-依匹妥莫单抗		mab	小鼠	上皮唾液蛋白	---

[0212]

依普妥珠单抗		mab	人源化	CD22	癌症，SLE
厄瑞努单抗		mab	人	CGRP	偏头痛
厄利珠单抗		$F(ab')_2$	人源化	ITGB2 (CD18)	心脏病发作、中风、创伤性休克
厄妥玛索单抗	Rexomun	3功能抗体	大鼠/小鼠杂种	HER2/neu，CD3	乳腺癌等
依他赛珠单抗	Abegrin	mab	人源化	整联蛋白 αvβ3	黑素瘤、前列腺癌、卵巢癌等
依卓利珠单抗		mab	人源化	整联蛋白 α7β7	炎性肠病
依维苏单抗		mab	人	促血管生成素 3	血脂异常
依沃苏单抗		mab	人	PCSK9	高胆固醇血症
埃比韦卢单抗		mab	人	乙型肝炎表面抗原	乙型肝炎
法索单抗	NeutroSpec	mab	小鼠	CD15	阑尾炎(诊断)
法拉莫单抗		mab	小鼠	干扰素受体	---
法乐妥珠单抗		mab	人源化	叶酸受体 1	卵巢癌
法司努单抗		mab	人	HNGF	急性坐骨神经痛
FBTA05	Lymphomun	3功能抗体	大鼠/小鼠杂种	CD20	慢性淋巴细胞性白血病
非维珠单抗		mab	人源化	呼吸道合胞病毒	呼吸道合胞病毒感染
菲扎吉努单抗		mab	人	IL-22	类风湿性关节炎，银屑病
菲巴珠单抗		mab	人源化	ephrin 受体 A3	---
菲拉妥珠单抗		mab	人源化	HGF	癌症等
菲吉妥木单抗		mab	人	IGF-1 受体 (CD221)	肾上腺皮质癌、非小细胞肺癌等
非利伏单抗		mab	人	A 型流感病毒血凝素	---
夫兰妥单抗		mab	人	TYRP1 (糖蛋白 75)	黑素瘤
夫来库单抗		mab	人	IL 20	类风湿性关节炎
芳托利珠单抗	HuZAF	mab	人源化	IFN-γ	克罗恩氏病等
弗雷鲁单抗		mab	人	CD3ε	---
弗雷韦卢单抗		mab	人	狂犬病毒糖	狂犬病(预防)

[0213]

				蛋白	
夫瑞利木单抗		mab	人	TGF-β	特发性肺纤维化、局灶节段性肾小球硬化、癌症
伏雷努单抗		mab	人	NGF	疼痛
伏妥昔单抗		mab	嵌合	EGFR	癌症
伽奈珠单抗		mab	人源化	降钙素	偏头痛
加利昔单抗		mab	嵌合	CD80	B-细胞淋巴瘤
加尼妥单抗		mab	人	IGF-1 受体(CD221)	癌症
冈特奈卢单抗		mab	人	β淀粉样蛋白	阿尔茨海默氏病
加威利莫单抗		mab	小鼠	CD147 (基础免疫球蛋白)	抗宿主病
奥-吉妥珠单抗	Mylotarg	mab	人源化	CD33	急性骨髓性白血病
格沃吉珠单抗		mab	人源化	IL-1β	糖尿病等
吉仑妥昔单抗	Rencarex	mab	嵌合	碳酸酐酶 9 (CA-IX)	透明细胞肾细胞癌[84]
维汀-格仑妥木单抗		mab	人	GPNMB	黑素瘤，乳腺癌
戈利木单抗	Simponi	mab	人	TNF-α	类风湿性关节炎、银屑病关节炎、强直性脊柱炎
戈利昔单抗		mab	嵌合	CD23 (IgE 受体)	过敏性哮喘
谷瑟库单抗		mab	人	IL23	银屑病
艾巴利珠单抗		mab	人源化	CD4	HIV 感染
替坦-艾瑞妥莫单抗	Zevalin	mab	小鼠	CD20	非霍奇金淋巴瘤
艾卢苏单抗		mab	人	VEGFR-1	癌症等
艾达赛珠单抗		mab	人源化	达比加群	逆转达比加群的抗凝作用
伊戈伏单抗	Indimacis-125	$F(ab')_2$	小鼠	CA-125	卵巢癌(诊断)
IMAB362		mab	人	CLDN18.2	胃肠腺癌和胰腺肿瘤
伊玛鲁单抗		mab	人	MIF	癌症
英赛罗单抗	Myoscint	mab	小鼠	心肌肌球蛋白	心脏成像
英加妥珠单抗		mab	人源化	EGFR	癌症
英拉苏单抗		mab	人	选择素 P	心血管疾病

[0214]

雷星-英达妥昔单抗		mab	嵌合	SDC1	癌症
维汀-英度妥单抗		mab	人	GUCY2C	癌症
英比利珠单抗		mab	人源化	CD19	癌症、系统性硬化症、多发性硬化症
英夫利西单抗	Remicade	mab	嵌合	TNF-α	类风湿性关节炎、强直性脊柱炎、银屑病关节炎、银屑病、克罗恩氏病、溃疡性结肠炎
艾诺利莫单抗		mab	小鼠	CD25 (IL-2受体的α链)	抗宿主病
奥星-艾诺妥珠单抗		mab	人源化	CD22	ALL
英特妥木单抗		mab	人	CD51	实体瘤(前列腺癌、黑素瘤)
艾匹利木单抗	Yervoy	mab	人	CD152	黑素瘤
艾雷妥木单抗		mab	人	CD30 (TNFRSF8)	霍奇金淋巴瘤
艾萨妥昔单抗		mab	嵌合	CD38	癌症
艾托利珠单抗		mab	人源化	CD6	---
艾塞吉珠单抗		mab	人源化	IL 17A	自身免疫疾病
克立昔单抗		mab	嵌合	CD4	慢性哮喘
拉贝珠单抗	CEA-Cide	mab	人源化	CEA	结肠直肠癌
兰帕利珠单抗		mab	人源化	CFD	继发于老年性黄斑变性的地图样萎缩
拉那鲁单抗		mab	人	激肽释放酶	血管性水肿
兰洛珠单抗		mab	人源化	GDF-8	肌消耗性病症
恩星-拉妥昔单抗		mab	嵌合	EGFR	---
乐瑞吉珠单抗		mab	人源化	IL-13	哮喘
乐玛来索单抗		mab	小鼠	NCA-90 (粒细胞抗原)	诊断剂
棱德里珠单抗		mab	人源化	C5	---
仑兹鲁单抗		mab	人	CSF2	---
乐迪利木单抗		mab	人	TGFβ2	减少青光眼手术之后的结疤
乐萨妥木单抗		mab	人	TRAIL-R2	癌症
利比韦卢单抗		mab	人	乙型肝炎表	乙型肝炎

[0215]

				面抗原	
维汀-利法妥珠单抗		mab	人源化	磷酸钠共转运蛋白	癌症
利格利珠单抗		mab	人源化	IGHE	严重哮喘和慢性自发性荨麻疹
沙泰坦-利洛托单抗		mab	小鼠	CD37	癌症
林妥珠单抗		mab	人源化	CD33	癌症
利瑞鲁单抗		mab	人	KIR2D	实体癌和血液学癌症
洛迪赛珠单抗		mab	人源化	PCSK9	高胆固醇血症
洛吉维单抗		mab	兽医	家犬 IL31	---
莫星-洛沃妥珠单抗		mab	人源化	CD56	癌症
鲁卡妥木单抗		mab	人	CD40	多发性骨髓瘤、非霍奇金淋巴瘤、霍奇金淋巴瘤
培戈-鲁利珠单抗		mab	人源化	CD28	自身免疫疾病
鲁昔单抗		mab	嵌合	CD23 (IgE 受体)	慢性淋巴细胞性白血病
鲁妥珠单抗		mab	人源化	ERBB3 (HER3)	癌症
MABp1	Xilonix	mab	人	IL1A	结肠直肠癌
玛帕妥木单抗		mab	人	TRAIL-R1	癌症
玛格妥昔单抗		mab	人源化	ch4D5	癌症
马司莫单抗		---	小鼠	T 细胞受体	---
马妥珠单抗		mab	人源化	EGFR	结肠直肠癌、肺癌和胃癌
玛弗利木单抗		mab	人	GMCSF 受体 α 链	类风湿性关节炎
美珀利珠单抗	Bosatria	mab	人源化	IL-5	哮喘和白细胞病
美特利木单抗		mab	人	TGFβ1	系统性硬皮病
米拉妥珠单抗		mab	人源化	CD74	多发性骨髓瘤和其他血液学恶性肿瘤
明瑞妥莫单抗		mab	小鼠	TAG-72	肿瘤检测(和疗法---)
索星-米妥昔单抗		mab	嵌合	叶酸受体 α	癌症
米妥莫单抗		mab	小鼠	GD3 神经节	小细胞肺癌

[0216]

				苷脂	
莫加利珠单抗		mab	人源化	CCR4	癌症
莫那利珠单抗		mab	人源化	KLRC1	---
莫罗木单抗		mab	人	恒河猴因子	---
莫他韦珠单抗	Numax	mab	人源化	呼吸道合胞病毒	呼吸道合胞病毒(预防)
帕舒托-莫塞妥莫单抗		mab	小鼠	CD22	癌症
莫罗单抗-CD3	Orthoclone OKT3	mab	小鼠	CD3	预防器官移植排斥
他那可单抗		Fab	小鼠	C242 抗原	结肠直肠癌
那米鲁单抗		mab	人	CSF2	---
他那莫单抗		Fab	小鼠	5T4	非小细胞肺癌小、肾细胞癌
恩星-那妥昔单抗		mab	嵌合	CD37	---
那呐妥单抗		mab	人	RON	癌症
那他利珠单抗	Tysabri	mab	人源化	整联蛋白 α4	多发性硬化症，克罗恩氏病
那赛昔珠单抗		mab	嵌合/人源化	DLL4	---
那韦伏单抗		mab	人	A 型流感病毒血凝素 HA	---
奈巴库单抗		mab	人	内毒素	败血症
奈西妥木单抗		mab	人	EGFR	非小细胞肺癌
奈莫利珠单抗		mab	人源化	IL31RA	湿疹[106]
奈瑞利莫单抗		mab	小鼠	TNF-α	---
奈伐苏单抗		mab	人	促血管生成素 2	癌症
尼莫妥珠单抗	Theracim，Theraloc	mab	人源化	EGFR	鳞状细胞癌、头颈癌、鼻咽癌、胶质瘤
尼沃鲁单抗	Opdivo	mab	人	PD-1	癌症
巯诺莫单抗	Verluma	Fab	小鼠	---	癌症(诊断)
奥托萨昔单抗		mab	嵌合	炭疽杆菌	炭疽芽孢杆菌
奥比妥珠单抗	Gazyva	mab	人源化	CD20	慢性淋巴细胞性白血病
奥卡妥珠单抗		mab	人源化	CD20	癌症
奥瑞利珠单抗		mab	人源化	CD20	类风湿性关节炎、红斑狼疮等
奥度莫单抗		mab	小鼠	LFA-1 (CD11a)	预防器官移植

[0217]

					排斥、免疫性疾病
奥法妥木单抗	Arzerra	mab	人	CD20	慢性淋巴细胞性白血病等
奥拉妥单抗		mab	人	PDGF-R α	癌症
奥洛吉珠单抗		mab	人源化	IL6	---
奥玛利珠单抗	Xolair	mab	人源化	IgE Fc 区	过敏性哮喘
奥那妥珠单抗		mab	人源化	人扩散因子受体激酶	癌症
昂妥昔珠单抗		mab	嵌合/人源化	TEM1	癌症
奥匹努单抗		mab	人	LINGO-1	多发性硬化症
莫奥珠单抗		scFv	人源化	EpCAM	癌症
奥瑞戈沃单抗	OvaRex	mab	小鼠	CA-125	卵巢癌
奥替苏单抗		mab	人	oxLDL	---
奥特昔珠单抗		mab	嵌合/人源化	CD3	1 型糖尿病
奥乐妥珠单抗		mab	人源化	CD37	癌症
奥塞鲁单抗		mab	人	OX-40	哮喘
奥扎奈珠单抗		mab	人源化	NOGO-A	ALS 和多发性硬化症
奥佐利珠单抗		mab	人源化	TNF-α	炎症
帕吉昔单抗		mab	嵌合	脂磷壁酸	败血症(葡萄球菌)
帕利韦珠单抗	Synagis，Abbosynagis	mab	人源化	呼吸道合胞病毒的 F 蛋白	呼吸道合胞病毒(预防)
潘瑞鲁单抗		mab	人	CTGF	---
帕尼妥木单抗	Vectibix	mab	人	EGFR	结肠直肠癌
帕尼库单抗		mab	人源化	MUC1 的肿瘤特异性糖基化	卵巢癌
帕诺巴库单抗		mab	人	铜绿假单胞菌	铜绿假单胞菌感染
帕萨妥珠单抗		mab	人	EGFL7	癌症
帕考利珠单抗		mab	人源化	IL-4	哮喘
帕妥昔珠单抗		mab	嵌合/人源化	叶酸水解酶	癌症
帕特利珠单抗		mab	人源化	LTA	TNF
帕曲妥单抗		mab	人	ERBB3 (HER3)	癌症
兰洛利珠单抗		mab	人源化	PDCD1	黑素瘤和其他癌症
帕尼单抗	Theragyn	---	小鼠	MUC1	癌症

[0218]

珀雷吉珠单抗		mab	人源化	IL 17A	关节炎
珀妥珠单抗	Omnitarg	mab	人源化	HER2/neu	癌症
培克珠单抗		scFv	人源化	C5	减少心脏手术的副作用
匹地利珠单抗		mab	人源化	PD-1	癌症和传染性疾病
维汀-匹那妥珠单抗		mab	人源化	CD22	癌症
阿巴伏单抗		mab	小鼠	腺癌抗原	腺癌(成像)
普拉鲁单抗		mab	人	人 TNF	疼痛和炎性疾病
洛扎利珠单抗		mab	人源化	CCR2	糖尿病肾病和动静脉移植物通畅
泊加丽珠单抗		mab	人源化	TNFR 超家族成员 4	---
维汀-珀拉妥珠单抗		mab	人源化	CD79B	癌症
珀奈珠单抗		mab	人源化	人 β-淀粉样蛋白	阿尔茨海默氏病
帕博利珠单抗		mab	人源化	ICOSL	---
普立昔单抗		mab	嵌合	CD4	克罗恩氏病，多发性硬化症
瑞托萨昔单抗		mab	嵌合	1型大肠杆菌志贺毒素	---
普瑞妥木单抗		mab	人	波形蛋白	脑癌
PRO 140		---	人源化	CCR5	HIV 感染
奎利珠单抗		mab	人源化	IGHE	哮喘
雷考妥莫单抗		mab	小鼠	N-羟乙酰神经氨酸	癌症
雷曲妥单抗		mab	人	纤连蛋白额外结构域-B	癌症
雷非韦卢单抗		mab	人	狂犬病毒糖蛋白	狂犬病(预防)
雷泮赛珠单抗		mab	人源化	神经细胞凋亡调节蛋白酶 1	血脂异常
雷姆赛卢单抗	Cyramza	mab	人	VEGFR2	实体瘤
雷珠单抗	Lucentis	Fab	人源化	VEGF-A	黄斑变性(湿形式)
雷昔巴库单抗		mab	人	炭疽毒素，保护性抗原	炭疽(预防和治疗)
瑞法奈珠单抗		mab	人源化	髓鞘相关糖蛋白	中风之后的运动功能恢复

[0219]

瑞加韦单抗		mab	人	细胞巨化病毒糖蛋白 B	细胞巨化病毒感染
瑞司利珠单抗		mab	人源化	IL-5	呼吸道、皮肤和胃肠道的炎症
瑞洛妥木单抗		mab	人	HGF	实体瘤
利努苏单抗		mab	人	血小板衍生生长因子受体 β	新生血管性老年性黄斑变性
利散吉珠单抗		mab	人源化	IL23A	---
利妥昔单抗	MabThera，Rituxan	mab	嵌合	CD20	淋巴瘤、白血病、一些自身免疫病症
培戈-利伐巴珠单抗		mab	人源化	铜绿假单胞菌 III 型分泌系统	---
洛巴妥木单抗		mab	人	IGF-1 受体 (CD221)	癌症
洛来度单抗		mab	人	RHD	---
洛莫索珠单抗		mab	人源化	硬化蛋白	骨质疏松症
隆他利珠单抗		mab	人源化	IFN-α	系统性红斑狼疮
特司林-洛伐妥珠单抗		mab	人源化	DLL3	---
洛维利珠单抗	LeukArrest	mab	人源化	CD11，CD18	出血性休克
卢普利珠单抗	Antova	mab	人源化	CD154 (CD40L)	风湿性疾病
戈维替康-沙西妥珠单抗		mab	人源化	肿瘤相关钙信号转导蛋白 2	癌症
萨玛利珠单抗		mab	人源化	CD200	癌症
沙培利单抗		mab	人源化	IL6R	---
萨瑞鲁单抗		mab	人	IL6	类风湿性关节炎，强直性脊柱炎
喷地肽沙妥莫单抗		mab	小鼠	TAG-72	癌症(诊断)
瑟库吉努单抗		mab	人	IL 17A	葡萄膜炎、类风湿性关节炎银屑病
瑟瑞妥单抗		mab	人	ERBB3 (HER3)	癌症
瑟托萨昔单抗		mab	嵌合	2 型大肠杆菌	---

[0220]

				志贺毒素	
司韦单抗		---	人	细胞巨化病毒	细胞巨化病毒感染
SGN-CD19A		mab	人源化	CD19	急性淋巴细胞性白血病和 B 细胞非霍奇金淋巴瘤
SGN-CD33A		mab	人源化	CD33	急性骨髓性白血病
西罗珠单抗		mab	人源化	FAP	癌症
司法利木单抗		mab	人源化	IFN-α	SLE、皮肌炎、多发性肌炎
司妥昔单抗		mab	嵌合	IL-6	癌症
辛妥珠单抗		mab	人源化	LOXL2	纤维变性
西普利珠单抗		mab	人源化	CD2	银屑病、抗宿主病(预防)
司卢库单抗		mab	人	IL-6	类风湿性关节炎
维汀-索非妥珠单抗		mab	人源化	CA-125	卵巢癌
索拉奈珠单抗		mab	人源化	β淀粉样蛋白	阿尔茨海默氏病
索利图单抗		BiTE	小鼠	EpCAM	---
索尼普单抗		---	人源化	鞘氨醇-1-磷酸	脉络膜和视网膜新生血管
松妥珠单抗		mab	人源化	上皮唾液蛋白	---
司达鲁单抗		mab	人	肌肉抑制素	肌营养不良
硫索单抗	LeukoScan	Fab'	小鼠	NCA-90（粒细胞抗原)	骨髓炎(成像)
苏韦珠单抗		mab	人源化	HIV-1	病毒感染
他巴鲁单抗		mab	人	BAFF	B 细胞癌症
替他珠单抗	AFP-Cide	mab	人源化	甲胎蛋白	癌症
托珠单抗		Fab	人源化	整联蛋白αIIbβ3	经皮冠状动脉介入治疗
他利珠单抗		mab	人源化	IgE	过敏反应
坦妥维单抗	Tactress	mab	兽医	CD52	---
他奈珠单抗		mab	人源化	NGF	疼痛
帕他普莫单抗		mab	小鼠	CD19	癌症[来源请求]
他瑞妥单抗		mab	人	Notch 受体	癌症
特非巴珠单抗	Aurexis	mab	人源化	聚集因子 A	金黄色葡萄球菌感染

[0221]

阿替莫单抗		Fab	小鼠	---	---
特那妥莫单抗		mab	小鼠	肌腱蛋白 C	癌症
特奈利昔单抗		mab	嵌合	CD40	自身免疫疾病和器官移植排斥的预防
特普利珠单抗		mab	人源化	CD3	1 型糖尿病
特普妥木单抗		mab	人	IGF-1 受体(CD221)	血液学肿瘤
特度鲁单抗		mab	人	C5	---
特托罗单抗		mab	人源化	CD37	癌症[141]
特折鲁单抗		mab	人	TSLP	哮喘，特应性皮炎
TGN1412		---	人源化	CD28	慢性淋巴细胞性白血病，类风湿性关节炎
替西木单抗(=曲美利木单抗)		mab	人	CTLA-4	癌症
替加妥珠单抗		mab	人源化	TRAIL-R2	癌症
替曲吉珠单抗		mab	人源化	IL23	免疫介导的炎性病症
替莫鲁单抗		mab	人	AOC3	---
维汀-替索妥单抗		mab	人	凝血因子 III	---
TNX-650		---	人源化	IL-13	霍奇金淋巴瘤
托西利珠单抗(=阿特立单抗)	Actemra，RoActemra	mab	人源化	IL-6 受体	类风湿性关节炎
托雷利珠单抗		mab	人源化	CD154 (CD40L)	类风湿性关节炎、狼疮性肾炎等
托萨托舒单抗		mab	人	金黄色葡萄球菌	---
托西莫单抗	Bexxar	---	小鼠	CD20	滤泡性淋巴瘤
托维妥单抗		mab	人	CD140a	癌症
曲洛吉努单抗		mab	人	IL-13	哮喘等
曲妥珠单抗	Herceptin	mab	人源化	HER2/neu	乳腺癌
曲妥珠单抗-美坦新偶联物	Kadcyla	mab	人源化	HER2/neu	乳腺癌
TRBS07	Ektomab	3 功能抗体	---	GD2 神经节苷脂	黑素瘤
曲加利珠单抗		mab	人源化	CD4	---
曲美利木单抗		mab	人	CTLA-4	癌症
曲戈卢单抗		mab	人	生长分化因	由于骨科废用

[0222]

				子 8	和肌肉减少引起的肌肉萎缩
塞莫白介素-2-妥考妥珠单抗		mab	人源化	EpCAM	癌症
妥韦单抗		---	人	乙型肝炎病毒	慢性乙型肝炎
乌利妥昔单抗		mab	嵌合	MS4A1	癌症
乌洛鲁单抗		mab	人	CXCR4 (CD184)	血液学恶性肿瘤
乌瑞鲁单抗		mab	人	4-1BB (CD137)	癌症等
厄托萨珠单抗		mab	人源化	大肠杆菌	由大肠杆菌引起的腹泻
优特吉努单抗	Stelara	mab	人	IL-12，IL-23	多发性硬化症、银屑病、银屑病关节炎
乌托鲁单抗		mab	人	4-1BB (CD137)	癌症
他立林-伐达妥昔单抗		mab	嵌合	CD33	---
维汀-万多妥珠单抗		mab	人源化	STEAP1	癌症
万替妥单抗		mab	人	卷曲受体	癌症
伐努赛珠单抗		mab	人源化	促血管生成素 2	癌症
伐帕利昔单抗		mab	嵌合	AOC3 (VAP-1)	---
伐立鲁单抗		mab	人	CD27	实体瘤和血液学恶性肿瘤
伐特利珠单抗		mab	人源化	ITGA2 (CD49b)	---
维多利珠单抗	Entyvio	mab	人源化	整联蛋白 α4β7	克罗恩氏病，溃疡性结肠炎
维妥珠单抗		mab	人源化	CD20	非霍奇金淋巴瘤
维帕利莫单抗		mab	小鼠	AOC3 (VAP-1)	炎症
维森苏单抗		mab	人	NRP1	实体恶性肿瘤
威司利珠单抗	Nuvion	mab	人源化	CD3	克罗恩氏病，溃疡性结肠炎
沃巴利珠单抗		mab	人源化	IL6R	炎性自身免疫疾病
沃洛赛昔单抗		mab	嵌合	整联蛋白 α5β1	实体瘤

[0223]

玛汀-沃瑟妥珠单抗		mab	人源化	CD70	癌症
伏妥莫单抗	HumaSPECT	mab	人	肿瘤抗原CTAA16.88	结肠直肠肿瘤
珍妥珠单抗		mab		IGF1，IGF2	---
扎鲁妥木单抗	HuMax-EGFr	mab	人	EGFR	头颈鳞状细胞癌
扎诺利木单抗	HuMax-CD4	mab	人	CD4	类风湿性关节炎、银屑病、T细胞淋巴瘤
扎妥昔单抗		mab	嵌合	HER1	癌症
齐拉木单抗		mab	人	CD147 (基础免疫球蛋白)	---
阿托-佐利莫单抗		mab	小鼠	CD5	系统性红斑狼疮，抗宿主病

[0224] 可在本文所述的方法、系统和组合物的情况下表达的治疗性蛋白 的其他实例包括治疗性单克隆抗体(mAb)、Fab、F(ab)2和scFv，诸 如广泛中和抗HIV单克隆，包括抗体10-1074(Caskey等人,Nat Med. 2017年2月;23(2):185-191,Epub 2017年1月16日,以引用的方式整 体并入本文);HIV-1抗体3BNC117(Scheid,等人,Nature.2016年7月 28日;535(7613):556-60,以引用的方式整体并入本文);以及VRC01 (参见例如Bar等人,N Engl J Med.2016年11月24 日;375(21):2037-2050,以引用的方式整体并入本文)。

[0225] 在一些实施方案中,以选择来在适当的受试者(例如,小鼠、人 等)中引发治疗性和/或预防性作用的剂量提供和/或施用本文的组合 物和系统。在一些实施方案中,提供治疗性剂量。在一些实施方案中， 提供预防性剂量。给药或施用方案由临床医师或在药理学领域的其他 技术人员基于熟知的药理学和治疗性/预防性考虑因素来定制,所述 考虑因素包括但不限于所需的药理作用水平、可获得的药理作用的实 际水平、毒性。一般来说,遵循熟知的用于施用药剂的药理学原理是 可取的(例如,通常可取的是有时不要改变超过50％并且不超过每3-4 个药剂半衰期)。对于具有相对少的或无剂量相关毒性的考虑因素的 组合物,并且在需要最大功效情况下,超过平均需要剂量的剂量并非 罕见。这种给药方法通常称为“最大剂量”策略。在某些实施方案中， 剂量(例如,治疗性或预防性)是约0.01mg/kg至约200mg/kg(例如， 0.01mg/kg、0.02mg/kg、0.05mg/kg、0.1mg/kg、0.2mg/kg、0.5mg/kg、 1.0mg/kg、2.0mg/kg、5.0mg/kg、10mg/kg、20mg/kg、50mg/kg、 100mg/kg、200mg/kg或其间的任何范围(例如,5.0mg/kg至100 mg/kg))。在一些实施方案中,受试者是在0.1kg(例如,小鼠)与150kg (例如,人)之间,例如0.1kg、0.2kg、0.5kg、1.0kg、2.0kg、5.0kg、 10kg、20kg、50kg、100kg、200kg或其间的任何范围(例如,40-125 kg)。在一些实施方案中,剂量包括在0.001mg与40,000mg之间(例 如,0.001mg、0.002mg、0.005mg、0.01mg、0.02mg、0.05mg、0.1 kg、0.2mg、0.5mg、1.0mg、2.0mg、5.0mg、10mg、20mg、50mg、 100mg、200mg、500mg、1,000mg、2,000mg、5,000mg、10,000mg、 20,000mg、40,000mg或其间的范围。

[0226] 实施例

[0227] 在所有的以下实施例中,所有的表达载体是不含CpG的表达载 体,Genscript px458-relA1(SEQ ID NO:8)和Genscript px458-relA4 (SEQ ID NO:9)除外,这两者是可

商购获得的携带CpG的序列(参见， www后接″genscript.com/CRISPR-gRNA-constructs.html.”)。

[0228] 实施例1

[0229] 长期治疗性利妥昔单抗表达

[0230] 此实施例描述所实施的实验,其证明在单次注射编码利妥昔单抗 的双盒或单盒质粒载体之后单克隆抗体利妥昔单抗在治疗性血清水 平下的长期表达。

[0231] 第一实施例:

[0232] 在第一实施例中,每组注射三只小鼠。每只小鼠接受单一IV注 射1050纳摩尔的含有2.5%的并入脂质体双层中的地塞米松棕榈酸酯(DP)的DOTAP阳离子脂质体。在此两分钟后接着单一IV注射75ug 编码抗CD20(利妥昔单抗)的两种不同的质粒DNA中的一种。在IV注射前2小时用IP注射40mg/kg地塞米松处理两个组。图5中所示 的质粒715.1 2a(P2A)(SEQ ID NO:3)编码通过2A自裂解肽分离的抗 CD20 mAb重链和轻链cDNA。图6中所示的质粒718.1(SEQ ID NO:4) 为分别编码抗CD20 mAb重链和轻链cDNA的双表达盒质粒载体。 在注射后24小时且之后以7天间隔通过ELISA确定抗CD20的血清 水平。ELISA试剂盒购自Eagle Biosciences。

[0233] 结果在图2A中示出。注射每种质粒在注射后24小时产生接近 或高于1ug/ml水平的血清抗CD20 mAb蛋白水平。血清抗CD20 mAb 蛋白水平在此范围内在两个组中维持接下来至少178天。血清抗 CD20 mAb蛋白水平在接受相同方案,但是DNA载体编码人G-CSF cDNA的小鼠中是不可检测的。这些数据证明,编码抗CD20 mAb的 双盒以及单盒质粒DNA载体可在单一IV注射之后产生延长的维持 的血清抗CD20 mAb蛋白水平。

[0234] 第二实施例:

[0235] 在第二实施例中,使用RPMI+10%FBS培养基将Raji细胞(5x10 4个细胞/孔)接种在96孔板中。第二天,将细胞与利妥昔单抗(0.5、1、 10ug/ml)或小鼠血清样品(20ul/孔,一式两份样品)一起在室温下孵育 1小时。然后向所有孔中加入20微升合并的正常人血浆(Innovative Research)(除利妥昔单抗对照条件外),并将板在37C下再孵育12小 时。根据制造商的说明使用PROMEGA细胞滴度Glo试剂测量细胞 活力。结果在图2B中示出,其中值作为相对于对照条件(无处理)的 变化百分比示出。所测试的每个小鼠样品的利妥昔单抗浓度在图2B 中示出。对照1-2样品是指来自注射对照质粒(编码G-CSF)的小鼠的 小鼠血清。条代表一式两份样品的标准差。

[0236] 通过ELISA针对抗CD20的浓度确定分析来自148天前顺序注 射阳离子脂质体,接着注射编码编码抗CD20 mAb或人G-CSF的质 粒DNA载体的小鼠的血清。置于条上的红色字体的数字代表对应血 清样品的利妥昔单抗的浓度(ng/ml)。使用细胞裂解测定,从148天前注射抗CD20 DNA载体的小鼠分离的血清在与用高浓度的重组利妥 昔单抗蛋白(Invivogen)处理的Raji细胞相当的水平下裂解CD-20+人 Raji细胞。这些数据(在图2B中)显示,注射抗CD20 DNA载体的小 鼠在单一DNA载体注射之后产生完全生物活性的利妥昔单抗mAb 蛋白,持续至少176天。

[0237] 第三实施例:

[0238] 在第三实施例中,每组注射三只小鼠。每只小鼠接受单一IV注 射1000纳摩尔的含有2.5%的并入脂质体双层中的地塞米松棕榈酸酯 (DP)的DOTAP阳离子脂质体。在此两分

钟后接着单一IV注射75ug 编码抗CD20(利妥昔单抗)的两种不同的质粒DNA中的一种。在IV注射前2小时用IP注射40mg/kg地塞米松处理两个组。图7中所示 的质粒902.8(P2A)(SEQ ID NO:5)编码通过2A自裂解肽分离的抗 CD20 mAb重链和轻链cDNA。图6中所示的质粒718.1(SEQ ID NO:4) 为分别编码抗CD20 mAb重链和轻链cDNA的双表达盒质粒载体。在注射后24小时且之后以7天间隔通过ELISA确定抗CD20的血清 水平。ELISA试剂盒购自Eagle Biosciences。图3中的结果显示,注 射每种质粒在注射后24小时产生接近或高于1ug/ml水平的血清抗 CD20 mAb蛋白水平。在注射之后57天时,两组的血清抗CD20 mAb 蛋白水平在此范围内。

[0239] 第四实施例:

[0240] 在第四实施例中,每组注射三只小鼠。每只小鼠接受单一IV注 射1000纳摩尔的DOTAP阳离子脂质体和1000纳摩尔的DMPC中性 脂质体,各自含有2.5%的并入脂质体双层中的地塞米松棕榈酸酯 (DP)。在此两分钟后接着单一IV注射75ug编码抗CD20(利妥昔单抗)的质粒DNA。在IV注射前2小时用IP注射40mg/kg地塞米松处 理两个组。质粒p718.1为分别编码抗CD20 mAb重链和轻链cDNA 的双表达盒质粒载体。图8示出质粒p113.2(SEQ ID NO:6)是相同的, 但在第二编码盒的上游包括单一超增强子。在注射后24小时通过 ELISA确定抗CD20的血清水平。ELISA试剂盒由Eagle Biosciences 提供。结果在图4中示出。两组在顺序注射后24小时均表达抗CD20。添加单一超增强子元件在此时间点处增加小鼠中的血清抗CD20 mAb蛋白的产生。

[0241] 实施例2

[0242] 生物活性核酸的表达

[0243] 此实施例描述所实施的实验,其证明IV顺序注射阳离子脂质体, 然后注射编码特异性靶向小鼠NFkB-p65的CPISPR/Cas9、shRNA、核酶或反义序列的质粒DNA载体各自抑制小鼠中的p65表达。

[0244] 第一实施例:

[0245] 在第一实施例中,每组注射三只或四只小鼠。每只小鼠接受单一 IV注射1000纳摩尔的含有2.5%的并入脂质体双层中的地塞米松棕榈 酸酯(DP)的DOTAP阳离子脂质体。在此两分钟后接着单一IV注射 75ug编码指示的基于CRISPR或核酶的质粒的质粒DNA以抑制内源 性小鼠NFkB-p65的表达。使用的质粒如下:核酶(图13,SEQ ID NO:7),CRISPR1(图14,SEQ ID NO:8),CRISPR2(图15,SEQ ID NO:9),和CRISPR(图16,SEQ ID NO:10)。对照组接受与抗NFkB-p65 CRISPR质粒相同的CRISPR/Cas9质粒,不同的是20bp靶向序列靶 向小鼠PECAM。在IV注射前2小时用IP注射40mg/kg地塞米松处 理所有组。

[0246] 组织制备和抗小鼠-p65 ELISA方法如下。通过在冰上解剖成500 uL制备的1X Triton裂解缓冲液来在注射之后24小时(抗p65核酶) 和在注射之后8天(抗p65 CRISPR1/2)生成肺裂解液。样品包括每只 动物的两个肺。每个样品进行均质化(Polytron PT 2100)30秒,加上 超声处理(Misonix XL2000 Microson超声细胞破碎器XL 2000),并且 在4C下离心10分钟,并且从组织沉淀抽吸裂解液。然后使用购自 Thermo Fisher的BCA总蛋白质测定确定来自每个裂解液的蛋白质浓 度。根据制造商的说明,将蛋白质标准化的裂解液一式两份加入到来 自Signaling Technologies的96孔板ELISA(PathScan总NF-κB p65 夹心ELISA试剂盒)中。然后在(分子装置Spectramax M5)板读取器中 分析板。在记录来自板的

吸光度之后,通过4PL分析拟合使用鼠B16 黑素瘤细胞上清液生成的标准曲线。误差条代表平均值的标准误差。

[0247] 此实施例的结果在图9中示出。这些数据证明,基于抗小鼠 NFkB-p65 CRISPR/Cas9以及核酶质粒的靶向载体分别在其全身性注 射后8天和1天减少内源性鼠p65的表达。

[0248] 第二实施例:

[0249] 此实施例的方法与上文相同。结果在图10中示出。这些数据证 明,基于抗小鼠NFkB-p65 CRISPR/Cas9质粒的靶向载体在其全身性 注射后13天减少小鼠中的内源性小鼠p65的表达。另外,对来自这 些小鼠的组织切片进行NFkB-p65免疫组织化学方法。

[0250] 将小鼠肺的石蜡包埋的切片用p65的C末端的一级兔Mab(抗 NF-kB p65抗体[E379](ab32536)-ABCAM)在Leica Bond自动染色仪 上进行分批(来自对照和经处理动物的切片)染色。之后进行过氧化物 酶标记。使用Hamamatsu NanoZoomer数字病理学系统在20X放大率 下在明视场中扫描IHC染色的切片。然后将数字图像导入到 Visiopharm软件中以用于定量分析。

