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(54) 发明名称
包封的RNA复制子和使用方法

(57) 摘要
本公开内容涉及溶瘤病毒衍生出的复制子及其衣壳化。本公开内容还涉及一个或多个编码有效负载分子的转基因向所述复制子中的掺入。本公开内容进一步涉及将编码溶瘤病毒的复制子和/或重组RNA分子包封到颗粒中以及所述复制子和/或颗粒用于治疗 and 预防癌症的用途。



1. 一种重组RNA复制子,其包含:
小核糖核酸病毒基因组,其中所述小核糖核酸病毒基因组包含在一个或多个蛋白编码区中的缺失或截短;和
异源多核苷酸。
2. 根据权利要求1所述的重组RNA复制子,其中所述小核糖核酸病毒基因组包含在一个或多个VP编码区中的缺失或截短。
3. 根据权利要求1或2所述的重组RNA复制子,其中所述小核糖核酸病毒基因组包含在VP1、VP3和VP2编码区中的每一个中的缺失或截短。
4. 根据权利要求1-3中任一项所述的重组RNA复制子,其中所述小核糖核酸病毒基因组包含VP1和VP3编码区的缺失以及VP2编码区的截短。
5. 根据权利要求1-4中任一项所述的重组RNA复制子,其中所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。
6. 根据权利要求1-5中任一项所述的重组RNA复制子,其中所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。
7. 根据权利要求6所述的重组RNA复制子,其中所述缺失或所述截短包含至少2000bp。
8. 根据权利要求1-7中任一项所述的重组RNA复制子,其中所述缺失的位点或所述截短的位点包含所述异源多核苷酸。
9. 根据权利要求1-7中任一项所述的重组RNA复制子,其中所述异源多核苷酸插入在2A编码区和2B编码区之间。
10. 根据权利要求1-7中任一项所述的重组RNA复制子,其中所述异源多核苷酸插入在3D编码区和3' 非翻译区(UTR)之间。
11. 根据权利要求1-10中任一项所述的重组RNA复制子,其中所述异源多核苷酸包含至少1000bp、至少2000bp或至少3000bp。
12. 根据权利要求1-11中任一项所述的重组RNA复制子,其中所述小核糖核酸病毒是塞内卡谷病毒(SVV)。
13. 根据权利要求12所述的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的一个或多个核苷酸。
14. 根据权利要求12所述的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:1的编号的核苷酸1261至3477(包括端点)。
15. 根据权利要求12或13所述的重组RNA复制子,其中所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp或至少2000bp。
16. 根据权利要求15所述的重组RNA复制子,其中所述缺失或所述截短包含至少2000bp。
17. 根据权利要求12至16中任一项所述的重组RNA复制子,其中所述SVV基因组包含5'前导蛋白编码序列。
18. 根据权利要求12至17中任一项所述的重组RNA复制子,其中所述SVV基因组包含VP4编码区。
19. 根据权利要求12至18中任一项所述的重组RNA复制子,其中所述SVV基因组包含VP2编码区或其截短体。

20. 根据权利要求19所述的重组RNA复制子,其中所述SVV基因组从5'至3'方向包含5'前导蛋白编码序列、VP4编码区和VP2编码区或其截短体。

21. 根据权利要求20所述的重组RNA复制子,其中包含5'前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的SVV基因组的部分与SEQ ID NO:1的核苷酸1至1260具有至少90%序列同一性。

22. 根据权利要求20或21所述的重组RNA复制子,其中所述SVV基因组从5'至3'方向包含5'前导蛋白编码序列、VP4编码区、VP2编码区或其截短体和异源多核苷酸。

23. 根据权利要求1-22中任一项所述的重组RNA复制子,其中所述SVV基因组包含顺式作用复制元件(CRE)。

24. 根据权利要求23所述的重组RNA复制子,其中所述CRE包含10-200bp。

25. 根据权利要求23或24所述的重组RNA复制子,其中所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260对应的区域内的一个或多个核苷酸。

26. 根据权利要求23或24所述的重组RNA复制子,其中所述CRE包含在与根据SEQ ID NO:1的核苷酸1117至核苷酸1260对应的区域内的一个或多个核苷酸。

27. 根据权利要求23-26中任一项所述的重组RNA复制子,其中所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。

28. 根据权利要求12-27中任一项所述的重组RNA复制子,其中所述SVV基因组进一步包含2A编码区。

29. 根据权利要求28所述的重组RNA复制子,其中所述2A编码区位于VP2编码区或其截短体和异源多核苷酸之间。

30. 根据权利要求12-29中任一项所述的重组RNA复制子,其中所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区中的一个或多个。

31. 根据权利要求12-29中任一项所述的重组RNA复制子,其中所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。

32. 根据权利要求31所述的重组RNA复制子,其中所述SVV基因组从5'至3'包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。

33. 根据权利要求32所述的重组RNA复制子,其中包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区的SVV基因组的部分与根据SEQ ID NO:1的核苷酸3505至7310具有至少90%序列同一性。

34. 根据权利要求30-33中任一项所述的重组RNA复制子,其中所述SVV基因组从5'至3'包含异源多核苷酸和2B编码区。

35. 根据权利要求1至11中任一项所述的重组RNA复制子,其中所述小核糖核酸病毒是柯萨奇病毒。

36. 根据权利要求35所述的重组RNA复制子,其中所述缺失或所述截短包含在根据SEQ ID NO:3的编号的核苷酸717至3332(包括端点)之间的一个或多个核苷酸。

37. 根据权利要求35所述的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:3的编号的核苷酸717至3332(包括端点)。

38. 根据权利要求35或36所述的重组RNA复制子,其中所述缺失或所述截短包含至少

500bp、至少1000bp、至少1500bp、至少2000bp或至少2600bp。

39. 根据权利要求35至38中任一项所述的重组RNA复制子,其中所述柯萨奇病毒基因组包含5' UTR。

40. 根据权利要求35至39中任一项所述的重组RNA复制子,其中包含5' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:4具有至少90%序列同一性。

41. 根据权利要求35至40中任一项所述的重组RNA复制子,其中所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR中的一个或多个。

42. 根据权利要求35至40中任一项所述的重组RNA复制子,其中所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

43. 根据权利要求42所述的重组RNA复制子,其中所述柯萨奇病毒基因组从5' 至3' 方向包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

44. 根据权利要求42所述的重组RNA复制子,其中包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:3中的核苷酸3492至7435具有至少90%序列同一性。

45. 根据权利要求41至44中任一项所述的重组RNA复制子,其中所述柯萨奇病毒基因组从5' 至3' 包含5' UTR、异源多核苷酸和2A编码区。

46. 根据权利要求1至11中任一项所述的重组RNA复制子,其中所述小核糖核酸病毒是脑心肌炎病毒(EMCV)。

47. 根据权利要求9和11-46中任一项所述的重组RNA复制子,其中所述重组RNA复制子包含插入在异源多核苷酸和2B编码区之间的内部核糖体进入位点(IRES)。

48. 根据权利要求1至47中任一项所述的重组RNA复制子,其中所述异源多核苷酸编码一个或多个有效负载分子。

49. 根据权利要求1至47中任一项所述的重组RNA复制子,其中所述异源多核苷酸编码两个或更多个有效负载分子。

50. 根据权利要求49所述的重组RNA复制子,其中所述两个或更多个有效负载分子通过一个或多个切割多肽可操作地连接。

51. 根据权利要求50所述的重组RNA复制子,其中所述切割多肽包含2A家族自切割肽、3C切割位点、弗林蛋白酶位点、IGSF1多肽或HIV蛋白酶位点。

52. 根据权利要求51所述的重组RNA复制子,其中所述切割多肽包含IGSF1多肽,并且其中所述IGSF1多肽包含与SEQ ID NO:75具有至少90%同一性的氨基酸序列。

53. 根据权利要求51所述的重组RNA复制子,其中所述切割多肽包含HIV蛋白酶位点。

54. 根据权利要求51所述的重组RNA复制子,其中所述切割多肽包含2A家族自切割肽。

55. 根据权利要求50至54中任一项所述的重组RNA复制子,其中所述切割多肽包含弗林蛋白酶位点。

56. 根据权利要求50至55中任一项所述的重组RNA复制子,其中所述异源多核苷酸编码包含两个或更多个有效负载分子和切割多肽的多肽,所述多肽从N-端至C-端包含:N'-有效

负载分子1-切割多肽-有效负载分子2-C'。

57. 根据权利要求53所述的重组RNA复制子,其中所述异源多核苷酸进一步包含编码HIV蛋白酶的编码区,并且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-C'。

58. 根据权利要求57所述的重组RNA复制子,其中所述异源多核苷酸进一步包含编码第三有效负载分子的编码区,并且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:

N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-HIV蛋白酶位点-有效负载分子3-C'。

59. 根据权利要求56至58中任一项所述的重组RNA复制子,进一步包含在所编码的多肽的C-端处的切割多肽。

60. 根据权利要求48至59中任一项所述的重组RNA复制子,其中所述有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、抗原、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。

61. 根据权利要求48至59中任一项所述的重组RNA复制子,其中所述有效负载分子选自:

a) 一种或多种细胞因子,包含IFN γ 、GM-CSF、IL-2、IL-12、IL-15、IL-18、IL-23和IL-36 γ ;

b) 一种或多种趋化因子,包含CXCL10、CCL4、CCL5和CCL21;

c) 一种或多种抗体,包含抗-PD1-VHH-Fc抗体、抗-CD47-VHH-Fc抗体和抗-TGF β -VHH(或scFv)-Fc抗体;

d) 一种或多种双组分多肽,包含结合DLL3和效应细胞靶抗原的双组分多肽、结合FAP和效应细胞靶抗原的双组分多肽、以及结合EpCAM和效应细胞靶抗原的双组分多肽;

e) 一种或多种肿瘤相关抗原,包含存活素、MAGE家族蛋白和根据表6的所有抗原;

f) 一种或多种肿瘤新抗原;

g) 一种或多种结合MHC-肽抗原复合物的双组分多肽;

h) 一种或多种促融合蛋白,包含单纯疱疹病毒(HSV)UL27/糖蛋白B/gB,HSV UL53/糖蛋白K/gK,呼吸道合胞体病毒(RSV)F蛋白,FASTp15,VSV-G,syncitin-1(来自人内源性逆转录病毒-W(HERV-W))或syncitin-2(来自HERVFRDE1),副粘病毒SV5-F,麻疹病毒-H,麻疹病毒-F,以及来自逆转录病毒或慢病毒诸如长臂猿白血病病毒(GALV)、鼠白血病病毒(MLV)、Mason-Pfizer猴病毒(MPMV)和马传染性贫血病毒(EIAV)的糖蛋白,任选地除去了R跨膜肽(R-版本);

i) 一种或多种其它有效负载分子,包含IL15R、PGDH、ADA、ADA2、HYAL1、HYAL2、CHIPS、MLKL(或仅它的4HB结构域)、GSDMD(或它的L192A突变体、或它的氨基酸1-233片段、或它的具有L192A突变的氨基酸1-233片段)、GSDME(或它的氨基酸1-237片段)、HMGB1(或仅它的Box B结构域)、蜂毒肽(例如, α -蜂毒肽)、SMAC/Diablo(或它的氨基酸56-239片段)、蛇LAAO、蛇解聚素、瘦素、FLT3L、TRAIL、Gasdermin D或其截短体和Gasdermin E或其截短体;

j) 一种或多种来自病原体的抗原,所述病原体包含登革热病毒、切昆贡亚病毒、结核分

枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒；或

k) 它们的任意组合。

62. 根据权利要求49至59中任一项所述的重组RNA复制子, 其中所述两个或更多个有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。

63. 根据权利要求49至59中任一项所述的重组RNA复制子, 其中所述异源多核苷酸编码两个或更多个有效负载分子, 其包含:

- a. IL-2和IL-36 γ ;
- b. CXCL10以及结合FAP和CD3的抗原结合分子;
- c. IL-2以及结合DLL3和CD3的抗原结合分子;
- d. IL-36 γ 以及结合DLL3和CD3的抗原结合分子;或
- e. IL-2、IL-36 γ 以及结合DLL3和CD3的抗原结合分子。

64. 根据权利要求1至63中任一项所述的重组RNA复制子, 进一步包含微RNA (miRNA) 靶序列(miR-TS) 盒, 其包含一个或多个miRNA靶序列。

65. 根据权利要求64所述的重组RNA复制子, 其中所述一个或多个miRNA包含miR-124、miR-1、miR-143、miR-128、miR-219、miR-219a、miR-122、miR-204、miR-217、miR-137和miR-126。

66. 一种重组DNA分子, 其从5' 至3' 包含启动子序列、5' 连接切割序列、编码根据权利要求1至65中任一项所述的重组RNA复制子的多核苷酸序列和3' 连接切割序列。

67. 根据权利要求66所述的重组DNA分子, 其中所述启动子序列是T7启动子序列。

68. 根据权利要求66或67所述的重组DNA分子, 其中所述5' 连接切割序列是核酶序列并且所述3' 连接切割序列是核酶序列。

69. 根据权利要求68所述的重组DNA分子, 其中所述5' 核酶序列是锤头核酶序列并且其中所述3' 核酶序列是丁型肝炎病毒核酶序列。

70. 根据权利要求66或67所述的重组DNA分子, 其中所述5' 连接切割序列是核酶序列并且所述3' 连接切割序列是限制性酶识别序列。

71. 根据权利要求70所述的重组DNA分子, 其中所述5' 核酶序列是锤头核酶序列、手枪核酶序列或经修饰的手枪核酶序列。

72. 根据权利要求70或71所述的重组DNA分子, 其中3' 限制性酶识别序列是IIS型限制性酶识别序列。

73. 根据权利要求72所述的重组DNA分子, 其中所述IIS型识别序列是SapI识别序列。

74. 根据权利要求66或67所述的重组DNA分子, 其中所述5' 连接切割序列是RNA酶H引物结合序列并且所述3' 连接切割序列是限制性酶识别序列。

75. 一种生产根据权利要求1-65中任一项所述的重组RNA复制子的方法, 所述方法包含体外转录根据权利要求66-74中任一项所述的DNA分子和纯化得到的重组RNA复制子。

76. 一种组合物, 其包含有效量的根据权利要求1-65中任一项所述的重组RNA复制子和适用于施用给哺乳动物受试者的载体。

77. 一种载体, 其包含根据权利要求1-65中任一项所述的重组RNA复制子。

78. 根据权利要求77所述的载体,其中所述载体是病毒载体。

79. 根据权利要求77所述的载体,其中所述载体是非病毒载体。

80. 一种颗粒,其包含根据权利要求1-65中任一项所述的重组RNA复制子。

81. 根据权利要求80所述的颗粒,其中所述颗粒选自纳米颗粒、外泌体、脂质体和脂质体复合物。

82. 根据权利要求81所述的颗粒,其中所述纳米颗粒是脂质纳米颗粒(LNP),其包含阳离子脂质、一种或多种辅助脂质和磷脂-聚合物缀合物。

83. 根据权利要求82所述的颗粒,其中所述阳离子脂质选自DLinDMA、DLin-KC2-DMA、DLin-MC3-DMA(MC3)、**COATSOME®**SS-LC(以前名称:SS-18/4PE-13)、**COATSOME®**SS-EC(以前名称:SS-33/4PE-15)、**COATSOME®**SS-OC、**COATSOME®**SS-OP、9-((4-二甲基氨基)丁酰基)氧基)十七烷二酸二((Z)-壬-2-烯-1-基)酯(L-319)或N-(2,3-二油酰氧基)丙基)-N,N,N-三甲基氯化铵(DOTAP)。

84. 根据权利要求82或83所述的颗粒,其中所述辅助脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸胆碱(DSPC);1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE);1,2-二油酰基-sn-甘油-3-磷酸胆碱(DOPC);1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE);和胆固醇。

85. 根据权利要求82所述的颗粒,其中所述阳离子脂质是1,2-二油酰基-3-三甲基铵-丙烷(DOTAP),并且其中中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE)或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。

86. 根据权利要求82-85中任一项所述的颗粒,其中所述PEG-脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇(DPG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG),或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。

87. 根据权利要求82-86中任一项所述的颗粒,其中所述PEG-脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)-5000](DSPE-PEG5K);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇-2000(DPG-PEG2K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DSG-PEG5K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DSG-PEG2K);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DMG-PEG5K);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DMG-PEG2K)。

88. 根据权利要求82所述的颗粒,其中所述阳离子脂质包含**COATSOME®**SS-OC,其中所述一种或多种辅助脂质包含胆固醇(Chol)和DSPC,并且其中所述磷脂-聚合物缀合物包含DPG-PEG2000。

89. 根据权利要求88所述的颗粒,其中SS-OC: DSPC: Chol: DPG-PEG2K(作为总脂质含量的百分比)的比率是A:B:C:D,其中:

a. A=40%-60%, B=10%-25%, C=20%-30%, 且D=0%-3%并且其中A+B+C+D=100%;

b. A=45%-50%, B=20%-25%, C=25%-30%, 且D=0%-1%并且其中A+B+C+D=100%

c. $A=40\%-60\%$, $B=10\%-30\%$, $C=20\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

d. $A=40\%-60\%$, $B=10\%-30\%$, $C=25\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

e. $A=45\%-55\%$, $B=10\%-20\%$, $C=30\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

f. $A=45\%-50\%$, $B=10\%-15\%$, $C=35\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

g. $A=45\%-65\%$, $B=5\%-20\%$, $C=20\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

h. $A=50\%-60\%$, $B=5\%-15\%$, $C=30\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

i. $A=55\%-60\%$, $B=5\%-15\%$, $C=30\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

j. $A=55\%-60\%$, $B=5\%-10\%$, $C=30\%-35\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$ 。

90. 根据权利要求88所述的颗粒, 其中SS-OC: DSPC: Chol: DPG-PEG2K (作为总脂质含量的百分比) 的比率是:

a. 约49:22:28.5:0.5;

b. 约49:11:38.5:1.5; 或

c. 约58:7:33.5:1.5。

91. 根据权利要求88所述的颗粒, 其中SS-OC: DSPC: Chol: DPG-PEG2K (作为总脂质含量的百分比) 的比率是约49:22:28.5:0.5。

92. 根据权利要求82所述的颗粒, 其中所述阳离子脂质是1,2-二油酰基-3-三甲基铵-丙烷(DOTAP), 并且其中中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE) 或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。

93. 根据权利要求82或92所述的颗粒, 所述颗粒进一步包含PEG-脂质, 其中所述PEG-脂质是1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-聚(乙二醇)(DSPE-PEG) 或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。

94. 根据权利要求80-93中任一项所述的颗粒, 所述颗粒进一步包含编码溶瘤病毒的第二重组RNA分子。

95. 根据权利要求94所述的颗粒, 其中所述溶瘤病毒是小核糖核酸病毒。

96. 根据权利要求95所述的颗粒, 其中所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。

97. 根据权利要求95所述的颗粒, 其中所述小核糖核酸病毒是塞内卡谷病毒(SVV)。

98. 根据权利要求95所述的颗粒, 其中所述小核糖核酸病毒是柯萨奇病毒。

99. 根据权利要求95所述的颗粒, 其中所述小核糖核酸病毒是脑心肌炎病毒(EMCV)。

100. 一种治疗组合物, 其包含多个根据权利要求82-99中任一项所述的脂质纳米颗粒。

101. 根据权利要求100所述的治疗组合物, 其中所述多个LNP具有约50nm至约120nm的

平均大小。

102. 根据权利要求100所述的治疗组合物,其中所述多个LNP具有约100nm的平均大小。

103. 根据权利要求100-102中任一项所述的治疗组合物,其中所述多个LNP具有约20mV至约-20mV、约10mV至约-10mV、约5mV至约-5mV、或约20mV至约-40mV、-50mV至约-20mV、约-40mV至约-20mV、或约-30mV至约-20mV之间的平均 ζ 电位。

104. 根据权利要求103所述的治疗组合物,其中所述多个LNP具有约-30mV、约-31mV、约-32mV、约-33mV、约-34mV、约-35mV、约-36mV、约-37mV、约-38mV、约-39mV或约-40mV的平均 ζ 电位。

105. 一种杀死癌细胞的方法,所述方法包含将所述癌细胞暴露于根据权利要求80-97中任一项所述的颗粒、根据权利要求77-79中任一项所述的载体、根据权利要求1-65中任一项所述的重组RNA复制子、或其组合物。

106. 根据权利要求105所述的方法,其中在体内、在体外或离体执行所述方法。

107. 一种治疗受试者中的癌症的方法,所述方法包含给遭受癌症的受试者施用有效量的根据权利要求80-97中任一项所述的颗粒、根据权利要求77-79中任一项所述的载体、根据权利要求1-65中任一项所述的重组RNA复制子、或其组合物。

108. 根据权利要求107所述的方法,其中将所述颗粒、所述重组RNA复制子或其组合物静脉内地、鼻内地、作为吸入剂施用,或直接注射进肿瘤中。

109. 根据权利要求107或108所述的方法,其中将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。

110. 根据权利要求107-109中任一项所述的方法,其中所述受试者是小鼠、大鼠、兔、猫、狗、马、非人灵长类动物或人。

111. 根据权利要求107-110中任一项所述的方法,其中所述癌症选自肺癌、乳腺癌、卵巢癌、子宫颈癌、前列腺癌、睾丸癌、结肠直肠癌、结肠癌、胰腺癌(例如,阉割抗性的神经内分泌前列腺癌)、肝癌、胃癌、头颈癌、甲状腺癌、恶性神经胶质瘤、胶质母细胞瘤、黑色素瘤、B-细胞慢性淋巴细胞性白血病、弥漫性大B细胞性淋巴瘤(DLBCL)、肉瘤、神经母细胞瘤、神经内分泌癌、横纹肌肉瘤、髓母细胞瘤、膀胱癌、边缘区淋巴瘤(MZL)、梅克尔细胞癌和肾细胞癌。

112. 根据权利要求111所述的方法,其中:

- a. 所述肺癌是小细胞肺癌或非小细胞肺癌;
- b. 所述肝癌是肝细胞癌(HCC);和/或
- c. 所述前列腺癌是治疗引发的神经内分泌前列腺癌。

113. 根据权利要求111所述的方法,其中所述癌症是神经内分泌癌。

114. 一种针对疾病免疫受试者的方法,所述方法包含给所述受试者施用有效量的根据权利要求80-97中任一项所述的颗粒、根据权利要求77-79中任一项所述的载体、根据权利要求1-65中任一项所述的重组RNA复制子、或其组合物。

115. 根据权利要求114所述的方法,其中将所述颗粒、所述重组RNA复制子或其组合物静脉内地、肌肉内地、真皮内地、鼻内地或作为吸入剂施用。

116. 根据权利要求114或115所述的方法,其中将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。

117. 根据权利要求114至116中任一项所述的方法, 其中所述疾病是传染性疾病。

118. 根据权利要求117所述的方法, 其中所述传染性疾病由病原体之一造成, 所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒。

119. 一种重组RNA复制子, 其包含小核糖核酸病毒基因组和异源多核苷酸。

120. 根据权利要求119所述的重组RNA复制子, 其中所述异源多核苷酸插入在2A编码区和2B编码区之间。

121. 根据权利要求119所述的重组RNA复制子, 其中所述异源多核苷酸插入在5' UTR和2A编码区之间。

122. 根据权利要求119所述的重组RNA复制子, 其中所述异源多核苷酸插入在3D编码区和3' UTR之间。

123. 根据权利要求119-122中任一项所述的重组RNA复制子, 其中所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。

包封的RNA复制子和使用方法

[0001] 相关申请的交叉引用

[0002] 本申请要求2020年5月29日提交的美国临时申请号63/032,000的优先权,其内容通过引用整体并入。

[0003] 序列表的通过引用并入

[0004] 随同本文以电子方式提交的文本文件的内容通过引用整体并入本文:序列表的计算机可读形式副本(文件名:ONCR_019_01W0_SeqList_ST25.txt,创建日期:2021年5月28日,文件大小:约771千字节)。

技术领域

[0005] 本公开内容总体上涉及免疫学、炎症和癌症治疗剂的领域。更具体地,本公开内容涉及具有改进的负载能力和编码有效负载分子的异源多核苷酸的病毒复制子,以及颗粒包封的病毒复制子。本公开内容进一步涉及增殖性障碍诸如癌症的治疗和预防。

背景技术

[0006] 本领域中仍然存在对与病毒和/或病毒复制子的治疗用途相关的组合物和方法的长期且未得到满足的需求,所述病毒和/或病毒复制子包含对一种或多种治疗分子的改进的负载能力和/或功能。本公开内容提供了这样的组合物和方法等。

发明内容

[0007] 本公开内容提供了重组RNA复制子,其包含:a)小核糖核酸病毒基因组,其中所述小核糖核酸病毒基因组包含在一个或多个蛋白编码区中的缺失或截短;和b)异源多核苷酸。在某些实施方案中,所述小核糖核酸病毒基因组包含在一个或多个VP编码区中的缺失或截短。在某些实施方案中,所述小核糖核酸病毒基因组包含在VP1、VP3和VP2编码区中的每一个中的缺失或截短。在某些实施方案中,所述小核糖核酸病毒基因组包含VP1和VP3编码区的缺失以及VP2编码区的截短。在某些实施方案中,所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。在某些实施方案中,所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。在某些实施方案中,所述缺失或所述截短包含至少2000bp。在某些实施方案中,所述缺失的位点或所述截短的位点包含所述异源多核苷酸。在某些实施方案中,所述异源多核苷酸插入在2A编码区和2B编码区之间。在某些实施方案中,所述异源多核苷酸插入在3D编码区和3'非翻译区(UTR)之间。在某些实施方案中,所述异源多核苷酸包含至少1000bp、至少2000bp或至少3000bp。

[0008] 本公开内容提供了重组RNA复制子,其包含:a)塞内卡谷病毒(SVV)基因组,其中所述SVV基因组包含在一个或多个蛋白编码区中的缺失或截短;和b)异源多核苷酸(即,所述复制子是SVV衍生出的复制子)。在某些实施方案中,所述缺失或所述截短包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的一个或多个核苷酸。在某些实施方案中,所述缺失或所述截短包含根据SEQ ID NO:1的编号的核苷酸1261至3477(包括端点)。在

某些实施方案中,所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp或至少2000bp。在某些实施方案中,所述缺失或所述截短包含至少2000bp。在某些实施方案中,所述SVV基因组包含5' 前导蛋白编码序列。在某些实施方案中,所述SVV基因组包含VP4编码区。在某些实施方案中,所述SVV基因组包含VP2编码区或其截短体。在某些实施方案中,所述SVV基因组从5' 至3' 方向包含5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体。在某些实施方案中,包含5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的SVV基因组的部分与SEQ ID NO:1的核苷酸1至1260具有至少90%序列同一性。在某些实施方案中,所述SVV基因组从5' 至3' 方向包含5' 前导蛋白编码序列、VP4编码区、VP2编码区或其截短体和异源多核苷酸。在某些实施方案中,所述SVV基因组包含顺式作用复制元件(CRE)。在某些实施方案中,所述CRE包含10-200bp。在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260对应的区域内的一个或多个核苷酸。在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1117至核苷酸1260对应的区域内的一个或多个核苷酸。在某些实施方案中,所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述SVV基因组进一步包含2A编码区。在某些实施方案中,所述2A编码区位于VP2编码区或其截短体和异源多核苷酸之间。在某些实施方案中,所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D (RdRp) 编码区中的一个或多个。在某些实施方案中,所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D (RdRp) 编码区。在某些实施方案中,所述SVV基因组从5' 至3' 包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D (RdRp) 编码区。在某些实施方案中,包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D (RdRp) 编码区的SVV基因组的部分与根据SEQ ID NO:1的核苷酸3505至7310具有至少90%序列同一性。在某些实施方案中,所述SVV基因组从5' 至3' 包含异源多核苷酸和2B编码区。

[0009] 本公开内容提供了重组RNA复制子,其包含:a) 柯萨奇病毒基因组,其中所述柯萨奇病毒基因组包含在一个或多个蛋白编码区中的缺失或截短;和b) 异源多核苷酸(即,所述复制子是柯萨奇病毒衍生出的复制子)。在某些实施方案中,所述缺失或所述截短包含根据SEQ ID NO:3的编号在核苷酸717至3332(包括端点)之间的一个或多个核苷酸。在某些实施方案中,所述缺失或所述截短包含根据SEQ ID NO:3的编号的核苷酸717至3332(包括端点)。在某些实施方案中,所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp或至少2600bp。在某些实施方案中,所述柯萨奇病毒基因组包含5' UTR。在某些实施方案中,包含5' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:4具有至少90%序列同一性。在某些实施方案中,所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR中的一个或多个。在某些实施方案中,所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。在某些实施方案中,所述柯萨奇病毒基因组从5' 至3' 方向包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。在某些实施方案中,包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:3中的核苷酸3492至7435具有至少90%序列同一性。在某些实施方案中,所述柯萨奇

病毒基因组从5'至3'包含5' UTR、异源多核苷酸和2A编码区。

[0010] 本公开内容提供了重组RNA复制子,其包含:a)脑心肌炎病毒(EMCV)基因组,其中所述EMCV基因组包含在一个或多个蛋白编码区中的缺失或截短;和b)异源多核苷酸(即,所述复制子是EMCV衍生出的复制子)。

[0011] 在某些实施方案中,所述重组RNA复制子包含插入在异源多核苷酸和2B编码区之间的内部核糖体进入位点(IRES)。

[0012] 在某些实施方案中,所述重组RNA复制子的异源多核苷酸编码一个或多个有效负载分子。在某些实施方案中,所述重组RNA复制子的异源多核苷酸编码两个或更多个有效负载分子。在某些实施方案中,所述两个或更多个有效负载分子通过一个或多个切割多肽可操作地连接。在某些实施方案中,所述切割多肽包含2A家族自切割肽、3C切割位点、弗林蛋白酶位点、IGSF1多肽或HIV蛋白酶位点。在某些实施方案中,所述切割多肽包含IGSF1多肽,且其中所述IGSF1多肽包含与SEQ ID NO:75具有至少90%同一性的氨基酸序列。在某些实施方案中,所述切割多肽包含HIV蛋白酶位点。在某些实施方案中,所述切割多肽包含2A家族自切割肽。在某些实施方案中,所述切割多肽包含弗林蛋白酶位点。在某些实施方案中,所述异源多核苷酸编码包含两个或更多个有效负载分子和切割多肽的多肽,所述多肽从N-端至C-端包含:N'-有效负载分子1-切割多肽-有效负载分子2-C'。在某些实施方案中,所述异源多核苷酸进一步包含编码HIV蛋白酶的编码区,且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-C'。在某些实施方案中,所述异源多核苷酸进一步包含编码第三有效负载分子的编码区,且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-HIV蛋白酶位点-有效负载分子3-C'。在某些实施方案中,本公开内容的重组RNA复制子进一步包含在所编码的多肽的C-端处的切割多肽。

[0013] 在某些实施方案中,所述有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、抗原、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。在某些实施方案中,所述有效负载分子选自:

[0014] a) 一种或多种细胞因子,包含IFN γ 、GM-CSF、IL-2、IL-12、IL-15、IL-18、IL-23和IL-36 γ ;

[0015] b) 一种或多种趋化因子,包含CXCL10、CCL4、CCL5和CCL21;

[0016] c) 一种或多种抗体,包含抗-PD1-VHH-Fc抗体、抗-CD47-VHH-Fc抗体和抗-TGF β -VHH(或scFv)-Fc抗体;

[0017] d) 一种或多种双组分多肽,包含结合DLL3和效应细胞靶抗原的双组分多肽、结合FAP和效应细胞靶抗原的双组分多肽、以及结合EpCAM和效应细胞靶抗原的双组分多肽;

[0018] e) 一种或多种肿瘤相关抗原,包含存活素、MAGE家族蛋白和根据表6的所有抗原;

[0019] f) 一种或多种肿瘤新抗原;

[0020] g) 一种或多种结合MHC-肽抗原复合物的双组分多肽;

[0021] h) 一种或多种促融合蛋白,包含单纯疱疹病毒(HSV)UL27/糖蛋白B/gB,HSV UL53/糖蛋白K/gK,呼吸道合胞体病毒(RSV)F蛋白,FASTp15,VSV-G,syncitin-1(来自人内源性逆转录病毒-W(HERV-W))或syncitin-2(来自HERVFRDE1),副粘病毒SV5-F,麻疹病毒-H,麻疹

病毒-F,来自逆转录病毒或慢病毒诸如长臂猿白血病病毒(GALV)、鼠白血病病毒(MLV)、Mason-Pfizer猴病毒(MPMV)和马传染性贫血病毒(EIAV)的糖蛋白,任选地除去了R跨膜肽(R-版本);

[0022] i) 一种或多种其它有效负载分子,包含IL15R、PGDH、ADA、ADA2、HYAL1、HYAL2、CHIPS、MLKL(或仅它的4HB结构域)、GSDMD(或它的L192A突变体、或它的氨基酸1-233片段、或它的具有L192A突变的氨基酸1-233片段)、GSDME(或它的氨基酸1-237片段)、HMGB1(或仅它的Box B结构域)、蜂毒肽(例如, α -蜂毒肽)、SMAC/Diablo(或它的氨基酸56-239片段)、蛇LAAO、蛇解聚素、瘦素、FLT3L、TRAIL、Gasdermin D或其截短体、Gasdermin E或其截短体;

[0023] j) 一种或多种来自病原体的抗原,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒;或

[0024] k) 它们的任意组合。

[0025] 在某些实施方案中,所述两个或更多个有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。在某些实施方案中,所述异源多核苷酸编码两个或更多个有效负载分子,其包含:

[0026] IL-2和IL-36 γ ;

[0027] CXCL10以及结合FAP和CD3的抗原结合分子;

[0028] IL-2以及结合DLL3和CD3的抗原结合分子;

[0029] IL-36 γ 以及结合DLL3和CD3的抗原结合分子;或

[0030] IL-2、IL-36 γ 以及结合DLL3和CD3的抗原结合分子。

[0031] 在某些实施方案中,本公开内容的重组RNA复制子进一步包含微RNA(miRNA)靶序列(miR-TS)盒,其包含一个或多个miRNA靶序列。在某些实施方案中,所述一个或多个miRNA包含miR-124、miR-1、miR-143、miR-128、miR-219、miR-219a、miR-122、miR-204、miR-217、miR-137和miR-126。

[0032] 本公开内容提供了重组DNA分子,其从5'至3'包含启动子序列、5'连接切割序列、编码本公开内容的重组RNA复制子的多核苷酸序列和3'连接切割序列。在某些实施方案中,所述启动子序列是T7启动子序列。在某些实施方案中,所述5'连接切割序列是核酶序列且所述3'连接切割序列是核酶序列。在某些实施方案中,所述5'核酶序列是锤头核酶序列且其中所述3'核酶序列是丁型肝炎病毒核酶序列。在某些实施方案中,所述5'连接切割序列是核酶序列且所述3'连接切割序列是限制性酶识别序列。在某些实施方案中,所述5'核酶序列是锤头核酶序列、手枪核酶序列或经修饰的手枪核酶序列。在某些实施方案中,3'限制性酶识别序列是IIS型限制性酶识别序列。在某些实施方案中,所述IIS型识别序列是SapI识别序列。在某些实施方案中,所述5'连接切割序列是RNA酶H引物结合序列且所述3'连接切割序列是限制性酶识别序列。

[0033] 本公开内容提供了生产重组RNA复制子的方法,其包含体外转录本公开内容的DNA分子和纯化得到的重组RNA复制子。

[0034] 本公开内容提供了组合物,其包含有效量的本公开内容的重组RNA复制子和适用于施用给哺乳动物受试者的载体。

[0035] 本公开内容提供了载体,其包含本公开内容的重组RNA复制子。在某些实施方案

中,所述载体是病毒载体。在某些实施方案中,所述载体是非病毒载体。

[0036] 本公开内容提供了颗粒,其包含本公开内容的重组RNA复制子。在某些实施方案中,所述颗粒选自纳米颗粒、外泌体、脂质体和脂质体复合物。在某些实施方案中,所述纳米颗粒是脂质纳米颗粒(LNP),其包含阳离子脂质、一种或多种辅助脂质和磷脂-聚合物缀合物。在某些实施方案中,所述阳离子脂质选自DLinDMA、DLin-KC2-DMA、DLin-MC3-DMA(MC3)、**COATSOME®SS-LC**(以前名称:SS-18/4PE-13)、**COATSOME®SS-EC**(以前名称:SS-33/4PE-15)、**COATSOME®SS-0C**、**COATSOME®SS-0P**、9-((4-二甲基氨基)丁酰基)氧基)十七烷二酸二((Z)-壬-2-烯-1-基)酯(L-319)或N-(2,3-二油酰氧基)丙基)-N,N,N-三甲基氯化铵(DOTAP)。在某些实施方案中,所述辅助脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸胆碱(DSPC);1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE);1,2-二油酰基-sn-甘油-3-磷酸胆碱(DOPC);1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE);和胆固醇。在某些实施方案中,所述阳离子脂质是1,2-二油酰基-3-三甲基铵-丙烷(DOTAP),且其中所述中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE)或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。在某些实施方案中,所述磷脂-聚合物缀合物选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇(DPG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG),或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。在某些实施方案中,所述磷脂-聚合物缀合物选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)-5000](DSPE-PEG5K);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇-2000(DPG-PEG2K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DSG-PEG5K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DSG-PEG2K);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DMG-PEG5K);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DMG-PEG2K)。在某些实施方案中,所述阳离子脂质包含**COATSOME®SS-0C**,其中所述一种或多种辅助脂质包含胆固醇(Chol)和DSPC,且其中所述磷脂-聚合物缀合物包含DPG-PEG2000。在某些实施方案中,SS-0C:DSPC:Chol:DPG-PEG2K(作为总脂质含量的百分比)的比率是A:B:C:D,其中:

[0037] (a) A=40%-60%, B=10%-25%, C=20%-30%, 且D=0%-3%并且其中A+B+C+D=100%;

[0038] (b) A=45%-50%, B=20%-25%, C=25%-30%, 且D=0%-1%并且其中A+B+C+D=100%

[0039] (c) A=40%-60%, B=10%-30%, C=20%-45%, 且D=0%-3%并且其中A+B+C+D=100%;

[0040] (d) A=40%-60%, B=10%-30%, C=25%-45%, 且D=0%-3%并且其中A+B+C+D=100%;

[0041] (e) A=45%-55%, B=10%-20%, C=30%-40%, 且D=1%-2%并且其中A+B+C+D=100%;

[0042] (f) A=45%-50%, B=10%-15%, C=35%-40%, 且D=1%-2%并且其中A+B+C+D=100%;

[0043] (g) A=45%-65%, B=5%-20%, C=20%-45%, 且D=0%-3%并且其中A+B+C+D=100%;

[0044] (h) A=50%-60%, B=5%-15%, C=30%-45%, 且D=0%-3%并且其中A+B+C+D=100%;

[0045] (i) A=55%-60%, B=5%-15%, C=30%-40%, 且D=1%-2%并且其中A+B+C+D=100%;或

[0046] (j) A=55%-60%, B=5%-10%, C=30%-35%, 且D=1%-2%并且其中A+B+C+D=100%。

[0047] 在某些实施方案中, SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是: 约49:22:28.5:0.5; 约49:11:38.5:1.5; 或约58:7:33.5:1.5。在某些实施方案中, SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约49:22:28.5:0.5。在某些实施方案中, 所述阳离子脂质是1,2-二油酰基-3-三甲基铵-丙烷(DOTAP), 且其中所述中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE) 或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。

[0048] 在某些实施方案中, 本公开内容的颗粒进一步包含磷脂-聚合物缀合物, 其中所述磷脂-聚合物缀合物是1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-聚(乙二醇)(DSPE-PEG) 或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。

[0049] 在某些实施方案中, 本公开内容的颗粒进一步包含编码溶瘤病毒的第二重组RNA分子。在某些实施方案中, 所述溶瘤病毒是小核糖核酸病毒。在某些实施方案中, 所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。在某些实施方案中, 所述小核糖核酸病毒是塞内卡谷病毒(SVV)。在某些实施方案中, 所述小核糖核酸病毒是柯萨奇病毒。在某些实施方案中, 所述小核糖核酸病毒是脑心肌炎病毒(EMCV)。

[0050] 本公开内容提供了治疗组合物, 其包含本公开内容的多个脂质纳米颗粒。在某些实施方案中, 所述多个LNP具有约50nm至约120nm的平均大小。在某些实施方案中, 所述多个LNP具有约100nm的平均大小。在某些实施方案中, 所述多个LNP具有约20mV至约-20mV、约10mV至约-10mV、约5mV至约-5mV、或约20mV至约-40mV、-50mV至约-20mV、约-40mV至约-20mV、或约-30mV至约-20mV之间的平均 ζ 电位。在某些实施方案中, 所述多个LNP具有约-30mV、约-31mV、约-32mV、约-33mV、约-34mV、约-35mV、约-36mV、约-37mV、约-38mV、约-39mV或约-40mV的平均 ζ 电位。

[0051] 本公开内容提供了杀死癌细胞的方法, 包含将所述癌细胞暴露于本公开内容的颗粒、载体、重组RNA复制子或组合物。在某些实施方案中, 在体内、在体外或离体执行所述方法。

[0052] 本公开内容提供了治疗受试者中的癌症的方法, 其包含给遭受癌症的受试者施用有效量的本公开内容的颗粒、载体、重组RNA复制子或组合物。在某些实施方案中, 将所述重组RNA复制子或其组合物静脉内地、鼻内地、作为吸入剂施用, 或直接注射进肿瘤中。在某些实施方案中, 将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。在某些实施方案中, 所述受试者是小鼠、大鼠、兔、猫、狗、马、非人灵长类动物或人。

[0053] 在某些实施方案中,所述癌症选自肺癌、乳腺癌、卵巢癌、子宫颈癌、前列腺癌(例如,阉割抗性的神经内分泌前列腺癌)、睾丸癌、结肠直肠癌、结肠癌、胰腺癌、肝癌、胃癌、头颈癌、甲状腺癌、恶性神经胶质瘤、胶质母细胞瘤、黑色素瘤、B-细胞慢性淋巴细胞性白血病、弥漫性大B细胞性淋巴瘤(DLBCL)、肉瘤、神经母细胞瘤、神经内分泌癌、横纹肌肉瘤、髓母细胞瘤、膀胱癌、边缘区淋巴瘤(MZL)、梅克尔细胞癌和肾细胞癌。在某些实施方案中,所述肺癌是小细胞肺癌或非小细胞肺癌;所述肝癌是肝细胞癌(HCC);和/或所述前列腺癌是治疗引发的神经内分泌前列腺癌。在某些实施方案中,所述癌症是神经内分泌癌。

[0054] 本公开内容提供了针对疾病免疫受试者的方法,其包含给所述受试者施用有效量的本公开内容的颗粒、载体、重组RNA复制子或组合物。在某些实施方案中,将所述颗粒、所述重组RNA复制子或其组合物静脉内地、肌肉内地、真皮内地、鼻内地或作为吸入剂施用。在某些实施方案中,将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。在某些实施方案中,所述疾病是传染性疾病。在某些实施方案中,所述传染性疾病由病原体之一造成,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒。

[0055] 本公开内容提供了包含小核糖核酸病毒基因组和异源多核苷酸的重组RNA复制子。在某些实施方案中,所述异源多核苷酸插入在2A编码区和2B编码区之间。在某些实施方案中,所述异源多核苷酸插入在5' UTR和2A编码区之间。在某些实施方案中,所述异源多核苷酸插入在3D编码区和3' UTR之间。在某些实施方案中,所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。

附图说明

[0056] 图1是描绘野生型SVV病毒基因组和一种示例性的SVV衍生出的重组RNA复制子的示意图。

[0057] 图2的一系列图显示了包含各种长度的异源多核苷酸的SVV的病毒复制率。

[0058] 图3A是描绘具有mCherry报道基因的各种SVV衍生出的重组RNA复制子构建体的示意图。图3B的一系列成像图显示了用复制子转染的H1299细胞中mCherry的表达。

[0059] 图4A的一系列成像图显示了用复制子Trunc5和/或野生型SVV病毒基因组转染的H1299细胞中mCherry的表达。图4B所含的图显示了用于评价病毒滴度的H446细胞中的IC₅₀测定的结果。

[0060] 图5A是描绘具有mCherry报道基因的各种SVV衍生出的重组RNA复制子构建体的示意图。图5B是显示体外T7 RNA合成的结果的凝胶图像。图5C的一系列成像图显示了用每种复制子转染的细胞的mCherry信号。

[0061] 图6A是描绘野生型SVV病毒基因组和携带mCherry报道基因的SVV衍生出的重组RNA复制子示意图。图6B是描绘携带不同报道基因的SVV衍生出T的重组RNA复制子runc10的示意图。

[0062] 图7A是描绘携带编码鼠IL-2有效负载的转基因的SVV-复制子Trunc10的示意图。图7B所含的两幅图显示了mIL-2表达的结果。图7C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0063] 图8A是描绘SVV-复制子Trunc10的示意图,其携带编码单链mIL-12 (scmIL-12) 的转基因,具有和没有信号序列。图8B的图显示了通过taqman测定分析的RNA拷贝数的结果。图8C所含的两幅图显示了鼠IL-12的表达。

[0064] 图9A是描绘SVV-复制子Trunc10的示意图,其携带编码人IL-36 γ 的转基因,具有天然信号序列或具有IL2信号序列。图9B所含的两幅图显示了转染或转衣壳化以后hIL-36 γ 的分泌。图9C所含的两幅图显示了通过taqman测定分析的RNA拷贝数的结果。

[0065] 图10A是描绘在单个有效负载下游掺入脑心肌炎病毒 (EMCV) IRES的双顺反子复制子的示意图。图10B的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0066] 图11A是描绘在多个有效负载下游掺入脑心肌炎病毒 (EMCV) IRES的双顺反子双重有效负载复制子的示意图,在第一有效负载和第二有效负载 (eGFP) 之间被弗林蛋白酶-T2A位点隔开。图11B的一系列图像显示了在感染后24小时mCherry和GFP的表达。

[0067] 图12A是描绘双重有效负载复制子示意图,所述复制子在RdRp和3' UTR之间在复制子的3' 末端掺入第二有效负载。图12B的图显示了转染以后hIL-36 γ 的分泌。图12C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0068] 图13A是分析his-标记的1DLT176-MTT10-DLL3-VHH-CD3 LiTE的表达的抗-His蛋白质印迹。图13B的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0069] 图14A是分析his-标记的rDLL3- α CD3-BiTE的表达的抗-His蛋白质印迹。图14B的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0070] 图15A是描绘Trunc10复制子的示意图,所述复制子包含在his-标记的抗mFAP BiTE和CXCL10之间的替代切割肽 (3C,或弗林蛋白酶-3C,或弗林蛋白酶T2A)。图15B的图显示了CXCL10的表达的结果。图15C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0071] 图16A是描绘Trunc10复制子的示意图,所述复制子包含在his-标记的抗-mFAP BiTE和CXCL10之间的替代切割肽 (T2A、P2A、F2A或E2A)。图16B的图显示了CXCL10的表达的结果。图16C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0072] 图17A是描绘复制子多核苷酸的构型的示意图,所述复制子多核苷酸编码通过IGSF1多肽可操作地连接的双重有效负载分子 (SEQ ID NO:75和76)。图17B的图显示了IL-36 γ 的表达的结果。图17C的图显示了IL-2的表达的结果。图17D的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0073] 图18A是描绘相同开放读码框中两个分泌型有效负载的HIV-1蛋白酶介导的加工的示意图。图18B的图显示了通过taqman测定分析的RNA拷贝数的结果。图18C所含的两幅图显示了两个有效负载的表达的结果。

[0074] 图19A是描绘包含BiTE和hIL-36 γ 的双重有效负载复制子的示意图。图19B的图显示了hIL-36 γ 的表达。图19C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0075] 图20A是描绘三重有效负载复制子T10-BiTE-IL3g6-IL2的示意图。图20B所含的两幅图显示了hIL-36和mIL-2的表达。图20C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0076] 图21A是描绘三重有效负载复制子T10-mIL2-BiTE-hIL-36 γ 的替代设计的示意图。图21B所含的两幅图显示了hIL-36和mIL-2的表达。图21C的图显示了通过taqman测定分析的RNA拷贝数的结果。

[0077] 图22A是描绘三重有效负载复制子T10-mIL2-hIL-36 γ -BiTE的另一种设计的示意图。图22B的图显示了通过taqman测定分析的RNA拷贝数的结果。图22C的一系列图显示了上清液和裂解物中hIL-36和mIL-2的表达。

[0078] 图23A的图显示了基于NCI-H69细胞的小鼠模型中体内hIL-36 γ 表达的结果。图23B的图显示了基于NCI-H446细胞的小鼠模型中体内hIL-36 γ 表达的结果。

[0079] 图24是描绘野生型柯萨奇病毒病毒基因组和一种示例性的柯萨奇病毒衍生出的携带mCherry报道基因的重组RNA复制子的示意图。

[0080] 图25A的一系列图像显示了用复制子和/或对照载体转染的细胞中的mCherry和GFP表达。图25B所含的两个图像显示了mCherry的表达,其证实了在与野生型病毒基因组一起的共转染中复制子的转衣壳化。

[0081] 图26的简图描绘了SVV衍生出的复制子和Neg-RNA的体外转录过程。5'和3'核酶(Rib)对SVV衍生出的复制子的自动催化切割产生了SVV衍生出的复制子,其具有复制所需的单独5'和3'末端。相反,Neg-RNA构建体缺乏核酶序列且不能复制和病毒粒子产生。

[0082] 图27的简图描绘了为了维持复制子的天然5'和3'单独末端使用连接切割序列从基因组转录物除去非病毒RNA多核苷酸。

[0083] 图28A-28B的示意图显示了用于产生单独5'末端的锤头核酶。图28A的示意图显示了在箭头处在5'末端退火和切割的最小锤头核酶(HHR)的结构模型(SEQ ID NO:108)。图28B的示意图显示了在箭头处切割5'末端的具有稳定化茎I(STBL)的核酶的结构模型(SEQ ID NO:109)。

[0084] 图29A-29B的示意图显示了用于产生单独5'末端的手枪核酶。图29A的示意图显示了野生型手枪核酶(SEQ ID NO:110,111)特征。图29B的示意图显示了来自多粘类芽孢杆菌(*P. Polymyxa*)的手枪核酶(SEQ ID NO:112),其具有加入的四环以融合通过mFOLD建模的P3链。虚线框是为了在病毒序列的背景下保持核酶的折叠而诱变处理的区域。在虚线框中显示的“GUC”序列被突变为“UCA”以产生手枪1,且“GUC”序列被突变为“TTA”以产生手枪2。

具体实施方式

[0085] 溶瘤病毒是具有能够感染和裂解肿瘤细胞的裂解生命周期的有复制能力的病毒。直接的肿瘤细胞裂解不仅导致细胞死亡,而且产生针对由局部抗原呈递细胞摄取和呈递的肿瘤抗原的适应性免疫应答。因此,溶瘤病毒通过直接细胞裂解和通过促进能够在病毒清除后维持抗肿瘤应答的抗原特异性适应性应答来对抗肿瘤细胞生长。

[0086] 可以将溶瘤病毒基因工程改造以表达有效负载分子-例如,通过将编码合乎需要的有效负载蛋白的异源多核苷酸掺入病毒基因组中。但是,由于病毒衣壳蛋白的包装能力,只有有限长度的多核苷酸可以整合到完整病毒基因组中而不会损害病毒的复制率、衣壳化和/或功能。此外,从单个合成的病毒基因组或病毒复制子表达多种功能性有效负载分子可能具有挑战性。有效负载分子掺入的这些限制限制了病毒治疗剂在转移性癌症的治疗中的使用。

[0087] 本领域需要溶瘤病毒衍生出的复制子,其包含改进的掺入编码有效负载分子的异源多核苷酸的能力,其可以用于各种治疗剂诸如抗癌治疗剂中。异源序列可以编码一个或多个在本文中称为有效负载分子的分子。在某些实施方案中,本公开内容的有效负载序列

和有效负载分子不介导病毒功能。在某些实施方案中,本公开内容的有效负载序列和有效负载分子可以分离自或衍生自特定物种,所述特定物种与意图施用病毒复制以表达有效负载序列或有效负载分子的受试者或细胞的物种匹配或同源。异源序列可以编码以下中的一种或多种:编码或非编码核酸序列、DNA序列、RNA序列、氨基酸序列、肽、多肽、蛋白或它们的任意组合。

[0088] 本公开内容提供了衍生自小核糖核酸病毒基因组的重组RNA复制子,其具有改进的掺入编码有效负载分子的异源多核苷酸的能力。在某些实施方案中,本公开内容的重组RNA复制子表达来自相同复制子的两个或更多个功能性有效负载分子。描述了表达两个或更多个有效负载分子的复制子的示例性构型。本公开内容进一步提供了包含重组RNA复制子的颗粒。在某些实施方案中,所述颗粒进一步包含完整病毒基因组。在某些实施方案中,所述重组RNA复制子可以被完整病毒基因组表达的衣壳蛋白转衣壳化。在某些实施方案中,使细胞与所述颗粒接触允许产生两组感染性病毒颗粒,一组包含重组RNA复制子,且另一组包含完整病毒基因组。在某些实施方案中,两组的病毒颗粒可以一起感染细胞,这允许在体内或在体外连续产生两组的病毒颗粒。在某些实施方案中,本公开内容提供了用于治疗 and 预防增殖性疾病和障碍(例如,癌症)的重组RNA复制子和使用方法。本公开内容能够全身性递送适用于治疗广泛的增殖性障碍(例如,癌症)的有效重组RNA复制子。

[0089] 在本文中使用的章节标题仅仅用于组织目的,不应解释为限制描述的主题。本文引用的所有文件或文件的部分,包括、但不限于专利、专利申请、文章、书籍和论文,出于任何目的特此明确地通过引用整体并入。在一个或多个并入的文件或文件的部分定义了与本申请中该术语的定义相矛盾的术语的情况下,以出现在本申请中的定义为准。但是,本文引用的任何参考文献、文章、出版物、专利、专利公开和专利申请的提及并不且不应被视为承认或任何形式的暗示:它们在世界上的任何国家构成有效的现有技术或形成普通一般知识的一部分。

[0090] 重组RNA复制子

[0091] 小核糖核酸病毒基因组遵循保守的4-3-4格式,其中单个多蛋白被病毒编码的蛋白酶切割成5'前导蛋白(仅存在于某些物种中)、四种结构蛋白和七种(3+4)非结构蛋白。小核糖核酸病毒基因组以5'非翻译区(UTR)开始,并包括内部核糖体进入位点(IRES)。与IRES相邻,5'前导蛋白是一种蛋白酶,其位于翻译的小核糖核酸病毒多蛋白的5'末端,尽管它并不存在于小核糖核酸病毒科的所有成员中。这之后是多蛋白的P1区域,分别按顺序编码衣壳蛋白VP4、VP2、VP3和VP1。这些蛋白分别由VP4编码区、VP2编码区、VP3编码区和VP1编码区编码(这四个编码区统称为“VP编码区”)。翻译的多蛋白的P2区域由2A、2B和2C组成。小核糖核酸病毒2A是这样的蛋白:其在小核糖核酸病毒基因组中可以不存在,或者在某些情况下以超过一个拷贝存在。小核糖核酸病毒多蛋白的最后一段是P3,包含3A、3B、3C和3D。3B(也被称作VPg)是一种与基因组的5'末端结合并在基因组复制中起重要作用的小蛋白。由3C编码的蛋白酶执行小核糖核酸病毒多蛋白的大部分切割以及抑制宿主转录。最后一种小核糖核酸病毒蛋白是3D,即RNA依赖性的RNA聚合酶(RdRp)。小核糖核酸病毒的3'UTR通常具有聚腺苷酸尾巴。

[0092] 本公开内容提供了包含小核糖核酸病毒基因组的重组RNA复制子,其中所述小核糖核酸病毒基因组包含在一个或多个编码区中的缺失和/或截短。在某些实施方案中,所述

编码区编码结构蛋白 (VP4、VP2、VP3和VP1)。在某些实施方案中,所述复制子的小核糖核酸病毒基因组包含所有VP编码区的缺失。在某些实施方案中,所述复制子的小核糖核酸病毒基因组包含VP1、VP3和VP2编码区中的每一个的缺失和/或截短。在某些实施方案中,所述复制子的小核糖核酸病毒基因组包含VP1和VP3编码区的缺失和VP2编码区的截短。在某些实施方案中,在小核糖核酸病毒基因组的VP编码区内的缺失和截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。在某些实施方案中,在小核糖核酸病毒基因组的VP编码区内的总缺失和截短是至少2000bp。

[0093] 在某些实施方案中,所述重组RNA复制子包含一个或多个异源多核苷酸。在某些实施方案中,所述异源多核苷酸插入所述缺失或截短的位点中。在某些实施方案中,所述异源多核苷酸插入在2A编码区和2B编码区之间。在某些实施方案中,所述异源多核苷酸插入在3D (RdRp) 编码区和3' 非翻译区 (UTR) 之间。在某些实施方案中,所述一个或多个异源多核苷酸包含至少1000bp、至少2000bp或至少3000bp。

[0094] 在某些实施方案中,所述小核糖核酸病毒基因组选自塞内卡病毒基因组、心病毒基因组、肠道病毒基因组和口蹄疫病毒基因组。在某些实施方案中,所述病毒基因组衍生自小核糖核酸病毒,其选自心病毒、Cosavirus、肠道病毒、嗜肝病毒、嵴病毒、副肠孤病毒、Rosavirus、Salivirus、Pasivirus、塞内卡病毒及其嵌合病毒基因组。在某些实施方案中,所述病毒基因组衍生自小核糖核酸病毒,其选自人鼻病毒、HRV (SEQ ID NO:5;GenBank登记号K02121.1)、脊髓灰质炎病毒、PV (SEQ ID NO:6;GenBank登记号AF111984.2)、柯萨奇病毒A、CVA (SEQ ID NO:7;GenBank登记号AF546702.1)、牛肠道病毒、BEV (SEQ ID NO:8;GenBank登记号NC_001859.1)、肠道病毒71、EV71 (SEQ ID NO:9;GenBank登记号KJ686308.1)、埃可病毒、ECHO (SEQ ID NO:10;GenBank登记号AF029859.2)、口蹄疫病毒、FMDV (SEQ ID NO:11;GenBank登记号DQ989323.1)、塞内卡谷病毒、SVV (SEQ ID NO:12;GenBank登记号NC_011349.1)、Theiler氏鼠脑脊髓炎病毒、TMEV (SEQ ID NO:13;GenBank登记号M20301.1)、门戈病毒、MEV (SEQ ID NO:14;GenBank登记号L22089.1)、脑心肌炎、EMCV (SEQ ID NO:15;GenBank登记号X74312.1) -每种病毒的NCBI GenBank登记号在括号中指出。在某些实施方案中,所述小核糖核酸病毒基因组是塞内卡谷病毒基因组。在某些实施方案中,所述小核糖核酸病毒基因组是柯萨奇病毒基因组。在某些实施方案中,所述小核糖核酸病毒基因组是脑心肌炎病毒基因组。在某些实施方案中,所述小核糖核酸病毒基因组是脊髓灰质炎病毒基因组 (包括嵌合脊髓灰质炎病毒诸如PVS-RIP0)。

[0095] 在某些实施方案中,本文所述的重组RNA复制子包含嵌合小核糖核酸病毒基因组 (例如,这样的病毒基因组,其包含一个衍生自第一种小核糖核酸病毒的部分,诸如衣壳蛋白或IRES,和另一个衍生自第二种小核糖核酸病毒的部分,诸如非结构蛋白酶或聚合酶编码区)。

[0096] 在某些实施方案中,所述重组RNA复制子保留正链和/或负链RNA合成的能力。在某些实施方案中,所述重组RNA复制子的正链和/或负链RNA合成率为对应的野生型病毒基因组的合成率的至少1%、至少5%、至少10%、至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%或至少100%。

[0097] 在某些实施方案中,所述重组RNA复制子保留与野生型病毒基因组相当的病毒复制率。在某些实施方案中,所述重组RNA复制子的病毒复制率为对应的野生型病毒基因组的

病毒复制率的至少1%、至少5%、至少10%、至少20%、至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少90%或至少100%。

[0098] 在某些实施方案中,将所述重组RNA复制子提供为重组核糖核酸(RNA)。在某些实施方案中,所述重组RNA复制子包含一个或多个核酸类似物。核酸类似物的例子包括2'-O-甲基-取代的RNA、2'-O-甲氧基-乙基碱基、2' 氟碱基、锁核酸(LNAs)、未锁核酸(UNA)、桥连核酸(BNA)、吗啉代和肽核酸(PNA)。在某些实施方案中,所述重组RNA复制子是环状RNA分子(circRNA)或单链RNA(ssRNA)。在某些实施方案中,所述单链RNA是有义或负义链。

[0099] 在某些实施方案中,所述重组RNA复制子是环状RNA分子(circRNA)。CircRNA分子缺乏外切核酸酶介导的降解所必需的游离末端,因此延长了RNA分子的半衰期,并随着时间的推移实现更稳定的蛋白生产。为了从circRNA分子产生功能性RNA复制子,有必要一旦进入细胞内就“打开”环状构建体,使得可以产生具有适当3' 和5' 天然末端的线性RNA复制子。因此,在某些实施方案中,将所述重组RNA复制子提供为circRNA分子并且进一步包含一个或多个额外的RNA序列,所述RNA序列有助于细胞内circRNA分子的线性化。这样的额外的RNA序列的例子包括siRNA靶位点、miRNA靶位点和指导RNA靶位点。对应的siRNA、miRNA或gRNA可以与circRNA分子共同配制。可替换地,可以基于同源miRNA在靶细胞中的表达来选择miRNA靶位点,使得circRNA分子的切割和复制子的复制限于表达特定miRNA的靶细胞。

[0100] 重组SVV复制子

[0101] 本公开内容提供了包含塞内卡谷病毒(SVV)病毒基因组的重组RNA复制子,其中所述SVV基因组包含在一个或多个SVV蛋白编码区中的缺失或截短。在某些实施方案中,所述复制子包含异源多核苷酸。

[0102] 在某些实施方案中,所述SVV基因组选自野生型SVV基因组(诸如SVV-A,SEQ ID NO:1)或突变体SVV基因组(诸如SVV-IR2,SEQ ID NO:2)。在某些实施方案中,本公开内容的重组RNA复制子包含嵌合SVV基因组。