[0251] 使用Visiopharm图像分析模块,通过HIC图像分析技术员随机 选择每个样品的肺实质的五个分散的代表性区域(ROI),并且手动勾 画以用于进一步的定量分析。使用三个特征,具有平均和多项式平滑 滤波器的RGB-B、对比红-蓝和具有最小H&E-曙红滤波器的HDAB-DAB,软件将初始数字图像转化为灰度值。使用Bayesian分 类方案,Visiopharm软件然后被训练来标记阳性棕色染色、苏木精复 染色和空白区域。使用此配置来将所有的ROI以分批模式进行处理 以生成所需的输出。

[0252] 表2

[0253]

	分类方案: Bayesian			
测量	Nfkb 面积(μm²)	组织面积(μm²)	总面积(μm²)	Nfkb 比
动物 143-39	123566.69	483901.69	607468.38	0.2034125
动物林格式对照	287497.75	467149.91	754647.69	0.3809695

[0254] 通过将NFkB面积除以肺实质的总面积来确定NFkB的比率。对 照(林格氏)与经处理的肺(143-39)比率之间的差值显示NfKb染色的 大约53%降低。此发现与染色部分的视觉观察一致。结果在图41中 示出。图41A示出林格氏处理的对照,并且图41B示出CRISPR/Cas9 抗NFkB p65处理的小鼠组织。这些结果证明,一次顺序IV注射 CRISPR/Cas9抗NFkB p65质粒DNA载体在13天前注射抗NFkB p65 相对于对照DNA载体的小鼠的整个肺中使p65蛋白水平降低超过 50%。

[0255] 第三实施例:

[0256] 此实施例的方法与上文相同。结果在图11中示出。这些数据证 明,基于抗小鼠NFkB-p65 CRISPR/Cas9以及反义质粒的靶向载体(图 19,SEQ ID NO:11)分别在其全身性注射后13天和1天减少内源性鼠 p65的表达。

[0257] 第四实施例:

[0258] 此实施例的方法与上文相同。结果在图12中示出。这些数据证 明,基于抗小鼠NFkB-p65 shRNA载体p65 shB(图20,SEQ ID NO:12) 和质粒p65 shA2(SEQ ID NO:55;图76)质粒的靶向载体在其全身性 注射后1天减少内源性小鼠p65的表达。对照质粒PECAM sh对照是 SEQ ID NO:56,图77。

[0259] 实施例3

[0260] 长期G-CSF表达

[0261] 此实施例描述所实施的实验,其证明单一IV顺序注射阳离子脂 质体,接着注射编码人G-CSF基因的质粒DNA载体在接下来的至少 582天在小鼠中产生上述治疗性人G-CSF血清蛋白水平(图17A)以及 升高的绝对嗜中性粒细胞计数(ANC)(图17B)。因此,单一IV顺序脂 质体DNA注射可在完全免疫小鼠中产生治疗性血清水平的DNA载 体编码蛋白,持续超过一年半。所采用的两种HG-CSF质粒是011215 #7(SEQ ID NO:45;图66)和011315#2(SEQ ID NO:46;图67);并 且阴性对照是质粒122014#235(SEQ ID NO:47;图68)。

[0262] 在另一个实施例中,将编码HG-CSF的质粒注射到大鼠中。将 10号和12号大鼠各自给予一次顺序注射,而将14号大鼠在初始注 射之后第7天和第21天再注射两次。将10号大鼠IV注射3000纳摩 尔DOTAP SUV,接着注射300ug编码HG-CSF的MAR较少的质粒 DNA。将12号大鼠注射3mg地塞米松(IP),接着IV注射3000纳摩 尔DOTAP SUV,并且然后注射300ug编码HG-CSF的MAR较少的 质粒DNA。将14号大鼠在实验开始时注射3000纳摩尔DOTAP SUV, 并且然后注射300ug编码HG-CSF的含有MAR的质粒DNA。之后 将14号大鼠在第7天注射3mg地塞米松(IP),接着IV注射3300纳 摩尔DOTAP SUV,并且然后注射330ug编码HG-CSF的含有MAR的质粒DNA。在第21天,将14号大鼠注射3mg地塞米松(IP),接 着IV注射4400纳摩尔DOTAP SUV,并且然后注射330ug编码 HG-CSF的含有MAR的质粒DNA。

[0263] 结果在图18中示出,其显示在顺序IV注射DOTAP阳离子脂质 体,接着注射编码HG-CSF的质粒DNA之后大鼠血清中的嗜中性粒 细胞升高。这些结果证明,重复顺序IV阳离子脂质体注射,接着注 射HG-CS质粒DNA载体可在接下来的至少100天良好地产生绝对嗜 中性粒细胞计数的持续升高。它们还显示,预注射地塞米松,接着单 一顺序IV阳离子脂质体注射,接着注射HG-CSF质粒DNA载体也 可产生绝对嗜中性粒细胞计数的持续升高。

[0264] 实施例4

[0265] 施用PCR生成的DNA载体明显增加蛋白质产物产生的水平和持续 时间

[0266] 此实施例描述所实施的实验,其证明与质粒DNA相比,施用PCR 生成的DNA载体明显增加小鼠中编码DNA载体基因的蛋白质产物 产生的水平和持续时间两者。

[0267] 环化PCR生成的DNA载体增加小鼠中血清人G-CSF产生的水平

[0268] 方法:为了通过PCR生成DNA表达载体,使用含有对应酶切位 点的引物对或使用Q5高保真聚合酶(New England Biolab)的具有茎环 构型的引物对(针对受保护的线性产物),通过PCR扩增HG-CSF表达 盒。将纯化的PCR产物以10U/ug用对应酶(BamHI)消化,然后在85C 下热灭活20min。在室温下,用80T4DNA连接酶单位/ug消化PCR 以1或50ng/ul进行纯化的消化PCR的连接,持续1小时,然后在 65C下热灭活20min。对于1ng/ul连接条件,在纯化前用Millipore filtration Ultra15减小体积。然后将连接的PCR产物从纯化柱用乳酸 林格氏溶液洗脱,之后经受最终0.2uM过滤。所有的纯化步骤使用 Purelink PCR纯化试剂盒(Thermofisher)进行。

[0269] 结果在图21中示出,其示出顺序IV注射1050纳摩尔的DOTAP 阳离子脂质体,接着注射70ug的HG-CSF质粒或不同形式的PCR 生成的HG-CSF表达盒DNA之后24小时的大鼠血清中人G-CSF的 水平。接受环化PCR生成的DNA的小鼠显示比接受线性PCR生成 的DNA或质粒DNA的那些小鼠更高的血清HG-CSF水平。

[0270] 环化PCR生成的DNA载体增加血清人G-CSF和ANC的水平和持续时间。此外,单一再

注射PCR生成的DNA明显增加小鼠中的长期高水平人G-CSF水平。

[0271] 图22示出在初始注射之后接下来至少302天的小鼠中小鼠血清 或血浆中的人G-CSF的水平(左轴)和全血中以每微升数千计的绝对 嗜中性粒细胞计数(ANC)(右轴)。对小鼠顺序IV注射阳离子脂质体，接着注射PCR生成的DNA。在第35天对一个组给予重复顺序注射 脂质和PCR DNA,在接下来的200天内产生显著更高的血清HG-CSF 水平。分析肝素化全血的ANC,并且通过ELISA分析血浆的HG-CSF。在注射之后300天,小鼠显示显著升高的嗜中性粒细胞水平。对照(模 拟物且未注射)中的平均ANC是2K/uL。因此,单一重复注射PCR 生成的载体DNA可明显升高表达载体的蛋白质产物以及ANC的血 清HG-CSF水平,持续延长的时间段。

[0272] 将R6K DNA序列包含到环化PCR生成的DNA载体中增加小鼠中血清人G-CSF产生的水平和持续时间

[0273] 方法:对27g小鼠IV注射DOTAP SUV阳离子脂质体,接着注 射编码HG-CSF的环化PCR DNA(具有或没有复制起点(R6K))。随后 每7或14天对小鼠放血一次。图23示出在一次顺序注射阳离子脂质 体,接着注射具有或没有R6K复制起点的PCR生成的DNA之后106 天的小鼠血清中的人G-CSF水平。因此,并入包含R6K的所选DNA 序列可显著增加DNA载体编码的蛋白质的血清水平,持续延长的时 间段。

[0274] 实施例5

[0275] 中性脂质和地塞米松棕榈酸酯增加血清水平

[0276] 此实施例描述所实施的实验,其证明将中性脂质和地塞米松棕榈 酸酯添加到人G-CSF表达载体的顺序IV施用显著增加小鼠中的人 G-CSF血清水平和ANC两者,持续延长的时间段。

[0277] 方法:对小鼠注射三种不同的脂质体制剂中的一种。单独的1050 纳摩尔DOTAP SUV,与1050纳摩尔DMPC中性脂质混合的1050 纳摩尔DOTAP SUV,或与1050纳摩尔DMPC混合的含有2.5％地塞 米松棕榈酸酯的1050纳摩尔SUV。脂质注射之后2分钟接着注射含 有编码人G-CSF的表达的质粒的MAR。随后每7或14天对小鼠放 血一次。分析肝素化全血的嗜中性粒细胞计数,并且通过ELISA分 析血浆的HG-CSF。未处理对照小鼠始终为<3K/uL。

[0278] 图24示出顺序注射具有或没有中性脂质或地塞米松棕榈酸酯的 阳离子脂质体，接着注射质粒DNA的小鼠中人G-CSF和对应的绝对 嗜中性粒细胞计数(ANC,右轴)水平。在注射之后99天,小鼠显示 显著升高的嗜中性粒细胞水平。接受中性脂质加上地塞米松棕榈酸酯 的小鼠显示随时间推移最高的ANC计数。

[0279] 实施例6

[0280] 使用第二增强子增加表达的蛋白质的血清水平

[0281] 此实施例描述所实施的实验,其证明在人G-CSF DNA表达质粒 中添加第二增强子可在顺序IV注射之后在小鼠中增加人G-CSF血清 水平。

[0282] 方法:首先对小鼠注射各自1000纳摩尔的含有2.5％地塞米松棕 榈酸酯的DOTP和含有2.5％地塞米松棕榈酸酯的DMPC。在此两分 钟后接着注射编码HG-CSF的质粒。所采用的四种质粒是 sv40-mCMVEF1(SEQ ID NO:13;图26);mCMV-mCMVEF1(SEQ ID NO:14;图27);mCMV-hCMVEF1(SEQ ID NO:15;图28);以及 mCMVEF1(SEQ ID NO:16;图29)。前三种表达构建体含有额外的增 强子序列。如先前所述对小鼠进行放血。

[0283] 图25示出此实施例的结果。如此图所示，增强子组合在顺序IV 注射之后1天和8天增加小鼠中的人G-CSF表达。示出脂质体，接 着编码人G-CSF并含有一系列不同的增强子元件的两种组合的质粒 的单一处理的结果。

[0284] 实施例7

[0285] 使用超增强子

[0286] 此实施例描述所实施的实验，其证明在人G-CSF DNA表达质粒 中添加超增强子序列可在顺序IV注射之后在小鼠中增加人G-CSF血 清水平。

[0287] 方法：首先对小鼠注射各自1000纳摩尔的含有2.5％地塞米松棕 榈酸酯的DOTP和含有2.5％地塞米松棕榈酸酯的DMPC中性脂质。 在此2分钟后接着注射具有或没有超增强子元件(hr3)的编码HG-CSF 的质粒。含有hr3的质粒如下：hr3-mCMVEF1#2(SEQ ID NO:17；

[0288] 图31)；hr3-mcmvEF1#5(SEQ ID NO:18；图32)；以及hr3-mcmvEF1 #18(SEQ ID NO:19；图33)。接受没有超增强子元件的质粒的组中的 一个(第4条)补充2.5％人血清白蛋白(HSA)。

[0289] 在图30中，示出顺序IV注射脂质体，接着注射质粒DNA之后 24小时的人G-CSF的小鼠血清水平。前三个组的质粒含有超增强子 元件。还示出质粒与人血清白蛋白(HSA)一起注射。含有超增强子元 件的三种不同DNA载体中的每种产生比缺乏超增强子的对应DNA 载体更高的血清人G-CSF水平。

[0290] 实施例8

[0291] 使用超增强子

[0292] 此实施例描述所实施的实验，其证明在人因子九DNA表达质粒 中添加超增强子、R6K或RNA-out DNA序列可在顺序IV注射之后 在小鼠中增加人因子九血清水平。

[0293] 方法：对27g小鼠IV注射DOTAP SUV阳离子脂质体，接着注 射编码人因子IX的DNA。使用质粒和环化PCR构建体两者，具有 或没有复制起点(R6K)。

[0294] 图34示出顺序IV注射脂质体和各种不同的FIX DNA表达质粒 之后24小时的人因子IX的血浆浓度。所使用的质粒是：FIX质粒(SEQ ID NO:20；图35)；FIX R6K1(SEQ ID NO:21；图36)；FIX R6K2(SEQ ID NO:22；图37)；FIX Superenh(SEQ ID NO:23；图38)；以及FIX RNA-out(SEQ ID NO:24；图39)。除对照FIX质粒(第1条)之外，质 粒包括具有R6K元件的两种不同的PCR生成的DNA，含有超增强 子的FIX质粒和使用RNA-out生成的FIX质粒。修饰的DNA载体中 的每种在注射之后1天产生更高的人FIX血清蛋白水平。

[0295] 实施例9

[0296] 注射之后10天和40天的CRISPR/Cas9介导的敲低

[0297] 此实施例描述所实施的实验，其证明在小鼠中进行顺序IV注射 之后10天和40天的小鼠NFkB-p65蛋白的抗p65 CRISPR/Cas9介导 的敲低。

[0298] 小鼠处理方法：每组注射三或四只小鼠。每只小鼠接受单一IV 注射1000纳摩尔的含有2.5％的并入脂质体双层中的地塞米松棕榈酸 酯(DP)的DOTAP阳离子脂质体。在此两分钟后接着单一IV注射75 ug编码指示的基于CRISPR或核酶的质粒的质粒DNA以抑制内源性 小鼠NFkB-p65的表达。PECAM CRISPR对照在SEQ ID NO:10中示 出，并且p65 CRISPR RelA1在SEQ ID NO:8中示出。质粒EF1/U6 RelA1(020117#5)(SEQ ID NO:57)在图79中示出；质粒EF1/U6 RelA4(020117#8)(SEQ ID NO:58)在图80中示出；并且质粒 hu1/EF1/U6

RelA1(021417#3)(SEQ ID NO:59)在图81中示出。对照 组接受与抗NFkB-p65 CRISPR质粒相同的CRISPR/Cas9质粒,不同 的是20bp靶向序列靶向小鼠PECAM。在IV注射前2小时用IP注 射40mg/kg地塞米松处理所有组。

[0299] 组织制备和抗小鼠-p65 ELISA方法。通过在冰上解剖成500uL 制备的1X Triton裂解缓冲液来在注射之后24小时(抗p65核酶)和在 注射之后8天(抗p65 CRISPR1/2)生成肺裂解液。样品包括每只动物 的两个肺。每个样品进行均质化(Polytron PT 2100)30秒,加上超声 处理(Misonix XL2000 Microson超声细胞破碎器XL 2000),并且在4C 下离心10分钟,并且从组织沉淀抽吸裂解液。然后使用购自Thermo Fisher的BCA总蛋白质测定确定来自每个裂解液的蛋白质浓度。根 据制造商的说明,将蛋白质标准化的裂解液一式两份加入到来自 Signaling Technologies的96孔板ELISA(PathScan总NF-κB p65夹心 ELISA试剂盒)中。然后在(分子装置Spectramax M5)板读取器中分析 板。在记录来自板的吸光度之后,通过4PL分析拟合使用鼠B16黑 素瘤细胞上清液生成的标准曲线。误差条代表平均值的标准误差。

[0300] 结果描述:在图78和图40中示出的这些数据证明,基于抗小鼠 NFkB-p65 CRISPR/Cas9以及核酶质粒的靶向载体在其全身性注射后 10天和40天减少小鼠中的内源性小鼠p65的表达。

[0301] 实施例10

[0302] 小鼠中的长期HG-CSF表达

[0303] 此实施例描述所实施的实验,其证明在单一顺序IV注射阳离子 脂质体,然后注射HG-CSF DNA表达载体之后582天处死的小鼠显 示在对照小鼠中不存在的脾脏和骨髓中的非常大量的嗜中性粒细胞。 方法如下。对照小鼠不进行注射。对处理的27g小鼠IV注射800纳 摩尔DOTAP SUV阳离子脂质体,接着注射90ug编码hG-CSF的质 粒DNA,并且在注射之后582天进行安乐死。将小鼠放血处死,并 且将器官保存在10%中性缓冲福尔马林中。图42示出骨髓中的IHC 结果。具体地,图42a(20x)和图42b(60x),对照骨髓,示出各种不 同的细胞类型混合物包围正常股骨髓腔的骨小梁,其中深色染色的红 系细胞特别明显。图42c(20x)和图42d(60x),经处理的骨髓,示出 单调的几乎实心片的浅色染色的细胞替代股骨骨髓浅色染色的髓样 细胞(多形核白细胞)中的骨小梁元素,其中椭圆形、凹陷椭圆形、带 和片段化形式替代股骨骨髓内的其他细胞类型。图43示出脾脏组织 中的IHC结果。图43a(20x)和图43b(60x),对照脾脏,示出显示各 种不同细胞群体的正常脾脏的白(淋巴)髓的红色/深色部分。图43c (20x)和图43d(60x),经处理的脾脏,示出浅色染色的髓样细胞(pmn), 其中椭圆形、凹陷椭圆形、带和片段化形式替代大多数其他细胞类型。

[0304] 实施例11

[0305] 大鼠中的长期HG-CSF表达

[0306] 此实施例描述所实施的实验,其证明在最后顺序IV注射阳离子 脂质体,然后注射HG-CSF DNA表达载体之后168天处死的大鼠显 示在对照大鼠中不存在的骨髓中的非常大量的嗜中性粒细胞。方法如 下。对照大鼠不进行注射。经处理的大鼠:将150g雌性大鼠在实验 开始时注射3000纳摩尔DOTAP SUV,并且然后注射300ug编码 HG-CSF的DNA表达载体。之后将经处理的大鼠在第7天注射3mg 地塞米松(IP),接着IV注射3300纳摩尔DOTAP SUV,并且然后注 射330ug编码HG-CSF的DNA表达载体。在第21天,将处理的大 鼠再注射3mg地塞米

松(IP),接着IV注射4400纳摩尔DOTAP SUV，并且然后注射330ug编码HG-CSF的DNA表达载体。对大鼠进行安 乐死,放血处死,并且将器官保存在10％中性缓冲福尔马林中。图 44示出骨髓中的IHC结果。具体地,图44a(20x)和图42b(60x),对 照骨髓,示出股骨骨髓中的各种不同的细胞类型,其中圆形的深色染 色的红细胞谱系特别明显。图44c(20x)和图44d(60x),经处理的骨 髓,示出股骨骨髓中的浅色染色的髓样细胞(多形核白细胞),其中椭圆形、凹陷椭圆形、带和片段化形式占优势。仍然有少量深色染色的 红细胞谱系细胞的簇。图45a示出40x下的对照大鼠椎体,而图45b 示出40x下的HGCSF大鼠椎体。

[0307] 实施例12

[0308] 抗人PCSK9单克隆抗体的表达

[0309] 此实施例描述顺序IV注射阳离子脂质体,接着注射编码抗人 PCSK9单克隆抗体的DNA表达载体,以减少小鼠中的LDL。每组注 射五只CD-1小鼠。在注射前2个月,将小鼠置于高胆固醇和胆酸饮 食下,以增加LDL胆固醇(Envigo Atherogenic Teklad Diet TD.02028)。然后每只小鼠接受单一IV注射1050纳摩尔含有2.5％的并入脂质体 双层中的地塞米松棕榈酸酯(DP)的DOTAP阳离子脂质体,之后2分 钟接着单一IV注射75ug编码抗人PCSK9单克隆抗体(mAb)的三种 不同质粒DNA中的一种或编码抗人CD20单克隆抗体的质粒DNA 作为对照组。在IV注射前2小时用IP注射40mg/kg地塞米松处理 所有组。DNARx-31H4-2A(SEQ ID NO:25;图46)和DNARx-21B12 (P2A)(SEQ ID NO:27;图48)编码通过2A自裂解肽分离的抗PCSK9 mAb重链和轻链cDNA。质粒DNARx-31H4(SEQ ID NO:26;图47) 和DNARx-21B12(SEQ ID NO:28;图49)为分别编码不同型式的抗 PCSK9 mAb重链和轻链cDNA的双表达盒质粒载体。在注射前1周， 然后在注射后24小时并且此后以7天间隔测量小鼠LDL胆固醇的血 清水平。血清LDL测定是光度测定法,涉及在另一种化合物的存在 下酶促分解LDL底物以形成染料。然后通过吸光度测定测量染料的 颜色强度,并且通过UC Davis兽医诊断实验室进行。预期经处理小 鼠中的LDL水平将降低,但在对照小鼠中不降低。

[0310] 实施例13

[0311] 抗人CD47单克隆抗体的表达

[0312] 此实施例描述顺序IV注射阳离子脂质体,接着注射编码抗人 CD47单克隆抗体的DNA表达载体,以抑制携带肿瘤的裸小鼠中的 Raji、人B细胞淋巴瘤肿瘤进展。每组注射五只无胸腺裸小鼠。小鼠 在肩部或斜腹中皮下接受$0.1x10^5$-$2x10^6$个Raji细胞。10至14天后,或在肿瘤达到70-100mm3的体积时,每只小鼠接受单一IV注射1050 纳摩尔含有2.5％的并入脂质体双层中的地塞米松棕榈酸酯(DP)的 DOTAP阳离子脂质体,之后2分钟接着单一IV注射75ug编码抗人 CD47单克隆抗体的DNA表达质粒或编码抗人PCSK9单克隆抗体的 质粒DNA作为对照组。在IV注射前2小时用IP注射40mg/kg地塞 米松处理所有组。DNARx-CD47-2A(P2A)(SEQ ID NO:29;图50)编 码通过2A自裂解肽分离的抗CD47 mAb重链和轻链cDNA。DNARx-CD47(SEQ ID NO:30;图51)为分别编码抗CD47 mAb重链 和轻链cDNA的双表达盒质粒载体。在DNA表达载体注射后,每周 一次或每周两次通过卡尺测量肿瘤体积。预期经处理小鼠中的肿瘤体 积将降低,但在对照小鼠中不降低。

[0313] 实施例14

[0314] 抗人CD47和抗人CD20单克隆抗体的表达

[0315] 此实施例描述顺序IV注射阳离子脂质体,接着注射编码抗人 CD47单克隆抗体、抗

人CD20单克隆抗体或者抗人CD47和抗CD20 单克隆抗体两者的DNA表达载体，以抑制携带肿瘤的裸小鼠中的 Raji、人B细胞淋巴瘤肿瘤进展。每组注射五只无胸腺裸小鼠。小鼠 在肩部或斜腹中皮下接受$0.1x10^5$-$2x10^6$个Raji细胞。10至14天后，或在肿瘤达到70-100mm^3的体积时，每只小鼠接受单一IV注射1050 纳摩尔含有2.5％的并入脂质体双层中的地塞米松棕榈酸酯(DP)的 DOTAP阳离子脂质体，之后2分钟接着单一IV注射75ug编码抗人 CD47单克隆抗体、抗人CD20单克隆抗体、抗人CD47加上抗CD20 单克隆抗体的DNA表达质粒或编码抗人PCSK9单克隆抗体的质粒 DNA作为对照组。在IV注射前2小时用IP注射40mg/kg地塞米松处理所有组。

[0316] DNARx-CD47-2A(P2A)(SEQ ID NO:29;图50)编码通过2A自 裂解肽分离的抗CD47 mAb重链和轻链cDNA，并且质粒715.1 2a (P2A)(SEQ ID NO:3)编码通过2A自裂解肽分离的抗CD20 mAb重链 和轻链cDNA。DNARx-CD47(SEQ ID NO:30;图51)为编码抗CD47 mAb重链和轻链cDNA的双表达盒质粒载体。在DNA表达载体注射 后，每周一次或每周两次通过卡尺测量肿瘤体积。预期经处理小鼠中 的肿瘤体积将降低，但在对照小鼠中不降低。

[0317] 实施例15

[0318] 抗流感干细胞抗原单克隆抗体的表达

[0319] 此实施例描述顺序IV注射阳离子脂质体，接着注射编码抗A型 流感干细胞抗原的DNA表达载体，以在小鼠中预防和/或治疗A型流 感。每组注射五只C57B16小鼠。在注射前，将小鼠接种2x MLD50 的PR/8/34(H1N1)、HKx31(H3N1)或B/Lee/40流感病毒株。通过以 增加量的病毒感染未接种疫苗的小鼠来确定攻击病毒的相应 MLD50。在注射后14-20天监测小鼠的体重减轻和死亡。然后每只 小鼠接受单一IV注射1050纳摩尔含有2.5％的并入脂质体双层中的 地塞米松棕榈酸酯(DP)的DOTAP阳离子脂质体，之后2分钟接着单 一IV注射75ug编码抗A型流感干细胞抗原单克隆抗体的三种不同 质粒DNA中的一种或编码抗人CD20单克隆抗体的质粒DNA作为 对照组。在IV注射前2小时用IP注射40mg/kg地塞米松处理所有组。

[0320] 质粒DNARx-D8-2A(SEQ ID NO:31;图52)、DNARx-F10-2A (SEQ ID NO:32;图53)和DNARx-A66-2A(P2A)(SEQ ID NO:33;图 54)编码通过2A自裂解肽分离的抗A型流感干细胞抗原mAb重链和 轻链cDNA。质粒DNARx-D8(SEQ ID NO:34;图55)、DNARx-F10 (SEQ ID NO:35;图56)和DNARx-A66(SEQ ID NO:36;图57)为分别 编码不同型式的抗A型流感干细胞抗原重链和轻链cDNA的双表达 盒质粒载体。质粒DNARx-HA-MITD(SEQ ID NO:37;图58)编码来 自具有I类MHC跨膜结构域和胞质结构域(MITD)的PR/8/34(H1N1) 的HA，并且质粒DNARx-SEC-部分HA-MITD(SEQ ID NO:38;图 59)编码来自具有I类MHC信号肽片段(SEC)和跨膜和胞质结构域 (MITD)的PR/8/34(H1N1)的部分HA。质粒DNARx-D8-2A-HA-MITD (SEQ ID NO:39;图60)、DNARx-F10-2A-HA-MITD(SEQ ID NO:40; 图61)、DNARx-A66-2A-HA-MITD (SEQ ID NO:41;图62)、DNARx-D8-2A-SEC-部分-HA-MITD(SEQ ID NO:42;图63)、DNARx-F10-2A-SEC-部分-HA-MITD(SEQ ID NO:43;图64)和 DNARx-A66-2A SEC-部分-MITD(SEQ ID NO:44;图65)为双表达盒 质粒，其中第一表达盒编码通过2A自裂解肽分离的抗A型流感干细 胞抗原mAb重链和轻链cDNA，并且第二表达盒编码来自具有I类 MHC跨膜结构域和胞质结构域(MITD)的PR/8/34(H1N1)的HA或者 来自具有I类MHC信号肽片段(SEC)和跨膜和胞质结构域(MITD)的 PR/8/34(H1N1)的部分HA。使用A型或B型流感特异性抗核蛋白抗 体

(Millipore,Bellerica,MA)通过ELISA检测小鼠血清中流感核蛋白 的存在。预期经处理的小鼠将使其流感得以预防或治疗,而对照小鼠 并不如此。

[0321] 实施例16

[0322] 抗小鼠PD-1单克隆抗体、卵清蛋白和gp-70的表达

[0323] 此实施例描述顺序IV注射阳离子脂质体,然后注射编码抗小鼠 PD-1单克隆抗体、卵清蛋白、gp-70、抗小鼠PD-1单克隆抗体加上 卵清蛋白或抗小鼠PD-1单克隆抗体加上gp-70的DNA表达载体,以 抑制携带肿瘤的小鼠中B16黑素瘤或CT26结肠肿瘤进展。向五只C57B16小鼠在斜腹中皮下注射每只动物$2x10^5$个B16细胞,或者向 五只BALBC小鼠在斜腹中皮下注射每只动物$2x10^5$个CT26细胞。在接种后第4天,每只小鼠接受单一IV注射1050纳摩尔含有2.5% 的并入脂质体双层中的地塞米松棕榈酸酯(DP)的DOTAP阳离子脂质 体,之后2分钟接着单一IV注射75ug编码抗小鼠PL-1单克隆抗体、卵清蛋白、gp-70的DNA表达质粒或编码抗人PCSK9单克隆抗体的 质粒DNA作为对照组。在IV注射前2小时用IP注射40mg/kg地塞 米松处理所有组。质粒DNARx-PD1-2A(P2A)(SEQ ID NO:48;图69) 编码通过2A自裂解肽分离的抗PD-1mAb重链和轻链cDNA,质粒 DNARx-SEC-OVA-MITD(SEQ ID NO:49;图70)编码卵清蛋白限制 性表位H2Kb和I类MHC信号肽片段(SEC)以及跨膜和胞质结构域 (MITD),质粒DNARx-SEC-gp70-MITD(SEQ ID NO:50;图71)编码 H-2Ld限制肽抗原AH1和I类MHC信号肽片段(SEC)以及跨膜和胞 质结构域(MITD)。质粒DNARx-PD1-2A OVA(SEQ ID NO:51;图72) 或DNARx-PD1-2A gp70(SEQ ID NO:52;图73)为双表达盒质粒载体, 其在第一表达盒中编码通过2A自裂解肽分离的抗PD-1mAb重链和 轻链cDNA,并且在第二表达盒中编码卵清蛋白限制性表位H2Kb或 H-2Ld限制肽抗原AH1和I类MHC信号肽片段(SEC)以及跨膜和胞 质结构域(MITD)。每3至4天通过卡尺测量肿瘤体积,并且对肿瘤 体积直径超过15mm和/或显示健康受损现象的动物进行安乐死。预 期经处理小鼠中的肿瘤体积将降低,但在对照小鼠中不降低。

[0324] 实施例17

[0325] 抗人抗CD20单克隆抗体、人G-CSF和链球菌Cas9的表达

[0326] 此实施例描述在小鼠中顺序IV注射阳离子脂质体,接着注射编 码抗人抗CD20单克隆抗体、人G-CSF、链球菌Cas9、抗CD20单克 隆抗体加上HG-CSF或抗CD20单克隆抗体加上Cas9的DNA表达载 体。每组注射五只CD-1小鼠。每只小鼠接受单一IV注射1050纳摩 尔含有2.5%的并入脂质体双层中的地塞米松棕榈酸酯(DP)的DOTAP 阳离子脂质体,之后2分钟接着单一IV注射75ug编码抗人CD20 单克隆抗体(mAb)、HG-CSF、Cas9、抗人CD20单克隆抗体加上 HG-CSF、抗人CD20单克隆抗体加上HG-CSF的质粒DNA或编码抗 人CD20单克隆抗体加上荧光素酶的质粒DNA作为对照组。在IV注 射前2小时用IP注射40mg/kg地塞米松处理所有组。质粒DNARx CD20-2A Cas9(SEQ ID NO:53;图74)或DNARx CD20-2A HG-CSF (SEQ ID NO:54;图75)为双表达盒质粒载体,第一表达盒编码通过 2A自裂解肽分离的抗CD20 mAb重链和轻链cDNA并通过 mCMV-EF1驱动,而第二表达盒编码Cas9或HG-CSF并且通过 hCMV-铁蛋白重链启动子驱动。如先前在方法中所述,在注射之后每 7天通过特异性ELISA测量抗CD20和HG-CSF的血清水平,而注射 之后每7天通过Cas9 ELISA和/或先前注射的小鼠的蛋白印迹形式小 鼠肺裂解液测量Cas9蛋白水平。两种测定将使用以下经验证的捕获 抗体:MAC133抗Cas9抗体,克隆7A9(Millipore)。

[0327] 实施例18

[0328] 使用中性脂质体增加抗人抗CD20单克隆抗体 的体内表达

[0329] 此实施例描述中性脂质体与阳离子脂质体的共同注射如何随时 间推移相对于注射相同的阳离子脂质体而没有中性脂质体增加小鼠 血清抗CD20单克隆抗体水平。对每组三只小鼠给予40mg/kg水平 下的地塞米松的IP注射。2小时后,首先向它们顺序注射1000纳摩 尔或1250纳摩尔DOTAP SUV,有或没有1000纳摩尔DMPC(1,2- 二肉豆蔻酰基-SN-甘油基-3-磷酰胆碱)中性脂质,并且然后注射75ug 含有利妥昔单抗(抗CD20单克隆抗体)cDNA的质粒载体。在24小时 之后并且此后每2-3周通过ELISA测量利妥昔单抗蛋白的血清水平。结果在图82中示出,其显示包含中性脂质和阳离子脂质体增加血清 抗CD20单克隆抗体水平。

[0330] 实施例19

[0331] 使用中性脂质体和地塞米松棕榈酸酯增加抗人抗CD20单克隆抗体 的体内表达

[0332] 此实施例描述将地塞米松棕榈酸酯并入中性脂质体中如何进一 步增加基因表达。对每组三只小鼠给予40mg/kg水平下的地塞米松 的IP注射。2小时后,首先向它们顺序注射1000纳摩尔含有2.5%地 塞米松棕榈酸酯的DOTAP SUV和1000纳摩尔含有1%、2.5%、5% 或10%地塞米松棕榈酸酯的DMPC中性脂质,并且然后注射75ug 含有利妥昔单抗cDNA的质粒载体。在24小时之后,通过ELISA测 量利妥昔单抗蛋白的血清水平。结果在图83中示出,其显示采用地 塞米松棕榈酸酯和中性脂质体进一步增加体内基因表达。

[0333] 实施例20

[0334] 在载体中包含Syn 21和/或Δ-p10增加体内基因表达

[0335] 此实施例描述包含抗CD20 mAb重链和轻链cDNA的Syn 21和/ 或Δ-p10序列5'或3'如何增加小鼠中的血清抗CD20 mAb水平。对 每组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后, 首先向它们顺序注射1000纳摩尔DOTAP SUV和1000纳摩尔DMPC 中性脂质,两者均含有2.5%地塞米松棕榈酸酯,并且然后注射75ug 含有利妥昔单抗cDNA的质粒载体。含有Syn 21和Δ-p10序列两者 的代表性载体构建体在SEQ ID NO:82(图85)中示出。在24小时之后, 通过ELISA测量利妥昔单抗蛋白的血清水平。结果在图84中示出, 其显示在载体中包含Syn 21和/或Δ-p10序列增加基因表达。

[0336] 实施例21

[0337] 在载体中包含hr3超增强子增加体内基因表达

[0338] 此实施例描述添加五引物hr3超增强子序列如何增加小鼠中的人 G CSF以及抗CD20单克隆抗体的表达。对每组三只小鼠给予40 mg/kg水平下的地塞米松的IP注射。2小时后,首先向它们顺序注射 1000纳摩尔DOTAP SUV和1000纳摩尔DMPC中性脂质,两者均含 有2.5%地塞米松棕榈酸酯,并且然后注射75ug含有人G-CSF或利 妥昔单抗cDNA的质粒载体。在24小时之后,通过ELISA测量hG-CSF 或利妥昔单抗蛋白的血清水平。结果在图86中示出,其显示当在质 粒中包含hr3超增强子时,G CSF表达增加(图86A)并且利妥昔单抗 抗CD20表达增加(图86b)。

[0339] 实施例22

[0340] 在3'或5'UTR区中包含R6K增加体内基因表达

[0341] 此实施例描述在人因子九cDNA的5'UTR或3'UTR中插入R6K 复制起点序列如何增

加小鼠中产生的人因子九血清水平的水平。对每 组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后， 首先向它们顺序注射1000纳摩尔DOTAP SUV和1000纳摩尔DMPC 中性脂质，两者均含有2.5％地塞米松棕榈酸酯，并且然后注射75ug (图87A)或60ug(图87B)含有因子IX cDNA的质粒载体。在24小时 之后，通过ELISA测量因子IX蛋白的血浆水平。结果在图87中示 出，其显示将R6K复制起点定位在因子IX基因的3'或5'UTR中增 加在75ug水平(图87A)和60ug水平(图87B)两者下的表达水平。