[0103] 对于SVV病毒基因组,所述VP4编码区包括根据SEQ ID NO:1的核苷酸904至核苷酸1116。所述VP2编码区包括根据SEQ ID NO:1的核苷酸1117至核苷酸1968。所述VP3编码区包括根据SEQ ID NO:1的核苷酸1969至核苷酸2685。所述VP1编码区包括根据SEQ ID NO:1的核苷酸2686至核苷酸3477。所述2A编码区包括根据SEQ ID NO:1的核苷酸3478至核苷酸3504。所述2B编码区包括根据SEQ ID NO:1的核苷酸3505至核苷酸3888。

[0104] 在某些实施方案中,所述复制子的SVV基因组包含在一个或多个VP编码区中的缺失和/或截短。在某些实施方案中,将本文所述的复制子与合成的病毒基因组联合施用给受试者。不希望受任何特定理论约束,有人认为,删除和/或截短复制子中的VP编码区将:1) 便利比病毒本身更大的有效负载盒的容纳,和/或2) 使复制子自身不能在细胞之间传播。

[0105] 在某些实施方案中,VP4、VP2、VP3和VP1编码区中的一个或至少一个被删除和/或截短。在某些实施方案中,包含VP4、VP2、VP3和VP1的VP编码区中的两个或至少两个被删除和/或截短。在某些实施方案中,包含VP2、VP3和VP1的VP编码区中的两个或至少两个被删除和/或截短。在某些实施方案中,包含VP4、VP2、VP3和VP1的VP编码区中的三个或至少三个被删除和/或截短。在某些实施方案中,所有的VP4、VP2、VP3和VP1编码区被删除和/或截短。在某些实施方案中,所述VP2编码区被截短且VP3编码区和VP1编码区中的一个被删除或截短。在某些实施方案中,所述VP2编码区被截短且VP3和VP1编码区都被删除和/或截短。在某些

实施方案中,所述复制子的SVV基因组包含VP1、VP3和VP2编码区中的每一个的缺失和/或截短。在某些实施方案中,所述复制子的SVV基因组包含VP1和VP3编码区的缺失和VP2编码区的截短。在某些实施方案中,所述复制子的SVV基因组包含遵循以下表1中列出的模式之一的在VP2-VP3-VP1区域中的一个或多个缺失或截短。

[0106] 表1. 在SVV基因组的VP2-VP3-VP1区域中的缺失或截短的模式

[0107]

模式**\编码区	VP2	VP3	VP1
1	T	N	N
2	T	N	T
3	T	N	D
4	T	T	N
5	T	T	T
6	T	T	D
7	T	D	N
8	T	D	T
9	T	D	D
10	N	N	N
11	N	N	T
12	N	N	D
13	N	T	N
14	N	T	T
15	N	T	D
16	N	D	N
17	N	D	T
18	N	D	D

[0108] **“D”指示缺失;“T”指示截短;“N”指示无截短或缺失。

[0109] 在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1和图1的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短、基本上由其组成或由其组成。在某些实施方案中,所述复制子的SVV基因组包含与根据SEQ ID NO:1的核苷酸1261至核苷酸3477(包括端点)对应的SVV基因组区域的缺失。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1407至核苷酸3477对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1599至核苷酸3477对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1683至核苷酸3477对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1924至核苷酸3477对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸2467至核苷酸3477对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1261至核苷酸3300对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1261至核苷酸3000对应的区域内的一个或多个缺失或截短。在某些实施

方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1261至核苷酸2700对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1261至核苷酸2400对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:1的核苷酸1261至核苷酸2100对应的区域内的一个或多个缺失或截短。所有范围都包括端点。

[0110] 在某些实施方案中,每个缺失或截短包含1个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含10个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含50个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含100个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含500个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含1000个或更多个核苷酸。

[0111] 在某些实施方案中,所述一个或多个缺失或截短包含共计至少500bp、至少600bp、至少700bp、至少800bp、至少900bp、至少1000bp、至少1100bp、至少1200bp、至少1300bp、至少1400bp、至少1500bp、至少1600bp、至少1700bp、至少1800bp、至少1900bp、至少2000bp、至少2100bp或至少2200bp的核苷酸。在某些实施方案中,所述一个或多个缺失或截短由共计500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp、2400bp (或之间的任何值)的核苷酸组成。在某些实施方案中,所述一个或多个缺失或截短由共计500-2400bp之间、500-2300bp之间、500-2200bp之间、500-2000bp之间、500-1500bp之间、500-1000bp之间、1000-2300bp之间、1000-2200bp之间、1000-2000bp之间、1000-1500bp之间、1500-2300bp之间、1500-2200bp之间、1500-2000bp之间、2000-2300bp或2000-2200bp之间的核苷酸组成。所有范围都包括端点。

[0112] 在某些实施方案中,所述复制子的SVV基因组包含5' UTR。在某些实施方案中,所述复制子的SVV基因组包含5' 前导蛋白编码序列。在某些实施方案中,所述复制子的SVV基因组包含非截短的VP4编码区。在某些实施方案中,所述复制子的SVV基因组包含VP2编码区或其截短体。

[0113] 在某些实施方案中,所述复制子的SVV基因组从5' 至3' 包含5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体。在某些实施方案中,包含5' UTR、5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的复制子的SVV基因组的部分与SEQ ID NO:1或SEQ ID NO:2的核苷酸1至1260具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性。在某些实施方案中,包含5' UTR、5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的复制子的SVV基因组的部分与SEQ ID NO:1或SEQ ID NO:2的核苷酸1至1260具有约70%、约75%、约80%、约85%、约90%、约93%、约95%、约97%、约98%、约99%、约99.5%或100%序列同一性。在某些实施方案中,包含5' UTR、5' 前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的复制子的SVV基因组的部分具有根据SEQ ID NO:1或SEQ ID NO:2的核苷酸1至1260的至多1个、至多5个、至多10个或至多20个核苷酸突变。

[0114] 在某些实施方案中,所述复制子的SVV基因组包含VP2编码区的5' 部分。在某些实施方案中,所述内源性VP2编码区的5' 部分是至少50bp、至少60bp、至少70bp、至少80bp、至少90bp、至少100bp、至少110bp、至少120bp、至少130bp、至少140bp或至少145bp的长度。在

某些实施方案中,所述内源性VP2编码区的5'部分包含约50bp、约60bp、约70bp、约80bp、约90bp、约100bp、约110bp、约120bp、约130bp、约140bp、约145bp、或之间的任何值。在某些实施方案中,所述内源性VP2编码区的5'部分是小于50bp、小于60bp、小于70bp、小于80bp、小于90bp、小于100bp、小于110bp、小于120bp、小于130bp、小于140bp或小于145bp的长度。所有范围都包括端点。

[0115] 在某些实施方案中,所述复制子的SVV基因组包含顺式作用复制元件(CRE)。在某些实施方案中,所述复制子的SVV基因组的VP2编码区或其截短体包含CRE。在某些实施方案中,所述复制子的SVV基因组中包含VP4编码区和VP2编码区或其截短体的区域包含CRE。

[0116] 在某些实施方案中,所述CRE包含约10bp、约20bp、约30bp、约40bp、约50bp、约60bp、约70bp、约80bp、约90bp、约100bp、约110bp、约120bp、约130bp、约140bp、约150bp、约160bp、约170bp、约180bp、约190bp、约200bp(或之间的任何值)的核苷酸。在某些实施方案中,所述CRE包含至少10bp、至少20bp、至少30bp、至少40bp、至少50bp、至少60bp、至少70bp、至少80bp、至少90bp、至少100bp、至少110bp、至少120bp、至少130bp、至少140bp、至少150bp、至少160bp、至少170bp、至少180bp、至少190bp或至少200bp的核苷酸。在某些实施方案中,所述CRE包含10-200bp之间、10-150bp之间、10-100bp之间、10-75bp之间、10-60bp之间、10-50bp之间、20-200bp之间、20-150bp之间、20-100bp之间、20-75bp之间、20-60bp之间、20-50bp之间、30-200bp之间、30-150bp之间、30-100bp之间、30-75bp之间、30-60bp之间、30-50bp之间、40-200bp之间、40-150bp之间、40-100bp之间、40-75bp之间、40-60bp之间、40-50bp之间、50-200bp之间、50-150bp之间、50-100bp之间、50-75bp之间或50-60bp之间的核苷酸。所有范围都包括端点。

[0117] 在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260对应的区域内的一个或多个核苷酸。在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260、核苷酸1050至核苷酸1260、核苷酸1100至核苷酸1260、核苷酸1150至核苷酸1260、核苷酸1200至核苷酸1260、核苷酸1000至核苷酸1250、核苷酸1050至核苷酸1250、核苷酸1100至核苷酸1250、核苷酸1150至核苷酸1250、核苷酸1200至核苷酸1250、核苷酸1000至核苷酸1200、核苷酸1050至核苷酸1200、核苷酸1100至核苷酸1200、核苷酸1150至核苷酸1200、核苷酸1000至核苷酸1150、核苷酸1050至核苷酸1150、核苷酸1100至核苷酸1150、核苷酸1000至核苷酸1100或核苷酸1050至核苷酸1100对应的区域内的一个或多个核苷酸。在某些实施方案中,所述CRE位于与根据SEQ ID NO:1的核苷酸1000至核苷酸1260、核苷酸1050至核苷酸1260、核苷酸1100至核苷酸1260、核苷酸1150至核苷酸1260、核苷酸1200至核苷酸1260、核苷酸1000至核苷酸1250、核苷酸1050至核苷酸1250、核苷酸1100至核苷酸1250、核苷酸1150至核苷酸1250、核苷酸1200至核苷酸1250、核苷酸1000至核苷酸1200、核苷酸1050至核苷酸1200、核苷酸1100至核苷酸1200、核苷酸1150至核苷酸1200、核苷酸1000至核苷酸1150、核苷酸1050至核苷酸1150、核苷酸1100至核苷酸1150、核苷酸1000至核苷酸1100或核苷酸1050至核苷酸1100对应的区域内。所有范围都包括端点。

[0118] 在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260对应的区域内的一个或多个核苷酸。在某些实施方案中,所述CRE包含与SEQ ID NO:1的核苷酸1000至核苷酸1260、核苷酸1050至核苷酸1260、核苷酸1100至核苷酸1260、核苷酸1150至核苷酸1260、核苷酸1200至核苷酸1260、核苷酸1000至核苷酸1250、核苷酸1050至核

核苷酸1250、核苷酸1100至核苷酸1250、核苷酸1150至核苷酸1250、核苷酸1200至核苷酸1250、核苷酸1000至核苷酸1200、核苷酸1050至核苷酸1200、核苷酸1100至核苷酸1200、核苷酸1150至核苷酸1200、核苷酸1000至核苷酸1150、核苷酸1050至核苷酸1150、核苷酸1100至核苷酸1150、核苷酸1000至核苷酸1100或核苷酸1050至核苷酸1100对应的多核苷酸序列。在某些实施方案中,所述CRE包含与对应于SEQ ID NO:1的核苷酸1000至核苷酸1260、核苷酸1050至核苷酸1260、核苷酸1100至核苷酸1260、核苷酸1150至核苷酸1260、核苷酸1200至核苷酸1260、核苷酸1000至核苷酸1250、核苷酸1050至核苷酸1250、核苷酸1100至核苷酸1250、核苷酸1150至核苷酸1250、核苷酸1200至核苷酸1250、核苷酸1000至核苷酸1200、核苷酸1050至核苷酸1200、核苷酸1100至核苷酸1200、核苷酸1150至核苷酸1200、核苷酸1000至核苷酸1150、核苷酸1050至核苷酸1150、核苷酸1100至核苷酸1150、核苷酸1000至核苷酸1100或核苷酸1050至核苷酸1100的多核苷酸序列具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。所有范围都包括端点。

[0119] 在某些实施方案中,所述CRE包含在与根据SEQ ID NO:1的核苷酸1117至核苷酸1260对应的区域内的一个或多个核苷酸。该CRE区域的多核苷酸序列由SEQ ID NO:149表示。在某些实施方案中,所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的10个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的20个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的30个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的40个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的50个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的60个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的70个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的80个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的90个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实

施方案中,所述CRE包含与SEQ ID NO:149的100个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的110个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的120个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的130个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。在某些实施方案中,所述CRE包含与SEQ ID NO:149的140个连续核苷酸区段具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。

[0120] 在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少500bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少600bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少700bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少800bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少900bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截

短,其中所述一个或多个缺失或截短包含共计至少1000bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1100bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1200bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1300bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1400bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1500bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1600bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1700bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少

1800bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少1900bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少2000bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少2100bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。在某些实施方案中,所述复制子的SVV基因组包含在与根据SEQ ID NO:1的编号的核苷酸1261至核苷酸3477(包括端点)对应的区域内所述SVV基因组的一个或多个缺失或截短,其中所述一个或多个缺失或截短包含共计至少2200bp,且其中所述复制子的SVV基因组包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的CRE多核苷酸序列。

[0121] 在某些实施方案中,所述复制子的SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区中的一个或多个。在某些实施方案中,所述复制子的SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。在某些实施方案中,所述复制子的SVV基因组包含2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。在某些实施方案中,所述复制子的SVV基因组从5'至3'包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。在某些实施方案中,包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区的复制子的SVV基因组的部分与根据SEQ ID NO:1的核苷酸3505至7310具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性。

[0122] 在某些实施方案中,所述重组RNA复制子从5'至3'包含5'前导蛋白编码序列、VP4编码区、VP2编码区或其截短体和异源多核苷酸。在某些实施方案中,所述复制子从5'至3'包含异源多核苷酸和2B编码区。在某些实施方案中,所述重组RNA复制子从5'至3'包含异源多核苷酸、2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)。

[0123] 在某些实施方案中,所述SVV基因组包含2A编码区。在某些实施方案中,所述2A编码区位于VP2编码区或其截短体和异源多核苷酸之间。在某些实施方案中,所述2A编码区位于异源多核苷酸和2B编码区之间。

[0124] 在某些实施方案中,所述SVV衍生出的复制子包含一个或多个异源多核苷酸。在某些实施方案中,所述复制子的异源多核苷酸包含至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。在某些实施方案中,所述一个或多个异源多核苷酸包含共计至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。

[0125] 在某些实施方案中,所述SVV衍生出的复制子包含与SEQ ID NO:20、22、24、26、28、30、32、34、36、38、40、42、44、46、48、50、52、54、56、58和60中的任一个具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性的序列。

[0126] 在某些实施方案中,所述SVV衍生出的复制子包含SVV基因组和异源多核苷酸;其中所述SVV基因组包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的缺失,其中所述缺失是至少500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp或2400bp总长度;其中所述SVV基因组包含CRE,所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%、至少99.5%或100%同一性的多核苷酸序列。

[0127] 在某些实施方案中,所述SVV衍生出的复制子包含SVV基因组和异源多核苷酸;其中所述SVV基因组包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的缺失,其中所述缺失是至少500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp或2400bp总长度;其中所述SVV基因组包含CRE,所述CRE包含与SEQ ID NO:149具有至少90%同一性的多核苷酸序列。

[0128] 在某些实施方案中,所述SVV衍生出的复制子包含SVV基因组和异源多核苷酸;其中所述SVV基因组包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的缺失,其中所述缺失是至少500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp或2400bp总长度;其中所述SVV基因组包含与根据SEQ ID NO:1的核苷酸1至1260具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%、至少99.5%或100%同一性的多核苷酸序列;其中所述SVV基因组包含与根据SEQ ID NO:1的核苷酸3505至7310具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%、至少99.5%或100%同一性的多核苷酸序列;且其中所述SVV基因组包含CRE,所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%、至少99.5%或100%同一性的多核苷酸序列。

[0129] 在某些实施方案中,所述SVV衍生出的复制子包含SVV基因组和异源多核苷酸;其中所述SVV基因组包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的缺失,其中所述缺失是至少500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp或2400bp总长度;其中所述SVV基因组包含与根据SEQ ID NO:1的核苷酸1至1260具有至少90%同一性的多核苷酸序列;其中所述SVV基因组包含与根据SEQ ID NO:1的核苷酸3505至

7310具有至少90%同一性的多核苷酸序列;且其中所述SVV基因组包含CRE,所述CRE包含与SEQ ID NO:149具有至少90%同一性的多核苷酸序列。

[0130] 重组柯萨奇病毒复制子

[0131] 本公开内容提供了包含柯萨奇病毒病毒基因组的重组RNA复制子,其中所述柯萨奇病毒基因组包含在一个或多个柯萨奇病毒蛋白编码区中的缺失或截短。在某些实施方案中,所述复制子包含异源多核苷酸。

[0132] 在某些实施方案中,所述柯萨奇病毒选自CVB3、CVA21和CVA9。示例性的柯萨奇病毒的核酸序列提供为GenBank参考编号M33854.1 (CVB3;SEQ ID NO:16),GenBank参考编号KT161266.1 (CVA21;SEQ ID NO:17),和GenBank参考编号D00627.1 (CVA9;SEQ ID NO:18)。在某些实施方案中,本文所述的重组RNA复制子编码嵌合柯萨奇病毒。

[0133] 对于柯萨奇病毒病毒基因组,所述VP4编码区包括根据SEQ ID NO:3的核苷酸714至核苷酸920。所述VP2编码区包括根据SEQ ID NO:3的核苷酸921至核苷酸1736。所述VP3编码区包括根据SEQ ID NO:3的核苷酸1737至核苷酸2456。所述VP1编码区包括根据SEQ ID NO:3的核苷酸2457至核苷酸3350。所述2A编码区包括根据SEQ ID NO:3的核苷酸3351至核苷酸3797。所述2B编码区包括根据SEQ ID NO:3的核苷酸3798至核苷酸4088。

[0134] 在某些实施方案中,所述重组RNA复制子包含柯萨奇病毒基因组,其包含SEQ ID NO:4的5' UTR序列。在这样的实施方案中,与其它先前描述的5' UTR序列相比,SEQ ID NO:4的5' UTR序列出乎意料地增加功能性柯萨奇病毒的产生。在某些实施方案中,所述重组RNA复制子包含根据SEQ ID NO:3的序列的经修饰的CVA21柯萨奇病毒基因组。

[0135] 在某些实施方案中,所述复制子的柯萨奇病毒基因组包含在一个或多个VP编码区中的缺失和/或截短。在某些实施方案中,VP4、VP2、VP3和VP1编码区中的一个或至少一个被删除和/或截短。在某些实施方案中,包含VP4、VP2、VP3和VP1的VP编码区中的两个或至少两个被删除和/或截短。在某些实施方案中,包含VP4、VP2、VP3和VP1的VP编码区中的三个或至少三个被删除和/或截短。在某些实施方案中,所有的VP4、VP2、VP3和VP1编码区被删除和/或截短。

[0136] 在某些实施方案中,所述复制子的柯萨奇病毒基因组包含在与根据SEQ ID NO:3的核苷酸714至核苷酸3350(包括端点)对应的区域内柯萨奇病毒基因组的一个或多个缺失或截短、基本上由其组成或由其组成。在某些实施方案中,所述复制子的柯萨奇病毒基因组包含与根据SEQ ID NO:3的核苷酸714至核苷酸3350(包括端点)对应的柯萨奇病毒基因组区域的缺失。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:3的核苷酸1000至核苷酸3350对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:3的核苷酸714至核苷酸3350、核苷酸1000至核苷酸3350、核苷酸1500至核苷酸3350、核苷酸2000至核苷酸3350、核苷酸2500至核苷酸3350、核苷酸714至核苷酸3000、核苷酸1000至核苷酸3000、核苷酸1500至核苷酸3000、核苷酸2000至核苷酸3000、核苷酸2500至核苷酸3000、核苷酸714至核苷酸2500、核苷酸1000至核苷酸2500、核苷酸1500至核苷酸2500、核苷酸2000至核苷酸2500、核苷酸714至核苷酸2000、核苷酸1000至核苷酸2000、核苷酸1500至核苷酸2000、核苷酸714至核苷酸1500或核苷酸1000至核苷酸1500(包括端点)对应的区域内的一个或多个缺失或截短。所有范围都包括端点。

[0137] 在某些实施方案中,所述复制子的柯萨奇病毒基因组包含在与根据SEQ ID NO:3

的核苷酸717至核苷酸3332(包括端点)对应的区域内柯萨奇病毒基因组的一个或多个缺失或截短、基本上由其组成或由其组成。在某些实施方案中,所述复制子的柯萨奇病毒基因组包含与根据SEQ ID NO:3的核苷酸717至核苷酸3332(包括端点)对应的柯萨奇病毒基因组区域的缺失。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:3的核苷酸1000至核苷酸3332对应的区域内的一个或多个缺失或截短。在某些实施方案中,所述复制子包含在与根据SEQ ID NO:3的核苷酸717至核苷酸3332、核苷酸1000至核苷酸3332、核苷酸1500至核苷酸3332、核苷酸2000至核苷酸3332、核苷酸2500至核苷酸3332、核苷酸717至核苷酸3000、核苷酸1000至核苷酸3000、核苷酸1500至核苷酸3000、核苷酸2000至核苷酸3000、核苷酸2500至核苷酸3000、核苷酸717至核苷酸2500、核苷酸1000至核苷酸2500、核苷酸1500至核苷酸2500、核苷酸2000至核苷酸2500、核苷酸717至核苷酸2000、核苷酸1000至核苷酸2000、核苷酸1500至核苷酸2000、核苷酸717至核苷酸1500或核苷酸1000至核苷酸1500(包括端点)对应的区域内的一个或多个缺失或截短。所有范围都包括端点。

[0138] 在某些实施方案中,每个缺失或截短包含1个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含10个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含50个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含100个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含500个或更多个核苷酸。在某些实施方案中,每个缺失或截短包含1000个或更多个核苷酸。所有范围都包括端点。

[0139] 在某些实施方案中,所述一个或多个缺失或截短包含共计至少500bp、至少600bp、至少700bp、至少800bp、至少900bp、至少1000bp、至少1100bp、至少1200bp、至少1300bp、至少1400bp、至少1500bp、至少1600bp、至少1700bp、至少1800bp、至少1900bp、至少2000bp、至少2100bp、至少2200bp、至少2300bp、至少2400bp、至少2500bp、至少2600bp、至少2615bp、至少2636bp、至少2650bp或至少2700bp的核苷酸。在某些实施方案中,所述一个或多个缺失或截短由共计500bp、600bp、700bp、800bp、900bp、1000bp、1100bp、1200bp、1300bp、1400bp、1500bp、1600bp、1700bp、1800bp、1900bp、2000bp、2100bp、2200bp、2300bp、2400bp、2500bp、2600bp、2700bp(或之间的任何值)的核苷酸组成。在某些实施方案中,所述一个或多个缺失或截短由共计500-2700bp之间、500-2600bp之间、500-2300bp之间、500-2000bp之间、500-1500bp之间、500-1000bp之间、1000-2700bp之间、1000-2600bp之间、1000-2300bp之间、1000-2000bp之间、1000-1500bp之间、1500-2700bp之间、1500-2600bp之间、1500-2300bp之间、1500-2200bp之间、1500-2000bp之间、2000-2700bp之间、2000-2600bp之间、2000-2300bp之间或2000-2200bp之间的核苷酸组成。所有范围都包括端点。

[0140] 在某些实施方案中,所述复制子的柯萨奇病毒基因组包含5' UTR。在某些实施方案中,所述复制子的柯萨奇病毒基因组的包含5' UTR的部分与SEQ ID NO:4具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性。在某些实施方案中,所述复制子的柯萨奇病毒基因组的包含5' UTR的部分与SEQ ID NO:4具有约70%、约75%、约80%、约85%、约90%、约93%、约95%、约97%、约98%、约99%、约99.5%或100%序列同一性。在某些实施方案中,所述复制子的柯萨奇病毒基因组的包含5' UTR的部分具有根据SEQ ID NO:4的至多1个、至多5个、至多10个或至多20个核苷酸突变。

[0141] 在某些实施方案中,所述复制子的柯萨奇病毒基因组包含2B编码区、2C编码区、3A

编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR中的一个或多个。在某些实施方案中,所述复制子的柯萨奇病毒基因组包含2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。在某些实施方案中,所述复制子的柯萨奇病毒基因组从5' 至3' 方向包含2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。在某些实施方案中,所述柯萨奇病毒基因组的包含2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR的部分与根据SEQ ID NO:3的核苷酸3797至7435具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性。

[0142] 在某些实施方案中,所述复制子从5' 至3' 包含5' UTR和异源多核苷酸。在某些实施方案中,所述复制子从5' 至3' 包含异源多核苷酸和2B编码区。在某些实施方案中,所述重组RNA复制子从5' 至3' 包含异源多核苷酸、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

[0143] 在某些实施方案中,所述复制子进一步包含2A编码区。在某些实施方案中,所述2A编码区位于5' UTR和异源多核苷酸之间。在某些实施方案中,所述2A编码区位于异源多核苷酸和2B编码区之间。在某些实施方案中,所述复制子从5' 至3' 包含5' UTR、异源多核苷酸和2A编码区。在某些实施方案中,所述复制子的柯萨奇病毒基因组从5' 至3' 方向包含异源多核苷酸、2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

[0144] 在某些实施方案中,所述复制子的柯萨奇病毒基因组从5' 至3' 方向包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。在某些实施方案中,包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR的柯萨奇病毒基因组的部分与根据SEQ ID NO:3的核苷酸3492至7435具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性。

[0145] 在某些实施方案中,所述柯萨奇病毒衍生出的复制子包含一个或多个异源多核苷酸。在某些实施方案中,所述复制子的异源多核苷酸具有至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp的长度。在某些实施方案中,所述一个或多个异源多核苷酸具有至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp的总长度。所有范围都包括端点。

[0146] 在某些实施方案中,所述柯萨奇病毒衍生出的复制子包含与SEQ ID NO:62具有至少70%、至少75%、至少80%、至少85%、至少90%、至少93%、至少95%、至少97%、至少98%、至少99%、至少99.5%或100%序列同一性的序列。

[0147] 异源多核苷酸和有效负载分子

[0148] 在某些实施方案中,所述复制子包含编码一个或多个有效负载分子的异源多核苷酸。

[0149] 在某些实施方案中,所述异源核苷酸插入在所述复制子的病毒基因组的2A编码区和2B编码区之间的病毒基因组位置。在某些实施方案中,所述异源核苷酸插入在所述复制子的病毒基因组的2A编码区上游的病毒基因组位置。在某些实施方案中,所述异源核苷酸

插入在3D (RdRp) 或3D pol编码区下游的病毒基因组位置。

[0150] 在某些实施方案中,所述异源核苷酸插入包含SVV病毒基因组的复制子中。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:1的核苷酸1117至3479对应的病毒基因组的区域。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:1的核苷酸3504至3505对应的病毒基因组的区域。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:1的核苷酸7209至7210对应的病毒基因组的区域。

[0151] 在某些实施方案中,所述异源核苷酸插入包含柯萨奇病毒病毒基因组的复制子。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:3的核苷酸713至3351对应的病毒基因组的区域。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:3的核苷酸3797至3798对应的病毒基因组的区域。在某些实施方案中,所述异源核苷酸插入与SEQ ID NO:3的核苷酸7334至7335对应的病毒基因组的区域。

[0152] 在某些实施方案中,将一个或多个miRNA靶序列插入编码有效负载分子的异源多核苷酸中。在某些实施方案中,将一个或多个miRNA靶序列掺入编码有效负载分子的异源多核苷酸的3' 或5' UTR中。在某些实施方案中,将一个或多个miRNA靶序列掺入编码有效负载分子的异源多核苷酸的编码区中。在这样的实施方案中,在表达对应的miRNA的细胞中,有效负载的翻译和随后表达没有发生,或大幅减少。在某些实施方案中,所述有效负载分子是蛋白。

[0153] 在某些实施方案中,所述有效负载分子是分泌型蛋白。在某些实施方案中,所述分泌型蛋白包含信号肽。在某些实施方案中,所述分泌型蛋白包含非天然信号肽。在某些实施方案中,所述信号肽促进有效负载分子的分泌。在某些实施方案中,所述分泌型蛋白不具有信号肽。

[0154] 在某些实施方案中,所述编码有效负载分子的异源多核苷酸与一个或多个病毒蛋白编码区形成连续开放读码框。在这里,连续开放读码框表示可以翻译成连续多肽的特定核苷酸三联体的序列。在某些实施方案中,所述有效负载分子和所述病毒蛋白通过切割多肽连接。在某些实施方案中,所述病毒蛋白是2B。

[0155] 在某些实施方案中,所述有效负载分子是细胞毒性肽。本文中使用的“细胞毒性肽”表示当在宿主细胞中表达时能够诱导细胞死亡和/或当被宿主细胞分泌时能够诱导相邻细胞的细胞死亡的蛋白。在某些实施方案中,所述细胞毒性肽是天冬氨酸特异性半胱氨酸蛋白酶、p53、白喉毒素(DT)、假单胞菌属外毒素A(PEA)、I型核酶灭活蛋白(RIP)(例如,皂草素和白树毒素)、II型RIP(例如,蓖麻蛋白)、志贺样毒素1(Slt1)、光敏活性氧物质(例如杀手红)。在某些实施方案中,所述细胞毒性肽由通过细胞凋亡导致细胞死亡的自杀基因(诸如天冬氨酸特异性半胱氨酸蛋白酶基因)编码。

[0156] 在某些实施方案中,所述有效负载分子是免疫调节肽。本文中使用的“免疫调节肽”是能够调节(例如,活化或抑制)特定免疫受体和/或途径的肽。在某些实施方案中,所述免疫调节肽可以作用于任何哺乳动物细胞,包括免疫细胞、组织细胞和间质细胞。在一个优选的实施方案中,所述免疫调节肽作用于免疫细胞诸如T细胞、NK细胞、NKT T细胞、B细胞、树突细胞、巨噬细胞、嗜碱性粒细胞、肥大细胞或嗜酸性粒细胞。示例性的免疫调节肽包括抗原结合分子诸如抗体或其抗原结合片段、细胞因子、趋化因子、可溶性受体、细胞表面受体配体、双组分多肽和酶。

[0157] 在某些实施方案中,所述有效负载分子是细胞因子诸如IFN γ 、GM-CSF、IL-1、IL-2、IL-12、IL-15、IL-18、IL-36 γ 、TNF α 、IFN α 、IFN β 、IFN γ 或TNFSF14。在某些实施方案中,所述有效负载分子是趋化因子诸如CXCL10、CXCL9、CCL21、CCL4或CCL5。在某些实施方案中,所述有效负载分子是细胞表面受体的配体诸如NKG2D配体、神经纤毛蛋白配体、Flt3配体、CD47配体(例如,SIRP1 α)。在某些实施方案中,所述有效负载分子是可溶性受体,诸如可溶性的细胞因子受体(例如,IL-13R、TGF β R1、TGF β R2、IL-35R、IL-15R、IL-2R、IL-12R和干扰素受体)或可溶性的先天性免疫受体(例如,Toll-样受体、补体受体等)。在某些实施方案中,所述有效负载分子是参与细胞内RNA和/或DNA传感的蛋白的显性激动剂突变体(例如STING、RIG-1或MDA-5的显性激动剂突变体)。

[0158] 在某些实施方案中,所述有效负载分子是抗原结合分子诸如抗体或其抗原结合片段(例如,单链可变片段(scFv)、F(ab)等)。在某些实施方案中,所述抗原结合分子特异性地结合细胞表面受体,诸如免疫检查点受体(例如,PD-1、PD-L1和CTLA4)或参与细胞生长和活化的另外细胞表面受体(例如,OX40、CD200R、CD47、CSF1R、41BB、CD40和NKG2D)。在某些实施方案中,所述抗原结合分子特异性地结合在表3和/或4中所示的抗原。

[0159] 在某些实施方案中,所述有效负载分子是蝎子多肽诸如氯代毒素、BmKn-2、neopladine 1、neopladine 2和mauriporin。在某些实施方案中,所述有效负载分子是蛇多肽诸如蛇毒解聚素、apoxin-I、具窝蝮蛇毒素-I、BJcuL、OHAP-1、rhodostomin、drCT-I、CTX-III、B1L和ACTX-6。在某些实施方案中,所述有效负载分子是蜘蛛多肽诸如latarcin和透明质酸酶。在某些实施方案中,所述有效负载分子是蜜蜂多肽诸如蜂毒肽和蜂毒明肽。在某些实施方案中,所述有效负载分子是蛙多肽诸如PsT-1、PdT-1和PdT-2。

[0160] 在某些实施方案中,所述有效负载分子是酶。在某些实施方案中,所述酶能够通过改变细胞外基质调节肿瘤微环境。在这样的实施方案中,所述酶可以包括、但不限于基质金属蛋白酶(例如,MMP9)、胶原酶、透明质酸酶、明胶酶或弹性蛋白酶。在某些实施方案中,所述酶是基因导向的酶前药治疗(GDEPT)系统的组成部分,诸如单纯疱疹病毒胸苷激酶、胞嘧啶脱氨酶、硝基还原酶、羧肽酶G2、嘌呤核苷磷酸化酶或细胞色素P450。在某些实施方案中,所述酶能够在靶细胞中诱导或活化细胞死亡途径(例如,天冬氨酸特异性半胱氨酸蛋白酶)。在某些实施方案中,所述酶能够降解细胞外代谢物或信息(例如精氨酸酶或15-羟基前列腺素脱氢酶)。

[0161] 在某些实施方案中,所述有效负载分子是双组分多肽(双组分抗原结合分子)。本文中使用的“双组分多肽”表示包含能够结合在非癌性效应细胞(例如,T细胞)上表达的细胞表面抗原的第一结构域和能够结合由靶细胞(例如,癌细胞、肿瘤细胞或不同类型的效应细胞)表达的细胞表面抗原的第二结构域的多聚体蛋白。在某些实施方案中,双组分多肽的各个多肽结构域可以包含抗体或其结合片段(例如,单链可变片段(scFv)或F(ab))、纳米抗体、双体、flexibody、DOCK-AND-LOCKTM抗体或单克隆抗-独特型抗体(mAb2)。在某些实施方案中,所述双组分多肽的结构可以是双可变结构域抗体(DVD-IgTM)、Tandab[®]、双特异性的T细胞接合剂(BiTETM)、DuoBody[®]或双亲和力重新靶向(DART)多肽。在某些实施方案中,所述双组分多肽是BiTE且包含特异性地结合在表3和/或4中所示的抗原的结构域。示例性的BiTE显示在下面表2中。

[0162] 表2:在临床前和临床研究中使用的经验证的BiTE

[0163]

靶标	名称	目标疾病	临床状态
CD19	兰妥莫单抗 /MT-103/MEDI-538	NHL, ALL	阶段 I/II/III
EpCAM	MT110	实体瘤	阶段 I
CEA	MT111/MEDI-565	胃肠道腺癌	阶段 I
PSMA	帕妥昔珠单抗 /BAY2010112/AMG112	前列腺	阶段 I
CD33	AMG330	AML	临床前
EGFR	C-BiTE 和 P-BiTE 抗体	结肠直肠癌	临床前
Her2	FynomAb, COVA420, HER2-BsAb	乳腺癌和胃癌	临床前
EphA2	bscEphA2xCD3	多发性实体瘤	临床前
MCSP	MCSP-BiTE	黑色素瘤	临床前
ADAM17	A300E	前列腺癌	临床前
PSCA	CD3-PSCA(MB1)	前列腺癌	临床前
17-A1	CD3/17-1A-双特异性的	结肠直肠癌	临床前
NKG2D 配体	scFv-NKG2D, huNKG2D-OKT3	多发性实体和液体肿瘤	临床前
DLL3	AMG757	小细胞肺癌	临床

[0164]

[0165] 在某些实施方案中,双组分多肽所结合的、在效应细胞上表达的细胞表面抗原选自下面表3。在某些实施方案中,所述双组分多肽结合CD3或其组分之一。CD3是一种蛋白复合物和T细胞共受体,其作为T细胞多分子受体(TCR)的组成部分在T淋巴细胞上表达。它包含CD3 γ 、CD3 δ 、CD3 ϵ 和/或CD3 ξ 受体链。在某些实施方案中,所述双组分多肽结合NKp46。NKp46(也被称作CD335)属于天然的细胞毒性受体(NCR)家族并且是具有2个Ig-样结构域和一个短细胞质尾巴的糖蛋白。在某些实施方案中,所述双组分多肽结合CD16。CD16(也被称作Fc γ RIII)是在天然杀伤细胞、嗜中性粒细胞、单核细胞和巨噬细胞的表面上发现的分化簇分子。在某些实施方案中,所述双组分多肽结合SIRP α 。SIRP α (也被称作信号调节蛋白 α)是一种来自主要由髓样细胞和干细胞或神经元表达的SIRP家族的调节性膜糖蛋白,其与跨膜蛋白CD47相互作用。

[0166] 在某些实施方案中,在肿瘤细胞或效应细胞上表达的细胞表面抗原选自下面表4。在某些实施方案中,在肿瘤细胞上表达的细胞表面抗原是肿瘤抗原。在某些实施方案中,所述肿瘤抗原选自CD19、EpCAM、CEA、PSMA、CD33、EGFR、Her2、EphA2、MCSP、ADAM17、PSCA、17-A1、NKG2D配体、CSF1R、FAP、GD2、DLL3或神经纤毛蛋白。在某些实施方案中,所述肿瘤抗原选自在表4中列出的那些。

[0167] 在某些实施方案中,所述双组分多肽选自结合DLL3和效应细胞靶抗原的分子、结

合FAP和效应细胞靶抗原的分子、以及结合EpCAM和效应细胞靶抗原的分子。在某些实施方案中,所述效应细胞靶抗原选自表3。在某些实施方案中,所述效应细胞靶抗原是T细胞靶抗原。在某些实施方案中,所述效应细胞靶抗原是CD3。在某些实施方案中,所述效应细胞靶抗原是CD3 ϵ 。

[0168] 表3:示例性的效应细胞靶抗原

T 细胞		NKT 细胞	NK 细胞	其它
CD3	CD30	CD3	CD16	CD48
CD3 γ	CD38	CD3 γ	CD94/NKG2 (例如, NKG2D)	轻
CD3 δ	CD40	CD3 δ	NKp30	CD44
CD3 ϵ	CD57	CD3 ϵ	NKp44	CD45
CD3 ξ	CD69	CD3 ξ	NKp46	IL-1R2
CD2	CD70	不变的 TCR	KAR	IL-1R α
CD4	CD73			IL-1R α 2
CD5	CD81			IL-13R α 2
CD6	CD82			IL-15R α
CD7	CD96			CCR5
CD8	CD134			CCR8
CD16	CD137			SIRP α
CD25	CD152			
CD27	CD278			
CD28				

[0170] 表4:示例性的靶细胞抗原

靶细胞抗原			
8H9	CRISP3	Lewis-Y	Fas
GnT-V, β 1,6-N	DC-SIGN	LIV-1 (SLC39A6)	SOX2
AFP	DHFR	Livin	STEAP1
ART1	EGP40	LAMP1	SLITRK6

[0172]

靶细胞抗原			
ART4	EZH2	MAGEA3	NaPi2a
ABCG2	EpCAM	MAGEA4	SOX1
B7-H3	EphA2	MAGEB6	SOX11
B7-H4	EphA2/Eck	MAGEA1	SPANXA1
B7-H6	EGFRvIII	MART-1	SART-1
BCMA	E-钙粘着蛋白	MCSP	SSX4
B-细胞周期蛋白	EGP2	MME	SSX5
BMI1	ETA	间皮素(MSLN)	存活素
CA-125	ERBB3	MAPK1	SSX2
钙粘着蛋白	ERBB3/4	MUC16	TAG72
CABYR	ERBB4	MUC1	TEM1
CTAG2	EPO	MRP-3	TEM8
CA6	F3	MyoD-1	TSGA10
CAIX	FAR	NCAM	TSSK6
CEA	FBP	连接素 4	甲状腺球蛋白
CEACAM5	FTHL17	巢蛋白	转铁蛋白受体
CEACAM6	胎儿 AchR	NEP	TACSTD2 (TROP2)
Cav-1	FAP	NY-ESO-1	TMEM97
CD10	FGFR3	hHLA-A	TRP-2
CD117	FR-a	H60	TULP2
CD123	Fra-I/Fosl 1	OLIG2	TROP2
CD133	GAGE1	5T4	酪氨酸酶
CD138	GD2	p53	TRP1
CD15	GD3	P-钙粘着蛋白	UPAR
CD171	Gli1	PB	VEGF
CD19	GP100	P-糖蛋白	VEGF 受体
CD20	GPA33	PMCT (SLC13A5)	VEGFR2
CD21		PRAME	BRAF
CD22	磷脂酰肌醇蛋白 聚糖-3	PROX1	WT-1
CD30	HIV gp120	PSA	XAGE2

[0173]

靶细胞抗原			
CD33	HLA-A	PSCA	ZNF165
CD37	HLA-A2	PSMA	$\alpha_v\beta_6$ 整联蛋白
CD38	HLA-AI	PSC1	β -连环蛋白
CD44v6	HLA-B	PVRL4	组织蛋白酶 B
CD44v7/8	HLA-C	Ras	CSAG2
CD74	HMW-MAA	ROR1	CTAG
Cd79b	Her2/Neu	SART2	EGFR
CD124 (IL-4R)	Her3	SART3	EGP40
CDH3	u70/80	纤连蛋白的癌胚 胎变体	EZH2
Ki-67	LICAM	腱糖蛋白	HIV sp120
CSPG4	ULBP1	LICAM	κ 轻链
CALLA	ULBP2	Rae-1 α	LDHC
CSAG2	ULBP3		TRP-1
COX-2	ULBP6	Rae-1 β	Fas-L
λ	MICA	Rae-1 δ	DLL3
LAYN	MICB	Rae-1 γ	MAGEA12
LeuM-1	Her3	PDGF	MAGEC2
KDR	EGF	SSX	BAGE
CD47	SIRP1 α	SSX2	BAGE1
	细胞周期蛋白 A	KKLC1	GAGE
	KMHN1	SAGE	XAGE
		SPA17	XAGE1B

[0174] 在某些实施方案中,所述双组分多肽特异性地结合根据下面表5标记为“x”的两种抗原的组合。在表5中具有相同抗原的那些“x”标记的组合指示,双组分多肽特异性地结合相同抗原的两种不同表位。在某些实施方案中,所述双组分多肽是BiTE。

[0175] 表5. 用于双组分多肽结合的两两种抗原的组合

[0176]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
8H9	x	x	x	x	x	x	x	x	x	x	x	x	x
GnT-V, β 1,6-N	x	x	x	x	x	x	x	x	x	x	x	x	x
AFP	x	x	x	x	x	x	x	x	x	x	x	x	x

[0177]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
ART1	x	x	x	x	x	x	x	x	x	x	x	x	x
ART4	x	x	x	x	x	x	x	x	x	x	x	x	x
ABCG2	x	x	x	x	x	x	x	x	x	x	x	x	x
B7-H3	x	x	x	x	x	x	x	x	x	x	x	x	x
B7-H4	x	x	x	x	x	x	x	x	x	x	x	x	x
B7-H6	x	x	x	x	x	x	x	x	x	x	x	x	x
BCMA	x	x	x	x	x	x	x	x	x	x	x	x	x
B-细胞周期蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
BMI1	x	x	x	x	x	x	x	x	x	x	x	x	x
CA-125	x	x	x	x	x	x	x	x	x	x	x	x	x
钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
CABYR	x	x	x	x	x	x	x	x	x	x	x	x	x
CTAG2	x	x	x	x	x	x	x	x	x	x	x	x	x
CA6	x	x	x	x	x	x	x	x	x	x	x	x	x
CAIX	x	x	x	x	x	x	x	x	x	x	x	x	x
CEA	x	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM5	x	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM6	x	x	x	x	x	x	x	x	x	x	x	x	x
Cav-1	x	x	x	x	x	x	x	x	x	x	x	x	x
CD10	x	x	x	x	x	x	x	x	x	x	x	x	x
CD117	x	x	x	x	x	x	x	x	x	x	x	x	x
CD123	x	x	x	x	x	x	x	x	x	x	x	x	x
CD133	x	x	x	x	x	x	x	x	x	x	x	x	x
CD138	x	x	x	x	x	x	x	x	x	x	x	x	x
CD15	x	x	x	x	x	x	x	x	x	x	x	x	x
CD171	x	x	x	x	x	x	x	x	x	x	x	x	x
CD19	x	x	x	x	x	x	x	x	x	x	x	x	x
CD20	x	x	x	x	x	x	x	x	x	x	x	x	x
CD21	x	x	x	x	x	x	x	x	x	x	x	x	x
CD22	x	x	x	x	x	x	x	x	x	x	x	x	x
CD30	x	x	x	x	x	x	x	x	x	x	x	x	x
CD33	x	x	x	x	x	x	x	x	x	x	x	x	x
CD37	x	x	x	x	x	x	x	x	x	x	x	x	x

[0178]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
CD38	x	x	x	x	x	x	x	x	x	x	x	x	x
CD44v6	x	x	x	x	x	x	x	x	x	x	x	x	x
CD44v7/8	x	x	x	x	x	x	x	x	x	x	x	x	x
CD74	x	x	x	x	x	x	x	x	x	x	x	x	x
Cd79b	x	x	x	x	x	x	x	x	x	x	x	x	x
CD124 (IL-4R)	x	x	x	x	x	x	x	x	x	x	x	x	x
CDH3	x	x	x	x	x	x	x	x	x	x	x	x	x
Ki-67	x	x	x	x	x	x	x	x	x	x	x	x	x
CSPG4	x	x	x	x	x	x	x	x	x	x	x	x	x
CALLA	x	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x	x
COX-2	x	x	x	x	x	x	x	x	x	x	x	x	x
λ	x	x	x	x	x	x	x	x	x	x	x	x	x
LAYN	x	x	x	x	x	x	x	x	x	x	x	x	x
LeuM-1	x	x	x	x	x	x	x	x	x	x	x	x	x
KDR	x	x	x	x	x	x	x	x	x	x	x	x	x
CD47	x	x	x	x	x	x	x	x	x	x	x	x	x
CRISP3	x	x	x	x	x	x	x	x	x	x	x	x	x
DC-SIGN	x	x	x	x	x	x	x	x	x	x	x	x	x
DHFR	x	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x	x
EpCAM	x	x	x	x	x	x	x	x	x	x	x	x	x
EphA2	x	x	x	x	x	x	x	x	x	x	x	x	x
EphA2/Eck	x	x	x	x	x	x	x	x	x	x	x	x	x
EGFRvIII	x	x	x	x	x	x	x	x	x	x	x	x	x
E-钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
EGP2	x	x	x	x	x	x	x	x	x	x	x	x	x
ETA	x	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3	x	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3/4	x	x	x	x	x	x	x	x	x	x	x	x	x
ERBB4	x	x	x	x	x	x	x	x	x	x	x	x	x

[0179]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
EPO	x	x	x	x	x	x	x	x	x	x	x	x	x
F3	x	x	x	x	x	x	x	x	x	x	x	x	x
FAR	x	x	x	x	x	x	x	x	x	x	x	x	x
FBP	x	x	x	x	x	x	x	x	x	x	x	x	x
FTHL17	x	x	x	x	x	x	x	x	x	x	x	x	x
胎儿 AchR	x	x	x	x	x	x	x	x	x	x	x	x	x
FAP	x	x	x	x	x	x	x	x	x	x	x	x	x
FGFR3	x	x	x	x	x	x	x	x	x	x	x	x	x
FR-a	x	x	x	x	x	x	x	x	x	x	x	x	x
Fra-1/Fosl 1	x	x	x	x	x	x	x	x	x	x	x	x	x
GAGE1	x	x	x	x	x	x	x	x	x	x	x	x	x
GD2	x	x	x	x	x	x	x	x	x	x	x	x	x
GD3	x	x	x	x	x	x	x	x	x	x	x	x	x
Gli1	x	x	x	x	x	x	x	x	x	x	x	x	x
GP100	x	x	x	x	x	x	x	x	x	x	x	x	x
GPA33	x	x	x	x	x	x	x	x	x	x	x	x	x
磷脂酰肌醇蛋白 聚糖-3	x	x	x	x	x	x	x	x	x	x	x	x	x
HIV gp120	x	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A	x	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A2	x	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A1	x	x	x	x	x	x	x	x	x	x	x	x	x
HLA-B	x	x	x	x	x	x	x	x	x	x	x	x	x
HLA-C	x	x	x	x	x	x	x	x	x	x	x	x	x
HMW-MAA	x	x	x	x	x	x	x	x	x	x	x	x	x
Her2/Neu	x	x	x	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x	x	x	x
u70/80	x	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x	x
ULBP1	x	x	x	x	x	x	x	x	x	x	x	x	x
ULBP2	x	x	x	x	x	x	x	x	x	x	x	x	x
ULBP3	x	x	x	x	x	x	x	x	x	x	x	x	x

[0180]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
ULBP6	x	x	x	x	x	x	x	x	x	x	x	x	x
MICA	x	x	x	x	x	x	x	x	x	x	x	x	x
MICB	x	x	x	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x	x	x	x
EGF	x	x	x	x	x	x	x	x	x	x	x	x	x
SIRP1 α	x	x	x	x	x	x	x	x	x	x	x	x	x
Lewis-Y	x	x	x	x	x	x	x	x	x	x	x	x	x
LIV-1 (SLC39A6)	x	x	x	x	x	x	x	x	x	x	x	x	x
Livin	x	x	x	x	x	x	x	x	x	x	x	x	x
LAMP1	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA3	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA4	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEB6	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA1	x	x	x	x	x	x	x	x	x	x	x	x	x
MART-1	x	x	x	x	x	x	x	x	x	x	x	x	x
MCSP	x	x	x	x	x	x	x	x	x	x	x	x	x
MME	x	x	x	x	x	x	x	x	x	x	x	x	x
间皮素(MSLN)	x	x	x	x	x	x	x	x	x	x	x	x	x
MAPK1	x	x	x	x	x	x	x	x	x	x	x	x	x
MUC16	x	x	x	x	x	x	x	x	x	x	x	x	x
MUC1	x	x	x	x	x	x	x	x	x	x	x	x	x
MRP-3	x	x	x	x	x	x	x	x	x	x	x	x	x
MyoD-1	x	x	x	x	x	x	x	x	x	x	x	x	x
NCAM	x	x	x	x	x	x	x	x	x	x	x	x	x
连接素 4	x	x	x	x	x	x	x	x	x	x	x	x	x
巢蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
NEP	x	x	x	x	x	x	x	x	x	x	x	x	x
NY-ESO-1	x	x	x	x	x	x	x	x	x	x	x	x	x
hHLA-A	x	x	x	x	x	x	x	x	x	x	x	x	x
H60	x	x	x	x	x	x	x	x	x	x	x	x	x
OLIG2	x	x	x	x	x	x	x	x	x	x	x	x	x
5T4	x	x	x	x	x	x	x	x	x	x	x	x	x

[0181]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
p53	x	x	x	x	x	x	x	x	x	x	x	x	x
P-钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
PB	x	x	x	x	x	x	x	x	x	x	x	x	x
P-糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
PMCT (SLC13A5)	x	x	x	x	x	x	x	x	x	x	x	x	x
PRAME	x	x	x	x	x	x	x	x	x	x	x	x	x
PROXI	x	x	x	x	x	x	x	x	x	x	x	x	x
PSA	x	x	x	x	x	x	x	x	x	x	x	x	x
PSCA	x	x	x	x	x	x	x	x	x	x	x	x	x
PSMA	x	x	x	x	x	x	x	x	x	x	x	x	x
PSC1	x	x	x	x	x	x	x	x	x	x	x	x	x
PVRL4	x	x	x	x	x	x	x	x	x	x	x	x	x
Ras	x	x	x	x	x	x	x	x	x	x	x	x	x
ROR1	x	x	x	x	x	x	x	x	x	x	x	x	x
SART2	x	x	x	x	x	x	x	x	x	x	x	x	x
SART3	x	x	x	x	x	x	x	x	x	x	x	x	x
纤连蛋白的癌胚 胎变体	x	x	x	x	x	x	x	x	x	x	x	x	x
腱糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 α	x	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 β	x	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 δ	x	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 γ	x	x	x	x	x	x	x	x	x	x	x	x	x
PDGF	x	x	x	x	x	x	x	x	x	x	x	x	x
Fas	x	x	x	x	x	x	x	x	x	x	x	x	x
SOX2	x	x	x	x	x	x	x	x	x	x	x	x	x
STEAP1	x	x	x	x	x	x	x	x	x	x	x	x	x
SLITRK6	x	x	x	x	x	x	x	x	x	x	x	x	x
NaPi2a	x	x	x	x	x	x	x	x	x	x	x	x	x
SOX1	x	x	x	x	x	x	x	x	x	x	x	x	x

[0182]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
SOX11	x	x	x	x	x	x	x	x	x	x	x	x	x
SPANXA1	x	x	x	x	x	x	x	x	x	x	x	x	x
SART-1	x	x	x	x	x	x	x	x	x	x	x	x	x
SSX4	x	x	x	x	x	x	x	x	x	x	x	x	x
SSX5	x	x	x	x	x	x	x	x	x	x	x	x	x
存活素	x	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x	x
TAG72	x	x	x	x	x	x	x	x	x	x	x	x	x
TEM1	x	x	x	x	x	x	x	x	x	x	x	x	x
TEM8	x	x	x	x	x	x	x	x	x	x	x	x	x
TSGA10	x	x	x	x	x	x	x	x	x	x	x	x	x
TSSK6	x	x	x	x	x	x	x	x	x	x	x	x	x
甲状腺球蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
转铁蛋白受体	x	x	x	x	x	x	x	x	x	x	x	x	x
TACSTD2 (TROP2)	x	x	x	x	x	x	x	x	x	x	x	x	x
TMEM97	x	x	x	x	x	x	x	x	x	x	x	x	x
TRP-2	x	x	x	x	x	x	x	x	x	x	x	x	x
TULP2	x	x	x	x	x	x	x	x	x	x	x	x	x
TROP2	x	x	x	x	x	x	x	x	x	x	x	x	x
酪氨酸酶	x	x	x	x	x	x	x	x	x	x	x	x	x
TRP1	x	x	x	x	x	x	x	x	x	x	x	x	x
UPAR	x	x	x	x	x	x	x	x	x	x	x	x	x
VEGF	x	x	x	x	x	x	x	x	x	x	x	x	x
VEGF 受体	x	x	x	x	x	x	x	x	x	x	x	x	x
VEGFR2	x	x	x	x	x	x	x	x	x	x	x	x	x
BRAF	x	x	x	x	x	x	x	x	x	x	x	x	x
WT-1	x	x	x	x	x	x	x	x	x	x	x	x	x
XAGE2	x	x	x	x	x	x	x	x	x	x	x	x	x
ZNF165	x	x	x	x	x	x	x	x	x	x	x	x	x
$\alpha\beta 6$ 整合蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x
β -连环蛋白	x	x	x	x	x	x	x	x	x	x	x	x	x

[0183]

	CD3	CD3 γ	CD3 δ	CD3 ϵ	CD3 ξ	CD2	CD4	CD5	CD6	CD7	CD8	CD16	CD25
组织蛋白酶 B	x	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x	x
CTAG	x	x	x	x	x	x	x	x	x	x	x	x	x
EGFR	x	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x	x
HIV sp120	x	x	x	x	x	x	x	x	x	x	x	x	x
κ 轻链	x	x	x	x	x	x	x	x	x	x	x	x	x
LDHC	x	x	x	x	x	x	x	x	x	x	x	x	x
TRP-1	x	x	x	x	x	x	x	x	x	x	x	x	x
Fas-L	x	x	x	x	x	x	x	x	x	x	x	x	x
DLL3	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA12	x	x	x	x	x	x	x	x	x	x	x	x	x
MAGEC2	x	x	x	x	x	x	x	x	x	x	x	x	x
BAGE	x	x	x	x	x	x	x	x	x	x	x	x	x
BAGE1	x	x	x	x	x	x	x	x	x	x	x	x	x
GAGE	x	x	x	x	x	x	x	x	x	x	x	x	x
XAGE	x	x	x	x	x	x	x	x	x	x	x	x	x
XAGE1B	x	x	x	x	x	x	x	x	x	x	x	x	x
SSX	x	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x	x
KKLC1	x	x	x	x	x	x	x	x	x	x	x	x	x
SAGE	x	x	x	x	x	x	x	x	x	x	x	x	x
SPA17	x	x	x	x	x	x	x	x	x	x	x	x	x
细胞周期蛋白 A	x	x	x	x	x	x	x	x	x	x	x	x	x
KMHN1	x	x	x	x	x	x	x	x	x	x	x	x	x

[0184] 表5. (续)

[0185]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
8H9	x	x	x	x	x	x	x	x	x	x	x	x
GnT-V, β 1,6-N	x	x	x	x	x	x	x	x	x	x	x	x

[0186]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
AFP	x	x	x	x	x	x	x	x	x	x	x	x
ART1	x	x	x	x	x	x	x	x	x	x	x	x
ART4	x	x	x	x	x	x	x	x	x	x	x	x
ABCG2	x	x	x	x	x	x	x	x	x	x	x	x
B7-H3	x	x	x	x	x	x	x	x	x	x	x	x
B7-H4	x	x	x	x	x	x	x	x	x	x	x	x
B7-H6	x	x	x	x	x	x	x	x	x	x	x	x
BCMA	x	x	x	x	x	x	x	x	x	x	x	x
B-细胞周期蛋白	x	x	x	x	x	x	x	x	x	x	x	x
BMI1	x	x	x	x	x	x	x	x	x	x	x	x
CA-125	x	x	x	x	x	x	x	x	x	x	x	x
钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x
CABYR	x	x	x	x	x	x	x	x	x	x	x	x
CTAG2	x	x	x	x	x	x	x	x	x	x	x	x
CA6	x	x	x	x	x	x	x	x	x	x	x	x
CAIX	x	x	x	x	x	x	x	x	x	x	x	x
CEA	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM5	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM6	x	x	x	x	x	x	x	x	x	x	x	x
Cav-1	x	x	x	x	x	x	x	x	x	x	x	x
CD10	x	x	x	x	x	x	x	x	x	x	x	x
CD117	x	x	x	x	x	x	x	x	x	x	x	x
CD123	x	x	x	x	x	x	x	x	x	x	x	x
CD133	x	x	x	x	x	x	x	x	x	x	x	x
CD138	x	x	x	x	x	x	x	x	x	x	x	x
CD15	x	x	x	x	x	x	x	x	x	x	x	x
CD171	x	x	x	x	x	x	x	x	x	x	x	x
CD19	x	x	x	x	x	x	x	x	x	x	x	x
CD20	x	x	x	x	x	x	x	x	x	x	x	x
CD21	x	x	x	x	x	x	x	x	x	x	x	x
CD22	x	x	x	x	x	x	x	x	x	x	x	x
CD30	x	x	x	x	x	x	x	x	x	x	x	x
CD33	x	x	x	x	x	x	x	x	x	x	x	x

[0187]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
CD37	x	x	x	x	x	x	x	x	x	x	x	x
CD38	x	x	x	x	x	x	x	x	x	x	x	x
CD44v6	x	x	x	x	x	x	x	x	x	x	x	x
CD44v7/8	x	x	x	x	x	x	x	x	x	x	x	x
CD74	x	x	x	x	x	x	x	x	x	x	x	x
Cd79b	x	x	x	x	x	x	x	x	x	x	x	x
CD124 (IL-4R)	x	x	x	x	x	x	x	x	x	x	x	x
CDH3	x	x	x	x	x	x	x	x	x	x	x	x
Ki-67	x	x	x	x	x	x	x	x	x	x	x	x
CSPG4	x	x	x	x	x	x	x	x	x	x	x	x
CALLA	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x
COX-2	x	x	x	x	x	x	x	x	x	x	x	x
λ	x	x	x	x	x	x	x	x	x	x	x	x
LAYN	x	x	x	x	x	x	x	x	x	x	x	x
LeuM-1	x	x	x	x	x	x	x	x	x	x	x	x
KDR	x	x	x	x	x	x	x	x	x	x	x	x
CD47	x	x	x	x	x	x	x	x	x	x	x	x
CRISP3	x	x	x	x	x	x	x	x	x	x	x	x
DC-SIGN	x	x	x	x	x	x	x	x	x	x	x	x
DHFR	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x
EpCAM	x	x	x	x	x	x	x	x	x	x	x	x
EphA2	x	x	x	x	x	x	x	x	x	x	x	x
EphA2/Eck	x	x	x	x	x	x	x	x	x	x	x	x
EGFRvIII	x	x	x	x	x	x	x	x	x	x	x	x
E-钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x
EGP2	x	x	x	x	x	x	x	x	x	x	x	x
ETA	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3/4	x	x	x	x	x	x	x	x	x	x	x	x

[0188]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
ERBB4	x	x	x	x	x	x	x	x	x	x	x	x
EPO	x	x	x	x	x	x	x	x	x	x	x	x
F3	x	x	x	x	x	x	x	x	x	x	x	x
FAR	x	x	x	x	x	x	x	x	x	x	x	x
FBP	x	x	x	x	x	x	x	x	x	x	x	x
FTHL17	x	x	x	x	x	x	x	x	x	x	x	x
胎儿 AchR	x	x	x	x	x	x	x	x	x	x	x	x
FAP	x	x	x	x	x	x	x	x	x	x	x	x
FGFR3	x	x	x	x	x	x	x	x	x	x	x	x
FR-a	x	x	x	x	x	x	x	x	x	x	x	x
Fra-1/Fosl 1	x	x	x	x	x	x	x	x	x	x	x	x
GAGE1	x	x	x	x	x	x	x	x	x	x	x	x
GD2	x	x	x	x	x	x	x	x	x	x	x	x
GD3	x	x	x	x	x	x	x	x	x	x	x	x
Gli1	x	x	x	x	x	x	x	x	x	x	x	x
GP100	x	x	x	x	x	x	x	x	x	x	x	x
GPA33	x	x	x	x	x	x	x	x	x	x	x	x
磷脂酰肌醇蛋白 聚糖-3	x	x	x	x	x	x	x	x	x	x	x	x
HIV gp120	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A2	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A1	x	x	x	x	x	x	x	x	x	x	x	x
HLA-B	x	x	x	x	x	x	x	x	x	x	x	x
HLA-C	x	x	x	x	x	x	x	x	x	x	x	x
HMW-MAA	x	x	x	x	x	x	x	x	x	x	x	x
Her2/Neu	x	x	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x	x	x
u70/80	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x
ULBP1	x	x	x	x	x	x	x	x	x	x	x	x
ULBP2	x	x	x	x	x	x	x	x	x	x	x	x

[0189]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
ULBP3	x	x	x	x	x	x	x	x	x	x	x	x
ULBP6	x	x	x	x	x	x	x	x	x	x	x	x
MICA	x	x	x	x	x	x	x	x	x	x	x	x
MICB	x	x	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x	x	x
EGF	x	x	x	x	x	x	x	x	x	x	x	x
SIRP1 α	x	x	x	x	x	x	x	x	x	x	x	x
Lewis-Y	x	x	x	x	x	x	x	x	x	x	x	x
LIV-1 (SLC39A6)	x	x	x	x	x	x	x	x	x	x	x	x
Livin	x	x	x	x	x	x	x	x	x	x	x	x
LAMP1	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA3	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA4	x	x	x	x	x	x	x	x	x	x	x	x
MAGEB6	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA1	x	x	x	x	x	x	x	x	x	x	x	x
MART-1	x	x	x	x	x	x	x	x	x	x	x	x
MCSP	x	x	x	x	x	x	x	x	x	x	x	x
MME	x	x	x	x	x	x	x	x	x	x	x	x
间皮素(MSLN)	x	x	x	x	x	x	x	x	x	x	x	x
MAPK1	x	x	x	x	x	x	x	x	x	x	x	x
MUC16	x	x	x	x	x	x	x	x	x	x	x	x
MUC1	x	x	x	x	x	x	x	x	x	x	x	x
MRP-3	x	x	x	x	x	x	x	x	x	x	x	x
MyoD-1	x	x	x	x	x	x	x	x	x	x	x	x
NCAM	x	x	x	x	x	x	x	x	x	x	x	x
连接素 4	x	x	x	x	x	x	x	x	x	x	x	x
巢蛋白	x	x	x	x	x	x	x	x	x	x	x	x
NEP	x	x	x	x	x	x	x	x	x	x	x	x
NY-ESO-1	x	x	x	x	x	x	x	x	x	x	x	x
hHLA-A	x	x	x	x	x	x	x	x	x	x	x	x
H60	x	x	x	x	x	x	x	x	x	x	x	x
OLIG2	x	x	x	x	x	x	x	x	x	x	x	x

[0190]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
5T4	x	x	x	x	x	x	x	x	x	x	x	x
p53	x	x	x	x	x	x	x	x	x	x	x	x
P-钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x
PB	x	x	x	x	x	x	x	x	x	x	x	x
P-糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x
PMCT (SLC13A5)	x	x	x	x	x	x	x	x	x	x	x	x
PRAME	x	x	x	x	x	x	x	x	x	x	x	x
PROXI	x	x	x	x	x	x	x	x	x	x	x	x
PSA	x	x	x	x	x	x	x	x	x	x	x	x
PSCA	x	x	x	x	x	x	x	x	x	x	x	x
PSMA	x	x	x	x	x	x	x	x	x	x	x	x
PSC1	x	x	x	x	x	x	x	x	x	x	x	x
PVRL4	x	x	x	x	x	x	x	x	x	x	x	x
Ras	x	x	x	x	x	x	x	x	x	x	x	x
ROR1	x	x	x	x	x	x	x	x	x	x	x	x
SART2	x	x	x	x	x	x	x	x	x	x	x	x
SART3	x	x	x	x	x	x	x	x	x	x	x	x
纤连蛋白的癌胚 胎变体	x	x	x	x	x	x	x	x	x	x	x	x
腱糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 α	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 β	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 δ	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 γ	x	x	x	x	x	x	x	x	x	x	x	x
PDGF	x	x	x	x	x	x	x	x	x	x	x	x
Fas	x	x	x	x	x	x	x	x	x	x	x	x
SOX2	x	x	x	x	x	x	x	x	x	x	x	x
STEAP1	x	x	x	x	x	x	x	x	x	x	x	x
SLITRK6	x	x	x	x	x	x	x	x	x	x	x	x
NaPi2a	x	x	x	x	x	x	x	x	x	x	x	x

[0191]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
SOX1	x	x	x	x	x	x	x	x	x	x	x	x
SOX11	x	x	x	x	x	x	x	x	x	x	x	x
SPANXA1	x	x	x	x	x	x	x	x	x	x	x	x
SART-1	x	x	x	x	x	x	x	x	x	x	x	x
SSX4	x	x	x	x	x	x	x	x	x	x	x	x
SSX5	x	x	x	x	x	x	x	x	x	x	x	x
存活素	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x
TAG72	x	x	x	x	x	x	x	x	x	x	x	x
TEM1	x	x	x	x	x	x	x	x	x	x	x	x
TEM8	x	x	x	x	x	x	x	x	x	x	x	x
TSGA10	x	x	x	x	x	x	x	x	x	x	x	x
TSSK6	x	x	x	x	x	x	x	x	x	x	x	x
甲状腺球蛋白	x	x	x	x	x	x	x	x	x	x	x	x
转铁蛋白受体	x	x	x	x	x	x	x	x	x	x	x	x
TACSTD2 (TROP2)	x	x	x	x	x	x	x	x	x	x	x	x
TMEM97	x	x	x	x	x	x	x	x	x	x	x	x
TRP-2	x	x	x	x	x	x	x	x	x	x	x	x
TULP2	x	x	x	x	x	x	x	x	x	x	x	x
TROP2	x	x	x	x	x	x	x	x	x	x	x	x
酪氨酸酶	x	x	x	x	x	x	x	x	x	x	x	x
TRP1	x	x	x	x	x	x	x	x	x	x	x	x
UPAR	x	x	x	x	x	x	x	x	x	x	x	x
VEGF	x	x	x	x	x	x	x	x	x	x	x	x
VEGF 受体	x	x	x	x	x	x	x	x	x	x	x	x
VEGFR2	x	x	x	x	x	x	x	x	x	x	x	x
BRAF	x	x	x	x	x	x	x	x	x	x	x	x
WT-1	x	x	x	x	x	x	x	x	x	x	x	x
XAGE2	x	x	x	x	x	x	x	x	x	x	x	x
ZNF165	x	x	x	x	x	x	x	x	x	x	x	x
$\alpha\beta 6$ 整联蛋白	x	x	x	x	x	x	x	x	x	x	x	x

[0192]

	CD27	CD28	CD30	CD38	CD40	CD57	CD69	CD70	CD73	CD81	CD82	CD96
β-连环蛋白	x	x	x	x	x	x	x	x	x	x	x	x
组织蛋白酶 B	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x
CTAG	x	x	x	x	x	x	x	x	x	x	x	x
EGFR	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x
HIV sp120	x	x	x	x	x	x	x	x	x	x	x	x
κ 轻链	x	x	x	x	x	x	x	x	x	x	x	x
LDHC	x	x	x	x	x	x	x	x	x	x	x	x
TRP-1	x	x	x	x	x	x	x	x	x	x	x	x
Fas-L	x	x	x	x	x	x	x	x	x	x	x	x
DLL3	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA12	x	x	x	x	x	x	x	x	x	x	x	x
MAGEC2	x	x	x	x	x	x	x	x	x	x	x	x
BAGE	x	x	x	x	x	x	x	x	x	x	x	x
BAGE1	x	x	x	x	x	x	x	x	x	x	x	x
GAGE	x	x	x	x	x	x	x	x	x	x	x	x
XAGE	x	x	x	x	x	x	x	x	x	x	x	x
XAGE1B	x	x	x	x	x	x	x	x	x	x	x	x
SSX	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x
KKLC1	x	x	x	x	x	x	x	x	x	x	x	x
SAGE	x	x	x	x	x	x	x	x	x	x	x	x
SPA17	x	x	x	x	x	x	x	x	x	x	x	x
细胞周期蛋白 A	x	x	x	x	x	x	x	x	x	x	x	x
KMHN1	x	x	x	x	x	x	x	x	x	x	x	x

[0193] 表5. (续)

[0194]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
8H9	x	x	x	x	x	x	x	x	x	x

[0195]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
GnT- V β 1,6-N	x	x	x	x	x	x	x	x	x	x
AFP	x	x	x	x	x	x	x	x	x	x
ART1	x	x	x	x	x	x	x	x	x	x
ART4	x	x	x	x	x	x	x	x	x	x
ABCG2	x	x	x	x	x	x	x	x	x	x
B7-H3	x	x	x	x	x	x	x	x	x	x
B7-H4	x	x	x	x	x	x	x	x	x	x
B7-H6	x	x	x	x	x	x	x	x	x	x
BCMA	x	x	x	x	x	x	x	x	x	x
B- 细胞周 期蛋白	x	x	x	x	x	x	x	x	x	x
BMI1	x	x	x	x	x	x	x	x	x	x
CA-125	x	x	x	x	x	x	x	x	x	x
钙粘着蛋 白	x	x	x	x	x	x	x	x	x	x
CABYR	x	x	x	x	x	x	x	x	x	x
CTAG2	x	x	x	x	x	x	x	x	x	x
CA6	x	x	x	x	x	x	x	x	x	x
CAIX	x	x	x	x	x	x	x	x	x	x
CEA	x	x	x	x	x	x	x	x	x	x
CEACAM5	x	x	x	x	x	x	x	x	x	x
CEACAM6	x	x	x	x	x	x	x	x	x	x
Cav-1	x	x	x	x	x	x	x	x	x	x
CD10	x	x	x	x	x	x	x	x	x	x
CD117	x	x	x	x	x	x	x	x	x	x
CD123	x	x	x	x	x	x	x	x	x	x
CD133	x	x	x	x	x	x	x	x	x	x
CD138	x	x	x	x	x	x	x	x	x	x
CD15	x	x	x	x	x	x	x	x	x	x
CD171	x	x	x	x	x	x	x	x	x	x
CD19	x	x	x	x	x	x	x	x	x	x

[0196]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
CD20	x	x	x	x	x	x	x	x	x	x
CD21	x	x	x	x	x	x	x	x	x	x
CD22	x	x	x	x	x	x	x	x	x	x
CD30	x	x	x	x	x	x	x	x	x	x
CD33	x	x	x	x	x	x	x	x	x	x
CD37	x	x	x	x	x	x	x	x	x	x
CD38	x	x	x	x	x	x	x	x	x	x
CD44v6	x	x	x	x	x	x	x	x	x	x
CD44v7/8	x	x	x	x	x	x	x	x	x	x
CD74	x	x	x	x	x	x	x	x	x	x
Cd79b	x	x	x	x	x	x	x	x	x	x
CD124 (IL- 4R)	x	x	x	x	x	x	x	x	x	x
CDH3	x	x	x	x	x	x	x	x	x	x
Ki-67	x	x	x	x	x	x	x	x	x	x
CSPG4	x	x	x	x	x	x	x	x	x	x
CALLA	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x
COX-2	x	x	x	x	x	x	x	x	x	x
λ	x	x	x	x	x	x	x	x	x	x
LAYN	x	x	x	x	x	x	x	x	x	x
LeuM-1	x	x	x	x	x	x	x	x	x	x
KDR	x	x	x	x	x	x	x	x	x	x
CD47	x	x	x	x	x	x	x	x	x	x
CRISP3	x	x	x	x	x	x	x	x	x	x
DC-SIGN	x	x	x	x	x	x	x	x	x	x
DHFR	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x
EpCAM	x	x	x	x	x	x	x	x	x	x
EphA2	x	x	x	x	x	x	x	x	x	x
EphA2/Eck	x	x	x	x	x	x	x	x	x	x

[0197]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
EGFRvIII	x	x	x	x	x	x	x	x	x	x
E-钙粘着 蛋白	x	x	x	x	x	x	x	x	x	x
EGP2	x	x	x	x	x	x	x	x	x	x
ETA	x	x	x	x	x	x	x	x	x	x
ERBB3	x	x	x	x	x	x	x	x	x	x
ERBB3/4	x	x	x	x	x	x	x	x	x	x
ERBB4	x	x	x	x	x	x	x	x	x	x
EPO	x	x	x	x	x	x	x	x	x	x
F3	x	x	x	x	x	x	x	x	x	x
FAR	x	x	x	x	x	x	x	x	x	x
FBP	x	x	x	x	x	x	x	x	x	x
FTHL17	x	x	x	x	x	x	x	x	x	x
胎儿 AchR	x	x	x	x	x	x	x	x	x	x
FAP	x	x	x	x	x	x	x	x	x	x
FGFR3	x	x	x	x	x	x	x	x	x	x
FR-a	x	x	x	x	x	x	x	x	x	x
Fra-1/Fosl 1	x	x	x	x	x	x	x	x	x	x
GAGE1	x	x	x	x	x	x	x	x	x	x
GD2	x	x	x	x	x	x	x	x	x	x
GD3	x	x	x	x	x	x	x	x	x	x
Gli1	x	x	x	x	x	x	x	x	x	x
GP100	x	x	x	x	x	x	x	x	x	x
GPA33	x	x	x	x	x	x	x	x	x	x
磷脂酰肌 醇蛋白聚 糖-3	x	x	x	x	x	x	x	x	x	x
HIV gp120	x	x	x	x	x	x	x	x	x	x
HLA-A	x	x	x	x	x	x	x	x	x	x
HLA-A2	x	x	x	x	x	x	x	x	x	x
HLA-AI	x	x	x	x	x	x	x	x	x	x
HLA-B	x	x	x	x	x	x	x	x	x	x

[0198]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
HLA-C	x	x	x	x	x	x	x	x	x	x
HMW- MAA	x	x	x	x	x	x	x	x	x	x
Her2/Neu	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x
u70/80	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x
ULBP1	x	x	x	x	x	x	x	x	x	x
ULBP2	x	x	x	x	x	x	x	x	x	x
ULBP3	x	x	x	x	x	x	x	x	x	x
ULBP6	x	x	x	x	x	x	x	x	x	x
MICA	x	x	x	x	x	x	x	x	x	x
MICB	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x
EGF	x	x	x	x	x	x	x	x	x	x
SIRP1 α	x	x	x	x	x	x	x	x	x	x
Lewis-Y	x	x	x	x	x	x	x	x	x	x
LIV-1 (SLC39A6)	x	x	x	x	x	x	x	x	x	x
Livin	x	x	x	x	x	x	x	x	x	x
LAMP1	x	x	x	x	x	x	x	x	x	x
MAGEA3	x	x	x	x	x	x	x	x	x	x
MAGEA4	x	x	x	x	x	x	x	x	x	x
MAGEB6	x	x	x	x	x	x	x	x	x	x
MAGEA1	x	x	x	x	x	x	x	x	x	x
MART-1	x	x	x	x	x	x	x	x	x	x
MCSP	x	x	x	x	x	x	x	x	x	x
MME	x	x	x	x	x	x	x	x	x	x
间皮素 (MSLN)	x	x	x	x	x	x	x	x	x	x
MAPK1	x	x	x	x	x	x	x	x	x	x
MUC16	x	x	x	x	x	x	x	x	x	x

[0199]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
MUC1	x	x	x	x	x	x	x	x	x	x
MRP-3	x	x	x	x	x	x	x	x	x	x
MyoD-1	x	x	x	x	x	x	x	x	x	x
NCAM	x	x	x	x	x	x	x	x	x	x
连接素 4	x	x	x	x	x	x	x	x	x	x
巢蛋白	x	x	x	x	x	x	x	x	x	x
NEP	x	x	x	x	x	x	x	x	x	x
NY-ESO-1	x	x	x	x	x	x	x	x	x	x
hHLA-A	x	x	x	x	x	x	x	x	x	x
H60	x	x	x	x	x	x	x	x	x	x
OLIG2	x	x	x	x	x	x	x	x	x	x
5T4	x	x	x	x	x	x	x	x	x	x
p53	x	x	x	x	x	x	x	x	x	x
P-钙粘着 蛋白	x	x	x	x	x	x	x	x	x	x
PB	x	x	x	x	x	x	x	x	x	x
P-糖蛋白	x	x	x	x	x	x	x	x	x	x
PMCT (SLC13A5)	x	x	x	x	x	x	x	x	x	x
PRAME	x	x	x	x	x	x	x	x	x	x
PROXI	x	x	x	x	x	x	x	x	x	x
PSA	x	x	x	x	x	x	x	x	x	x
PSCA	x	x	x	x	x	x	x	x	x	x
PSMA	x	x	x	x	x	x	x	x	x	x
PSC1	x	x	x	x	x	x	x	x	x	x
PVRL4	x	x	x	x	x	x	x	x	x	x
Ras	x	x	x	x	x	x	x	x	x	x
ROR1	x	x	x	x	x	x	x	x	x	x
SART2	x	x	x	x	x	x	x	x	x	x
SART3	x	x	x	x	x	x	x	x	x	x
纤连蛋白	x	x	x	x	x	x	x	x	x	x

[0200]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
的 癌 胚 胎 变体										
臍糖蛋白	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x
Rae-1 α	x	x	x	x	x	x	x	x	x	x
Rae-1 β	x	x	x	x	x	x	x	x	x	x
Rae-1 δ	x	x	x	x	x	x	x	x	x	x
Rae-1 γ	x	x	x	x	x	x	x	x	x	x
PDGF	x	x	x	x	x	x	x	x	x	x
Fas	x	x	x	x	x	x	x	x	x	x
SOX2	x	x	x	x	x	x	x	x	x	x
STEAP1	x	x	x	x	x	x	x	x	x	x
SLITRK6	x	x	x	x	x	x	x	x	x	x
NaPi2a	x	x	x	x	x	x	x	x	x	x
SOX1	x	x	x	x	x	x	x	x	x	x
SOX11	x	x	x	x	x	x	x	x	x	x
SPANXA1	x	x	x	x	x	x	x	x	x	x
SART-1	x	x	x	x	x	x	x	x	x	x
SSX4	x	x	x	x	x	x	x	x	x	x
SSX5	x	x	x	x	x	x	x	x	x	x
存活素	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x
TAG72	x	x	x	x	x	x	x	x	x	x
TEM1	x	x	x	x	x	x	x	x	x	x
TEM8	x	x	x	x	x	x	x	x	x	x
TSGA10	x	x	x	x	x	x	x	x	x	x
TSSK6	x	x	x	x	x	x	x	x	x	x
甲状球蛋白	x	x	x	x	x	x	x	x	x	x
转铁蛋白 受体	x	x	x	x	x	x	x	x	x	x

[0201]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
TACSTD2 (TROP2)	x	x	x	x	x	x	x	x	x	x
TMEM97	x	x	x	x	x	x	x	x	x	x
TRP-2	x	x	x	x	x	x	x	x	x	x
TULP2	x	x	x	x	x	x	x	x	x	x
TROP2	x	x	x	x	x	x	x	x	x	x
酪氨酸酶	x	x	x	x	x	x	x	x	x	x
TRP1	x	x	x	x	x	x	x	x	x	x
UPAR	x	x	x	x	x	x	x	x	x	x
VEGF	x	x	x	x	x	x	x	x	x	x
VEGF 受体	x	x	x	x	x	x	x	x	x	x
VEGRR2	x	x	x	x	x	x	x	x	x	x
BRAF	x	x	x	x	x	x	x	x	x	x
WT-1	x	x	x	x	x	x	x	x	x	x
XAGE2	x	x	x	x	x	x	x	x	x	x
ZNF165	x	x	x	x	x	x	x	x	x	x
$\alpha\beta 6$ 整联 蛋白	x	x	x	x	x	x	x	x	x	x
β -连环蛋白	x	x	x	x	x	x	x	x	x	x
组织蛋白 酶 B	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x
CTAG	x	x	x	x	x	x	x	x	x	x
EGFR	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x
HIV sp120	x	x	x	x	x	x	x	x	x	x
κ 轻链	x	x	x	x	x	x	x	x	x	x
LDHC	x	x	x	x	x	x	x	x	x	x
TRP-1	x	x	x	x	x	x	x	x	x	x
Fas-L	x	x	x	x	x	x	x	x	x	x

[0202]

	CD134	CD137	CD152	CD278	不变的 TCR	CD94/NKG 2 (例如, NKG2D)	NKp30	NKp44	NKp46	KAR
DLL3	x	x	x	x	x	x	x	x	x	x
MAGEA12	x	x	x	x	x	x	x	x	x	x
MAGEC2	x	x	x	x	x	x	x	x	x	x
BAGE	x	x	x	x	x	x	x	x	x	x
BAGE1	x	x	x	x	x	x	x	x	x	x
GAGE	x	x	x	x	x	x	x	x	x	x
XAGE	x	x	x	x	x	x	x	x	x	x
XAGE1B	x	x	x	x	x	x	x	x	x	x
SSX	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x
KKLC1	x	x	x	x	x	x	x	x	x	x
SAGE	x	x	x	x	x	x	x	x	x	x
SPA17	x	x	x	x	x	x	x	x	x	x
细胞周期 蛋白 A	x	x	x	x	x	x	x	x	x	x
KMHN1	x	x	x	x	x	x	x	x	x	x

[0203] 表5. (续)

[0204]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Rα	IL- 1Ra2	IL- 13Ra2	IL- 15Ra	CCR5	CCR8	SIRPα
8H9	x	x	x	x	x	x	x	x	x	x	x	x
GnT- V _β 1,6-N	x	x	x	x	x	x	x	x	x	x	x	x
AFP	x	x	x	x	x	x	x	x	x	x	x	x
ART1	x	x	x	x	x	x	x	x	x	x	x	x
ART4	x	x	x	x	x	x	x	x	x	x	x	x
ABCG2	x	x	x	x	x	x	x	x	x	x	x	x
B7-H3	x	x	x	x	x	x	x	x	x	x	x	x
B7-H4	x	x	x	x	x	x	x	x	x	x	x	x
B7-H6	x	x	x	x	x	x	x	x	x	x	x	x
BCMA	x	x	x	x	x	x	x	x	x	x	x	x
B- 细胞周	x	x	x	x	x	x	x	x	x	x	x	x

[0205]

	CD48	轻	CD44	CD45	IL-1R2	IL-1Ra	IL-1Ra2	IL-13Ra2	IL-15Ra	CCR5	CCR8	SIRPα
期蛋白												
BMI1	x	x	x	x	x	x	x	x	x	x	x	x
CA-125	x	x	x	x	x	x	x	x	x	x	x	x
钙粘着蛋白	x	x	x	x	x	x	x	x	x	x	x	x
CABYR	x	x	x	x	x	x	x	x	x	x	x	x
CTAG2	x	x	x	x	x	x	x	x	x	x	x	x
CA6	x	x	x	x	x	x	x	x	x	x	x	x
CAIX	x	x	x	x	x	x	x	x	x	x	x	x
CEA	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM5	x	x	x	x	x	x	x	x	x	x	x	x
CEACAM6	x	x	x	x	x	x	x	x	x	x	x	x
Cav-1	x	x	x	x	x	x	x	x	x	x	x	x
CD10	x	x	x	x	x	x	x	x	x	x	x	x
CD117	x	x	x	x	x	x	x	x	x	x	x	x
CD123	x	x	x	x	x	x	x	x	x	x	x	x
CD133	x	x	x	x	x	x	x	x	x	x	x	x
CD138	x	x	x	x	x	x	x	x	x	x	x	x
CD15	x	x	x	x	x	x	x	x	x	x	x	x
CD171	x	x	x	x	x	x	x	x	x	x	x	x
CD19	x	x	x	x	x	x	x	x	x	x	x	x
CD20	x	x	x	x	x	x	x	x	x	x	x	x
CD21	x	x	x	x	x	x	x	x	x	x	x	x
CD22	x	x	x	x	x	x	x	x	x	x	x	x
CD30	x	x	x	x	x	x	x	x	x	x	x	x
CD33	x	x	x	x	x	x	x	x	x	x	x	x
CD37	x	x	x	x	x	x	x	x	x	x	x	x
CD38	x	x	x	x	x	x	x	x	x	x	x	x
CD44v6	x	x	x	x	x	x	x	x	x	x	x	x
CD44v7/8	x	x	x	x	x	x	x	x	x	x	x	x
CD74	x	x	x	x	x	x	x	x	x	x	x	x
Cd79b	x	x	x	x	x	x	x	x	x	x	x	x

[0206]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Rα	IL- 1Rα2	IL- 13Rα2	IL- 15Rα	CCR5	CCR8	SIRPα
CD124 (IL-4R)	x	x	x	x	x	x	x	x	x	x	x	x
CDH3	x	x	x	x	x	x	x	x	x	x	x	x
Ki-67	x	x	x	x	x	x	x	x	x	x	x	x
CSPG4	x	x	x	x	x	x	x	x	x	x	x	x
CALLA	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x
COX-2	x	x	x	x	x	x	x	x	x	x	x	x
λ	x	x	x	x	x	x	x	x	x	x	x	x
LAYN	x	x	x	x	x	x	x	x	x	x	x	x
LeuM-1	x	x	x	x	x	x	x	x	x	x	x	x
KDR	x	x	x	x	x	x	x	x	x	x	x	x
CD47	x	x	x	x	x	x	x	x	x	x	x	x
CRISP3	x	x	x	x	x	x	x	x	x	x	x	x
DC-SIGN	x	x	x	x	x	x	x	x	x	x	x	x
DHFR	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x
EpCAM	x	x	x	x	x	x	x	x	x	x	x	x
EphA2	x	x	x	x	x	x	x	x	x	x	x	x
EphA2/Eck	x	x	x	x	x	x	x	x	x	x	x	x
EGFRvIII	x	x	x	x	x	x	x	x	x	x	x	x
E-钙粘着 蛋白	x	x	x	x	x	x	x	x	x	x	x	x
EGP2	x	x	x	x	x	x	x	x	x	x	x	x
ETA	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3	x	x	x	x	x	x	x	x	x	x	x	x
ERBB3/4	x	x	x	x	x	x	x	x	x	x	x	x
ERBB4	x	x	x	x	x	x	x	x	x	x	x	x
EPO	x	x	x	x	x	x	x	x	x	x	x	x
F3	x	x	x	x	x	x	x	x	x	x	x	x
FAR	x	x	x	x	x	x	x	x	x	x	x	x
FBP	x	x	x	x	x	x	x	x	x	x	x	x

[0207]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Rα	IL- 1Rα2	IL- 13Rα2	IL- 15Rα	CCR5	CCR8	SIRPα
FTHL17	x	x	x	x	x	x	x	x	x	x	x	x
胎儿 AchR	x	x	x	x	x	x	x	x	x	x	x	x
FAP	x	x	x	x	x	x	x	x	x	x	x	x
FGFR3	x	x	x	x	x	x	x	x	x	x	x	x
FR-a	x	x	x	x	x	x	x	x	x	x	x	x
Fra-I/Fos1 l	x	x	x	x	x	x	x	x	x	x	x	x
GAGE1	x	x	x	x	x	x	x	x	x	x	x	x
GD2	x	x	x	x	x	x	x	x	x	x	x	x
GD3	x	x	x	x	x	x	x	x	x	x	x	x
Glil	x	x	x	x	x	x	x	x	x	x	x	x
GP100	x	x	x	x	x	x	x	x	x	x	x	x
GPA33	x	x	x	x	x	x	x	x	x	x	x	x
磷脂酰肌 醇蛋白聚 糖-3	x	x	x	x	x	x	x	x	x	x	x	x
HIV gp120	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A	x	x	x	x	x	x	x	x	x	x	x	x
HLA-A2	x	x	x	x	x	x	x	x	x	x	x	x
HLA-AI	x	x	x	x	x	x	x	x	x	x	x	x
HLA-B	x	x	x	x	x	x	x	x	x	x	x	x
HLA-C	x	x	x	x	x	x	x	x	x	x	x	x
HMW- MAA	x	x	x	x	x	x	x	x	x	x	x	x
Her2/Neu	x	x	x	x	x	x	x	x	x	x	x	x
Her3	x	x	x	x	x	x	x	x	x	x	x	x
u70/80	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x
ULBP1	x	x	x	x	x	x	x	x	x	x	x	x
ULBP2	x	x	x	x	x	x	x	x	x	x	x	x
ULBP3	x	x	x	x	x	x	x	x	x	x	x	x
ULBP6	x	x	x	x	x	x	x	x	x	x	x	x
MICA	x	x	x	x	x	x	x	x	x	x	x	x
MICB	x	x	x	x	x	x	x	x	x	x	x	x

[0208]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Rα	IL- 1Rα2	IL- 13Rα2	IL- 15Rα	CCR5	CCR8	SIRPα
Her3	x	x	x	x	x	x	x	x	x	x	x	x
EGF	x	x	x	x	x	x	x	x	x	x	x	x
SIRP1α	x	x	x	x	x	x	x	x	x	x	x	x
Lewis-Y	x	x	x	x	x	x	x	x	x	x	x	x
LIV-1 (SLC39A6)	x	x	x	x	x	x	x	x	x	x	x	x
Livin	x	x	x	x	x	x	x	x	x	x	x	x
LAMP1	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA3	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA4	x	x	x	x	x	x	x	x	x	x	x	x
MAGEB6	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA1	x	x	x	x	x	x	x	x	x	x	x	x
MART-1	x	x	x	x	x	x	x	x	x	x	x	x
MCSP	x	x	x	x	x	x	x	x	x	x	x	x
MME	x	x	x	x	x	x	x	x	x	x	x	x
间皮素 (MSLN)	x	x	x	x	x	x	x	x	x	x	x	x
MAPK1	x	x	x	x	x	x	x	x	x	x	x	x
MUC16	x	x	x	x	x	x	x	x	x	x	x	x
MUC1	x	x	x	x	x	x	x	x	x	x	x	x
MRP-3	x	x	x	x	x	x	x	x	x	x	x	x
MyoD-1	x	x	x	x	x	x	x	x	x	x	x	x
NCAM	x	x	x	x	x	x	x	x	x	x	x	x
连接素 4	x	x	x	x	x	x	x	x	x	x	x	x
巢蛋白	x	x	x	x	x	x	x	x	x	x	x	x
NEP	x	x	x	x	x	x	x	x	x	x	x	x
NY-ESO-1	x	x	x	x	x	x	x	x	x	x	x	x
hHLA-A	x	x	x	x	x	x	x	x	x	x	x	x
H60	x	x	x	x	x	x	x	x	x	x	x	x
OLIG2	x	x	x	x	x	x	x	x	x	x	x	x
5T4	x	x	x	x	x	x	x	x	x	x	x	x
p53	x	x	x	x	x	x	x	x	x	x	x	x
P-钙粘着	x	x	x	x	x	x	x	x	x	x	x	x

[0209]

	CD48	轻	CD44	CD45	IL-1R2	IL-1R α	IL-1R α 2	IL-13R α 2	IL-15R α	CCR5	CCR8	SIRP α
蛋白												
PB	x	x	x	x	x	x	x	x	x	x	x	x
P-糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x
PMCT (SLC13A5)	x	x	x	x	x	x	x	x	x	x	x	x
PRAME	x	x	x	x	x	x	x	x	x	x	x	x
PROX1	x	x	x	x	x	x	x	x	x	x	x	x
PSA	x	x	x	x	x	x	x	x	x	x	x	x
PSCA	x	x	x	x	x	x	x	x	x	x	x	x
PSMA	x	x	x	x	x	x	x	x	x	x	x	x
PSC1	x	x	x	x	x	x	x	x	x	x	x	x
PVRL4	x	x	x	x	x	x	x	x	x	x	x	x
Ras	x	x	x	x	x	x	x	x	x	x	x	x
ROR1	x	x	x	x	x	x	x	x	x	x	x	x
SART2	x	x	x	x	x	x	x	x	x	x	x	x
SART3	x	x	x	x	x	x	x	x	x	x	x	x
纤连蛋白 的 癌 胚 胎 变 体	x	x	x	x	x	x	x	x	x	x	x	x
腱糖蛋白	x	x	x	x	x	x	x	x	x	x	x	x
LICAM	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 α	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 β	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 δ	x	x	x	x	x	x	x	x	x	x	x	x
Rae-1 γ	x	x	x	x	x	x	x	x	x	x	x	x
PDGF	x	x	x	x	x	x	x	x	x	x	x	x
Fas	x	x	x	x	x	x	x	x	x	x	x	x
SOX2	x	x	x	x	x	x	x	x	x	x	x	x
STEAP1	x	x	x	x	x	x	x	x	x	x	x	x
SLITRK6	x	x	x	x	x	x	x	x	x	x	x	x
NaPi2a	x	x	x	x	x	x	x	x	x	x	x	x
SOX1	x	x	x	x	x	x	x	x	x	x	x	x

[0210]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Rα	IL- 1Rα2	IL- 13Rα2	IL- 15Rα	CCR5	CCR8	SIRPα
SOX11	x	x	x	x	x	x	x	x	x	x	x	x
SPANXA1	x	x	x	x	x	x	x	x	x	x	x	x
SART-1	x	x	x	x	x	x	x	x	x	x	x	x
SSX4	x	x	x	x	x	x	x	x	x	x	x	x
SSX5	x	x	x	x	x	x	x	x	x	x	x	x
存活素	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x
TAG72	x	x	x	x	x	x	x	x	x	x	x	x
TEM1	x	x	x	x	x	x	x	x	x	x	x	x
TEM8	x	x	x	x	x	x	x	x	x	x	x	x
TSGA10	x	x	x	x	x	x	x	x	x	x	x	x
TSSK6	x	x	x	x	x	x	x	x	x	x	x	x
甲状腺球蛋白	x	x	x	x	x	x	x	x	x	x	x	x
转铁蛋白受体	x	x	x	x	x	x	x	x	x	x	x	x
TACSTD2 (TROP2)	x	x	x	x	x	x	x	x	x	x	x	x
TMEM97	x	x	x	x	x	x	x	x	x	x	x	x
TRP-2	x	x	x	x	x	x	x	x	x	x	x	x
TULP2	x	x	x	x	x	x	x	x	x	x	x	x
TROP2	x	x	x	x	x	x	x	x	x	x	x	x
酪氨酸酶	x	x	x	x	x	x	x	x	x	x	x	x
TRP1	x	x	x	x	x	x	x	x	x	x	x	x
UPAR	x	x	x	x	x	x	x	x	x	x	x	x
VEGF	x	x	x	x	x	x	x	x	x	x	x	x
VEGF 受体	x	x	x	x	x	x	x	x	x	x	x	x
VEGRR2	x	x	x	x	x	x	x	x	x	x	x	x
BRAF	x	x	x	x	x	x	x	x	x	x	x	x
WT-1	x	x	x	x	x	x	x	x	x	x	x	x
XAGE2	x	x	x	x	x	x	x	x	x	x	x	x
ZNF165	x	x	x	x	x	x	x	x	x	x	x	x

[0211]

	CD48	轻	CD44	CD45	IL- 1R2	IL- 1Ra	IL- 1Ra2	IL- 13Ra2	IL- 15Ra	CCR5	CCR8	SIRPα
αvβ6 整联蛋白	x	x	x	x	x	x	x	x	x	x	x	x
β-连环蛋白	x	x	x	x	x	x	x	x	x	x	x	x
组织蛋白酶 B	x	x	x	x	x	x	x	x	x	x	x	x
CSAG2	x	x	x	x	x	x	x	x	x	x	x	x
CTAG	x	x	x	x	x	x	x	x	x	x	x	x
EGFR	x	x	x	x	x	x	x	x	x	x	x	x
EGP40	x	x	x	x	x	x	x	x	x	x	x	x
EZH2	x	x	x	x	x	x	x	x	x	x	x	x
HIV sp120	x	x	x	x	x	x	x	x	x	x	x	x
κ 轻链	x	x	x	x	x	x	x	x	x	x	x	x
LDHC	x	x	x	x	x	x	x	x	x	x	x	x
TRP-1	x	x	x	x	x	x	x	x	x	x	x	x
Fas-L	x	x	x	x	x	x	x	x	x	x	x	x
DLL3	x	x	x	x	x	x	x	x	x	x	x	x
MAGEA12	x	x	x	x	x	x	x	x	x	x	x	x
MAGEC2	x	x	x	x	x	x	x	x	x	x	x	x
BAGE	x	x	x	x	x	x	x	x	x	x	x	x
BAGE1	x	x	x	x	x	x	x	x	x	x	x	x
GAGE	x	x	x	x	x	x	x	x	x	x	x	x
XAGE	x	x	x	x	x	x	x	x	x	x	x	x
XAGE1B	x	x	x	x	x	x	x	x	x	x	x	x
SSX	x	x	x	x	x	x	x	x	x	x	x	x
SSX2	x	x	x	x	x	x	x	x	x	x	x	x
KKLC1	x	x	x	x	x	x	x	x	x	x	x	x
SAGE	x	x	x	x	x	x	x	x	x	x	x	x
SPA17	x	x	x	x	x	x	x	x	x	x	x	x
细胞周期蛋白 A	x	x	x	x	x	x	x	x	x	x	x	x
KMHN1	x	x	x	x	x	x	x	x	x	x	x	x

[0212] 在某些实施方案中,所述有效负载分子是抗原。在某些实施方案中,所述抗原是选自在表4中列出的那些的蛋白或其部分。在某些实施方案中,所述抗原是肿瘤相关抗原(TAA)或其部分。在某些实施方案中,所述肿瘤相关抗原在肿瘤细胞的细胞表面上表达。在

某些实施方案中,所述抗原或其部分的表达诱导针对肿瘤细胞的免疫应答。在某些实施方案中,所述肿瘤相关抗原选自CD19、EpCAM、CEA、PSMA、CD33、EGFR、Her2、EphA2、MCSP、ADAM17、PSCA、17-A1、NKGD2配体、CSF1R、FAP、GD2、DLL3、神经纤毛蛋白、存活素或MAGE家族蛋白。在某些实施方案中,所述肿瘤相关抗原是存活素。在某些实施方案中,所述肿瘤相关抗原是MAGE(黑色素瘤抗原基因)家族蛋白。所述MAGE家族蛋白包含MAGE-B1、MAGEA1、MAGEA10、MAGEA11、MAGEA12、MAGEA2B、MAGEA3、MAGEA4、MAGEA6、MAGEA8、MAGEA9、MAGEB1、MAGEB10、MAGEB16、MAGEB18、MAGEB2、MAGEB3、MAGEB4、MAGEB5、MAGEB6、MAGEB6B、MAGEC1、MAGEC2、MAGEC3、MAGED1、MAGED2、MAGED4、MAGEE1、MAGEE2、MAGEF1、MAGEH1、MAGEL2、NDN、NDNL2或它们的任意组合。在某些实施方案中,所述肿瘤相关抗原选自下面表6中的抗原。在某些实施方案中,所述复制子编码本公开内容的二、三、四、五种或更多种肿瘤相关抗原。

[0213] 在某些实施方案中,所述有效负载分子包含本公开内容的肿瘤相关抗原(TAA)的片段(即,肽片段)或由其组成。在某些实施方案中,所述TAA的片段具有约10个氨基酸(aa)、约15个氨基酸、约20个氨基酸、约30个氨基酸、约40个氨基酸、约50个氨基酸、约60个氨基酸、约70个氨基酸、约80个氨基酸、约90个氨基酸、约100个氨基酸或之间的任何值的长度。在某些实施方案中,所述TAA的片段具有至少10个氨基酸、至少15个氨基酸、至少20个氨基酸、至少30个氨基酸、至少40个氨基酸、至少50个氨基酸、至少60个氨基酸、至少70个氨基酸、至少80个氨基酸、至少90个氨基酸或至少100个氨基酸的长度。在某些实施方案中,所述复制子包含二、三、四、五种或更多种有效负载分子,各自包含不同TAA的片段或由其组成。在某些实施方案中,所述复制子包含二、三、四、五种或更多种有效负载分子,各自包含相同TAA的不同片段或由其组成。在某些实施方案中,所述复制子包含有效负载分子的二、三、四、五个或更多个拷贝,各自包含相同TAA的相同片段或由其组成。在某些实施方案中,所述有效负载分子包含TAA的相同肽片段的重复,诸如相同肽片段的2、3、4、5、6、7、8、9、10或超过10个重复。

[0214] 表6. 肿瘤相关抗原

[0215]

肿瘤相关抗原
MAGEA1
MAGEA3
MAGEA4
MAGEA12
MAGEC2
BAGE (B 黑色素瘤抗原)
BAGE1 (B 黑色素瘤抗原 1)
GAGE (G 抗原)
GAGE1 (G 抗原 1)
XAGE (X 抗原)
XAGE1B (X 抗原家族成员 1B)
CTAG (癌/睾丸抗原)
CTAG2 (LAGE1)
CTAG1 (NY-ESO-1)
SSX (滑膜肉瘤 X)
SSX2 (滑膜肉瘤 X 断点 2)
KKLC1 (Kita-kyushu 肺癌抗原 1)
SAGE (肉瘤抗原)
SPA17 (精子自身抗原蛋白 17)
细胞周期蛋白 A
KMHN1 (CCDC110)
存活素
EBV 编码的潜在膜蛋白 1 (LMP1)
EBV 编码的潜在膜蛋白 2 (LMP2)
衍生自人乳头瘤病毒(HPV)的病毒抗原
衍生自人乳头瘤病毒(HPV)株 6 的病毒抗原
衍生自人乳头瘤病毒(HPV)株 7 的病毒抗原
衍生自人乳头瘤病毒(HPV)株 11 的病毒抗原
衍生自人乳头瘤病毒(HPV)株 16 的病毒抗原
衍生自人乳头瘤病毒(HPV)株 18 的病毒抗原
衍生自人乳头瘤病毒(HPV)株 31 的病毒抗原
衍生自爱泼斯坦-巴尔病毒(EBV)的病毒抗原

[0216]	肿瘤相关抗原
	衍生自人 T-淋巴营养性病毒(HTLV)的病毒抗原的病毒抗原
	衍生自梅克尔细胞多形瘤病毒(MCV)的病毒抗原
	衍生自卡波西氏肉瘤-相关的疱疹病毒的病毒抗原
	衍生自巨细胞病毒(CMV)的病毒抗原

[0217] 在某些实施方案中,所述有效负载分子包含肿瘤新抗原或由其组成。术语“肿瘤新抗原”表示存在于受试者的肿瘤细胞或组织中、但不存在于受试者的相应正常细胞或组织中的新抗原。肿瘤新抗原可以是肽或蛋白。在某些实施方案中,所述肿瘤新抗原是患者特异性的或受试者特异性的。在某些实施方案中,所述复制子编码多种包含肿瘤新抗原的有效负载分子,诸如2、3、4、5、6、7、8、9、10或超过10种包含肿瘤新抗原的有效负载分子。在某些实施方案中,所述复制子可以编码相同肿瘤新抗原的多个拷贝。

[0218] 在某些实施方案中,所述有效负载分子是对主要组织相容性复合物(MHC)-肽抗原复合物具有特异性结合的双组分多肽。在某些实施方案中,所述双组分多肽特异性地结合MHC-肽抗原复合物。在某些实施方案中,所述MHC是I类MHC。在某些实施方案中,所述肽抗原衍生自TAA或肿瘤新抗原。在某些实施方案中,所述双组分多肽包含特异性地结合MHC-肽抗原复合物的T-细胞受体(TCR)的片段(例如TCR的细胞外结构域)。在某些实施方案中,所述双组分多肽也结合根据表3的效应细胞抗原之一。在某些实施方案中,所述双组分多肽特异性地结合CD3。在某些实施方案中,所述双组分多肽特异性地结合CD3 ϵ 。

[0219] 在某些实施方案中,所述重组RNA复制子包含一个或多个有效负载分子,其中所述有效负载分子包含:

[0220] a) 一种或多种细胞因子,包含IFN γ 、GM-CSF、IL-2、IL-12、IL-15、IL-18、IL-23和IL-36 γ ;

[0221] b) 一种或多种趋化因子,包含CXCL10、CCL4、CCL5和CCL21;

[0222] c) 一种或多种抗体,包含抗-PD1-VHH-Fc抗体、抗-CD47-VHH-Fc抗体和抗-TGF β -VHH(或scFv)-Fc抗体;

[0223] d) 一种或多种双组分多肽,包含结合DLL3和效应细胞靶抗原的双组分多肽、结合FAP和效应细胞靶抗原的双组分多肽、以及结合EpCAM和效应细胞靶抗原的双组分多肽;

[0224] e) 一种或多种肿瘤相关抗原,包含存活素、MAGE家族蛋白和根据表6的所有抗原;

[0225] f) 一种或多种肿瘤新抗原;

[0226] g) 一种或多种结合MHC-肽抗原复合物的双组分多肽;

[0227] h) 一种或多种促融合蛋白,包含单纯疱疹病毒(HSV) UL27/糖蛋白B/gB, HSV UL53/糖蛋白K/gK, 呼吸道合胞体病毒(RSV) F蛋白, FASTp15, VSV-G, syncitin-1(来自人内源性逆转录病毒-W(HERV-W))或syncitin-2(来自HERVFRDE1), 副粘病毒SV5-F, 麻疹病毒-H, 麻疹病毒-F, 以及来自逆转录病毒或慢病毒诸如长臂猿白血病毒(GALV)、鼠白血病毒(MLV)、Mason-Pfizer猴病毒(MPMV)和马传染性贫血病毒(EIAV)的糖蛋白, 任选地除去了R跨膜肽(R-版本);

[0228] i) 一种或多种其它有效负载分子, 包含IL15R、PGDH、ADA、ADA2、HYAL1、HYAL2、CHIPS、MLKL(或仅它的4HB结构域)、GSDMD(或它的L192A突变体、或它的氨基酸1-233片段、

或它的具有L192A突变的氨基酸1-233片段)、GSDME(或它的氨基酸1-237片段)、HMGB1(或仅它的Box B结构域)、蜂毒肽(例如, α -蜂毒肽)、SMAC/Diablo(或它的氨基酸56-239片段)、蛇LAAO、蛇解聚素、瘦素、FLT3L、TRAIL、Gasdermin D或其截短体和Gasdermin E或其截短体;

[0229] j) 一种或多种来自病原体的抗原,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒;或

[0230] k) 它们的任意组合。

[0231] 促融合蛋白是促进细胞与细胞膜融合的蛋白。由本公开内容的复制子编码的有效负载分子或至少一个有效负载分子可以是促融合蛋白,其包含单纯疱疹病毒(HSV) UL27/糖蛋白B/gB, HSV UL53/糖蛋白K/gK, 呼吸道合胞体病毒(RSV) F蛋白, FASTp15, VSV-G, syncitin-1(来自人内源性逆转录病毒-W(HERV-W))或syncitin-2(来自HERVFRDE1), 副粘病毒SV5-F, 麻疹病毒-H, 麻疹病毒-F, 以及来自逆转录病毒或慢病毒诸如长臂猿白血病病毒(GALV)、鼠白血病病毒(MLV)、Mason-Pfizer猴病毒(MPMV)和马传染性贫血病毒(EIAV)的糖蛋白,任选地除去了R跨膜肽(R-版本)。

[0232] 在某些实施方案中,所述有效负载分子是GM-CSF。在某些实施方案中,所述有效负载分子是与SEQ ID NO:81具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的GM-CSF多肽。

[0233] 在某些实施方案中,所述有效负载分子是IL-2。在某些实施方案中,所述有效负载分子是与SEQ ID NO:82具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-2多肽。在某些实施方案中,所述有效负载分子是与SEQ ID NO:83具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-2多肽。

[0234] 在某些实施方案中,所述有效负载分子是IL-12 β 亚基。在某些实施方案中,所述有效负载分子是与SEQ ID NO:84具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-12 β 亚基多肽。在某些实施方案中,所述有效负载分子是IL-12 α 亚基。在某些实施方案中,所述有效负载分子是与SEQ ID NO:85具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-12 α 亚基多肽。在某些实施方案中,所述有效负载分子是IL-23 α 亚基。在某些实施方案中,所述有效负载分子是与SEQ ID NO:86具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-23 α 亚基多肽。

[0235] 在某些实施方案中,所述有效负载分子是IL-18。在某些实施方案中,所述有效负载分子是与SEQ ID NO:87具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-18多肽。

[0236] 在某些实施方案中,所述有效负载分子是IL-36 γ 。在某些实施方案中,所述有效负载分子是与SEQ ID NO:88具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-36 γ 多肽。在某些实施方案中,所述有效负载分子是与SEQ ID NO:89具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-36 γ 多肽。

[0237] 在某些实施方案中,所述有效负载分子是CXCL10。在某些实施方案中,所述有效负载分子是与SEQ ID NO:90具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CXCL10多肽。在某些实施方案中,所述有效负载分子是与SEQ ID NO:91具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CXCL10多肽。

[0238] 在某些实施方案中,所述有效负载分子是CCL4。在某些实施方案中,所述有效负载分子是与SEQ ID NO:92具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CCL4多肽。

[0239] 在某些实施方案中,所述有效负载分子是CCL5。在某些实施方案中,所述有效负载分子是与SEQ ID NO:93具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CCL5多肽。

[0240] 在某些实施方案中,所述有效负载分子是CCL21。在某些实施方案中,所述有效负载分子是与SEQ ID NO:94具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CCL21多肽。

[0241] 在某些实施方案中,所述有效负载分子是抗-PD1-VHH-Fc。在某些实施方案中,所述有效负载分子是与SEQ ID NO:95具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的抗-PD1-VHH-Fc (hIgG4) 多肽。

[0242] 在某些实施方案中,所述有效负载分子是抗-DLL3双组分多肽。在某些实施方案中,所述抗-DLL3双组分多肽是抗-DLL3双特异性的T-细胞接合剂(BiTE)。在某些实施方案中,所述抗-DLL3双组分多肽或抗-DLL3双特异性的T-细胞接合剂(BiTE)包含能够结合效应细胞的细胞表面抗原的第一结构域和能够结合DLL3的第二结构域。在某些实施方案中,所述第一结构域结合CD3。在某些实施方案中,所述第二结构域(结合DLL3)是scFv或纳米抗体(VHH)。在某些实施方案中,所述DLL3结合结构域选自在国际PCT申请号PCT/US2021/030836(其通过引用整体并入本文)中描述的那些。在某些实施方案中,所述DLL3抗原包含与SEQ ID NO:96具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的氨基酸序列。

[0243] 在某些实施方案中,所述有效负载分子包含抗-FAP重链可变区。在某些实施方案中,所述有效负载分子包含与SEQ ID NO:97具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的抗-FAP重链可变区多肽。在某些实施方案中,所述有效负载分子包含抗-FAP轻链可变区。在某些实施方案中,所述有效负载分子包含与SEQ ID NO:98具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的抗-FAP轻链可变区多肽。

[0244] 在某些实施方案中,所述有效负载分子包含抗-CD3重链可变区。在某些实施方案中,所述有效负载分子包含与SEQ ID NO:99具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的抗-CD3重链可变区多肽。在某些实施方案中,所述有效负载分子包含抗-CD3轻链可变区。在某些实施方案中,所述有效负载分子包含与SEQ ID NO:100具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的抗-CD3轻链可变区多肽。

[0245] 在某些实施方案中,所述有效负载分子是兰妥莫单抗。在某些实施方案中,所述有

效负载分子是与SEQ ID NO:101具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的兰妥莫单抗-样多肽。

[0246] 在某些实施方案中,所述有效负载分子是MT110。在某些实施方案中,所述有效负载分子是与SEQ ID NO:102具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MT110-样多肽。

[0247] 在某些实施方案中,所述有效负载分子是帕妥昔珠单抗。在某些实施方案中,所述有效负载分子是与SEQ ID NO:103具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的帕妥昔珠单抗-样多肽。

[0248] 在某些实施方案中,所述有效负载分子是AMG330。在某些实施方案中,所述有效负载分子是与SEQ ID NO:104具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的AMG330-样多肽。

[0249] 在某些实施方案中,所述有效负载分子是COVA420重链。在某些实施方案中,所述有效负载分子是与SEQ ID NO:105具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的COVA420重链-样多肽。在某些实施方案中,所述有效负载分子是COVA420轻链。在某些实施方案中,所述有效负载分子是与SEQ ID NO:106具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的COVA420轻链-样多肽。

[0250] 在某些实施方案中,所述有效负载分子是存活素。在某些实施方案中,所述有效负载分子是与SEQ ID NO:107具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的存活素多肽。

[0251] 在某些实施方案中,所述有效负载分子是IFN γ 。在某些实施方案中,所述有效负载分子是与SEQ ID NO:113具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IFN γ 多肽。

[0252] 在某些实施方案中,所述有效负载分子是IL-15。在某些实施方案中,所述有效负载分子是与SEQ ID NO:114具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的IL-15多肽。

[0253] 在某些实施方案中,所述有效负载分子是IL15R。在某些实施方案中,所述IL15R包含IL15RA和/或IL15RB。在某些实施方案中,所述IL15RA与SEQ ID NO:115具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性。在某些实施方案中,所述IL15RB多肽与SEQ ID NO:116具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性。

[0254] 在某些实施方案中,所述有效负载分子是PGDH。在某些实施方案中,所述有效负载分子是与SEQ ID NO:117具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的PGDH多肽。

[0255] 在某些实施方案中,所述有效负载分子是ADA2。在某些实施方案中,所述有效负载分子是与SEQ ID NO:118具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的ADA2多肽。

[0256] 在某些实施方案中,所述有效负载分子是HYAL1。在某些实施方案中,所述有效负载分子是与SEQ ID NO:119具有至少70%、至少75%、至少80%、至少85%、至少90%、至少

95%、至少98%、至少99%或100%序列同一性的HYAL1多肽。

[0257] 在某些实施方案中,所述有效负载分子是HYAL2。在某些实施方案中,所述有效负载分子是与SEQ ID NO:120具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的HYAL2多肽。

[0258] 在某些实施方案中,所述有效负载分子是MLKL。在某些实施方案中,所述有效负载分子是与SEQ ID NO:121具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MLKL多肽。在某些实施方案中,所述有效负载分子包含MLKL 4HB结构域或由其组成。

[0259] 在某些实施方案中,所述有效负载分子是GSDMD。在某些实施方案中,所述有效负载分子是与SEQ ID NO:122具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的GSDMD多肽。在某些实施方案中,所述有效负载分子是GSDMD 1-233片段和/或L192A突变体。

[0260] 在某些实施方案中,所述有效负载分子是GSDME。在某些实施方案中,所述有效负载分子是与SEQ ID NO:123具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的GSDME多肽。在某些实施方案中,所述有效负载分子是GSDME 1-237片段。

[0261] 在某些实施方案中,所述有效负载分子是HMGB1。在某些实施方案中,所述有效负载分子是与SEQ ID NO:124具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的HMGB1多肽。在某些实施方案中,所述有效负载分子包含HMGB1 Box B结构域或由其组成。

[0262] 在某些实施方案中,所述有效负载分子是蜂毒肽。在某些实施方案中,所述有效负载分子是与SEQ ID NO:125具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的蜂毒肽多肽。

[0263] 在某些实施方案中,所述有效负载分子是SMAC/Diablo。在某些实施方案中,所述有效负载分子是与SEQ ID NO:126具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的SMAC/Diablo多肽。在某些实施方案中,所述有效负载分子包含SMAC/Diablo氨基酸56-239片段或由其组成。

[0264] 在某些实施方案中,所述有效负载分子是蛇LAA0。在某些实施方案中,所述有效负载分子是与SEQ ID NO:127具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的蛇LAA0多肽。

[0265] 在某些实施方案中,所述有效负载分子是瘦素。在某些实施方案中,所述有效负载分子是与SEQ ID NO:128具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的瘦素多肽。

[0266] 在某些实施方案中,所述有效负载分子是FLT3L。在某些实施方案中,所述有效负载分子是与SEQ ID NO:129具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的FLT3L多肽。

[0267] 在某些实施方案中,所述有效负载分子是TRAIL。在某些实施方案中,所述有效负载分子是与SEQ ID NO:130具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的TRAIL多肽。

[0268] 在某些实施方案中,所述有效负载分子是MAGEA1。在某些实施方案中,所述有效负载分子是与SEQ ID NO:131具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MAGEA1多肽。

[0269] 在某些实施方案中,所述有效负载分子是MAGEA3。在某些实施方案中,所述有效负载分子是与SEQ ID NO:132具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MAGEA3多肽。

[0270] 在某些实施方案中,所述有效负载分子是MAGEA4。在某些实施方案中,所述有效负载分子是与SEQ ID NO:133具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MAGEA4多肽。

[0271] 在某些实施方案中,所述有效负载分子是MAGEA12。在某些实施方案中,所述有效负载分子是与SEQ ID NO:134具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MAGEA12多肽。

[0272] 在某些实施方案中,所述有效负载分子是MAGEC2。在某些实施方案中,所述有效负载分子是与SEQ ID NO:135具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的MAGEC2多肽。

[0273] 在某些实施方案中,所述有效负载分子是BAGE1 (B黑色素瘤抗原1)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:136具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的BAGE1 (B黑色素瘤抗原1)多肽。

[0274] 在某些实施方案中,所述有效负载分子是GAGE1 (G抗原1)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:137具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的GAGE1 (G抗原1)多肽。

[0275] 在某些实施方案中,所述有效负载分子是XAGE1B (X抗原家族成员1B)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:138具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的XAGE1B (X抗原家族成员1B)多肽。

[0276] 在某些实施方案中,所述有效负载分子是CTAG2 (LAGE1)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:139具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CTAG2 (LAGE1)多肽。

[0277] 在某些实施方案中,所述有效负载分子是CTAG1 (NY-ESO-1)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:140具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的CTAG1 (NY-ESO-1)多肽。

[0278] 在某些实施方案中,所述有效负载分子是SSX2 (滑膜肉瘤X断点2)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:141具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的SSX2 (滑膜肉瘤X断点2)多肽。

[0279] 在某些实施方案中,所述有效负载分子是KKLC1 (Kita-kyushu肺癌抗原1)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:142具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的KKLC1 (Kita-

kyushu肺癌抗原1)多肽。

[0280] 在某些实施方案中,所述有效负载分子是SAGE(肉瘤抗原)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:143具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的SAGE(肉瘤抗原)多肽。

[0281] 在某些实施方案中,所述有效负载分子是SPA17(精子自身抗原蛋白17)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:144具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的SPA17(精子自身抗原蛋白17)多肽。

[0282] 在某些实施方案中,所述有效负载分子是细胞周期蛋白A。在某些实施方案中,所述有效负载分子是与SEQ ID NO:145具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的细胞周期蛋白A多肽。

[0283] 在某些实施方案中,所述有效负载分子是KMHN1(CCDC110)。在某些实施方案中,所述有效负载分子是与SEQ ID NO:146具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的KMHN1(CCDC110)多肽。

[0284] 在某些实施方案中,所述有效负载分子是LMP-1。在某些实施方案中,所述有效负载分子是与SEQ ID NO:147具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的LMP-1多肽。

[0285] 在某些实施方案中,所述有效负载分子是LMP-2。在某些实施方案中,所述有效负载分子是与SEQ ID NO:148具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%或100%序列同一性的LMP-2多肽。

[0286] 在某些实施方案中,所述有效负载分子是不由受试者自身的基因组编码的抗原。在某些实施方案中,所述有效负载分子是由病原微生物表达的抗原。病原微生物包含细菌、病毒、寄生虫和真菌。在某些实施方案中,所述有效负载分子是来自病原体之一的抗原,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒。

[0287] 切割多肽

[0288] 在某些实施方案中,一个或多个切割多肽可操作地连接至有效负载分子。这样的切割多肽的存在允许将有效负载分子与由复制子编码的多肽的其余部分分离。在某些实施方案中,所述复制子包含编码两个或更多个有效负载分子的异源多核苷酸,所述有效负载分子可操作地连接至一个或多个切割多肽,这允许所述有效负载分子的分离。在某些实施方案中,另外的肽接头(诸如甘氨酸-丝氨酸接头)可以存在于有效负载分子和切割多肽之间。

[0289] 所述切割多肽包含2A家族自切割肽、3C切割位点、弗林蛋白酶位点、IGSF1和HIV-1蛋白酶位点。应当注意,超过一种切割多肽可以可操作地连接至有效负载分子,且不同的切割多肽可以用在相同复制子中。例如,不同的切割多肽可以可操作地连接至有效负载分子的N-端和C-端。另外,两个或更多个切割多肽可以连接在一起或连续连接以形成更长的切割多肽,其可以具有改进的切割性能。

[0290] 在某些实施方案中,所述切割多肽包含2A家族自切割肽或由其组成。自切割肽存

在于小核糖核酸病毒科的成员中,包括口蹄疫病毒属诸如口蹄疫病毒(FMDV)、马甲型鼻炎病毒(ERAV)、Thosea assigna病毒(TaV)和猪捷申病毒-1(PTV-1)(Donnelly, M L, 等人, J.Gen.Virol., 82, 1027-101 (2001); Ryan, M D, 等人, J.Gen.Virol., 72, 2727-2732 (2001) 和心病毒属诸如Theilovirus(例如, Theiler氏鼠脑脊髓炎)和脑心肌炎病毒。从FMDV、ERAV、PTV-1和TaV衍生出的2A肽在本文中有时分别被称作“F2A”、“E2A”、“P2A”和“T2A”。口蹄疫病毒2A多肽通常含有Dx1Ex2NPG (SEQ ID NO:63) 基序, 其中x1经常是缬氨酸或异亮氨酸。不希望受任何特定理论约束, 认为2A序列介导脯氨酸和甘氨酸之间的“核糖体跳跃”, 从而损害P和G之间的正常肽键形成而不影响下游翻译。示例性的2A自切割肽可以在下表7中找到。另外的示例性的2A自切割肽可以在美国专利号9,497,943和Souza-Moreira等人, FEMS Yeast Res. 2018年8月1日; 18 (5) (它们通过引用并入本文) 中找到。在某些实施方案中, 所述切割多肽包含根据表7的2A自切割肽之一。在某些实施方案中, 所述切割多肽包含由根据表7中的2A自切割肽之一的至多1个、至多2个、至多3个或至多4个突变组成的氨基酸序列。

[0291] 表7. 示例性的2A自切割肽

[0292]

名称	序列	SEQ ID NO
T2A	EGRGSLTTCGDVEENPGP	64
P2A	ATNFSLLKQAGDVEENPGP	65
E2A	QCTNYALLKLAGDVESNPGP	66
F2A	VKQTLNFDLLKLAGDVESNPGP	67
SVV 2A	SGDIETNPGP	68

[0293] 在某些实施方案中, 所述切割多肽包含SVV 2A自切割肽或由其组成。在某些实施方案中, 所述SVV 2A自切割肽具有SGDIETNPGP (SEQ ID NO:68) 的氨基酸序列。在某些实施方案中, 所述SVV 2A自切割肽具有由根据SGDIETNPGP (SEQ ID NO:68) 的至多1个、至多2个或至多3个突变组成的氨基酸序列。