[0342] 实施例23

[0343] 单一载体注射之后的长期抗CD20抗体表达

[0344] 此实施例描述单一利妥昔单抗DNA注射之后148、232和284 天产生的小鼠血清利妥昔单抗水平如何保持治疗有效(图88A)，从而 诱导与重组利妥昔单抗蛋白相当的CD20+人肿瘤细胞裂解水平。对 每组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后， 首先向它们顺序注射1050纳摩尔含有2.5％地塞米松棕榈酸酯的 DOTAP SUV，并且然后注射75ug含有利妥昔单抗cDNA的质粒载 体。在24小时之后并且此后每1-2周通过ELISA测量利妥昔单抗蛋 白的血清水平。结果在图88中示出。图88A示出在284天内在不同 时间点处的长期利妥昔单抗水平，从而显示长期表达。图88B示出抗 CD20小鼠血清能够在与利妥昔单抗蛋白相当的水平下诱导人肿瘤细 胞裂解。

[0345] 实施例24

[0346] 单一载体注射之后的长期抗IL5抗体表达

[0347] 此实施例描述一次顺序IV注射编码抗人白介素-5mAb(美泊利 单抗;2B6)重链和轻链cDNA的双盒单质粒DNA载体(SEQ ID NO:83;图90)如何在小鼠中产生治疗性抗IL-5mAb血清水平，持续> 92天，如通过ELISA所测定的。对每组三只小鼠给予40mg/kg水平 下的地塞米松的IP注射。2小时后，首先向它们顺序注射1120纳摩 尔含有2.5％地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔含有 5％地塞米松棕榈酸酯的DMPC MLB，并且然后注射85ug含有抗IL-5 cDNA的质粒载体(2B6)。在24小时之后并且此后每1-2周通过ELISA 测量抗IL-5mAb的血清水平。结果在图89中示出，其显示表达至少 92天的治疗性抗IL-5mAb(2B6)血清水平。

[0348] 实施例25

[0349] 单一载体注射之后的长期抗流感抗体表达

[0350] 此实施例描述一次顺序IV注射编码抗流感5J8 mAb重链和轻链 cDNA的双盒单质粒DNA载体(SEQ ID NO:84;图92)如何产生通过 ELISA测量的治疗性抗A型流感mAb血清水平(图91A)，有效中和 Ca109流行性流感株(图91B)，持续>85天。对每组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后，首先向它们顺序注射 1120纳摩尔含有2.5％地塞米松棕榈酸酯的DOTAP SUV以及1000 纳摩尔含有5％地塞米松棕榈酸酯的DMPC MLV，并且然后注射85 ug含有抗流感抗体的cDNA的质粒载体。在24小时之后并且此后每 1-2周通过ELISA测量抗流感蛋白的血清水平。中和方法如下。热杀 死来自在不同时间点注射抗流感cDNA的小鼠的血清，在 DMEM/BSA中1:40稀释，然后与X-179Ca109 H1N1病毒的100x TCID50混合。1小时后，将30,000个MDCK2细胞连同TPCK处理 的胰蛋白酶加入血清/病毒混合物中。在16-18小时温育后，使用针对 病毒核蛋白的A型流感特异性免疫测定对MDCK2细胞的感染进行 评分。

[0351] 实施例26

[0352] 长期表达

[0353] 此实施例描述顺序IV注射编码抗人白介素-5mAb(美泊利单抗；2B6)重链和轻链cDNA和人G-CSF cDNA的单质粒DNA载体(SEQ ID NO:85,图94)如何产生通过ELISA测量的治疗性抗IL-5mAb以 及hG-CSF血清水平,持续>66天。对每组三只小鼠给予40mg/kg 水平下的地塞米松的IP注射。2小时后,首先向它们顺序注射1120 纳摩尔含有2.5％地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔 含有5％地塞米松棕榈酸酯的DMPC MLV,并且然后注射88ug含有 抗IL-5mAb和hG-CSF的cDNA的质粒载体。在24小时之后并且此 后每1-3周通过ELISA测量每种蛋白质的血清水平。结果在图96中 示出,其显示抗IL-5mAb以及hG-CSF在小鼠中的表达水平在治疗 性水平下持续至少66天。

[0354] 实例27

[0355] 双盒提供增加的表达

[0356] 此实施例描述含有两个hG-CSF盒的双表达盒单质粒载体随时间 推移产生比单盒hG-CSF载体更高的绝对嗜中性粒细胞计数。对每组 三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后,首 先向它们顺序注射1000纳摩尔DOTAP SUV和1000纳摩尔DMPC MLV,两者均含有2.5％地塞米松棕榈酸酯,并且然后注射75ug含 有hG-CSF的双盒cDNA的质粒载体。在24小时之后并且此后每1-2 周通过ELISA测量hG-CSF蛋白的血浆水平。由全血测定绝对嗜中性 粒细胞计数(ANC)。图95示出此实施例的结果,其显示相同编码蛋 白的双盒表达在小鼠中提供比编码蛋白的单盒表达更高的血清水平。

[0357] 实施例28

[0358] 双盒提供增加的表达

[0359] 此实施例描述双表达盒单质粒载体(每个盒含有相同的通过猪捷 申病毒-1 2A(P2A)自裂解肽序列分离的抗人IL-5重链和轻链mAb cDNA)如何在小鼠中产生比编码抗人IL-5mAb的单盒DNA载体更高 的抗人IL-5血清mAb水平。对每组三只小鼠给予40mg/kg水平下的 地塞米松的IP注射。2小时后,首先向它们顺序注射1120纳摩尔含 有2.5％地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔含有5％ 地塞米松棕榈酸酯的DMPC MLV,并且然后注射88ug含有IL-5的 cDNA的质粒载体。在24小时之后,通过ELISA测量IL-5蛋白的血 清水平。结果在图96中示出,其显示表达抗人IL-5重链和轻链的双 盒载体产生比编码抗人IL-5的单盒DNA载体更高的抗人IL-5血清 mAb水平。

[0360] 实施例29

[0361] 双盒提供增加的表达

[0362] 此实施例描述双表达盒单质粒载体(每个盒含有相同的通过猪捷 申病毒-1 2A(P2A)自裂解肽序列分离的抗A型流感重链和轻链单克 隆抗体5J8 cDNA)如何在小鼠中产生比编码DNA载体的单盒抗人 IL-5mAb更高的抗5J8 mAb血清水平。对每组三只小鼠给予40mg/kg 水平下的地塞米松的IP注射。2小时后,首先向它们顺序注射1120 纳摩尔含有2.5％地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔 含有5％地塞米松棕榈酸酯的DMPC MLV,并且然后注射88ug含有IL-5的cDNA的质粒载体。在24小时之后,通过ELISA测量IL-5蛋白的血清水平。结果在图97中示出,其显示表达抗5J8 mAb的双 盒载体产生比编码抗5J8的单盒DNA载体更高的抗5J8血清mAb水 平。

[0363] 实施例30

[0364] 不同mAb的双盒单质粒表达以及两种表达不同mAb的单盒质粒的 共同注射

[0365] 此实施例描述一次IV注射双表达盒单质粒载体如何在小鼠中产 生两种单克隆抗体的显著血清水平,在所述双表达盒单质粒载体中, 一个盒含有通过猪捷申病毒-1 2A(P2A)自裂解肽序列分离的抗A型 流感重链和轻链单克隆抗体5J8 cDNA,并且第二个盒含有通过猪捷 申病毒-1 2A(P2A)自裂解肽分离的抗人IL-5重链和轻链单克隆抗体 cDNA(2B6)。此外,一次IV共同注射分别编码完整重链和轻链单克 隆抗体抗流感5J8和抗人IL-5(2B6)的两种不同单表达盒DNA载体也 在小鼠中产生两种单克隆抗体的显著血清水平。对每组三只小鼠给予 40mg/kg水平下的地塞米松的IP注射。2小时后,首先向它们顺序 注射1120纳摩尔含有2.5%地塞米松棕榈酸酯的DOTAP SUV以及 1000纳摩尔含有5%地塞米松棕榈酸酯的DMPC MLV,并且然后注 射88ug质粒载体。在24小时之后,通过ELISA测量蛋白质的血清 水平。结果在图98中示出,其示出双盒单质粒如何在体内表达不同 的mAb,并且共同注射的两个单盒质粒如何在体内表达不同的mAb。

[0366] 实施例31

[0367] 不同mAb的双盒单质粒表达

[0368] 此实施例描述一次IV注射双表达盒单质粒载体如何在小鼠中产 生两种单克隆抗体的显著血清水平,在所述双表达盒单质粒载体中, 一个盒含有通过猪捷申病毒-1 2A(P2A)自裂解肽序列分离的抗A型 流感重链和轻链单克隆抗体5J8 cDNA,并且第二个盒含有通过猪捷 申病毒-1 2A(P2A)自裂解肽分离的抗人IL-5重链(2B6)和轻链单克隆 抗体cDNA。对每组三只小鼠给予40mg/kg水平下的地塞米松的IP 注射。2小时后,首先向它们顺序注射1120纳摩尔含有2.5%地塞米 松棕榈酸酯的DOTAP SUV以及1000纳摩尔含有5%地塞米松棕榈酸 酯的DMPC MLV,并且然后注射88ug质粒载体。在24小时之后, 通过ELISA测量蛋白质的血清水平。结果在图99中示出。图99A示 出在43天内抗人IL-5mAb的血清表达水平,并且图99B示出在43 天内抗A型流感mAb的血清表达水平。

[0369] 实施例32

[0370] 不同mAb的三盒单质粒表达

[0371] 此实施例描述一次IV注射三表达盒单质粒载体如何在小鼠中产 生全部三种不同单克隆抗体的显著血清水平,在所述三表达盒单质粒 载体中,一个盒含有通过猪捷申病毒-1 2A(P2A)自裂解肽序列分离的 抗A型流感重链和轻链单克隆抗体5J8 cDNA,第二个盒含有通过猪 捷申病毒-1 2A(P2A)自裂解肽分离的抗人IL-5重链和轻链单克隆抗 体cDNA,并且第三个盒含有通过猪捷申病毒-1 2A(P2A)自裂解肽分 离的抗人CD20重链和轻链单克隆抗体cDNA。此外,一次IV共同 注射分别编码完整重链和轻链单克隆抗体抗流感5J8、抗人IL-5和抗 人CD20 mAb的三种不同单表达盒DNA载体也在小鼠中产生全部三 种不同单克隆抗体的显著血清水平。对每组三只小鼠给予40mg/kg 水平下的地塞米松的IP注射。2小时后,首先向它们顺序注射1120 纳摩尔含有2.5%地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔 含有5%地塞米松棕榈酸酯的DMPC MLV,并且然后注射88ug质粒 载体。在24小时之后,通过ELISA测量蛋白质的血清水平。结果在 图100中示出,其显示利妥昔单抗(抗CD20)、抗IL5 mAb和抗流感 mAb均从单一载体(左侧)以及通过共同注射三个单独载体(右侧)的同时表达。

[0372] 实施例33

[0373] 表达抗PCSK9 mAb以降低LDL水平

[0374] 此实施例描述一次IV注射表达抗PCSK9 mAb的单质粒载体如 何降低小鼠中的LDL水平。对每组三只小鼠给予40mg/kg水平下的 地塞米松的IP注射。2小时后,首先向它们顺序注射各自1000纳摩 尔的DOTAP SUV和DMPC MLV,两者均含有2.5%地塞米松棕榈酸 酯,并且然后注射75ug质粒载体。在注射之后15天测量LDL胆固 醇的血浆水平,并且根据相对于注射之前同一小鼠的LDL胆固醇测 量值的比例进行作图。图101示出结果,其显示表达抗PCSK9 mAb 的单质粒载体降低小鼠中的LDL水平。

[0375] 实施例34

[0376] 表达抗PCSK9 mAb提供长期LDL水平降低

[0377] 此实施例描述体内表达抗PCSK9 mAb如何提供长期LDL水平 降低。在注射之前评定小鼠的血清LDL水平。在注射当天,对每组 三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后,首 先向它们顺序注射1000纳摩尔DOTAP SUV和1000纳摩尔DMPC MLV,两者均含有2.5%地塞米松棕榈酸酯,并且然后注射75ug编 码抗PCSK9 mAb的轻链和重链的质粒载体。在此之后每7-21天测量 LDL胆固醇的血清水平。结果在图102中示出,其显示表达抗PCSK9 mAb的小鼠中的长期LDL水平降低。

[0378] 实施例35

[0379] 表达抗PCSK9 mAb降低食用脂肪饮食的小鼠中的LDL水平

[0380] 此实施例描述体内表达抗PCSK9 mAb如何提供与对照(抗CD20 mAb表达)相比食用脂肪饮食的小鼠中的LDL水平降低。在注射之前 评定小鼠的血清LDL水平。在注射当天,对每组三只小鼠给予40 mg/kg水平下的地塞米松的IP注射。2小时后,首先向它们顺序注射1000纳摩尔DOTAP SUV和1000纳摩尔DMPC MLV,两者均含有 2.5%地塞米松棕榈酸酯,并且然后注射75ug质粒载体。在注射之后 的当天,将小鼠切换为脂肪胆固醇提高的饮食。在此之后每7-14天 测量LDL胆固醇的血清水平。图103示出结果,其显示表达抗PCSK9 mAb的小鼠随时间推移具有与表达对照抗CD20抗体的对照小鼠相 比更低的LDL水平。

[0381] 实施例36

[0382] mAb表达的持久性

[0383] 此实施例描述如何长期表达mAb,包括利妥昔单抗(抗CD20 mAb)、抗流感mAb(FI6)和抗流感mAb(5J8)和抗IL5 mAb。对每组 三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时后,对 它们进行顺序注射。顺序注射利妥昔单抗包括在40mg/kg水平下注 射地塞米松。2小时后,首先向它们顺序注射1050纳摩尔含有2.5% 地塞米松棕榈酸酯的DOTAP SUV,并且然后注射75ug含有利妥昔 单抗cDNA的质粒载体。顺序注射抗流感和抗IL-5抗体包括1120纳 摩尔含有2.5%地塞米松棕榈酸酯的DOTAP SUV以及1000纳摩尔含 有5%地塞米松棕榈酸酯的DMPC MLV,并且然后注射88ug质粒载 体。在24小时之后并且然后此后每7-21天通过ELISA测量蛋白质的 血清水平。结果在图104中示出,其显示抗流感FI6 mAb表达约25 天,抗流感5J8 mAb和抗IL4 mAB表达超过100天,并且利妥昔单 抗表达超过275天。

[0384] 实施例37

[0385] 各种质粒载体剂量

[0386] 此实施例描述来自四种不同剂量的表达利妥昔单抗的质粒载体 的表达水平的比

较。对每组三只小鼠给予40mg/kg水平下的地塞米 松的IP注射。2小时后，如下对它们进行顺序注射。首先注射脂质体， 其由1000纳摩尔含有5％地塞米松棕榈酸酯的DMPC MLV以及1000、1080、1170或1250纳摩尔含有2.5％地塞米松棕榈酸酯的 DOTAP SUV构成；然后以75、81、88或95ug的剂量注射质粒载体。 在24小时之后，通过ELISA测量蛋白质的血清水平。结果在图105 中示出，其显示来自全部四个质粒剂量的良好表达水平。

[0387] 实施例38

[0388] 增强的mAb表达

[0389] 此实施例描述ALB和AZU信号序列如何增强5J8 mAb的表达。 对每组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2小时 后，首先向它们顺序注射1120纳摩尔含有2.5％地塞米松棕榈酸酯的 DOTAP SUV以及1000纳摩尔含有5％地塞米松棕榈酸酯的DMPC MLV，并且然后注射88ug质粒载体。在24小时之后，通过ELISA 测量蛋白质的血清水平。结果在图106中示出，其显示通过使用ALB 和AZU信号序列增强5J8 mAb的表达。

[0390] 实施例39

[0391] 体内P53表达

[0392] 此实施例描述在IV注射之后24小时人p53基因如何在小鼠肺中 广泛表达，并且还描述人p53基因如何在血管内皮细胞中占优势地表 达。对每组三只小鼠给予40mg/kg水平下的地塞米松的IP注射。2 小时后，首先向它们顺序注射均为1000纳摩尔的含有按重量计2.5％ 地塞米松棕榈酸酯的DOTAP SUV脂质体和DMPC中性脂质，然后2 分钟后，每只小鼠注射75ug编码人p53的质粒载体(图108，SEQ ID NO:86)。注射后24小时收获肺并且针对免疫组织化学进行处理。针 对人p53对肺切片进行染色(棕色)。图107A示出对照小鼠肺组织，并且图107B示出针对p53染色的人p53注射小鼠肺组织，显示p53 基因在小鼠肺中广泛地表达。针对人p53和小鼠CD31(PECAM)(血 管内皮细胞特异性标记物)对来自经处理小鼠的肺组织进行双重染 色。图107C和图107D中p53和CD31的共定位显示p53注射的小 鼠中占优势的血管内皮细胞人p53表达。图107C和图107D示出相 同的组织切片，具有不同的染色。两个图中的CD31染色均是广泛的， 因为肺泡壁内衬有连续内皮组织。

[0393] 本申请中提到的所有公布和专利以引用的方式并入本文。本发明 的所描述的方法和组合物的各种改进和变化对于本领域技术人员将 显而易见，而不背离本发明的范围和精神。虽然已结合具体优选的实 施方案描述了本发明，但应理解的是，要求保护的本发明不应不适当 地局限于所述具体实施方案。事实上，对于相关领域的技术人员来说 显而易见的用于进行本发明的所描述模式的各种修改意图在以下权 利要求的范围内。

[0001] 序列表

[0002] <110> DNARx公司(DNARx)

[0003] <120> 用于体内核酸表达的系统和方法

[0004] <130> DNARX-35131/WO-1/ORD

[0005] <150> US 62/475,477

[0006] <151> 2017-03-23

[0007] <160> 86

[0008] <170> PatentIn version 3.5

[0009] <210> 1

[0010] <211> 615

[0011] <212> DNA

[0012] <213> 人工序列(Artificial sequence)

[0013] <220>

[0014] <223> 合成

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[0019] ctccaggaga agctgtgtgc cacctacaag ctgtgccacc ctgaggagct ggtgctgctg 240

[0020] ggacactctc tgggcatccc ctgggctccc ctgagcagct gccccagcca ggccctgcag 300

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[0026] cttgcccagc cctga 615

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[0028] <211> 207

[0029] <212> PRT

[0030] <213> 智人(Homo sapiens)

[0031] <400> 2

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[0034] Leu Leu Leu Trp His Ser Ala Leu Trp Thr Val Gln Glu Ala Thr Pro

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[0037] 35 40 45

[0038] Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys

[0039] 50 55 60

[0040] Leu Val Ser Glu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu

[0041] 65 70 75 80

[0042] Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
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[0457] <211> 9290

[0458] <212> DNA

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[0461] <223> 合成

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不含CpG的hG-CSF蛋白(SEQ ID NO:2)

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图1

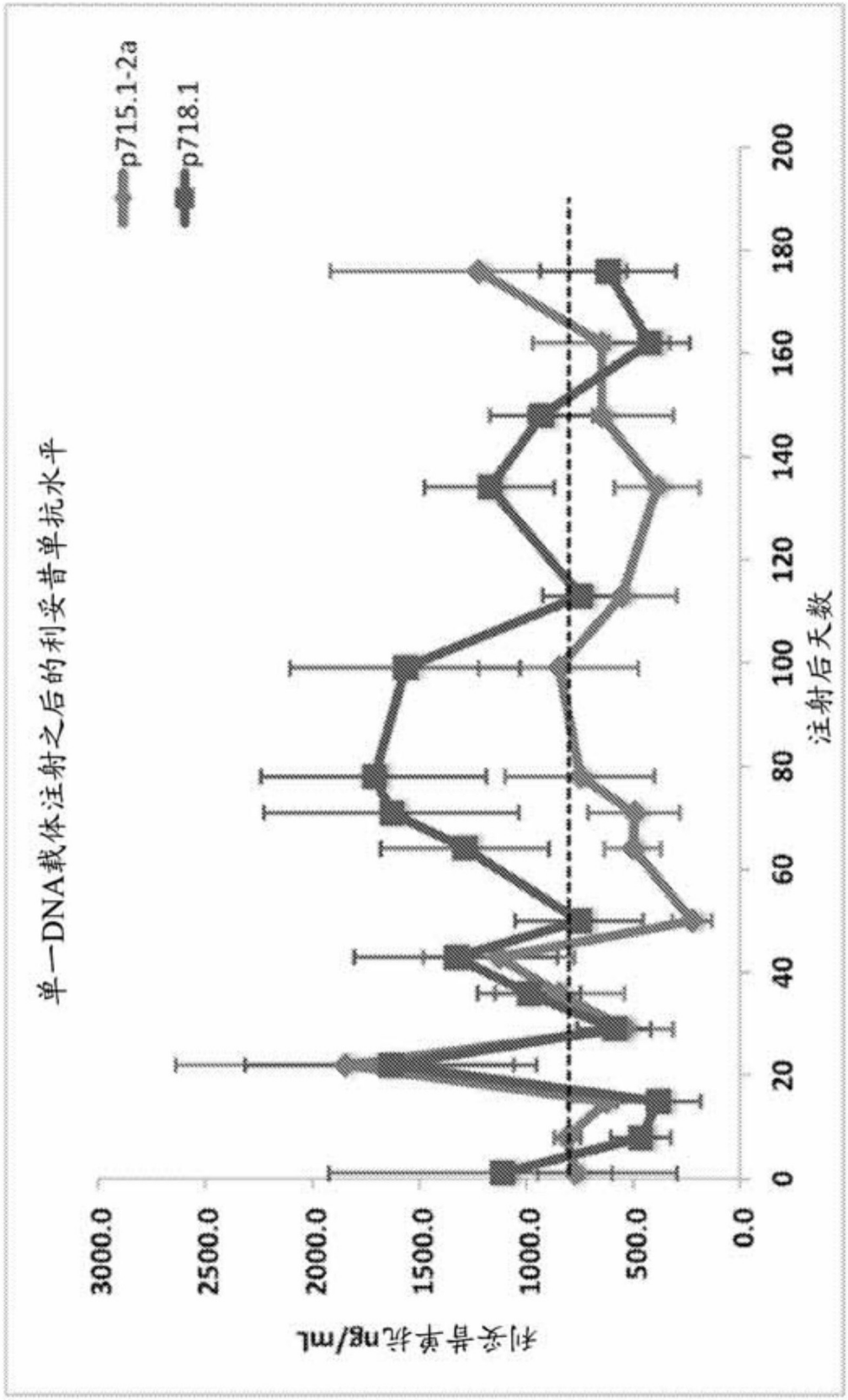

单一DNA载体注射之后的利妥昔单抗水平
p715.1-2a
p718.1
利妥昔单抗ng/mL
3000.0
2500.0
2000.0
1500.0
1000.0
500.0
0.0
0
20
40
60
80
100
120
140
160
180
200
注射后天数

图2A

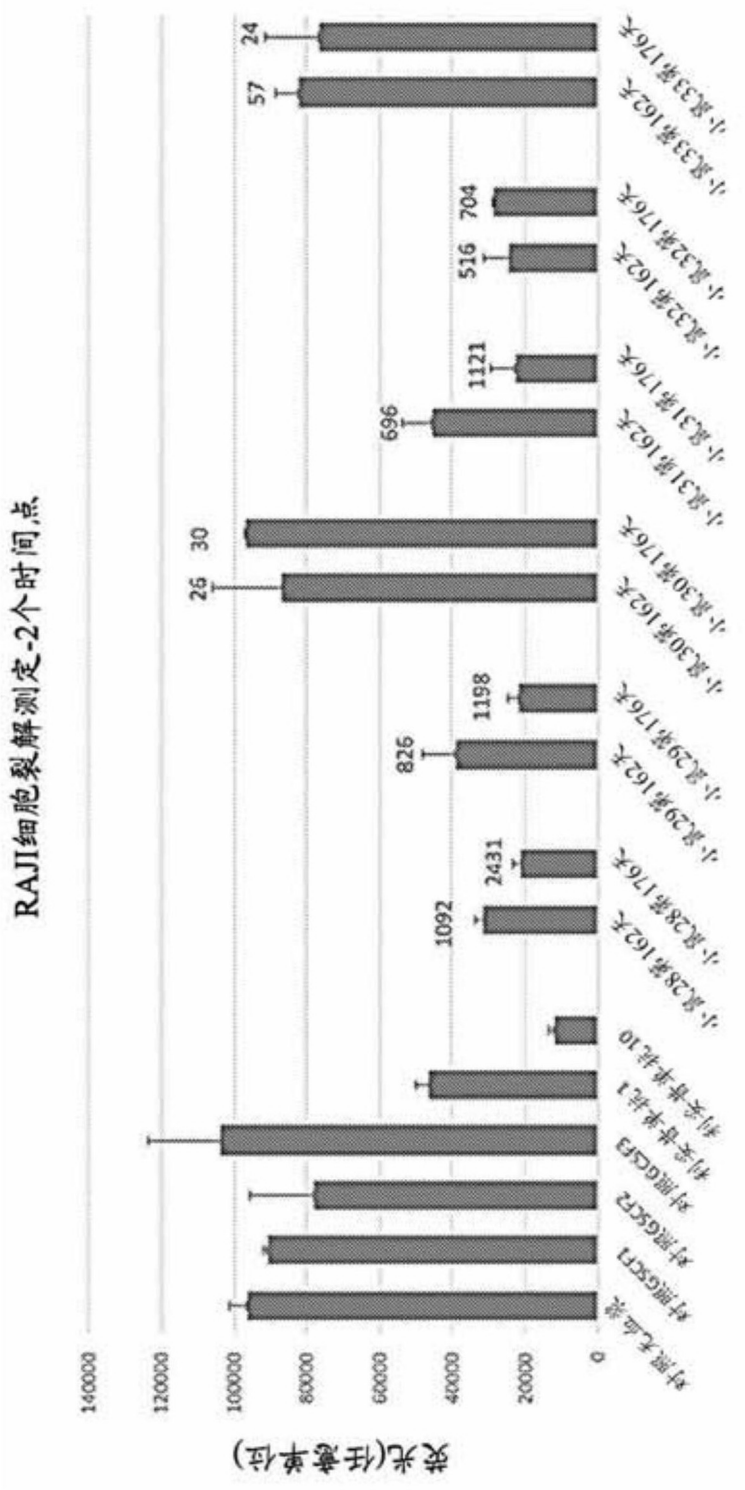

RAJI细胞裂解测定-2个时间点
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80000
60000
40000
20000
0
24
57
704
516
1121
696
30
26
1198
826
2431
1092
小鼠33条162天
小鼠33条176天
小鼠32条162天
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小鼠28条176天
利妥昔单抗10
利妥昔单抗1
对照GCF3
对照GCF2
对照GCF1
对照无血清

图2B

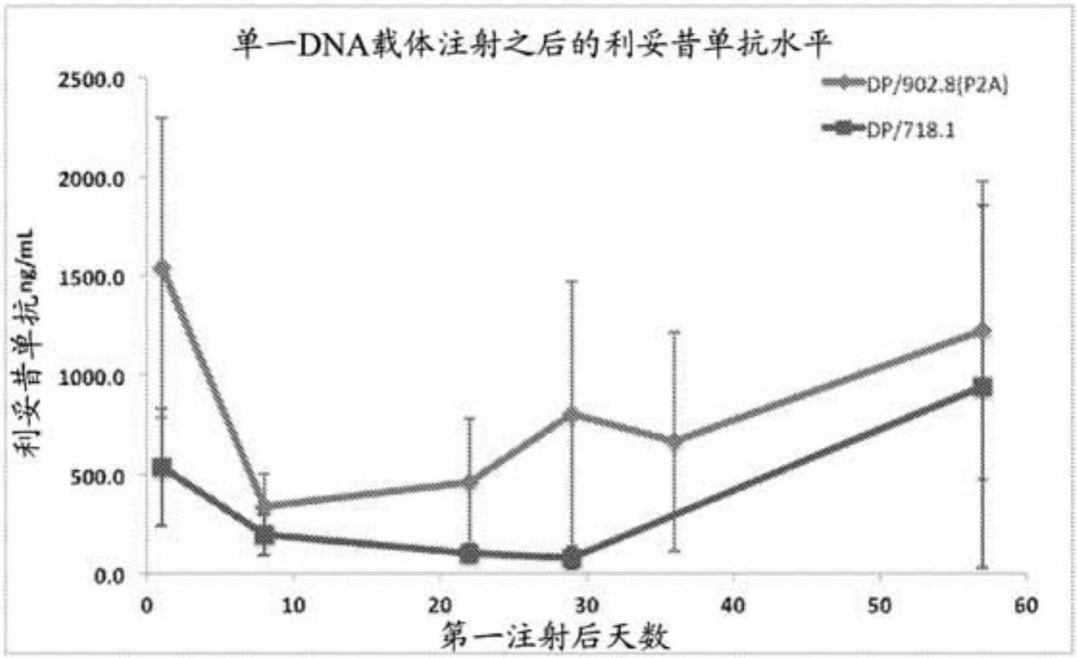

单一DNA载体注射之后的利妥昔单抗水平
DP/902.8(P2A)
DP/718.1
2500.0
2000.0
1500.0
1000.0
500.0
0.0
利妥昔单抗ng/mL
0
10
20
30
40
50
60
第一注射后天数

图3

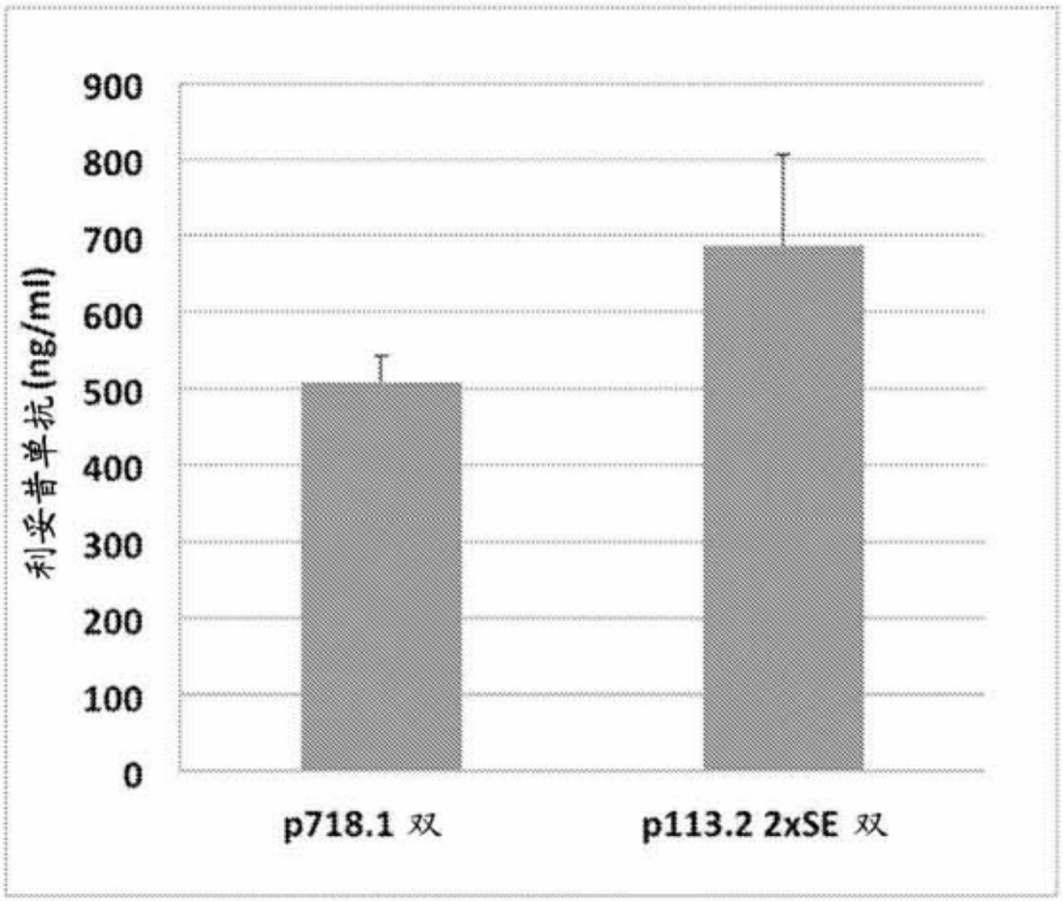

900
800
700
600
500
400
300
200
100
0
利妥昔单抗(ng/ml)
p718.1 双
p113.2 2xSE 双

图4

715.1 2a : RINhe-ΔmCMVΔEF1I126-BstEII-**GAK-Δ抗CD20-H-F2(RAKR)-P2A-Δ抗CD20-L**-BglII-MixpA/BV2
(SEQ ID NO:3)

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图5

718.1：双盒抗CD20

DraIIRINhe ΔmCMV-EF1-I126-BstEII-**aCD20H**-BglII-polyA-ΔhCMV-EF1-I126-BstEII-**aCD20L**-BglII-polyA BV2

(SEQ ID NO:4)

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图6

902.8 (P2A) : 完整G5: F3P2A (双顺反子抗CD20)

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- Δ抗 CD20-H-F3(RKRR)-P2A-Δ抗 CD20-L-BglII-MixpA-BV2

(SEQ ID NO:5)

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图7

113.2 :超增强子双盒抗CD20 (SEQ ID NO:6)

DraIIRINhe-超增强子-ΔmCMV-EF1-I126-BstEII-**aCD20H**-BglII-polyA-超增强子-ΔhCMV-EF1-I126-BstEII-**aCD20L**-BglII-polyA BV2

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图8

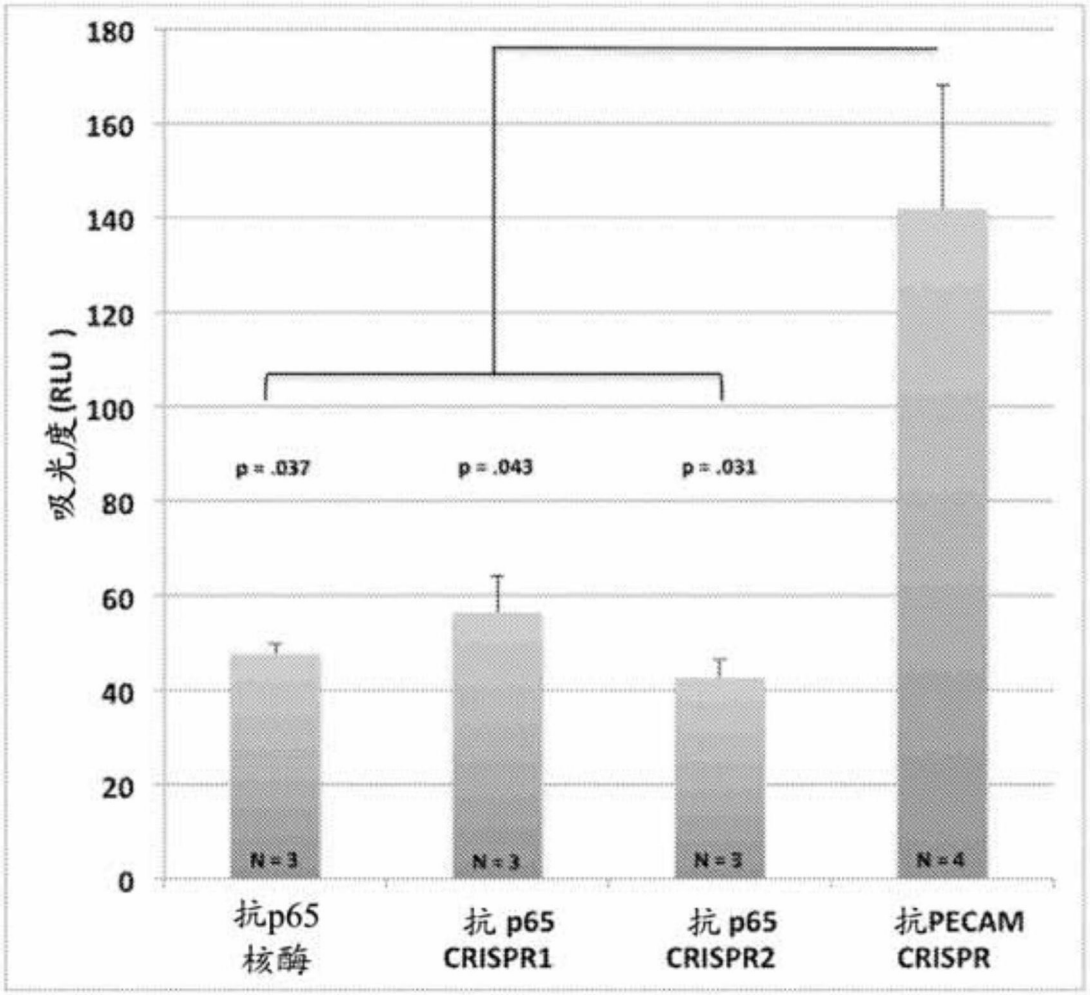

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抗p65
核酶
抗 p65
CRISPR1
抗 p65
CRISPR2
抗PECAM
CRISPR