[0294] 在某些实施方案中, 所述切割多肽包含柯萨奇病毒2A切割位点或由其组成。在某些实施方案中, 所述柯萨奇病毒2A切割位点具有GFGHQ (SEQ ID NO:69) 的氨基酸序列。在某些实施方案中, 所述柯萨奇病毒2A切割位点具有由根据GFGHQ (SEQ ID NO:69) 的至多1个、至多2个或至多3个突变组成的氨基酸序列。

[0295] 在某些实施方案中, 所述切割多肽包含3C切割位点或由其组成。在某些实施方案中, 所述3C切割位点是具有氨基酸序列IVYELQGP (SEQ ID NO:70) 的SVV 3C切割位点。在某些实施方案中, 所述3C切割位点具有由根据IVYELQGP (SEQ ID NO:70) 的至多1个、至多2个或至多3个突变组成的氨基酸序列。在某些实施方案中, 所述切割多肽包含融合素位点和3C切割位点。在某些实施方案中, 所述切割多肽包含RRKRIVYELQGP (SEQ ID NO:71) 的氨基酸序列或由其组成。在某些实施方案中, 所述3C切割位点具有由根据RRKRIVYELQGP (SEQ ID NO:71) 的至多1个、至多2个、至多3个或至多4个突变组成的氨基酸序列。

[0296] 在某些实施方案中, 所述切割多肽包含一个或多个切割位点或由其组成, 所述切割位点可以被由哺乳动物细胞产生的蛋白酶切割。在某些实施方案中, 所述蛋白酶是弗林蛋白酶。在某些实施方案中, 所述切割多肽包含一个弗林蛋白酶位点或由其组成。在某些实施方案中, 所述切割多肽包含两个或更多个弗林蛋白酶位点或由其组成。在某些实

施方案中,所述弗林蛋白酶位点具有Arg-X-X-Arg (SEQ ID NO:72)的共有序列。在某些实施方案中,所述弗林蛋白酶位点具有Arg-X-Lys/Arg-Arg (SEQ ID NO:73)的共有序列。在某些实施方案中,所述弗林蛋白酶位点具有RRKR (SEQ ID NO:74)的氨基酸序列。在某些实施方案中,所述切割多肽包含一个或多个GS接头(氨基酸序列Gly-Ser)。在某些实施方案中,所述切割多肽包含一个或多个GSG接头(氨基酸序列Gly-Ser-Gly)。在某些实施方案中,所述切割多肽采用“GSG接头-2A肽”的构型。在某些实施方案中,所述切割多肽采用“弗林蛋白酶位点-2A肽”的构型。在某些实施方案中,所述切割多肽采用“弗林蛋白酶位点-GSG接头-2A肽”的构型。

[0297] 在某些实施方案中,所述切割多肽包含IGSF1多肽或由其组成。在某些实施方案中,所述IGSF1多肽包含NEAIRLSLIMQLVALLLVWLWIRWKCRRLRIREAWLLGTAQGVTMLFIVTALLCCGLCNG (SEQ ID NO:75)的氨基酸序列或由其组成。在某些实施方案中,所述IGSF1多肽包含与SEQ ID NO:75具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或至少98%同一性的氨基酸序列或由其组成。在某些实施方案中,除了IGSF1多肽以外,所述切割多肽还包含一个或多个弗林蛋白酶位点。在某些实施方案中,所述切割多肽包含含有肽的弗林蛋白酶位点或由其组成,所述肽具有GSRRKRGSRRKRGS (SEQ ID NO:76)的氨基酸序列。在某些实施方案中,所述切割多肽包含GSRRKRGSRRKRGSNEAIRLSLIMQLVALLLVWLWIRWKCRRLRIREAWLLGTAQGVTMLFIVTALLCCGLCNG (SEQ ID NO:77)的氨基酸序列或由其组成。在某些实施方案中,所述切割多肽包含与SEQ ID NO:77具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或至少98%同一性的氨基酸序列或由其组成。在某些实施方案中,所述有效负载分子中的两个可操作地连接至包含IGSF多肽的切割多肽。在某些实施方案中,所述有效负载分子中的两个可操作地连接至包含IGSF多肽和一个或多个弗林蛋白酶位点的切割多肽。在某些实施方案中,所述有效负载分子中的两个可操作地连接至包含SEQ ID NO:77的氨基酸序列或由其组成的切割多肽。

[0298] 在某些实施方案中,所述切割多肽包含一个或多个可以被非哺乳动物蛋白酶识别的切割位点或由其组成。在某些实施方案中,所述非哺乳动物蛋白酶是HIV蛋白酶。在某些实施方案中,所述切割多肽包含HIV蛋白酶位点或由其组成。在某些实施方案中,所述HIV蛋白酶位点包含PR切割序列或由其组成,所述PR切割序列具有IFLETS (SEQ ID NO:78)的氨基酸序列。在某些实施方案中,所述HIV蛋白酶位点包含PR切割序列或由其组成,所述PR切割序列具有根据IFLETS (SEQ ID NO:78)的至多一个、至多两个、或至多三个突变或保守突变。在某些实施方案中,所述切割多肽包含GS接头和PR切割序列。在某些实施方案中,所述切割多肽包含GSGIFLETS (SEQ ID NO:79)的氨基酸序列或由其组成。在某些实施方案中,所述切割多肽包含特定氨基酸序列或由其组成,所述特定氨基酸序列具有根据GSGIFLETS (SEQ ID NO:79)的至多一个、至多两个、至多三个或至多四个突变或保守突变。

[0299] 在某些实施方案中,所述异源核酸包含HIV蛋白酶编码序列。在某些实施方案中,所述HIV蛋白酶包含特定氨基酸序列或由其组成,所述特定氨基酸序列与SEQ ID NO:80具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少98%同一性、至少99%同一性或100%同一性:

[0300] QITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWPKMIGGIGGFIKVRQYDQILIEICGH KAIGTVLVGPTPVNIIGRNLLTQIGCTLNF (SEQ ID NO:80)

[0301] 在某些实施方案中,所述异源多核苷酸包含编码区,其编码可操作地连接至一个或多个切割多肽的有效负载分子。在某些实施方案中,所述有效负载分子可操作地连接至两个切割多肽。在某些实施方案中,至少一个切割多肽侧接有效负载分子的N-端和/或至少一个切割多肽侧接有效负载分子的C-端。在某些实施方案中,所述切割肽和所述有效负载分子采用以下构型:

[0302] N'-切割多肽1-有效负载分子-切割多肽2-C'。

[0303] 在某些实施方案中,另外的切割多肽可以存在于在该段落中在上面描述的构型的N'和/或C'末端处。在某些实施方案中,所述另外的切割多肽包含2A自切割肽。在某些实施方案中,在C-端处的切割多肽2包含T2A自切割肽或由其组成。在某些实施方案中,在N-端处的切割多肽1包含2A自切割肽或由其组成。在某些实施方案中,另外的肽接头(诸如甘氨酸-丝氨酸接头)可以存在于有效负载分子和切割多肽之间。

[0304] 多个有效负载分子的共表达

[0305] 在某些实施方案中,本公开内容提供了重组RNA复制子,其包含编码两个或更多个有效负载分子的异源核苷酸。在某些实施方案中,本公开内容的重组RNA复制子能够从一个复制子表达两个或更多个有效负载分子。

[0306] 在某些实施方案中,所述两个或更多个有效负载分子由连续的异源多核苷酸编码。在某些实施方案中,至少一个有效负载分子由第二异源多核苷酸编码。在某些实施方案中,所述两个或更多个异源多核苷酸插入在病毒基因组的不同位置。

[0307] 在某些实施方案中,至少一个有效负载分子是分泌型蛋白。在某些实施方案中,所述分泌型蛋白包含天然信号肽或非天然信号肽。在某些实施方案中,所述有效负载分子中的两个是分泌型蛋白。在某些实施方案中,所述有效负载分子中的至少两个是分泌型蛋白。在某些实施方案中,所有的有效负载分子是分泌型蛋白。在某些实施方案中,至少一个有效负载分子是分泌型蛋白,其包含用于分泌的天然信号肽序列。在某些实施方案中,至少一个有效负载分子是分泌型蛋白,其包含用于分泌的非天然信号肽序列。在某些实施方案中,至少一个有效负载分子是没有信号肽序列的分泌型蛋白。

[0308] 在某些实施方案中,每个有效负载分子在其C-端可操作地连接至切割多肽。在某些实施方案中,每个有效负载分子在其N-端和其C-端可操作地连接至切割多肽。

[0309] 在某些实施方案中,所述异源多核苷酸包含编码区,其编码可操作地连接至切割多肽的两个或更多个有效负载分子。在某些实施方案中,所述两个或更多个有效负载分子和所述切割多肽采用以下构型:

[0310] N'-有效负载分子1-切割多肽-有效负载分子2-C'。

[0311] 在某些实施方案中,另外的切割多肽可以存在于在该段落中在上面描述的构型的N'和/或C'末端处。在某些实施方案中,所述另外的切割多肽包含2A自切割肽。在某些实施方案中,T2A自切割肽侧接有效负载分子2的C-端。在某些实施方案中,另外的肽接头(诸如甘氨酸-丝氨酸接头)可以存在于有效负载分子和切割多肽之间。

[0312] 在某些实施方案中,所述异源多核苷酸包含编码区,其编码可操作地连接至切割多肽的两个有效负载分子,所述切割多肽包含IGSF多肽或由其组成。在某些实施方案中,所述IGSF1多肽具有以下氨基酸序列:NEAIRLSLIMQLVALLLVVLWIRWKCRRRLRIEAWLLGTAQGVMTL FIVTALLCCGLCNG (SEQ ID NO:75)。

[0313] 在某些实施方案中,所述IGSF1多肽与SEQ ID NO:75具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或至少98%同一性。在某些实施方案中,所述切割多肽包含含有特定肽的弗林蛋白酶位点,所述特定肽具有GSRRKRGSRKRGS (SEQ ID NO:76)的氨基酸序列。在某些实施方案中,所述切割多肽包含以下氨基酸序列或由其组成:GSRRKRGSRKRGSNEAIRLSLIMQLVALLLVVLWIRWKCRRRLRIREAWLLGTAQGVMTLFIIVTALLCCGLCNG (SEQ ID NO:77)。

[0314] 在某些实施方案中,所述切割多肽包含与SEQ ID NO:77具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%或至少98%同一性的氨基酸序列或由其组成。

[0315] 在某些实施方案中,所述异源多核苷酸包含编码区,其编码可操作地连接至切割多肽的两个有效负载分子,所述切割多肽包含一个或多个HIV蛋白酶位点或由其组成。在某些实施方案中,所述HIV蛋白酶位点包含PR切割序列或由其组成,所述PR切割序列具有IFLETS (SEQ ID NO:78)的氨基酸序列,或具有根据IFLETS (SEQ ID NO:78)的至多一个、至多两个、或至多三个突变或保守突变的氨基酸序列。在某些实施方案中,所述切割多肽包含GS接头和PR切割序列。在某些实施方案中,所述切割多肽包含GSGIFLETS (SEQ ID NO:79)的氨基酸序列或由其组成。在某些实施方案中,所述切割多肽包含特定氨基酸序列或由其组成,所述特定氨基酸序列具有根据GSGIFLETS (SEQ ID NO:79)的至多一个、至多两个、至多三个或至多四个突变或保守突变。

[0316] 在某些实施方案中,所述异源核酸进一步包含HIV蛋白酶编码区。在某些实施方案中,所述HIV蛋白酶通过切割多肽可操作地连接至一个或多个有效负载分子,所述切割多肽包含HIV蛋白酶位点或由其组成。在某些实施方案中,所述HIV蛋白酶位于两个有效负载分子之间。

[0317] 在某些实施方案中,所述异源核酸包含编码区,其编码两个有效负载分子和HIV蛋白酶。在某些实施方案中,所述异源核酸包含编码区,其编码采用以下构型的多肽:

[0318] N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-C'。

[0319] 在某些实施方案中,另外的切割多肽可以存在于在该段落中在上面描述的构型的N'和/或C'末端处。在某些实施方案中,所述另外的切割多肽包含HIV蛋白酶位点。在某些实施方案中,所述另外的切割多肽包含2A自切割肽。在某些实施方案中,T2A自切割肽侧接有效负载分子2的C-端。在某些实施方案中,另外的肽接头(诸如甘氨酸-丝氨酸接头)可以存在于有效负载分子和HIV蛋白酶位点之间。

[0320] 在某些实施方案中,所述异源核酸包含编码区,其编码三个有效负载分子和HIV蛋白酶。在某些实施方案中,所述异源核酸包含编码区,其编码采用以下构型的多肽:

[0321] N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-HIV蛋白酶位点-有效负载分子3-C'。

[0322] 在某些实施方案中,另外的切割多肽可以存在于在该段落中在上面描述的构型的N'和/或C'末端处。在某些实施方案中,所述另外的切割多肽包含HIV蛋白酶位点。在某些实施方案中,所述另外的切割多肽包含2A自切割肽。在某些实施方案中,T2A自切割肽侧接有效负载分子3的C-端。在某些实施方案中,另外的肽接头(诸如甘氨酸-丝氨酸接头)可以存在于有效负载分子和HIV蛋白酶位点之间。

[0323] 在某些实施方案中,所述两个或更多个有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。在某些实施方案中,至少一个有效负载分子是分泌型蛋白。在某些实施方案中,所述两个或更多个有效负载分子是分泌型蛋白。在某些实施方案中,所述有效负载分子选自在本公开内容的“异源多核苷酸和有效负载分子”部分中描述的有效负载分子。

[0324] 在某些实施方案中,所述两个或更多个有效负载分子包含:

[0325] a. IL-2和IL-36 γ ;

[0326] b. CXCL10以及结合FAP和CD3的抗原结合分子;

[0327] c. IL-2以及结合DLL3和CD3的抗原结合分子;

[0328] d. IL-36 γ 以及结合DLL3和CD3的抗原结合分子;或

[0329] e. IL-2、IL-36 γ 以及结合DLL3和CD3的抗原结合分子

[0330] 在某些实施方案中,所述两个或更多个有效负载分子包含抗-DLL3双组分多肽、抗-FAP双组分多肽、抗-PD1-VHH-Fc抗体、IL-2、IL-12、IL-18、IL-23、IL-36 γ 、CCL21、CXCL10或其任意组合。在某些实施方案中,所述抗-DLL3双组分多肽是抗-DLL3/抗-CD3双组分多肽。在某些实施方案中,所述抗-FAP双组分多肽是抗-FAP/抗-CD3双组分多肽。

[0331] 在某些实施方案中,本公开内容的复制子或所述复制子的异源多核苷酸包含根据下面表8中列出的有效负载分子组合之一的两个或至少两个有效负载分子的编码区。在某些实施方案中,所述复制子是SVV衍生出的复制子。在某些实施方案中,所述复制子是CVA21衍生出的复制子。根据下面表8,两个有效负载分子的每种组合被标记为“x”。在表8中具有相同有效负载分子的那些“x”标记的组合指示,所述复制子包含有效负载分子的两个拷贝。

[0332] 表8. 两个有效负载分子组合

[0333]

	IFNg	GM-CSF	IL-2	IL-12	IL-15	IL-18	IL-23	IL-36 γ	CXCL10	CCL4	CCL5
IFNg	X	X	X	X	X	X	X	X	X	X	X
GM-CSF	X	X	X	X	X	X	X	X	X	X	X
IL-2	X	X	X	X	X	X	X	X	X	X	X
IL-12	X	X	X	X	X	X	X	X	X	X	X
IL-15	X	X	X	X	X	X	X	X	X	X	X
IL-18	X	X	X	X	X	X	X	X	X	X	X
IL-23	X	X	X	X	X	X	X	X	X	X	X
IL-36 γ	X	X	X	X	X	X	X	X	X	X	X
CXCL10	X	X	X	X	X	X	X	X	X	X	X
CCL4	X	X	X	X	X	X	X	X	X	X	X
CCL5	X	X	X	X	X	X	X	X	X	X	X
CCL21	X	X	X	X	X	X	X	X	X	X	X
抗-PD1-VHH-Fc	X	X	X	X	X	X	X	X	X	X	X
抗-TGFb-VHH(或scFv)-Fc	X	X	X	X	X	X	X	X	X	X	X
抗-CD47-VHH-Fc	X	X	X	X	X	X	X	X	X	X	X
抗-DLL3 双组分多肽	X	X	X	X	X	X	X	X	X	X	X
抗-FAP 双组分多肽	X	X	X	X	X	X	X	X	X	X	X
抗-EpCAM 双组分多肽	X	X	X	X	X	X	X	X	X	X	X
存活素	X	X	X	X	X	X	X	X	X	X	X
MAGE 家族蛋白	X	X	X	X	X	X	X	X	X	X	X
IL15R	X	X	X	X	X	X	X	X	X	X	X
PGDH	X	X	X	X	X	X	X	X	X	X	X
ADA	X	X	X	X	X	X	X	X	X	X	X

[0334]

	IFNg	GM-CSF	IL-2	IL-12	IL-15	IL-18	IL-23	IL-36 γ	CXCL10	CCL4	CCL5
ADA2	X	X	X	X	X	X	X	X	X	X	X
HYAL1	X	X	X	X	X	X	X	X	X	X	X
HYAL2	X	X	X	X	X	X	X	X	X	X	X
CHIPS	X	X	X	X	X	X	X	X	X	X	X
MLKL (或仅它的 4HB 结构域)	X	X	X	X	X	X	X	X	X	X	X
GSDMD (或它的 L192A 突变体、或它的氨基酸 1-233 片段、或它的具有 L192A 突变的氨基酸 1-233 片段)	X	X	X	X	X	X	X	X	X	X	X
GSDME (或它的氨基酸 1-237 片段)	X	X	X	X	X	X	X	X	X	X	X
HMGB1 (或仅它的 Box B 结构域)	X	X	X	X	X	X	X	X	X	X	X
蜂毒肽(例如, α -蜂毒肽)	X	X	X	X	X	X	X	X	X	X	X
SMAC/Diablo (或它的氨基酸 56-239 片段)	X	X	X	X	X	X	X	X	X	X	X
蛇 LAAO	X	X	X	X	X	X	X	X	X	X	X
蛇解聚素	X	X	X	X	X	X	X	X	X	X	X
瘦素	X	X	X	X	X	X	X	X	X	X	X

[0335]

	IFNg	GM-CSF	IL-2	IL-12	IL-15	IL-18	IL-23	IL-36 γ	CXCL10	CCL4	CCL5
FLT3L	X	X	X	X	X	X	X	X	X	X	X
TRAIL	X	X	X	X	X	X	X	X	X	X	X
Gasdermin D 或其截短体	X	X	X	X	X	X	X	X	X	X	X
Gasdermin E 或其截短体	X	X	X	X	X	X	X	X	X	X	X
肿瘤相关抗原	X	X	X	X	X	X	X	X	X	X	X
肿瘤新抗原	X	X	X	X	X	X	X	X	X	X	X
结合 MHC- 肽抗原复合物的双组分 多肽	X	X	X	X	X	X	X	X	X	X	X
促融合蛋白	X	X	X	X	X	X	X	X	X	X	X

[0336]

表8. (续)

[0337]

	CCL21	抗-PD1-VHH-Fc	抗-TGFb-VHH(或scFv)-Fc	抗-CD47-VHH-Fc	抗-DLL3双组分多肽	抗-FAP双组分多肽	抗-EpCAM双组分多肽	存活素
IFNg	X	X	X	X	X	X	X	X
GM-CSF	X	X	X	X	X	X	X	X
IL-2	X	X	X	X	X	X	X	X
IL-12	X	X	X	X	X	X	X	X
IL-15	X	X	X	X	X	X	X	X
IL-18	X	X	X	X	X	X	X	X
IL-23	X	X	X	X	X	X	X	X
IL-36 γ	X	X	X	X	X	X	X	X
CXCL10	X	X	X	X	X	X	X	X
CCL4	X	X	X	X	X	X	X	X
CCL5	X	X	X	X	X	X	X	X
CCL21	X	X	X	X	X	X	X	X

[0338]

	CCL21	抗- PD1- VHH- Fc	抗- TGFb- VHH(或 scFv)-Fc	抗- CD47- VHH- Fc	抗-DLL3 双组分多 肽	抗-FAP 双 组分多肽	抗-EpCAM 双组分多 肽	存活素
抗-PD1- VHH-Fc	X	X	X	X	X	X	X	X
抗-TGFb- VHH(或 scFv)-Fc	X	X	X	X	X	X	X	X
抗-CD47- VHH-Fc	X	X	X	X	X	X	X	X
抗-DLL3 双 组分多肽	X	X	X	X	X	X	X	X
抗-FAP 双 组分多肽	X	X	X	X	X	X	X	X
抗-EpCAM 双组分多肽	X	X	X	X	X	X	X	X
存活素	X	X	X	X	X	X	X	X
MAGE 家族 蛋白	X	X	X	X	X	X	X	X
IL15R	X	X	X	X	X	X	X	X
PGDH	X	X	X	X	X	X	X	X
ADA	X	X	X	X	X	X	X	X
ADA2	X	X	X	X	X	X	X	X
HYAL1	X	X	X	X	X	X	X	X
HYAL2	X	X	X	X	X	X	X	X
CHIPS	X	X	X	X	X	X	X	X
MLKL (或 仅它的 4HB 结构域)	X	X	X	X	X	X	X	X

[0339]

	CCL21	抗- PD1- VHH- Fc	抗- TGFb- VHH(或 scFv)-Fc	抗- CD47- VHH- Fc	抗-DLL3 双组分多 肽	抗-FAP 双 组分多肽	抗-EpCAM 双组分多 肽	存活素
GSDMD (或 它的 L192A 突变体、或 它的氨基酸 1-233 片 段、或它的 具有 L192A 突变的氨基 酸 1-233 片 段)	X	X	X	X	X	X	X	X
GSDME (或 它的氨基酸 1-237 片段)	X	X	X	X	X	X	X	X
HMGB1 (或 仅它的 Box B 结构域)	X	X	X	X	X	X	X	X
蜂毒肽(例 如, α -蜂毒 肽)	X	X	X	X	X	X	X	X
SMAC/Diab lo (或它的 氨基酸 56- 239 片段)	X	X	X	X	X	X	X	X
蛇 LAAO	X	X	X	X	X	X	X	X
蛇解聚素	X	X	X	X	X	X	X	X
瘦素	X	X	X	X	X	X	X	X
FLT3L	X	X	X	X	X	X	X	X
TRAIL	X	X	X	X	X	X	X	X
Gasdermin D 或其截短 体	X	X	X	X	X	X	X	X

[0340]

	CCL21	抗- PD1- VHH- Fc	抗- TGFb- VHH(或 scFv)-Fc	抗- CD47- VHH- Fc	抗-DLL3 双组分多 肽	抗-FAP 双 组分多肽	抗-EpCAM 双组分多 肽	存活素
Gasdermin E 或其截短体	X	X	X	X	X	X	X	X
肿瘤相关抗 原	X	X	X	X	X	X	X	X
肿瘤新抗原	X	X	X	X	X	X	X	X
结合 MHC- 肽抗原复合 物的双组分 多肽	X	X	X	X	X	X	X	X
促融合蛋白	X	X	X	X	X	X	X	X

[0341] 表8. (续)

[0342]

	MAGE 家族 蛋白	IL15R	PGDH	ADA	ADA2	HYAL1	HYAL2	CHIPS	MLKL (或仅 它的 4HB 结 构域)
IFNg	X	X	X	X	X	X	X	X	X
GM-CSF	X	X	X	X	X	X	X	X	X
IL-2	X	X	X	X	X	X	X	X	X
IL-12	X	X	X	X	X	X	X	X	X
IL-15	X	X	X	X	X	X	X	X	X
IL-18	X	X	X	X	X	X	X	X	X
IL-23	X	X	X	X	X	X	X	X	X
IL-36 γ	X	X	X	X	X	X	X	X	X
CXCL10	X	X	X	X	X	X	X	X	X
CCL4	X	X	X	X	X	X	X	X	X
CCL5	X	X	X	X	X	X	X	X	X
CCL21	X	X	X	X	X	X	X	X	X
抗-PD1- VHH-Fc	X	X	X	X	X	X	X	X	X
抗-TGFb- VHH(或	X	X	X	X	X	X	X	X	X

[0343]

	MAGE 家族 蛋白	IL15R	PGDH	ADA	ADA2	HYAL1	HYAL2	CHIPS	MLKL (或仅 它的 4HB 结 构域)
scFv)-Fc									
抗-CD47- VHH-Fc	X	X	X	X	X	X	X	X	X
抗-DLL3 双 组分多肽	X	X	X	X	X	X	X	X	X
抗-FAP 双组 分多肽	X	X	X	X	X	X	X	X	X
抗-EpCAM 双组分多肽	X	X	X	X	X	X	X	X	X
存活素	X	X	X	X	X	X	X	X	X
MAGE 家族 蛋白	X	X	X	X	X	X	X	X	X
IL15R	X	X	X	X	X	X	X	X	X
PGDH	X	X	X	X	X	X	X	X	X
ADA	X	X	X	X	X	X	X	X	X
ADA2	X	X	X	X	X	X	X	X	X
HYAL1	X	X	X	X	X	X	X	X	X
HYAL2	X	X	X	X	X	X	X	X	X
CHIPS	X	X	X	X	X	X	X	X	X
MLKL (或仅 它的 4HB 结 构域)	X	X	X	X	X	X	X	X	X
GSDMD (或 它的 L192A 突变体、或 它的氨基酸 1-233 片段、 或它的具有 L192A 突变 的氨基酸 1- 233 片段)	X	X	X	X	X	X	X	X	X

[0344]

	MAGE 家族 蛋白	IL15R	PGDH	ADA	ADA2	HYAL1	HYAL2	CHIPS	MLKL (或仅 它的 4HB 结 构域)
GSDME (或 它的氨基酸 1-237 片段)	X	X	X	X	X	X	X	X	X
HMGB1 (或 仅它的 Box B 结构域)	X	X	X	X	X	X	X	X	X
蜂毒肽(例 如, α -蜂毒 肽)	X	X	X	X	X	X	X	X	X
SMAC/Diablo (或它的氨基 酸 56-239 片 段)	X	X	X	X	X	X	X	X	X
蛇 LAAO	X	X	X	X	X	X	X	X	X
蛇解聚素	X	X	X	X	X	X	X	X	X
瘦素	X	X	X	X	X	X	X	X	X
FLT3L	X	X	X	X	X	X	X	X	X
TRAIL	X	X	X	X	X	X	X	X	X
Gasdermin D 或其截短体	X	X	X	X	X	X	X	X	X
Gasdermin E 或其截短体	X	X	X	X	X	X	X	X	X
肿瘤相关抗 原	X	X	X	X	X	X	X	X	X
肿瘤新抗原	X	X	X	X	X	X	X	X	X
结合 MHC- 肽抗原复合 物的双组分 多肽	X	X	X	X	X	X	X	X	X
促融合蛋白	X	X	X	X	X	X	X	X	X

[0345] 表8. (续)

[0346]

	GSDMD (或它的 L192A 突变体、或 它的氨基酸 1-233 片段、或它的具有 L192A 突变的氨基 酸 1-233 片段)	GSDME (或它的 氨基酸 1-237 片段)	HMGB1 (或仅它 的 Box B 结构 域)	蜂毒肽 (例 如, α - 蜂毒 肽)	SMAC/ Diablo (或它的 氨基酸 56-239 片段)	蛇 LAAO	蛇解 聚素	瘦素
IFN γ	X	X	X	X	X	X	X	X
GM-CSF	X	X	X	X	X	X	X	X
IL-2	X	X	X	X	X	X	X	X
IL-12	X	X	X	X	X	X	X	X
IL-15	X	X	X	X	X	X	X	X
IL-18	X	X	X	X	X	X	X	X
IL-23	X	X	X	X	X	X	X	X
IL-36 γ	X	X	X	X	X	X	X	X
CXCL10	X	X	X	X	X	X	X	X
CCL4	X	X	X	X	X	X	X	X
CCL5	X	X	X	X	X	X	X	X
CCL21	X	X	X	X	X	X	X	X
抗-PD1- VHH-Fc	X	X	X	X	X	X	X	X
抗-TGF β - VHH(或 scFv)-Fc	X	X	X	X	X	X	X	X
抗-CD47- VHH-Fc	X	X	X	X	X	X	X	X
抗-DLL3 双 组分多肽	X	X	X	X	X	X	X	X
抗-FAP 双组 分多肽	X	X	X	X	X	X	X	X
抗-EpCAM 双组分多肽	X	X	X	X	X	X	X	X
存活素	X	X	X	X	X	X	X	X
MAGE 家族 蛋白	X	X	X	X	X	X	X	X

[0347]

	GSDMD (或它的 L192A 突变体、或 它的氨基酸 1-233 片段、或它的具有 L192A 突变的氨基 酸 1-233 片段)	GSDME (或它的 氨基酸 1-237 片段)	HMGB1 (或仅它 的 Box B 结构 域)	蜂毒肽 (例 如, α - 蜂毒 肽)	SMAC/ Diablo (或它的 氨基酸 56-239 片段)	蛇 LAAO	蛇解 聚素	瘦素
IL15R	X	X	X	X	X	X	X	X
PGDH	X	X	X	X	X	X	X	X
ADA	X	X	X	X	X	X	X	X
ADA2	X	X	X	X	X	X	X	X
HYAL1	X	X	X	X	X	X	X	X
HYAL2	X	X	X	X	X	X	X	X
CHIPS	X	X	X	X	X	X	X	X
MLKL (或仅 它的 4HB 结 构域)	X	X	X	X	X	X	X	X
GSDMD (或 它的 L192A 突变体、或 它的氨基酸 1-233 片段、 或它的具有 L192A 突变 的氨基酸 1- 233 片段)	X	X	X	X	X	X	X	X
GSDME (或 它的氨基酸 1-237 片段)	X	X	X	X	X	X	X	X
HMGB1 (或 仅它的 Box B 结构域)	X	X	X	X	X	X	X	X
蜂毒肽(例 如, α -蜂毒 肽)	X	X	X	X	X	X	X	X

[0348]

	GSDMD (或它的 L192A 突变体、或 它的氨基酸 1-233 片段、或它的具有 L192A 突变的氨基 酸 1-233 片段)	GSDME (或它的 氨基酸 1-237 片段)	HMGB1 (或仅它 的 Box B 结构 域)	蜂毒肽 (例 如, α - 蜂毒 肽)	SMAC/ Diablo (或它的 氨基酸 56-239 片段)	蛇 LAAO	蛇解 聚素	瘦素
SMAC/Diablo (或它的氨基 酸 56-239 片 段)	X	X	X	X	X	X	X	X
蛇 LAAO	X	X	X	X	X	X	X	X
蛇解聚素	X	X	X	X	X	X	X	X
瘦素	X	X	X	X	X	X	X	X
FLT3L	X	X	X	X	X	X	X	X
TRAIL	X	X	X	X	X	X	X	X
Gasdermin D 或其截短体	X	X	X	X	X	X	X	X
Gasdermin E 或其截短体	X	X	X	X	X	X	X	X
肿瘤相关抗 原	X	X	X	X	X	X	X	X
肿瘤新抗原	X	X	X	X	X	X	X	X
结合 MHC- 肽抗原复合 物的双组分 多肽	X	X	X	X	X	X	X	X
促融合蛋白	X	X	X	X	X	X	X	X

[0349] 表8. (续)

[0350]

	FLT3L	TRAIL	Gasdermin D 或其截 短体	Gasdermin E 或其截 短体	肿瘤相 关抗原	肿瘤新 抗原	结合 MHC- 肽抗原 复合物 的双组 分多肽	促融 合蛋 白

[0351]

	FLT3L	TRAIL	Gasdermin D 或其截 短体	Gasdermin E 或其截 短体	肿瘤相 关抗原	肿瘤新 抗原	结合 MHC- 肽抗原 复合物的双组 分多肽	促融 合蛋 白
IFNg	X	X	X	X	X	X	X	X
GM-CSF	X	X	X	X	X	X	X	X
IL-2	X	X	X	X	X	X	X	X
IL-12	X	X	X	X	X	X	X	X
IL-15	X	X	X	X	X	X	X	X
IL-18	X	X	X	X	X	X	X	X
IL-23	X	X	X	X	X	X	X	X
IL-36 γ	X	X	X	X	X	X	X	X
CXCL10	X	X	X	X	X	X	X	X
CCL4	X	X	X	X	X	X	X	X
CCL5	X	X	X	X	X	X	X	X
CCL21	X	X	X	X	X	X	X	X
抗-PD1-VHH- Fc	X	X	X	X	X	X	X	X
抗-TGFb- VHH(或 scFv)- Fc	X	X	X	X	X	X	X	X
抗-CD47- VHH-Fc	X	X	X	X	X	X	X	X
抗-DLL3 双组 分多肽	X	X	X	X	X	X	X	X
抗-FAP 双组 分多肽	X	X	X	X	X	X	X	X
抗-EpCAM 双 组分多肽	X	X	X	X	X	X	X	X
存活素	X	X	X	X	X	X	X	X
MAGE 家族蛋 白	X	X	X	X	X	X	X	X

[0352]

	FLT3L	TRAIL	Gasdermin D 或其截 短体	Gasdermin E 或其截 短体	肿瘤相 关抗原	肿瘤新 抗原	结合 MHC- 肽抗原 复合物的双组 分多肽	促融 合蛋 白
IL15R	X	X	X	X	X	X	X	X
PGDH	X	X	X	X	X	X	X	X
ADA	X	X	X	X	X	X	X	X
ADA2	X	X	X	X	X	X	X	X
HYAL1	X	X	X	X	X	X	X	X
HYAL2	X	X	X	X	X	X	X	X
CHIPS	X	X	X	X	X	X	X	X
MLKL (或仅 它的 4HB 结 构域)	X	X	X	X	X	X	X	X
GSDMD (或它 的 L192A 突变 体、或它的氨 基酸 1-233 片 段、或它的具 有 L192A 突变 的氨基酸 1- 233 片段)	X	X	X	X	X	X	X	X
GSDME (或它 的氨基酸 1- 237 片段)	X	X	X	X	X	X	X	X
HMGB1 (或仅 它的 Box B 结 构域)	X	X	X	X	X	X	X	X
蜂毒肽(例 如, α -蜂毒肽)	X	X	X	X	X	X	X	X
SMAC/Diablo (或它的氨基 酸 56-239 片	X	X	X	X	X	X	X	X

[0353]

	FLT3L	TRAIL	Gasdermin D 或其截 短体	Gasdermin E 或其截 短体	肿瘤相 关抗原	肿瘤新 抗原	结合 MHC- 肽抗原 复合物的 双组 分多肽	促融 合蛋 白
段)								
蛇 LAAO	X	X	X	X	X	X	X	X
蛇解聚素	X	X	X	X	X	X	X	X
瘦素	X	X	X	X	X	X	X	X
FLT3L	X	X	X	X	X	X	X	X
TRAIL	X	X	X	X	X	X	X	X
Gasdermin D 或其截短体	X	X	X	X	X	X	X	X
Gasdermin E 或其截短体	X	X	X	X	X	X	X	X
肿瘤相关抗原	X	X	X	X	X	X	X	X
肿瘤新抗原	X	X	X	X	X	X	X	X
结合 MHC-肽 抗原复合物的 双组分多肽	X	X	X	X	X	X	X	X
促融合蛋白	X	X	X	X	X	X	X	X

[0354] 在某些实施方案中,本公开内容的复制子或所述复制子的异源多核苷酸包含根据下面表9中列出的有效负载分子组合之一的三个或至少三个有效负载分子的编码区。在某些实施方案中,所述复制子是SVV衍生出的复制子。在某些实施方案中,所述复制子是CVA21衍生出的复制子。

[0355] 表9. 三个有效负载分子组合

[0356]

#	有效负载分子组合	#	有效负载分子组合
1	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体	61	抗-FAP 双组分多肽, IL-23, CXCL10
2	抗-DLL3c, 抗-FAP 双组分多肽,	62	抗-FAP 双组分多肽, IL-

[0357]

#	有效负载分子组合	#	有效负载分子组合
	IL-2		36γ, CCL21
3	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, IL-12	63	抗-FAP 双组分多肽, IL-36γ, CXCL10
4	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, IL-18	64	抗-FAP 双组分多肽, CCL21, CXCL10
5	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, IL-23	65	抗-PD1-VHH-Fc 抗体, IL-2, IL-12
6	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, IL-36γ	66	抗-PD1-VHH-Fc 抗体, IL-2, IL-18
7	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, CCL21	67	抗-PD1-VHH-Fc 抗体, IL-2, IL-23
8	抗-DLL3 双组分多肽, 抗-FAP 双组分多肽, CXCL10	68	抗-PD1-VHH-Fc 抗体, IL-2, IL-36γ
9	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-2	69	抗-PD1-VHH-Fc 抗体, IL-2, CCL21
10	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-12	70	抗-PD1-VHH-Fc 抗体, IL-2, CXCL10
11	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-18	71	抗-PD1-VHH-Fc 抗体, IL-12, IL-18
12	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-23	72	抗-PD1-VHH-Fc 抗体, IL-12, IL-23
13	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-36γ	73	抗-PD1-VHH-Fc 抗体, IL-12, IL-36γ
14	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, CCL21	74	抗-PD1-VHH-Fc 抗体, IL-12, CCL21
15	抗-DLL3 双组分多肽, 抗-PD1-VHH-Fc 抗体, CXCL10	75	抗-PD1-VHH-Fc 抗体, IL-12, CXCL10
16	抗-DLL3 双组分多肽, IL-2, IL-12	76	抗-PD1-VHH-Fc 抗体, IL-18, IL-23
17	抗-DLL3 双组分多肽, IL-2, IL-18	77	抗-PD1-VHH-Fc 抗体, IL-18, IL-36γ
18	抗-DLL3 双组分多肽, IL-2, IL-23	78	抗-PD1-VHH-Fc 抗体, IL-18, CCL21

[0358]

#	有效负载分子组合	#	有效负载分子组合
19	抗-DLL3 双组分多肽, IL-2, IL-36 γ	79	抗-PD1-VHH-Fc 抗体, IL-18, CXCL10
20	抗-DLL3 双组分多肽, IL-2, CCL21	80	抗-PD1-VHH-Fc 抗体, IL-23, IL-36 γ
21	抗-DLL3 双组分多肽, IL-2, CXCL10	81	抗-PD1-VHH-Fc 抗体, IL-23, CCL21
22	抗-DLL3 双组分多肽, IL-12, IL-18	82	抗-PD1-VHH-Fc 抗体, IL-23, CXCL10
23	抗-DLL3 双组分多肽, IL-12, IL-23	83	抗-PD1-VHH-Fc 抗体, IL-36 γ , CCL21
24	抗-DLL3 双组分多肽, IL-12, IL-36 γ	84	抗-PD1-VHH-Fc 抗体, IL-36 γ , CXCL10
25	抗-DLL3 双组分多肽, IL-12, CCL21	85	抗-PD1-VHH-Fc 抗体, CCL21, CXCL10
26	抗-DLL3 双组分多肽, IL-12, CXCL10	86	IL-2, IL-12, IL-18
27	抗-DLL3 双组分多肽, IL-18, IL-23	87	IL-2, IL-12, IL-23
28	抗-DLL3 双组分多肽, IL-18, IL-36 γ	88	IL-2, IL-12, IL-36 γ
29	抗-DLL3 双组分多肽, IL-18, CCL21	89	IL-2, IL-12, CCL21
30	抗-DLL3 双组分多肽, IL-18, CXCL10	90	IL-2, IL-12, CXCL10
31	抗-DLL3 双组分多肽, IL-23, IL-36 γ	91	IL-2, IL-18, IL-23
32	抗-DLL3 双组分多肽, IL-23, CCL21	92	IL-2, IL-18, IL-36 γ
33	抗-DLL3 双组分多肽, IL-23, CXCL10	93	IL-2, IL-18, CCL21
34	抗-DLL3 双组分多肽, IL-36 γ , CCL21	94	IL-2, IL-18, CXCL10
35	抗-DLL3 双组分多肽, IL-36 γ ,	95	IL-2, IL-23, IL-36 γ

[0359]

#	有效负载分子组合	#	有效负载分子组合
	CXCL10		
36	抗-DLL3 双组分多肽, CCL21, CXCL10	96	IL-2, IL-23, CCL21
37	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-2	97	IL-2, IL-23, CXCL10
38	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-12	98	IL-2, IL-36 γ , CCL21
39	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-18	99	IL-2, IL-36 γ , CXCL10
40	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-23	100	IL-2, CCL21, CXCL10
41	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, IL-36 γ	101	IL-12, IL-18, IL-23
42	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, CCL21	102	IL-12, IL-18, IL-36 γ
43	抗-FAP 双组分多肽, 抗-PD1-VHH-Fc 抗体, CXCL10	103	IL-12, IL-18, CCL21
44	抗-FAP 双组分多肽, IL-2, IL-12	104	IL-12, IL-18, CXCL10
45	抗-FAP 双组分多肽, IL-2, IL-18	105	IL-12, IL-23, IL-36 γ
46	抗-FAP 双组分多肽, IL-2, IL-23	106	IL-12, IL-23, CCL21
47	抗-FAP 双组分多肽, IL-2, IL-36 γ	107	IL-12, IL-23, CXCL10
48	抗-FAP 双组分多肽, IL-2, CCL21	108	IL-12, IL-36 γ , CCL21
49	抗-FAP 双组分多肽, IL-2, CXCL10	109	IL-12, IL-36 γ , CXCL10
50	抗-FAP 双组分多肽, IL-12, IL-18	110	IL-12, CCL21, CXCL10
51	抗-FAP 双组分多肽, IL-12, IL-23	111	IL-18, IL-23, IL-36 γ
52	抗-FAP 双组分多肽, IL-12, IL-36 γ	112	IL-18, IL-23, CCL21
53	抗-FAP 双组分多肽, IL-12, CCL21	113	IL-18, IL-23, CXCL10
54	抗-FAP 双组分多肽, IL-12, CXCL10	114	IL-18, IL-36 γ , CCL21
55	抗-FAP 双组分多肽, IL-18, IL-23	115	IL-18, IL-36 γ , CXCL10

[0360]

#	有效负载分子组合	#	有效负载分子组合
56	抗-FAP 双组分多肽, IL-18, IL-36 γ	116	IL-18, CCL21, CXCL10
57	抗-FAP 双组分多肽, IL-18, CCL21	117	IL-23, IL-36 γ , CCL21
58	抗-FAP 双组分多肽, IL-18, CXCL10	118	IL-23, IL-36 γ , CXCL10
59	抗-FAP 双组分多肽, IL-23, IL-36 γ	119	IL-23, CCL21, CXCL10
60	抗-FAP 双组分多肽, IL-23, CCL21	120	IL-36 γ , CCL21, CXCL10

[0361] 在某些实施方案中,在表8或表9中的抗-DLL3双组分多肽结合DLL3和在表3中列出的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-DLL3双组分多肽结合DLL3和选自CD3、NKp46和CD16的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-DLL3双组分多肽是BiTE。

[0362] 在某些实施方案中,在表8或表9中的抗-FAP双组分多肽结合FAP和在表3中列出的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-FAP双组分多肽结合FAP和选自CD3、NKp46和CD16的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-FAP双组分多肽是BiTE。

[0363] 在某些实施方案中,在表8或表9中的抗-EpCAM双组分多肽结合EpCAM和在表3中列出的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-EpCAM双组分多肽结合EpCAM和选自CD3、NKp46和CD16的效应细胞抗原之一。在某些实施方案中,在表8或表9中的抗-EpCAM双组分多肽是BiTE。

[0364] 在某些实施方案中,各种塞内卡谷病毒(SVV)衍生出的重组RNA复制子包含编码一种或多种免疫调节蛋白(例如,抗-DLL3双特异性的T-细胞接合剂(BiTE))的异源多核苷酸。在某些实施方案中,所述SVV衍生出的重组RNA复制子进一步包含一种或多种细胞因子(例如,IL-2、IL-12、IL-36 γ)和/或一种或多种趋化因子(例如,CCL21、CCL4)的编码区。在某些实施方案中,所述SVV衍生出的重组RNA复制子包含根据下面表10的两个或更多个有效负载分子的编码区。

[0365] 表10. SVV衍生出的复制子的有效负载分子

[0366]

SVV衍生出的复制子	有效负载分子
复制子构建体#A1:	抗-DLL3BiTE, IL-2
复制子构建体#A2:	抗-DLL3BiTE, IL-12
复制子构建体#A3:	抗-DLL3BiTE, IL-36 γ
复制子构建体#A4:	抗-DLL3BiTE, CCL21
复制子构建体#A5:	抗-DLL3BiTE, CCL4
复制子构建体#A6:	抗-DLL3BiTE, IL-2, IL-12

复制子构建体#A7:	抗-DLL3BiTE, IL-2, IL-36 γ
复制子构建体#A8:	抗-DLL3BiTE, IL-2, CCL21
复制子构建体#A9:	抗-DLL3BiTE, IL-2, CCL4
复制子构建体#A10:	抗-DLL3BiTE, IL-12, IL-36 γ
复制子构建体#A11:	抗-DLL3BiTE, IL-12, CCL21
复制子构建体#A12:	抗-DLL3BiTE, IL-12, CCL4
复制子构建体#A13:	抗-DLL3BiTE, IL-36 γ , CCL21
复制子构建体#A14:	抗-DLL3BiTE, IL-36 γ , CCL4
复制子构建体#A15:	抗-DLL3BiTE, CCL21, CCL4

[0367] 在某些实施方案中,所述柯萨奇病毒A21 (CVA21) 衍生出的重组RNA复制子包含编码一种或多种免疫调节蛋白(例如,抗-DLL3双特异性的T-细胞接合剂(BiTE))的异源多核苷酸。在某些实施方案中,所述CVA21衍生出的重组RNA复制子进一步包含一种或多种细胞因子(例如,IL-2、IL-12、IL-36 γ)和/或一种或多种趋化因子(例如,CCL21、CCL4)的编码区。在某些实施方案中,所述CVA21衍生出的重组RNA复制子包含根据下面表11的两个或更多个有效负载分子的编码区。

[0368] 表11.CVA21衍生出的复制子的有效负载分子

CVA21 衍生出的复制子	有效负载分子
复制子构建体#C1:	抗-DLL3BiTE, IL-2
复制子构建体#C2:	抗-DLL3BiTE, IL-12
复制子构建体#C3:	抗-DLL3BiTE, IL-36 γ
复制子构建体#C4:	抗-DLL3BiTE, CCL21
复制子构建体#C5:	抗-DLL3BiTE, CCL4
复制子构建体#C6:	抗-DLL3BiTE, IL-2, IL-12
复制子构建体#C7:	抗-DLL3BiTE, IL-2, IL-36 γ
复制子构建体#C8:	抗-DLL3BiTE, IL-2, CCL21
复制子构建体#C9:	抗-DLL3BiTE, IL-2, CCL4

CVA21 衍生出的复制子	有效负载分子
复制子构建体#C10:	抗-DLL3BiTE, IL-12, IL-36 γ
复制子构建体#C11:	抗-DLL3BiTE, IL-12, CCL21
复制子构建体#C12:	抗-DLL3BiTE, IL-12, CCL4
复制子构建体#C13:	抗-DLL3BiTE, IL-36 γ , CCL21
复制子构建体#C14:	抗-DLL3BiTE, IL-36 γ , CCL4
复制子构建体#C15:	抗-DLL3BiTE, CCL21, CCL4

[0371] 内部核糖体进入位点

[0372] 在某些实施方案中,所述重组RNA复制子包含在5' UTR之外的IRES。在某些实施方

案中,所述IRES位于5' UTR和2B编码区之间。在某些实施方案中,所述IRES位于2A编码区和2B编码区之间。在某些实施方案中,所述IRES位于有效负载分子编码序列和2B编码区之间。在某些实施方案中,所述IRES位于CRE和2B编码区之间。在某些实施方案中,所述IRES位于5' UTR和异源多核苷酸之间。在某些实施方案中,所述IRES位于CRE和异源多核苷酸之间。在某些实施方案中,所述IRES位于VP编码区和异源多核苷酸之间。在某些实施方案中,所述IRES位于2A编码区和异源多核苷酸之间。在某些实施方案中,所述IRES是EMCV IRES。在某些实施方案中,所述复制子是包含SVV基因组的复制子。

[0373] 转衣壳化

[0374] 在某些实施方案中,本公开内容的重组RNA复制子可以被另一种编码溶瘤病毒的重组RNA分子(例如,RNA病毒基因组)转衣壳化。这样的重组RNA分子可以包含病毒基因组(例如,合成的病毒基因组)。在某些实施方案中,这样的重组RNA分子或RNA病毒基因组当通过非病毒递送媒介物引入细胞时能够产生感染性的、裂解的病毒,并且不需要另外的外源基因或蛋白存在于细胞中即可复制和产生感染性病毒。在某些实施方案中,这样的RNA病毒基因组都包含VP编码区。表达的病毒蛋白然后介导病毒复制并组装成包含RNA病毒基因组的感染性病毒颗粒(其可以包含衣壳蛋白、包膜蛋白和/或膜蛋白)。在某些实施方案中,本公开内容的重组RNA复制子可以通过从这样的RNA病毒基因组表达的衣壳蛋白转衣壳化。在某些实施方案中,当所述重组RNA复制子和所述RNA病毒基因组存在于相同细胞中(例如,通过颗粒将它们递送进细胞中)时,所述重组RNA复制子可以被转衣壳化。这样,当引入相同宿主细胞中时,本文所述的重组RNA复制子和RNA病毒基因组可以产生两组病毒颗粒-一组包含重组RNA复制子,另一组包含RNA病毒基因组,它们二者能够感染另一种宿主细胞。

[0375] miRNA靶序列(miR-TS)盒

[0376] 在某些实施方案中,所述重组RNA复制子包含一个或多个微RNA(miRNA)靶序列(miR-TS)盒,其中所述miR-TS盒包含一个或多个miRNA靶序列,且其中一个或多个对应miRNA在细胞中的表达抑制所述复制子在细胞中的复制。在某些实施方案中,所述一个或多个miRNA选自miR-124、miR-1、miR-143、miR-128、miR-219、miR-219a、miR-122、miR-204、miR-217、miR-137和miR-126。在某些实施方案中,所述miR-TS盒包含miR-124靶序列的一个或多个拷贝、miR-1靶序列的一个或多个拷贝和miR-143靶序列的一个或多个拷贝。在某些实施方案中,所述miR-TS盒包含miR-128靶序列的一个或多个拷贝、miR-219靶序列的一个或多个拷贝和miR-122靶序列的一个或多个拷贝。在某些实施方案中,所述miR-TS盒包含miR-128靶序列的一个或多个拷贝、miR-204靶序列的一个或多个拷贝和miR-219靶序列的一个或多个拷贝。在某些实施方案中,所述miR-TS盒包含miR-217靶序列的一个或多个拷贝、miR-137靶序列的一个或多个拷贝和miR-126靶序列的一个或多个拷贝。

[0377] 在某些实施方案中,将包含一个或多个miR-TS盒的重组RNA复制子掺入一个或多个必需病毒基因(蛋白编码区)的5' 非翻译区(UTR)或3' UTR。在某些实施方案中,将包含一个或多个miR-TS盒的重组RNA复制子掺入一个或多个非必需基因的5' 非翻译区(UTR)或3' UTR。在某些实施方案中,将包含一个或多个miR-TS盒的重组RNA复制子掺入一个或多个必需病毒基因的5' 或3'。

[0378] 生产重组RNA复制子的方法

[0379] 在某些实施方案中,使用一种或多种DNA载体模板在体外产生本公开内容的重组

RNA复制子,所述模板包含编码重组RNA复制子的多核苷酸。术语“载体”在本文中用于表示能够转移、编码或运输另一种核酸分子的核酸分子。被转移的核酸通常插入到载体核酸分子中。载体可以包括指导细胞中自主复制的序列,和/或可以包括足以允许整合到宿主细胞DNA中的序列。在某些实施方案中,使用一种或多种病毒载体产生本公开内容的重组RNA复制子。

[0380] 在某些实施方案中,通过将编码重组RNA复制子的多核苷酸引入(例如,借助于转染、转导、电穿孔等)到合适的体外宿主细胞中来产生本公开内容的重组RNA复制子。合适的宿主细胞包括昆虫和哺乳动物细胞系。将宿主细胞培养适当量的时间以允许多核苷酸的表达和重组RNA复制子的产生。然后将重组RNA复制子从宿主细胞中分离并配制用于治疗用途(例如,包封在颗粒中)。图26显示了具有3'和5'核酶的重组RNA复制子的体外合成的示意图(使用SVV衍生出的复制子作为实施例,但它也适用于其它复制子)。相同的示意图适用于使用连接切割序列的其它组合合成重组RNA复制子。

[0381] 在某些实施方案中,本公开内容的重组RNA复制子的复制需要对于复制子的病毒基因组而言天然的单独5'和3'末端。由体外T7 RNA聚合酶或哺乳动物RNA Pol II产生的RNA转录物含有哺乳动物5'和3' UTR,不含有产生感染性的RNA病毒所需的单独天然末端。例如,T7 RNA聚合酶需要在模板多核苷酸的5'末端上的鸟苷残基才能启动转录。但是,SVV用在其5'末端上的尿苷残基开始。因此,必须除去包含SVV病毒基因组的复制子的体外转录所需的T7前导序列,以生成生产功能性复制子所需的天然5' SVV末端。因此,在某些实施方案中,适用于生产本公开内容的重组RNA复制子的多核苷酸需要另外的非病毒5'和3'序列,其能够产生对于病毒而言天然的单独5'和3'末端。这样的序列在本文中被称作连接切割序列(JCS)。在某些实施方案中,连接切割序列的作用是在病毒RNA和哺乳动物mRNA序列的连接处切割T7 RNA聚合酶或Pol II编码的RNA转录物,从而从转录物除去非病毒RNA多核苷酸,以便保持病毒基因组的内源性5'和3'单独末端(参见图27中所示的示意图)。在某些实施方案中,连接切割序列用于在编码重组RNA复制子的DNA质粒的线性化期间产生适当的末端(例如,在质粒模板的线性化后和重组RNA复制子的体外转录之前,使用3'限制性酶识别序列产生适当的3'末端)。

[0382] 连接切割序列的性质和非病毒RNA从病毒基因组转录物的除去可以通过多种方法完成。例如,在某些实施方案中,所述连接切割序列是RNA干扰(RNAi)分子的靶标。本文中使用的“RNA干扰分子”表示通过内源基因沉默途径(例如,Dicer和RNA诱导的沉默复合物(RISC))介导靶mRNA序列的降解的RNA多核苷酸。示例性的RNA干扰剂包括微RNA(miRNA)、人工miRNA(amiRNA)、短发夹RNA(shRNA)和小干扰RNA(siRNA)。此外,本领域中目前已知的或将在未来定义的用于在特定位点切割RNA转录物的任何系统都可以用于产生对于病毒而言天然的单独末端。

[0383] 在某些实施方案中,所述RNAi分子是miRNA。miRNA表示长度为约18-25个核苷酸的天然存在的非编码小RNA分子,其至少部分地与靶mRNA序列互补。在动物中,miRNA的基因被转录为初级miRNA(pri-miRNA),它是双链的并形成茎-环结构。然后初级miRNA在细胞核中被包含类别2RNA酶III、Drosha和微处理器亚基DCGR8的微处理器复合物切割,以形成70-100个核苷酸的前体miRNA(前-miRNA)。前-miRNA形成发夹结构并被转运到细胞质,在此它被RNA酶III酶Dicer加工成约18-25个核苷酸的miRNA双链体。尽管双链体的任一条链都可

selection-charts/type-iis-restriction-enzymes的New England Biolabs网站。在某些实施方案中,所述连接切割序列是SapI限制性酶识别位点。

[0390] 在某些实施方案中,所述连接切割序列是核酶编码序列并且介导重组RNA复制子中间体的自我切割以产生最终重组RNA复制子和随后感染性RNA病毒产生所需的天然单独5' 和3' 末端。示例性的核酶包括锤头核酶(例如,图28A-28B中所示的锤头核酶)、Varkud卫星(VS)核酶、发夹核酶、GIR1分支核酶、glmS核酶、twister核酶、twister姊妹核酶、手枪核酶(例如,图29A-29B中所示的手枪1和手枪2)、斧头核酶和丁型肝炎病毒核酶。在某些实施方案中,所述5' 和/或3' 连接切割序列是核酶编码序列。

[0391] 在某些实施方案中,所述连接切割序列是编码配体诱导型自切割核酶(被称作“适体酶”)的序列。适体酶是含有对配体特异的整合适体结构域的核酶序列。与适体结构域结合的配体触发核酶的酶活性的活化,从而导致RNA转录物的切割。示例性的适体酶包括茶碱依赖性适体酶(例如,与茶碱依赖性适体连接的锤头核酶)、四环素依赖性适体酶(例如,与Tet依赖性适体连接的锤头核酶)、鸟嘌呤依赖性适体酶(例如,与鸟嘌呤依赖性适体连接的锤头核酶)。在某些实施方案中,所述5' 和/或3' 连接切割序列是适体酶编码序列。

[0392] 在某些实施方案中,所述连接切割序列是RNAi分子(例如,siRNA分子、shRNA分子、miRNA分子或amiRNA分子)、gRNA分子或RNA酶H引物的靶序列。在这样的实施方案中,所述连接切割序列至少部分地与RNAi分子、gRNA分子或引物分子的序列互补。用于对比和确定序列同一性百分比和互补性百分比的序列比对方法是本领域众所周知的。用于对比的序列的最佳比对可以例如通过下述方法实现:Needleman和Wunsch, (1970) J. Mol. Biol. 48:443的同源性比对算法, Pearson和Lipman的检索相似性方法, (1988) Proc. Nat'l Acad. Sci. USA 85:2444, 这些算法的计算机化实现(在威斯康辛州遗传学软件包中的GAP、BESTFIT、FASTA和TFASTA, Genetics Computer Group, 575 Science Dr., Madison, WI), 手工比对和目检(参见, 例如, Brent等人, (2003) Current Protocols in Molecular Biology), 使用本领域已知的算法, 包括BLAST和BLAST 2.0算法, 其分别描述于Altschul等人, (1977) Nuc. Acids Res. 25:3389-3402; 和Altschul等人, (1990) J. Mol. Biol. 215:403-410。用于执行BLAST分析的软件可通过国家生物技术信息中心(National Center for Biotechnology Information)公开获得。

[0393] 在某些实施方案中,所述5' 连接切割序列和3' 连接切割序列来自同一组(例如,都是RNAi靶序列,都是核酶编码序列等)。例如,在某些实施方案中,所述连接切割序列是RNAi靶序列(例如,siRNA、shRNA、amiRNA或miRNA靶序列),并掺入编码重组RNA复制子的多核苷酸的5' 和3' 末端。在这样的实施方案中,所述5' 和3' RNAi靶序列可以相同(即,相同siRNA、amiRNA或miRNA的靶标)或不同(即,5' 序列是一种siRNA、shmiRNA或miRNA的靶标,且3' 序列是另一种siRNA、amiRNA或miRNA的靶标)。在某些实施方案中,所述连接切割序列是指导RNA靶序列,并掺入编码重组RNA复制子的多核苷酸的5' 和3' 末端。在这样的实施方案中,所述5' 和3' gRNA靶序列可以是相同的(即,相同gRNA的靶标)或不同的(即,5' 序列是一种gRNA的靶标且3' 序列是另一种gRNA的靶标)。在某些实施方案中,所述连接切割序列是初级-mRNA编码序列,并掺入编码重组RNA复制子的多核苷酸的5' 和3' 末端。在某些实施方案中,所述连接切割序列是核酶编码序列,并掺入编码重组RNA复制子的多核苷酸序列的5' 和3' 紧邻处。

[0394] 在某些实施方案中,所述5' 连接切割序列和3' 连接切割序列来自同一组,但是不同的变体或类型。例如,在某些实施方案中,所述5' 和3' 连接切割序列可以是RNAi分子的靶序列,其中所述5' 连接切割序列是siRNA靶序列且所述3' 连接切割序列是miRNA靶序列(或反之亦然)。在某些实施方案中,所述5' 和3' 连接切割序列可以是核酶编码序列,其中所述5' 连接切割序列是锤头核酶编码序列且所述3' 连接切割序列是丁型肝炎病毒核酶编码序列。

[0395] 在某些实施方案中,所述5' 连接切割序列和3' 连接切割序列是不同的类型。例如,在某些实施方案中,所述5' 连接切割序列是RNAi靶序列(例如,siRNA、amiRNA或miRNA靶序列)且所述3' 连接切割序列是核酶序列、适体酶序列、初级-miRNA序列或gRNA靶序列。在某些实施方案中,所述5' 连接切割序列是核酶序列且所述3' 连接切割序列是RNAi靶序列(例如,siRNA、amiRNA或miRNA靶序列)、适体酶序列、初级-miRNA编码序列或gRNA靶序列。在某些实施方案中,所述5' 连接切割序列是适体酶序列且所述3' 连接切割序列是RNAi靶序列(例如,siRNA、amiRNA或miRNA靶序列)、核酶序列、初级-miRNA序列或gRNA靶序列。在某些实施方案中,所述5' 连接切割序列是初级-miRNA序列且所述3' 连接切割序列是RNAi靶序列(例如,siRNA、amiRNA或miRNA靶序列)、核酶序列、适体酶序列或gRNA靶序列。在某些实施方案中,所述5' 连接切割序列是gRNA靶序列且所述3' 连接切割序列是RNAi靶序列(例如,siRNA、amiRNA或miRNA靶序列)、核酶序列、初级-miRNA序列或适体酶序列。

[0396] 连接切割序列相对于编码重组RNA复制子的多核苷酸的示例性排列显示在下面表12和13中。

[0397] 表12:对称的连接切割序列(JSC)排列

[0398]

5'	JCS		JCS	3'
	siRNA TS	复制子	siRNA TS	
	miR TS	复制子	miR TS	
	AmiR TS	复制子	AmiR TS	
	gRNA TS	复制子	gRNA TS	
	pri-miR	复制子	pri-miR	
	核酶	复制子	核酶	
	适体酶	复制子	适体酶	
	RNA酶H引物TS	复制子	RNA酶H引物TS	

[0399] 表13:不对称的JCS排列

[0400]