图9

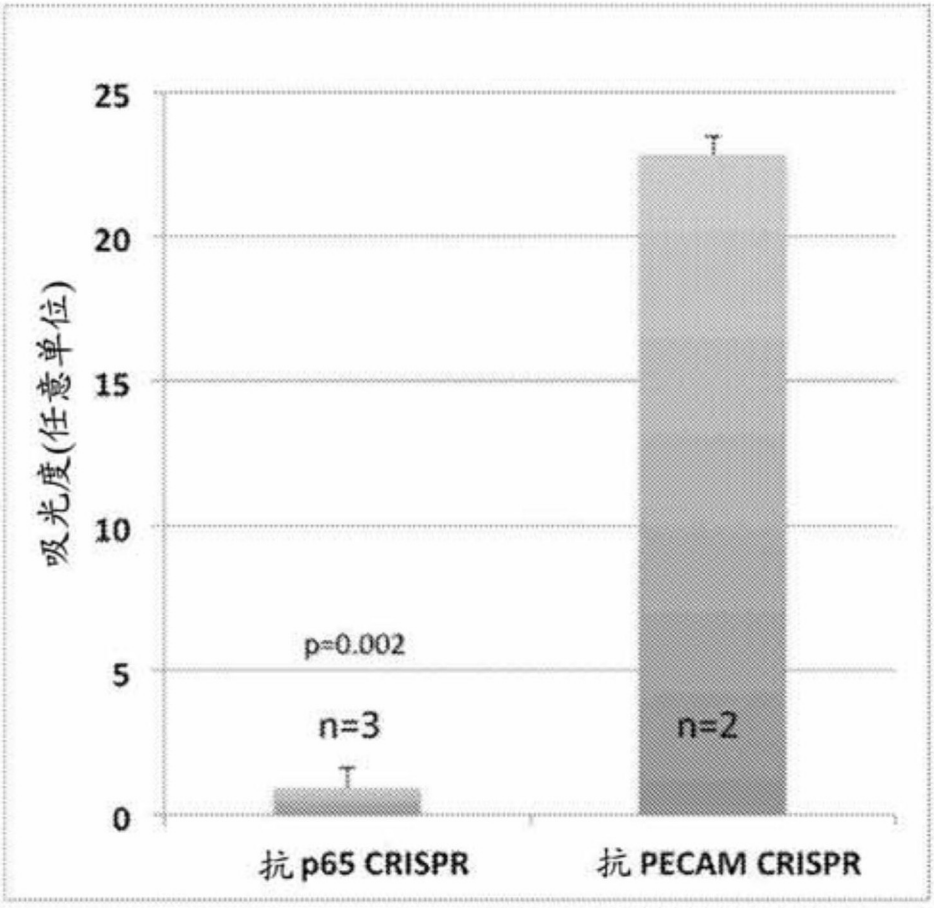


图10

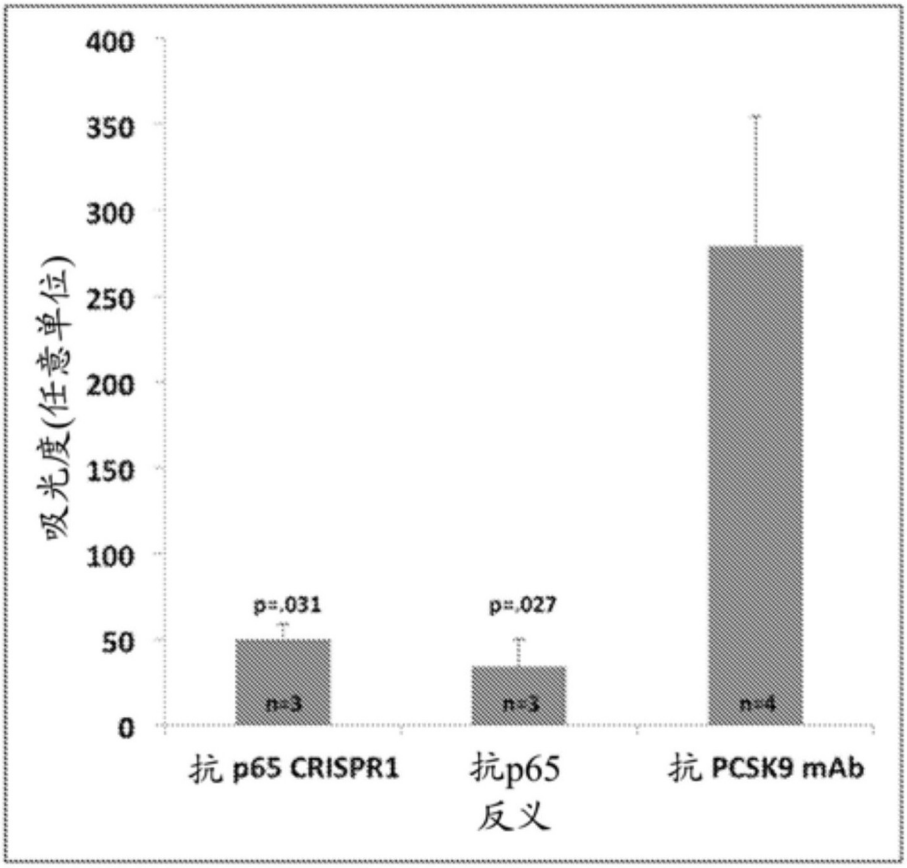

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抗 PCSK9 mAb

图11

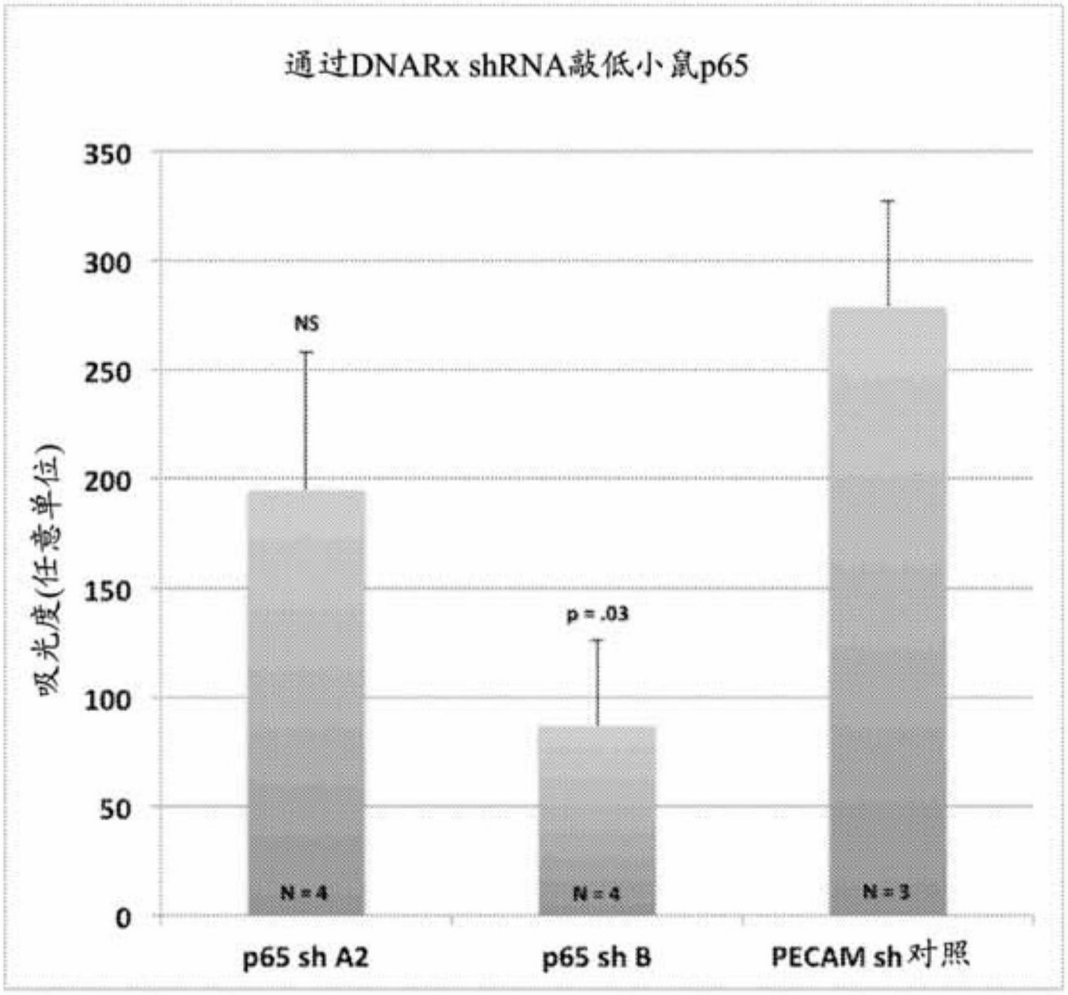

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p65 sh A2
p65 sh B
PECAM sh对照

图12

抗p65核酶 ：DraIIIRINhe-ΔmCMVΔEF1I126-BstEII-__p65核酶-1__-BglII-MixpA/BV2 (081016 #

2)

(SEQ ID NO:7)

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图13

抗p65 CRISPR1 : Genscript px458-relA1 (SEQ ID NO:8)

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抗 p65 CRISPR2 : Genscript px458-relA4 (SEQ ID NO:9)

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图15

抗 PECAM CRISPR : Genscript px458-PECAM1-4 (SEQ ID NO:10)

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图16

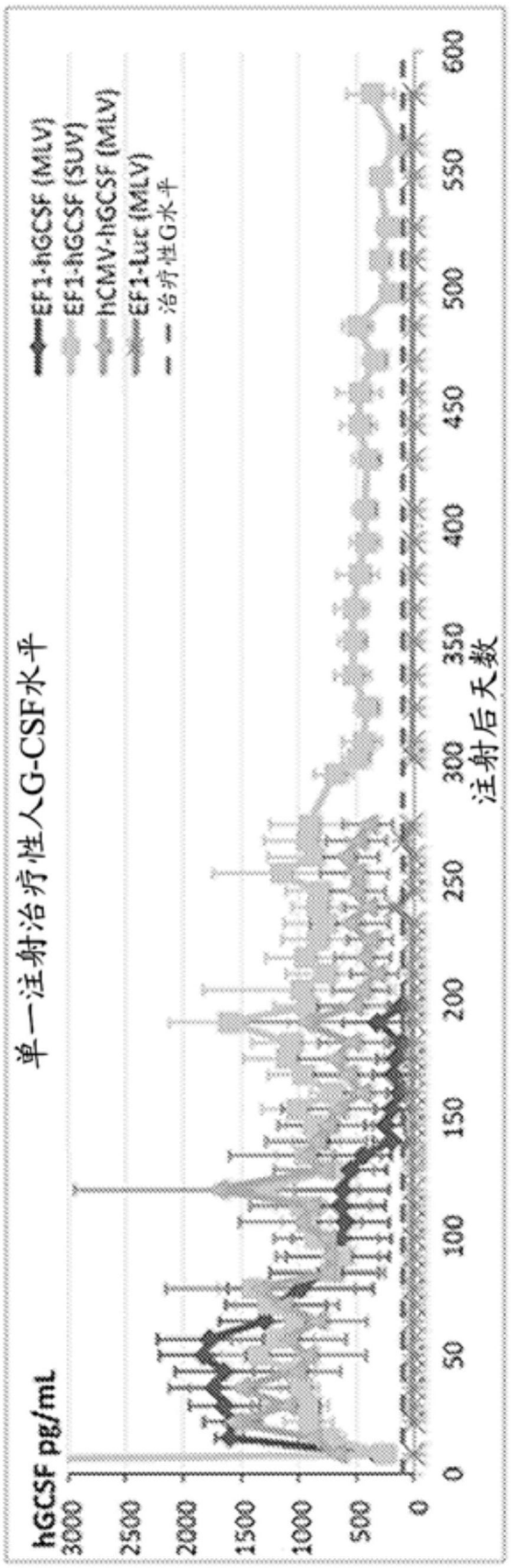

单一注射治疗性人G-CSF水平
hGCSF pg/mL
3000
2500
2000
1500
1000
500
0
0
50
100
150
200
250
300
350
400
450
500
550
600
注射后天数
EF1-hGCSF (MLV)
EF1-hGCSF (SUV)
hCMV-hGCSF (MLV)
EF1-Luc (MLV)
治疗性G水平

图17A

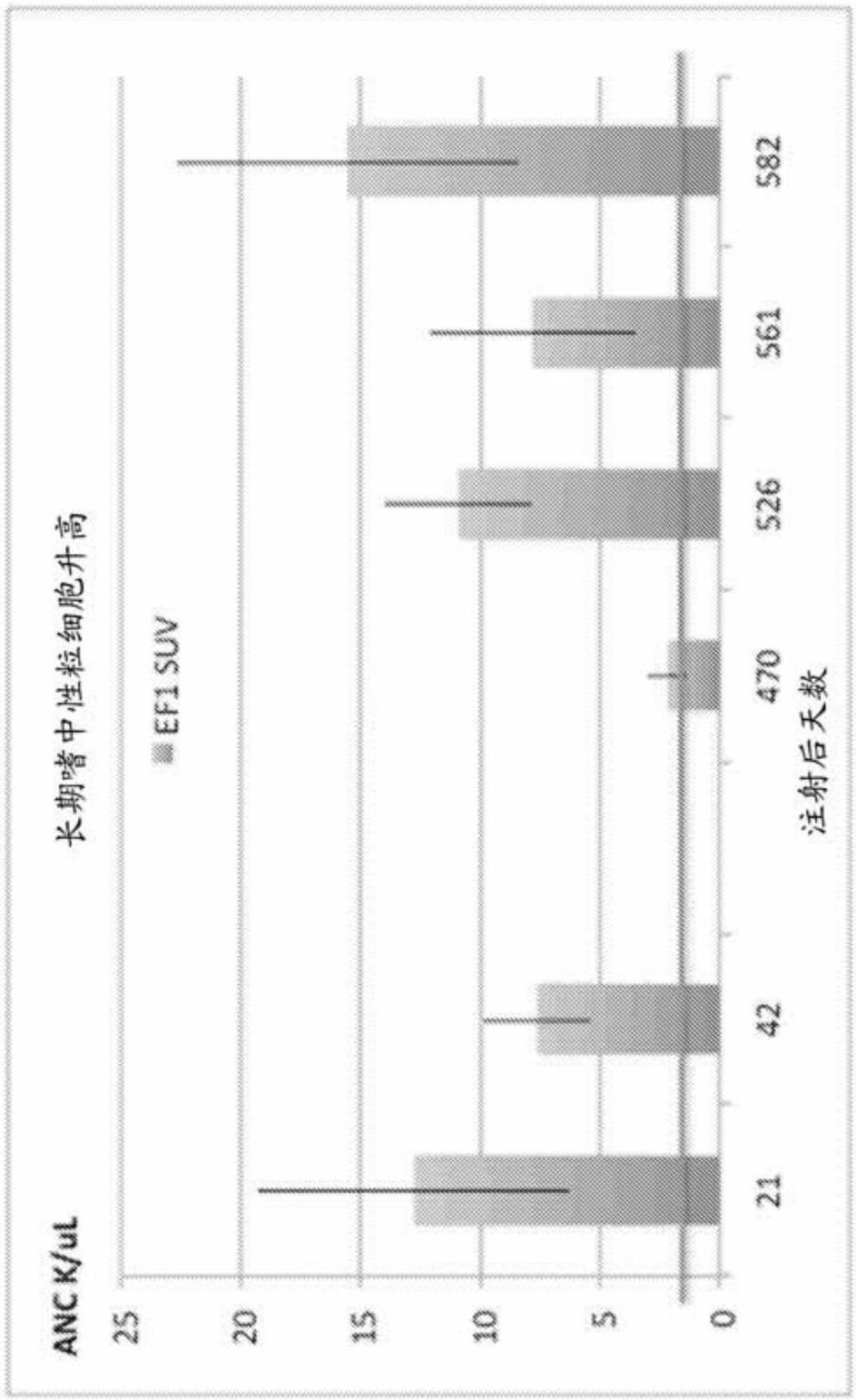

长期嗜中性粒细胞升高
EF1 SUV
ANC K/uL
25
20
15
10
5
0
21
42
470
526
561
582
注射后天数

图17B

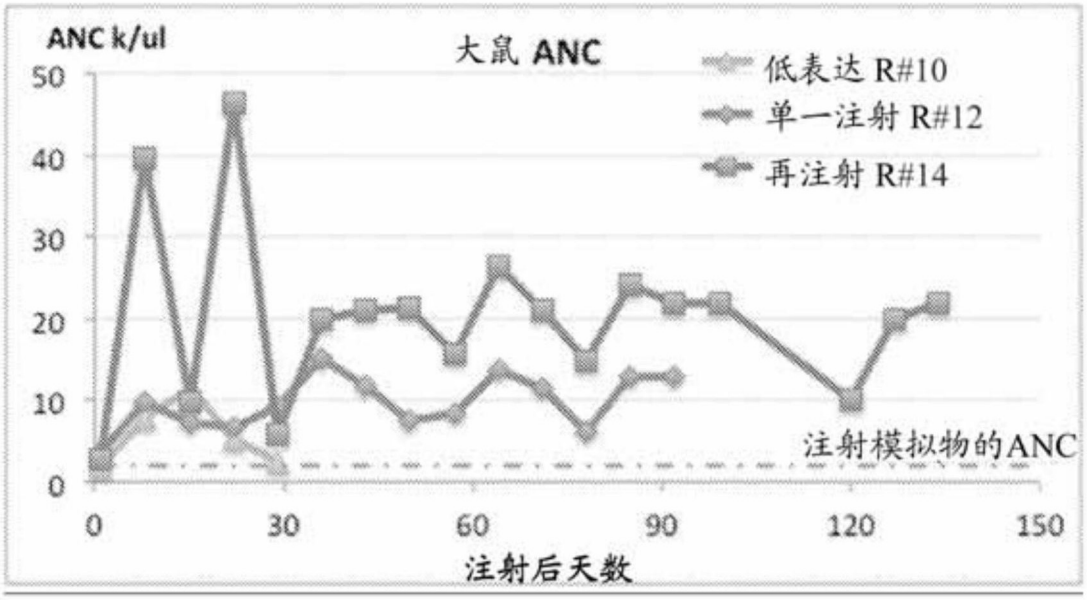


图18

抗p65反义: DraIIRINhe ΔmCMV-7SK-AS-p65-Ch-ΔmCMV EF1-I126-tdTomato/BV2 (092416 # 4)

(SEQ ID NO:11)

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图19

p65 shB: NheΔhCMVΔhCMVRVp65 shB-TTTTT-XbaI-HindIII-Amp (SEQ ID NO:12)

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CATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTC
GTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTC
AGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAA
CCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTG
GAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCAC
CAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATT
GAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTG
ACGTCTAAGAAACCATTATTATCATGACATTAACCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTCTCGCGCGTTTCGGTGATGACGGTGAAAACCTCTGACACA
TGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGGCGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTA
ACTATGCGGCATCAGAGCAGATTGTACTGAGAGTGCACCATATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCCATTCGCCATTC
AGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTAACGCCA
GGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTCCTTAATAGTTGCAGCCAAATCCTTCCTGTCAGATTTGGCTGCAACTATTAAGGTTTTT

图20

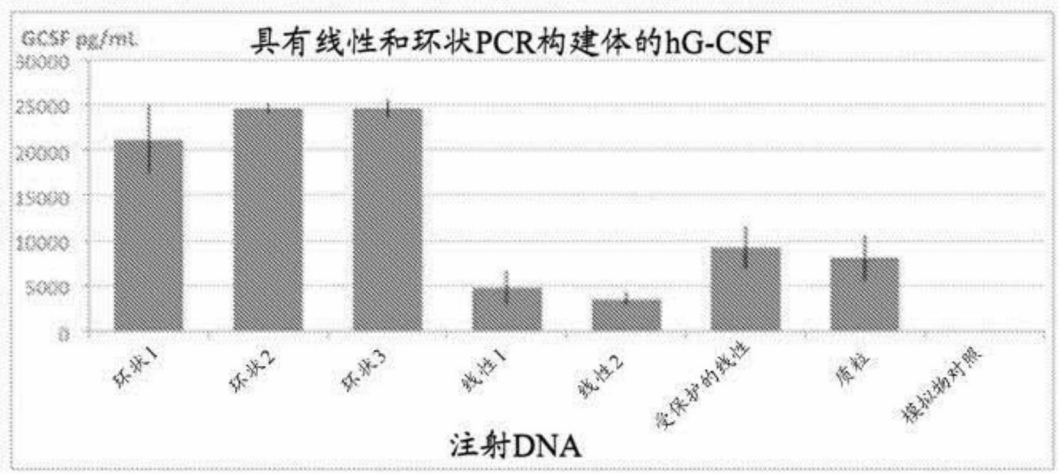


图21

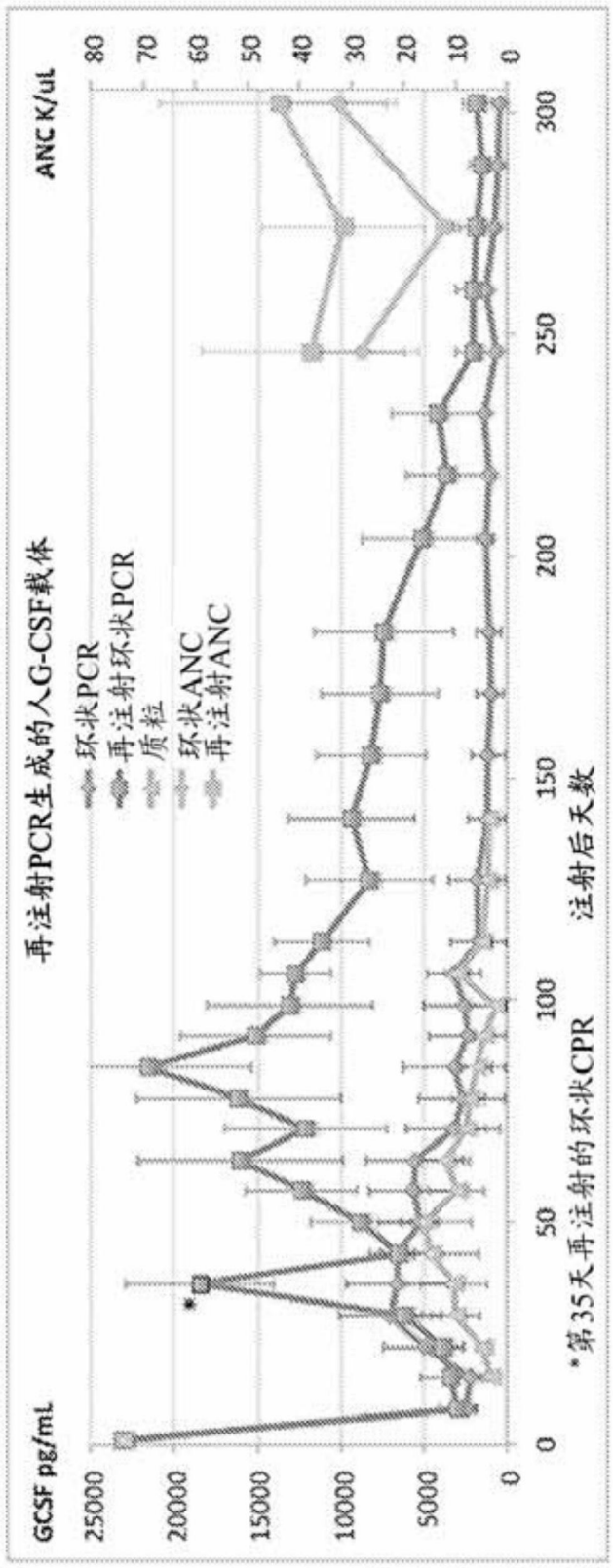

再注射PCR生成的人G-CSF载体
GCSF pg/mL
ANC K/ul
环状PCR
再注射环状PCR
质粒
环状ANC
再注射ANC
*第35天再注射的环状CPR
注射后天数
25000
20000
15000
10000
5000
0
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300

图22

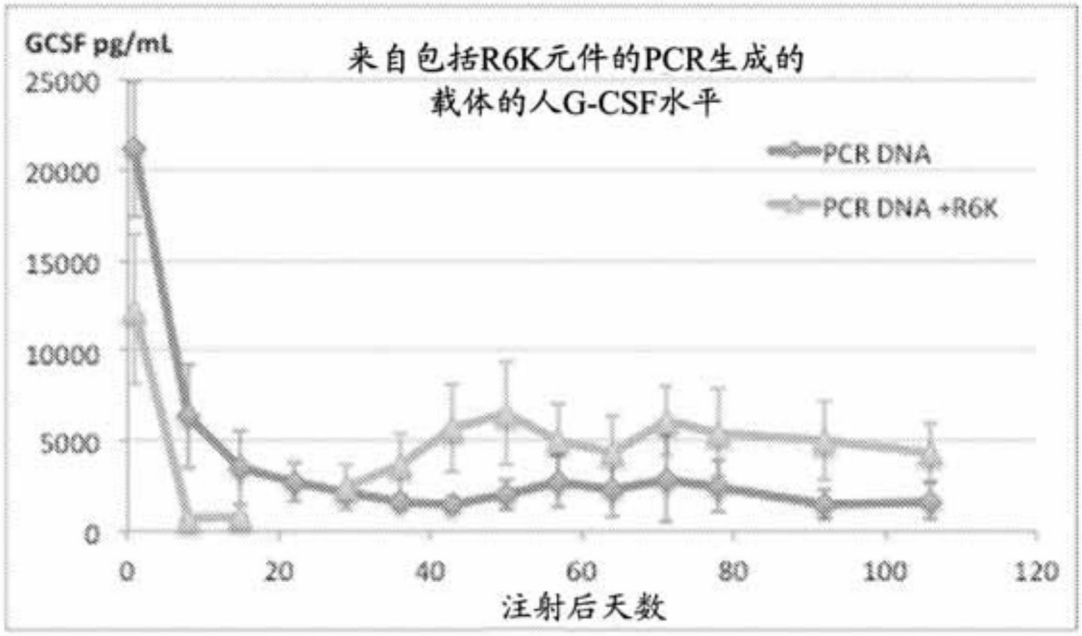

GCSF pg/mL
来自包括R6K元件的PCR生成的
载体的人G-CSF水平
PCR DNA
PCR DNA +R6K
25000
20000
15000
10000
5000
0
0
20
40
60
80
100
120
注射后天数

图23

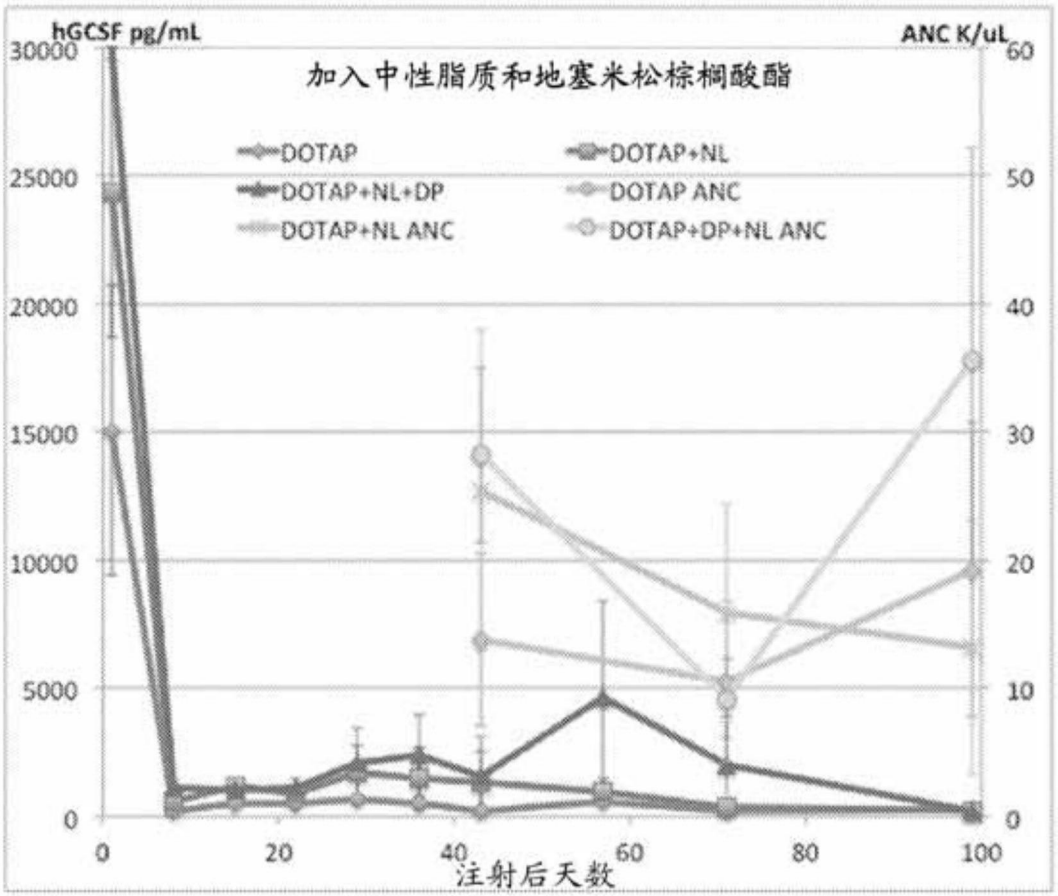

hGCSF pg/mL
ANC K/uL
加入中性脂质和地塞米松棕榈酸酯
DOTAP
DOTAP+NL
DOTAP+NL+DP
DOTAP ANC
DOTAP+NL ANC
DOTAP+DP+NL ANC
30000
25000
20000
15000
10000
5000
0
60
50
40
30
20
10
0
0
20
40
60
80
100
注射后天数

图24

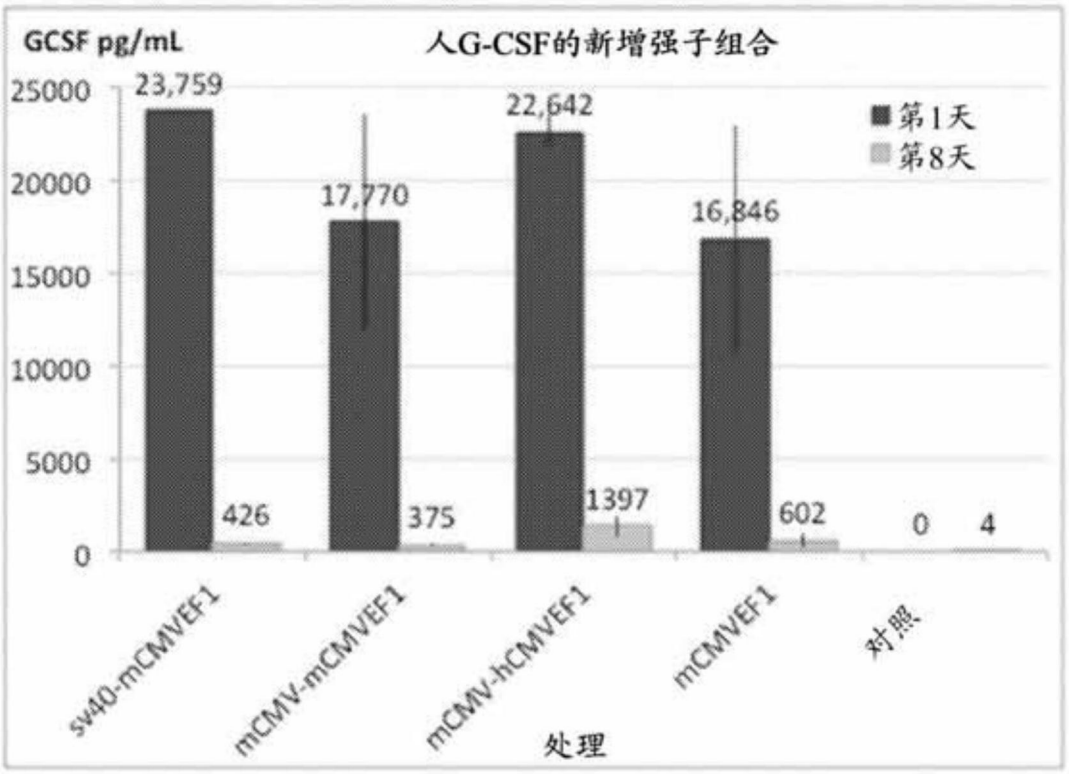


图25

sv40-mCMV-EF1 : DraIIIRINhe-sv40-ΔmCMV-EF1-I126-BstEII-**ΔGCSF**-BglII-polyA-BV2 (SEQ ID NO:13)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGGGCCTGAAATAACCTCTGAAAGAGGAACTTGGTTAGGTACCTTCTGAGGCTGAAAGAACCAGCTGTGGAATGT
GTGTCAGTTAGGGTGTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTAGTCAGCAACCAGGTGTGGAAAGTCCCCAGGCTCC
CCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTAGTCAGCAACCATAGTCCCAGTCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACT
CAATAGGGACTTTCCATTGGGTTTTGCCCAGTACATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTC
CAATGGGTTTTGCCCAGTACATAAGGTCAATGGGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCC
AGTACATAAGGTCAATAGGGGTGAATCAACAGGAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAA
TAGGGGGTGAGTCAATGGGTTTTTCCCATTATTGGCACATACATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGG
CAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGT
GGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGTAA
GTCACTGACTGTCTATGCCTGGGAAAGGGTGGGCAGGAGATGGGGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTC
TCTTTCCTCTCCTGACAGGTTGGTAACCAAGCTTTCCATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAGCTGCTGCTGTGGCACAGTGCACT
CTGGACAGTGCAGGAAGCCACCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCA
GCTCTCCAGGAGAAGCTGTGTGCCACCTACAAGCTGTGCCACCCTGAGGAGCTGGTGCTGCTGGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCC
CAGCCAGGCCCTGCAGCTGGCAGGCTGCTTGAGCCAACTCCATAGTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTC
CCACCTTGGACACACTGCAGCTGGATGTTGCTGACTTTGCCACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCCCACCCAGGGTGCC
ATGCCTGCCTTTGCCTCTGCTTTCCAGAGAAGGGCAGGAGGGGTCCTGGTTGCCCTCCCATCTGCAGAGCTTCCTGGAGGTGTCCTACAGAGTTCTAAGACACCTTGCC
CAGCCCTGATAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCTCTAGTGATCAGCAGTTCAACCTGTT
GATAGTATGTACTAAGCTCTCATGTTTAATGTACTAAGCTCTCATGTTTAATGAACTAAACCCTCATGGCTAATGTACTAAGCTCTCATGGCTAATGTACTAAGCTCTCA
TGTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAGAATATATAAGG
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ATTTTTGAAAAAGTCTTTTCTGTAATGAAGGAGAAAACTCACCCAGGCAGTTCCATAGGATGGCAAGATCCTGGTATCTGTCTGCAATTCCAACTCTTCCAACATCAAT
ACAACCTATTAATTTCCCCTCATCAAAAATAAGGTTATCAAGTGAGAAATCACCATGAGTGACCACTGAATCTGGTGAGAATGGCAAAAGATTATGCATTTCTTTCCAG
ACTTGTTCAACAGGCCAGCCATTTCTCTCATCATCAAAATCACTGGCATCAACCAAACCATTATTCATTCTTGATTGGGCCTGAGCCAGTCTAAATACTCTATCAGAGTT
AAAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTCCAATACCTGGAATGC
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CCATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCC
AACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACC
TCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图26

mCMV-mCMV-EF1 : DraIIIRINhe-ΔmCMV -ΔmCMV-EF1-I126-BstEII-**ΔGCSF**-BglII-polyA-BV2
(SEQ ID NO:14)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
GGCACATACATAAGGTCAATAGGGGTGTCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAG
TACATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAAT
GGGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACA
GGAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTA
TTGGCACATACATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGA
AGTTGGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGT
GGGGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGT
GGGCAGGAGATGGGGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTCTCTTTCCTCTCCTGACAGGTTGGTAACCAAG
CTTTCCATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAGCTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCCCTGGG
CCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCAGCTCTCCAGGAGAAGCTGTGTGCCACCTAC
AAGCTGTGCCACCCTGAGGAGCTGGTGCTGCTGGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGCTGCTT
GAGCCAACTCCATAGTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGATGTTGC
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ATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTTATC
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CATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACAGAA
CCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAA
ATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGAT
ATACTATGCCAATGTTTAATTGTCAG

图27

mCMV-hCMV-EF1 : DraIIIRINhe-ΔmCMV-**ΔhCMV**-EF1-I126-BstEII-**ΔGCSF**-BglII-polyA-BV2
(SEQ ID NO:15)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
GGCACATACATAAGGTCAATAGGGGTGTCTAGCat**GTTACATAACTTATGGTAAATGGCCTGCCTGGCTGACTGCCCAATGACCCCTGCCCAATGATGTCAATAATG**
ATGTATGTTCCCATGTAATGCCAATAGGGACTTTCCATTGATGTCAATGGGTGGAGTATTTATGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAA
GTATGCCCCCTATTGATGTCAATGATGGTAAATGGCCTGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTATGTATTAGTC
ATTGCTATTATCTAGCACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGGAGG
GGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAACCAT
ATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGTGGGCAGGAGATGG
GGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTCTCTTTCCTCTCCTGACAGGTTGGTAACCAAGCTTTCCATGGCTGG
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TGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCAGCTCTCCAGGAGAAGCTGTGTGCCACCTACAAGCTGTGCCACCC
TGAGGAGCTGGTGCTGCTGGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGCTGCTTGAGCCAACTCCATA
GTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGATGTTGCTGACTTTGCCACCA
CCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCTGCCTTTGCCTCTGCTTTCCAGAGAAGGGCAGGAGGGGT
CCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAGGTGTCCTACAGAGTTCTAAGACACCTTGCCCAGCCCTGATAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCT
AGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCTCTAGTGATCAGCAGTTCAACCTGTTGATAGTATGTACTAAGCTCTCATGTTTAATGTACTAAGCTCTCAT
GTTTAATGAACTAAACCCTCATGGCTAATGTACTAAGCTCTCATGGCTAATGTACTAAGCTCTCATGTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATAT
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GAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTC**C**AATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATC
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TGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCA
ATGTTTAATTGTCA**G**

图28

mCMV- EF1 : DraIIIRINhe-ΔmCMV-EF1-I126-BstEII-**ΔGCSF**-BglII-polyA-BV2
(SEQ ID NO:16)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
GGCACATACATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAG
TTGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGG
GGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGTGG
GCAGGAGATGGGGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTCTCTTTCCTCTCCTGACAGGTTGGTAACCAAGCTT
TCCATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAGCTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCCCTGGGCCC
TGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCAGCTCTCCAGGAGAAGCTGTGTGCCACCTACAAG
CTGTGCCACCCTGAGGAGCTGGTGCTGCTGGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGCTGCTTGAG
CCAACTCCATAGTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGATGTTGCTGA
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CAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAGGTGTCCTACAGAGTTCTAAGACACCTTGCCCAGCCCTGATAGATCTACTTCTGGCTAATAAAAG
ATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCTCTAGTGATCAGCAGTTCAACCTGTTGATAGTATGTACTAAGCTCTCATGTTTAATGTAC
TAAGCTCTCATGTTTAATGAACTAAACCCTCATGGCTAATGTACTAAGCTCTCATGGCTAATGTACTAAGCTCTCATGTTTCATGTACTAAGCTCTCATGTTTGAACAAT
AAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTTATCCT
CATATGAGCTCTTAGAAAAACTCATCCAGCATCAAATGAAACTGCAATTTATTCATATCAGGATTATCAATACCATATTTTTGAAAAAGTCTTTTCTGTAATGAAGGAG
AAAACTCACCCAGGCAGTTCCATAGGATGGCAAGATCCTGGTATCTGTCTGCAATTCCAACTCTTCCAACATCAATACAACCTATTAATTTCCCCTCATCAAAAATAAG
GTTATCAAGTGAGAAATCACCATGAGTGACCACTGAATCTGGTGAGAATGGCAAAAGATTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTTCTCTCATCA
TCAAAATCACTGGCATCAACCAAACCATTATTCATTCTTGATTGGGCCTGAGCCAGTCTAAATACTCTATCAGAGTTAAAAGGACAATTACAAACAGGAATGGAATGC
AATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTC**C**AATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACC
ATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACAGAAC
CTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAA
TCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATA
TACTATGCCAATGTTTAATTGTCA**G**

图29

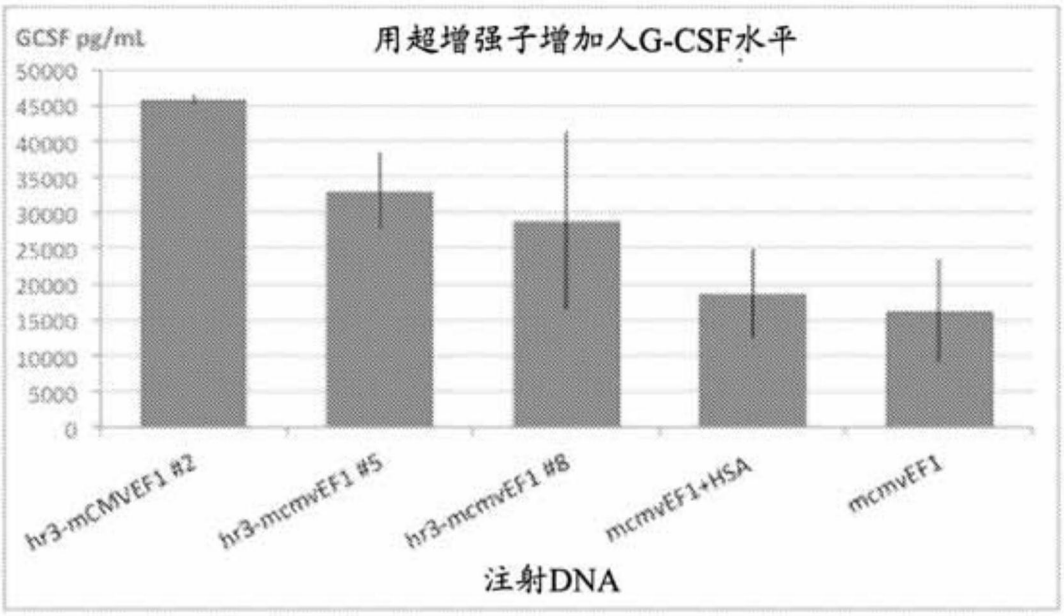


图30

hr3-mCMV-EF1-2 : DraIIIRINhe-hr3-ΔmCMV-EF1-I126-BstEII-**ΔGCSF**-BglII-polyA-BV2 (110716 #2)
(SEQ ID NO:17)

CACTATGTGGACATGAATTCAATTGGCTAGCAAAACAAATGACATCATTCCTGATTATAATAATTTTAATTGTGCTTTACAAGTAGAATTCTACTTGTAAAGAGAGTTT
AATTTGAAAAACAAATTAGTCATTATTAAACATGTTAACAATTGTGTATAAAAATGACATCAGTTTAATGATGACATCATCTCTTGATTATGTTTTACAAGTAGAATTCT
ACTTGTAAAGCTGGTTCAGTTTTGAAAAACAAATGACATCATCTCTTGATTATGTTTTACAAGTAGAATTCTACTTGTAAAAGTGAGTTTAGTTTTAAAAAACAAATGA
CATCATTCAGTTTTGAAAAACAAATGACATCATCTCTTGATTGTGTTTTACAAGTAGAATTCTACTTGTAAAGTGAGTTCAGTTTTGAAAAACAAATGACCCTCTCATAC
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GTTTTGCCCAGTACATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTAC
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GTGAATCAACAGGAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGG
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GGGAAAGGGTGGGCAGGAGATGGGGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTCTCTTTCCTCTCCTGACAGGTT
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CCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCAGCTCTCCAGGAGAAGCTGTG
TGCCACCTACAAGCTGTGCCACCCTGAGGAGCTGGTGCTGCTGGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGG
CAGGCTGCTTGAGCCAACTCCATAGTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTCCCACCTTGGACACACTGCAGC
TGGATGTTGCTGACTTTGCCACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCTGCCTTTGCCTCTGCTT
TCCAGAGAAGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAGGTGTCCTACAGAGTTCTAAGACACCTTGCCCAGCCCTGATAGATCTACTTCT
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GGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTCCAATACCTGGAATGCTGTTTTCCCTGGGATGGCA
GTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCA
TTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTT
ATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTA
TACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图31

hr3-hCMV-hCMV-HTLV-5 : DraIIIRI-Δhr3-NheΔhCMVΔhCMVRVΔHTLV -BstEII-ΔhGCSF-BglII-MixpA/BV2
(110716 #5: 反向hr3)

(SEQ ID NO:18)

CACTATGTGGACATGAATTCTCATAGCTAGAAATCTTGTAAAGATTATTTATTAAAATTGTTCAACAATTGTATGAGAGGGTCATTTGTTTTTCAAAACTGAACTCACTT
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TAAAATTATTATAATCAGGAATGATGTCATTTGTTTTGCTAGC**TGTTACATAACTTATGGTAAATGGCCTGCCTGGCTGACTGCCCAATGACCCCTGCCCAATGATGT**
CAATAATGATGTATGTTCCCATGTAATGCCAATAGGGACTTTCCATTGATGTCAATGGGTGGAGTATTTATGGTAACTGCCCACTTGGCAGTACATCAAGTGTATC
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CCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCA
CCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCA**G**

图32

hr3- hCMV-hCMV-HTLV -8 : DraIIIRINhe-Δhr3-ΔhCMVΔhCMVRVΔHTLV -BstEII-ΔhGCSF-BglII-MixpA/BV2 (110716 #8)

(SEQ ID NO:19)

CACTATGTGGACATGAATTCTCATAGCTAGCAAAACAAATGACATCATTCCTGATTATAATAATTTTAATTGTGCTTTACAAGTAGAATTCTACTTGTAAAGAGAGTTTA
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TGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCT
GACCATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGC
CCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCA
CCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCA**G**

图33

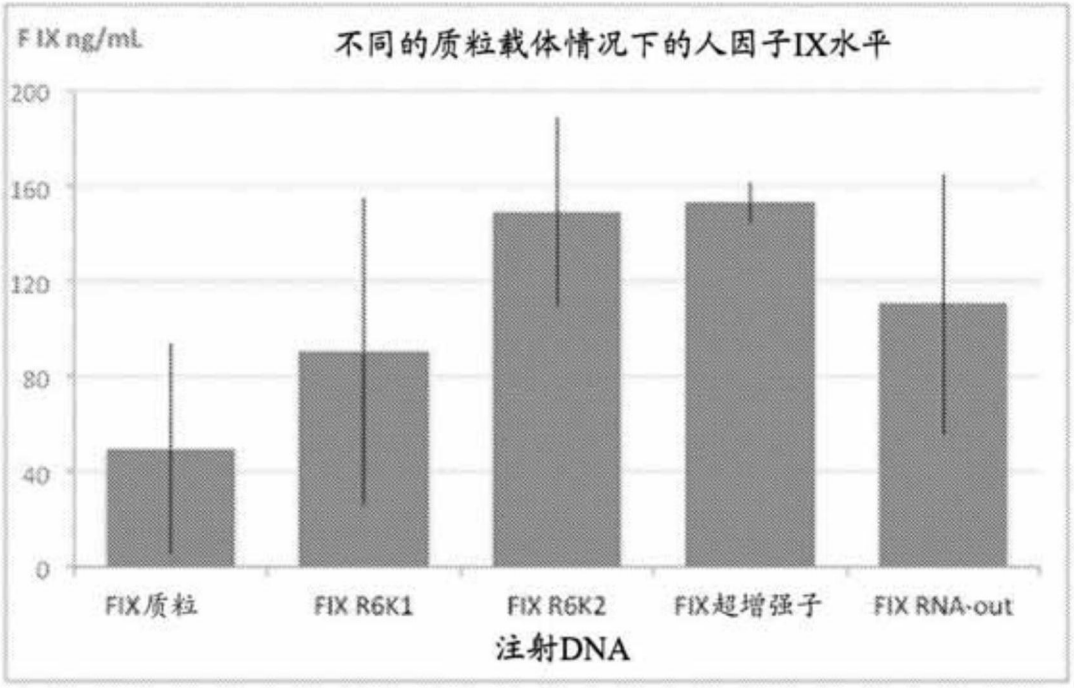

FIX ng/mL
不同的质粒载体情况下的人因子IX水平
200
160
120
80
40
0
FIX质粒
FIX R6K1
FIX R6K2
FIX超增强子
FIX RNA-out
注射DNA

图34

FIX质粒： DraIIIRINhe-ΔmCMV-EF1-I126-BstEII-**ΔFIX**-BglII-polyA-BV2 (062316#4)
(SEQ ID NO:20)

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GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
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AAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTCCAATACCTGGAATGCTG
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CATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTC
CTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图35

FIX R6K1: XbaRINhe-ΔmCMV-EF1-I126-BstEII-**ΔFIX**-BglII-R6K-Kan-polyA (121616 # 4)
(SEQ ID NO:21)

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CTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCAT

图36

FIX R6K1: DraIIIRINhe-ΔmCMV-EF1-RV-MIP-GA-R6K-Kan-MIP-BstEII-ΔFIX-BglII-polyA (121616 # 8) (SEQ ID NO:22)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
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ATGCCAATGTTTAATTGTCAG

图37

FIX超增强子: DraIIIRINhe-超增强子-ΔmCMV-EF1-I126-BstEII-**ΔFIX**-BglII-polyA-BV2
(121616 # 12)

(SEQ ID NO:23)

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AATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAG
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GCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCT
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图38

FIX RNAout: NTC9385R-ΔhFIX: Nature Technology (natx.com/): RNAout-cmv-ΔFIX

(SEQ ID NO:24)

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GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCCC
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图39

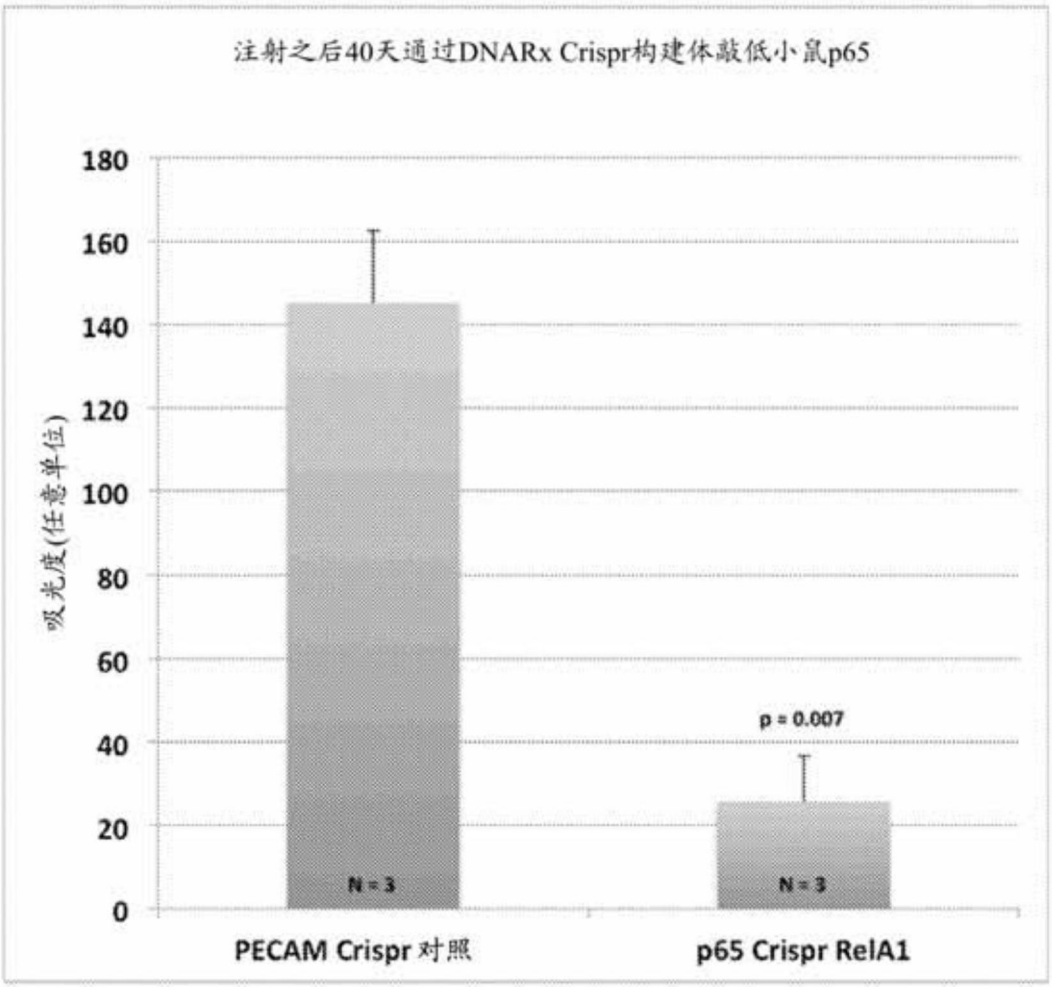

注射之后40天通过DNARx Crispr构建体敲低小鼠p65
吸光度(任意单位)
180
160
140
120
100
80
60
40
20
0
p = 0.007
N = 3
N = 3
PECAM Crispr 对照
p65 Crispr RelA1

图40

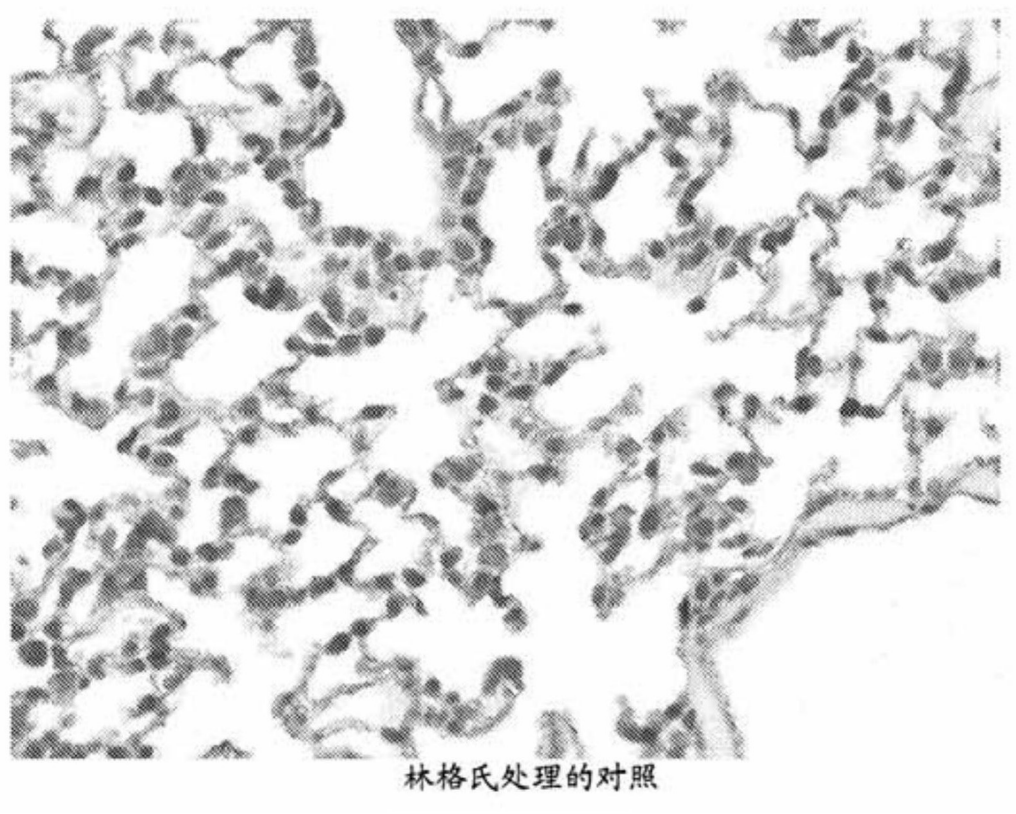


图41A

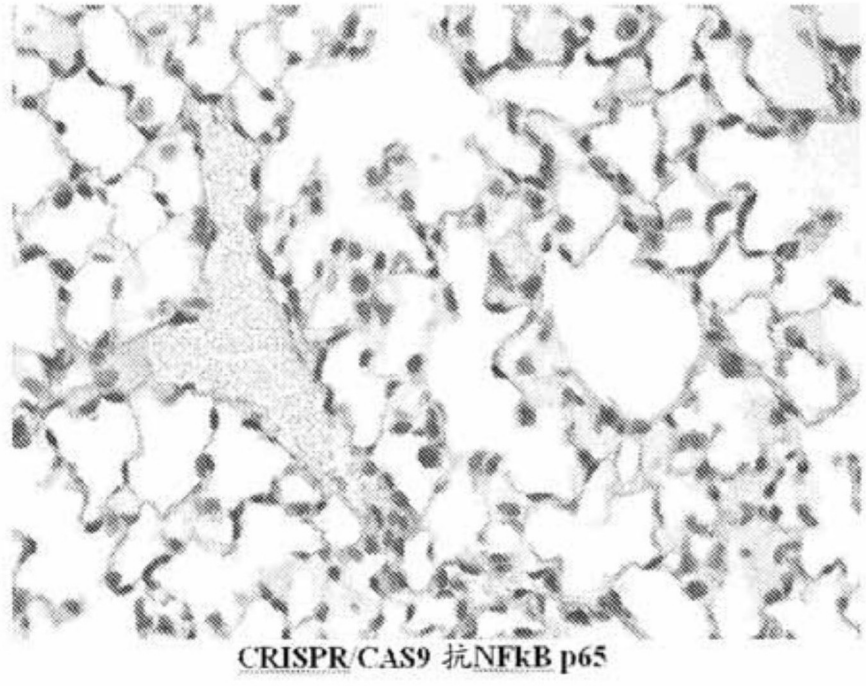


图41B

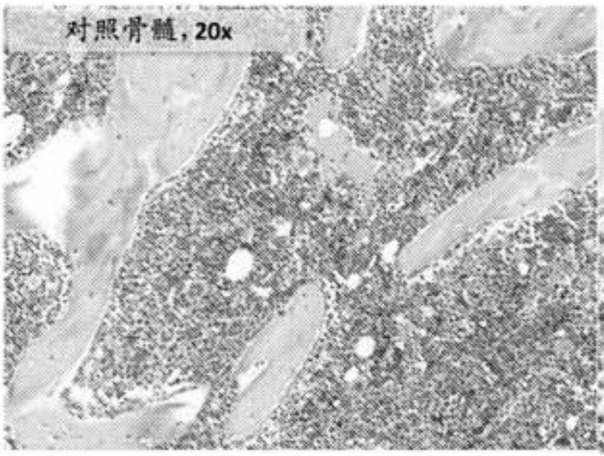


图 42A

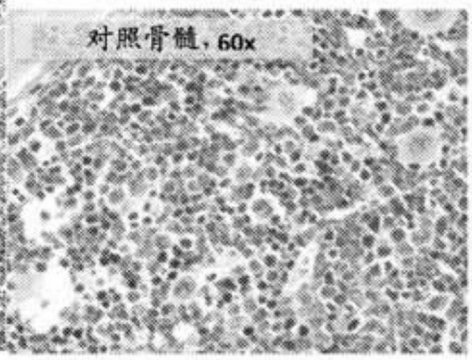


图 42B

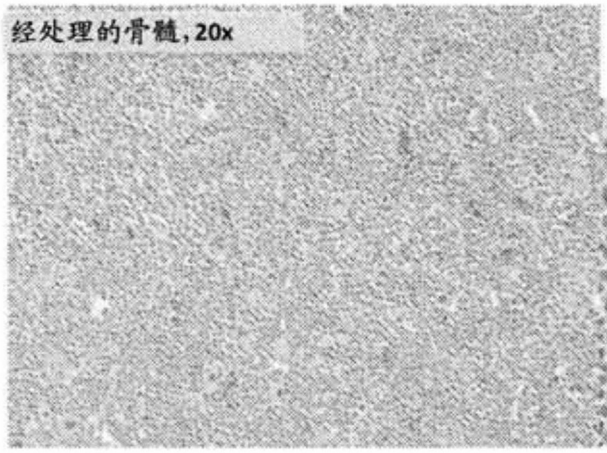


图 42C

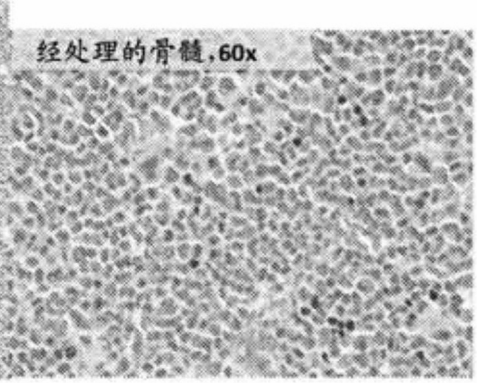


图 42D

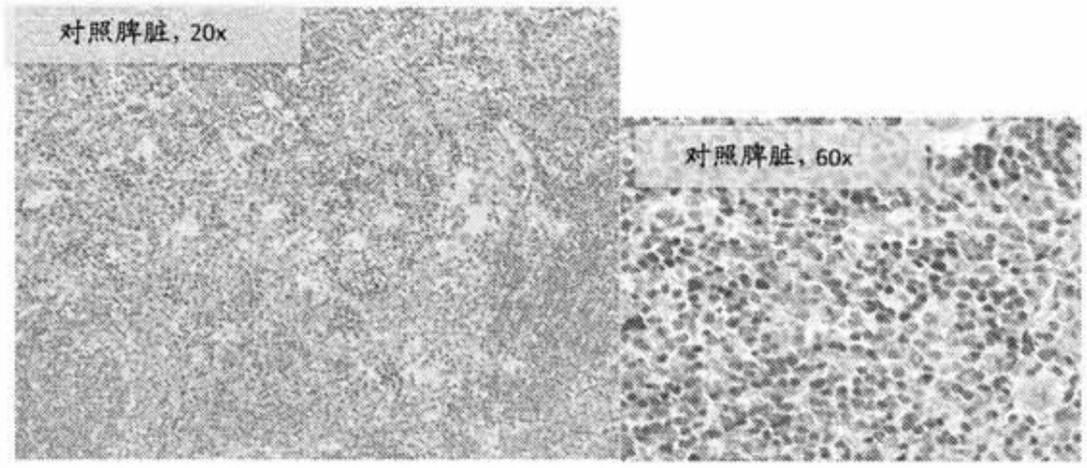


图 43A 图 43B

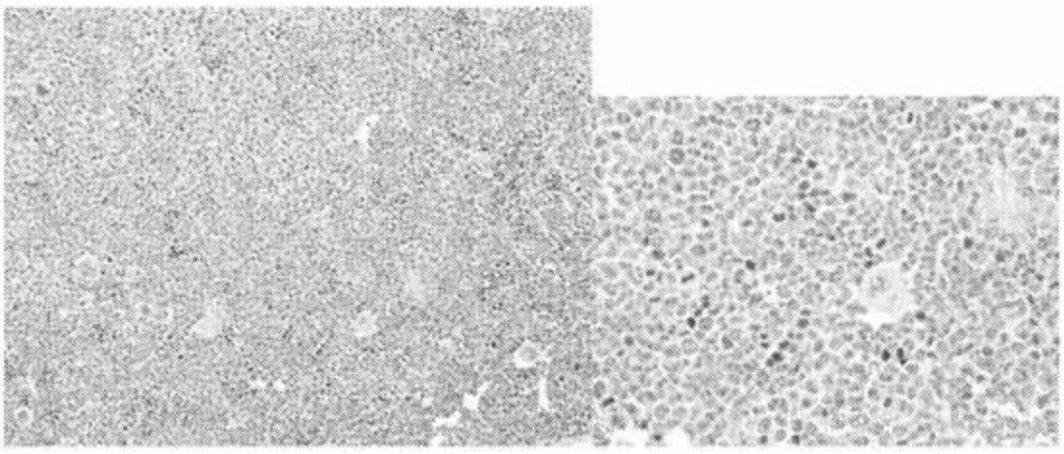


图 43C 图 43D

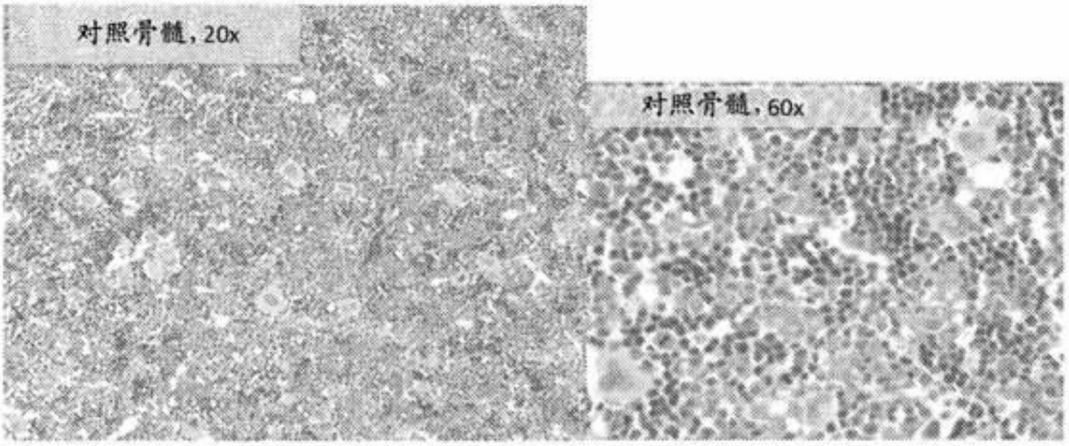


图 44A 图 44B

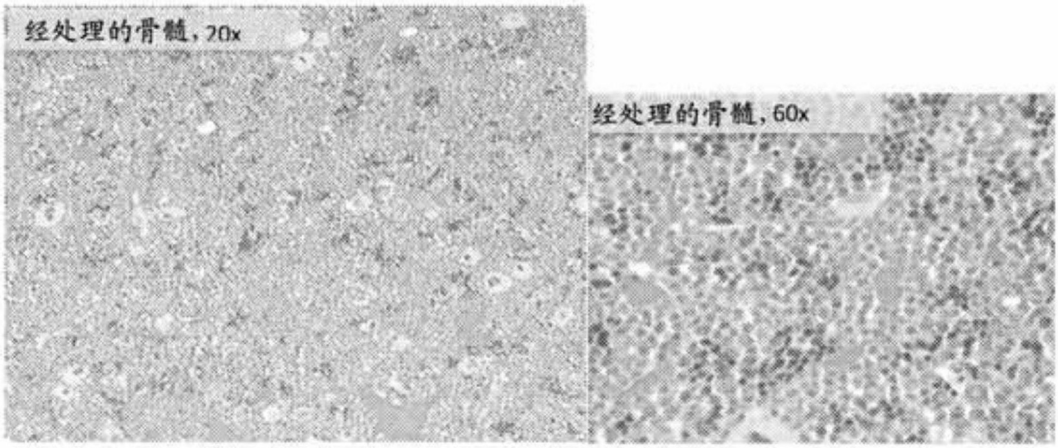


图 44C 图 44D

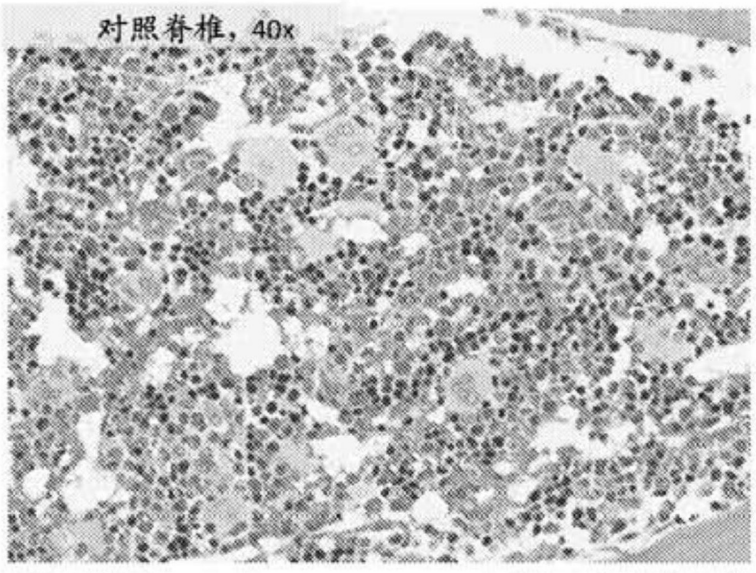


图45A

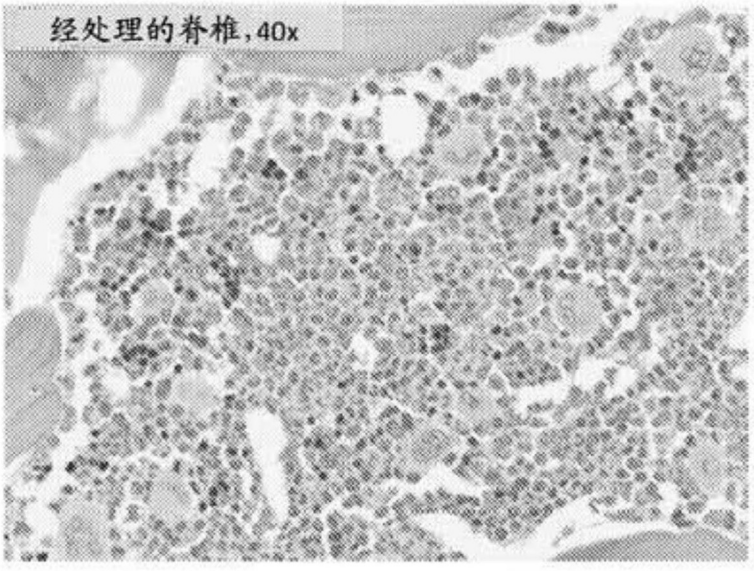


图45B

DNARx-31H4-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- Δ31H4-H-F3(RKRR)-P2A-Δ31H4-L-BglII-MixpA-BV2
(SEQ ID NO:25)

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图46

DNARx-31H4: 双盒抗 PCSK9-31H4

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-Δ31H4-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-Δ31H4-L -BglII-polyA BV2

(SEQ ID NO:26)

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图47

DNARx-21B12-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- Δ21B12-H-F3(RKRR)-P2A-Δ21B12-L-BglII-MixpA-BV2
(SEQ ID NO:27)

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图48

DNARx-21B12:双盒抗PCSK9-21B12

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-Δ21B12-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-Δ21B12-L -BglII-polyA BV2

(SEQ ID NO:28)

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图49

DNARx-CD47-2A: aCD47-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- ΔaCD47-H-F3(RKRR)-P2A-ΔaCD47-L-BglII-MixpA-BV2

(SEQ ID NO:29)

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图50

DNARx-CD47:双盒 aCD47

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔaCD47-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-ΔaCD47-L -BglII-polyA BV2

(SEQ ID NO:30)

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图51

DNARx-D8-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- ΔD8-H-F3(RKRR)-P2A-ΔD8-L-BglII-MixpA-BV2

(SEQ ID NO:31)

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图52

DNARx-F10-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- ΔF10-H-F3(RKRR)-P2A-ΔF10-L-BglII-MixpA-BV2
(SEQ ID NO:32)