5'	<u>JCS</u>		<u>JCS</u>	3'
	siRNA TS	复制子	miR TS	
	siRNA TS	复制子	AmiR TS	
	siRNA TS	复制子	gRNA TS	
	siRNA TS	复制子	pri-miR	
	siRNA TS	复制子	核酶	
	siRNA TS	复制子	适体酶	
	siRNA TS	复制子	RNA 酶 H 引物 TS	
	siRNA TS	复制子	限制性酶 RS	
	miR TS	复制子	siRNA TS	

[0401]

5'	JCS		JCS	3'
	miR TS	复制子	AmiR TS	
	miR TS	复制子	gRNA TS	
	miR TS	复制子	pri-miR	
	miR TS	复制子	核酶	
	miR TS	复制子	适体酶	
	miR TS	复制子	RNA 酶 H 引物 TS	
	miR TS	复制子	限制性酶 RS	
	AmiR TS	复制子	siRNA TS	
	AmiR TS	复制子	miR TS	
	AmiR TS	复制子	gRNA TS	
	AmiR TS	复制子	pri-miR	
	AmiR TS	复制子	核酶	
	AmiR TS	复制子	适体酶	
	AmiR TS	复制子	RNA 酶 H 引物 TS	
	AmiR TS	复制子	限制性酶 RS	
	gRNA TS	复制子	siRNA TS	
	gRNA TS	复制子	miR TS	
	gRNA TS	复制子	AmiR TS	
	gRNA TS	复制子	pri-miR	
	gRNA TS	复制子	核酶	
	gRNA TS	复制子	适体酶	
	gRNA TS	复制子	RNA 酶 H 引物 TS	
	gRNA TS	复制子	限制性酶 RS	
	pri-miR	复制子	siRNA TS	
	pri-miR	复制子	miR TS	
	pri-miR	复制子	AmiR TS	
	pri-miR	复制子	gRNA TS	
	pri-miR	复制子	核酶	
	pri-miR	复制子	适体酶	
	pri-miR	复制子	RNA 酶 H 引物 TS	
	pri-miR	复制子	限制性酶 RS	
	核酶	复制子	siRNA TS	
	核酶	复制子	miR TS	

[0402]	5'	<u>JCS</u>		<u>JCS</u>	3'
		核酶	复制子	AmiR TS	
		核酶	复制子	gRNA TS	
		核酶	复制子	pri-miR	
		核酶	复制子	适体酶	
		核酶	复制子	RNA 酶 H 引物 TS	
		核酶	复制子	限制性酶 RS	
		适体酶	复制子	siRNA TS	
		适体酶	复制子	miR TS	
		适体酶	复制子	AmiR TS	
		适体酶	复制子	gRNA TS	
		适体酶	复制子	pri-miR	
		适体酶	复制子	核酶	
		适体酶	复制子	RNA 酶 H 引物 TS	
		适体酶	复制子	限制性酶 RS	
		RNA 酶 H 引物 TS	复制子	siRNA TS	
		RNA 酶 H 引物 TS	复制子	miR TS	
		RNA 酶 H 引物 TS	复制子	AmiR TS	
		RNA 酶 H 引物 TS	复制子	gRNA TS	
		RNA 酶 H 引物 TS	复制子	pri-miR	
		RNA 酶 H 引物 TS	复制子	核酶	
		RNA 酶 H 引物 TS	复制子	适体酶	
		RNA 酶 H 引物 TS	复制子	限制性酶 RS	

[0403] 在某些实施方案中,通过体外RNA转录在体外产生本公开内容的重组RNA复制子(参见图27中的示意图)。然后将重组RNA复制子纯化和配制用于治疗用途(例如,包封进脂质纳米颗粒中)。在某些实施方案中,所述DNA多核苷酸从5'至3'包含:(i)启动子序列(例如,T7聚合酶启动子);(ii)5'核酶序列;(iii)编码重组RNA复制子的多核苷酸;和(iv)3'核酶序列。在某些实施方案中,所述DNA多核苷酸从5'至3'包含:(i)启动子序列(例如,T7聚合酶启动子);(ii)5'锤头核酶序列(例如,野生型HHR或经修饰的HHR诸如在图28A-28B中提供的);(iii)编码重组RNA复制子的多核苷酸;和(iv)3'丁型肝炎病毒核酶序列。

[0404] 在某些实施方案中,所述DNA多核苷酸从5'至3'包含:(i)启动子序列(例如,T7聚合酶启动子);(ii)5'锤头核酶序列(例如,野生型HHR或经修饰的HHR诸如在图28A-28B中提供的);(iii)编码重组RNA复制子的多核苷酸;和(iv)3'丁型肝炎病毒核酶序列。在某些实施方案中,所述DNA多核苷酸从5'至3'包含:(i)启动子序列(例如,T7聚合酶启动子);(ii)5'锤头核酶序列(例如,野生型HHR或经修饰的HHR诸如在图28A-28B中提供的);(iii)编码重组RNA复制子的多核苷酸;和(iv)3'丁型肝炎病毒核酶序列。

[0405] 在某些实施方案中,所述DNA多核苷酸从5'至3'包含:(i)启动子序列(例如,T7聚

合酶启动子); (ii) 5' 核酶序列; (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' 限制性酶识别位点。在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' 锤头核酶序列 (例如, 野生型HHR或经修饰的HHR诸如在图28A-28B中提供的); (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。

[0406] 在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' 锤头核酶序列 (例如, 野生型HHR或经修饰的HHR诸如在图28A-28B中提供的); (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。

[0407] 在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' 手枪核酶序列 (例如, 在图29A-29B中显示的手枪1或手枪2核酶序列); (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' 手枪1核酶序列; (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' 手枪2核酶序列; (iii) 编码野生型SVV基因组的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。在某些实施方案中, 所述DNA多核苷酸包含与SEQ ID NO:15具有至少95%、96%、97%、98%或99%同一性的核酸序列。在某些实施方案中, 所述DNA多核苷酸包含SEQ ID NO:15或由其组成。

[0408] 在某些实施方案中, 所述DNA多核苷酸从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' RNA酶H引物结合位点; (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' 限制性酶识别位点。在某些实施方案中, 所述DNA载体包含多核苷酸, 其从5' 至3' 包含: (i) 启动子序列 (例如, T7聚合酶启动子); (ii) 5' RNA酶H引物结合位点; (iii) 编码重组RNA复制子的多核苷酸; 和 (iv) 3' SapI限制性酶识别位点。

[0409] 包含重组RNA复制子的颗粒

[0410] 在某些实施方案中, 本公开内容的重组RNA复制子被包封在“颗粒”中。本文中使用的颗粒表示非组织衍生出的物质组合物, 诸如脂质体、脂质体复合物、纳米颗粒、纳米囊、微米颗粒、微米球、脂质颗粒、外泌体、囊泡等。在某些实施方案中, 所述颗粒是非蛋白性的和非免疫原性的。在这样的实施方案中, 本公开内容的重组RNA复制子的包封允许递送病毒基因组而不诱导全身性的抗病毒免疫应答, 并且减轻中和抗病毒抗体的作用。此外, 本公开内容的重组RNA复制子的包封保护基因组免于降解并促进向靶宿主细胞中的引入。在某些实施方案中, 所述颗粒是纳米颗粒。在某些实施方案中, 所述颗粒是脂质纳米颗粒。在某些实施方案中, 所述颗粒是外泌体。

[0411] 本公开内容提供了颗粒, 其包含本公开内容的重组RNA复制子。在某些实施方案中, 所述颗粒是脂质纳米颗粒。在某些实施方案中, 所述颗粒进一步包含编码溶瘤病毒的第二重组RNA分子。在某些实施方案中, 所述编码溶瘤病毒的第二重组RNA分子包含RNA病毒基因组 (例如, 溶瘤病毒的RNA病毒基因组)。在某些实施方案中, 所述溶瘤病毒是小核糖核酸病毒。在某些实施方案中, 所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。在某些实施方案中, 所述小核糖核酸病毒是塞内卡谷病毒 (SVV)。在某些实施方案中, 所述小核糖核酸病毒是柯萨奇病毒。在某些实施方案中, 所述小核糖核酸病毒是脑心肌炎病毒 (EMCV)。在某些实施方案中, 所述RNA病毒基因组包含完整VP1、VP2、VP3和VP4编码区。在某

些实施方案中,所述包含完整VP1、VP2、VP3和VP4编码区的RNA病毒基因组属于与所述复制子的病毒基因组相同的病毒种或相同的病毒属。在某些实施方案中,所述重组RNA复制子可以通过从包含完整VP编码区的RNA病毒基因组表达的衣壳蛋白转衣壳化。在某些实施方案中,当所述重组RNA复制子和所述RNA病毒基因组存在于相同细胞中(例如,通过颗粒将它们递送进细胞中)时,所述重组RNA复制子可以被转衣壳化。

[0412] 在某些实施方案中,所述颗粒在受试者中是可生物降解的。在这样的实施方案中,可以将多剂量的颗粒施用给受试者,而不在受试者中积累颗粒。合适的颗粒的例子包括聚苯乙烯颗粒、聚(乳酸-共聚-羟乙酸)PLGA颗粒、基于多肽的阳离子聚合物颗粒、环糊精颗粒、壳聚糖颗粒、基于脂质的颗粒、聚(β -氨基酯)颗粒、低分子量聚乙烯亚胺颗粒、聚磷酸酯颗粒、二硫化物交联的聚合物颗粒、聚酰氨基胺颗粒、聚乙烯亚胺(PEI)颗粒和PLURIONICS稳定化的聚丙烯硫化物颗粒。

[0413] 在某些实施方案中,将本公开内容的多核苷酸包封在无机颗粒中。在某些实施方案中,所述无机颗粒是金纳米颗粒(GNP)、金纳米棒(GNR)、磁性纳米颗粒(MNP)、磁性纳米管(MNT)、碳纳米角(CNH)、碳富勒烯、碳纳米管(CNT)、磷酸钙纳米颗粒(CPNP)、介孔二氧化硅纳米颗粒(MSN)、二氧化硅纳米管(SNT)或星形中空二氧化硅纳米颗粒(SHNP)。

[0414] 在某些实施方案中,本公开内容的颗粒在尺寸上是纳米级的,以提高溶解度、避免体内聚集引起的可能并发症以及促进胞饮作用。在某些实施方案中,所述颗粒具有约小于约1000nm的平均直径。在某些实施方案中,所述颗粒具有小于约500nm的平均直径。在某些实施方案中,所述颗粒具有约30至约100nm之间、约50至约100nm之间、或约75至约100nm之间的平均直径。在某些实施方案中,所述颗粒具有约30至约75nm之间、或约30至约50nm之间的平均直径。在某些实施方案中,所述颗粒具有约100至约500nm之间的平均直径。在某些实施方案中,所述颗粒具有约200至400nm之间的平均直径。在某些实施方案中,所述颗粒具有约350nm的平均大小。

[0415] 外泌体

[0416] 在某些实施方案中,本公开内容的重组RNA复制子被包封在外泌体中。外泌体是胞吞来源的小膜囊泡,其在多泡体与亲本细胞(例如,释放外泌体的细胞,在本文中也称作供体细胞)的质膜融合后释放到细胞外环境中。外泌体的表面包含衍生自亲本细胞的细胞膜的脂质双层,并且可以进一步包含在亲本细胞表面上表达的膜蛋白。在某些实施方案中,外泌体还可以含有来自亲本细胞的胞质溶胶。外泌体由许多不同的细胞类型产生,包括上皮细胞、B和T淋巴细胞、肥大细胞(MC)和树突细胞(DC),并已在血浆、尿、支气管肺泡灌洗液、肠上皮细胞和肿瘤组织中鉴定。因为外泌体的组成取决于它们来源的亲本细胞类型,所以不存在“外泌体特异性的”蛋白。但是,许多外泌体包含与外泌体在亲本细胞中所起源的细胞内囊泡相关的蛋白(例如,与核内体和溶酶体相关和/或由其表达的蛋白)。例如,外泌体可以富含抗原呈递分子诸如主要组织相容性复合物I和II(MHC-I和MHC-II)、四次穿膜蛋白(例如,CD63)、几种热激蛋白、细胞骨架组分诸如肌动蛋白和微管蛋白、参与细胞内膜融合、细胞-细胞相互作用(例如CD54)的蛋白、信号转导蛋白和细胞溶质酶。

[0417] 通过外泌体膜与靶细胞的质膜的融合,外泌体可以介导细胞蛋白从一个细胞(例如,亲本细胞)向靶细胞或受体细胞的转移。因此,修饰被外泌体包封的材料提供了一种机制,通过该机制可以将外源性试剂(诸如本文所述的多核苷酸)引入靶细胞。已被修饰以含

有一种或多种外源性试剂(例如,本文所述的多核苷酸)的外泌体在本文中被称作“经修饰的外泌体”。在某些实施方案中,通过将外源性试剂(例如,本文所述的多核苷酸)引入亲本细胞中而产生经修饰的外泌体。在这样的实施方案中,将外源核酸引入产生外泌体的亲本细胞中,从而将外源核酸本身或外源核酸的转录物掺入由亲本细胞产生的经修饰的外泌体中。通过本领域已知的方式,例如外源核酸的转导、转染、转化和/或显微注射,可以将外源核酸引入亲本细胞。

[0418] 在某些实施方案中,通过将本公开内容的重组RNA复制子直接引入外泌体中来产生经修饰的外泌体。在某些实施方案中,将本公开内容的重组RNA复制子引入完整外泌体中。“完整外泌体”表示包含衍生自产生它们的亲本细胞的蛋白和/或遗传物质的外泌体。获得完整外泌体的方法是本领域已知的(参见例如,Alvarez-Erviti L.等人,Nat Biotechnol.2011年4月;29(4):34-5;Ohno S,等人,Mol Ther 2013年1月;21(1):185-91;和欧洲专利公开号2010663)。

[0419] 在某些实施方案中,将重组RNA复制子引入空外泌体。“空外泌体”表示缺乏衍生自亲本细胞的蛋白和/或遗传物质(例如,DNA或RNA)的外泌体。产生空外泌体(例如,缺乏亲本细胞衍生出的遗传物质)的方法是本领域已知的,包括紫外线暴露、介导核酸向外泌体中的负载的内源蛋白的突变/缺失、以及电穿孔和化学处理以打开外泌体膜中的孔使得内源性遗传物质通过开放的孔从外泌体中排出。在某些实施方案中,空外泌体通过以下方式产生:通过用具有从约9至约14的pH的水溶液处理打开外泌体以获得外泌体膜,除去囊泡内的组分(例如,囊泡内的蛋白和/或核酸),并重新组装外泌体膜以形成空外泌体。在某些实施方案中,通过超速离心或密度梯度超速离心除去囊泡内的组分(例如,囊泡内的蛋白和/或核酸)。在某些实施方案中,通过声处理、机械振动、穿过多孔膜的挤出、电流或这些技术中的一种或多种的组合,重新组装所述膜。在特定实施方案中,通过声处理重新组装所述膜。

[0420] 在某些实施方案中,用本文所述的重组RNA复制子装载完整或空外泌体以产生经修饰的外泌体可以使用常规分子生物学技术诸如体外转化、转染和/或显微注射来实现。在某些实施方案中,通过电穿孔将外源性试剂(例如,本文所述的多核苷酸)直接引入完整或空外泌体中。在某些实施方案中,通过脂转染(例如,转染)将外源性试剂(例如,本文所述的多核苷酸)直接引入完整或空外泌体中。适用于生产根据本公开内容的外泌体的脂转染试剂盒是本领域已知的和商购可得的(例如,来自Roche的FuGENE®HD转染试剂,和来自Invitrogen的LIPOFECTAMINE™ 2000)。在某些实施方案中,通过使用热激的转化将外源性试剂(例如,本文所述的多核苷酸)直接引入完整或空外泌体中。在这样的实施方案中,将从亲本细胞分离的外泌体在二价阳离子诸如Ca²⁺(在CaCl₂中)存在下冷却,以使外泌体膜透化。然后将外泌体与外源核酸一起温育并短暂热激(例如,在42℃温育30-120秒)。在特定实施方案中,通过在除去囊泡内组分后将试剂与外泌体膜混合或共温育,可以实现用外源性试剂(例如,本文所述的多核苷酸)对空外泌体的负载。因此,从外泌体膜重新组装的经修饰的外泌体将会将外源性试剂掺入囊泡内空间中。用于产生外泌体包封的核酸的其它方法是本领域已知的(参见例如,美国专利号9,889,210、9,629,929和9,085,778;国际PCT公开号WO 2017/161010和WO 2018/039119)。

[0421] 从许多不同的亲本细胞,包括细胞系、骨髓衍生出的细胞和从原代患者样品衍生出的细胞,可以获得外泌体。通过本领域已知的方式,可以从亲本细胞培养物的上清液分离

从亲本细胞释放的外泌体。例如,外泌体的物理性能可以用于将它们与介质或其它源材料分离,包括基于电荷(例如,电泳分离)、大小(例如,过滤、分子筛分等)、密度(例如,常规或梯度离心)和Svedberg常数(例如,或没有外力的沉降等)的分离。可替换地或另外,分离可以基于一种或多种生物学性能,并且包括可以采用表面标志物的方法(例如,对于沉淀,与固相可逆结合、FACS分离、特异性配体结合、非特异性配体结合等)。使用针对外泌体相关蛋白诸如CD63的荧光标记的抗体,通过流式细胞计量术可以确定外泌体表面蛋白的分析。用于表征外泌体的其它标志物描述于国际PCT公开号W0 2017/161010。在又进一步考虑的方法中,还可以使用化学和/或物理方法融合外泌体,包括PEG诱导的融合和/或超声融合。

[0422] 在某些实施方案中,尺寸排阻色谱法可以用于分离外泌体。在某些实施方案中,如本领域公知的,可以在色谱分离后通过离心技术(对一种或多种色谱级分)进一步分离外泌体。在某些实施方案中,外泌体的分离可以包含方法的组合,所述方法包括、但不限于如前所述的差速离心(参见Raposo,G.等人,J.Exp.Med.183,1161-1172(1996))、超速离心、基于尺寸的膜过滤、浓缩和/或速率区带离心。

[0423] 在某些实施方案中,所述外泌体膜包含磷脂、糖脂、脂肪酸、鞘脂、磷酸甘油酯、甾醇、胆固醇和磷脂酰丝氨酸中的一种或多种。此外,所述膜可以包含一种或多种多肽以及一种或多种多糖,诸如聚糖。用于改变一种或多种膜组分的相对量的示例性外泌体膜组合物和方法描述于国际PCT公开号W0 2018/039119中。

[0424] 在某些实施方案中,所述颗粒是外泌体且具有约30至约100nm之间、约30至约200nm之间、或约30至约500nm之间的直径。在某些实施方案中,所述颗粒是外泌体且具有约10nm至约100nm之间、约20nm至约100nm之间、约30nm至约100nm之间、约40nm至约100nm之间、约50nm至约100nm之间、约60nm至约100nm之间、约70nm至约100nm之间、约80nm至约100nm之间、约90nm至约100nm之间、约100nm至约200nm之间、约100nm至约150nm之间、约150nm至约200nm之间、约100nm至约250nm之间、约250nm至约500nm之间、或约10nm至约1000nm之间的直径。在某些实施方案中,所述颗粒是外泌体且具有约20nm至300nm之间、约40nm至200nm之间、约20nm至250nm之间、约30nm至150nm之间、或约30nm至100nm之间的直径。

[0425] 脂质纳米颗粒

[0426] 在某些实施方案中,将本文所述的重组RNA复制子包封在脂质纳米颗粒(LNP)中。在某些实施方案中,所述LNP包含一种或多种脂质诸如甘油三酯(例如三硬脂精)、甘油二酯(例如山嵛酸甘油酯)、甘油单酯(例如单硬脂酸甘油酯)、脂肪酸(例如硬脂酸)、类固醇(例如胆固醇)和蜡类(例如棕榈酸鲸蜡酯)。在某些实施方案中,所述LNP包含一种或多种阳离子脂质和一种或多种辅助脂质。在某些实施方案中,所述LNP包含一种或多种阳离子脂质、胆固醇和一种或多种中性脂质。

[0427] 阳离子脂质表示在选定的pH(诸如生理pH)携带净正电荷的多种脂质种类中的任一种。这样的脂质包括、但不限于1,2-二亚油烯基氧基-N,N-二甲基氨基丙烷(DLinDMA)、1,2-二亚麻烯基氧基-N,N-二甲基氨基丙烷(DLenDMA)、双十八烷基二甲基铵(DODMA)、二硬脂酰二甲基铵(DSDMA)、N,N-二油烯基-N,N-二甲基氯化铵(DODAC);N-(2,3-二油烯基氧基)丙基-N,N,N-三甲基氯化铵(DOTMA);N,N-二硬脂酰-N,N-二甲基溴化铵(DDAB);N-(2,3-二油酰氧基)丙基-N,N,N-三甲基氯化铵(DOTAP);3-(N-(N',N'-二甲基氨基乙烷)-氨甲酰基)

胆固醇 (DC-Chol) 和 N-(1,2-二肉豆蔻基氧基丙-3-基)-N,N-二甲基-N-羟基乙基溴化铵 (DMRIE)。例如,在生理 pH 以下具有正电荷的阳离子脂质包括、但不限于 DODAP、DODMA 和 DMDMA。在某些实施方案中,所述阳离子脂质包含 C₁₈ 烷基链、在首基和烷基链之间的醚键以及 0 至 3 个双键。这样的脂质包括例如 DSDMA、DLinDMA、DLenDMA 和 DODMA。阳离子脂质可以包含醚键和 pH 可滴定的首基。这样的脂质包括例如 DODMA。

[0428] 在某些实施方案中,所述阳离子脂质包含可质子化的叔胺首基。这样的脂质在本文中被称作可电离脂质。可电离脂质表示包含可电离的胺首基并且通常包含小于约 7 的 pKa 的脂质种类。因此,在具有酸性 pH 的环境中,可电离的胺首基被质子化,使得可电离脂质优先与带负电荷的分子(例如,核酸诸如本文所述的重组多核苷酸)相互作用,从而促进纳米颗粒组装和包封。因此,在某些实施方案中,可电离脂质可以增加核酸在脂质纳米颗粒中的负载。在 pH 大于约 7 的环境中(例如,约 7.4 的生理 pH),可电离脂质包含中性电荷。当包含可电离脂质的颗粒被吸收至核内体的低 pH 环境(例如, pH < 7) 时,可电离脂质再次质子化并与阴离子胞内体膜缔合,从而促进由颗粒包封的内容物的释放。在某些实施方案中,所述 LNP 包含可电离脂质,例如, 7.5S-可切割的和 pH-响应性的脂质样材料(诸如 **COATSOME®** SS-系列)。

[0429] 在某些实施方案中,所述阳离子脂质是选自 DLinDMA、DLin-KC2-DMA、DLin-MC3-DMA (MC3)、**COATSOME®**SS-LC (以前名称:SS-18/4PE-13)、**COATSOME®**SS-EC (以前名称:SS-33/4PE-15)、**COATSOME®**SS-OC、**COATSOME®**SS-OP、二((Z)-壬-2-烯-1-基)9-((4-二甲基氨基)丁酰基)氧基)十七烷二酸酯(L-319)或 N-(2,3-二油酰氧基)丙基)-N,N,N-三甲基氯化铵(DOTAP)的可电离脂质。在某些实施方案中,所述阳离子可电离脂质是 DLin-MC3-DMA (MC3)。在某些实施方案中,所述阳离子可电离脂质是 **COATSOME®**SS-LC。在某些实施方案中,所述阳离子可电离脂质是 **COATSOME®**SS-EC。在某些实施方案中,所述阳离子可电离脂质是 **COATSOME®**SS-OC。在某些实施方案中,所述阳离子可电离脂质是 **COATSOME®**SS-OP。在某些实施方案中,所述阳离子可电离脂质是 L-319。在某些实施方案中,所述阳离子可电离脂质是 DOTAP。

[0430] 在某些实施方案中,所述 LNP 包含一种或多种非阳离子辅助脂质(中性脂质)。示例性的中性辅助脂质包括(1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺)(DLPE)、1,2-二植烷酰基-sn-甘油-3-磷酸乙醇胺(DiPPE)、1,2-二硬脂酰基-sn-甘油-3-磷酸胆碱(DSPC)、1,2-二棕榈酰基-sn-甘油-3-磷酸胆碱(DPPC)、1,2-二油烯基-sn-甘油-3-磷酸乙醇胺(DOPE)、1,2-二棕榈酰基-sn-甘油-3-磷酸乙醇胺(DPPE)、1,2-二肉豆蔻酰基-sn-甘油-3-磷酸乙醇胺(DMPE)、(1,2-二油酰基-sn-甘油-3-磷酸-(1'-消旋-甘油)(DOPG)、1,2-二油酰基-sn-甘油-3-磷酸胆碱(DOPC)、1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺(DSPE)、神经酰胺、鞘磷脂和胆固醇。在某些实施方案中,所述一种或多种辅助脂质选自 1,2-二硬脂酰基-sn-甘油-3-磷酸胆碱(DSPC); 1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE); 1,2-二油酰基-sn-甘油-3-磷酸胆碱(DOPC); 1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE); 和胆固醇。在某些实施方案中,所述 LNP 包含 DSPC。在某些实施方案中,所述 LNP 包含 DOPC。在某些实施方案中,所述 LNP 包含 DLPE。在某些实施方案中,所述 LNP 包含 DOPE。

[0431] 也涵盖聚乙二醇(PEG)修饰的磷脂和衍生化的脂质诸如衍生化的神经酰胺(PEG-

CER) (包括N-辛酰基-鞘氨醇-1-[琥珀酰(甲氧基聚乙二醇)-2000] (C8 PEG-2000神经酰胺))在本文所述的脂质体和药物组合物中的应用和包含,优选地与本文中公开的化合物和脂质中的一种或多种组合。

[0432] 在某些实施方案中,所述脂质纳米颗粒可以进一步包含一种或多种PEG修饰的脂质,其包含与包含一个或多个C6-C20烷基的脂质共价连接的至多5kDa长度的聚乙二醇链。在某些实施方案中,所述LNP进一步包含1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-聚(乙二醇) (DSPE-PEG) 或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)] (DSPE-PEG-胺)。在某些实施方案中,所述LNP进一步包含PEG修饰的脂质,其选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)-5000] (DSPE-PEG5K); 1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇-2000 (DPG-PEG2K); 1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-5000 (DSG-PEG5K); 1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-2000 (DSG-PEG2K); 1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-5000 (DMG-PEG5K); 和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-2000 (DMG-PEG2K)。在某些实施方案中,所述LNP进一步包含DSPE-PEG5K。在某些实施方案中,所述LNP进一步包含DPG-PEG2K。在某些实施方案中,所述LNP进一步包含DSG-PEG2K。在某些实施方案中,所述LNP进一步包含DMG-PEG2K。在某些实施方案中,所述LNP进一步包含DSG-PEG5K。在某些实施方案中,所述LNP进一步包含DMG-PEG5K。在某些实施方案中,所述PEG修饰的脂质占脂质纳米颗粒中的总脂质含量的约0.1%至约1%。在某些实施方案中,所述PEG修饰的脂质占脂质纳米颗粒中的总脂质含量的约0.1%、约0.2%、约0.3%、约0.4%、约0.5%、约0.6%、约0.7%、约0.8%、约0.9%、约1.0%、约1.5%、约2.0%、约2.5%或约3.0%。

[0433] 在某些实施方案中,所述脂质用可切割的PEG脂质修饰。具有可切割键的PEG衍生物的例子包括用肽键(Kulkarni等人.(2014).Mmp-9 responsive PEG cleavable nanovesicles for efficient delivery of chemotherapeutics to pancreatic cancer.Mol Pharmaceutics 11:2390-9;Lin等人.(2015).Drug/dye-loaded, multifunctional peg-chitosan-iron oxide nanocomposites for methotrexate synergistically self-targeted cancer therapy and dual model imaging.ACS Appl Mater Interfaces 7:11908-20.)、二硫键(Yan等人(2014).A method to accelerate the gelation of disulfide-crosslinked hydrogels.Chin J Polym Sci 33:118-27;Wu和Yan(2015).Copper nanopowder catalyzed cross-coupling of diaryl disulfides with aryl iodides in PEG-400.Synlett 26:537-42)、乙烯基醚键、胺键(Kelly等人.(2016).Polymeric prodrug combination to exploit the therapeutic potential of antimicrobial peptides against cancer cells.Org Biomol Chem 14:9278-86.)和酯键(Xu等人.(2008).Esterase-catalyzed dePEGylation of pH-sensitive vesicles modified with cleavable PEG-lipid derivatives.J Control Release 130:238-45)修饰的那些。也参见,Fang等人,(2017)Cleavable PEGylation:a strategy for overcoming the“PEG dilemma”in efficient drug delivery.Drug Delivery 24:2,22-32。

[0434] 在某些实施方案中,所述PEG脂质是活化的PEG脂质。示例性的活化的PEG脂质包括PEG-NH₂、PEG-MAL、PEG-NHS和PEG-ALD。这样的官能化的PEG脂质可用于将靶向部分缀合至

脂质纳米颗粒以将颗粒引导至特定靶细胞或组织(例如,通过抗原结合分子、肽、聚糖等的附着)。

[0435] 在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是DOTAP。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是DLin-MC3-DMA (MC3)。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是**COATSOME®SS-EC**。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是**COATSOME®SS-LC**。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是**COATSOME®SS-OC**。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是**COATSOME®SS-OP**。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述阳离子脂质是L-319。

[0436] 在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述一种或多种辅助脂质包含胆固醇。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述一种或多种辅助脂质包含DLPE。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述一种或多种辅助脂质包含DSPC。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述一种或多种辅助脂质包含DOPE。在某些实施方案中,所述LNP包含一种阳离子脂质和一种或多种辅助脂质,其中所述一种或多种辅助脂质包含DOPC。

[0437] 在某些实施方案中,所述LNP包含一种阳离子脂质和至少两种辅助脂质,其中所述阳离子脂质是DOTAP,且所述至少两种辅助脂质包含胆固醇和DLPE。在某些实施方案中,所述LNP包含一种阳离子脂质和至少两种辅助脂质,其中所述阳离子脂质是MC3,且所述至少两种辅助脂质包含胆固醇和DSPC。在某些实施方案中,所述至少两种辅助脂质包含胆固醇和DOPE。在某些实施方案中,所述至少两种辅助脂质包含胆固醇和DSPC。在某些实施方案中,所述LNP包含一种阳离子脂质和至少三种辅助脂质,其中所述阳离子脂质是DOTAP,且所述至少三种辅助脂质包含胆固醇、DLPE和DSPE。在某些实施方案中,所述LNP包含一种阳离子脂质和至少三种辅助脂质,其中所述阳离子脂质是MC3,且所述至少三种辅助脂质包含胆固醇、DSPC和DMG。在某些实施方案中,所述至少三种辅助脂质包含胆固醇、DOPE和DSPE。在某些实施方案中,所述至少三种辅助脂质包含胆固醇、DSPC和DMG。在某些实施方案中,所述LNP包含DOTAP、胆固醇和DLPE。在某些实施方案中,所述LNP包含MC3、胆固醇和DSPC。在某些实施方案中,所述LNP包含DOTAP、胆固醇和DOPE。在某些实施方案中,所述LNP包含DOTAP、胆固醇、DLPE和DSPE。在某些实施方案中,所述LNP包含MC3、胆固醇、DSPC和DMG。在某些实施方案中,所述LNP包含DOTAP、胆固醇、DLPE和DSPE-PEG。在某些实施方案中,所述LNP包含MC3、胆固醇、DSPC和DMG-PEG。在某些实施方案中,所述LNP包含DOTAP、胆固醇、DOPE和DSPE。在某些实施方案中,所述LNP包含DOTAP、胆固醇、DOPE和DSPE-PEG。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇和DPG-PEG(例如,DPG-PEG2K)。

[0438] 在某些实施方案中,所述LNP包含DOTAP、胆固醇(Chol)和DLPE,其中DOTAP:Chol:DLPE(作为总脂质含量的百分比)的比率是约50:35:15。在某些实施方案中,所述LNP包含

DOTAP、胆固醇 (Chol) 和DLPE,其中DOTAP:Chol:DOPE (作为总脂质含量的百分比) 的比率是约50:35:15。在某些实施方案中,所述LNP包含DOTAP、胆固醇 (Chol)、DLPE、DSPE-PEG,其中DOTP:Chol:DLPE (作为总脂质含量的百分比) 的比率是约50:35:15且其中所述颗粒包含约0.2% DSPE-PEG。在某些实施方案中,所述LNP包含MC3、胆固醇 (Chol)、DSPC和DMG-PEG,其中MC3:Chol:DSPC:DMG-PEG (作为总脂质含量的百分比) 的比率是约49:38.5:11:1.5。

[0439] 在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=40%-60%,B=10%-25%,C=20%-30%,且D=0%-3%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=45%-50%,B=20%-25%,C=25%-30%,且D=0%-1%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约49:22:28.5:0.5。

[0440] 在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=40%-60%,B=10%-30%,C=20%-45%,且D=0%-3%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=40%-60%,B=10%-30%,C=25%-45%,且D=0%-3%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=45%-55%,B=10%-20%,C=30%-40%,且D=1%-2%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=45%-50%,B=10%-15%,C=35%-40%,且D=1%-2%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是49:11:38.5:1.5。

[0441] 在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=45%-65%,B=5%-20%,C=20%-45%,且D=0%-3%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=50%-60%,B=5%-15%,C=30%-45%,且D=0%-3%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=55%-60%,B=5%-15%,C=30%-40%,且D=1%-2%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,其中SS-OC:DSPC:Chol:DPG-PEG2K (作为总脂质含量的百分比) 的比率是约A:B:C:D,其中A=55%-60%,B=5%-10%,C=30%-35%,且D=1%-2%并且其中A+B+C+D=100%。在某些实施方案中,所述LNP包含SS-OC、DSPC、胆固醇 (Chol) 和DPG-PEG2K,

其中SS-OC:DSPC:Chol:DPG-PEG2K(作为总脂质含量的百分比)的比率是58:7:33.5:1.5。

[0442] 在某些实施方案中,所述纳米颗粒涂有糖胺聚糖(GAG)以调节或促进靶细胞对纳米颗粒的摄取。GAG可以是肝素/硫酸肝素、硫酸软骨素/硫酸皮肤素、硫酸角蛋白或透明质酸(HA)。在一个特定实施方案中,所述纳米颗粒的表面涂有HA并靶向颗粒以供肿瘤细胞摄取。在某些实施方案中,所述脂质纳米颗粒涂有精氨酸-甘氨酸-天冬氨酸盐三-肽(RGD肽)(参见Ruoslahti, *Advanced Materials*, 24, 2012, 3747-3756; 和Bellis等人, *Biomaterials*, 32 (18), 2011, 4205-4210)。

[0443] 在某些实施方案中,所述LNP具有约50nm至约500nm的平均大小。例如,在某些实施方案中,所述LNP具有约50nm至约200nm、约100nm至约200nm、约150nm至约200nm、约50nm至约150nm、约100nm至约150nm、约150nm至约500nm、约200nm至约500nm、约300nm至约500nm、约350nm至约500nm、约400nm至约500nm、约425nm至约500nm、约450nm至约500nm、或约475nm至约500nm的平均大小。在某些实施方案中,所述多个LNP具有约50nm至约120nm的平均大小。在某些实施方案中,所述多个LNP具有约50nm、60nm、70nm、80nm、90nm、100nm、110nm或约120nm的平均大小。在某些实施方案中,所述多个LNP具有约100nm的平均大小。

[0444] 在某些实施方案中,所述LNP具有中性电荷(例如,约0mV至1mV之间的平均 ζ 电位)。在某些实施方案中,所述LNP具有约40mV至约-40mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约40mV至约0mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约35mV至约0mV、约30mV至约0mV、约25mV至约0mV、约20mV至约0mV、约15mV至约0mV、约10mV至约0mV、或约5mV至约0mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约20mV至约-40mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约20mV至约-20mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约10mV至约-20mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约10mV至约-10mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约10mV、约9mV、约8mV、约7mV、约6mV、约5mV、约4mV、约3mV、约2mV、约1mV、约0mV、约-1mV、约-2mV、约-3mV、约-4mV、约-5mV、约-6mV、约-7mV、约-8mV、约-9mV、约-9mV或约-10mV的平均 ζ 电位。

[0445] 在某些实施方案中,所述LNP具有约0mV至-20mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有小于约-20mV的平均 ζ 电位。例如,在某些实施方案中,所述LNP具有小于约-30mV、小于约35mV或小于约-40mV的平均 ζ 电位。在某些实施方案中,所述LNP具有约-50mV至约-20mV、约-40mV至约-20mV、或约-30mV至约-20mV之间的平均 ζ 电位。在某些实施方案中,所述LNP具有约0mV、约-1mV、约-2mV、约-3mV、约-4mV、约-5mV、约-6mV、约-7mV、约-8mV、约-9mV、约-10mV、约-11mV、约-12mV、约-13mV、约-14mV、约-15mV、约-16mV、约-17mV、约-18mV、约-19mV、约-20mV、约-21mV、约-22mV、约-23mV、约-24mV、约-25mV、约-26mV、约-27mV、约-28mV、约-29mV、约-30mV、约-31mV、约-32mV、约-33mV、约-34mV、约-35mV、约-36mV、约-37mV、约-38mV、约-39mV或约-40mV的平均 ζ 电位。

[0446] 在某些实施方案中,所述脂质纳米颗粒包含本文所述的重组核酸分子且包含约3:1(L:N)的脂质(L)与核酸(N)之比。在某些实施方案中,所述脂质纳米颗粒包含本文所述的重组核酸分子且包含约4:1、约5:1、约6:1、约7:1、约8:1、约9:1或约10:1的L:N比率。在某些实施方案中,所述脂质纳米颗粒包含本文所述的重组核酸分子且包含约7:1的脂质(L)与核酸(N)之比。在某些实施方案中,所述脂质纳米颗粒包含本文所述的重组核酸分子且包含约4.5:1、约4.6:1、约4.7:1、约4.8:1、约4.9:1、约5:1、约5.1:1、约5.2:1、约5.3:1、约5.4:1或

约5.5:1的L:N比率。在某些实施方案中,所述脂质纳米颗粒包含本文所述的重组核酸分子且包含约6.5:1、6.6:1、6.7:1、6.8:1、6.9:1、7:1、7.1:1、7.2:1、7.3:1、7.4:1和7.5:1的L:N比率。

[0447] 在某些实施方案中,所述LNP包含选自在表14中列出的制剂之一的脂质制剂。

[0448] 表14. 示例性的含有脂质纳米颗粒的复制子

[0449]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
70001-5C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70009- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7

[0450]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
70009- 2.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70009- 3.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70032- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70032- 2.C	PB, pH 5.8	MC3 (49%)	胆固醇 (38.5%)	DSPC (11%)	DMG- PEG2K (1.5%)	7
70032- 3.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	5
70032- 4.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	3
70032- 5.C	PB, pH 7.4	DOTAP (50%)	胆固醇 (34.8%)	DLPE (15%)	DSPE- PEG5K (0.2%)	5.33
70032-6C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70041- 2.C	MB, pH 3.0	SS-EC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70041- 3.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70041- 4.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7

[0451]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
70046- 4.C	MB, pH 3.0	SS-EC (56%)	胆固醇 (28.0%)	DOPC (9%)	DSG- PEG5K (7%)	9
70046- 5.C	MB, pH 3.0	SS-LC (56%)	胆固醇 (28.0%)	DOPC (9%)	DSG- PEG5K (7%)	9
70046- 6.C	MB, pH 3.0	SS-OC (56%)	胆固醇 (28.0%)	DOPC (9%)	DSG- PEG5K (7%)	9
70053- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70053- 2.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70059- 1.C	MB, pH 3.0	SS-EC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70059- 2.C	MB, pH 3.0	SS-EC (49%)	胆固醇 (39.5%)	DSPC (11%)	DSPE- PEG5K (0.5%)	7
70059- 3.C	MB, pH 3.0	SS-EC (49%)	胆固醇 (39.0%)	DSPC (11%)	DSPE- PEG5K (1.0%)	7
70065- 2.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.5%)	DSPC (11%)	DMG- PEG2K (0.5%)	7
70065- 3.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.0%)	DSPC (11%)	DMG- PEG2K (1.0%)	7
70065- 4.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (38.5%)	DSPC (11%)	DMG- PEG2K (1.5%)	7

[0452]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
70065- 5.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.5%)	DSPC (11%)	DMG- PEG5K (0.5%)	7
70065- 6.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (39.0%)	DSPC (11%)	DMG- PEG5K (1.0%)	7
70070- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70070- 4.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DMG- PEG2K (0.2%)	7
70070- 5.C	PB, pH 5.8	MC3 (49%)	胆固醇 (38.0%)	DSPC (11%)	DMG- PEG2K (2.0%)	7
70070- 6.C	PB, pH 5.8	MC3 (49%)	胆固醇 (35.0%)	DSPC (11%)	DMG- PEG2K (5.0%)	7
70077- 3.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70077- 4.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70077- 5.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (48.5%)	DSPC (2%)	DSG- PEG2K (0.5%)	7
70077- 6.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (48.0%)	DSPC (2%)	DPG- PEG2K (1.0%)	7
70077- 7.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (47.0%)	DSPC (2%)	DMG- PEG2K (2.0%)	7

[0453]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
70077- 8.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (38.5%)	DSPC (12%)	DMG- PEG2K (0.5%)	7
70077- 9.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (37.0%)	DSPC (12%)	DSG- PEG2K (2.0%)	7
70077- 10.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
70077- 11.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.0%)	DSPC (22%)	DMG- PEG2K (1.0%)	7
70087- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
70087- 2.C	MB, pH 3.0	SS-OC (60%)	胆固醇 (28.5%)	DSPC (11%)	DPG- PEG2K (0.5%)	7
70087- 3.C	MB, pH 3.0	SS-OC (60%)	胆固醇 (28.5%)	DSPC (11%)	DSG- PEG2K (0.5%)	7
70087- 4.C	MB, pH 3.0	SS-OC (60%)	胆固醇 (28.5%)	DSPC (11%)	DMG- PEG2K (0.5%)	7
70087- 5.C	MB, pH 3.0	SS-OC (60%)	胆固醇 (27.0%)	DSPC (11%)	DPG- PEG2K (1.5%)	7
80010- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
80010- 2.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7

[0454]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
80010- 3.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DMG- PEG2K (0.5%)	7
80010- 4.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DSG- PEG2K (0.5%)	7
80010- 5.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.0%)	DSPC (22%)	DPG- PEG2K (1.0%)	7
80016- 1.C	PB, pH 5.8	MC3 (49%)	胆固醇 (39.8%)	DSPC (11%)	DSPE- PEG5K (0.2%)	7
80016- 2.C	MB, pH 3.0	MC3 (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80016- 3.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (26.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	5.5
80016- 6.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80016- 7.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (27.5%)	DSPC (22%)	DPG- PEG2K (1.5%)	7
80016- 9.C	MB, pH 3.0	L-319 (49%)	胆固醇 (28.5%)	DSPC (22%)	DMG- PEG2K (0.2%)	7
80016- 10.C	MB, pH 3.0	L-319 (49%)	胆固醇 (27.5%)	DSPC (22%)	DMG- PEG2K (1.5%)	7
80016- 11.C	MB, pH 3.0	L-319 (49%)	胆固醇 (26.5%)	DSPC (22%)	DMG- PEG2K (2.5%)	7

[0455]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
80033- 1.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80033- 2.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80033- 3.C	MB, pH 3.0	SS-OP (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80048- 1.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (35.5%)	DSPC (15%)	DPG- PEG2K (0.5%)	9
80048- 2.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	5
80048- 3.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (21.5%)	DSPC (29%)	DPG- PEG2K (0.5%)	7
80048- 4.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (21.5%)	DOPE (29%)	DPG- PEG2K (0.5%)	5
80048- 5.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DOPE (22%)	DPG- PEG2K (0.5%)	9
80048- 6.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (35.5%)	DOPE (15%)	DPG- PEG2K (0.5%)	7
80048- 7.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (35.5%)	DLPE (15%)	DPG- PEG2K (0.5%)	5
80048- 8.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DLPE (22%)	DPG- PEG2K (0.5%)	7

[0456]

制剂 ID	缓冲液	可电离 脂质(%)	胆固醇(%)	辅助脂 质(%)	聚乙二醇化 的脂质(%)	N:P
80048- 9.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (21.5%)	DLPE (29%)	DPG- PEG2K (0.5%)	9
80059.1.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DLPE (22%)	DPG- PEG2K (0.5%)	7
80059- 2.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DLPE (22%)	DPG- PEG2K (0.5%)	7
80130- 1.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80130- 2.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80130- 3.C	MB, pH 3.0	SS-LC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7
80139- 1.C	MB, pH 3.0	SS-OC (49%)	胆固醇 (28.5%)	DSPC (22%)	DPG- PEG2K (0.5%)	7

[0457] 治疗组合物和使用方法

[0458] 本公开内容的一个方面涉及包含本文所述的重组RNA复制子或包含本文所述的重组RNA复制子的颗粒的治疗组合物,以及用于治疗癌症的方法。本文所述的组合物可以以适合所需递送途径的任何方式配制。通常,制剂包括所有生理上可接受的组合物,包括其衍生物或前药、溶剂化物、立体异构体、外消旋体或互变异构体、以及任何药学上可接受的载体、稀释剂和/或赋形剂。

[0459] 在某些实施方案中,包含重组RNA复制子(和任选地RNA病毒基因组)的LNP在施用给受试者时能够产生溶瘤病毒,其中编码的溶瘤病毒能够减小远离施用部位的肿瘤的大小。例如,LNP的静脉内施用可能导致肿瘤组织中的复制子复制和肿瘤大小的减小。在某些实施方案中,本公开内容的LNP能够定位至远离LNP施用部位的肿瘤或癌性组织。这样的效果使得本公开内容的LNP包封的复制子能够用于治疗不易接近并因此不适合肿瘤内递送治疗的肿瘤。

[0460] 短语“药学上可接受的”在本文中用于表示这样的化合物、物质、组合物和/或剂型:在合理的医学判断范围内,其适用于接触人类和动物的组织,而没有过度的毒性、刺激、

变应性应答或其它问题或并发症,与合理的收益/风险比相称。

[0461] 本文中使用的“药学上可接受的载体、稀释剂或赋形剂”包括、但不限于已经被美国食品和药品管理局批准为可接受用于用在人类或家养动物中的任何佐剂、载体、赋形剂、助流剂、甜味剂、稀释剂、防腐剂、染料/着色剂、增味剂、表面活性剂、润湿剂、分散剂、助悬剂、稳定剂等渗剂、溶剂、表面活性剂或乳化剂。示例性的药学上可接受的载体包括、但不限于:糖类,诸如乳糖、葡萄糖和蔗糖;淀粉,诸如玉米淀粉和马铃薯淀粉;纤维素和它的衍生物,诸如羧甲基纤维素钠、乙基纤维素和醋酸纤维素;黄蓍胶;麦芽;明胶;滑石;可可脂、蜡类、动物和植物脂肪、石蜡、有机硅、皂粘土、硅酸、氧化锌;油,诸如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油;二醇类,诸如丙二醇;多元醇,诸如甘油、山梨醇、甘露醇和聚乙二醇;酯类,诸如油酸乙酯和月桂酸乙酯;琼脂;缓冲剂,诸如氢氧化镁和氢氧化铝;海藻酸;无热原水;等张盐水;林格氏溶液;乙醇;磷酸盐缓冲溶液;和在药物制剂中采用的任意其它相容的物质。

[0462] “药学上可接受的盐”包括酸加成盐和碱加成盐。药学上可接受的盐包括酸加成盐(与蛋白的游离氨基形成),和与以下酸形成的盐:无机酸诸如、例如盐酸、氢溴酸、硫酸、硝酸、磷酸等,和有机酸诸如、但不限于乙酸、2,2-二氯乙酸、己二酸、海藻酸、抗坏血酸、天冬氨酸、苯磺酸、苯甲酸、4-乙酰氨基苯甲酸、樟脑酸、樟脑-10-磺酸、癸酸、己酸、辛酸、碳酸、肉桂酸、柠檬酸、环拉酸、十二烷基硫酸、乙烷-1,2-二磺酸、乙磺酸、2-羟基乙磺酸、甲酸、富马酸、半乳糖二酸、龙胆酸、葡萄糖庚糖酸、葡糖酸、葡糖醛酸、谷氨酸、戊二酸、2-氧代-戊二酸、甘油磷酸、羟乙酸、马尿酸、异丁酸、乳酸、乳糖酸、月桂酸、马来酸、苹果酸、丙二酸、扁桃酸、甲磺酸、粘酸、萘-1,5-二磺酸、萘-2-磺酸、1-羟基-2-萘甲酸、烟酸、油酸、乳清酸、草酸、棕榈酸、扑酸、丙酸、焦谷氨酸、丙酮酸、水杨酸、4-氨基水杨酸、癸二酸、硬脂酸、琥珀酸、酒石酸、硫氰酸、对甲苯磺酸、三氟乙酸、十一烯酸等。与游离羧基形成的盐还可以衍生自无机碱诸如、例如钠盐、钾盐、锂盐、铵盐、钙盐、镁盐、铁盐、锌盐、铜盐、锰盐、铝盐等。衍生自有机碱的盐包括、但不限于伯胺、仲胺和叔胺的盐,被取代的胺,包括天然存在的被取代的胺、环胺和碱性离子交换树脂,诸如氨、异丙胺、三甲胺、二乙胺、三乙胺、三丙胺、二乙醇胺、乙醇胺、地阿诺、2-二甲基氨基乙醇、2-二乙基氨基乙醇、二环己胺、赖氨酸、精氨酸、组氨酸、咖啡因、普鲁卡因、哈胺(hydrabamine)、胆碱、甜菜碱、苄乙苄胺、苄星青霉素、乙二胺、葡糖胺、甲基还原葡糖胺、可可碱、三乙醇胺、氨丁三醇、嘌呤、哌嗪、哌啶、N-乙基哌啶、多胺树脂等。特别优选的有机碱是异丙胺、二乙胺、乙醇胺、三甲胺、二环己胺、胆碱和咖啡因。

[0463] 本公开内容提供了杀死癌细胞或靶细胞的方法,包含在足以将所述组合物细胞内递送至癌细胞的条件下,将所述细胞暴露于本文所述的RNA多核苷酸或颗粒或其组合物。本文中使用的“杀死癌细胞”表示癌细胞借助于细胞凋亡或坏死的死亡。通过本领域已知的方法,包括、但不限于肿瘤大小测量、细胞计数和流式细胞计量术(用于检测细胞死亡标志物诸如膜联蛋白V和碘化丙啶的掺入),可以确定癌细胞的杀死。

[0464] 本公开内容进一步提供了在有此需要的受试者中治疗或预防癌症的方法,其中将有效量的本文所述的治疗组合物施用给所述受试者。施用途径自然会随着所治疗的疾病的位置和性质而变化,并且可以包括例如真皮内、透皮、真皮下、胃肠外、鼻、静脉内、肌肉内、鼻内、皮下、经皮、气管内、腹膜内、肿瘤内、灌注、灌洗、直接注射和口服施用。本文所述的封装的多核苷酸组合物可用于治疗转移性癌症,其中全身施用可能是将所述组合物递送至多

个器官和/或细胞类型所必需的。因此,在某些实施方案中,全身施用本文所述的组合物。

[0465] 本公开内容进一步提供了针对疾病免疫受试者的方法,其中将有效量的本文所述的治疗组合物施用给所述受试者。施用途径自然会随着免疫接种剂的位置和性质而变化,并且可以包括例如真皮内、透皮、真皮下、胃肠外、鼻、静脉内、肌肉内、鼻内、皮下、经皮、气管内、腹膜内、肿瘤内、灌注、灌洗、直接注射和口服施用。

[0466] 本公开内容进一步提供了用于用作药物的本公开内容的颗粒、本公开内容的载体、本公开内容的重组RNA复制子或其组合物。在某些实施方案中,所述药物是用于杀死癌细胞。在某些实施方案中,所述药物是用于治疗癌症。在某些实施方案中,所述药物是用于针对疾病免疫接种。

[0467] 在本文中互换使用的“有效量”或“有效剂量”表示导致疾病或病症的症状的改善或补救的本文所述组合物的量和/或剂量。所述改善是疾病或病症、或者疾病或病症的症状的任何改善或补救。所述改善是可观察的或可测量的改善,或者可以是受试者的健康状况的总体感觉的改善。因此,本领域技术人员认识到,治疗可以改善疾病状况,但可能不是疾病的完全治愈。受试者的改善可能包括、但不限于减少的肿瘤负荷、减少的肿瘤细胞增殖、增加的肿瘤细胞死亡、免疫途径的活化、增加的达到肿瘤进展的时间、减少的癌症疼痛、增加的存活或生活质量的改善。因此,基于药剂的性质,诸如质量/体积、细胞数目/体积、颗粒数目/体积、(药剂的质量)/(受试者的质量)、细胞数目/(受试者的质量)或颗粒数目/(受试者的质量),可以以多种方式表示特定药剂的有效量。特定药剂的有效量也可以表示为半数最大有效浓度(EC_{50}),其表示导致特定生理学应答的幅度为参比水平和最大应答水平之间的一半的药剂浓度。

[0468] 在某些实施方案中,有效剂量的施用可以通过施用单剂量的本文所述的组合物来实现。本文中使用的“剂量”表示一次递送的组合物的量。在某些实施方案中,将重组RNA分子的剂量测量为50%组织培养物感染剂量($TCID_{50}$)。在某些实施方案中,所述 $TCID_{50}$ 是至少约 10^3 至 $10^9 TCID_{50}/mL$,例如,至少约 $10^3 TCID_{50}/mL$ 、约 $10^4 TCID_{50}/mL$ 、约 $10^5 TCID_{50}/mL$ 、约 $10^6 TCID_{50}/mL$ 、约 $10^7 TCID_{50}/mL$ 、约 $10^8 TCID_{50}/mL$ 或约 $10^9 TCID_{50}/mL$ 。在某些实施方案中,可以通过给定体积中的颗粒数目(例如,颗粒/ mL)来测量剂量。在某些实施方案中,通过在每个颗粒中存在的本文所述的RNA多核苷酸的基因组拷贝数(例如,颗粒数目/ mL ,其中每个颗粒包含所述多核苷酸的至少一个基因组拷贝),可以进一步细化剂量。在某些实施方案中,有效剂量的递送可能需要施用多剂量的本文所述的组合物。因此,有效剂量的施用可能需要施用至少2、3、4、5、6、7、8、9、10、20、30、40、50或更多剂本文所述的组合物。

[0469] 在其中施用多剂本文所述组合物的实施方案中,每一剂不需要由相同的操作者和/或在相同的地理位置施用。此外,可以根据预定的时间表进行定量施用。例如,预定的定量施用计划可以包含每天、每隔一天、每周、每两周、每月、每两个月、每年、每半年等施用一剂本文所述的组合物。对于给定的患者,可以在必要时调整预定的定量施用计划(例如,可以增加或减少施用的组合物的量,和/或可以增加或减少剂量的频率,和/或可以增加或减少要施用的剂量总数)。

[0470] 定义

[0471] 在本说明书中,任何浓度范围、百分比范围、比率范围或整数范围应当理解为包括在列举的范围内的任意整数的值,且当适当时,包括其分数(诸如整数的十分之一和百分之

一),除非另外指出。应当理解,本文中使用的术语“一个”和“一种”表示所列举的组分中的“一个/种或多个/种”,除非另外指出。备选方案(例如,“或”)的应用应当被理解是指备选方案中的任一个、两个或它们的任意组合。本文中使用的术语“包括”和“包含”同义地使用。本文中使用的“多个”可以表示一个或多个组分(例如,一个或多个miRNA靶序列)。

[0472] 如在本申请中使用的,术语“约”和“大约”等同地使用。在本申请中使用的任何数字,不论有没有约/大约,都意在覆盖相关领域的普通技术人员所理解的任何正常波动。在某些实施方案中,术语“大约”或“约”表示在所述参考值的任一个方向(大于或更小)落入25%、20%、19%、18%、17%、16%、15%、14%、13%、12%、11%、10%、9%、8%、7%、6%、5%、4%、3%、2%、1%或更小内的值的范围,除非另有说明或另外从上下文中显而易见(这样的数字会超过可能值的100%的情况除外)。在某些实施方案中,术语“大约”或“约”表示在所述参考值的任一个方向(大于或更小)落入10%内的值的范围,除非另有说明或另外从上下文中显而易见(这样的数字会超过可能值的100%的情况除外)。

[0473] “减少”或“降低”表示与参考值相比,特定值减少或降低至少5%,例如,5%、6%、7%、8%、9%、10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、99%或100%。特定值的减少或降低也可以表示为该值与参考值相比的倍数变化,例如,与参考值相比,至少1、2、3、4、5、6、7、8、9、10、15、20、30、40、50、60、70、80、90、100、200、500、1000倍或更多的减少。

[0474] “增加”表示与参考值相比,特定值增加至少5%,例如,5%、6%、7%、8%、9%、10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、99%、100%、200%、300%、400%、500%或更多。特定值的增加也可以表示为该值与参考值相比的倍数变化,例如,与参考值的水平相比,至少1倍、2、3、4、5、6、7、8、9、10、15、20、30、40、50、60、70、80、90、100、200、500、1000倍或更多的增加。

[0475] 术语“序列同一性”表示在两个多核苷酸或多肽序列之间相同且在相同相对位置的碱基或氨基酸的百分比。因此,一个多核苷酸或多肽序列与另一多核苷酸或多肽序列相比具有一定百分比的序列同一性。对于序列对比,通常一个序列充当参考序列,测试序列与其进行对比。术语“参考序列”表示与测试序列进行对比的分子。术语“突变”表示核酸或氨基酸的置换、删除或添加。术语“保守突变”表示多肽中单个氨基酸或少量氨基酸的置换,其中新氨基酸具有与被置换的氨基酸相似的化学和物理性质(电荷、亲水性等)。

[0476] “互补”表示通过碱基堆积和特异性氢键合在两个包含天然或非天然存在的(例如,如上所述修饰的)碱基(核苷酸)或其类似物的序列之间配对的能力。例如,如果在核酸的一个位置的碱基能够与靶标的相应位置的碱基形成氢键,则认为在该位置的碱基相互互补。核酸可以包含通用碱基或惰性脱碱基间隔物,它们对氢键合没有正或负贡献。碱基配对可能包括规范的沃森-克里克碱基配对和非-沃森-克里克碱基配对(例如,Wobble碱基配对和Hoogsteen碱基配对)。应当理解,对于互补碱基配对,腺苷型碱基(A)与胸苷型碱基(T)或尿嘧啶型碱基(U)互补,胞嘧啶型碱基(C)与鸟苷型碱基(G)互补,并且通用碱基诸如3-硝基吡咯或5-硝基吡咯可以与任何A、C、U或T杂交并被认为是互补的。Nichols等人,Nature,1994;369:492-493和Loakes等人,Nucleic Acids Res.,1994;22:4039-4043。肌苷(I)在本领域中也已经被认为是通用碱基并且被认为与任何A、C、U或T互补。参见Watkins和SantaLucia,Nucl.Acids Research,2005;33(19):6258-6267。

[0477] “表达盒”或“表达构建体”表示可操作地连接至启动子的多核苷酸序列。

[0478] “可操作地连接”表示并列连接,其中如此描述的组件处于允许它们以它们的预期方式起作用的关系。例如,如果启动子影响多核苷酸序列的转录或表达,则所述启动子可操作地连接至所述多核苷酸序列;如果切割多肽允许有效负载分子在某些合乎需要的条件下分离(例如,与多肽的其余部分),则所述切割多肽可操作地连接至所述有效负载分子。

[0479] 术语“受试者”包括动物,诸如哺乳动物。在某些实施方案中,所述哺乳动物是灵长类动物。在某些实施方案中,所述哺乳动物是人。在某些实施方案中,受试者是家畜诸如牛、绵羊、山羊、奶牛、猪等;或驯化的动物诸如狗和猫。在某些实施方案中(例如,特别是在研究环境中),受试者是啮齿类动物(例如,小鼠、大鼠、仓鼠)、兔、灵长类动物、或猪诸如近交猪等。术语“受试者”和“患者”在本文中可互换地使用。在某些实施方案中,本公开内容的方法用于治疗人受试者。本公开内容的方法还可以用于治疗非人灵长类动物(例如,猴、狒狒和黑猩猩)、小鼠、大鼠、牛、马、猫、狗、猪、兔、山羊、鹿、绵羊、雪貂、沙鼠、豚鼠、仓鼠、蝙蝠、禽类和爬行动物。

[0480] 本文中使用的“预防”或“防止”可以指完全预防疾病的症状、延迟疾病的症状的发作、或减轻随后发展的疾病症状的严重程度。

[0481] 本文中的“癌症”表示或描述哺乳动物中的生理状况,其通常以失调的细胞生长为特征。癌症的例子包括、但不限于癌、淋巴瘤、母细胞瘤、肉瘤(包括脂肉瘤、成骨性肉瘤、血管肉瘤、内皮肉瘤、平滑肌肉瘤、脊索瘤、淋巴管肉瘤、淋巴管内皮肉瘤、横纹肌肉瘤、纤维肉瘤、粘液肉瘤和软骨肉瘤)、神经内分泌肿瘤、间皮瘤、滑膜瘤、许旺细胞瘤、脑膜瘤、腺癌、黑色素瘤和白血病或淋巴样恶性肿瘤。这样的癌症的更具体的例子包括:鳞状细胞癌(例如,上皮鳞状细胞癌)、肺癌(包括小细胞肺癌、非小细胞肺癌、肺腺癌和肺鳞状癌)、小细胞肺癌、腹膜癌、肝细胞癌、胃癌(gastric or stomach cancer)(包括胃肠癌)、胰腺癌、胶质母细胞瘤、宫颈癌、卵巢癌、肝癌、膀胱癌、肝细胞癌、乳腺癌、结肠癌、直肠癌、结直肠癌、子宫内膜或子宫癌、唾液腺癌、肾癌(kidney or renal cancer)(例如,肾细胞癌)、神经内分泌癌、前列腺癌(例如,阉割抗性的神经内分泌前列腺癌)、外阴癌、甲状腺癌、B-细胞慢性淋巴细胞性白血病、弥漫性大B细胞性淋巴瘤(DLBCL)、边缘区淋巴瘤(MZL)、梅克尔细胞癌、肝癌、肛门癌、阴茎癌、睾丸癌、食管癌、胆道肿瘤、尤因瘤、基底细胞癌、腺癌、汗腺癌、皮脂腺癌、乳头状癌、乳头状腺癌、囊腺癌、髓样癌、支气管原癌、肾细胞癌、肝细胞癌、胆管癌、绒毛膜癌、精原细胞瘤、胚胎性癌、威尔曼瘤、睾丸肿瘤、肺癌、膀胱癌、上皮癌、神经胶质瘤(例如,恶性神经胶质瘤)、星形细胞瘤、髓母细胞瘤、颅咽管瘤、室管膜瘤、松果体瘤、血管母细胞瘤、听神经瘤、少突神经胶质瘤、脑膜瘤、黑色素瘤、神经母细胞瘤、视网膜母细胞瘤、白血病,淋巴瘤,多发性骨髓瘤,Waldenstrom氏巨球蛋白血症、骨髓增生异常疾病、重链病、神经内分泌肿瘤、许旺细胞瘤和其它癌、以及头颈癌。在某些实施方案中,所述癌症是神经内分泌癌。此外,使用本文中公开的公开内容也可以治疗良性的(即,非癌性的)过度增殖性疾病、障碍和病症,包括良性前列腺肥大(BPH)、脑膜瘤、许旺细胞瘤、神经纤维瘤病、瘢痕疙瘩、肌瘤和子宫肌瘤等。

[0482] “施用”在本文中表示将药剂或组合物引入受试者。

[0483] 本文中使用的“治疗”表示将药剂或组合物递送至受试者以影响生理结果。在某些实施方案中,治疗表示治疗哺乳动物(例如人)的疾病,包括(a)抑制疾病,即阻止疾病发展

或预防疾病进展; (b) 缓解疾病, 即造成疾病状态的消退; 和 (c) 治愈疾病。

[0484] 细胞的“群体”表示大于1的任何细胞数量, 但优选地是至少 1×10^3 个细胞、至少 1×10^4 个细胞、至少 1×10^5 个细胞、至少 1×10^6 个细胞、至少 1×10^7 个细胞、至少 1×10^8 个细胞、至少 1×10^9 个细胞、至少 1×10^{10} 个细胞或更多细胞。细胞群体可以表示体外群体 (例如, 培养中的细胞群体) 或体内群体 (例如, 存在于特定组织中的细胞群体)。

[0485] “效应子功能”表示与针对靶细胞或靶抗原的免疫应答的产生、维持和/或增强相关的免疫细胞的功能。

[0486] 术语“微RNA”、“miRNA”和“miR”在本文中可互换地使用并表示长度为约21-25个核苷酸的小的非编码内源性RNA, 其通过指导其靶信使RNA (mRNA) 的降解或翻译抑制来调节基因表达。

[0487] 本文中使用的术语“组合物”表示本文所述的重组RNA分子或颗粒包封的重组RNA分子的制剂, 其能够施用或递送至受试者或细胞。

[0488] 术语“具有复制能力的病毒基因组”表示编码病毒复制和感染性病毒颗粒的产生所必需的所有病毒基因的病毒基因组。

[0489] 术语“溶瘤病毒”表示已经被修饰成或天然地优先感染癌细胞的病毒。

[0490] 术语“载体”在本文中用于表示能够转移或运输另一个核酸分子的核酸分子。

[0491] 术语“复制子”表示能够指导自身拷贝产生的核酸。本文中使用的术语“复制子”包括RNA以及DNA。通常, 病毒复制子至少含有病毒的基因组的一部分。病毒复制子可以含有不完整病毒基因组, 但仍能够指导自身拷贝的产生。

[0492] 术语“上游”当参考核酸使用时表示相对于参考核苷酸序列朝向5'定位的核苷酸序列, 并且当参考多肽使用时表示相对于参考氨基酸序列朝向N-端定位氨基酸序列。术语“下游”当参考核酸使用时表示相对于参考核苷酸序列朝向3'定位的核苷酸序列, 并且当参考多肽使用时表示相对于参考氨基酸序列朝向C-端定位氨基酸序列。

[0493] 术语“顺式作用复制元件”表示RNA病毒或复制子的RNA基因组的一部分, 其必须以顺式存在, 也就是说, 作为复制的必要条件作为每条病毒链的一部分存在。在某些实施方案中, 所述顺式作用复制元件由病毒RNA的一个或多个区段组成。

[0494] 本文中使用的与氨基酸或核酸位置相关的术语“与……对应”或“对应于”表示当将第一多肽/多核苷酸序列和参考多肽/多核苷酸序列比对时, 与参考多肽/多核苷酸序列中的给定氨基酸/核酸对齐的第一多肽/多核苷酸序列中的位置。本领域技术人员使用为此目的设计的软件执行比对, 例如, Clustal Omega 1.2.4版, 用该版本的默认参数。

[0495] 分子和细胞生物化学的一般方法可以参见标准教科书诸如Molecular Cloning: A Laboratory Manual, 第3版 (Sambrook等人, HarBor Laboratory Press 2001); Short Protocols in Molecular Biology, 第4版 (Ausubel等人. 编, John Wiley&Sons 1999); Protein Methods (Bollag等人, John Wiley&Sons 1996); Nonviral Vectors for Gene Therapy (Wagner等人. 编, Academic Press 1999); Viral Vectors (Kaplift和Loewy编, Academic Press 1995); Immunology Methods Manual (I. Lefkovits编, Academic Press 1997); 和Cell and Tissue Culture: Laboratory Procedures in Biotechnology (Doyle和Griffiths, John Wiley&Sons 1998), 其公开内容通过引用并入本文。

[0496] 其它编号的实施方案

[0497] 本公开内容的其它编号的实施方案提供如下：

[0498] 实施方案1.一种重组RNA复制子,其包含：

[0499] 小核糖核酸病毒基因组,其中所述小核糖核酸病毒基因组包含在一个或多个蛋白编码区中的缺失或截短;和

[0500] 异源多核苷酸。

[0501] 实施方案2.实施方案1的重组RNA复制子,其中所述小核糖核酸病毒基因组包含在一个或多个VP编码区中的缺失或截短。

[0502] 实施方案3.实施方案1或2的重组RNA复制子,其中所述小核糖核酸病毒基因组包含在VP1、VP3和VP2编码区中的每一个中的缺失或截短。

[0503] 实施方案4.实施方案1-3中的任一个的重组RNA复制子,其中所述小核糖核酸病毒基因组包含VP1和VP3编码区的缺失以及VP2编码区的截短。

[0504] 实施方案5.实施方案1-4中的任一个的重组RNA复制子,其中所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。

[0505] 实施方案6.实施方案1-5中的任一个的重组RNA复制子,其中所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp、至少2500bp或至少3000bp。

[0506] 实施方案7.实施方案6的重组RNA复制子,其中所述缺失或所述截短包含至少2000bp。

[0507] 实施方案8.实施方案1-7中的任一个的重组RNA复制子,其中所述缺失的位点或所述截短的位点包含所述异源多核苷酸

[0508] 实施方案9.实施方案1-7中的任一个的重组RNA复制子,其中所述异源多核苷酸插入在2A编码区和2B编码区之间。

[0509] 实施方案10.实施方案1-7中的任一个的重组RNA复制子,其中所述异源多核苷酸插入在3D编码区和3'非翻译区(UTR)之间。

[0510] 实施方案11.实施方案1-10中的任一个的重组RNA复制子,其中所述异源多核苷酸包含至少1000bp、至少2000bp或至少3000bp。

[0511] 实施方案12.实施方案1-11中的任一个的重组RNA复制子,其中所述小核糖核酸病毒是塞内卡谷病毒(SVV)。

[0512] 实施方案13.实施方案12的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:1的编号在核苷酸1261和3477(包括端点)之间的一个或多个核苷酸。

[0513] 实施方案14.实施方案12的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:1的编号的核苷酸1261至3477(包括端点)。

[0514] 实施方案15.实施方案12或13的重组RNA复制子,其中所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp或至少2000bp。

[0515] 实施方案16.实施方案15的重组RNA复制子,其中所述缺失或所述截短包含至少2000bp。

[0516] 实施方案17.实施方案12至16中的任一个的重组RNA复制子,其中所述SVV基因组包含5'前导蛋白编码序列。

[0517] 实施方案18.实施方案12至17中的任一个的重组RNA复制子,其中所述SVV基因组包含VP4编码区。

[0518] 实施方案19.实施方案12至18中的任一个的重组RNA复制子,其中所述SVV基因组包含VP2编码区或其截短体。

[0519] 实施方案20.实施方案19的重组RNA复制子,其中所述SVV基因组从5'至3'方向包含5'前导蛋白编码序列、VP4编码区和VP2编码区或其截短体。

[0520] 实施方案21.实施方案20的重组RNA复制子,其中包含5'前导蛋白编码序列、VP4编码区和VP2编码区或其截短体的SVV基因组的部分与SEQ ID NO:1的核苷酸1至1260具有至少90%序列同一性。

[0521] 实施方案22.实施方案20或21的重组RNA复制子,其中所述SVV基因组从5'至3'方向包含5'前导蛋白编码序列、VP4编码区、VP2编码区或其截短体和异源多核苷酸。

[0522] 实施方案23.实施方案1-22中的任一个的重组RNA复制子,其中所述SVV基因组包含顺式作用复制元件(CRE)。

[0523] 实施方案24.实施方案23的重组RNA复制子,其中所述CRE包含10-200bp。

[0524] 实施方案25.实施方案23或24的重组RNA复制子,其中所述CRE包含在与根据SEQ ID NO:1的核苷酸1000至核苷酸1260对应的区域内的一个或多个核苷酸。

[0525] 实施方案26.实施方案23或24的重组RNA复制子,其中所述CRE包含在与根据SEQ ID NO:1的核苷酸1117至核苷酸1260对应的区域内的一个或多个核苷酸。

[0526] 实施方案27.实施方案23-26中的任一个的重组RNA复制子,其中所述CRE包含与SEQ ID NO:149具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%或100%同一性的多核苷酸序列。

[0527] 实施方案28.实施方案12-27中的任一个的重组RNA复制子,其中所述SVV基因组进一步包含2A编码区。

[0528] 实施方案29.实施方案28的重组RNA复制子,其中所述2A编码区位于VP2编码区或其截短体和异源多核苷酸之间。

[0529] 实施方案30.实施方案12-29中的任一个的重组RNA复制子,其中所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区中的一个或多个。

[0530] 实施方案31.实施方案12-29中的任一个的重组RNA复制子,其中所述SVV基因组包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。

[0531] 实施方案32.实施方案31的重组RNA复制子,其中所述SVV基因组从5'至3'包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区。

[0532] 实施方案33.实施方案32的重组RNA复制子,其中包含2B编码区、2C编码区、3A编码区、3B编码区、3Cpro编码区和3D(RdRp)编码区的SVV基因组的部分与根据SEQ ID NO:1的核苷酸3505至7310具有至少90%序列同一性。

[0533] 实施方案34.实施方案30-33中的任一个的重组RNA复制子,其中所述SVV基因组从5'至3'包含异源多核苷酸和2B编码区。

[0534] 实施方案35.实施方案1至11中的任一个的重组RNA复制子,其中所述小核糖核酸病毒是柯萨奇病毒。

[0535] 实施方案36.实施方案35的重组RNA复制子,其中所述缺失或所述截短包含在根据SEQ ID NO:3的编号的核苷酸717至3332(包括端点)之间的一个或多个核苷酸。

[0536] 实施方案37.实施方案35的重组RNA复制子,其中所述缺失或所述截短包含根据SEQ ID NO:3的编号的核苷酸717至3332(包括端点)。

[0537] 实施方案38.实施方案35或36的重组RNA复制子,其中所述缺失或所述截短包含至少500bp、至少1000bp、至少1500bp、至少2000bp或至少2600bp。

[0538] 实施方案39.实施方案35至38中的任一个的重组RNA复制子,其中所述柯萨奇病毒基因组包含5' UTR。

[0539] 实施方案40.实施方案35至39中的任一个的重组RNA复制子,其中包含5' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:4具有至少90%序列同一性。

[0540] 实施方案41.实施方案35至40中的任一个的重组RNA复制子,其中所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR中的一个或多个。

[0541] 实施方案42.实施方案35至40中的任一个的重组RNA复制子,其中所述柯萨奇病毒基因组包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

[0542] 实施方案43.实施方案42的重组RNA复制子,其中所述柯萨奇病毒基因组从5' 至3' 方向包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR。

[0543] 实施方案44.实施方案42的重组RNA复制子,其中包含2A编码区、2B编码区、2C编码区、3A编码区、3B编码区、VPg编码区、3C编码区、3D pol编码区和3' UTR的柯萨奇病毒基因组的部分与SEQ ID NO:3中的核苷酸3492至7435具有至少90%序列同一性。

[0544] 实施方案45.实施方案41至44中的任一个的重组RNA复制子,其中所述柯萨奇病毒基因组从5' 至3' 包含5' UTR、异源多核苷酸和2A编码区。

[0545] 实施方案46.实施方案1至11中的任一个的重组RNA复制子,其中所述小核糖核酸病毒是脑心肌炎病毒(EMCV)。

[0546] 实施方案47.实施方案9和11-46中的任一个的重组RNA复制子,其中所述重组RNA复制子包含插入在异源多核苷酸和2B编码区之间的内部核糖体进入位点(IRES)。

[0547] 实施方案48.实施方案1至47中的任一个的重组RNA复制子,其中所述异源多核苷酸编码一个或多个有效负载分子。

[0548] 实施方案49.实施方案1至47中的任一个的重组RNA复制子,其中所述异源多核苷酸编码两个或更多个有效负载分子。

[0549] 实施方案50.实施方案49的重组RNA复制子,其中所述两个或更多个有效负载分子通过一个或多个切割多肽可操作地连接。

[0550] 实施方案51.实施方案50的重组RNA复制子,其中所述切割多肽包含2A家族自切割肽、3C切割位点、弗林蛋白酶位点、IGSF1多肽或HIV蛋白酶位点。

[0551] 实施方案52.实施方案51的重组RNA复制子,其中所述切割多肽包含IGSF1多肽,且其中所述IGSF1多肽包含与SEQ ID NO:75具有至少90%同一性的氨基酸序列。

[0552] 实施方案53.实施方案51的重组RNA复制子,其中所述切割多肽包含HIV蛋白酶位点。

[0553] 实施方案54.实施方案51的重组RNA复制子,其中所述切割多肽包含2A家族自切割

肽。

[0554] 实施方案55.实施方案50至54中的任一个的重组RNA复制子,其中所述切割多肽包含弗林蛋白酶位点。

[0555] 实施方案56.实施方案50至55中的任一个的重组RNA复制子,其中所述异源多核苷酸编码包含两个或更多个有效负载分子和切割多肽的多肽,所述多肽从N-端至C-端包含:N'-有效负载分子1-切割多肽-有效负载分子2-C'。

[0556] 实施方案57.实施方案53的重组RNA复制子,其中所述异源多核苷酸进一步包含编码HIV蛋白酶的编码区,且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-C'。

[0557] 实施方案58.实施方案57的重组RNA复制子,其中所述异源多核苷酸进一步包含编码第三有效负载分子的编码区,且其中所述异源多核苷酸包含编码多肽的编码区,所述多肽从N-端至C-端包含:

[0558] N'-有效负载分子1-HIV蛋白酶位点-HIV蛋白酶-HIV蛋白酶位点-有效负载分子2-HIV蛋白酶位点-有效负载分子3-C'。

[0559] 实施方案59.实施方案56至58中的任一个的重组RNA复制子,进一步包含在所编码的多肽的C-端处的切割多肽。

[0560] 实施方案60.实施方案48至59中的任一个的重组RNA复制子,其中所述有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、抗原、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。

[0561] 实施方案61.实施方案48至59中的任一个的重组RNA复制子,其中所述有效负载分子选自:

[0562] a) 一种或多种细胞因子,包含IFN γ 、GM-CSF、IL-2、IL-12、IL-15、IL-18、IL-23和IL-36 γ ;

[0563] b) 一种或多种趋化因子,包含CXCL10、CCL4、CCL5和CCL21;

[0564] c) 一种或多种抗体,包含抗-PD1-VHH-Fc抗体、抗-CD47-VHH-Fc抗体和抗-TGF β -VHH(或scFv)-Fc抗体;

[0565] d) 一种或多种双组分多肽,包含结合DLL3和效应细胞靶抗原的双组分多肽、结合FAP和效应细胞靶抗原的双组分多肽、以及结合EpCAM和效应细胞靶抗原的双组分多肽;

[0566] e) 一种或多种肿瘤相关抗原,包含存活素、MAGE家族蛋白和根据表6的所有抗原;

[0567] f) 一种或多种肿瘤新抗原;

[0568] g) 一种或多种结合MHC-肽抗原复合物的双组分多肽;

[0569] h) 一种或多种促融合蛋白,包含单纯疱疹病毒(HSV)UL27/糖蛋白B/gB,HSV UL53/糖蛋白K/gK,呼吸道合胞体病毒(RSV)F蛋白,FASTp15,VSV-G,syncitin-1(来自人内源性逆转录病毒-W(HERV-W))或syncitin-2(来自HERVFRDE1),副粘病毒SV5-F,麻疹病毒-H,麻疹病毒-F,以及来自逆转录病毒或慢病毒诸如长臂猿白血病毒(GALV)、鼠白血病毒(MLV)、Mason-Pfizer猴病毒(MPMV)和马传染性贫血病毒(EIAV)的糖蛋白,任选地除去了R跨膜肽(R-版本);

[0570] i) 一种或多种其它有效负载分子,包含IL15R、PGDH、ADA、ADA2、HYAL1、HYAL2、

CHIPS、MLKL (或仅它的4HB结构域)、GSDMD (或它的L192A突变体、或它的氨基酸1-233片段、或它的具有L192A突变的氨基酸1-233片段)、GSDME (或它的氨基酸1-237片段)、HMGB1 (或仅它的Box B结构域)、蜂毒肽 (例如, α -蜂毒肽)、SMAC/Diablo (或它的氨基酸56-239片段)、蛇LAAO、蛇解聚素、瘦素、FLT3L、TRAIL、Gasdermin D或其截短体和Gasdermin E或其截短体;

[0571] j) 一种或多种来自病原体的抗原,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒;或

[0572] k) 它们的任意组合。

[0573] 实施方案62.实施方案49至59中的任一个的重组RNA复制子,其中所述两个或更多个有效负载分子选自荧光蛋白、酶、细胞因子、趋化因子、能够结合细胞表面受体的抗原结合分子和细胞表面受体的配体。

[0574] 实施方案63.实施方案49至59中的任一个的重组RNA复制子,其中所述异源多核苷酸编码两个或更多个有效负载分子,其包含:

[0575] a. IL-2和IL-36 γ ;

[0576] b. CXCL10以及结合FAP和CD3的抗原结合分子;

[0577] c. IL-2以及结合DLL3和CD3的抗原结合分子;

[0578] d. IL-36 γ 以及结合DLL3和CD3的抗原结合分子;或

[0579] e. IL-2、IL-36 γ 以及结合DLL3和CD3的抗原结合分子。

[0580] 实施方案64.实施方案1至63中的任一个的重组RNA复制子,进一步包含微RNA(miRNA)靶序列(miR-TS)盒,其包含一个或多个miRNA靶序列。

[0581] 实施方案65.实施方案64的重组RNA复制子,其中所述一个或多个miRNA包含miR-124、miR-1、miR-143、miR-128、miR-219、miR-219a、miR-122、miR-204、miR-217、miR-137和miR-126。

[0582] 实施方案66.一种重组DNA分子,其从5'至3'包含启动子序列、5'连接切割序列、编码实施方案1-65中的任一个的重组RNA复制子的多核苷酸序列和3'连接切割序列。

[0583] 实施方案67.实施方案66的重组DNA分子,其中所述启动子序列是T7启动子序列。

[0584] 实施方案68.实施方案66或67的重组DNA分子,其中所述5'连接切割序列是核酶序列且所述3'连接切割序列是核酶序列。

[0585] 实施方案69.实施方案68的重组DNA分子,其中所述5'核酶序列是锤头核酶序列且其中所述3'核酶序列是丁型肝炎病毒核酶序列。

[0586] 实施方案70.实施方案66或67的重组DNA分子,其中所述5'连接切割序列是核酶序列且所述3'连接切割序列是限制性酶识别序列。

[0587] 实施方案71.实施方案70的重组DNA分子,其中所述5'核酶序列是锤头核酶序列、手枪核酶序列或经修饰的手枪核酶序列。

[0588] 实施方案72.实施方案70或71的重组DNA分子,其中3'限制性酶识别序列是IIS型限制性酶识别序列。

[0589] 实施方案73.实施方案72的重组DNA分子,其中所述IIS型识别序列是SapI识别序列。

[0590] 实施方案74.实施方案66或67的重组DNA分子,其中所述5'连接切割序列是RNA酶H

引物结合序列且所述3'连接切割序列是限制性酶识别序列。

[0591] 实施方案75.一种生产实施方案1-65中的任一个的重组RNA复制子的方法,包含体外转录实施方案66-74中的任一个的DNA分子和纯化得到的重组RNA复制子。

[0592] 实施方案76.一种组合物,其包含有效量的实施方案1-65中的任一个的重组RNA复制子和适用于施用给哺乳动物受试者的载体。

[0593] 实施方案77.一种载体,其包含实施方案1-65中的任一个的重组RNA复制子。

[0594] 实施方案78.实施方案77的载体,其中所述载体是病毒载体。

[0595] 实施方案79.实施方案77的载体,其中所述载体是非病毒载体。

[0596] 实施方案80.一种颗粒,其包含实施方案1-65中的任一个的重组RNA复制子。

[0597] 实施方案81.实施方案80的颗粒,其中所述颗粒选自纳米颗粒、外泌体、脂质体和脂质体复合物。

[0598] 实施方案82.实施方案81的颗粒,其中所述纳米颗粒是脂质纳米颗粒(LNP),其包含阳离子脂质、一种或多种辅助脂质和磷脂-聚合物缀合物。

[0599] 实施方案83.实施方案82的颗粒,其中所述阳离子脂质选自DLinDMA、DLin-KC2-DMA、DLin-MC3-DMA(MC3)、**COATSOME®**SS-LC(以前名称:SS-18/4PE-13)、**COATSOME®**SS-EC(以前名称:SS-33/4PE-15)、**COATSOME®**SS-OC、**COATSOME®**SS-OP、9-((4-二甲基氨基)丁酰基)氧基)十七烷二酸二((Z)-壬-2-烯-1-基)酯(L-319)或N-(2,3-二油酰氧基)丙基)-N,N,N-三甲基氯化铵(DOTAP)。

[0600] 实施方案84.实施方案82或83的颗粒,其中所述辅助脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸胆碱(DSPC);1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE);1,2-二油酰基-sn-甘油-3-磷酸胆碱(DOPC);1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE);和胆固醇。

[0601] 实施方案85.实施方案82的颗粒,其中所述阳离子脂质是1,2-二油酰基-3-三甲铵-丙烷(DOTAP),且其中所述中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE)或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。

[0602] 实施方案86.实施方案82-85中的任一个的颗粒,其中所述PEG-脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇(DPG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯(DSG-PEG);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯(DMG-PEG),或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。

[0603] 实施方案87.实施方案82-86中的任一个的颗粒,其中所述PEG-脂质选自1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)-5000](DSPE-PEG5K);1,2-二棕榈酰基-消旋-甘油甲氧基聚乙二醇-2000(DPG-PEG2K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DSG-PEG5K);1,2-二硬脂酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DSG-PEG2K);1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-5000(DMG-PEG5K);和1,2-二肉豆蔻酰基-消旋-甘油-3-甲基聚氧乙烯-2000(DMG-PEG2K)。

[0604] 实施方案88.实施方案82的颗粒,其中所述阳离子脂质包含**COATSOME®**SS-OC,其中所述一种或多种辅助脂质包含胆固醇(Chol)和DSPC,且其中所述磷脂-聚合物缀合

物包含DPG-PEG2000。

[0605] 实施方案89.实施方案88的颗粒,其中SS-OC:DSPC:Chol:DPG-PEG2K(作为总脂质含量的百分比)的比率是A:B:C:D,其中:

[0606] a. $A=40\%-60\%$, $B=10\%-25\%$, $C=20\%-30\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

[0607] b. $A=45\%-50\%$, $B=20\%-25\%$, $C=25\%-30\%$, 且 $D=0\%-1\%$ 并且其中 $A+B+C+D=100\%$

[0608] c. $A=40\%-60\%$, $B=10\%-30\%$, $C=20\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

[0609] d. $A=40\%-60\%$, $B=10\%-30\%$, $C=25\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

[0610] e. $A=45\%-55\%$, $B=10\%-20\%$, $C=30\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

[0611] f. $A=45\%-50\%$, $B=10\%-15\%$, $C=35\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

[0612] g. $A=45\%-65\%$, $B=5\%-20\%$, $C=20\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

[0613] h. $A=50\%-60\%$, $B=5\%-15\%$, $C=30\%-45\%$, 且 $D=0\%-3\%$ 并且其中 $A+B+C+D=100\%$;

[0614] i. $A=55\%-60\%$, $B=5\%-15\%$, $C=30\%-40\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$;

[0615] j. $A=55\%-60\%$, $B=5\%-10\%$, $C=30\%-35\%$, 且 $D=1\%-2\%$ 并且其中 $A+B+C+D=100\%$ 。

[0616] 实施方案90.实施方案88的颗粒,其中SS-OC:DSPC:Chol:DPG-PEG2K(作为总脂质含量的百分比)的比率是:

[0617] a. 约49:22:28.5:0.5;

[0618] b. 约49:11:38.5:1.5;或

[0619] c. 约58:7:33.5:1.5。

[0620] 实施方案91.实施方案88的颗粒,其中SS-OC:DSPC:Chol:DPG-PEG2K(作为总脂质含量的百分比)的比率是约49:22:28.5:0.5。

[0621] 实施方案92.实施方案82的颗粒,其中所述阳离子脂质是1,2-二油酰基-3-三甲基铵-丙烷(DOTAP),且其中所述中性脂质是1,2-二月桂酰基-sn-甘油-3-磷酸乙醇胺(DLPE)或1,2-二油酰基-sn-甘油-3-磷酸乙醇胺(DOPE)。

[0622] 实施方案93.实施方案82或92的颗粒,进一步包含PEG-脂质,其中所述PEG-脂质是1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-聚(乙二醇)(DSPE-PEG)或1,2-二硬脂酰基-sn-甘油-3-磷酸乙醇胺-N-[氨基(聚乙二醇)](DSPE-PEG-胺)。

[0623] 实施方案94.实施方案80-93中的任一个的颗粒,进一步包含编码溶瘤病毒的第二重组RNA分子。

[0624] 实施方案95.实施方案94的颗粒,其中所述溶瘤病毒是小核糖核酸病毒。

[0625] 实施方案96.实施方案95的颗粒,其中所述小核糖核酸病毒选自塞内卡病毒、心病病毒和肠道病毒。

[0626] 实施方案97.实施方案95的颗粒,其中所述小核糖核酸病毒是塞内卡谷病毒(SVV)。

[0627] 实施方案98.实施方案95的颗粒,其中所述小核糖核酸病毒是柯萨奇病毒。

[0628] 实施方案99.实施方案95的颗粒,其中所述小核糖核酸病毒是脑心肌炎病毒(EMCV)。

[0629] 实施方案100.一种治疗组合物,其包含多个根据实施方案82-99中的任一个的脂质纳米颗粒。

[0630] 实施方案101.实施方案100的治疗组合物,其中所述多个LNP具有约50nm至约120nm的平均大小。

[0631] 实施方案102.实施方案100的治疗组合物,其中所述多个LNP具有约100nm的平均大小。

[0632] 实施方案103.实施方案100-102中的任一个的治疗组合物,其中所述多个LNP具有约20mV至约-20mV、约10mV至约-10mV、约5mV至约-5mV、或约20mV至约-40mV、-50mV至约-20mV、约-40mV至约-20mV、或约-30mV至约-20mV之间的平均 ζ 电位。

[0633] 实施方案104.实施方案103的治疗组合物,其中所述多个LNP具有约-30mV、约-31mV、约-32mV、约-33mV、约-34mV、约-35mV、约-36mV、约-37mV、约-38mV、约-39mV或约-40mV的平均 ζ 电位。

[0634] 实施方案105.一种杀死癌细胞的方法,其包含将所述癌细胞暴露于实施方案80-97中的任一个的颗粒、实施方案77-79中的任一个的载体、实施方案1-65中的任一个的重组RNA复制子、或其组合物。

[0635] 实施方案106.实施方案105的方法,其中在体内、在体外或离体执行所述方法。

[0636] 实施方案107.一种治疗受试者中的癌症的方法,其包含给遭受癌症的受试者施用有效量的实施方案80-97中的任一个的颗粒、实施方案77-79中的任一个的载体、实施方案1-65中的任一个的重组RNA复制子、或其组合物。

[0637] 实施方案108.实施方案107的方法,其中将所述颗粒、所述重组RNA复制子或其组合物静脉内地、鼻内地、作为吸入剂施用,或直接注射进肿瘤中。

[0638] 实施方案109.实施方案107或108的方法,其中将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。

[0639] 实施方案110.实施方案107-109中的任一个的方法,其中所述受试者是小鼠、大鼠、兔、猫、狗、马、非人灵长类动物或人。

[0640] 实施方案111.实施方案107-110中的任一个的方法,其中所述癌症选自肺癌、乳腺癌、卵巢癌、子宫颈癌、前列腺癌、睾丸癌、结肠直肠癌、结肠癌、胰腺癌(例如,阉割抗性的神经内分泌前列腺癌)、肝癌、胃癌、头颈癌、甲状腺癌、恶性神经胶质瘤、胶质母细胞瘤、黑色素瘤、B-细胞慢性淋巴细胞性白血病、弥漫性大B细胞性淋巴瘤(DLBCL)、肉瘤、神经母细胞瘤、神经内分泌癌、横纹肌肉瘤、髓母细胞瘤、膀胱癌、边缘区淋巴瘤(MZL)、梅克尔细胞癌和肾细胞癌。

[0641] 实施方案112.实施方案111的方法,其中:

- [0642] a.所述肺癌是小细胞肺癌或非小细胞肺癌;
- [0643] b.所述肝癌是肝细胞癌(HCC);和/或
- [0644] c.所述前列腺癌是治疗引发的神经内分泌前列腺癌。
- [0645] 实施方案113.实施方案111的方法,其中所述癌症是神经内分泌癌。
- [0646] 实施方案114.一种针对疾病免疫受试者的方法,其包含给所述受试者施用有效量的实施方案80-97中的任一个的颗粒、实施方案77-79中的任一个的载体、实施方案1-65中的任一个的重组RNA复制子、或其组合物。
- [0647] 实施方案115.实施方案114的方法,其中将所述颗粒、所述重组RNA复制子或其组合物静脉内地、肌肉内地、真皮内地、鼻内地或作为吸入剂施用。
- [0648] 实施方案116.实施方案114或115的方法,其中将所述颗粒、所述重组RNA复制子或其组合物重复施用给所述受试者。
- [0649] 实施方案117.实施方案114至116中的任一个的方法,其中所述疾病是传染性疾病。
- [0650] 实施方案118.实施方案117的方法,其中所述传染性疾病由病原体之一造成,所述病原体包含登革热病毒、切昆贡亚病毒、结核分枝杆菌、人免疫缺陷病毒、SARS-CoV-2、冠状病毒、乙型肝炎病毒、披膜病毒科病毒、黄病毒科病毒、甲型流感病毒、流感B病毒和兽医病毒。
- [0651] 实施方案119.一种重组RNA复制子,其包含小核糖核酸病毒基因组和异源多核苷酸。
- [0652] 实施方案120.实施方案119的重组RNA复制子,其中所述异源多核苷酸插入在2A编码区和2B编码区之间。
- [0653] 实施方案121.实施方案119的重组RNA复制子,其中所述异源多核苷酸插入在5'UTR和2A编码区之间。
- [0654] 实施方案122.实施方案119的重组RNA复制子,其中所述异源多核苷酸插入在3D编码区和3'UTR之间。
- [0655] 实施方案123.实施方案119-122中的任一个的重组RNA复制子,其中所述小核糖核酸病毒选自塞内卡病毒、心病毒和肠道病毒。
- [0656] 实施例
- [0657] 给出以下实施例是为了说明本公开内容的各种实施方案的目的,并不意味着以任何方式限制本公开内容。本发明的实施例,连同本文所述的方法一起,目前是优选实施方案的代表,是示例性的,并且不旨在限制本公开内容的范围。本领域技术人员将想到被包括在由权利要求的范围限定的本公开内容的精神内的其中的变化和其它用途。
- [0658] 实施例1:异源多核苷酸的插入会减少SVV病毒复制
- [0659] 进行实验以评估塞内卡谷病毒(SVV)的病毒复制能力,所述病毒在病毒基因组中插入了不同长度的异源多核苷酸(表15)。简而言之,在第1天用0.015pmol的编码重组SVV病毒基因组的质粒转染NCI-H1299细胞。在第4天收获细胞并过滤上清液以收集病毒。在第5天,用收集的病毒感染NCI-H446细胞并进行CTG测定以估计病毒复制率。结果显示在图2和表15中。异源多核苷酸的插入造成病毒复制率的降低。
- [0660] 表15.包含异源多核苷酸的SVV的病毒复制

[0661]	构建体	有效负载大小 (bp)	IC50
	BV-SVV-wt	n/a	8.03E-09
	BV-SVV-mCherry	702	1.09E-06
	BV-SVV-nLuc	513	2.36E-05
	BV-SVV-mCXCL10	294	8.55E-05
	BV-SVV-m_scIL12	1629	4.43E-01
	BV-SVV-mFAP-CD3-BITE	1518	1.80E+00
	BV-SVV-mGMCSF	423	1.90E+00

[0662] 实施例2:在VP2区域内的SVV顺式作用复制元件 (CRE) 的鉴定

[0663] 进行实验以评估在编码一种或多种VP蛋白的病毒基因组区域内的缺失/截短是否影响SVV病毒复制。根据表16和图3A产生包含mCherry报道基因以及编码VP蛋白的区域中的缺失和/或截短的SVV衍生出的重组RNA复制子。通过体外T7转录产生相应的重组RNA复制子。用所得的RNA转染NCI-H1299细胞,并在转染以后24小时评价mCherry表达。结果表明,1599bp-3478bp之间的缺失对SVV病毒复制具有最小影响,而1116bp-1599bp之间的核苷酸缺失(在VP2编码区内)大大降低了SVV病毒复制(图3B)。因此,顺式作用复制元件(或顺式作用复制元件的至少一部分)存在于SVV病毒基因组的1116bp-1599bp之间。

[0664] 表16. 在VP编码区中具有缺失的SVV复制子

[0665]	复制子	SEQ ID NO: (对于复制子)	SEQ ID NO: (对于 DNA 载体模板)	缺失	复制子长度
	SVVmCh	20	19	0 bp	8.0 kb
	Trunc1	22	21	1011 bp	7.1 kb
	Trunc4	28	27	1554 bp	6.5 kb
	Trunc2	24	23	1795 bp	6.3 kb
	Trunc5	30	29	1878 bp	6.2 kb
	Trunc6	32	31	2362 bp	5.7 kb
	Trunc7	34	33	2812 bp	5.3 kb
	Trunc3	26	25	3478 bp	4.6 kb

[0666] 实施例3:以最小效力损失将Trunc5复制子用SVVwt转衣壳化

[0667] 进行实验以评估Trunc5复制子在被野生型SVV转衣壳化以后是否可以保持效力并确定对野生型SVV的适合性成本。简而言之,将Trunc5复制子和/或野生型SVV病毒基因组用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒 (NEB) 进行体外转录 (IVT)。将NCI-H1299细胞使用Lipofectamine RNAiMax (Invitrogen) 用0.5或1 μ g的每种或两种得到的RNA分子共转染。在转染以后48小时,将上清液收集并通过0.45 μ m过滤器过滤。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后24小时观察mCherry的表达(图4A)。在与SVVwt共转染以后检测到mCherry的表达,但在仅用复制子转染以后未检测到,表明Trunc5被转衣壳化。使用在NCI-H446细胞中进行的IC50测定,对比了来自SVVwt转染相对于SVVwt和Trunc5-SVV复制子共转染的过滤上清液的病毒滴度(图4B)。SVVwt与Trunc5的共转

染导致病毒滴度的最小降低。

[0668] 实施例4:Trunc10维持CRE并使有效负载容量最大化

[0669] 进行进一步实验以缩小CRE的位置并分析在SVV VP编码区内可耐受的缺失的长度。根据表17和图5A产生包含mCherry报道基因以及编码VP蛋白的区域中的缺失和/或截短的SVV衍生出的重组RNA复制子。根据在实施例2中描述的方案进行实验。图5B显示了通过体外T7 RNA合成产生的RNA分子,且图5C显示了各种复制子的mCherry信号。结果表明,1260bp-3478bp之间的缺失(Trunc10复制子)对SVV病毒复制具有最小影响。

[0670] 表17. 在VP编码区中具有缺失的SVV复制子

[0671]	复制子	SEQ ID NO:	SEQ ID NO: (对于	缺失	复制子长
		(对于复制子)	DNA 载体模板)		度
	SVVmCh	20	19	0 bp	8.0 kb
[0672]	Trunc5	30	29	1878 bp	6.2 kb
	Trunc6	32	31	2362 bp	5.7 kb
	Trunc8	36	35	2071 bp	6.0 kb
	Trunc10	38	37	2218 bp	5.8 kb

[0673] 实施例5:具有单个有效负载的SVV复制子具有复制和转衣壳化能力

[0674] 构建复制子用于能力的体外和体内试验(图6A-6B)。如在图6B中所示,将各种有效负载(mCherry、纳米萤光素酶或eGFP)插入复制子中,并根据实施例2-4中的方案试验所得复制子。结果表明,所有这些复制子都具有复制和转衣壳化能力。

[0675] 实施例6:具有鼠IL-2有效负载的SVV-Trunc10复制子

[0676] 进行实验以试验通过SVV-Trunc10复制子对鼠IL-2有效负载蛋白的表达。图7A显示了携带编码鼠IL-2有效负载的转基因的SVV-复制子Trunc10的构建。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用mIL-2 ELISA(R&D)检测鼠IL-2的表达(图7B)。此外,将病毒RNA分离并用正链和负链特异性的taqman测定进行分析(图7C)。结果表明,SVV-Trunc10-mIL-2复制子在转染和转衣壳化以后表达和分泌mIL-2,并能够合成正链和负链病毒RNA。

[0677] 实施例7:具有单链mIL-12有效负载的SVV-Trunc10复制子

[0678] 进行实验以试验通过SVV-Trunc10复制子对单链mIL-12(scmlL-12)有效负载蛋白的表达。图8A描绘了携带编码单链mIL-12(scmlL-12)的转基因的SVV-复制子Trunc10的构建,具有和没有信号序列。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol(Qiagen)中。将100 μ l

过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。将RNA分离并用正链和负链特异性的taqman测定进行分析(图8B),这表明所述复制子能够合成正链和负链病毒RNA,且有效负载分泌与正或负病毒RNA合成无关。用mIL-2 ELISA (R&D) 检测鼠IL-12的表达(图8C),这表明Trunc10-scmIL-12复制子在转染和转衣壳化以后表达和分泌mIL-12。信号序列的缺失减少了IL-12分泌。总之,结果表明,Trunc10-scmIL-12和Trunc10-scmIL-12 Δ ss复制子能够合成正链和负链病毒RNA,但是完整信号序列促进在转染和转衣壳化以后mIL-12的表达和分泌。

[0679] 实施例8:SVV-Trunc10-hIL-36 γ 复制子

[0680] 进行实验以试验通过SVV-Trunc10复制子对人IL-36 γ 有效负载蛋白的表达。图9A描绘了携带编码人IL-36 γ 的转基因的SVV-复制子Trunc10的构建,具有天然信号序列或具有IL2信号序列。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用hIL-36 γ ELISA (R&D) 检测hIL-36 γ 的表达。两种复制子在转染和转衣壳化以后表达和分泌hIL-36 γ ,并且IL-2信号序列的添加没有改善表达或分泌(图9B)。将RNA分离并用正链和负链特异性的taqman测定进行分析。结果(图9C)表明,两种复制子能够合成正链和负链病毒RNA。总之,结果证实,SVV-Trunc10-hIL-36 γ 和SVV-Trunc10-IL2ss-hIL-36 γ -18S复制子在转染和转衣壳化以后表达和分泌hIL-36 γ ,并能够合成正链和负链病毒RNA。

[0681] 实施例9:在双顺反子复制子中的第二IRES没有改善复制子功能

[0682] 图10A描绘了在单个有效负载下游掺入第二脑心肌炎病毒(EMCV) IRES的双顺反子复制子的构建。试验了第二IRES对复制子功能改善的影响。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g SVVmCherry转染。在转染后48小时,用QIAzol (Qiagen)收集RNA。将RNA分离并用正链和负链特异性的taqman测定进行分析(图10B)。结果表明,复制子的负链合成因第二ECMV IRES的添加而受损,并且在hDLL3-BiTE或mIL-2有效负载下游的第二IRES掺入没有改善病毒RNA合成。

[0683] 实施例10:多个弗林蛋白酶T2A位点对于双顺反子双重有效负载复制子中的有效负载表达是无效的

[0684] 图11A描绘了在多个有效负载下游掺入第二脑心肌炎病毒(EMCV) IRES的双顺反子双重有效负载复制子的构建,其中在第一有效负载和第二有效负载(eGFP)之间被弗林蛋白酶-T2A位点隔开。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,观察细胞的GFP表达,并将来自复制子和SVVmCherry的共转染的上清液收集和通过0.45 μ m过滤器过滤。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后24小时检查细胞的mCherry和GFP表达(图11B)。在Trunc10-hDLL3-BiTE-GFP-eIRES或Trunc10-mIL2-GFP-eIRES的转染以后或转衣壳化以后,检测到GFP的最小表达,表明双顺反子复制子具有

第二有效负载的受损表达。

[0685] 实施例11:在复制子的3'末端掺入第二有效负载的双有效负载复制子对复制无效

[0686] 图12A描绘了在复制子的3'末端在RdRp和3' UTR之间掺入第二有效负载的双重有效负载复制子的构建。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用hIL-36 γ ELISA (R&D)检测hIL-36 γ 的表达。复制子在转染以后分泌小于2pg/mL的hIL-36,并且hIL-36分泌在转衣壳化以后不是可检测的(图12B)。将RNA分离并用正链和负链特异性的taqman测定进行分析,这表明复制子是正链和负链病毒RNA合成有缺陷的(图12C)。结果证实,在3'末端处的有效负载插入导致转染以后非常低的IL-36 γ 表达,抑制转衣壳化,并减少正链和负链合成。

[0687] 实施例12:使用Trunc10复制子表达1DLT176-MTT10-DLL3-VHH-CD3

[0688] 构建了用于表达his-标记的1DLT176-MTT10-DLL3-VHH-CD3 LiTE的单个有效负载复制子。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用抗-His蛋白质印迹检测his-标记的1DLT176-MTT10-DLL3-VHH-CD3 LiTE的表达。与LiTE表达相关的特定条带用箭头指示并在转染的和转衣壳化的样品的上清液中检测到(图13A)。将RNA分离并用正链和负链特异性的taqman测定进行分析(图13B)。结果提示,Trunc10-1DLT176-MTT10-DLL3-VHH-CD3复制子能够表达LiTE有效负载,且能够合成正链和负链病毒RNA。

[0689] 实施例13:使用Trunc10复制子表达rDLL3- α CD3-H/L-BiTE和T10-rDLL3- α CD3-L/H-BiTE

[0690] 构建了用于表达his-标记的rDLL3- α CD3-BiTE的单个有效负载复制子。H/L的方向是重链然后轻链,而L/H.A则相反。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax (Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用抗-His蛋白质印迹检测his-标记的rDLL3- α CD3-BiTE的表达(图14A)。与LiTE表达相关的特定条带用箭头指示并在转染的和转衣壳化的样品的上清液中检测到。将RNA分离并用正链和负链特异性的taqman测定进行分析(图14B)。结果证实,两种表达Trunc10-rDLL3- α CD3 BiTE的复制子能够表达BiTE有效负载,能够转衣壳化,且能够合成正链和负链病毒RNA。重链和轻链的取向没有影响复制子功能。

[0691] 实施例14:使用Trunc10复制子表达多个有效负载的替代切割肽

[0692] 构建了在his-标记的mFAP和CXCL10之间包含替代切割肽(3C、或弗林蛋白酶-3C、

或弗林蛋白酶T2A)的Trunc10复制子,以试验这些替代切割肽中的任一种是否能够从单个复制子有效表达多个有效负载(图15A和SEQ ID NO:40、42、44)。将复制子模板(SEQ ID NO:39、41、43)和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用CXCL10特异性的ELISA(R&D)分析CXCL10的表达。在转染或转衣壳化以后没有检测到CXCL10的表达(图15B)。将RNA分离并用正链和负链特异性的taqman测定进行分析(图15C),这表明所有这些复制子都是正链和负链病毒RNA合成有缺陷的。因此,与原始弗林蛋白酶T2A位点相比,3C-fT2A和弗林蛋白酶3C切割位点没有促进双重有效负载表达或负或正链合成。

[0693] 构建了在his-标记的mFAP和CXCL10之间包含替代切割肽(T2A、P2A、F2A或E2A)的Trunc10复制子,以试验这些替代切割肽中的任一种是否能够从单个复制子有效表达多个有效负载(图16A和SEQ ID NO:48、50、52、54)。将复制子模板(SEQ ID NO:47、49、51、53)和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用CXCL10特异性的ELISA(R&D)检查CXCL10的表达(图16B),这表明与弗林蛋白酶-T2A复制子相比,T2A、P2A、F2A和E2A复制子增强了CXCL10的表达,但是在转衣壳化以后没有检测到CXCL10表达。将RNA分离并用正链和负链特异性的taqman测定进行分析(图16C),这表明所有复制子能够合成正链和负链病毒RNA,这与弗林蛋白酶-T2A复制子相比得到改善。

[0694] 实施例15:具有N末端弗林蛋白酶位点的IGSF1内部结构域接头允许从单个ORF分泌2个多肽

[0695] 试验具有N末端弗林蛋白酶位点的IGSF1内部结构域接头作为用于从单个复制子表达多个有效负载的切割多肽。将宿主IGSF1介导的加工接头设计成能够从相同开放读码框(ORF)表达和分泌2个有效负载。人IGSF1蛋白含有一个跨膜结构域和一个串联的信号序列/信号肽酶位点以促进第二个分泌型有效负载的分泌。在IGSF1接头的N端上,包括2x弗林蛋白酶切割位点用于两种肽的ER加工并确保N端有效负载的释放。在该实施例中,N-端有效负载分子是鼠IL-12,且C-端有效负载分子是在ORF内的IL-36 γ amma(图17A和SEQ ID NO:60)。将ORF插入Trunc10复制子中进行试验。

[0696] 将复制子模板(SEQ ID NO:59)和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用hIL-36 γ 和mIL-2 ELISA(R&D)检测人IL-36 γ 和鼠IL-2的表达。在转染和转衣壳化(TE)以后检测到两个有效负载的表达(图17B-17C)。将RNA分离并用正链和负链特异性的taqman测

定进行分析(图17D),这表明所有复制子能够合成正链和负链病毒RNA并与单个有效负载GFP复制子相当地复制。总之,结果证实了使用IGSF1介导的加工在IL2和IL36之间切割的成功策略,这使得能够从单个复制子表达两个有效负载。IL36和IL2都在转染和转衣壳化以后表达。正链和负链RNA合成与T10-eGFP复制子相当。

[0697] 实施例16:HIV-蛋白酶介导的蛋白酶解增强两个有效负载的有效负载表达

[0698] 图18A描绘了相同开放读码框中两个分泌型有效负载的HIV-1蛋白酶介导的加工的示意图。两个有效负载被HIV-1蛋白酶的连接二聚体或单体和侧接HIV蛋白酶切割(PR)位点隔开。在该实施例中,N-端有效负载分子是鼠IL-12且C-端有效负载分子是在ORF内的IL-36 γ 。将ORF插入Trunc10复制子中进行试验(SEQ ID NO:56、58)。将复制子模板(SEQ ID NO:55、57)和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。将RNA分离并用正链和负链特异性的taqman测定进行分析(图18B),这表明所有复制子能够合成正链和负链病毒RNA并且与单个有效负载GFP复制子相当地复制。用hIL-36 γ 和mIL-2 ELISA(R&D)检测人IL-36 γ 和鼠IL-2的表达。在转染和转衣壳化以后检测到两个有效负载的表达(图18C)。总之,这些结果证实,HIV-蛋白酶的单个拷贝能够从单个复制子有效表达两个有效负载,并且IL-36 γ 和IL2在转染和转衣壳化以后成功表达。正链和负链RNA合成与Trunc10-eGFP复制子相当。总之,这些结果证实,HIV-蛋白酶能够实现来自单个ORF的双重有效负载。

[0699] 图19A描绘一种双重有效负载复制子T10-BiTE-hIL-36 γ ,其包含单体HIV-1蛋白酶以及在his-标记的hDLL3-BiTE和人IL-36 γ 之间的侧接蛋白酶切割位点,其被试验来自单个基于Trunc10的复制子的两个有效负载的表达。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并穿过0.45 μ m过滤器过滤,并将RNA收集在QIAzol试剂(Qiagen)中。将100 μ l过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用hIL-36 γ ELISA(R&D)检查人IL-36 γ 的表达。在转染和转衣壳化以后检测到hIL-36 γ 的表达(图19B)。将RNA分离并用正链和负链特异性的taqman测定进行分析(图19C),这表明所有复制子能够合成正链和负链病毒RNA。总之,这些结果证实,HIV-蛋白酶的单个拷贝能够在转染和转衣壳化以后从双重有效负载复制子表达hIL-36。与T10-eGFP复制子相比,正链和负链RNA合成减少。

[0700] 实施例17:来自单个复制子的三重有效负载的HIV-蛋白酶介导的表达

[0701] 图20A描绘一种三重有效负载复制子T10-BiTE-IL3g6-IL2,其包含单体HIV-1蛋白酶以及在his-标记的hDLL3-BiTE、人IL-36 γ 和鼠IL-2之间的侧接蛋白酶切割位点,其被试验来自单个复制子Trunc10(T10)的三个有效负载的表达。将复制子和SVV-mCherry模板用NotI限制性酶线性化,并用HiScribe T7 RNA合成试剂盒(NEB)进行体外转录(IVT)。将H1299细胞使用Lipofectamine RNAiMax(Invitrogen)用1 μ g复制子RNA或1 μ g复制子RNA+1 μ g SVVmCherry转染。在转染后48小时,将上清液收集并通过0.45 μ m过滤器过滤,并将RNA

收集在QIAzol试剂(Qiagen)中。将100 μ L过滤的上清液转移到新鲜的H1299细胞单层上,并在感染后48小时收集上清液。用hIL-36 γ 或mIL-2特异性的ELISA(R&D)检查人IL-36 γ 和鼠IL-2的表达。在转染和转衣壳化以后没有检测到hIL-36的表达,且在转染和转衣壳化以后检测到mIL-2的低表达(图20B)。将RNA分离并用正链和负链特异性的taqman测定进行分析(图20C),这表明所有复制子能够合成正链和负链病毒RNA,但是与单个有效负载复制子相比,该能力降低。

[0702] 图21A描绘了三重有效负载复制子T10-mIL2-BiTE-hIL-36 γ 的一种替代设计,其将IL-2编码区置于其它两个有效负载编码区之前,并使用单体HIV-1蛋白酶以及在鼠IL-2、his-标记的hDLL3-BiTE和人IL-36 γ 之间的侧接蛋白酶切割位点。按照与上述相同的方案,对该构建体试验了来自单个复制子的三个有效负载的表达。在转染以后检测到hIL-36的表达,但在转衣壳化(TE)以后其表达水平降低。在裂解物中在转染和转衣壳化以后检测到mIL-2的低表达,但它不分泌到上清液中(图21B)。将RNA分离并用正链和负链特异性的taqman测定进行分析(图21C),这表明所有复制子能够合成正链和负链病毒RNA。

[0703] 图22A描绘了三重有效负载复制子T10-mIL2-hIL-36 γ -BiTE的另一种设计,其将hDLL3-BiTE放置为最后的有效负载,并且包含单体HIV-1蛋白酶以及在鼠IL-2、人IL-36 γ 和his-标记的hDLL3-BiTE之间的侧接蛋白酶切割位点。按照与上述相同的方案,对该构建体试验了来自单个复制子的三个有效负载的表达。将RNA分离并用正链和负链特异性的taqman测定进行分析(图22B),这表明所有复制子能够合成正链和负链病毒RNA。在转染以后检测到hIL-36和mIL-2的表达,但在转衣壳化以后未检测到,并且在裂解物中检测到相对于上清液更高的mIL-2表达(图22C)。总之,结果表明,从三重有效负载复制子T10-mIL2-hIL36-BiTE BiTE,可以在转染以后在上清液和裂解物中检测到低水平的hIL-36和mIL-2表达,但在转衣壳化以后未检测到,并且正链和负链合成略低于T10-eGFP。

[0704] 实施例18:使用SVV衍生出的RNA复制子的有效负载表达的体内研究

[0705] 在动物模型中试验了使用SVV衍生出的复制子的有效负载表达。

[0706] 将NCI-H69细胞(8×10^6 个细胞/0.1mL在无血清PBS和Matrigel®的1:1混合物中)皮下地植入无胸腺裸雌性小鼠的右肋腹。当中位肿瘤大小达到大约150mm³(120-180mm³范围)时,将小鼠分组为每个治疗组3只小鼠的组。在一个治疗组中,将小鼠经由肿瘤内施用用脂质纳米颗粒(LNP)的混合物治疗,所述脂质纳米颗粒包封野生型SVV RNA病毒基因组(SVV-WT)或SVV-Trunc10-hIL-36 γ RNA复制子(如在实施例8中所述)。在对照组中,将小鼠经由肿瘤内施用用LNP的混合物治疗,所述LNP包封野生型SVV RNA病毒基因组和SVV-阴性对照RNA(SVV-Neg)。在定量施用后48小时、72小时和6天以后收集肿瘤样品,粉碎样品组织,并制备肿瘤裂解物。通过ELISA确定IL-36 γ 表达水平。结果显示在图23A中。在定量施用后48和72小时在肿瘤样品中检测到人IL-36 γ 的表达。

[0707] 在另一组实验中,将NCI-H446细胞(5×10^6 个细胞/0.1mL在无血清PBS和Matrigel®1:1混合物中)皮下地植入无胸腺裸雌性小鼠的右肋腹。当中位肿瘤大小达到大约150mm³(120-180mm³范围)时,将小鼠分组为每个治疗组3只小鼠的组。在一个治疗组中,将小鼠经由肿瘤内施用用脂质纳米颗粒(LNP)的混合物治疗,所述脂质纳米颗粒包封野生型SVV RNA病毒基因组(SVV-WT)和编码人IL-36 γ (R-IL36g)的SVV-复制子RNA。在对照组中,将小鼠经由肿瘤内施用用LNP的混合物治疗,所述LNP包封野生型SVV RNA病毒基因组和

SVV-阴性对照RNA (SVV-Neg)。在定量施用后48小时、72小时和7天以后收集肿瘤样品,粉碎样品组织,并制备肿瘤裂解物。通过ELISA确定IL-36 γ 表达水平。结果显示在图23B中。在定量施用后48和72小时在肿瘤样品中检测到人IL-36 γ 的表达。

[0708] 实施例19:柯萨奇病毒A21复制子的构建和来自它的有效负载表达

[0709] 如在图24中所示,通过除去VP结构蛋白 (VP1、VP2、VP3) 并用侧翼为2A蛋白酶位点的荧光蛋白mCherry ORF替换它们,产生CVA21-复制子 (SEQ ID NO:62)。使用根据SEQ ID NO:61的DNA载体模板,可以产生复制子。

[0710] 试验了包含mCherry有效负载的CVA21-复制子的有效负载表达。将六孔板中的 1×10^5 个NCI-H1299细胞使用RNAiMax试剂用500ng单独GFP mRNA (转染对照)、与CVA21-WT RNA等摩尔比 (对照2) 或与CVA21-复制子RNA等摩尔比转染 (图25A)。转染对照显示H1299细胞的最大转染效率。对照2显示,GFP信号被CVA21-mRNA转染部分抑制。CVA21-复制子显示出自始至终与转染对照匹配的mCherry信号,表明非常有效的转染和高表达。因此,CVA21复制子RNA能够在NCI-H1299细胞中表达有效负载蛋白。

[0711] 接下来,进行实验以确定CVA21 mCherry复制子是否可以在有WT CVA21病毒存在下转衣壳化。将六孔板中的 1×10^5 个NCI-H1299细胞使用RNAiMax试剂用500ng单独CVA21-复制子RNA (阴性对照) 或用500ng CVA21-WT RNA转染。在转染以后48小时,将上清液收集,离心,通过45 μ M过滤,并然后将100 μ L用于感染新的12孔板孔的 (1×10^5 个细胞) H1299细胞。在用复制子:WT病毒上清液感染的孔中观察到强感染和mCherry信号,表明mCherry复制子被WT-RNA产生的衣壳成功衣壳化,而缺乏CVA21-WT的阴性对照没有显示mCherry信号 (图25B)。总之,这些结果证实,在有野生型CVA21病毒存在下,携带有效负载的CVA21复制子可以成功地转衣壳化。

[0712] 实施例20:包含SVV衍生出的重组RNA复制子和编码SVV病毒基因组的RNA分子的脂质纳米颗粒用于肺癌治疗的体内效力

[0713] 构建了各种塞内卡谷病毒 (SVV) 衍生出的重组RNA复制子。这些重组RNA复制子包含编码一种或多种免疫调节蛋白 (例如,抗-DLL3双特异性的T-细胞接合剂 (BiTE)) 的异源多核苷酸。这些重组RNA复制子中的一些进一步包含一种或多种细胞因子 (例如,IL-2、IL-12、IL-36 γ) 和/或一种或多种趋化因子 (例如,CCL21、CCL4) 的编码区。所述SVV衍生出的RNA复制子中的一些包含根据下述表18的一个或多个有效负载分子的编码区:

[0714] 表18.SVV衍生出的复制子的有效负载分子

[0715]

SVV 衍生出的复制	有效负载分子

[0716]	子	
	复制子构建体#A1:	抗-DLL3BiTE, IL-2
	复制子构建体#A2:	抗-DLL3BiTE, IL-12
	复制子构建体#A3:	抗-DLL3BiTE, IL-36 γ
	复制子构建体#A4:	抗-DLL3BiTE, CCL21
	复制子构建体#A5:	抗-DLL3BiTE, CCL4
	复制子构建体#A6:	抗-DLL3BiTE, IL-2, IL-12
	复制子构建体#A7:	抗-DLL3BiTE, IL-2, IL-36 γ
	复制子构建体#A8:	抗-DLL3BiTE, IL-2, CCL21
	复制子构建体#A9:	抗-DLL3BiTE, IL-2, CCL4
	复制子构建体#A10:	抗-DLL3BiTE, IL-12, IL-36 γ
	复制子构建体#A11:	抗-DLL3BiTE, IL-12, CCL21
	复制子构建体#A12:	抗-DLL3BiTE, IL-12, CCL4
	复制子构建体#A13:	抗-DLL3BiTE, IL-36 γ , CCL21
	复制子构建体#A14:	抗-DLL3BiTE, IL-36 γ , CCL4
	复制子构建体#A15:	抗-DLL3BiTE, CCL21, CCL4

[0717] 对于每种SVV衍生出的复制子,制备了包含SVV衍生出的RNA复制子和编码SVV病毒基因组的RNA分子的脂质纳米颗粒。进行动物实验以评价这些脂质纳米颗粒在体内抑制肺肿瘤生长的效力,将其与包含编码SVV病毒基因组的RNA分子、但没有RNA复制子的脂质纳米颗粒的效力进行对比。

[0718] 简而言之,在第1、2和3天给8-周龄NSG小鼠注射人PBMC。在第10天,将H1299-DLL3细胞(5×10^6 个细胞/0.1mL在无血清PBS和Matrigel®的1:1混合物中)皮下地植入PBMC-人源化的小鼠的右肋腹。当中位肿瘤大小是大约 150mm^3 ($120\text{-}180\text{mm}^3$ 范围)时,将小鼠分组为每个治疗组8-10只小鼠的组。用含有编码SVV病毒基因组的RNA分子和特定SVV衍生出的RNA复制子的LNP治疗小鼠(通过静脉内和/或肿瘤内施用)。在对照组中,用含有编码SVV病毒基因组的RNA分子的LNP治疗小鼠。每周测量肿瘤体积2次以评估每个治疗组的效力。

[0719] 实施例21:包含CVA21衍生出的重组RNA复制子和编码CVA21病毒基因组的RNA分子的脂质纳米颗粒用于黑色素瘤治疗的体内效力

[0720] 构建了各种柯萨奇病毒A21 (CVA21) 衍生出的重组RNA复制子。这些重组RNA复制子包含编码一种或多种免疫调节蛋白(例如,抗-DLL3双特异性的T-细胞接合剂(BiTE))的异源多核苷酸。这些重组RNA复制子中的一些进一步包含一种或多种细胞因子(例如,IL-2、IL-12、IL-36 γ)和/或一种或多种趋化因子(例如,CCL21、CCL4)的编码区。CVA21衍生出的RNA复制子中的一些包含根据下述表19的一个或多个有效负载分子的编码区:

[0721] 表19.CVA21衍生出的复制子的有效负载分子

CVA21 衍生出的复制子	有效负载分子
复制子构建体#C1:	抗-DLL3BiTE, IL-2
复制子构建体#C2:	抗-DLL3BiTE, IL-12
复制子构建体#C3:	抗-DLL3BiTE, IL-36 γ
复制子构建体#C4:	抗-DLL3BiTE, CCL21
复制子构建体#C5:	抗-DLL3BiTE, CCL4
复制子构建体#C6:	抗-DLL3BiTE, IL-2, IL-12
[0722]	复制子构建体#C7: 抗-DLL3BiTE, IL-2, IL-36 γ
复制子构建体#C8:	抗-DLL3BiTE, IL-2, CCL21
复制子构建体#C9:	抗-DLL3BiTE, IL-2, CCL4
复制子构建体#C10:	抗-DLL3BiTE, IL-12, IL-36 γ
复制子构建体#C11:	抗-DLL3BiTE, IL-12, CCL21
复制子构建体#C12:	抗-DLL3BiTE, IL-12, CCL4
复制子构建体#C13:	抗-DLL3BiTE, IL-36 γ , CCL21
复制子构建体#C14:	抗-DLL3BiTE, IL-36 γ , CCL4
复制子构建体#C15:	抗-DLL3BiTE, CCL21, CCL4

[0723] 对于每种CVA21衍生出的复制子,制备了包含CVA21衍生出的RNA复制子和编码CVA21病毒基因组的RNA分子的脂质纳米颗粒。进行动物实验以评价这些脂质纳米颗粒在体内抑制黑色素瘤肿瘤生长的效力,将其与包含编码CVA21病毒基因组的RNA分子、但没有RNA复制子的脂质纳米颗粒的效力进行对比。

[0724] 简而言之,在第1、2和3天给8-周龄NSG小鼠注射人PBMC。在第10天,将SK-MEL-28-EpCAM细胞 (5×10^6 个细胞/0.1mL在无血清PBS和 **Matrigel®** 的1:1混合物中)皮下地植入PBMC-人源化的小鼠的右胁腹。当中位肿瘤大小是大约150mm³ (120-180mm³范围)时,将小鼠分组为每个治疗组8-10只小鼠的组。用含有编码CVA21病毒基因组的RNA分子和特定CVA21衍生出的RNA复制子的LNP治疗小鼠(通过静脉内和/或肿瘤内施用)。在对照组中,用含有编码CVA21病毒基因组的RNA分子的LNP治疗小鼠。每周测量肿瘤体积2次以评估每个治疗组的效力。

[0725] 通过引用并入

[0726] 本文引用的所有参考文献、文章、出版物、专利、专利公开和专利申请通过引用整体并入用于所有目的。但是,本文中引用的任何参考文献、文章、出版物、专利、专利公开和专利申请的提及没有且不应视作承认或以任何形式暗示:它们在世界上的任何国家构成有效的现有技术或形成普通一般知识的一部分。

[0727] 尽管本文已经显示和描述了本公开内容的优选实施方案;本领域技术人员将显而易见,这样的实施方案仅作为示例提供。在不背离本公开内容的前提下,本领域技术人员现在将想到许多变化、改变和替换。应当理解,在实施本公开内容时可以采用对本文描述的本

公开内容的实施方案的各种替代方案。以下权利要求旨在限定本公开内容的范围,并且由此覆盖在这些权利要求及其等同方案的范围内的方法和结构。

序列表

<110> 昂克诺斯公司 (Oncorus, Inc.)