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图53

DNARx-A66-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- ΔA66-H-F3(RKRR)-P2A-ΔA66-L-BglII-MixpA-BV2
(SEQ ID NO:33)

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CAATGTTTAATTGTCA**G**

图54

DNARx-D8 :双盒抗D8

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔD8-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-ΔD8-L -BglII-polyA BV2

(SEQ ID NO:34)

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TTAATTGTCAG

图55

DNARx-F10: 双盒抗F10

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔF10-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-ΔF10-L -BglII-polyA BV2

(SEQ ID NO:35)

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ATACTATGCCAATGTTTAATTGTCAG

图56

DNARx-A66: 双盒抗A66

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔA66-H-BglII-polyA- ΔhCMV-EF1-I126-BstEII-ΔA66-L -BglII-polyA BV2

(SEQ ID NO:36)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
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GTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAA
TGTTTAATTGTCAG

图57

DNARx-HA-MITD

DraIIRINhe-ΔmCMVΔEF1I126-BstEII-HA-MITD-BglII-MixpA-BV2

(SEQ ID NO:37)

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CTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图58

DNARx-SEC-部分HA-MITD

DraIIRINhe-ΔmCMVΔEF1I126-BstEII-SEC-部分HA-MITD-BglII-MixpA-BV2
(SEQ ID NO:38)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
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CAATGTTTAATTGTCAG

图59

DNARx-D8-2A-HA-MITD :双盒抗D8-2A-HA-MITD (SEQ ID NO:39)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔD8H-2A-D8L-BglII-polyA-ΔhCMV-EF1-I126-BstEII-HA-MITD-BglII-polyA BV2

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DNARx-F10-2A-HA-MITD : 双盒抗F10-2A-HA-MITD (SEQ ID NO:40)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔF10H-2A-F10L-BglII-polyA- ΔhCMV-EF1-I126-BstEII-HA-MITD-BglII-polyA BV2

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DNARx-A66-2A-HA-MITD：双盒抗 A66-2A-HA-MITD (SEQ ID NO:41)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔA66H-2A-A66L-BglII-polyA- ΔhCMV-EF1-I126-BstEII-HA-MITD-BglII-polyA BV2

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AAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTT
ATCCTCATATGAGCTCTTAGAAAAACTCATCCAGCATCAAATGAAACTGCAATTTATTCATATCAGGATTATCAATACCATATTTTTGAAAAAGTCTTTTCTGTAATGAAGGAGAAAACTCACCC
AGGCAGTTCCATAGGATGGCAAGATCCTGGTATCTGTCTGCAATTCCAACTCTTCCAACATCAATACAACCTATTAATTTCCCCTCATCAAAAATAAGGTTATCAAGTGAGAAATCACCATGAGT
GACCACTGAATCTGGTGAGAATGGCAAAAGATTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTTCTCTCATCATCAAAATCACTGGCATCAACCAAACCATTATTCATTCTTGATT
GGGCCTGAGCCAGTCTAAATACTCTATCAGAGTTAAAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATT
CTTCCAATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTC
TGACCATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTA
GCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGC
AGATATACTATGCCAATGTTTAATTGTCAG

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DNARx-D8-2A-SEC-部分-HA-MITD：双盒抗D8-2A-SEC-部分-HA-MITD (SEQ ID NO:42)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔD8H-2A-D8L-BglII-polyA- ΔhCMV-EF1-I126-BstEII-SEC-部分-HA-MITD-BglII-polyA BV2

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
GGCACATACATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAG
TTGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGG
GGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGTGG
GCAGGAGATGGGGCAGTGCAGGAAAAGTGGCACTATGAACCCTGCAGCCCTAGACAATTGTACTAACCTTCTTCTCTTTCCTCTCCTGACAGGTTGGTAACCAAGCCA
CCATGGGACTGGGACTCCAGTGGGTGTTCTTTGTGGCCCTGCTGAAAGGGGTGCACTGTGAAGTCAGACTGCTGGAAAGTGGTGGTGGCCTGCAGGTTCAGCTGGT
GCAGTCTGGGGCTGAAGTGAAGAAACCTGGCAGCTCTGTGAAGGTGTCCTGCAAGGCTAGTGGTGGCACCTTCTCTGCCTATGCCTTCACCTGGGTCAGACAGGCTC
CTGGACAGGGCCTTGAATGGATGGGAGGCATCACAGGCATGTTTGGCACAGCCAACTATGCCCAGAAATTCCAGGGCAGAGTGACCATCACAGCTGATGAGCTGAC
CAGCACAGCCTACATGGAACTGAGCAGCCTGACCTCTGAGGACACAGCCCTGTACTACTGTGCCAGAGGCCTGTACTATTATGAGTCTAGCCTGGACTACTGGGGCC
AGGGCACACTGGTTACAGTGTCTAGTGCCAGCACAAAGGGCCCATCTGTGTTCCCTCTGGCACCCAGCAGCAAGTCTACCAGTGGTGGAACAGCTGCCCTGGGCTGT
CTGGTCAAGGACTACTTTCCTGAGCCAGTGACAGTGTCCTGGAACTCTGGGGCTCTGACATCTGGGGTGCACACATTCCCTGCTGTGCTCCAGTCCTCTGGCCTGTAC
AGCCTCAGCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAAGGCTGA
GCCCAAGAGCTGTGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAGCTGCTTGGAGGGACCTTCTGTGTTTCTGTTCCCTCCAAAGCCAAAGGACACCCTGAT
GATCAGCAGAACCCCTGAAGTGACATGTGTGGTGGTTGATGTGTCCCATGAGGACCCAGAAGTGAAGTTCAATTGGTATGTGGATGGTGTTGAGGTGCACAATGCC
AAGACCAAGCCTAGAGAGGAACAGTACAACAGCACCTACAGAGTGGTGTCTGTGCTGACAGTGCTGCATCAGGACTGGCTGAATGGCAAAGAGTACAAGTGCAAG
GTGTCCAACAAGGCCCTGCCTGCTCCTATTGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTAGGGAACCCCAGGTTTACACACTGCCACCTAGCAGGGATGAGCT
GACCAAGAACCAGGTGTCCCTGACCTGCCTGGTTAAGGGCTTCTACCCCTCTGACATTGCTGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACA
ACCCCTCCTGTGCTGGACTCTGATGGCTCATTCTTCCTGTACTCCAAGCTCACAGTGGACAAGTCCAGATGGCAGCAAGGCAATGTGTTCAGCTGCTCTGTGATGCAT
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CACCCTGGCAAGGCCCCTAAGCTGATGATCTATGAAGTGACCAAGAGGCCCTCTGGGGTGCCAGACAGATTCTCTGCCAGCAAGTCTGGCAACACAGCCAGCCTGAC
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CTTTCCTACTTGGCAGTACATCTATGTATTAGTCATTGCTATTACCATGGATTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACAT
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CCACCTTTTTCCCCAGGGTGGGGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGATGCACCTACTAGAT
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CAGATCCTGGTCCTACATTGTGGAAACCCCTAGCTCTGAGAATGGCATCTGCTACCCTGGGGACTTCATTGACTATGAGGAACTGAAAGAACAGCTGTCCTCTGTGTC
CAGCTTTGAGAGATTTGAAATCTTCCCCAAAGAGAGCAGCTGGCCCAACCACAACACCAACAAAGGGGTCACAGCTGCCTGTAGCCATGAGGGCAAGAGCAGCTTCT
ACAGAAACCTGCTGTGGCTGACAGAGAAAGAGGGCAGCTACCCCAAGCTGAAGAACTCCTATGTGAACAAGAAGGGCAAAGAGGTCCTGGTTCTCTGGGGCATCCA
CCATCCTAGCAACAGCAAAGAGCAGCAGAACCTGTACCAGAATGAGAATGCCTATGTGTCTGTGGTCACAAGCAACTACAACAGAAGGTTCACCCCTGAGATTGCTG
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TATGTATGCCTTTGCTCTGAGCAGAGGCTTTGGCTCTGGCATCATCACCTCTGTGGATGGGGTCAAGCTGGAATCCATGGGCATCATTGTGGGCATTGTGGCAGGCCT
GGCTGTGCTGGCAGTGGTGGTTATTGGAGCTGTGGTGGCTGCTGTGATGTGCAGAAGAAAGTCCTCTGGAGGCAAAGGTGGCAGCTACTCTCAGGCTGCCTGTTCT
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CAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTT
TCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图63

DNARx-F10-2A-SEC-部分-HA-MITD：双盒抗F10-2A-SEC-部分-HA-MITD (SEQ ID NO:43)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔF10H-2A-F10L-BglII-polyA- ΔhCMV-EF1-I126-BstEII-SEC-部分-HA-MITD-BglII-polyA BV2

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
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GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
GGCACATACATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAG
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AGAACAGCCTACATGGACCTGAGAAGTCTTAGGAGTGAAGATACAGCTGTGTACTACTGTGCTAGAAGCCCCAGCTACATCTGCTCTGGTGGCACCTGTGTGTTTGA
CCACTGGGGCCAGGGAACCCTGGTCACAGTTTCTTCTGCCAGCACAAAGGGCCCATCTGTGTTCCCTCTGGCACCCAGCAGCAAGTCTACCAGTGGTGGAACAGCTG
CCCTGGGCTGTCTGGTCAAGGACTACTTTCCTGAGCCAGTGACAGTGTCCTGGAACTCTGGGGCTCTGACATCTGGGGTGCACACATTCCCTGCTGTGCTCCAGTCCT
CTGGCCTGTACAGCCTCAGCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGAC
AAGAAGGCTGAGCCCAAGAGCTGTGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAGCTGCTTGGAGGACCTTCTGTGTTTCTGTTCCCTCCAAAGCCAAAG
GACACCCTGATGATCAGCAGAACCCCTGAAGTGACATGTGGTGGTTGATGTGTCCCATGAGGACCCAGAAGTGAAGTTCAATTGGTATGTGGATGGTGTTGAGG
TGCACAATGCCAAGACCAAGCCTAGAGAGGAACAGTACAACAGCACCTACAGAGTGGTGTCTGTGCTGACAGTGCTGCATCAGGACTGGCTGAATGGCAAAGAGTA
CAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATTGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTAGGGAACCCCAGGTTTACACACTGCCACCTAGCA
GGGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTTAAGGGCTTCTACCCCTCTGACATTGCTGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAA
CTACAAGACAACCCCTCCTGTGCTGGACTCTGATGGCTCATTCTTCCTGTACTCCAAGCTCACAGTGGACAAGTCCAGATGGCAGCAAGGCAATGTGTTCAGCTGCTC
TGTGATGCATGAGGCCCTGCACAACCACTACACACAGAAGTCCCTGAGCCTGTCTCCTGGCAAGAAGAAGAAGGAGTGGAAGTGGAGCTACTAACTTCAGCCTG
CTGAAGCAGGCTGGAGATGTGGAGGAGAACCCTGGACCTATGGACTTCCAGGTGCAGATCATCAGCTTTCTGCTGATCTCTGCCTCTGTGATCATGAGCAGAGGCCA
GCCTGGACTGACACAGCCTCCATCTGTGTCCAAGGGCCTGAGACAGACAGCCACACTGACCTGCACAGGCAACAGCAACAATGTGGGCAATCAAGGGGCTGCCTGG
CTCCAGCAGCATCAGGGACATCCTCCAAAGCTGCTGAGCTACAGAAACAATGACAGACCCTCTGGCATCTCTGAGAGATTCTCTGCCTCTAGGAGTGGCAACACAGC
CAGCCTGACCATCACTGGACTCCAGCCAGAGGATGAGGCTGACTACTACTGCTCCACCTGGGACAGCAGCCTGTCTGCTGTGGTTTTTGGTGGTGGCACCAAGCTGA
CAGTGCTGAGAACAGTGGCTGCCCCTTCTGTGTTCATCTTCCCACCATCTGATGAGCAGCTGAAGTCTGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACTTCTACCC
TAGAGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTCCAGTCTGGCAACTCCCAAGAGTCTGTGACAGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGC
AGCACCCTGACACTGAGCAAGGCTGACTATGAGAAGCACAAAGTCTATGCCTGTGAAGTGACCCACCAGGGCCTGTCTAGCCCTGTGACCAAGAGCTTCAACAGGG
GAGAGAGCTGAAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCATGTTACATAACTTATGGTAAATG
GCCTGCCTGGCTGACTGCCCAATGACCCCTGCCCAATGATGTCAATAATGATGTATGTTCCCATGTAATGCCAATAGGGACTTTCCATTGATGTCAATGGGTGGAGTA
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TGACCTTATGGGACTTTCCTACTTGGCAGTACATCTATGTATTAGTCATTGCTATTACCATGGATTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGG
GCAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATG
TGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGAT
GCACCTACTAGATATCTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGTGGGCAGGAGGTGGGGCAGTGCAGGAAAAGTGGCACTGTGAACCCTGCAGCCCT
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GGCTCTGACAGAAACATGGGCTGGCTCCAGACTGAAGGGCATTGCTCCTCTGCAACTGGGCAAGTGCAACATTGCTGGCTGGCTGCTGGGCAACCCTGAGTGTGAT
CCTCTGCTGCCTGTCAGATCCTGGTCCTACATTGTGGAAACCCCTAGCTCTGAGAATGGCATCTGCTACCCTGGGGACTTCATTGACTATGAGGAACTGAAAGAACAG
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CAAGAGCAGCTTCTACAGAAACCTGCTGTGGCTGACAGAGAAAGAGGGCAGCTACCCCAAGCTGAAGAACTCCTATGTGAACAAGAAGGGCAAAGAGGTCCTGGTT
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ATTGTGGCAGGCCTGGCTGTGCTGGCAGTGGTGGTTATTGGAGCTGTGGTGGCTGCTGTGATGTGCAGAAGAAAGTCCTCTGGAGGCAAAGGTGGCAGCTACTCTC
AGGCTGCCTGTTCTGATTCTGCCCAGGGCTCTGATGTGTCCCTGACAGCTTAAAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTT
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TGAATCTGGTGAGAATGGCAAAAGATTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTTCTCTCATCATCAAAATCACTGGCATCAACCAAACCATTATTC
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TCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCT
GGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

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DNARx-A66-2A-SEC-部分-HA-MITD：双盒抗A66-2A-SEC-部分-HA-MITD (SEQ ID NO:44)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔA66H-2A-A66L-BglII-polyA- ΔhCMV-EF1-I126-BstEII-SEC-部分 -HA-MITD-BglII-polyA BV2

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
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GAAAGTCCCATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATT
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TACAAGACAACCCCTCCTGTGCTGGACTCTGATGGCTCATTCTTCCTGTACTCCAAGCTCACAGTGGACAAGTCCAGATGGCAGCAAGGCAATGTGTTCAGCTGCTCT
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TGAAGCAGGCTGGAGATGTGGAGGAGAACCCTGGACCTATGGACTTCCAGGTGCAGATCATCAGCTTTCTGCTGATCTCTGCCTCTGTGATCATGAGCAGAGGCCGA
GATTGTGCTGACACAGAGCCCTGCCACACTGTCTCTTAGCCCTGGGGAGAGAGCCACACTGAGCTGTAGAGCCAGCCAGTCTGTGTCCTCTTACCTGGCCTGGTATCA
GCAGAAGCCTGGACAGGCTCCCAGACTGCTGATCTATGATGCCAGCAACAGAGCCACAGGCATCCCTGCCAGATTCAGTGGCTCTGGCAGTGGCACAGACTTCACCC
TGACCATCAGCAGACTGGAACCAGAGGACTTTGCTGTGTACTTCTGCCAGCAGTATGGCAGCAGCCCTCAGTTTGGCCAGGGCACAAGACTGGAAATCAAGAGAAC
AGTGGCTGCCCCTTCTGTGTTCATCTTCCCACCATCTGATGAGCAGCTGAAGTCTGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACTTCTACCCTAGAGAAGCCAAG
GTGCAGTGGAAGGTGGACAATGCCCTCCAGTCTGGCAACTCCCAAGAGTCTGTGACAGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACAC
TGAGCAAGGCTGACTATGAGAAGCACAAAGTCTATGCCTGTGAAGTGACCCACCAGGGCCTGTCTAGCCCTGTGACCAAGAGCTTCAACAGGGGAGAGAGCTGAAG
ATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCATGTTACATAACTTATGGTAAATGGCCTGCCTGGCTG
ACTGCCCAATGACCCCTGCCCAATGATGTCAATAATGATGTATGTTCCCATGTAATGCCAATAGGGACTTTCCATTGATGTCAATGGGTGGAGTATTTATGGTAACTGC
CCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTATGCCCCCTATTGATGTCAATGATGGTAAATGGCCTGCCTGGCATTATGCCCAGTACATGACCTTATGGGA
CTTTCCTACTTGGCAGTACATCTATGTATTAGTCATTGCTATTACCATGGATTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACAT
GGCCCACAGTCCCTGAGAAGTTGGGGGGAGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCT
CCACCTTTTTCCCCAGGGTGGGGGAGAACCATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGGATGCACCTACTAGAT
ATCTTGGTAAGTCACTGACTGTCTATGCCTGGGAAAGGGTGGGCAGGAGGTGGGGCAGTGCAGGAAAAGTGGCACTGTGAACCCTGCAGCCCTAGACAATTGTACT
AACCTTCTTCTCTTTCCTCTCCTGACAGGTTGGTAACCAAGCCACCATGAGAGTGACAGCCCCTAGAACAGTCCTGCTGCTCCTGTCTGCTGCCCTGGCTCTGACAGAA
ACATGGGCTGGCTCCAGACTGAAGGGCATTGCTCCTCTGCAACTGGGCAAGTGCAACATTGCTGGCTGGCTGCTGGGCAACCCTGAGTGTGATCCTCTGCTGCCTGT
CAGATCCTGGTCCTACATTGTGGAAACCCCTAGCTCTGAGAATGGCATCTGCTACCCTGGGGACTTCATTGACTATGAGGAACTGAAAGAACAGCTGTCCTCTGTGTC
CAGCTTTGAGAGATTTGAAATCTTCCCCAAAGAGAGCAGCTGGCCCAACCACAACACCAACAAAGGGGTCACAGCTGCCTGTAGCCATGAGGGCAAGAGCAGCTTCT
ACAGAAACCTGCTGTGGCTGACAGAGAAAGAGGGCAGCTACCCCAAGCTGAAGAACTCCTATGTGAACAAGAAGGGCAAAGAGGTCCTGGTTCTCTGGGGCATCCA
CCATCCTAGCAACAGCAAAGAGCAGCAGAACCTGTACCAGAATGAGAATGCCTATGTGTCTGTGGTCACAAGCAACTACAACAGAAGGTTCACCCCTGAGATTGCTG
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GGCTGTGCTGGCAGTGGTGGTTATTGGAGCTGTGGTGGCTGCTGTGATGTGCAGAAGAAAGTCCTCTGGAGGCAAAGGTGGCAGCTACTCTCAGGCTGCCTGTTCT
GATTCTGCCCAGGGCTCTGATGTGTCCCTGACAGCTTAAAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTC
TAGCTCTAGTGATCAGCAGTTCAACCTGTTGATAGTATGTACTAAGCTCTCATGTTTAATGTACTAAGCTCTCATGTTTAATGAACTAAACCCTCATGGCTAATGTACTA
AGCTCTCATGGCTAATGTACTAAGCTCTCATGTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAG
TTTTATAAGAAAAAAAAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTTATCCTCATATGAGCTCTTAGAAAAACTCATCCAGCATCAAATGAAACTGCA
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GTCTGCAATTCCAACTCTTCCAACATCAATACAACCTATTAATTTCCCCTCATCAAAAATAAGGTTATCAAGTGAGAAATCACCATGAGTGACCACTGAATCTGGTGAG
AATGGCAAAAGATTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTTCTCTCATCATCAAAATCACTGGCATCAACCAAACCATTATTCATTCTTGATTGGGC
CTGAGCCAGTCTAAATACTCTATCAGAGTTAAAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGA
ATCAGGATATTCTTCCAATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAG
GCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATA
CAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTT
TCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图65

011215 # 7: βGlo-RINhe-ΔmCMVΔEF1I126-BstEII-**hG-CSF**-BglII-IFN S/MAR-MixpA/BV2: EF1-hGCSF (高表达者)

(SEQ ID NO:45)

CACTATGTGTTAATTAAAATTATCTCTAAGGCATGTGAACTGGCTGTCTTGGTTTTCATCTGTACTTCATCTGCTACCTCTGTGACCTGAAACATATTTATAATTCCATTA
AGCTGTGCATATGATAGATTTATCATATGTATTTTCCTTAAAGGATTTTTGTAAGAACTAATTGAATTGATACCTGTAAAGTCTTTATCACACTACCCAATAAATAATAA
ATCTCTTTGTTCAGCTCTCTGTTTCTATAAATATGTACCAGTTTTATTGTTTTTAGTGGTAGTGATTTTATTCTCTTTCTATATATATACACACACATGTGTGCATTCATAA
ATATATACAATTTTTATGAATAAAAAATTATTAGCAATCAATATTGAAAACCACTGATTTTTGTTTATGTGAGCAAACAGCAGATTAAAAGGAATTTCAATTGCCTGCA
GGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACATAAGGT
CAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATGGGAGGTAA
GCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAGGAAAGTCC
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CATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGG
AGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAAC
CATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGgtaagtcactgactgtctatgcctgggaaagggtgggcagggagatggggcagtgcag
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GCTGATGGCCCTGCAGCTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGT
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CTGGGAATGGCCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCTGCCTTTGCCTCTGCTTTCCAGAGAAGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAG
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GTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAGAATATATAAGGC
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AAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTCCAATACCTGGAATGCT
GTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGAC
CATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCA
ACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCT
CCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图66

011315 #2: βGlo-RINhe-**ΔhCMV**ΔCMVΔHTLV-BstEII-**hG-CSF**-BglII-IFN S/MAR-MixpA/BV2 : hCMV-hGCSF(低表达者)

(SEQ ID NO:46)

CACTATGTGTTAATTAAAATTATCTCTAAGGCATGTGAACTGGCTGTCTTGGTTTTCATCTGTACTTCATCTGCTACCTCTGTGACCTGAAACATATTTATAATTCCATTA
AGCTGTGCATATGATAGATTTATCATATGTATTTTCCTTAAAGGATTTTTGTAAGAACTAATTGAATTGATACCTGTAAAGTCTTTATCACACTACCCAATAAATAATAA
ATCTCTTTGTTCAGCTCTCTGTTTCTATAAATATGTACCAGTTTTATTGTTTTTAGTGGTAGTGATTTTATTCTCTTTCTATATATATACACACACATGTGTGCATTCATAA
ATATATACAATTTTTATGAATAAAAAATTATTAGCAATCAATATTGAAAACCACTGATTTTTGTTTATGTGAGCAAACAGCAGATTAAAAGGAATTTCAATTGCCTGCA
GGACATGAATTCTCATAGCTAGCAT**GTTACATAACTTATGGTAAATGGCCTGCCTGGCTGACTGCCCAATGACCCCTGCCCAATGATGTCAATAATGATGTATGTTC**
CCATGTAATGCCAATAGGGACTTTCCATTGATGTCAATGGGTGGAGTATTTATGGTAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTATGCCCC
CTATTGATGTCAATGATGGTAAATGGCCTGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTATGTATTAGTCATTGCTATTA
CCATGGTGATGGGTTTTGGCAGTACATCAATGGGTGTGGATAGTGGTTTGACCCATGGGGATTTCCAAGTCTCCACCCCATTGATGCCAATGGGAGTTTGTTTTGGCA
CCAAAATCAATGGGACTTTCCAAAATGTTGTAACAACTCTGCCCCATTGATGGAAATGGGTGGTAGGTGTGTGTGGTGGGAGGTCTATATAAGCAGAGCTTGTTTAG
TGAACTGGATGCACCTACTAGATATCCATATGGCTATCATCTCTCCTTCAATATCCATCATCCCTACCTGAGGCATCCATCCAATCATGTTGAGTATATTTCTGCATCCTC
CATCCTGTGGTGCCTCCTGAACTGATTCATCATTCTAGGTAAGTTTAAAGCTCAGGTATAGACATGGCCTTTGTCATGATCTCCCTTGGAGCCTACCTAGACTCATCAT
GCTCTCCAATCTTTGCCTGACCCTGCTTGCTCAACTCTAATTCTTTGTTTATTTTTCTGTTCTGATCATTTACAGATCCAAGCTGTGACATGATCCCTACCATATGTTGGA
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AGCCACCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGGGATGGGGCAGCTCTCCAGGAGAAG
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GCTGGCAGGCTGCTTGAGCCAACTCCATAGTGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCTGAGTTGGGTCCCACCTTGGACACACT
GCAGCTGGATGTTGCTGACTTTGCCACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCCCACCCAGGGTGCCATGCCTGCCTTTGCCT
CTGCTTTCCAGAGAAGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGGAGGTGTCCTACAGAGTTCTAAGACACCTTGCCCAGCCCTGATAGATCT
ACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTTGTGTCTGCATTCTAGCCTGCAGGAATTCAGTCAATATGTTCACCCCAAAAAAGCTGT
TTGTTAACTTGTCAACCTCATTCTAAAATGTATATAGAAGCCCAAAAGACAATAACAAAAATATTCTTGTAGAACAAAATGGGAAAGAATGTTCCACTAAATATCAAG
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ATATGGCATTTTACAATGGGAAAATGATGGTCTTTTTCTTTTTTAGAAAAACAGGGAAATATATTTATATGTAAAAAATAAAAGGGAACCCATATGTCATACCATACAC
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AGAATGACAGAAAATATTTGCAACACCCCAGTAAAGAGAATTGTAATATGCAGATTATAAAAAGAAGTCTTACAAATCAGTAAAAAATAAAACTAGACAAAAATTTG
AACAGATGAAAGAGAAACTCTAAATAATCATTACACATGAGAAACTCAATCTCAGAAATCAGAGAACTATCATTGCATATACACTAAATTAGAGAAATATTAAAAGGC
TAAGTAACATCTGTGGCTTAATTAATCTAGTGATCAGCAGTTCAACCTGTTGATAGTATGTACTAAGCTCTCATGTTTAATGTACTAAGCTCTCATGTTTAATGAACTAA
ACCCTCATGGCTAATGTACTAAGCTCTCATGGCTAATGTACTAAGCTCTCATGTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTA
AATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAAAAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTTATCCTCATATGAGCTCTTAGAAAAACTCAT
CCAGCATCAAATGAAACTGCAATTTATTCATATCAGGATTATCAATACCATATTTTTGAAAAAGTCTTTTCTGTAATGAAGGAGAAAACTCACCCAGGCAGTTCCATAG
GATGGCAAGATCCTGGTATCTGTCTGCAATTCCAACTCTTCCAACATCAATACAACCTATTAATTTCCCCTCATCAAAAATAAGGTTATCAAGTGAGAAATCACCATGA
GTGACCACTGAATCTGGTGAGAATGGCAAAAGATTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTTCTCTCATCATCAAAATCACTGGCATCAACCAAAC
CATTATTCATTCTTGATTGGGCCTGAGCCAGTCTAAATACTCTATCAGAGTTAAAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGG
CATCAACAATATTTTCACCTGAATCAGGATATTCTTCCAATACCTGGAATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAA
ATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCT
GGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCT
TGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图67

122014 # 235: βGlo-RINhe-ΔmCMVΔEF1I126-BstEII-**soLux**-BglII-IFN S/MAR-MixpA/BV2 : EF1-Luc
(SEQ ID NO:47)

CACTATGTGTTAATTAAAATTATCTCTAAGGCATGTGAACTGGCTGTCTTGGTTTTCATCTGTACTTCATCTGCTACCTCTGTGACCTGAAACATATTTATAATTCCATTA
AGCTGTGCATATGATAGATTTATCATATGTATTTTCCTTAAAGGATTTTTGTAAGAACTAATTGAATTGATACCTGTAAAGTCTTTATCACACTACCCAATAAATAATAA
ATCTCTTTGTTCAGCTCTCTGTTTCTATAAATATGTACCAGTTTTATTGTTTTTAGTGGTAGTGATTTTATTCTCTTTCTATATATATACACACACATGTGTGCATTCATAA
ATATATACAATTTTTATGAATAAAAAATTATTAGCAATCAATATTGAAAACCACTGATTTTTGTTTATGTGAGCAAACAGCAGATTAAAAGGAATTTCAATTGCCTGCA
GGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACATAAGGT
CAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATGGGAGGTAA
GCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAGGAAAGTCC
CATTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATTGGCACATA
CATAAGGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGGG
AGGGGTGGGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAAC
CATATATAAGTGCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGgtaagtcactgactgtctatgcctgggaaagggtgggcaggagatggggcagtgcag
gaaaagtggcactatgaacccTGCAGCCCTAGAcaattgtactaaccttcttctctttcctctcctgacagGTTGGTAACCAAGCTTTCCATGGAGGATGCTAAGAACATCAAGAAGGGGCC
TGCCCCCTTCTACCCCCTGGAGGATGGCACAGCTGGGGAGCAGCTGCACAAGGCTATGAAGAGATATGCCCTGGTGCCTGGCACTATTGCCTTCACAGATGCTCACA
TTGAAGTGGACATCACCTATGCTGAGTACTTTGAGATGTCAGTGAGGCTGGCTGAGGCTATGAAAAGATATGGGCTGAACACTAATCACAGGATTGTGGTGTGTTCA
GAGAACTCACTGCAGTTCTTCATGCCTGTGCTGGGAGCCCTGTTCATTGGAGTGGCTGTGGCCCCTGCTAATGACATCTACAATGAGAGGGAGCTGCTGAACTCTATG
GGCATCAGTCAGCCTACAGTGGTGTTTGTGTCTAAGAAGGGCCTGCAGAAAATCCTGAATGTGCAGAAGAAGCTGCCTATCATTCAGAAAATCATCATCATGGACTC
TAAGACAGACTATCAGGGCTTTCAGTCTATGTACACCTTTGTGACTAGTCACCTGCCCCCTGGCTTCAATGAGTATGACTTTGTGCCTGAGTCATTTGACAGGGACAAG
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TGCTGATGTACAGATTTGAGGAGGAGCTGTTCCTGAGATCACTGCAGGACTACAAAATTCAGTCAGCCCTGCTGGTGCCTACCCTGTTCAGCTTCTTTGCTAAGTCTAC
CCTGATTGACAAGTATGACCTGTCTAACCTGCATGAGATTGCCTCAGGGGGAGCCCCCCTGTCTAAGGAAGTGGGGGAAGCTGTGGCTAAGAGATTTCACCTGCCTG
GCATCAGGCAGGGCTATGGCCTGACAGAGACTACCTCAGCTATTCTGATCACCCCTGAGGGGGATGACAAGCCTGGGGCTGTGGGCAAAGTGGTGCCTTTCTTTGA
GGCTAAAGTGGTGGACCTGGACACAGGCAAGACCCTGGGAGTGAATCAGAGGGGGGAGCTGTGTGTGAGAGGCCCTATGATCATGTCAGGCTATGTGAACAACCC
TGAGGCTACTAATGCCCTGATTGATAAGGATGGCTGGCTGCACTCAGGGGACATTGCCTACTGGGATGAGGATGAGCACTTCTTCATTGTGGACAGGCTGAAGTCAC
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CAGGGGGGGAGTGGTCTTTGTGGATGAAGTGCCTAAGGGCCTCACAGGCAAGTTAGATGCTAGGAAGATCAGGGAGATCCTCATCAAGGCTAAGAAGGGGGGCA
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GTTCACCCCAAAAAAGCTGTTTGTTAACTTGTCAACCTCATTCTAAAATGTATATAGAAGCCCAAAAGACAATAACAAAAATATTCTTGTAGAACAAAATGGGAAAGA
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ATCACTGGCATCAACCAAACCATTATTCATTCTTGATTGGGCCTGAGCCAGTCTAAATACTCTATCAGAGTTAAAAGGACAATTACAAACAGGAATGGAATGCAATCT
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ATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACAGAACCTTT
GCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAG
CATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACT
ATGCCAATGTTTAATTGTCAG

图68

DNARx-PD1-2A

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- ΔPD1-H-F3(RKRR)-P2A-ΔPD1-L-BglII-MixpA-BV2
(SEQ ID NO:48)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
CATAAGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATG
GGAGGTAAGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAG
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GAGTTAAAAGGACAATTACAAACAGGAATGGAATGCAATCTTCTCAGGAACACTGCCAGGGCATCAACAATATTTTCACCTGAATCAGGATATTCTTC**C**AATACCTGG
AATGCTGTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAG
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TGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGT
GCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCA**G**

图69

DNARx-SEC-OVA-MITD

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- SEC-OVA-MITD-BglII-MixpA-BV2
(SEQ ID NO:49)

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTA
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ATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图70

DNARx-SEC-gp70-MITD

DraIIRINhe-ΔmCMVΔEF1I126-BstEII- SEC-gp70-MITD-BglII-MixpA-BV2
(SEQ ID NO:50)

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图71

DNARx-PDl-2A-OVA: 双盒抗PD1-2A和抗OVA

DraIIRINhe-ΔmCMV-EF1-I126BstEII-ΔPD1-H-2A-ΔPD1-LBglIIpolyA-ΔhCMV-EF1-I126BstEII-SEC-OVA-MITDBglIIpolyA BV2

(SEQ ID NO:51)

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ACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATCTCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGT
TTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAGTTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCA**G**

图72

DNARx-PD1-2A-gp70: 双盒抗PD1-2A和gp70

DraIIRINhe-ΔmCMV-EF1-I126BstEII-ΔPD1-H-2A-ΔPD1-LBglIIpolyA-ΔhCMV-EF1-I126BstEII-SEC-gp70-MITDBglIIpolyA BV2

(SEQ ID NO:52)

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DNARx-CD20-2A CAS9: 双盒抗CD20-2A和CAS9 (SEQ ID NO:53)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔaCD20H-2A-aCD20L-BglII-polyA- ΔhCMV-hFerH-HTLVBstEII-CAS9-BglII-polyA BV2

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DNARx-CD20-2A HG-CSF: 双盒抗CD20-2A和HG-CSF (SEQ ID NO:54)

DraIIRINhe- ΔmCMV-EF1-I126-BstEII-ΔaCD20H-2A-aCD20L-BglII-polyA- ΔhCMV-hFerH-HTLVBstEII-HG-CSF-BglII-polyA BV2

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图75

p65 shA2: NheΔhCMVΔhCMVRVp65 shA2-TTTTT-XbaI-HindIII-Amp
(SEQ ID NO:55)

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图76

PECAM sh 对照 ： NheΔhCMVΔhCMVRVD3PECAM sh-TTTTT-XbaI-HindIII-Amp
(SEQ ID NO:56)

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图77

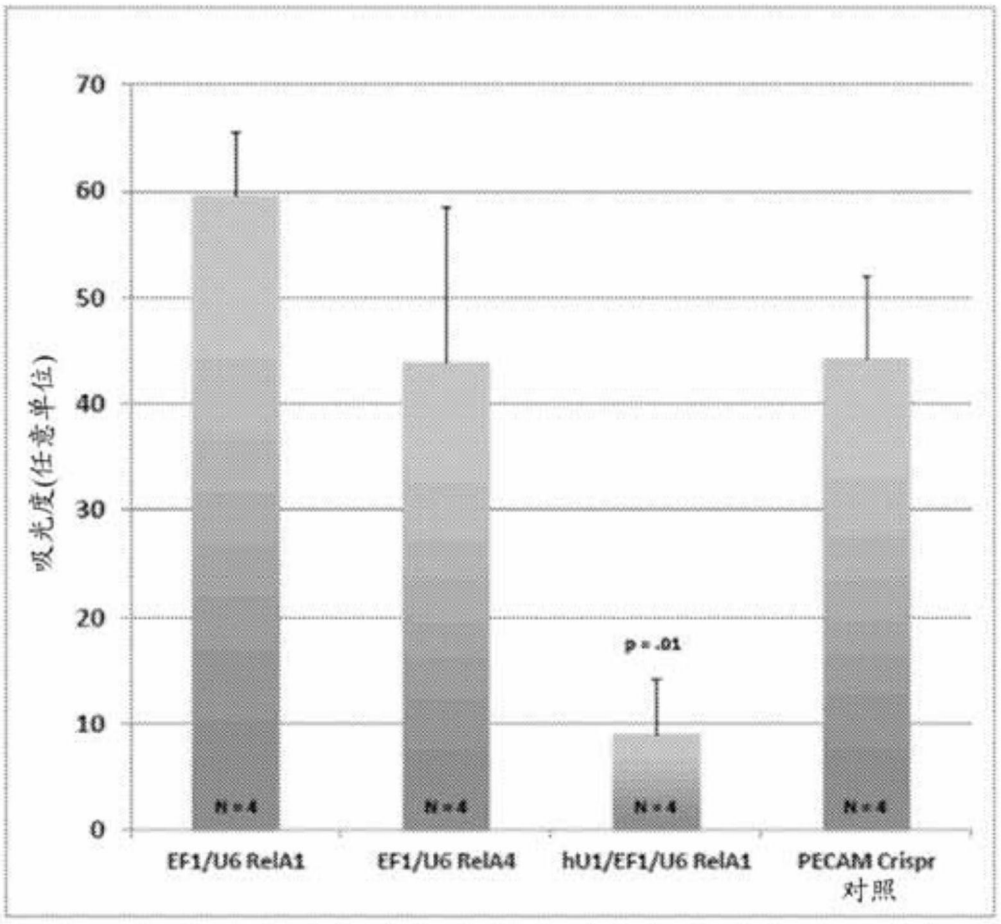

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EF1/U6 RelA4
hU1/EF1/U6 RelA1
PECAM Crispr
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图78

020117 # 5 : RlNhe-ΔmCMVΔEFl126-BstEII-spCas9-BglII-MixpA-U6- rel 1-gRNA 支架 -TTTTTT- 额外碱基 -BV2 (SEQ ID NO:57)

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图79

020117 # 8 : RINhe-ΔmCMVΔEFI126-BstEII-spCas9-BglII-MixpA-U6- rel 4-gRNA 支架 -TTTTTT- 额外碱基 -BV2 (SEQ ID NO:58)

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图80

021417 # 3 : RINhe- U1-rel 1-gRNA 支架 -BglII-3'Box -ΔmCMVΔEFI126-BstEII-spCas9-BglII-MixpA-U6- rel 1-gRNA 支架 -TTTTTT- 额外碱基 -BV2(三盒) (SEQ ID NO:59)

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图81

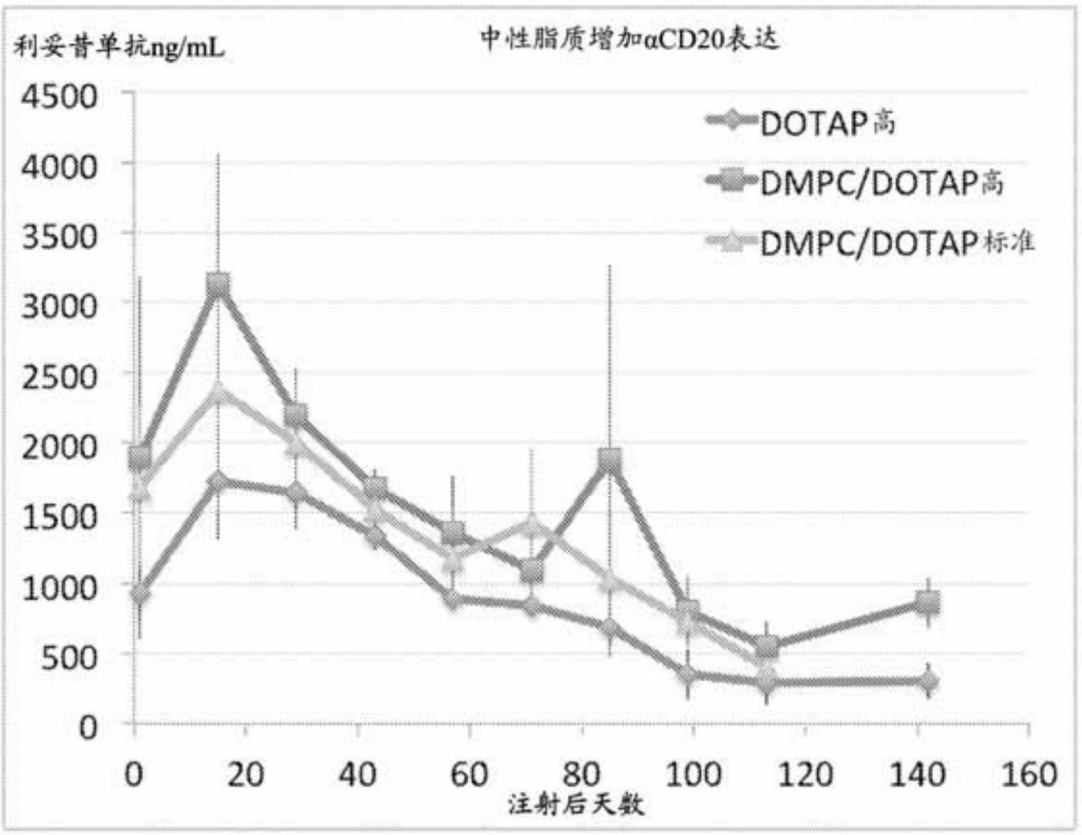

利妥昔单抗ng/mL
中性脂质增加αCD20表达
DOTAP高
DMPC/DOTAP高
DMPC/DOTAP标准
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
160
注射后天数

图82

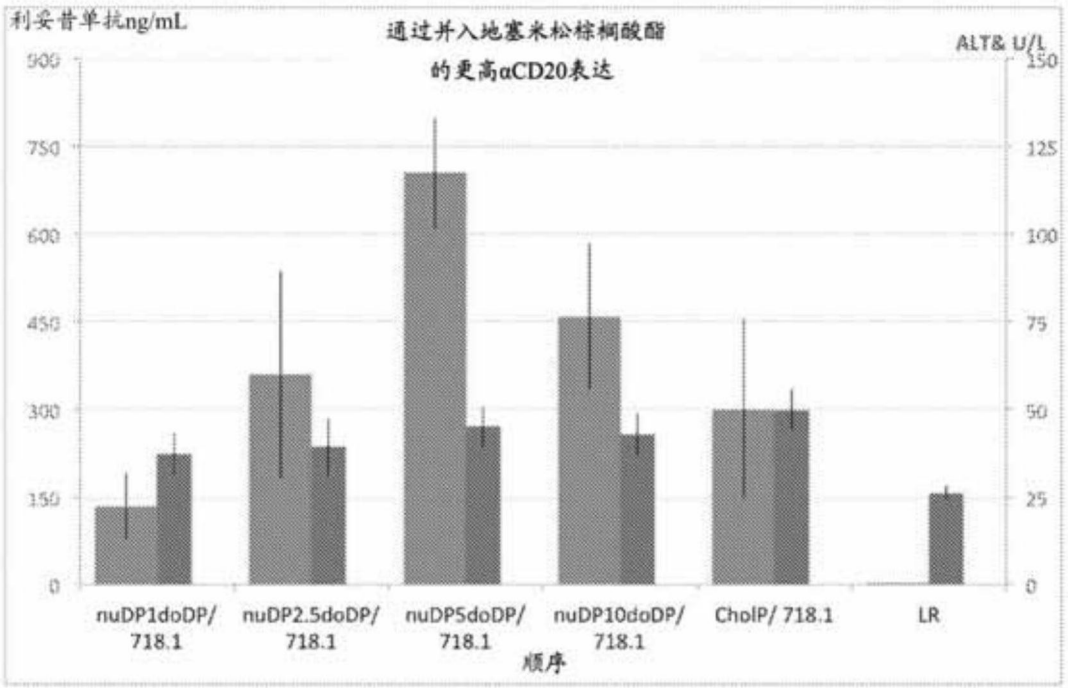

利妥昔单抗ng/mL
通过并入地塞米松棕榈酸酯
的更高αCD20表达
ALT& U/L
900
750
600
450
300
150
0
150
125
100
75
50
25
0
nuDP1doDP/ 718.1
nuDP2.5doDP/ 718.1
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CholP/ 718.1
LR
顺序

图83

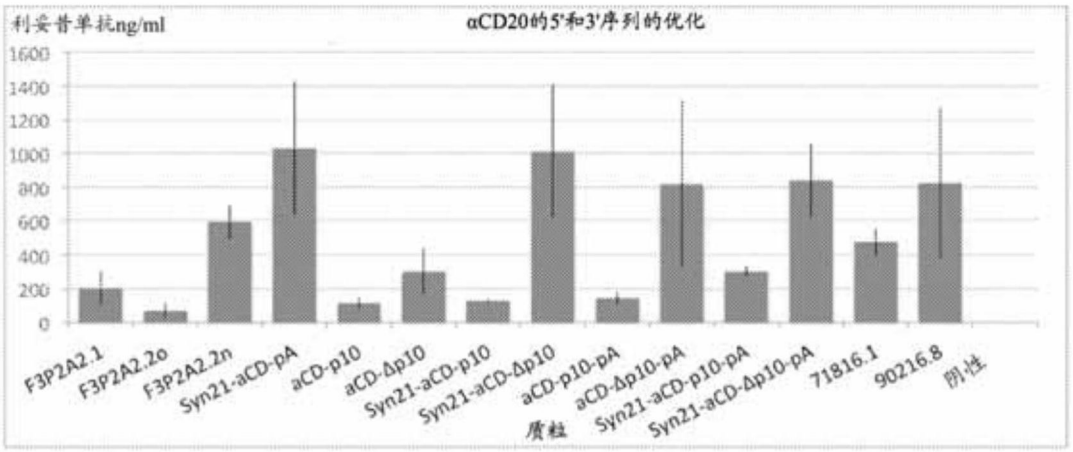

利妥昔单抗ng/ml
αCD20的5'和3'序列的优化
1600
1400
1200
1000
800
600
400
200
0
F3P2A2.1
F3P2A2.2o
F3P2A2.2n
Syn21-aCD-pA
aCD-p10
aCD-Δp10
Syn21-aCD-p10
Syn21-aCD-Δp10
aCD-p10-pA
aCD-Δp10-pA
Syn21-aCD-p10-pA
Syn21-aCD-Δp10-pA
71816.1
90216.8
阴性
质粒

图84

062817 # 8: DraIIRINhe-ΔmCMVΔEF1I126-BstEII-**syn21**-ΔaCD20-H-***F3(RKRR)-P2A-2***-ΔaCD20-L-BglII-**Δp10**-pA/BV2 **(SEQ ID NO:82)**

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图85

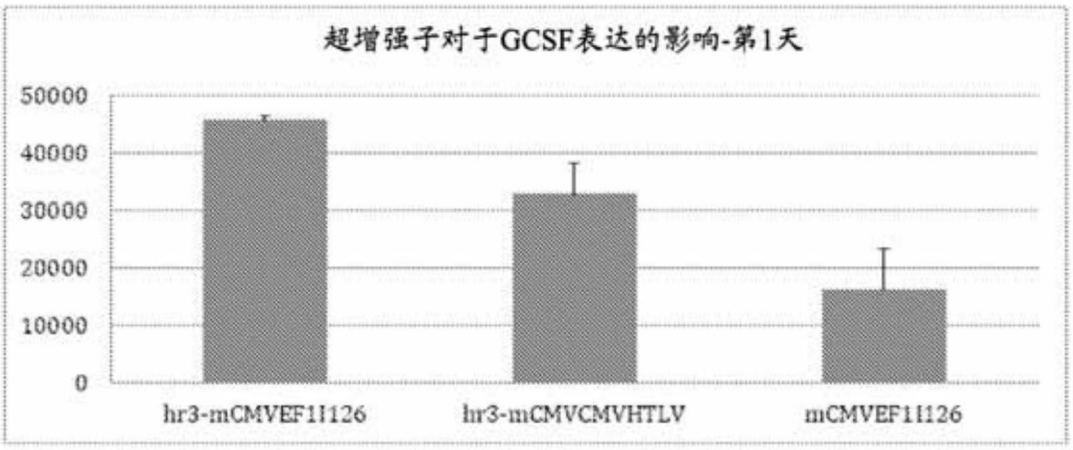

超增强子对于GCSF表达的影响-第1天
50000
40000
30000
20000
10000
0
hr3-mCMVEF1I126
hr3-mCMVCMVHTLV
mCMVEF1I126

图86A

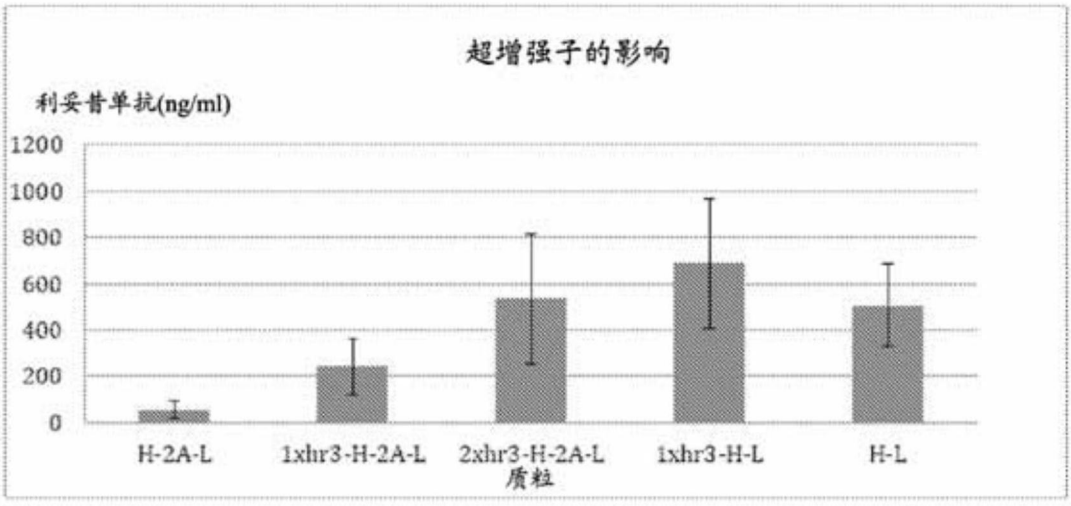

超增强子的影响
利妥昔单抗(ng/ml)
1200
1000
800
600
400
200
0
H-2A-L
1xhr3-H-2A-L
2xhr3-H-2A-L
1xhr3-H-L
H-L
质粒

图86B

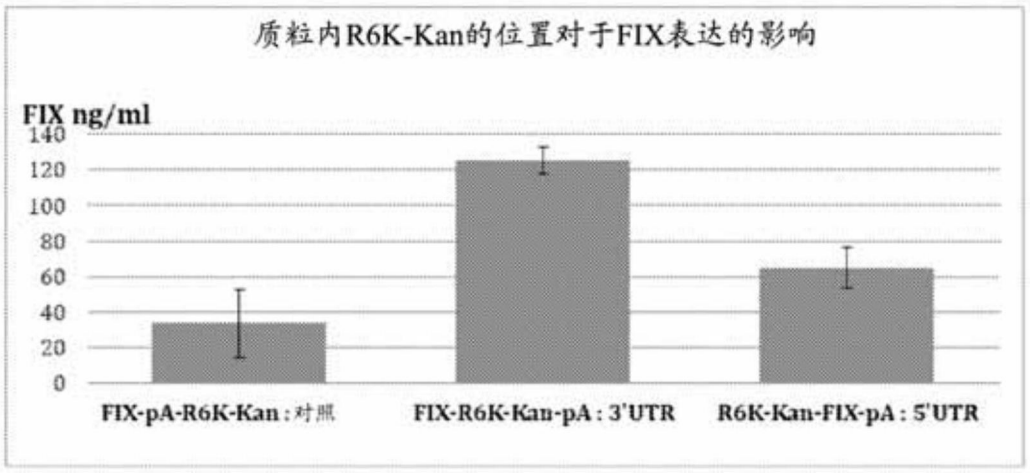

质粒内R6K-Kan的位置对于FIX表达的影响
FIX ng/ml
140
120
100
80
60
40
20
0
FIX-pA-R6K-Kan：对照
FIX-R6K-Kan-pA：3'UTR
R6K-Kan-FIX-pA：5'UTR

图87A

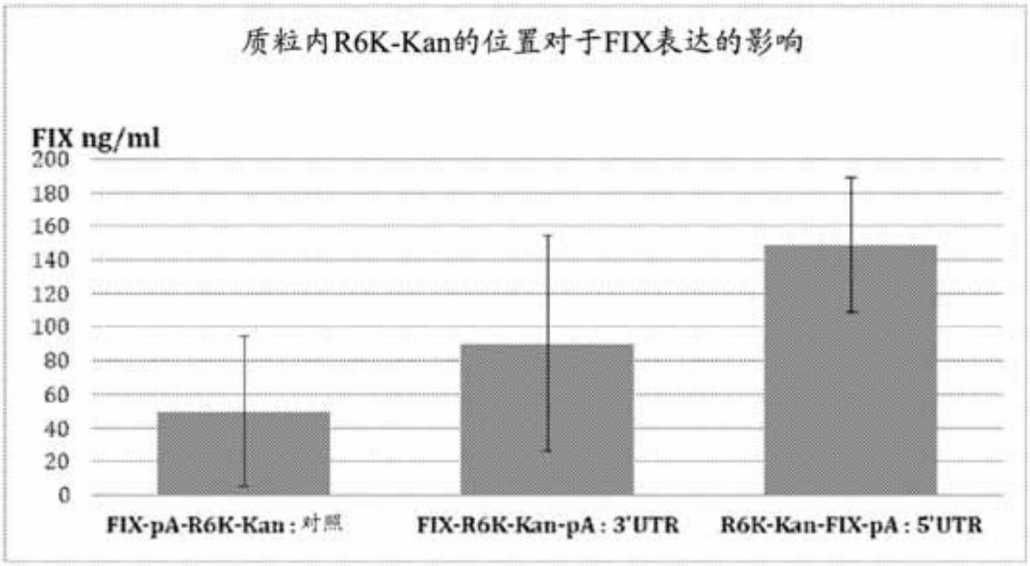

质粒内R6K-Kan的位置对于FIX表达的影响
FIX ng/ml
200
180
160
140
120
100
80
60
40
20
0
FIX-pA-R6K-Kan：对照
FIX-R6K-Kan-pA：3'UTR
R6K-Kan-FIX-pA：5'UTR

图87B

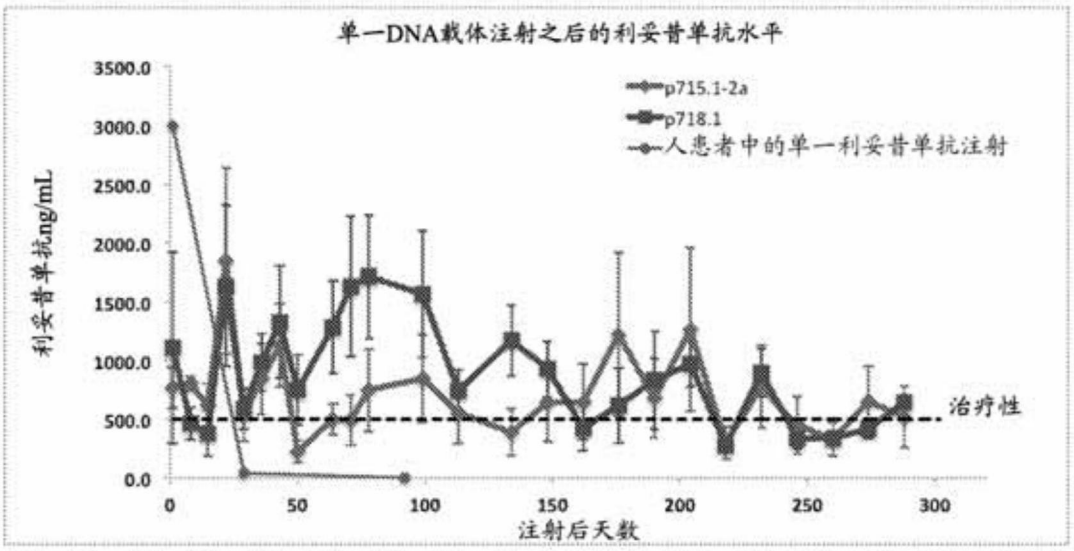


图88A

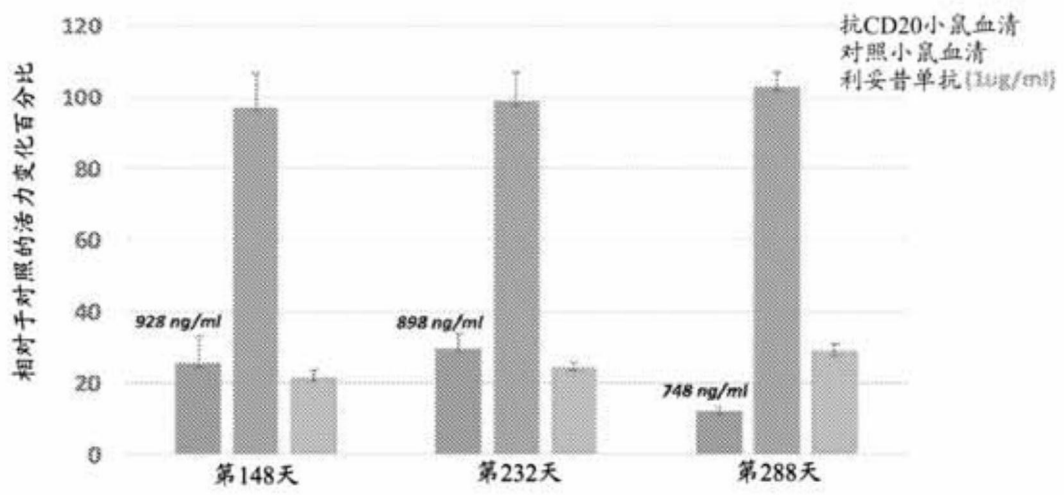


图88B

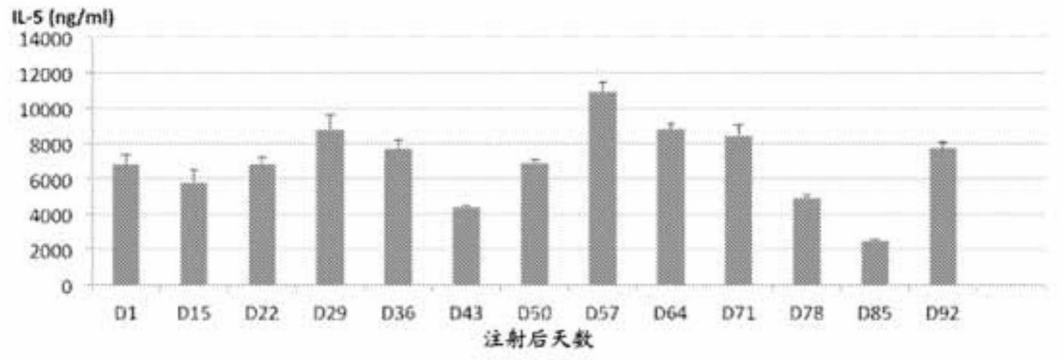


图89

双 NewM H-L -BV3

DraIII-**βGlo RI**-Nhe-ΔmCMVΔEF1-I126-BstEII -**NewM 2B6-H-hIgG**-BglII-MixpA-**21q21 S/MAR**-**ΔhCMV**-ΔEF1-RV-I126-BstEII-**GA-NewM 2B6-L-hIgK**-BglII-MixpA-**IFNβ S/MAR**-BV3 **(SEQ ID NO:83)**

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图90

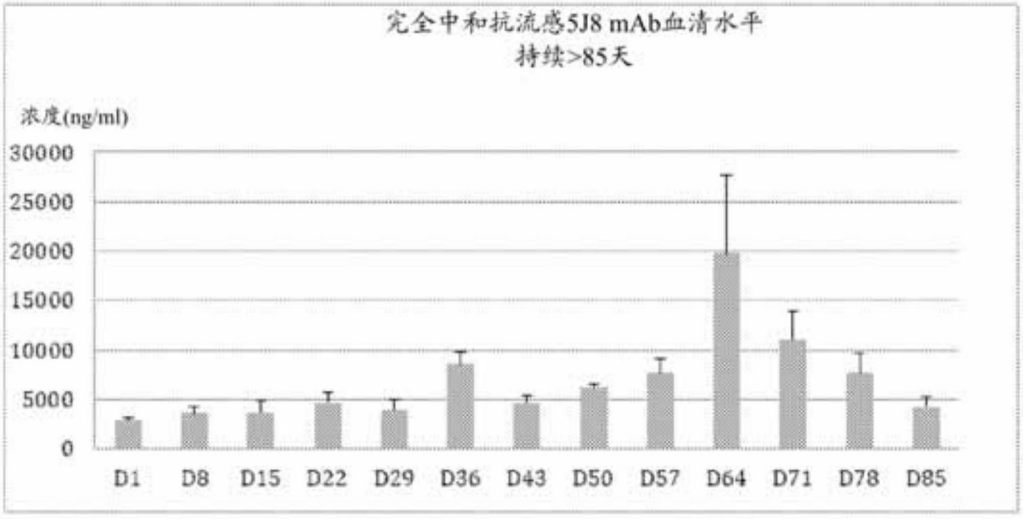

完全中和抗流感5J8 mAb血清水平
持续>85天
浓度(ng/ml)
30000
25000
20000
15000
10000
5000
0
D1
D8
D15
D22
D29
D36
D43
D50
D57
D64
D71
D78
D85

图91A

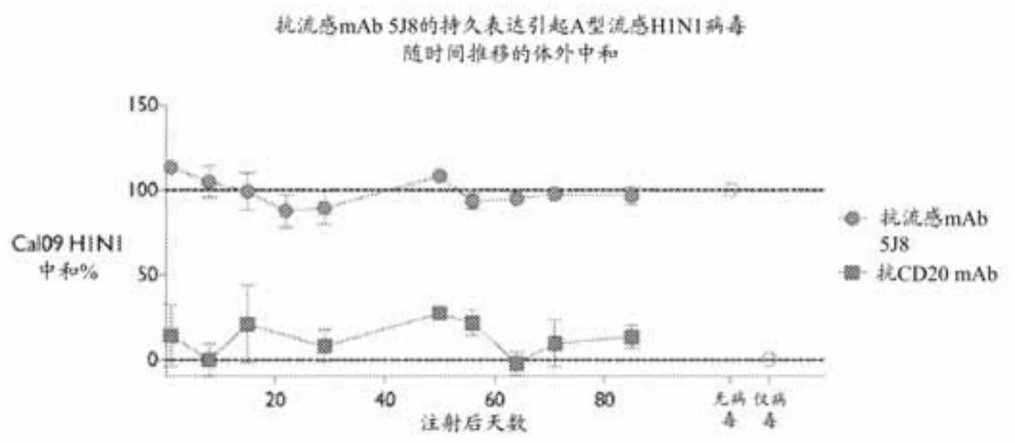

抗流感mAb 5J8的持久表达引起A型流感H1N1病毒
随时间推移的体外中和
Cal09 H1N1
中和%
150
100
50
0
20
40
60
80
注射后天数
无病毒
仅病毒
抗流感mAb 5J8
抗CD20 mAb

图91B

双 5J8 H-L -BV3

DraIII-βGlo RI-Nhe-ΔmCMVΔEF1-I126-BstEII-5J8H-hIgG-BglII-MixpA-21q21 S/MAR-ΔhCMV-ΔEF1-RV-I126-BstEII-5J8L-hIgL-BglII-MixpA-IFNβ S/MAR-BV3 (SEQ ID NO:84)

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图92

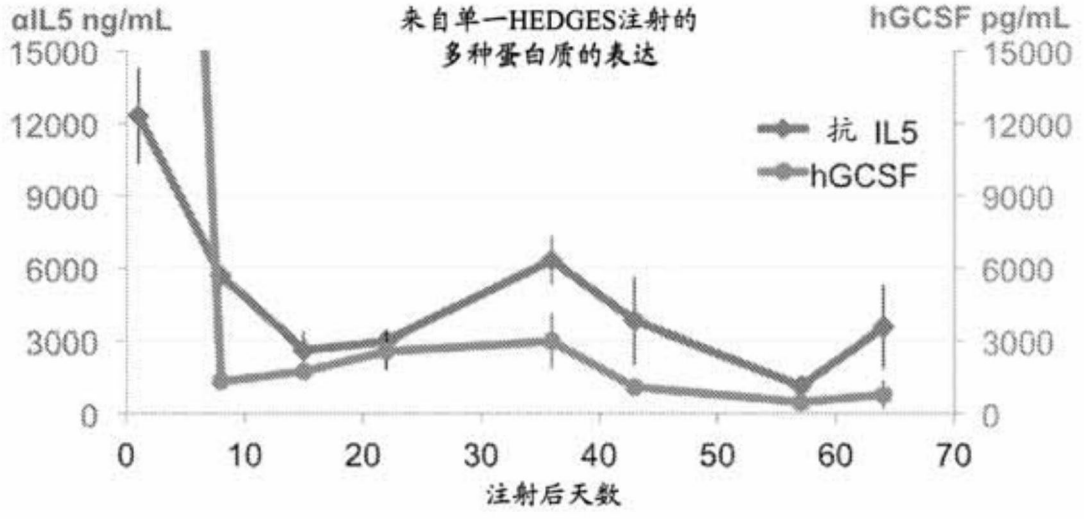

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来自单一HEDGES注射的
多种蛋白质的表达
hGCSF pg/mL
15000
12000
9000
6000
3000
0
抗 IL5
hGCSF
0
10
20
30
40
50
60
70
注射后天数

图93

101217 # 6 : NewM-G-BV3 DraIII-**βGlo RI**-NheI-ΔmCMVΔEF1I126-BstEII-**NewM 2B6-H-*F3P2A*-L**-BglII-MixpA-**21q21 S/MAR**-ΔmCMV -ΔEF1I126-BstEII-**ΔhGCSF**-BglII-MixpA-**IFNβ S/MAR**-BV3 **(SEQ ID NO:85)**

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图94

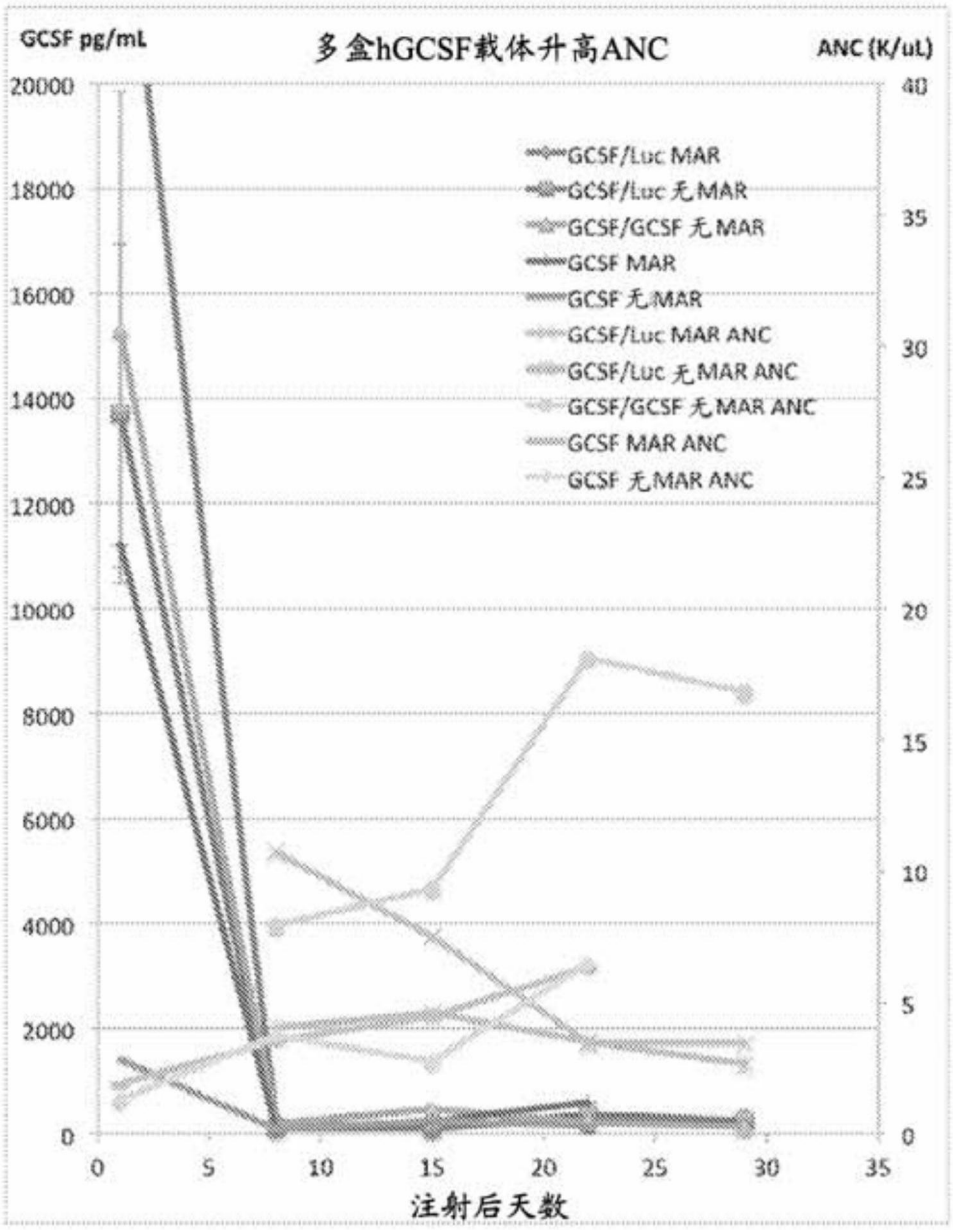

GCSF pg/mL
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ANC (K/uL)
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16000
14000
12000
10000
8000
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35
30
25
20
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10
5
0
0
5
10
15
20
25
30
35
注射后天数
GCSF/Luc MAR
GCSF/Luc 无MAR
GCSF/GCSF 无MAR
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图95

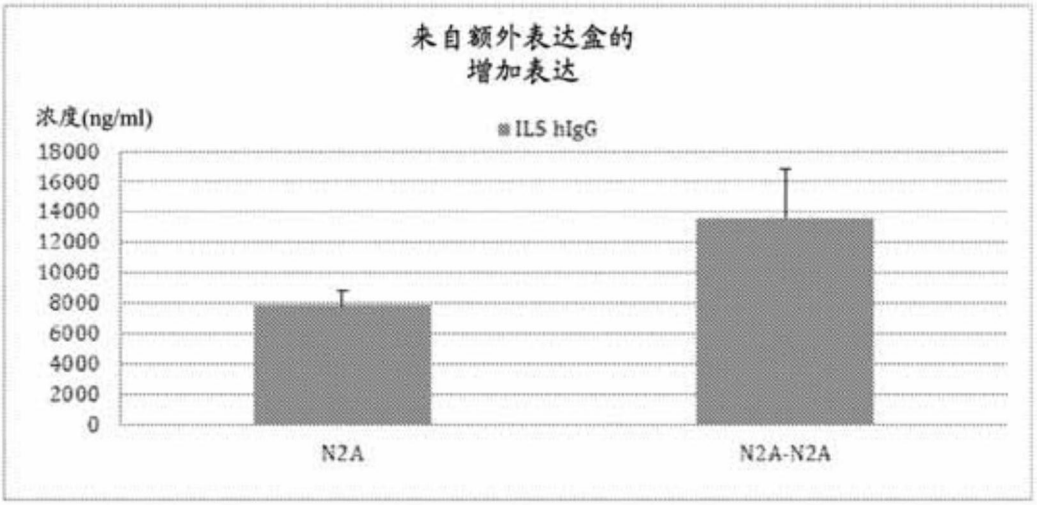

来自额外表达盒的
增加表达
浓度(ng/ml)
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16000
14000
12000
10000
8000
6000
4000
2000
0
N2A
N2A-N2A