<120> 包封的RNA复制子和使用方法

<130> ONCR-019/01W0 324865-2246

<150> US 63/032,000

<151> 2020-05-29

<160> 149

<170> PatentIn 3.5版

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<213> 塞内卡病毒塞内卡谷病毒

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1 5

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35 40 45
Trp Leu Leu Gly Thr Ala Gln Gly Val Thr Met Leu Phe Ile Val Thr
50 55 60
Ala Leu Leu Cys Cys Gly Leu Cys Asn Gly
65 70

<210> 78

<211> 6

<212> PRT

<213> 人工序列

<220>

<223> HIV蛋白酶位点

<400> 78

Ile Phe Leu Glu Thr Ser
1 5

<210> 79

<211> 9

<212> PRT

<213> 人工序列

<220>

<223> HIV蛋白酶位点

<400> 79

Gly Ser Gly Ile Phe Leu Glu Thr Ser

1 5

<210> 80

<211> 98

<212> PRT

<213> 人工序列

<220>

<223> HIV蛋白酶

<400> 80

Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly Gly

1 5 10 15

Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val Leu

20 25 30

Glu Glu Met Ser Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly Gly

35 40 45

Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Leu Ile Glu

50 55 60

Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr Pro

65 70 75 80

Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr Leu

85 90 95

Asn Phe

<210> 81

<211> 127

<212> PRT

<213> 智人

<400> 81

Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gln Pro Trp Glu His Val

1 5 10 15

Asn Ala Ile Gln Glu Ala Arg Arg Leu Leu Asn Leu Ser Arg Asp Thr

20 25 30

Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp

35 40 45

Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys Gln

50 55 60

Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met Met

65 70 75 80

Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys

85 90 95

Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp
 100 105 110
 Phe Leu Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val Gln Glu
 115 120 125
 <210> 82
 <211> 133
 <212> PRT
 <213> 智人
 <400> 82
 Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
 1 5 10 15
 Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
 20 25 30
 Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
 35 40 45
 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
 50 55 60
 Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
 65 70 75 80
 Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
 85 90 95
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
 100 105 110
 Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
 115 120 125
 Ile Ser Thr Leu Thr
 130
 <210> 83
 <211> 135
 <212> PRT
 <213> 小家鼠
 <400> 83
 Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln His Leu Glu Gln
 1 5 10 15
 Leu Leu Met Asp Leu Gln Glu Leu Leu Ser Arg Met Glu Asn Tyr Arg
 20 25 30
 Asn Leu Lys Leu Pro Arg Met Leu Thr Phe Lys Phe Tyr Leu Pro Lys
 35 40 45
 Gln Ala Thr Glu Leu Lys Asp Leu Gln Cys Leu Glu Asp Glu Leu Gly

50	55	60															
Pro	Leu	Arg	His	Val	Leu	Asp	Leu	Thr	Gln	Ser	Lys	Ser	Phe	Gln	Leu		
65					70					75					80		
Glu	Asp	Ala	Glu	Asn	Phe	Ile	Ser	Asn	Ile	Arg	Val	Thr	Val	Val	Lys		
				85					90						95		
Leu	Lys	Gly	Ser	Asp	Asn	Thr	Phe	Glu	Cys	Gln	Phe	Asp	Asp	Glu	Ser		
			100					105						110			
Ala	Thr	Val	Val	Asp	Phe	Leu	Arg	Arg	Trp	Ile	Ala	Phe	Cys	Gln	Ser		
		115					120							125			
Ile	Ile	Ser	Thr	Ser	Pro	Gln											
130						135											
<210>	84																
<211>	306																
<212>	PRT																
<213>	智人																
<400>	84																
Ile	Trp	Glu	Leu	Lys	Lys	Asp	Val	Tyr	Val	Val	Glu	Leu	Asp	Trp	Tyr		
1				5				10					15				
Pro	Asp	Ala	Pro	Gly	Glu	Met	Val	Val	Leu	Thr	Cys	Asp	Thr	Pro	Glu		
			20					25					30				
Glu	Asp	Gly	Ile	Thr	Trp	Thr	Leu	Asp	Gln	Ser	Ser	Glu	Val	Leu	Gly		
		35					40					45					
Ser	Gly	Lys	Thr	Leu	Thr	Ile	Gln	Val	Lys	Glu	Phe	Gly	Asp	Ala	Gly		
50						55				60							
Gln	Tyr	Thr	Cys	His	Lys	Gly	Gly	Glu	Val	Leu	Ser	His	Ser	Leu	Leu		
65				70						75					80		
Leu	Leu	His	Lys	Lys	Glu	Asp	Gly	Ile	Trp	Ser	Thr	Asp	Ile	Leu	Lys		
				85					90						95		
Asp	Gln	Lys	Glu	Pro	Lys	Asn	Lys	Thr	Phe	Leu	Arg	Cys	Glu	Ala	Lys		
			100					105						110			
Asn	Tyr	Ser	Gly	Arg	Phe	Thr	Cys	Trp	Trp	Leu	Thr	Thr	Ile	Ser	Thr		
		115					120						125				
Asp	Leu	Thr	Phe	Ser	Val	Lys	Ser	Ser	Arg	Gly	Ser	Ser	Asp	Pro	Gln		
130						135							140				
Gly	Val	Thr	Cys	Gly	Ala	Ala	Thr	Leu	Ser	Ala	Glu	Arg	Val	Arg	Gly		
145				150						155					160		
Asp	Asn	Lys	Glu	Tyr	Glu	Tyr	Ser	Val	Glu	Cys	Gln	Glu	Asp	Ser	Ala		
				165					170					175			
Cys	Pro	Ala	Ala	Glu	Glu	Ser	Leu	Pro	Ile	Glu	Val	Met	Val	Asp	Ala		

374

130	135	140
Met Gln Ala Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser Ser		
145	150	155
Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu		160
	165	170
Leu His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met Ser		175
	180	185
Tyr Leu Asn Ala Ser		190
195		
<210> 86		
<211> 170		
<212> PRT		
<213> 智人		
<400> 86		
Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln Cys Gln Gln		
1	5	10
Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His Pro Leu Val		15
	20	25
Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr Thr Asn Asp		30
	35	40
Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln Gly Leu Arg		45
	50	55
Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly Leu Ile Phe		60
65	70	75
Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu Pro Ser Leu		80
	85	90
Leu Pro Asp Ser Pro Val Gly Gln Leu His Ala Ser Leu Leu Gly Leu		95
	100	105
Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr Gln Gln Ile		110
	115	120
Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu Leu Arg Phe		125
	130	135
Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala Ala Arg Val		140
145	150	155
Phe Ala His Gly Ala Ala Thr Leu Ser Pro		160
	165	170
<210> 87		
<211> 157		
<212> PRT		

<213> 智人

<400> 87

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

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<210> 88

<211> 152

<212> PRT

<213> 智人

<400> 88

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

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Val Lys Pro Phe Leu Phe Tyr Arg Ala Lys Thr Gly Arg Thr Ser Thr
 100 105 110
 Leu Glu Ser Val Ala Phe Pro Asp Trp Phe Ile Ala Ser Ser Lys Arg
 115 120 125
 Asp Gln Pro Ile Ile Leu Thr Ser Glu Leu Gly Lys Ser Tyr Asn Thr
 130 135 140
 Ala Phe Glu Leu Asn Ile Asn Asp
 145 150

<210> 89

<211> 152

<212> PRT

<213> 小家鼠

<400> 89

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

<210> 90

<211> 77

<212> PRT

<213> 智人

<400> 90

Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys Ile Ser Ile Ser Asn

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

<210> 91

<211> 77

<212> PRT

<213> 小家鼠

<400> 91

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

<210> 92

<211> 92

<212> PRT

<213> 智人

<400> 92

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

Trp Val Gln Glu Tyr Val Tyr Asp Leu Glu Leu Asn
85 90

<210> 93

<211> 68

<212> PRT

<213> 智人

<400> 93

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

<210> 94

<211> 111

<212> PRT

<213> 智人

<400> 94

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

<210> 95

<211> 346

<212> PRT

<213> 人工序列

<220>

<223> 抗-PD1-VHH-Fc (hIgG4)

<400> 95

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

275	280	285
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe		
290	295	300
Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn		
305	310	315
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr		
325	330	335
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
340	345	
<210> 96		
<211> 592		
<212> PRT		
<213> 智人		
<400> 96		
Ala Gly Val Phe Glu Leu Gln Ile His Ser Phe Gly Pro Gly Pro Gly		
1	5	10
Pro Gly Ala Pro Arg Ser Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu		
20	25	30
Phe Phe Arg Val Cys Leu Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu		
35	40	45
Ser Pro Cys Ala Leu Gly Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr		
50	55	60
Thr Glu Gln Pro Gly Ala Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly		
65	70	75
Leu Leu Gln Val Pro Phe Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe		
85	90	95
Ile Ile Glu Thr Trp Arg Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro		
100	105	110
Ala Trp Ser Leu Leu Ala Arg Val Ala Gly Arg Arg Arg Leu Ala Ala		
115	120	125
Gly Gly Pro Trp Ala Arg Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu		
130	135	140
Arg Phe Ser Tyr Arg Ala Arg Cys Glu Pro Pro Ala Val Gly Thr Ala		
145	150	155
Cys Thr Arg Leu Cys Arg Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro		
165	170	175
Gly Leu Arg Pro Cys Ala Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu		
180	185	190
Val Cys Arg Ala Gly Cys Ser Pro Glu His Gly Phe Cys Glu Gln Pro		

195	200	205
Gly Glu Cys Arg Cys Leu Glu Gly Trp Thr Gly Pro Leu Cys Thr Val		
210	215	220
Pro Val Ser Thr Ser Ser Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala		
225	230	235
Thr Thr Gly Cys Leu Val Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro		
245	250	255
Cys Ala Asn Gly Gly Ser Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys		
260	265	270
Thr Cys Pro Arg Gly Phe Tyr Gly Leu Arg Cys Glu Val Ser Gly Val		
275	280	285
Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly Leu Cys Val Gly Gly		
290	295	300
Ala Asp Pro Asp Ser Ala Tyr Ile Cys His Cys Pro Pro Gly Phe Gln		
305	310	315
Gly Ser Asn Cys Glu Lys Arg Val Asp Arg Cys Ser Leu Gln Pro Cys		
325	330	335
Arg Asn Gly Gly Leu Cys Leu Asp Leu Gly His Ala Leu Arg Cys Arg		
340	345	350
Cys Arg Ala Gly Phe Ala Gly Pro Arg Cys Glu His Asp Leu Asp Asp		
355	360	365
Cys Ala Gly Arg Ala Cys Ala Asn Gly Gly Thr Cys Val Glu Gly Gly		
370	375	380
Gly Ala His Arg Cys Ser Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys		
385	390	395
Arg Glu Arg Ala Asp Pro Cys Ala Ala Arg Pro Cys Ala His Gly Gly		
405	410	415
Arg Cys Tyr Ala His Phe Ser Gly Leu Val Cys Ala Cys Ala Pro Gly		
420	425	430
Tyr Met Gly Ala Arg Cys Glu Phe Pro Val His Pro Asp Gly Ala Ser		
435	440	445
Ala Leu Pro Ala Ala Pro Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg		
450	455	460
Tyr Leu Leu Pro Pro Ala Leu Gly Leu Leu Val Ala Ala Gly Val Ala		
465	470	475
Gly Ala Ala Leu Leu Leu Val His Val Arg Arg Arg Gly His Ser Gln		
485	490	495
Asp Ala Gly Ser Arg Leu Leu Ala Gly Thr Pro Glu Pro Ser Val His		
500	505	510

Ala Leu Pro Asp Ala Leu Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly
515 520 525
Asp Gly Pro Ser Ser Ser Val Asp Trp Asn Arg Pro Glu Asp Val Asp
530 535 540
Pro Gln Gly Ile Tyr Val Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu
545 550 555 560
Val Ala Thr Pro Leu Phe Pro Pro Leu His Thr Gly Arg Ala Gly Gln
565 570 575
Arg Gln His Leu Leu Phe Pro Tyr Pro Ser Ser Ile Leu Ser Val Lys
580 585 590

<210> 97

<211> 117

<212> PRT

<213> 人工序列

<220>

<223> 抗-FAP重链可变区

<400> 97

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

<210> 98

<211> 107

<212> PRT

<213> 人工序列

<220>

<223> 抗-FAP轻链可变区

<400> 98

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

<210> 99

<211> 116

<212> PRT

<213> 人工序列

<220>

<223> CD3重链可变区

<400> 99

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

<210> 100

<211> 108

<212> PRT

<213> 人工序列

<220>

<223> CD3轻链可变区

<400> 100

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

<210> 101

<211> 498

<212> PRT

<213> 人工序列

<220>

<223> 博纳吐单抗

<400> 101

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

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

	405		410		415
Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser Gly					
	420		425		430
Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly					
	435		440		445
Val Pro Tyr Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu					
	450		455		460
Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln					
465		470		475	480
Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu					
	485		490		495
Leu Lys					
<210> 102					
<211> 496					
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<400> 102					
Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly					
1	5		10		15
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser					
	20		25		30
Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln					
	35		40		45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val					
	50		55		60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr					
65		70		75	80
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn					
	85		90		95
Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile					
	100		105		110
Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser					
	115		120		125
Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly					
	130		135		140
Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn					
145		150		155	160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp		
165	170	175
Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys		
180	185	190
Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala		
195	200	205
Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe		
210	215	220
Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln		
225	230	235
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Val Gln		
245	250	255
Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys		
260	265	270
Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His		
275	280	285
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile		
290	295	300
Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg		
305	310	315
Phe Thr Ile Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu		
325	330	335
Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Tyr		
340	345	350
Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val		
355	360	365
Thr Val Ser Ser Gly Glu Gly Thr Ser Thr Gly Ser Gly Gly Ser Gly		
370	375	380
Gly Ser Gly Gly Ala Asp Asp Ile Val Leu Thr Gln Ser Pro Ala Thr		
385	390	395
Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser		
405	410	415
Gln Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala		
420	425	430
Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser Gly Val Pro		
435	440	445
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile		
450	455	460
Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp		

465	470	475	480
Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys			
	485	490	495
<210> 103			
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<223> 帕妥昔单抗			
<400> 103			
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr			
	20	25	30
Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
	35	40	45
Ala Ile Ile Ser Asp Gly Gly Tyr Tyr Thr Tyr Tyr Ser Asp Ile Ile			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr			
65	70	75	80
Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys			
	85	90	95
Ala Arg Gly Phe Pro Leu Leu Arg His Gly Ala Met Asp Tyr Trp Gly			
	100	105	110
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly			
	115	120	125
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro			
	130	135	140
Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys			
145	150	155	160
Ala Ser Gln Asn Val Asp Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro			
	165	170	175
Gly Gln Ala Pro Lys Ser Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser			
	180	185	190
Asp Val Pro Ser Arg Phe Ser Gly Ser Ala Ser Gly Thr Asp Phe Thr			
	195	200	205
Leu Thr Ile Ser Ser Val Gln Ser Glu Asp Phe Ala Thr Tyr Tyr Cys			
	210	215	220
Gln Gln Tyr Asp Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu			

225	230	235	240
Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser			
	245	250	255
Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala			
	260	265	270
Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln			
	275	280	285
Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr			
	290	295	300
Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr			
305	310	315	320
Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn			
	325	330	335
Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn			
	340	345	350
Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr			
	355	360	365
Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser			
	370	375	380
Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr			
385	390	395	400
Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly			
	405	410	415
Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly			
	420	425	430
Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly			
	435	440	445
Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu			
	450	455	460
Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val			
465	470	475	480
Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr			
	485	490	495
Val Leu			
<210> 104			
<211> 505			
<212> PRT			
<213> 人工序列			
<220>			

290	295	300
Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp		
305	310	315 320
Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr		
325	330	335
Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr		
340	345	350
Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp		
355	360	365
Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly		
370	375	380
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val		
385	390	395 400
Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu		
405	410	415
Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn		
420	425	430
Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly		
435	440	445
Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu		
450	455	460
Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp		
465	470	475 480
Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe		
485	490	495
Gly Gly Gly Thr Lys Leu Thr Val Leu		
500	505	
<210> 105		
<211> 527		
<212> PRT		
<213> 人工序列		
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<223> COVA420重链		
<400> 105		
Gly Val Thr Leu Phe Val Ala Leu Tyr Asp Tyr Thr Ser Tyr Asn Thr		
1	5	10 15
Arg Asp Leu Ser Phe His Lys Gly Glu Lys Phe Gln Ile Leu Arg Met		
20	25	30
Glu Asp Gly Val Trp Trp Glu Ala Arg Ser Leu Thr Thr Gly Glu Thr		

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

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys															
355								360						365	
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser															
370								375						380	
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys															
385								390						395	400
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile															
														410	415
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro															
														420	430
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu															
														435	445
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn															
														450	460
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser															
465								470						475	480
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg															
														485	495
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu															
														500	510
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys															
														515	525
<210> 106															
<211> 213															
<212> PRT															
<213> 人工序列															
<220>															
<223> COVA420轻链															
<400> 106															
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly															
1														5	10 15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met															
														20	25 30
Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr															
														35	40 45
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser															
														50	55 60
Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu															
65														70	75 80

Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr			
	85	90	95
Phe Gly Gln Gly Thr Lys Leu Gln Ile Thr Arg Thr Val Ala Ala Pro			
	100	105	110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr			
	115	120	125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys			
	130	135	140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu			
145	150	155	160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser			
	165	170	175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala			
	180	185	190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe			
	195	200	205
Asn Arg Gly Glu Cys			
210			
<210> 107			
<211> 142			
<212> PRT			
<213> 智人			
<400> 107			
Met Gly Ala Pro Thr Leu Pro Pro Ala Trp Gln Pro Phe Leu Lys Asp			
1	5	10	15
His Arg Ile Ser Thr Phe Lys Asn Trp Pro Phe Leu Glu Gly Cys Ala			
	20	25	30
Cys Thr Pro Glu Arg Met Ala Glu Ala Gly Phe Ile His Cys Pro Thr			
	35	40	45
Glu Asn Glu Pro Asp Leu Ala Gln Cys Phe Phe Cys Phe Lys Glu Leu			
	50	55	60
Glu Gly Trp Glu Pro Asp Asp Asp Pro Ile Glu Glu His Lys Lys His			
65	70	75	80
Ser Ser Gly Cys Ala Phe Leu Ser Val Lys Lys Gln Phe Glu Glu Leu			
	85	90	95
Thr Leu Gly Glu Phe Leu Lys Leu Asp Arg Glu Arg Ala Lys Asn Lys			
	100	105	110
Ile Ala Lys Glu Thr Asn Asn Lys Lys Lys Glu Phe Glu Glu Thr Ala			
	115	120	125

Lys Lys Val Arg Arg Ala Ile Glu Gln Leu Ala Ala Met Asp
130 135 140

<210> 108

<211> 61

<212> RNA

<213> 未知

<220>

<223> 最小锤头核酶 (HHR)

<400> 108

guaccuuauC aaacugauga gucccugagg acgaaacgag uaagcucguc uuugaaaugg 60
g 61

<210> 109

<211> 75

<212> RNA

<213> 未知

<220>

<223> 具有稳定化的茎I (STBL) 的核酶的结构模型

<400> 109

ugguaccuua ccauuucaaa cugaugaguc cgugaggacg aaacgaguaa gcucgucuuu 60
gaaaugggggg gcugg 75

<210> 110

<211> 65

<212> RNA

<213> 未知

<220>

<223> 野生型手枪核酶

<220>

<221> 杂项特征

<222> (2) .. (2)

<223> n是任何核糖核苷酸

<220>

<221> 杂项特征

<222> (6) .. (6)

<223> n是任何核糖核苷酸

<220>

<221> 杂项特征

<222> (8) .. (9)

<223> n是任何核糖核苷酸

<220>

<221> 杂项特征
<222> (15) .. (15)
<223> n是任何核糖核苷酸
<220>
<221> 杂项特征
<222> (17) .. (17)
<223> n是任何核糖核苷酸
<220>
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<222> (25) .. (25)
<223> n是任何核糖核苷酸
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<222> (27) .. (27)
<223> n是任何核糖核苷酸
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<222> (35) .. (36)
<223> n是任何核糖核苷酸
<220>
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<222> (44) .. (57)
<223> n是任何核糖核苷酸
<220>
<221> 杂项特征
<222> (48) .. (53)
<223> 可以存在或至多6个残基可以不存在
<220>
<221> 杂项特征
<222> (62) .. (62)
<223> n是任何核糖核苷酸
<220>
<221> 杂项特征
<222> (64) .. (65)
<223> n是任何核糖核苷酸
<400> 110
rnucgnynnr gcganynuua ayarnynuua rgcynnrregc guynnnnnnnn nnnnnnnrrgg 60
unrrnn 65
<210> 111

<211> 68

<212> RNA

<213> 未知

<220>

<223> 野生型手枪核酶

<400> 111

ggacucgucu gagcgaguau aaacaggguca uuaagcucag agcguucacc gggguucggug 60
agguuggc 68

<210> 112

<211> 72

<212> RNA

<213> 多粘类芽孢杆菌

<400> 112

ggacucgucu gagcgaguau aaacaggguca uuaagcucag agcguucacc ggggaaauuc 60
ggugagguug gc 72

<210> 113

<211> 138

<212> PRT

<213> 智人

<400> 113

Gln Asp Pro Tyr Val Lys Glu Ala Glu Asn Leu Lys Lys Tyr Phe Asn
1 5 10 15

Ala Gly His Ser Asp Val Ala Asp Asn Gly Thr Leu Phe Leu Gly Ile
20 25 30

Leu Lys Asn Trp Lys Glu Glu Ser Asp Arg Lys Ile Met Gln Ser Gln
35 40 45

Ile Val Ser Phe Tyr Phe Lys Leu Phe Lys Asn Phe Lys Asp Asp Gln
50 55 60

Ser Ile Gln Lys Ser Val Glu Thr Ile Lys Glu Asp Met Asn Val Lys
65 70 75 80

Phe Phe Asn Ser Asn Lys Lys Lys Arg Asp Asp Phe Glu Lys Leu Thr
85 90 95

Asn Tyr Ser Val Thr Asp Leu Asn Val Gln Arg Lys Ala Ile His Glu
100 105 110

Leu Ile Gln Val Met Ala Glu Leu Ser Pro Ala Ala Lys Thr Gly Lys
115 120 125

Arg Lys Arg Ser Gln Met Leu Phe Arg Gly
130 135

<210> 114

<211> 114

<212> PRT

<213> 智人

<400> 114

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

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Thr Ser

<210> 115

<211> 237

<212> PRT

<213> 智人

<400> 115

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

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115	120	125
Ser Thr Gly Thr Thr Glu Ile	Ser Ser His Glu	Ser Ser His Gly Thr
130	135	140
Pro Ser Gln Thr Thr Ala Lys	Asn Trp Glu Leu Thr Ala	Ser Ala Ser
145	150	155
His Gln Pro Pro Gly Val Tyr	Pro Gln Gly His Ser Asp	Thr Thr Val
165	170	175
Ala Ile Ser Thr Ser Thr Val	Leu Leu Cys Gly Leu Ser	Ala Val Ser
180	185	190
Leu Leu Ala Cys Tyr Leu Lys	Ser Arg Gln Thr Pro Pro	Leu Ala Ser
195	200	205
Val Glu Met Glu Ala Met Glu	Ala Leu Pro Val Thr Trp	Gly Thr Ser
210	215	220
Ser Arg Asp Glu Asp Leu Glu	Asn Cys Ser His His	Leu
225	230	235
<210> 116		
<211> 525		
<212> PRT		
<213> 智人		
<400> 116		
Ala Val Asn Gly Thr Ser Gln	Phe Thr Cys Phe Tyr Asn	Ser Arg Ala
1	5	10
Asn Ile Ser Cys Val Trp Ser	Gln Asp Gly Ala Leu Gln	Asp Thr Ser
20	25	30
Cys Gln Val His Ala Trp Pro	Asp Arg Arg Arg Trp Asn	Gln Thr Cys
35	40	45
Glu Leu Leu Pro Val Ser Gln	Ala Ser Trp Ala Cys Asn	Leu Ile Leu
50	55	60
Gly Ala Pro Asp Ser Gln Lys	Leu Thr Thr Val Asp Ile	Val Thr Leu
65	70	75
Arg Val Leu Cys Arg Glu Gly	Val Arg Trp Arg Val Met	Ala Ile Gln
85	90	95
Asp Phe Lys Pro Phe Glu Asn	Leu Arg Leu Met Ala Pro	Ile Ser Leu
100	105	110
Gln Val Val His Val Glu Thr	His Arg Cys Asn Ile Ser	Trp Glu Ile
115	120	125
Ser Gln Ala Ser His Tyr Phe	Glu Arg His Leu Glu Phe	Glu Ala Arg
130	135	140
Thr Leu Ser Pro Gly His Thr	Trp Glu Glu Ala Pro Leu	Leu Thr Leu

145	150	155	160
Lys Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr			
	165	170	175
Gln Tyr Glu Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr			
	180	185	190
Thr Trp Ser Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala			
	195	200	205
Ala Leu Gly Lys Asp Thr Ile Pro Trp Leu Gly His Leu Leu Val Gly			
	210	215	220
Leu Ser Gly Ala Phe Gly Phe Ile Ile Leu Val Tyr Leu Leu Ile Asn			
225	230	235	240
Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val Leu Lys Cys Asn Thr			
	245	250	255
Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser Ser Glu His Gly Gly			
	260	265	270
Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro Ser Ser Ser Phe Ser			
	275	280	285
Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu Glu Val Leu Glu Arg			
	290	295	300
Asp Lys Val Thr Gln Leu Leu Leu Gln Gln Asp Lys Val Pro Glu Pro			
305	310	315	320
Ala Ser Leu Ser Ser Asn His Ser Leu Thr Ser Cys Phe Thr Asn Gln			
	325	330	335
Gly Tyr Phe Phe Phe His Leu Pro Asp Ala Leu Glu Ile Glu Ala Cys			
	340	345	350
Gln Val Tyr Phe Thr Tyr Asp Pro Tyr Ser Glu Glu Asp Pro Asp Glu			
	355	360	365
Gly Val Ala Gly Ala Pro Thr Gly Ser Ser Pro Gln Pro Leu Gln Pro			
	370	375	380
Leu Ser Gly Glu Asp Asp Ala Tyr Cys Thr Phe Pro Ser Arg Asp Asp			
385	390	395	400
Leu Leu Leu Phe Ser Pro Ser Leu Leu Gly Gly Pro Ser Pro Pro Ser			
	405	410	415
Thr Ala Pro Gly Gly Ser Gly Ala Gly Glu Glu Arg Met Pro Pro Ser			
	420	425	430
Leu Gln Glu Arg Val Pro Arg Asp Trp Asp Pro Gln Pro Leu Gly Pro			
	435	440	445
Pro Thr Pro Gly Val Pro Asp Leu Val Asp Phe Gln Pro Pro Pro Glu			
	450	455	460

Leu Val Leu Arg Glu Ala Gly Glu Glu Val Pro Asp Ala Gly Pro Arg
 465 470 475 480
 Glu Gly Val Ser Phe Pro Trp Ser Arg Pro Pro Gly Gln Gly Glu Phe
 485 490 495
 Arg Ala Leu Asn Ala Arg Leu Pro Leu Asn Thr Asp Ala Tyr Leu Ser
 500 505 510
 Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His Leu Val
 515 520 525
 <210> 117
 <211> 266
 <212> PRT
 <213> 智人
 <400> 117
 Met His Val Asn Gly Lys Val Ala Leu Val Thr Gly Ala Ala Gln Gly
 1 5 10 15
 Ile Gly Arg Ala Phe Ala Glu Ala Leu Leu Leu Lys Gly Ala Lys Val
 20 25 30
 Ala Leu Val Asp Trp Asn Leu Glu Ala Gly Val Gln Cys Lys Ala Ala
 35 40 45
 Leu Asp Glu Gln Phe Glu Pro Gln Lys Thr Leu Phe Ile Gln Cys Asp
 50 55 60
 Val Ala Asp Gln Gln Gln Leu Arg Asp Thr Phe Arg Lys Val Val Asp
 65 70 75 80
 His Phe Gly Arg Leu Asp Ile Leu Val Asn Asn Ala Gly Val Asn Asn
 85 90 95
 Glu Lys Asn Trp Glu Lys Thr Leu Gln Ile Asn Leu Val Ser Val Ile
 100 105 110
 Ser Gly Thr Tyr Leu Gly Leu Asp Tyr Met Ser Lys Gln Asn Gly Gly
 115 120 125
 Glu Gly Gly Ile Ile Ile Asn Met Ser Ser Leu Ala Gly Leu Met Pro
 130 135 140
 Val Ala Gln Gln Pro Val Tyr Cys Ala Ser Lys His Gly Ile Val Gly
 145 150 155 160
 Phe Thr Arg Ser Ala Ala Leu Ala Ala Asn Leu Met Asn Ser Gly Val
 165 170 175
 Arg Leu Asn Ala Ile Cys Pro Gly Phe Val Asn Thr Ala Ile Leu Glu
 180 185 190
 Ser Ile Glu Lys Glu Glu Asn Met Gly Gln Tyr Ile Glu Tyr Lys Asp
 195 200 205

His Ile Lys Asp Met Ile Lys Tyr Tyr Gly Ile Leu Asp Pro Pro Leu
 210 215 220
 Ile Ala Asn Gly Leu Ile Thr Leu Ile Glu Asp Asp Ala Leu Asn Gly
 225 230 235 240
 Ala Ile Met Lys Ile Thr Thr Ser Lys Gly Ile His Phe Gln Asp Tyr
 245 250 255
 Asp Thr Thr Pro Phe Gln Ala Lys Thr Gln
 260 265
 <210> 118
 <211> 482
 <212> PRT
 <213> 智人
 <400> 118
 Ile Asp Glu Thr Arg Ala His Leu Leu Leu Lys Glu Lys Met Met Arg
 1 5 10 15
 Leu Gly Gly Arg Leu Val Leu Asn Thr Lys Glu Glu Leu Ala Asn Glu
 20 25 30
 Arg Leu Met Thr Leu Lys Ile Ala Glu Met Lys Glu Ala Met Arg Thr
 35 40 45
 Leu Ile Phe Pro Pro Ser Met His Phe Phe Gln Ala Lys His Leu Ile
 50 55 60
 Glu Arg Ser Gln Val Phe Asn Ile Leu Arg Met Met Pro Lys Gly Ala
 65 70 75 80
 Ala Leu His Leu His Asp Ile Gly Ile Val Thr Met Asp Trp Leu Val
 85 90 95
 Arg Asn Val Thr Tyr Arg Pro His Cys His Ile Cys Phe Thr Pro Arg
 100 105 110
 Gly Ile Met Gln Phe Arg Phe Ala His Pro Thr Pro Arg Pro Ser Glu
 115 120 125
 Lys Cys Ser Lys Trp Ile Leu Leu Glu Asp Tyr Arg Lys Arg Val Gln
 130 135 140
 Asn Val Thr Glu Phe Asp Asp Ser Leu Leu Arg Asn Phe Thr Leu Val
 145 150 155 160
 Thr Gln His Pro Glu Val Ile Tyr Thr Asn Gln Asn Val Val Trp Ser
 165 170 175
 Lys Phe Glu Thr Ile Phe Phe Thr Ile Ser Gly Leu Ile His Tyr Ala
 180 185 190
 Pro Val Phe Arg Asp Tyr Val Phe Arg Ser Met Gln Glu Phe Tyr Glu
 195 200 205

Asp Asn Val Leu Tyr Met Glu Ile Arg Ala Arg Leu Leu Pro Val Tyr			
210	215	220	
Glu Leu Ser Gly Glu His His Asp Glu Glu Trp Ser Val Lys Thr Tyr			
225	230	235	240
Gln Glu Val Ala Gln Lys Phe Val Glu Thr His Pro Glu Phe Ile Gly			
	245	250	255
Ile Lys Ile Ile Tyr Ser Asp His Arg Ser Lys Asp Val Ala Val Ile			
	260	265	270
Ala Glu Ser Ile Arg Met Ala Met Gly Leu Arg Ile Lys Phe Pro Thr			
	275	280	285
Val Val Ala Gly Phe Asp Leu Val Gly His Glu Asp Thr Gly His Ser			
	290	295	300
Leu His Asp Tyr Lys Glu Ala Leu Met Ile Pro Ala Lys Asp Gly Val			
305	310	315	320
Lys Leu Pro Tyr Phe Phe His Ala Gly Glu Thr Asp Trp Gln Gly Thr			
	325	330	335
Ser Ile Asp Arg Asn Ile Leu Asp Ala Leu Met Leu Asn Thr Thr Arg			
	340	345	350
Ile Gly His Gly Phe Ala Leu Ser Lys His Pro Ala Val Arg Thr Tyr			
	355	360	365
Ser Trp Lys Lys Asp Ile Pro Ile Glu Val Cys Pro Ile Ser Asn Gln			
	370	375	380
Val Leu Lys Leu Val Ser Asp Leu Arg Asn His Pro Val Ala Thr Leu			
385	390	395	400
Met Ala Thr Gly His Pro Met Val Ile Ser Ser Asp Asp Pro Ala Met			
	405	410	415
Phe Gly Ala Lys Gly Leu Ser Tyr Asp Phe Tyr Glu Val Phe Met Gly			
	420	425	430
Ile Gly Gly Met Lys Ala Asp Leu Arg Thr Leu Lys Gln Leu Ala Met			
	435	440	445
Asn Ser Ile Lys Tyr Ser Thr Leu Leu Glu Ser Glu Lys Asn Thr Phe			
	450	455	460
Met Glu Ile Trp Lys Lys Arg Trp Asp Lys Phe Ile Ala Asp Val Ala			
465	470	475	480
Thr Lys			
<210> 119			
<211> 414			
<212> PRT			
<213> 智人			

<400> 119

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

Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met Asp			
305	310	315	320
Thr Thr Leu Gly Pro Phe Ile Leu Asn Val Thr Ser Gly Ala Leu Leu			
	325	330	335
Cys Ser Gln Ala Leu Cys Ser Gly His Gly Arg Cys Val Arg Arg Thr			
	340	345	350
Ser His Pro Lys Ala Leu Leu Leu Leu Asn Pro Ala Ser Phe Ser Ile			
	355	360	365
Gln Leu Thr Pro Gly Gly Gly Pro Leu Ser Leu Arg Gly Ala Leu Ser			
	370	375	380
Leu Glu Asp Gln Ala Gln Met Ala Val Glu Phe Lys Cys Arg Cys Tyr			
385	390	395	400
Pro Gly Trp Gln Ala Pro Trp Cys Glu Arg Lys Ser Met Trp			
	405	410	

<210> 120

<211> 428

<212> PRT

<213> 智人

<400> 120

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

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

<210> 121

<211> 471

<212> PRT

<213> 智人

<400> 121

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

305	310	315	320
His His Ser Glu Ala Pro Glu Leu His Gly Lys Ile Arg Ser Ser Asn			
	325	330	335
Phe Leu Val Thr Gln Gly Tyr Gln Val Lys Leu Ala Gly Phe Glu Leu			
	340	345	350
Arg Lys Thr Gln Thr Ser Met Ser Leu Gly Thr Thr Arg Glu Lys Thr			
	355	360	365
Asp Arg Val Lys Ser Thr Ala Tyr Leu Ser Pro Gln Glu Leu Glu Asp			
	370	375	380
Val Phe Tyr Gln Tyr Asp Val Lys Ser Glu Ile Tyr Ser Phe Gly Ile			
385	390	395	400
Val Leu Trp Glu Ile Ala Thr Gly Asp Ile Pro Phe Gln Gly Cys Asn			
	405	410	415
Ser Glu Lys Ile Arg Lys Leu Val Ala Val Lys Arg Gln Gln Glu Pro			
	420	425	430
Leu Gly Glu Asp Cys Pro Ser Glu Leu Arg Glu Ile Ile Asp Glu Cys			
	435	440	445
Arg Ala His Asp Pro Ser Val Arg Pro Ser Val Asp Glu Ile Leu Lys			
	450	455	460
Lys Leu Ser Thr Phe Ser Lys			
465	470		
<210> 122			
<211> 484			
<212> PRT			
<213> 智人			
<400> 122			
Met Gly Ser Ala Phe Glu Arg Val Val Arg Arg Val Val Gln Glu Leu			
1	5	10	15
Asp His Gly Gly Glu Phe Ile Pro Val Thr Ser Leu Gln Ser Ser Thr			
	20	25	30
Gly Phe Gln Pro Tyr Cys Leu Val Val Arg Lys Pro Ser Ser Ser Trp			
	35	40	45
Phe Trp Lys Pro Arg Tyr Lys Cys Val Asn Leu Ser Ile Lys Asp Ile			
	50	55	60
Leu Glu Pro Asp Ala Ala Glu Pro Asp Val Gln Arg Gly Arg Ser Phe			
65	70	75	80
His Phe Tyr Asp Ala Met Asp Gly Gln Ile Gln Gly Ser Val Glu Leu			
	85	90	95
Ala Ala Pro Gly Gln Ala Lys Ile Ala Gly Gly Ala Ala Val Ser Asp			

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

Glu Arg Ser Thr Met Ser Leu Pro Pro Gly Leu Leu Gly Asn Ser Trp
 420 425 430
 Gly Glu Gly Ala Pro Ala Trp Val Leu Leu Asp Glu Cys Gly Leu Glu
 435 440 445
 Leu Gly Glu Asp Thr Pro His Val Cys Trp Glu Pro Gln Ala Gln Gly
 450 455 460
 Arg Met Cys Ala Leu Tyr Ala Ser Leu Ala Leu Leu Ser Gly Leu Ser
 465 470 475 480
 Gln Glu Pro His
 <210> 123
 <211> 496
 <212> PRT
 <213> 智人
 <400> 123
 Met Phe Ala Lys Ala Thr Arg Asn Phe Leu Arg Glu Val Asp Ala Asp
 1 5 10 15
 Gly Asp Leu Ile Ala Val Ser Asn Leu Asn Asp Ser Asp Lys Leu Gln
 20 25 30
 Leu Leu Ser Leu Val Thr Lys Lys Lys Arg Phe Trp Cys Trp Gln Arg
 35 40 45
 Pro Lys Tyr Gln Phe Leu Ser Leu Thr Leu Gly Asp Val Leu Ile Glu
 50 55 60
 Asp Gln Phe Pro Ser Pro Val Val Val Glu Ser Asp Phe Val Lys Tyr
 65 70 75 80
 Glu Gly Lys Phe Ala Asn His Val Ser Gly Thr Leu Glu Thr Ala Leu
 85 90 95
 Gly Lys Val Lys Leu Asn Leu Gly Gly Ser Ser Arg Val Glu Ser Gln
 100 105 110
 Ser Ser Phe Gly Thr Leu Arg Lys Gln Glu Val Asp Leu Gln Gln Leu
 115 120 125
 Ile Arg Asp Ser Ala Glu Arg Thr Ile Asn Leu Arg Asn Pro Val Leu
 130 135 140
 Gln Gln Val Leu Glu Gly Arg Asn Glu Val Leu Cys Val Leu Thr Gln
 145 150 155 160
 Lys Ile Thr Thr Met Gln Lys Cys Val Ile Ser Glu His Met Gln Val
 165 170 175
 Glu Glu Lys Cys Gly Gly Ile Val Gly Ile Gln Thr Lys Thr Val Gln
 180 185 190
 Val Ser Ala Thr Glu Asp Gly Asn Val Thr Lys Asp Ser Asn Val Val

195	200	205
Leu Glu Ile Pro Ala Ala Thr Thr Ile Ala Tyr Gly Val Ile Glu Leu		
210	215	220
Tyr Val Lys Leu Asp Gly Gln Phe Glu Phe Cys Leu Leu Arg Gly Lys		
225	230	235
Gln Gly Gly Phe Glu Asn Lys Lys Arg Ile Asp Ser Val Tyr Leu Asp		
245	250	255
Pro Leu Val Phe Arg Glu Phe Ala Phe Ile Asp Met Pro Asp Ala Ala		
260	265	270
His Gly Ile Ser Ser Gln Asp Gly Pro Leu Ser Val Leu Lys Gln Ala		
275	280	285
Thr Leu Leu Leu Glu Arg Asn Phe His Pro Phe Ala Glu Leu Pro Glu		
290	295	300
Pro Gln Gln Thr Ala Leu Ser Asp Ile Phe Gln Ala Val Leu Phe Asp		
305	310	315
Asp Glu Leu Leu Met Val Leu Glu Pro Val Cys Asp Asp Leu Val Ser		
325	330	335
Gly Leu Ser Pro Thr Val Ala Val Leu Gly Glu Leu Lys Pro Arg Gln		
340	345	350
Gln Gln Asp Leu Val Ala Phe Leu Gln Leu Val Gly Cys Ser Leu Gln		
355	360	365
Gly Gly Cys Pro Gly Pro Glu Asp Ala Gly Ser Lys Gln Leu Phe Met		
370	375	380
Thr Ala Tyr Phe Leu Val Ser Ala Leu Ala Glu Met Pro Asp Ser Ala		
385	390	395
Ala Ala Leu Leu Gly Thr Cys Cys Lys Leu Gln Ile Ile Pro Thr Leu		
405	410	415
Cys His Leu Leu Arg Ala Leu Ser Asp Asp Gly Val Ser Asp Leu Glu		
420	425	430
Asp Pro Thr Leu Thr Pro Leu Lys Asp Thr Glu Arg Phe Gly Ile Val		
435	440	445
Gln Arg Leu Phe Ala Ser Ala Asp Ile Ser Leu Glu Arg Leu Lys Ser		
450	455	460
Ser Val Lys Ala Val Ile Leu Lys Asp Ser Lys Val Phe Pro Leu Leu		
465	470	475
Leu Cys Ile Thr Leu Asn Gly Leu Cys Ala Leu Gly Arg Glu His Ser		
485	490	495

<210> 124

<211> 215

<212> PRT

<213> 智人

<400> 124

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

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<210> 125

<211> 26

<212> PRT

<213> 意大利蜜蜂

<400> 125

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Gly Ile Gly Ala Val Leu Lys Val Leu Thr Thr Gly Leu Pro Ala Leu
1           5           10           15
Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln

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	20		25
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Met	Ala	Ala	Leu
	Lys	Ser	Trp
	Leu	Ser	Arg
	Ser	Val	Thr
	Ser	Phe	Phe
1	5	10	15
Arg	Tyr	Arg	Gln
	Cys	Leu	Cys
	Val	Pro	Val
	Val	Ala	Asn
	Phe	Lys	Lys
	20	25	30
Arg	Cys	Phe	Ser
	Glu	Leu	Ile
	Arg	Pro	Trp
	His	Lys	Thr
	Val	Thr	Ile
	35	40	45
Gly	Phe	Gly	Val
	Thr	Leu	Cys
	Ala	Val	Pro
	Ile	Ala	Gln
	Lys	Ser	Glu
	50	55	60
Pro	His	Ser	Leu
	Ser	Ser	Glu
	Ala	Leu	Met
	Arg	Arg	Ala
	Val	Ser	Leu
65	70	75	80
Val	Thr	Asp	Ser
	Thr	Ser	Thr
	Phe	Leu	Ser
	Gln	Thr	Thr
	Tyr	Ala	Leu
	85	90	95
Ile	Glu	Ala	Ile
	Thr	Glu	Tyr
	Thr	Lys	Ala
	Val	Tyr	Thr
	Leu	Thr	Ser
	100	105	110
Leu	Tyr	Arg	Gln
	Tyr	Thr	Ser
	Leu	Leu	Gly
	Lys	Met	Asn
	Ser	Glu	Glu
	115	120	125
Glu	Asp	Glu	Val
	Trp	Gln	Val
	Ile	Ile	Gly
	Ala	Arg	Ala
	Glu	Met	Thr
	130	135	140
Ser	Lys	His	Gln
	Glu	Tyr	Leu
	Lys	Leu	Glu
	Thr	Thr	Trp
	Met	Thr	Ala
145	150	155	160
Val	Gly	Leu	Ser
	Glu	Met	Ala
	Ala	Glu	Ala
	Ala	Tyr	Gln
	Thr	Gly	Ala
	165	170	175
Asp	Gln	Ala	Ser
	Ile	Thr	Ala
	Arg	Asn	His
	Ile	Gln	Leu
	Val	Lys	Leu
	180	185	190
Gln	Val	Glu	Glu
	Val	His	Gln
	Leu	Ser	Arg
	Lys	Ala	Glu
	Thr	Lys	Leu
	195	200	205
Ala	Glu	Ala	Gln
	Ile	Glu	Glu
	Leu	Arg	Gln
	Lys	Thr	Gln
	Glu	Glu	Gly
	210	215	220
Glu	Glu	Arg	Ala
	Glu	Ser	Glu
	Gln	Glu	Ala
	Tyr	Leu	Arg
	Glu	Asp	
225	230	235	
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<211>	485		
<212>	PRT		

<213> 鲍特鲍斯蛇

<400> 127

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

290	295	300
Glu Pro Pro Leu Pro Pro Lys Lys Ala His Ala Leu Arg Ser Val His		
305	310	315
Tyr Arg Ser Gly Thr Lys Ile Phe Leu Thr Cys Thr Lys Lys Phe Trp		
325	330	335
Glu Asp Asp Gly Ile His Gly Gly Lys Ser Thr Thr Asp Leu Pro Ser		
340	345	350
Arg Phe Ile Tyr Tyr Pro Asn His Asn Phe Pro Ser Gly Val Gly Val		
355	360	365
Ile Ile Ala Tyr Gly Ile Gly Asp Asp Ala Asn Phe Phe Gln Ala Leu		
370	375	380
Asp Phe Lys Asp Cys Gly Asp Ile Val Ile Asn Asp Leu Ser Leu Ile		
385	390	395
His Gln Leu Pro Lys Glu Glu Ile Gln Ala Phe Cys Arg Pro Ser Met		
405	410	415
Ile Gln Arg Trp Ser Leu Asp Lys Tyr Ala Met Gly Gly Ile Thr Thr		
420	425	430
Phe Thr Pro Tyr Gln Phe Gln His Phe Ser Glu Ala Leu Thr Ala Pro		
435	440	445
Val Asp Arg Ile Tyr Phe Ala Gly Glu Tyr Thr Ala Gln Ala His Gly		
450	455	460
Trp Ile Asp Ser Thr Ile Lys Ser Gly Leu Thr Ala Ala Arg Asp Val		
465	470	475
Asn Arg Ala Ser Glu		480
485		
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<212> PRT		
<213> 智人		
<400> 128		
Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys Thr Leu Ile Lys Thr		
1	5	10
Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr Gln Ser Val Ser Ser		
20	25	30
Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro Gly Leu His Pro Ile		
35	40	45
Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala Val Tyr Gln Gln Ile		
50	55	60
Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln Ile Ser Asn Asp Leu		

65	70	75	80
Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala Phe Ser Lys Ser Cys			
	85	90	95
His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu Asp Ser Leu Gly Gly			
	100	105	110
Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val Val Ala Leu Ser Arg			
	115	120	125
Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser Pro			
	130	135	140
Gly Cys			
145			
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<400> 129			
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala			
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Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val			
	20	25	30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp			
	35	40	45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala			
	50	55	60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His			
65	70	75	80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe			
	85	90	95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu			
	100	105	110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu			
	115	120	125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser			
	130	135	140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu			
145	150	155	160
Leu Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Leu Ala Ala Ala			
	165	170	175
Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly			

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

Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile
 245 250 255
 Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala
 260 265 270
 Ser Phe Phe Gly Ala Phe Leu Val Gly
 275 280
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 <211> 309
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 <400> 131
 Met Ser Leu Glu Gln Arg Ser Leu His Cys Lys Pro Glu Glu Ala Leu
 1 5 10 15
 Glu Ala Gln Gln Glu Ala Leu Gly Leu Val Cys Val Gln Ala Ala Thr
 20 25 30
 Ser Ser Ser Ser Pro Leu Val Leu Gly Thr Leu Glu Glu Val Pro Thr
 35 40 45
 Ala Gly Ser Thr Asp Pro Pro Gln Ser Pro Gln Gly Ala Ser Ala Phe
 50 55 60
 Pro Thr Thr Ile Asn Phe Thr Arg Gln Arg Gln Pro Ser Glu Gly Ser
 65 70 75 80
 Ser Ser Arg Glu Glu Glu Gly Pro Ser Thr Ser Cys Ile Leu Glu Ser
 85 90 95
 Leu Phe Arg Ala Val Ile Thr Lys Lys Val Ala Asp Leu Val Gly Phe
 100 105 110
 Leu Leu Leu Lys Tyr Arg Ala Arg Glu Pro Val Thr Lys Ala Glu Met
 115 120 125
 Leu Glu Ser Val Ile Lys Asn Tyr Lys His Cys Phe Pro Glu Ile Phe
 130 135 140
 Gly Lys Ala Ser Glu Ser Leu Gln Leu Val Phe Gly Ile Asp Val Lys
 145 150 155 160
 Glu Ala Asp Pro Thr Gly His Ser Tyr Val Leu Val Thr Cys Leu Gly
 165 170 175
 Leu Ser Tyr Asp Gly Leu Leu Gly Asp Asn Gln Ile Met Pro Lys Thr
 180 185 190
 Gly Phe Leu Ile Ile Val Leu Val Met Ile Ala Met Glu Gly Gly His
 195 200 205
 Ala Pro Glu Glu Glu Ile Trp Glu Glu Leu Ser Val Met Glu Val Tyr
 210 215 220

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

Ile Phe Ala Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp		
180	185	190
Asn Gln Ile Met Pro Lys Ala Gly Leu Leu Ile Ile Val Leu Ala Ile		
195	200	205
Ile Ala Arg Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu		
210	215	220
Leu Ser Val Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Ile Leu Gly		
225	230	235
Asp Pro Lys Lys Leu Leu Thr Gln His Phe Val Gln Glu Asn Tyr Leu		
245	250	255
Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu		
260	265	270
Trp Gly Pro Arg Ala Leu Val Glu Thr Ser Tyr Val Lys Val Leu His		
275	280	285
His Met Val Lys Ile Ser Gly Gly Pro His Ile Ser Tyr Pro Pro Leu		
290	295	300
His Glu Trp Val Leu Arg Glu Gly Glu Glu		
305	310	
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<211> 317		
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Met Ser Ser Glu Gln Lys Ser Gln His Cys Lys Pro Glu Glu Gly Val		
1	5	10
Glu Ala Gln Glu Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Thr		
20	25	30
Thr Glu Glu Gln Glu Ala Ala Val Ser Ser Ser Ser Pro Leu Val Pro		
35	40	45
Gly Thr Leu Glu Glu Val Pro Ala Ala Glu Ser Ala Gly Pro Pro Gln		
50	55	60
Ser Pro Gln Gly Ala Ser Ala Leu Pro Thr Thr Ile Ser Phe Thr Cys		
65	70	75
Trp Arg Gln Pro Asn Glu Gly Ser Ser Ser Gln Glu Glu Glu Gly Pro		
85	90	95
Ser Thr Ser Pro Asp Ala Glu Ser Leu Phe Arg Glu Ala Leu Ser Asn		
100	105	110
Lys Val Asp Glu Leu Ala His Phe Leu Leu Arg Lys Tyr Arg Ala Lys		
115	120	125

Glu Leu Val Thr Lys Ala Glu Met Leu Glu Arg Val Ile Lys Asn Tyr		
130	135	140
Lys Arg Cys Phe Pro Val Ile Phe Gly Lys Ala Ser Glu Ser Leu Lys		
145	150	155
Met Ile Phe Gly Ile Asp Val Lys Glu Val Asp Pro Ala Ser Asn Thr		
	165	170
Tyr Thr Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly		
	180	185
Asn Asn Gln Ile Phe Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Gly		
	195	200
Thr Ile Ala Met Glu Gly Asp Ser Ala Ser Glu Glu Glu Ile Trp Glu		
	210	215
Glu Leu Gly Val Met Gly Val Tyr Asp Gly Arg Glu His Thr Val Tyr		
225	230	235
Gly Glu Pro Arg Lys Leu Leu Thr Gln Asp Trp Val Gln Glu Asn Tyr		
	245	250
Leu Glu Tyr Arg Gln Val Pro Gly Ser Asn Pro Ala Arg Tyr Glu Phe		
	260	265
Leu Trp Gly Pro Arg Ala Leu Ala Glu Thr Ser Tyr Val Lys Val Leu		
	275	280
Glu His Val Val Arg Val Asn Ala Arg Val Arg Ile Ala Tyr Pro Ser		
	290	295
Leu Arg Glu Ala Ala Leu Leu Glu Glu Glu Glu Gly Val		
305	310	315
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Glu Ala Gln Gly Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Ala		
	20	25
Thr Glu Glu Gln Glu Thr Ala Ser Ser Ser Ser Thr Leu Val Glu Val		
	35	40
Thr Leu Arg Glu Val Pro Ala Ala Glu Ser Pro Ser Pro Pro His Ser		
	50	55
Pro Gln Gly Ala Ser Thr Leu Pro Thr Thr Ile Asn Tyr Thr Leu Trp		
65	70	75
		80

Ser	Gln	Ser	Asp	Glu	Gly	Ser	Ser	Asn	Glu	Glu	Gln	Glu	Gly	Pro	Ser	
				85					90					95		
Thr	Phe	Pro	Asp	Leu	Glu	Thr	Ser	Phe	Gln	Val	Ala	Leu	Ser	Arg	Lys	
				100					105					110		
Met	Ala	Glu	Leu	Val	His	Phe	Leu	Leu	Leu	Lys	Tyr	Arg	Ala	Arg	Glu	
				115					120					125		
Pro	Phe	Thr	Lys	Ala	Glu	Met	Leu	Gly	Ser	Val	Ile	Arg	Asn	Phe	Gln	
				130					135					140		
Asp	Phe	Phe	Pro	Val	Ile	Phe	Ser	Lys	Ala	Ser	Glu	Tyr	Leu	Gln	Leu	
145					150					155					160	
Val	Phe	Gly	Ile	Glu	Val	Val	Glu	Val	Val	Arg	Ile	Gly	His	Leu	Tyr	
				165					170					175		
Ile	Leu	Val	Thr	Cys	Leu	Gly	Leu	Ser	Tyr	Asp	Gly	Leu	Leu	Gly	Asp	
				180					185					190		
Asn	Gln	Ile	Val	Pro	Lys	Thr	Gly	Leu	Leu	Ile	Ile	Val	Leu	Ala	Ile	
				195					200					205		
Ile	Ala	Lys	Glu	Gly	Asp	Cys	Ala	Pro	Glu	Glu	Lys	Ile	Trp	Glu	Glu	
				210					215					220		
Leu	Ser	Val	Leu	Glu	Ala	Ser	Asp	Gly	Arg	Glu	Asp	Ser	Val	Phe	Ala	
225					230					235					240	
His	Pro	Arg	Lys	Leu	Leu	Thr	Gln	Asp	Leu	Val	Gln	Glu	Asn	Tyr	Leu	
				245					250					255		
Glu	Tyr	Arg	Gln	Val	Pro	Gly	Ser	Asp	Pro	Ala	Cys	Tyr	Glu	Phe	Leu	
				260					265					270		
Trp	Gly	Pro	Arg	Ala	Leu	Val	Glu	Thr	Ser	Tyr	Val	Lys	Val	Leu	His	
				275					280					285		
His	Leu	Leu	Lys	Ile	Ser	Gly	Gly	Pro	His	Ile	Ser	Tyr	Pro	Pro	Leu	
				290					295					300		
His	Glu	Trp	Ala	Phe	Arg	Glu	Gly	Glu	Glu							
305					310											
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Pro	Thr	Ser	Val	Glu	Leu	Glu	Asp	Trp	Val	Asp	Ala	Gln	His	Pro	Thr	
				20					25					30		

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

340	345	350
Asp Ala Thr Val Met Ala Ser Glu	Ser Leu Ser Val Met Ser Ser Asn	
355	360	365
Val Ser Phe Ser Glu		
370		
<210> 136		
<211> 26		
<212> PRT		
<213> 智人		
<400> 136		
Arg Leu Met Lys Glu Glu Ser Pro Val Val Ser Trp Arg Leu Glu Pro		
1	5	10
Glu Asp Gly Thr Ala Leu Cys Phe Ile Phe		
20	25	
<210> 137		
<211> 117		
<212> PRT		
<213> 智人		
<400> 137		
Met Ser Trp Arg Gly Arg Ser Thr Tyr Tyr Trp Pro Arg Pro Arg Arg		
1	5	10
Tyr Val Gln Pro Pro Glu Met Ile Gly Pro Met Arg Pro Glu Gln Phe		
20	25	30
Ser Asp Glu Val Glu Pro Ala Thr Pro Glu Glu Gly Glu Pro Ala Thr		
35	40	45
Gln Arg Gln Asp Pro Ala Ala Ala Gln Glu Gly Glu Asp Glu Gly Ala		
50	55	60
Ser Ala Gly Gln Gly Pro Lys Pro Glu Ala Asp Ser Gln Glu Gln Gly		
65	70	75
His Pro Gln Thr Gly Cys Glu Cys Glu Asp Gly Pro Asp Gly Gln Glu		
85	90	95
Met Asp Pro Pro Asn Pro Glu Glu Val Lys Thr Pro Glu Glu Gly Glu		
100	105	110
Gly Gln Ser Gln Cys		
115		
<210> 138		
<211> 81		
<212> PRT		
<213> 智人		

<400> 138

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

<210> 139

<211> 210

<212> PRT

<213> 智人

<400> 139

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

Glu Gln Arg Pro Gly Thr Pro Gly Pro Pro Pro Glu Gly Ala Gln
 180 185 190
 Gly Asp Gly Cys Arg Gly Val Ala Phe Asn Val Met Phe Ser Ala Pro
 195 200 205
 His Ile
 210
 <210> 140
 <211> 180
 <212> PRT
 <213> 智人
 <400> 140
 Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1 5 10 15
 Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
 20 25 30
 Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
 35 40 45
 Gly Ala Ala Arg Ala Ser Gly Pro Gly Gly Gly Ala Pro Arg Gly Pro
 50 55 60
 His Gly Gly Ala Ala Ser Gly Leu Asn Gly Cys Cys Arg Cys Gly Ala
 65 70 75 80
 Arg Gly Pro Glu Ser Arg Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe
 85 90 95
 Ala Thr Pro Met Glu Ala Glu Leu Ala Arg Arg Ser Leu Ala Gln Asp
 100 105 110
 Ala Pro Pro Leu Pro Val Pro Gly Val Leu Leu Lys Glu Phe Thr Val
 115 120 125
 Ser Gly Asn Ile Leu Thr Ile Arg Leu Thr Ala Ala Asp His Arg Gln
 130 135 140
 Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
 145 150 155 160
 Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Pro Pro Ser
 165 170 175
 Gly Gln Arg Arg
 180
 <210> 141
 <211> 188
 <212> PRT
 <213> 智人

<400> 141

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

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<210> 142

<211> 113

<212> PRT

<213> 智人

<400> 142

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

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65	70	75	80
Leu Val Asn Leu Ser Met Val Glu Asn Lys Leu Val Glu Leu Glu His			
	85	90	95
Thr Leu Leu Ser Lys Gly Phe Arg Gly Ala Ser Pro His Arg Lys Ser			
	100	105	110
Thr			
<210> 143			
<211> 904			
<212> PRT			
<213> 智人			
<400> 143			
Met Gln Ala Ser Pro Leu Gln Thr Ser Gln Pro Thr Pro Pro Glu Glu			
1	5	10	15
Leu His Ala Ala Ala Tyr Val Phe Thr Asn Asp Gly Gln Gln Met Arg			
	20	25	30
Ser Asp Glu Val Asn Leu Val Ala Thr Gly His Gln Ser Lys Lys Lys			
	35	40	45
His Ser Arg Lys Ser Lys Arg His Ser Ser Ser Lys Arg Arg Lys Ser			
	50	55	60
Met Ser Ser Trp Leu Asp Lys Gln Glu Asp Ala Ala Val Thr His Ser			
65	70	75	80
Ile Cys Glu Glu Arg Ile Asn Asn Gly Gln Pro Val Ala Asp Asn Val			
	85	90	95
Leu Ser Thr Ala Pro Pro Trp Pro Asp Ala Thr Ile Ala His Asn Ile			
	100	105	110
Arg Glu Glu Arg Met Glu Asn Gly Gln Ser Arg Thr Asp Lys Val Leu			
	115	120	125
Ser Thr Ala Pro Pro Gln Leu Val His Met Ala Ala Ala Gly Ile Pro			
	130	135	140
Ser Met Ser Thr Arg Asp Leu His Ser Thr Val Thr His Asn Ile Arg			
145	150	155	160
Glu Glu Arg Met Glu Asn Gly Gln Pro Gln Pro Asp Asn Val Leu Ser			
	165	170	175
Thr Gly Pro Thr Gly Leu Ile Asn Met Ala Ala Thr Pro Ile Pro Ala			
	180	185	190
Met Ser Ala Arg Asp Leu Tyr Ala Thr Val Thr His Asn Val Cys Glu			
	195	200	205
Gln Lys Met Glu Asn Val Gln Pro Ala Pro Asp Asn Val Leu Leu Thr			
	210	215	220