图96

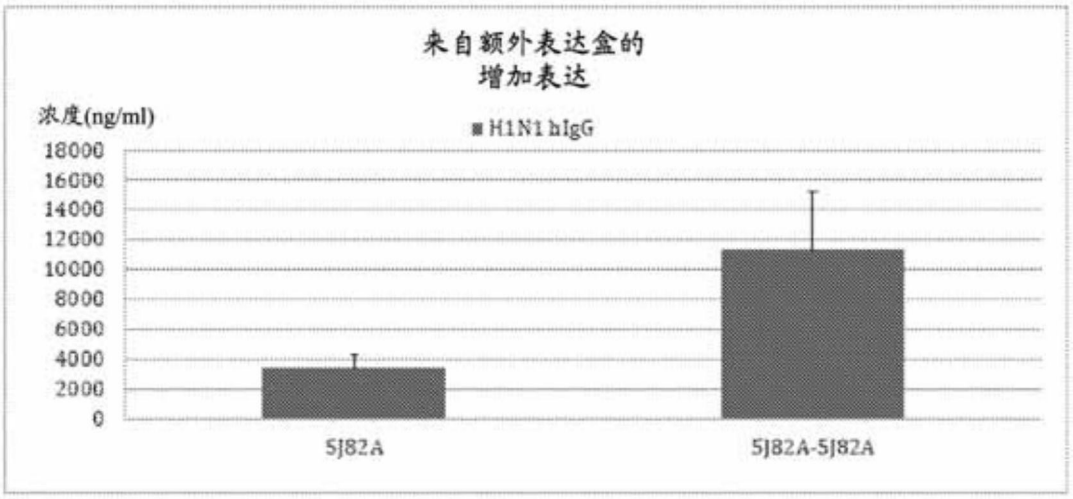

来自额外表达盒的
增加表达
浓度(ng/ml)
H1N1 hIgG
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14000
12000
10000
8000
6000
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2000
0
5J82A
5J82A-5J82A

图97

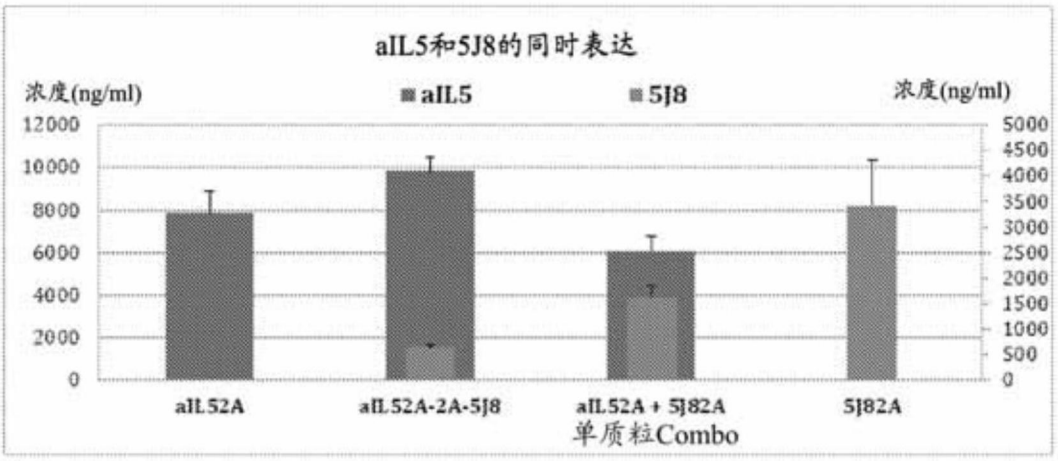


图98

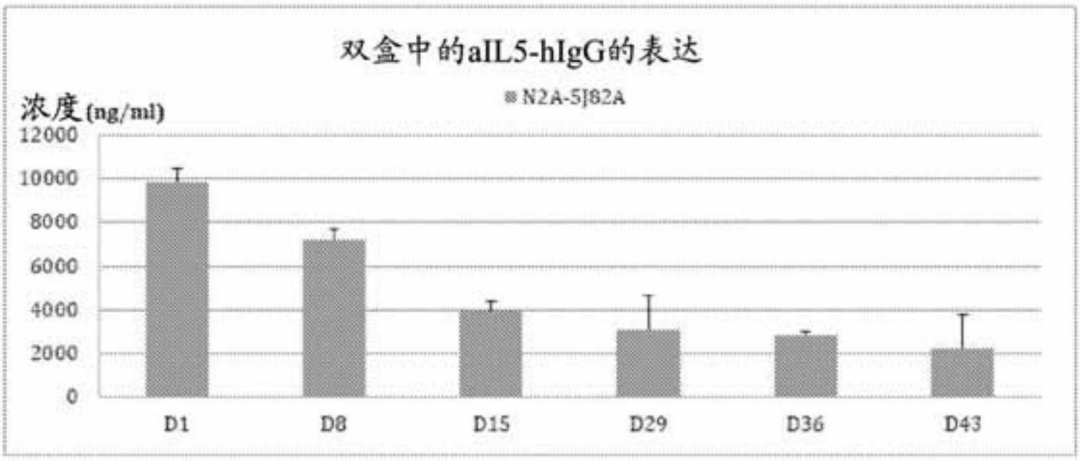


图99A

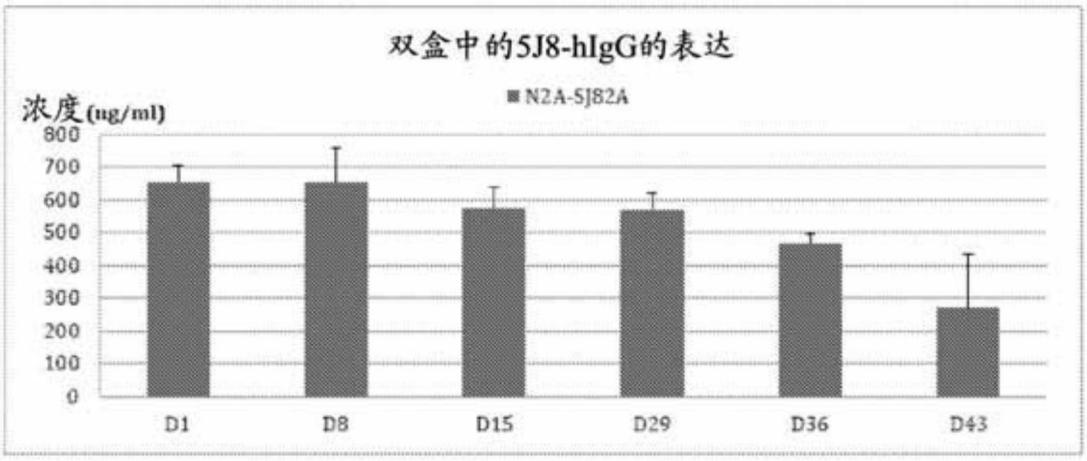


图99B

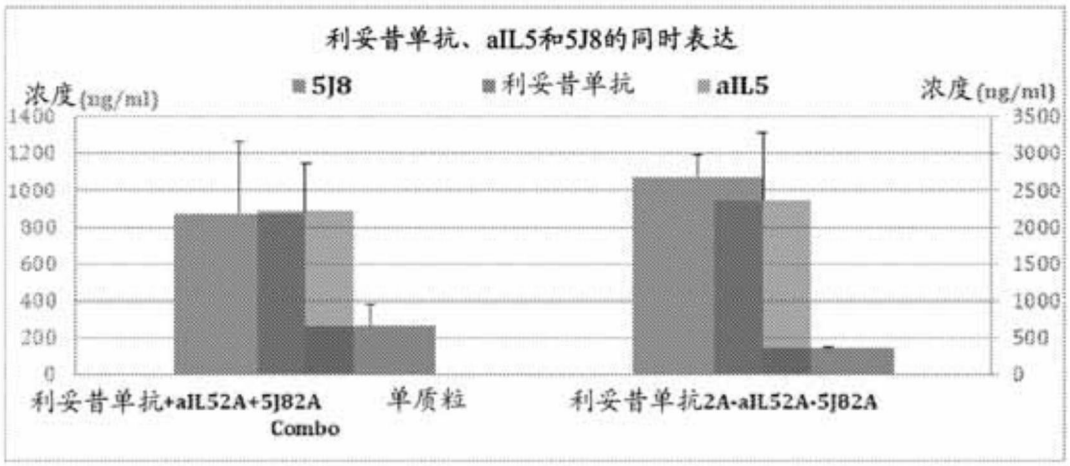

利妥昔单抗、aIL5和5J8的同时表达
浓度(ng/ml)
5J8
利妥昔单抗
aIL5
浓度(ng/ml)
1400
1200
1000
800
600
400
200
0
3500
3000
2500
2000
1500
1000
500
0
利妥昔单抗+aIL52A+5J82A Combo
单质粒
利妥昔单抗2A-aIL52A-5J82A

图100

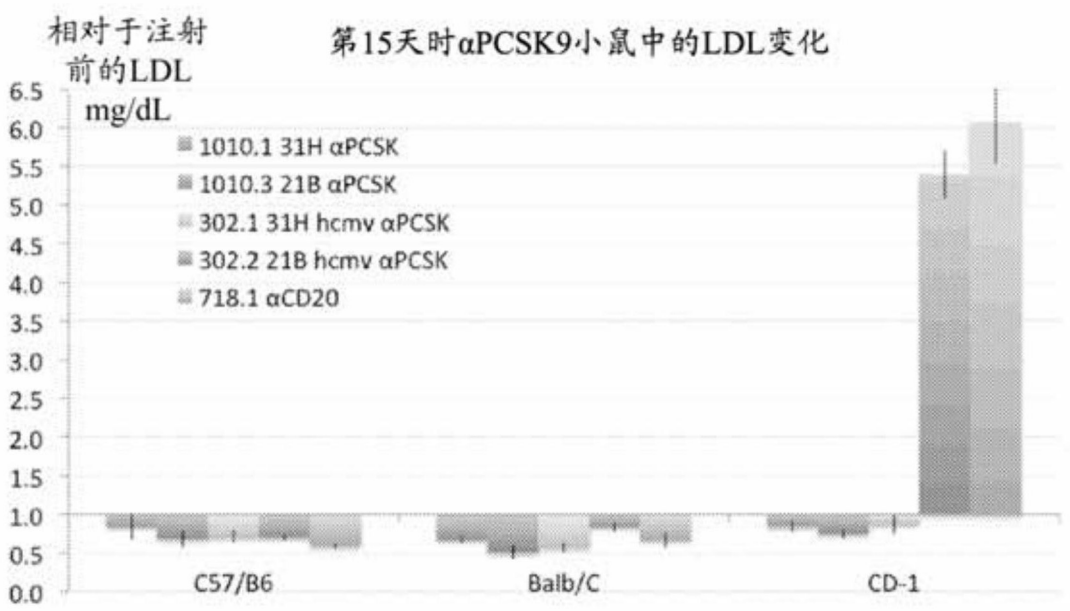

相对于注射前的LDL mg/dL
第15天时αPCSK9小鼠中的LDL变化
1010.1 31H αPCSK
1010.3 21B αPCSK
302.1 31H hcmv αPCSK
302.2 21B hcmv αPCSK
718.1 αCD20
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
C57/B6
Balb/C
CD-1

图101

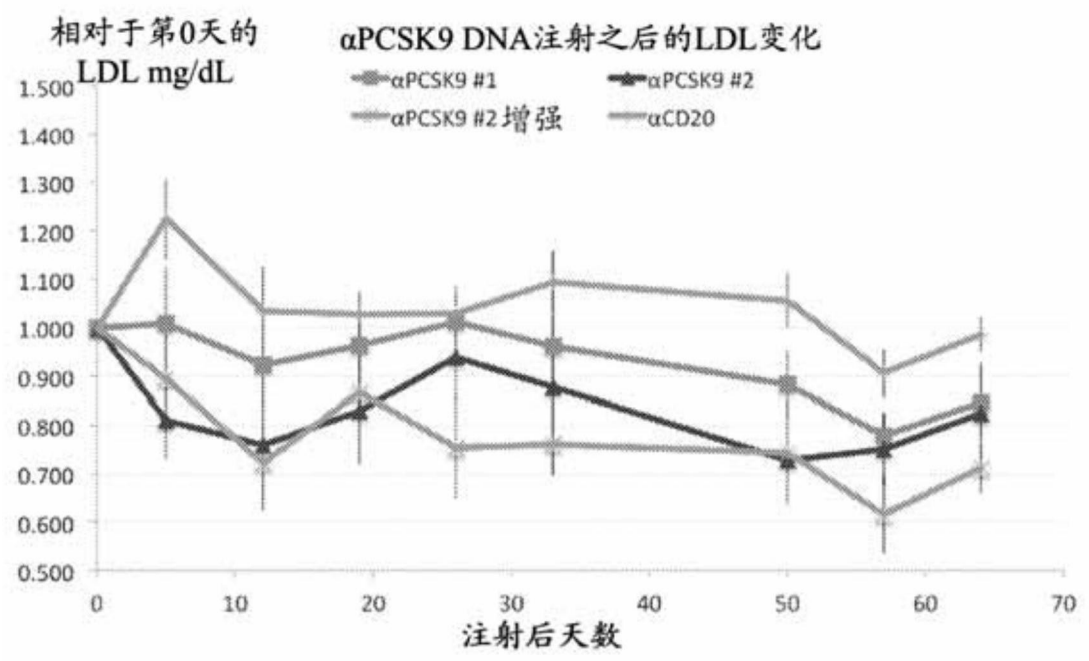

相对于第0天的
LDL mg/dL
αPCSK9 DNA注射之后的LDL变化
αPCSK9 #1
αPCSK9 #2
αPCSK9 #2增强
αCD20
1.500
1.400
1.300
1.200
1.100
1.000
0.900
0.800
0.700
0.600
0.500
0
10
20
30
40
50
60
70
注射后天数

图102

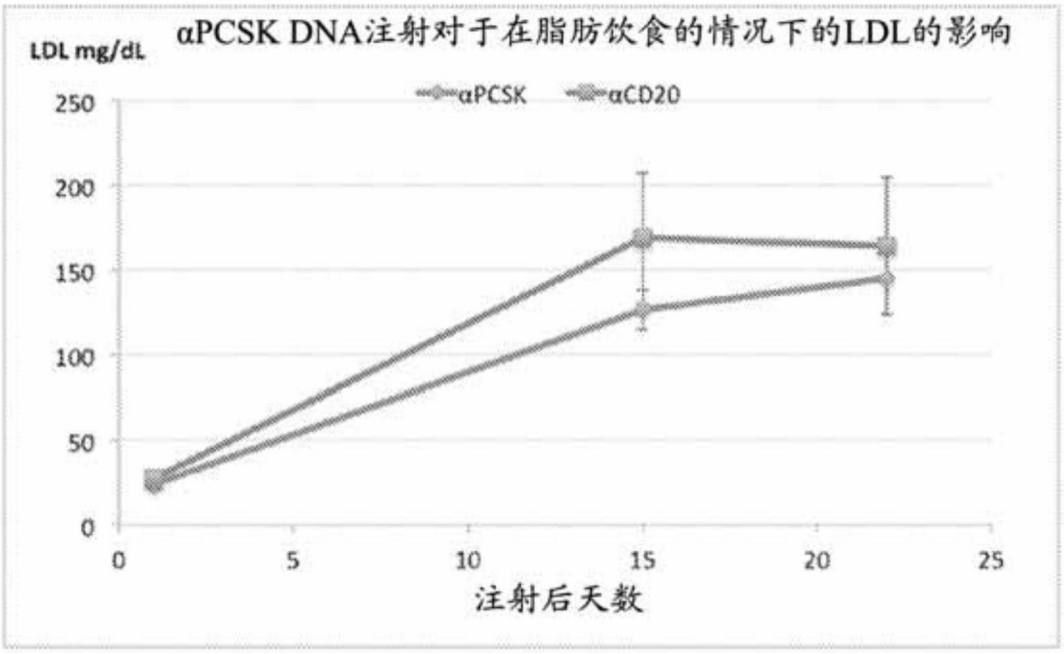

LDL mg/dL
αPCSK DNA注射对于在脂肪饮食的情况下的LDL的影响
αPCSK
αCD20
250
200
150
100
50
0
0
5
10
15
20
25
注射后天数

图103

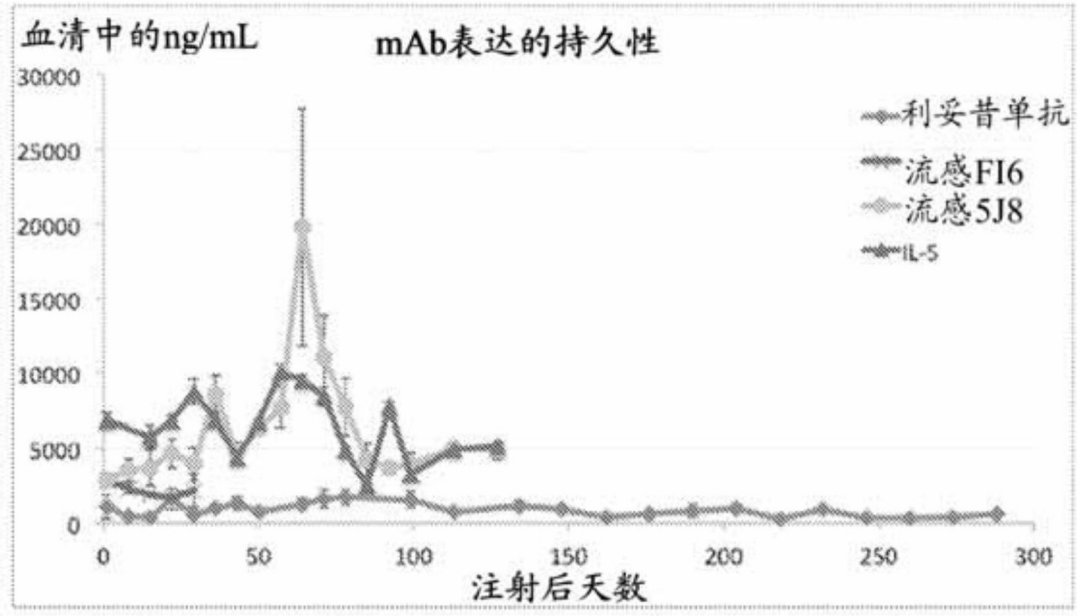

血清中的ng/mL
mAb表达的持久性
30000
25000
20000
15000
10000
5000
0
0
50
100
150
200
250
300
注射后天数
利妥昔单抗
流感FI6
流感5J8
IL-5

图104

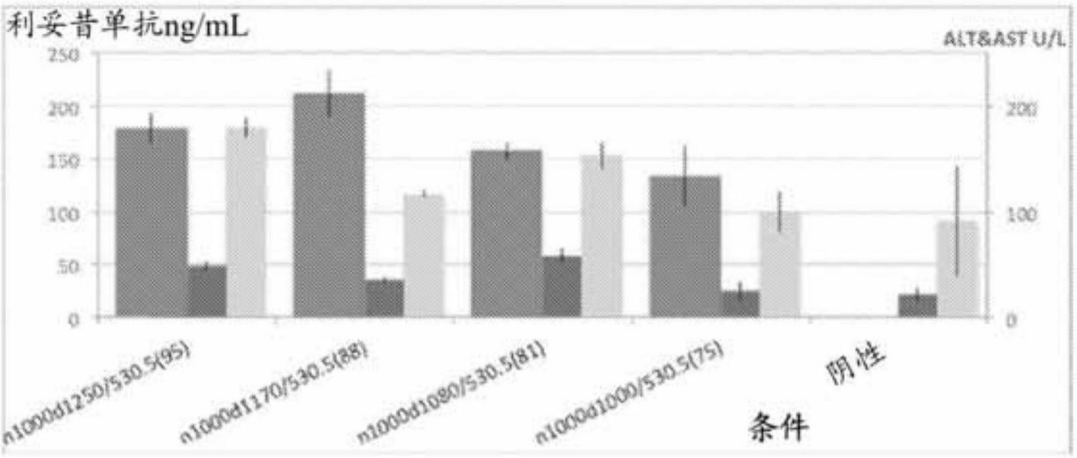

利妥昔单抗ng/mL
ALT&AST U/L
250
200
150
100
50
0
200
100
0
n1000d1250/530.5(95)
n1000d1170/530.5(88)
n1000d1080/530.5(81)
n1000d1000/530.5(75)
阴性
条件

图105

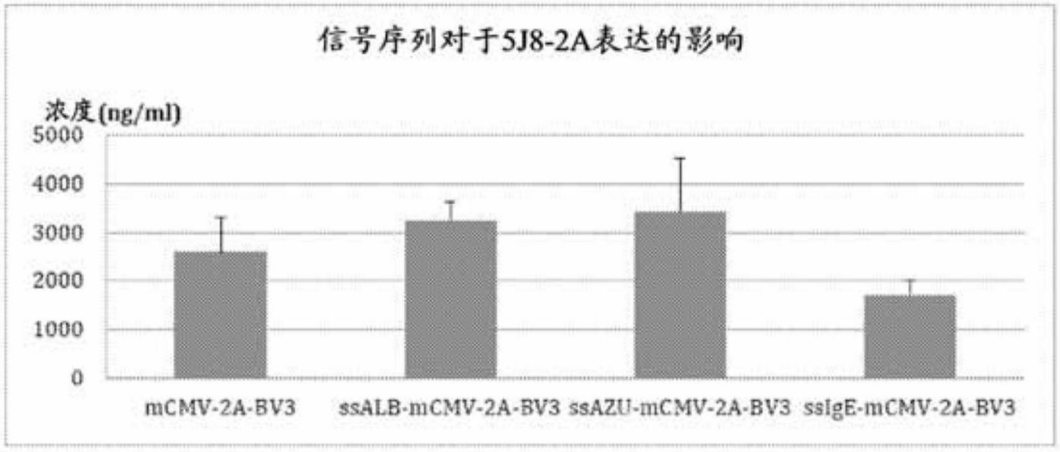

信号序列对于5J8-2A表达的影响
浓度(ng/ml)
5000
4000
3000
2000
1000
0
mCMV-2A-BV3
ssALB-mCMV-2A-BV3
ssAZU-mCMV-2A-BV3
ssIgE-mCMV-2A-BV3

图106

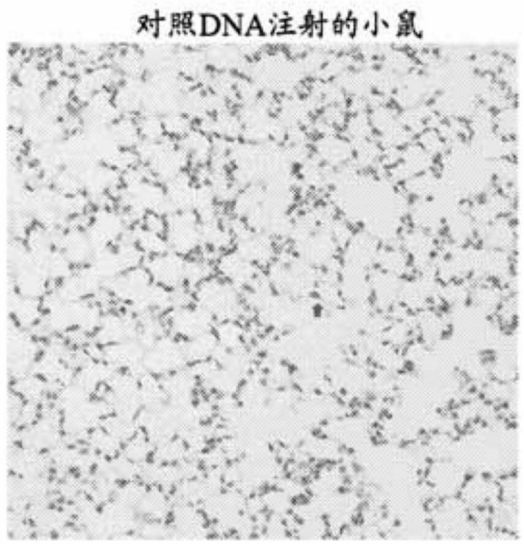

对照DNA注射的小鼠

图107A

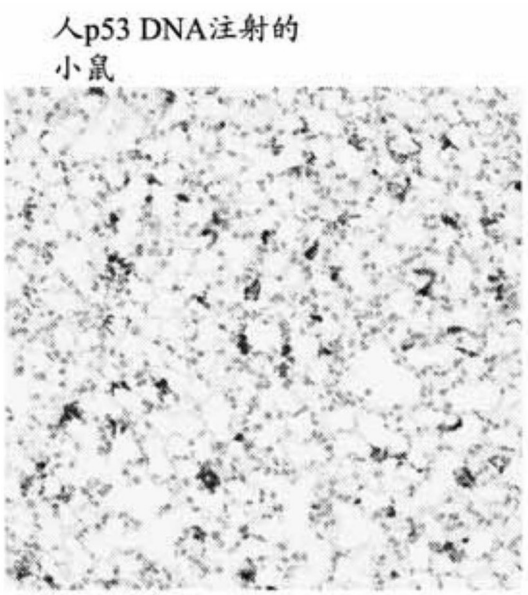


图107B

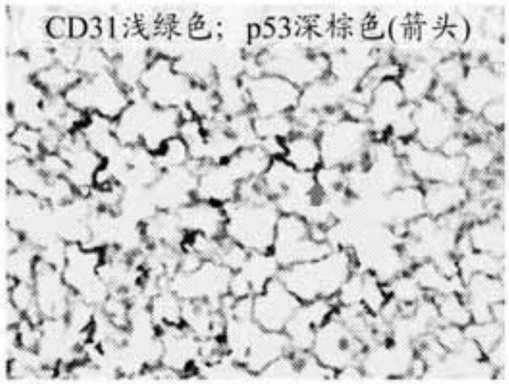


图107C

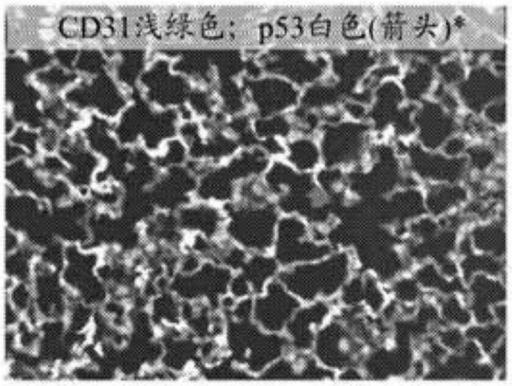


图107D

p53: RINhe-ΔmCMVΔEF1I126-BstEII-p53-BglII-MixpA/BV2 **(SEQ ID NO:86)**

CACTATGTGGACATGAATTCAATTGGCTAGCAGGAGTCAATGGGAAAAACCCATTGGAGCCAAGTACACTGACTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACATA
AGGTCAATAGGGGGTGAGTCAACAGGAAAGTCCCATTGGAGCCAAGTACATTGAGTCAATAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATGGGAGGTA
AGCCAATGGGTTTTTCCCATTACTGACATGTATACTGAGTCATTAGGGACTTTCCAATGGGTTTTGCCCAGTACATAAGGTCAATAGGGGTGAATCAACAGGAAAGTCCCA
TTGGAGCCAAGTACACTGAGTCAATAGGGACTTTCCATTGGGTTTTGCCCAGTACAAAAGGTCAATAGGGGGTGAGTCAATGGGTTTTTCCCATTATTGGCACATACATAA
GGTCAATAGGGGTGACTAGTGGAGAAGAGCATGCTTGAGGGCTGAGTGCCCCTCAGTGGGCAGAGAGCACATGGCCCACAGTCCCTGAGAAGTTGGGGGGGAGGGGTG
GGCAATTGAACTGGTGCCTAGAGAAGGTGGGGCTTGGGTAAACTGGGAAAGTGATGTGGTGTACTGGCTCCACCTTTTTCCCCAGGGTGGGGGAGAACCATATATAAGT
GCAGTAGTCTCTGTGAACATTCAAGCTTCTGCCTTCTCCCTCCTGTGAGTTTGgtaagtcactgactgtctatgcctgggaaagggtgggcaggagatggggcagtgcaggaaaagtggcactatgaa
cccTGCAGCCCTAGAcaattgtactaaccttcttctctttcctctcctgacagGTTGGTAACCAAGCCACCATGGAAGAACCCCAGTCTGACCCCTCTGTGGAACCTCCTCTGAGCCAAGAG
ACATTCTCTGACCTGTGGAAGCTGCTGCCTGAGAACAATGTGCTGAGCCCTCTGCCTAGCCAGGCCATGGATGATCTGATGCTGTCCCCTGATGACATTGAGCAGTGGTTC
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GCTCTGAACAAGATGTTCTGTCAGCTGGCCAAGACCTGTCCTGTGCAGCTGTGGGTTGACAGCACACCTCCTCCAGGCACAAGAGTCAGAGCCATGGCCATCTACAAGCA
GAGCCAGCACATGACAGAGGTTGTCAGAAGATGCCCTCACCATGAGAGGTGCTCTGATTCTGATGGACTGGCCCCTCCTCAGCACCTGATCAGAGTGGAAGGCAACCTGA
GAGTGGAATACCTGGATGACAGAAACACCTTCAGGCACTCTGTGGTGGTGCCCTATGAGCCTCCTGAAGTGGGCTCTGATTGCACCACCATCCACTACAACTACATGTGCA
ACAGCAGCTGCATGGGAGGCATGAACAGAAGGCCCATCCTGACCATCATCACCCTGGAAGATAGCTCTGGCAACCTGCTGGGCAGAAACAGCTTTGAAGTCAGAGTGTG
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CACCAGCAGCAGCCCTCAGCCTAAGAAAAAGCCCCTGGATGGGGAGTACTTCACACTCCAGATCAGAGGCAGGGAAAGATTTGAGATGTTCAGGGAACTGAATGAGGCC
CTGGAACTGAAGGATGCCCAGGCTGGAAAAGAGCCTGGAGGCAGCAGAGCCCATAGCAGCCACCTGAAGTCTAAGAAGGGCCAGAGCACCAGCAGACACAAGAAACTG
ATGTTCAAGACAGAGGGCCCTGACTCTGACTGAAGATCTACTTCTGGCTAATAAAAGATCAGAGCTCTAGTGATCTGTGTGTTGGTTTTTGTGTCTGCATTCTAGCTCTAG
TGATCAGCAGTTCAACCTGTTGATAGTATGTACTAAGCTCTCATGTTTAATGTACTAAGCTCTCATGTTTAATGAACTAAACCCTCATGGCTAATGTACTAAGCTCTCATGGC
TAATGTACTAAGCTCTCATGTTTCATGTACTAAGCTCTCATGTTTGAACAATAAAATTAATATAAATCAGCAACTTAAATAGCCTCTAAGGTTTTAAGTTTTATAAGAAAAAA
AAGAATATATAAGGCTTTTAAAGGTTTTAAGGTTTCCTAGGTTATCCTCATATGAGCTCTTAGAAAAACTCATCCAGCATCAAATGAAACTGCAATTTATTCATATCAGGATT
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GTTTTCCCTGGGATGGCAGTGGTGAGTAACCATGCATCATCAGGAGTTCTGATAAAATGCTTGATGGTTGGAAGAGGCATAAATTCAGTCAGCCAGTTTAGTCTGACCATC
TCATCTGTAACATCATTGGCAACAGAACCTTTGCCATGTTTCAGAAACAACTCTGGGGCATCTGGCTTCCCATACAATCTATAGATTGTGGCACCTGATTGCCCAACATTATC
TCTAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCTTGGCCTGGAGCAAGAGGTTTCTCTTTGAATATGGCTCATACATGTGCACCTCCTATAGTGAG
TTGTATTATACTATGCAGATATACTATGCCAATGTTTAATTGTCAG

图108

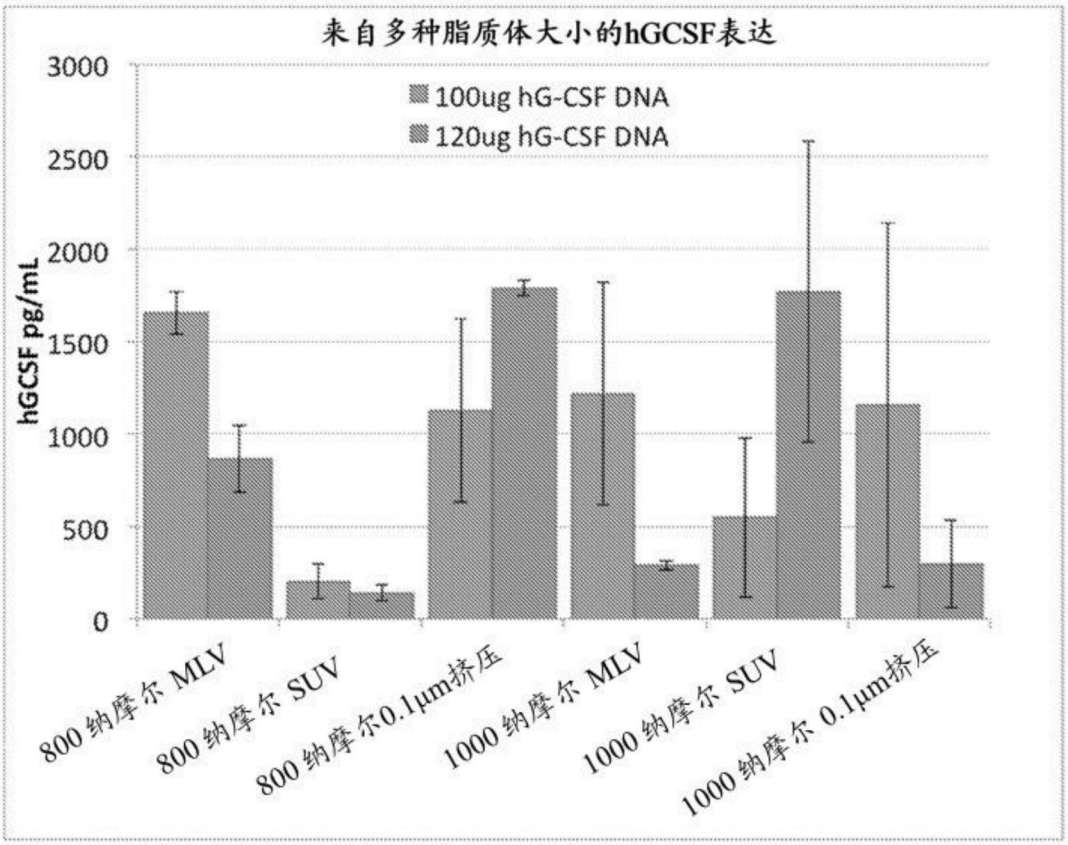

来自多种脂质体大小的hGCSF表达
hGCSF pg/mL
3000
2500
2000
1500
1000
500
0
100ug hG-CSF DNA
120ug hG-CSF DNA
800 纳摩尔 MLV
800 纳摩尔 SUV
800 纳摩尔0.1μm挤压
1000 纳摩尔 MLV
1000 纳摩尔 SUV
1000 纳摩尔 0.1μm挤压

图109

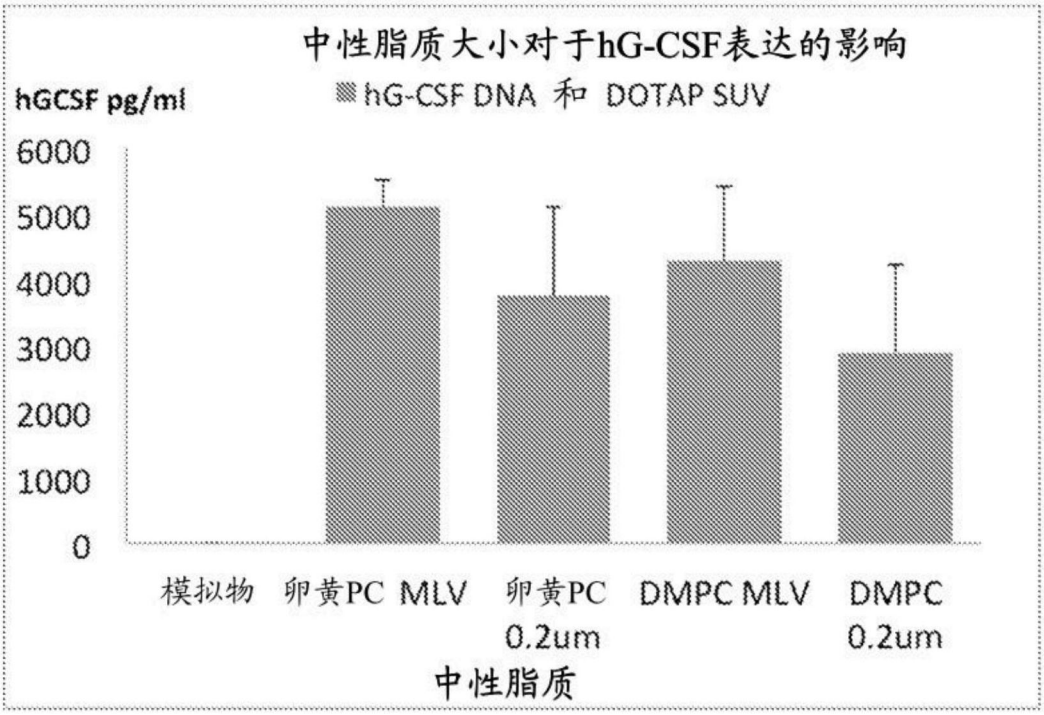

中性脂质大小对于hG-CSF表达的影响
hGCSF pg/ml
hG-CSF DNA 和 DOTAP SUV
6000
5000
4000
3000
2000
1000
0
模拟物
卵黄PC MLV
卵黄PC 0.2um
DMPC MLV
DMPC 0.2um
中性脂质

图110