Leu Arg Pro Arg Arg Ile Asn Met Thr Asp Thr Gly Ile Ser Pro Met			
225	230	235	240
Ser Thr Arg Asp Pro Tyr Ala Thr Ile Thr Tyr Asn Val Pro Glu Glu			
	245	250	255
Lys Met Glu Lys Gly Gln Pro Gln Pro Asp Asn Ile Leu Ser Thr Ala			
	260	265	270
Ser Thr Gly Leu Ile Asn Val Ala Gly Ala Gly Thr Pro Ala Ile Ser			
	275	280	285
Thr Asn Gly Leu Tyr Ser Thr Val Pro His Asn Val Cys Glu Glu Lys			
	290	295	300
Met Glu Asn Asp Gln Pro Gln Pro Asn Asn Val Leu Ser Thr Val Gln			
305	310	315	320
Pro Val Ile Ile Tyr Leu Thr Ala Thr Gly Ile Pro Gly Met Asn Thr			
	325	330	335
Arg Asp Gln Tyr Ala Thr Ile Thr His Asn Val Cys Glu Glu Arg Val			
	340	345	350
Val Asn Asn Gln Pro Leu Pro Ser Asn Ala Leu Ser Thr Val Leu Pro			
	355	360	365
Gly Leu Ala Tyr Leu Ala Thr Ala Asp Met Pro Ala Met Ser Thr Arg			
	370	375	380
Asp Gln His Ala Thr Ile Ile His Asn Leu Arg Glu Glu Lys Lys Asp			
385	390	395	400
Asn Ser Gln Pro Thr Pro Asp Asn Val Leu Ser Ala Val Thr Pro Glu			
	405	410	415
Leu Ile Asn Leu Ala Gly Ala Gly Ile Pro Pro Met Ser Thr Arg Asp			
	420	425	430
Gln Tyr Ala Thr Val Asn His His Val His Glu Ala Arg Met Glu Asn			
	435	440	445
Gly Gln Arg Lys Gln Asp Asn Val Leu Ser Asn Val Leu Ser Gly Leu			
	450	455	460
Ile Asn Met Ala Gly Ala Ser Ile Pro Ala Met Ser Ser Arg Asp Leu			
465	470	475	480
Tyr Ala Thr Ile Thr His Ser Val Arg Glu Glu Lys Met Glu Ser Gly			
	485	490	495
Lys Pro Gln Thr Asp Lys Val Ile Ser Asn Asp Ala Pro Gln Leu Gly			
	500	505	510
His Met Ala Ala Gly Gly Ile Pro Ser Met Ser Thr Lys Asp Leu Tyr			
	515	520	525
Ala Thr Val Thr Gln Asn Val His Glu Glu Arg Met Glu Asn Asn Gln			

530	535	540
Pro Gln Pro Ser Tyr Asp	Leu Ser Thr Val	Leu Pro Gly Leu Thr Tyr
545	550	555
Leu Thr Val Ala Gly Ile	Pro Ala Met Ser Thr Arg	Asp Gln Tyr Ala
565	570	575
Thr Val Thr His Asn Val	His Glu Glu Lys Ile Lys	Asn Gly Gln Ala
580	585	590
Ala Ser Asp Asn Val Phe	Ser Thr Val Pro Pro	Ala Phe Ile Asn Met
595	600	605
Ala Ala Thr Gly Val Ser	Ser Met Ser Thr Arg	Asp Gln Tyr Ala Ala
610	615	620
Val Thr His Asn Ile Arg	Glu Glu Lys Ile Asn	Asn Ser Gln Pro Ala
625	630	635
Pro Gly Asn Ile Leu Ser	Thr Ala Pro Pro Trp	Leu Arg His Met Ala
645	650	655
Ala Ala Gly Ile Ser Ser	Thr Ile Thr Arg Asp	Leu Tyr Val Thr Ala
660	665	670
Thr His Ser Val His Glu	Glu Lys Met Thr Asn	Gly Gln Gln Ala Pro
675	680	685
Asp Asn Ser Leu Ser Thr	Val Pro Pro Gly Cys	Ile Asn Leu Ser Gly
690	695	700
Ala Gly Ile Ser Cys Arg	Ser Thr Arg Asp Leu	Tyr Ala Thr Val Ile
705	710	715
His Asp Ile Gln Glu Glu	Glu Met Glu Asn Asp	Gln Thr Pro Pro Asp
725	730	735
Gly Phe Leu Ser Asn Ser	Asp Ser Pro Glu Leu	Ile Asn Met Thr Gly
740	745	750
His Cys Met Pro Pro Asn	Ala Leu Asp Ser Phe	Ser His Asp Phe Thr
755	760	765
Ser Leu Ser Lys Asp Glu	Leu Leu Tyr Lys Pro	Asp Ser Asn Glu Phe
770	775	780
Ala Val Gly Thr Lys Asn	Tyr Ser Val Ser Ala	Gly Asp Pro Pro Val
785	790	795
Thr Val Met Ser Leu Val	Glu Thr Val Pro Asn	Thr Pro Gln Ile Ser
805	810	815
Pro Ala Met Ala Lys Lys	Ile Asn Asp Asp Ile	Lys Tyr Gln Leu Met
820	825	830
Lys Glu Val Arg Arg Phe	Gly Gln Asn Tyr Glu	Arg Ile Phe Ile Leu
835	840	845

Leu Glu Glu Val Gln Gly Ser Met Lys Val Lys Arg Gln Phe Val Glu
 850 855 860
 Phe Thr Ile Lys Glu Ala Ala Arg Phe Lys Lys Val Val Leu Ile Gln
 865 870 875 880
 Gln Leu Glu Lys Ala Leu Lys Glu Ile Asp Ser His Cys His Leu Arg
 885 890 895
 Lys Val Lys His Met Arg Lys Arg
 900

<210> 144

<211> 151

<212> PRT

<213> 智人

<400> 144

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

<210> 145

<211> 432

<212> PRT

<213> 智人

<400> 145

Met Leu Gly Asn Ser Ala Pro Gly Pro Ala Thr Arg Glu Ala Gly Ser

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

434

Pro Ser Gln Ile His Ser Glu Asp Thr Leu Thr Leu Arg Thr Ser Thr		
	165	170 175
Asp Asn Leu Ser Ser Asn Ile Ile Ile His Pro Ser Glu Asn Ser Asp		
	180	185 190
Ile Leu Lys Asn Tyr Asn Asn Phe Tyr Arg Phe Leu Pro Thr Ala Pro		
	195	200 205
Pro Asn Val Met Ser Gln Ala Asp Thr Val Ile Leu Asp Lys Ser Lys		
	210	215 220
Ile Thr Val Pro Phe Leu Lys His Gly Phe Cys Glu Asn Leu Asp Asp		
225	230	235 240
Ile Cys His Ser Ile Lys Gln Met Lys Glu Glu Leu Gln Lys Ser His		
	245	250 255
Asp Gly Glu Val Ala Leu Thr Asn Glu Leu Gln Thr Leu Gln Thr Asp		
	260	265 270
Pro Asp Val His Arg Asn Gly Lys Tyr Asp Met Ser Pro Ile His Gln		
	275	280 285
Asp Lys Met Asn Phe Ile Lys Glu Glu Asn Leu Asp Gly Asn Leu Asn		
	290	295 300
Glu Asp Ile Lys Ser Lys Arg Ile Ser Glu Leu Glu Ala Leu Val Lys		
305	310	315 320
Lys Leu Leu Pro Phe Arg Glu Thr Val Ser Lys Phe His Val His Phe		
	325	330 335
Cys Arg Lys Cys Lys Lys Leu Ser Lys Ser Glu Met His Arg Gly Lys		
	340	345 350
Lys Asn Glu Lys Asn Asn Lys Glu Ile Pro Ile Thr Gly Lys Asn Ile		
	355	360 365
Thr Asp Leu Lys Phe His Ser Arg Val Pro Arg Tyr Thr Leu Ser Phe		
	370	375 380
Leu Asp Gln Thr Lys His Glu Met Lys Asp Lys Glu Arg Gln Pro Phe		
385	390	395 400
Leu Val Lys Gln Gly Ser Ile Ile Ser Glu Asn Glu Lys Thr Ser Lys		
	405	410 415
Val Asn Ser Val Thr Glu Gln Cys Val Ala Lys Ile Gln Tyr Leu Gln		
	420	425 430
Asn Tyr Leu Lys Glu Ser Val Gln Ile Gln Lys Lys Val Met Glu Leu		
	435	440 445
Glu Ser Glu Asn Leu Asn Leu Lys Ser Lys Met Lys Pro Leu Ile Phe		
	450	455 460
Thr Thr Gln Ser Leu Ile Gln Lys Val Glu Thr Tyr Glu Lys Gln Leu		

465	470	475	480
Lys Asn Leu Val Glu Glu Lys Ser Thr Ile Gln Ser Lys Leu Ser Lys			
	485	490	495
Thr Glu Glu Tyr Ser Lys Glu Cys Leu Lys Glu Phe Lys Lys Ile Ile			
	500	505	510
Ser Lys Tyr Asn Val Leu Gln Gly Gln Asn Lys Thr Leu Glu Glu Lys			
	515	520	525
Asn Ile Gln Leu Ser Leu Glu Lys Gln Gln Met Met Glu Ala Leu Asp			
	530	535	540
Gln Leu Lys Ser Lys Glu His Lys Thr Gln Ser Asp Met Ala Ile Val			
545	550	555	560
Asn Asn Glu Asn Asn Arg Met Ser Ile Glu Met Glu Ala Met Lys Thr			
	565	570	575
Asn Ile Leu Leu Ile Gln Asp Glu Lys Glu Met Leu Glu Lys Lys Thr			
	580	585	590
His Gln Leu Leu Lys Glu Lys Ser Ser Leu Gly Asn Glu Leu Lys Glu			
	595	600	605
Ser Gln Leu Glu Ile Ile Gln Leu Lys Glu Lys Glu Arg Leu Ala Lys			
	610	615	620
Thr Glu Gln Glu Thr Leu Leu Gln Ile Ile Glu Thr Val Lys Asp Glu			
625	630	635	640
Lys Leu Asn Leu Glu Thr Thr Leu Gln Glu Ser Thr Ala Ala Arg Gln			
	645	650	655
Ile Met Glu Arg Glu Ile Glu Asn Ile Gln Thr Tyr Gln Ser Thr Ala			
	660	665	670
Glu Glu Asn Phe Leu Gln Glu Ile Lys Asn Ala Lys Ser Glu Ala Ser			
	675	680	685
Ile Tyr Lys Asn Ser Leu Ser Glu Ile Gly Lys Glu Cys Glu Met Leu			
	690	695	700
Ser Lys Met Val Met Glu Thr Lys Thr Asp Asn Gln Ile Leu Lys Glu			
705	710	715	720
Glu Leu Lys Lys His Ser Gln Glu Asn Ile Lys Phe Glu Asn Ser Ile			
	725	730	735
Ser Arg Leu Thr Glu Asp Lys Ile Leu Leu Glu Asn Tyr Val Arg Ser			
	740	745	750
Ile Glu Asn Glu Arg Asp Thr Leu Glu Phe Glu Met Arg His Leu Gln			
	755	760	765
Arg Glu Tyr Leu Ser Leu Ser Asp Lys Ile Cys Asn Gln His Asn Asp			
	770	775	780

Pro Ser Lys Thr Thr Tyr Ile Ser Arg Arg Glu Lys Phe His Phe Asp
 785 790 795 800
 Asn Tyr Thr His Glu Asp Thr Ser Ser Pro Gln Ser Arg Pro Leu Ala
 805 810 815
 Ser Asp Leu Lys Gly Tyr Phe Lys Val Lys Asp Arg Thr Leu Lys His
 820 825 830
 His
 <210> 147
 <211> 386
 <212> PRT
 <213> 淋巴隐病毒人丙型疱疹病毒4
 <400> 147
 Met Glu His Asp Leu Glu Arg Gly Pro Pro Gly Pro Arg Arg Pro Pro
 1 5 10 15
 Arg Gly Pro Pro Leu Ser Ser Ser Leu Gly Leu Ala Leu Leu Leu Leu
 20 25 30
 Leu Leu Ala Leu Leu Phe Trp Leu Tyr Ile Val Met Ser Asp Trp Thr
 35 40 45
 Gly Gly Ala Leu Leu Val Leu Tyr Ser Phe Ala Leu Met Leu Ile Ile
 50 55 60
 Ile Ile Leu Ile Ile Phe Ile Phe Arg Arg Asp Leu Leu Cys Pro Leu
 65 70 75 80
 Gly Ala Leu Cys Ile Leu Leu Leu Met Ile Thr Leu Leu Leu Ile Ala
 85 90 95
 Leu Trp Asn Leu His Gly Gln Ala Leu Phe Leu Gly Ile Val Leu Phe
 100 105 110
 Ile Phe Gly Cys Leu Leu Val Leu Gly Ile Trp Ile Tyr Leu Leu Glu
 115 120 125
 Met Leu Trp Arg Leu Gly Ala Thr Ile Trp Gln Leu Leu Ala Phe Phe
 130 135 140
 Leu Ala Phe Phe Leu Asp Leu Ile Leu Leu Ile Ile Ala Leu Tyr Leu
 145 150 155 160
 Gln Gln Asn Trp Trp Thr Leu Leu Val Asp Leu Leu Trp Leu Leu Leu
 165 170 175
 Phe Leu Ala Ile Leu Ile Trp Met Tyr Tyr His Gly Gln Arg His Ser
 180 185 190
 Asp Glu His His His Asp Asp Ser Leu Pro His Pro Gln Gln Ala Thr
 195 200 205
 Asp Asp Ser Gly His Glu Ser Asp Ser Asn Ser Asn Glu Gly Arg His

210	215	220
His Leu Leu Val Ser Gly Ala Gly Asp Gly Pro Pro Leu Cys Ser Gln		
225	230	235
Asn Leu Gly Ala Pro Gly Gly Gly Pro Asp Asn Gly Pro Gln Asp Pro		240
	245	250
Asp Asn Thr Asp Asp Asn Gly Pro Gln Asp Pro Asp Asn Thr Asp Asp		255
	260	265
Asn Gly Pro His Asp Pro Leu Pro Gln Asp Pro Asp Asn Thr Asp Asp		270
	275	280
Asn Gly Pro Gln Asp Pro Asp Asn Thr Asp Asp Asn Gly Pro His Asp		285
290	295	300
Pro Leu Pro His Ser Pro Ser Asp Ser Ala Gly Asn Asp Gly Gly Pro		
305	310	315
Pro Gln Leu Thr Glu Glu Val Glu Asn Lys Gly Gly Asp Gln Gly Pro		320
	325	330
Pro Leu Met Thr Asp Gly Gly Gly Gly His Ser His Asp Ser Gly His		335
	340	345
Gly Gly Gly Asp Pro His Leu Pro Thr Leu Leu Leu Gly Ser Ser Gly		350
	355	360
Ser Gly Gly Asp Asp Asp Asp Pro His Gly Pro Val Gln Leu Ser Tyr		365
370	375	380
Tyr Asp		
385		
<210> 148		
<211> 497		
<212> PRT		
<213> 淋巴隐病毒人丙型疱疹病毒4		
<400> 148		
Met Gly Ser Leu Glu Met Val Pro Met Gly Ala Gly Pro Pro Ser Pro		
1	5	10
Gly Gly Asp Pro Asp Gly Tyr Asp Gly Gly Asn Asn Ser Gln Tyr Pro		15
	20	25
Ser Ala Ser Gly Ser Ser Gly Asn Thr Pro Thr Pro Pro Asn Asp Glu		30
	35	40
Glu Arg Glu Ser Asn Glu Glu Pro Pro Pro Pro Tyr Glu Asp Pro Tyr		45
	50	55
Trp Gly Asn Gly Asp Arg His Ser Asp Tyr Gln Pro Leu Gly Thr Gln		60
65	70	75
Asp Gln Ser Leu Tyr Leu Gly Leu Gln His Asp Gly Asn Asp Gly Leu		80

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

Ala Gly Ile Leu Phe Ile Leu Ala Ile Leu Thr Glu Trp Gly Ser Gly
405 410 415
Asn Arg Thr Tyr Gly Pro Val Phe Met Cys Leu Gly Gly Leu Leu Thr
420 425 430
Met Val Ala Gly Ala Val Trp Leu Thr Val Met Ser Asn Thr Leu Leu
435 440 445
Ser Ala Trp Ile Leu Thr Ala Gly Phe Leu Ile Phe Leu Ile Gly Phe
450 455 460
Ala Leu Phe Gly Val Ile Arg Cys Cys Arg Tyr Cys Cys Tyr Tyr Cys
465 470 475 480
Leu Thr Leu Glu Ser Glu Glu Arg Pro Pro Thr Pro Tyr Arg Asn Thr
485 490 495

Val

<210> 149

<211> 144

<212> RNA

<213> 人工序列

<220>

<223> 顺式作用复制元件 (CRE)

<400> 149

gaucacaaca ccgaagaaau ggaaaacucu gcugaucgag ucacaacgca aacggcgggc 60
aacacugcca uaaacacgca aucaucauug gguguguugu gugccuacgu ugaagacccg 120
accaaauucug auccuccguc cagc 144

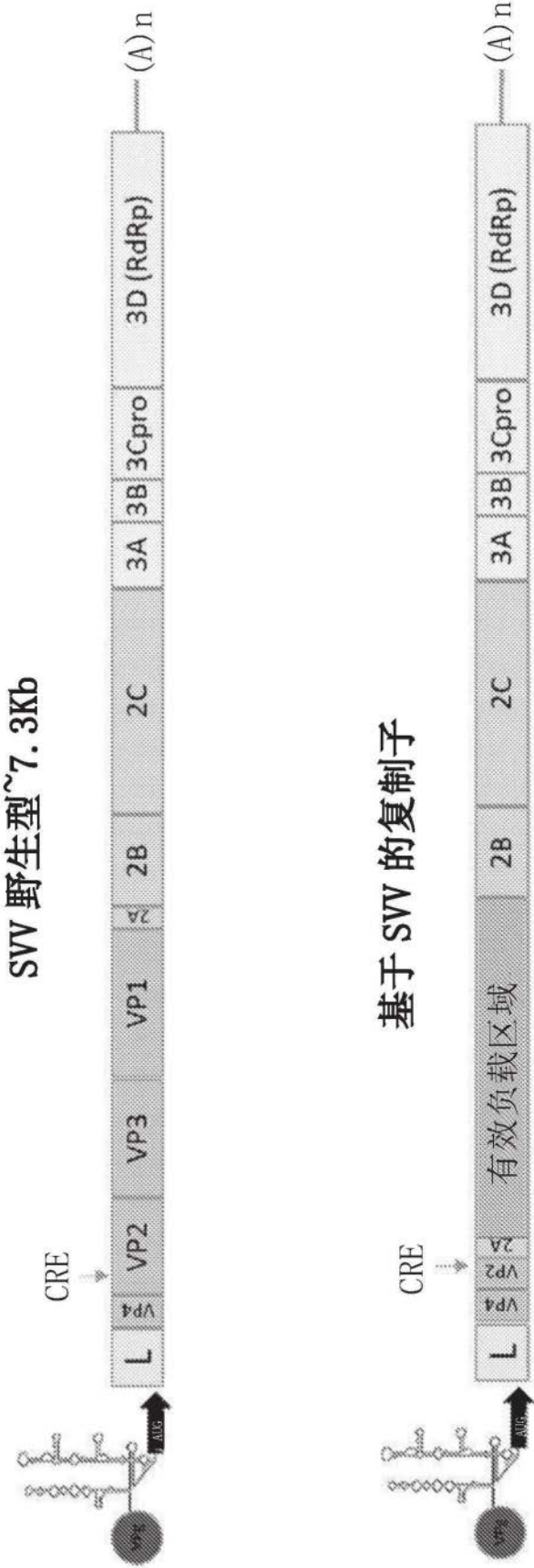


图1

Y 轴：相对于模拟的%存活
X 轴： $\log_{10}$ (稀释因子)

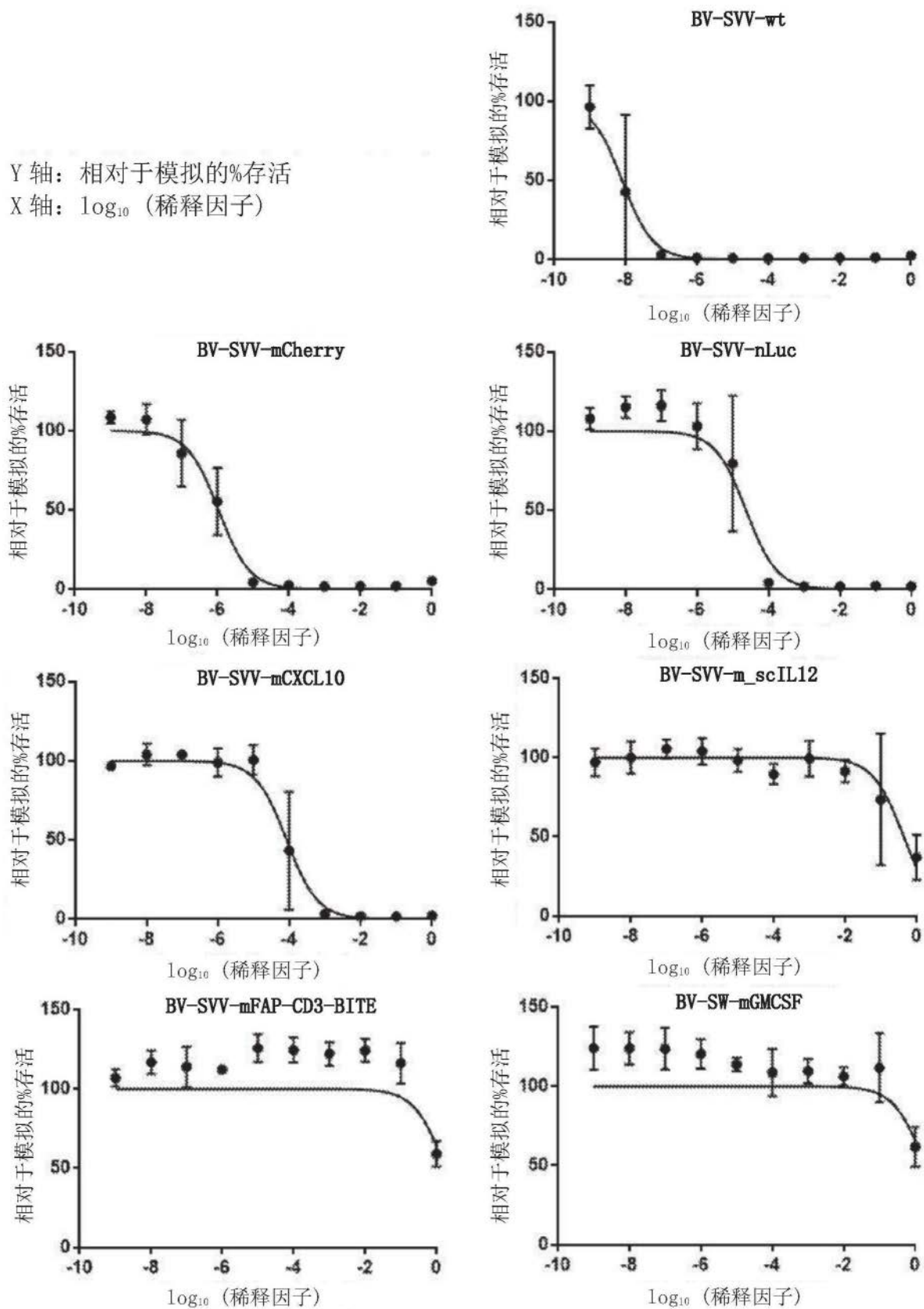


图2

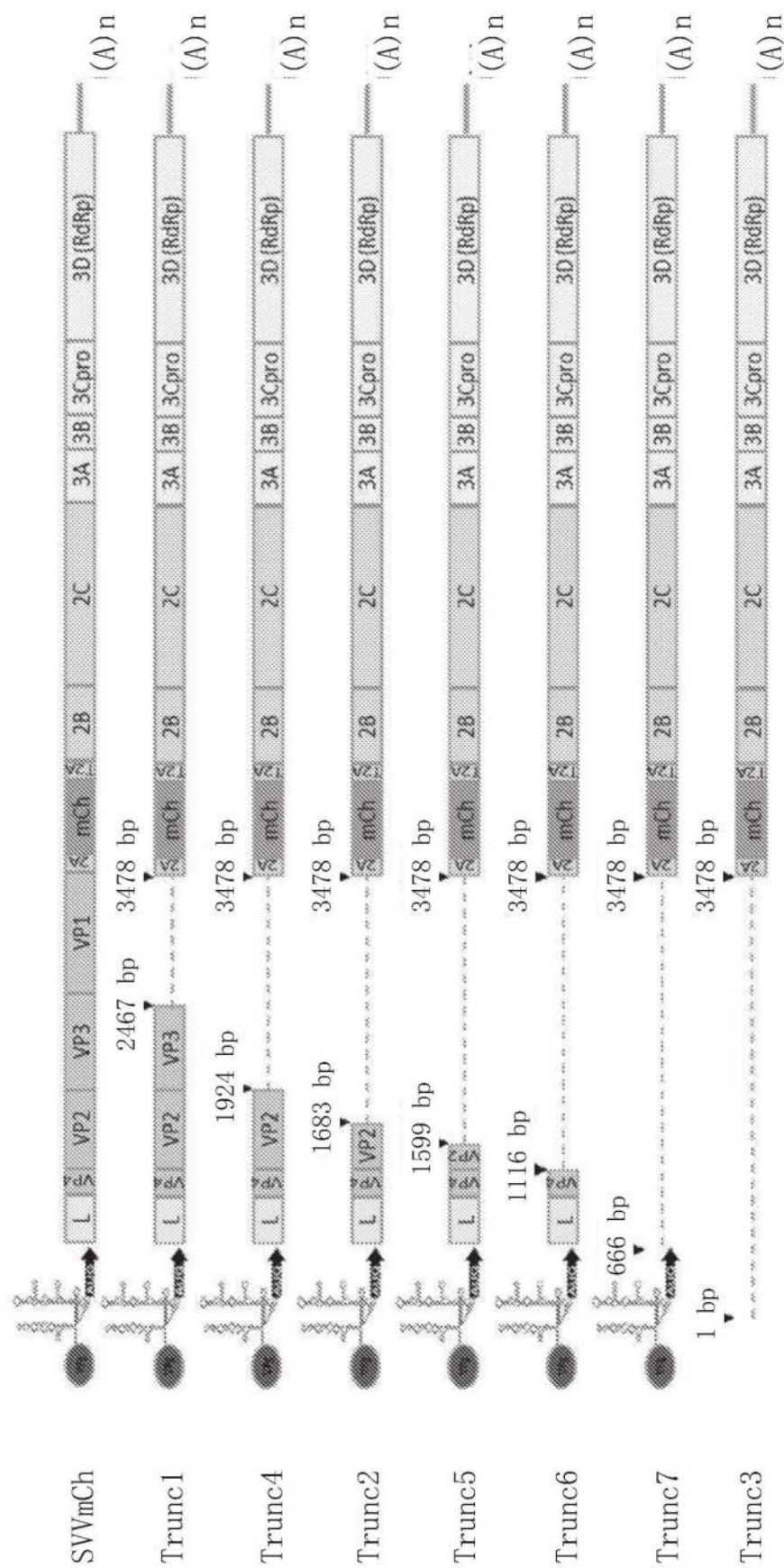


图3A

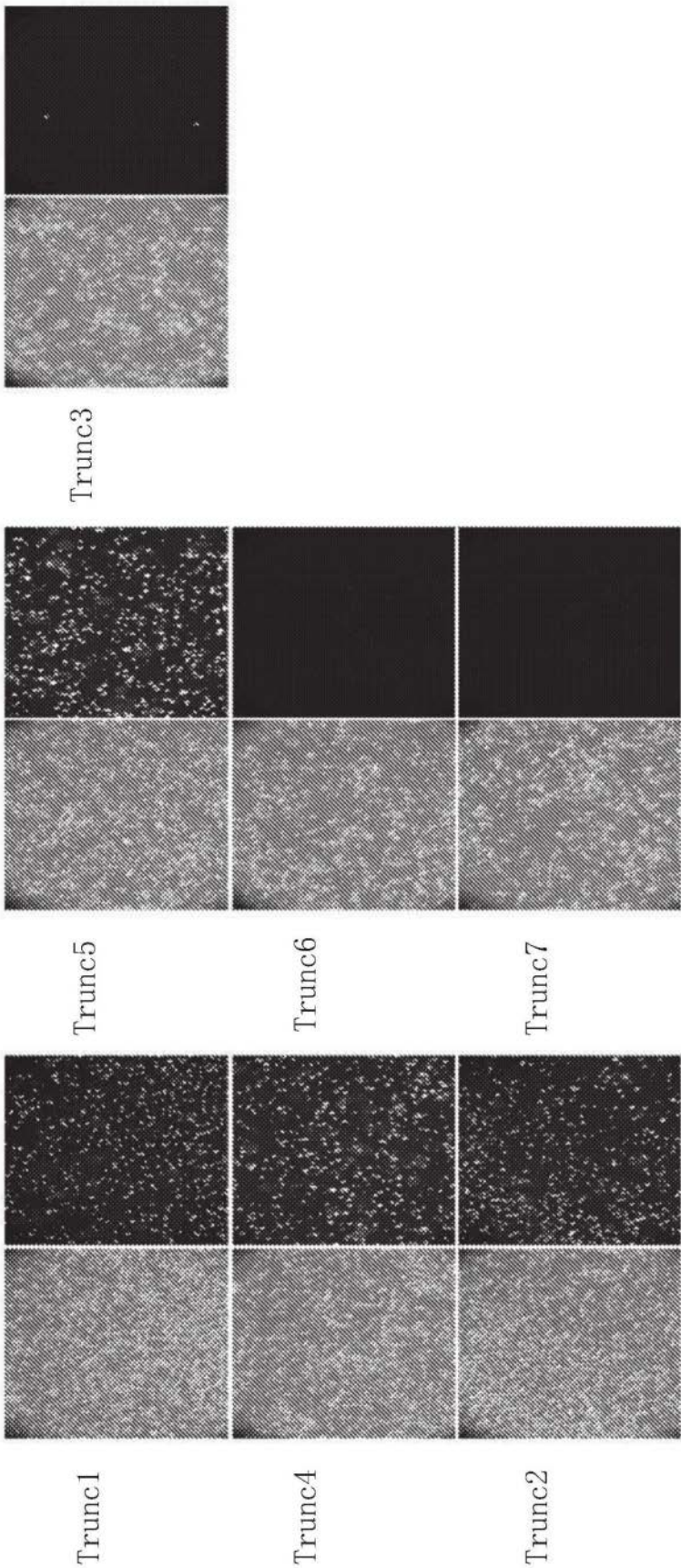


图3B

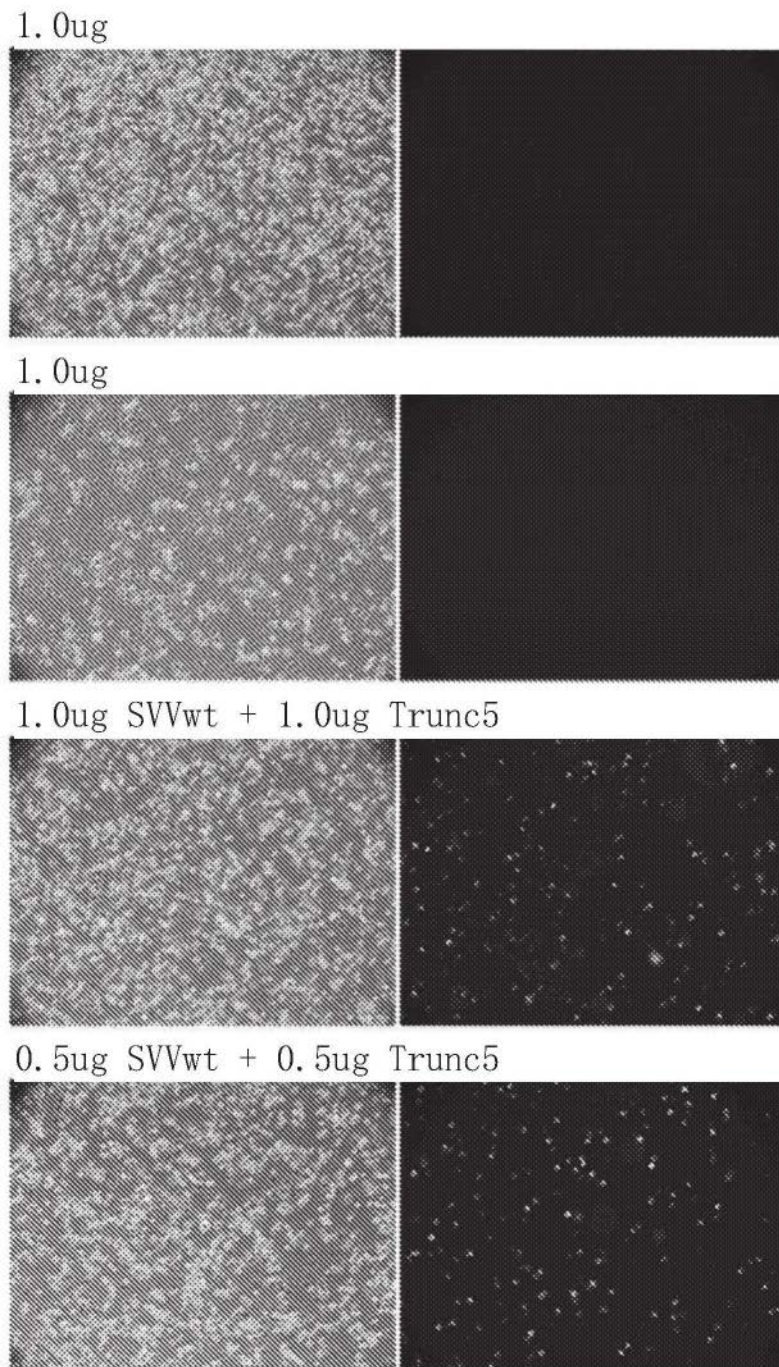
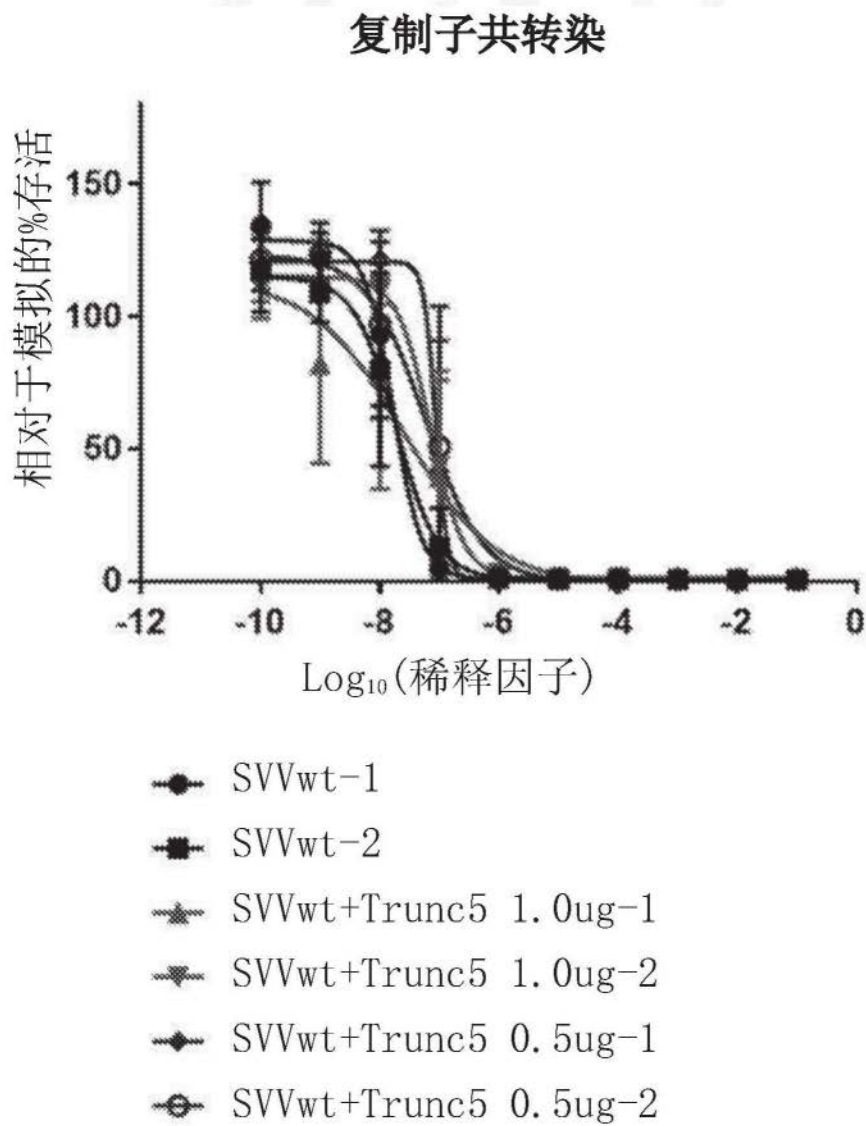


图4A



样品	IC50	平均值
SVVwt 1.0ug	1.69E-08	1.791E-08
	1.9E-08	
SVVwt+Trunc5 1ug	2.51E-08	4.797E-08
	7.09E-08	
SVVwt+Trunc5 0.5ug	3.63E-08	7.215E-08
	5.8E-08	

图4B

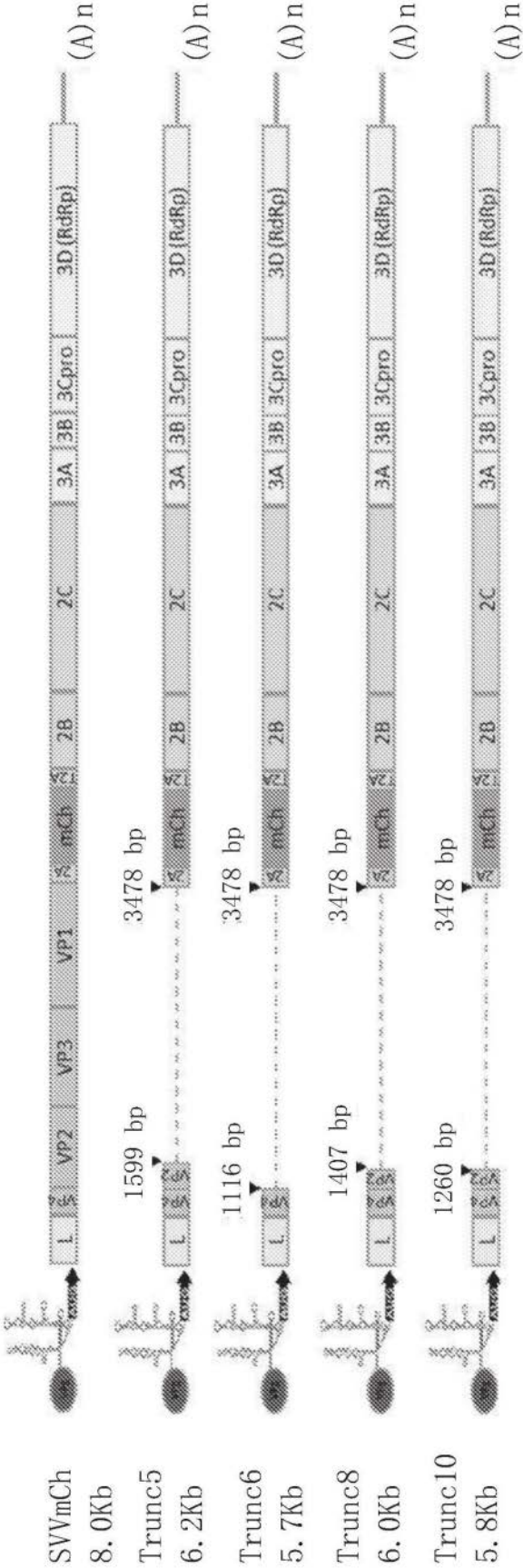


图5A

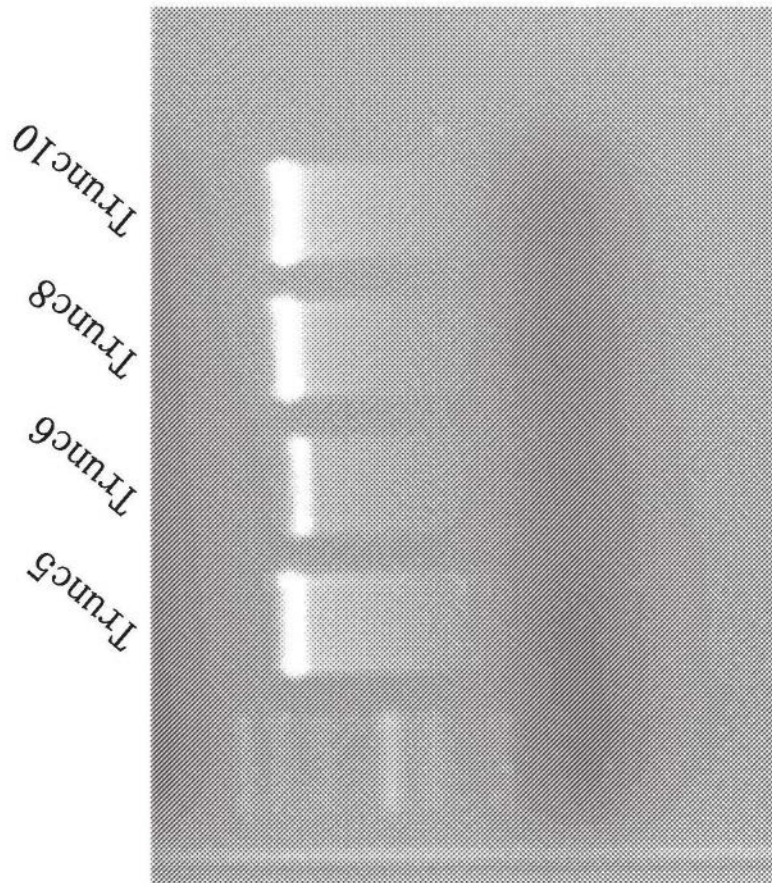


图5B

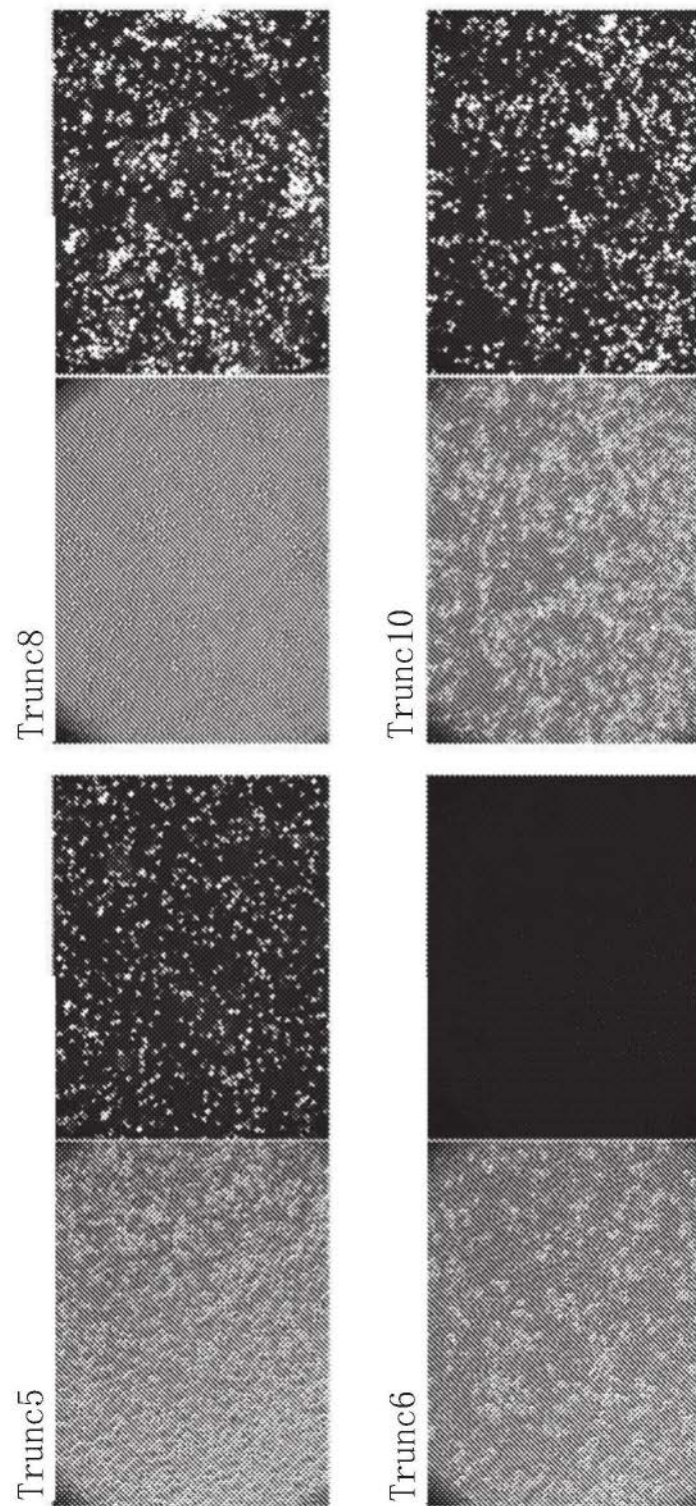


图5C

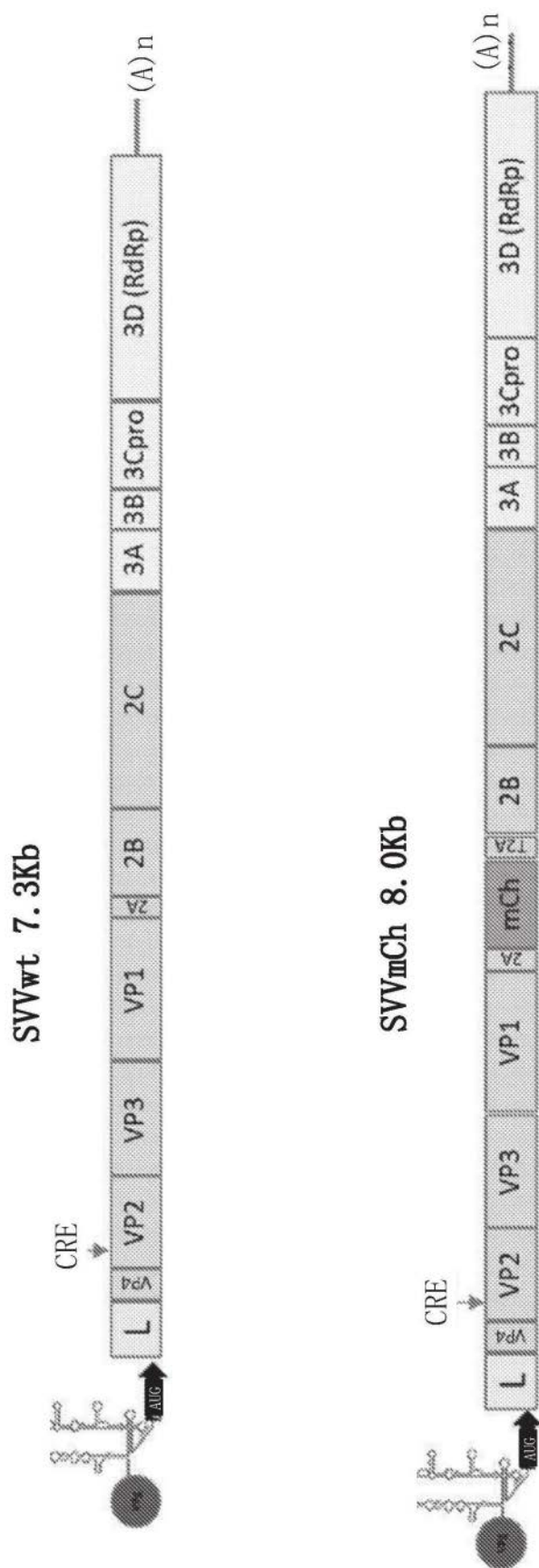


图6A

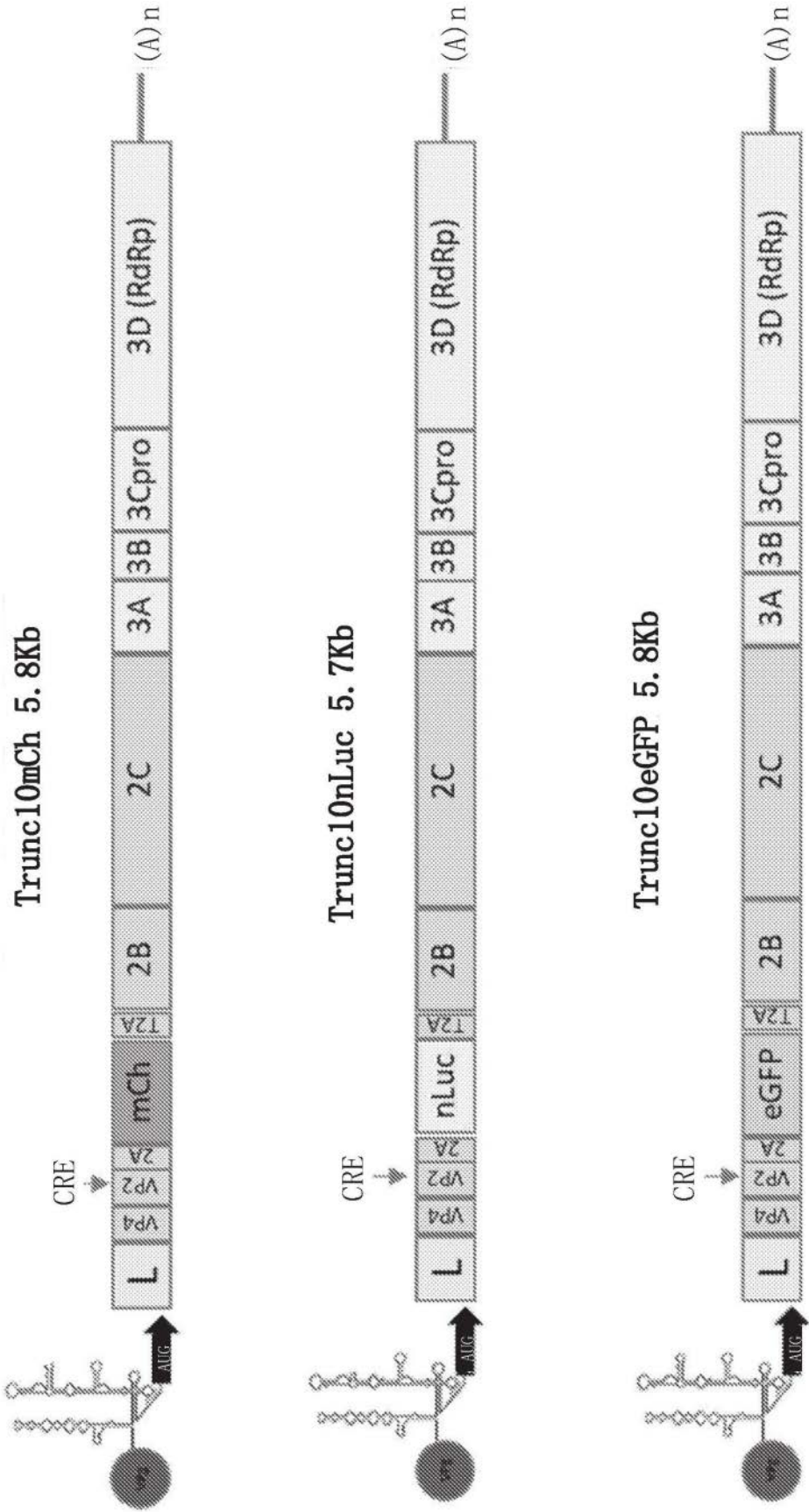


图6B



图7A

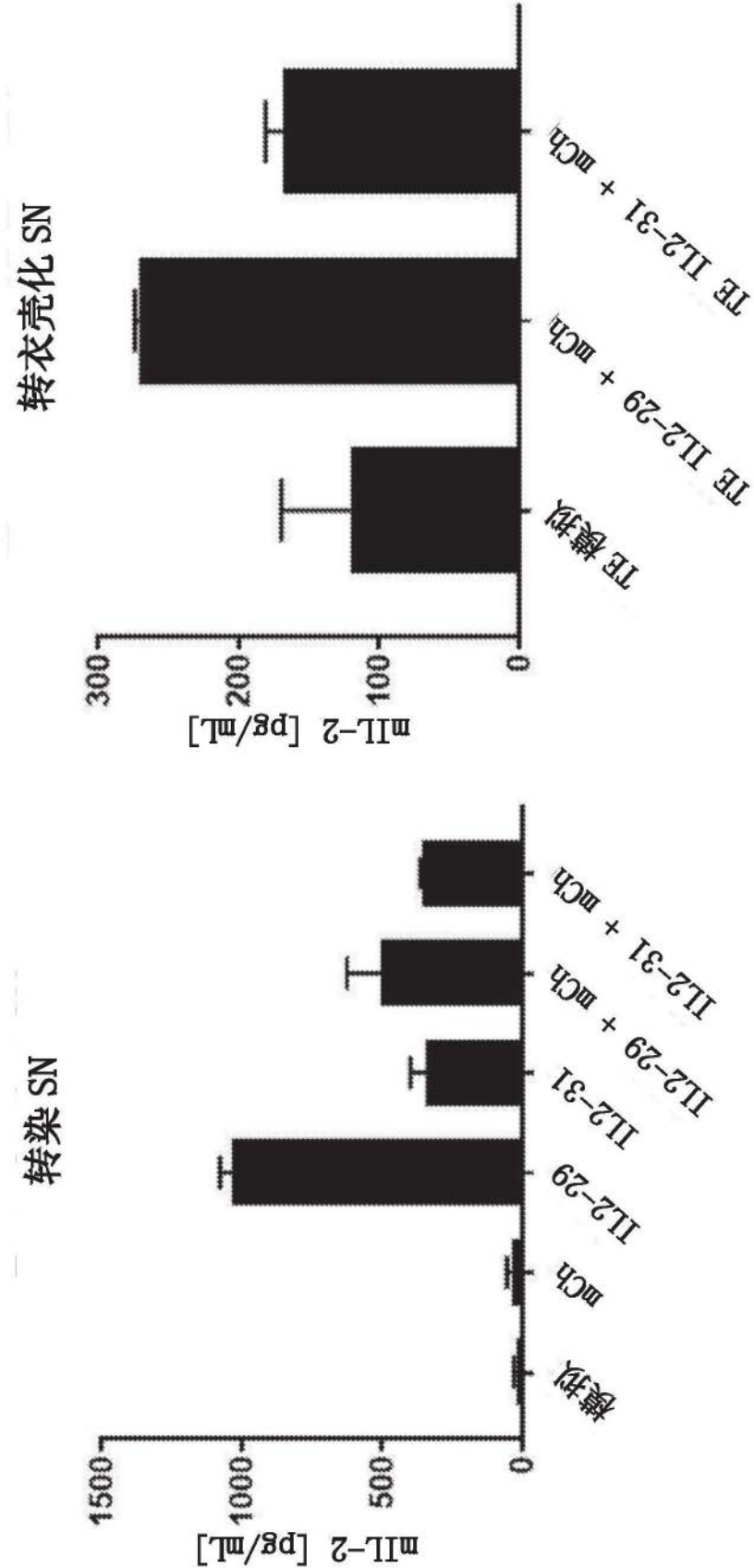


图7B

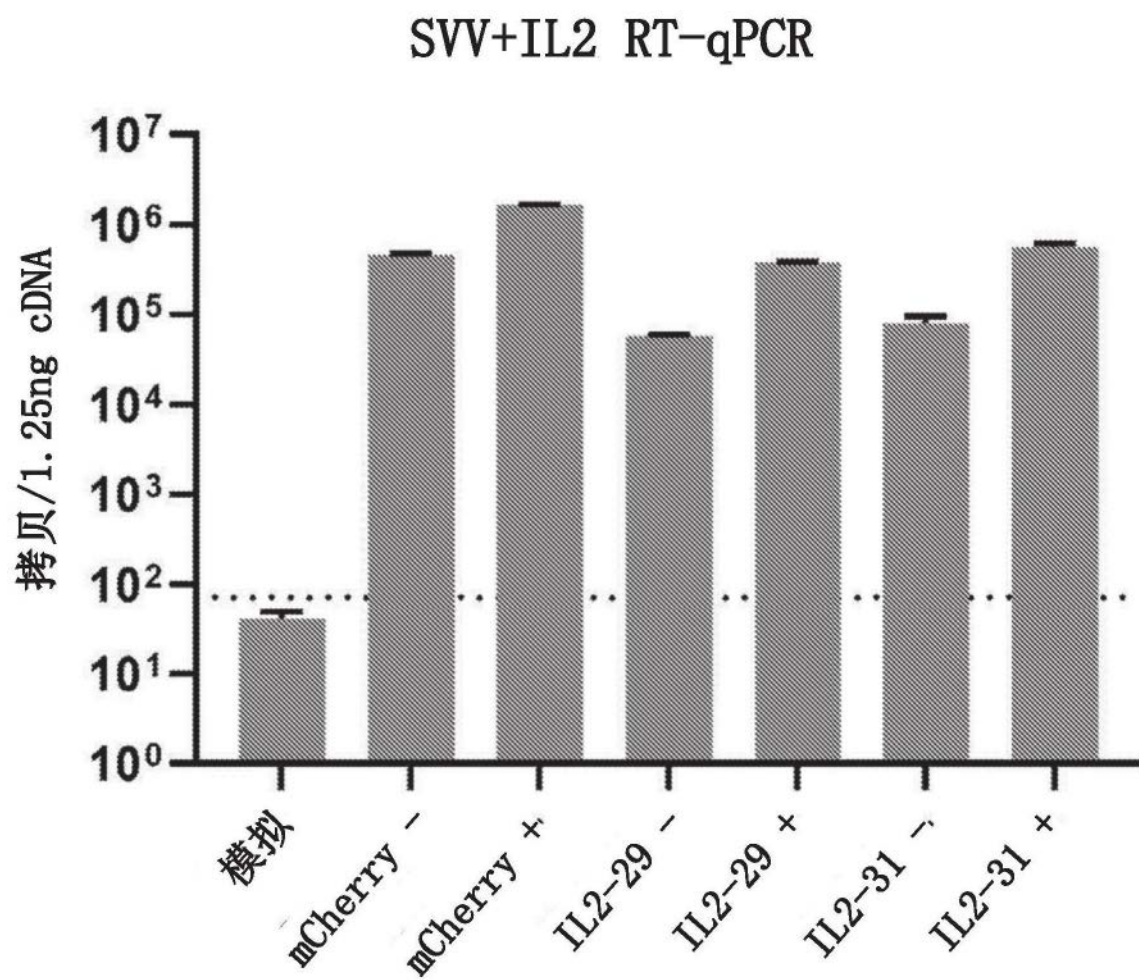


图7C

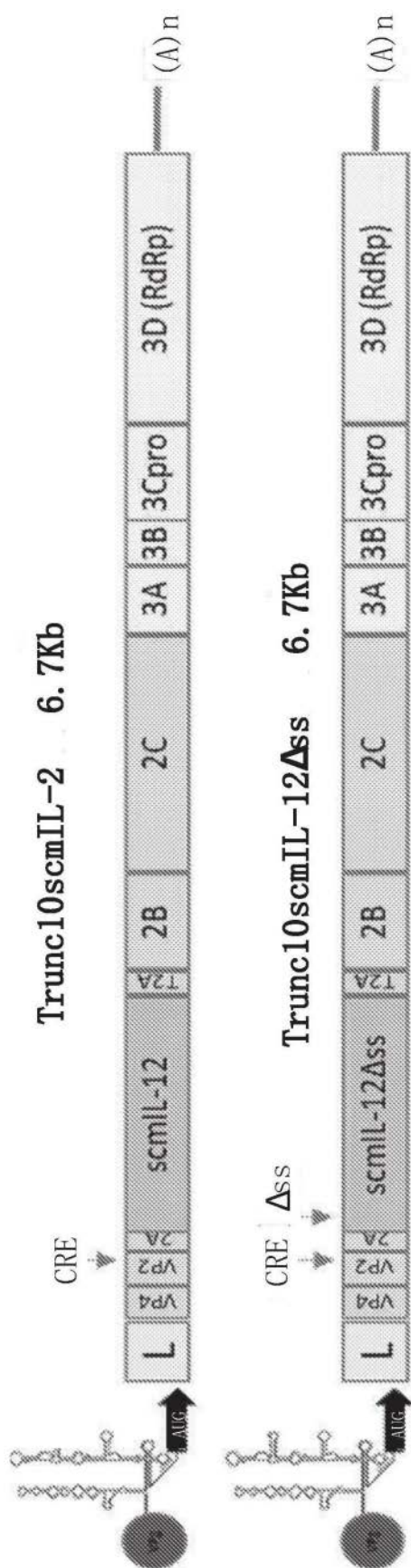


图8A

SVV 复制子 IL-12 RT-qPCR

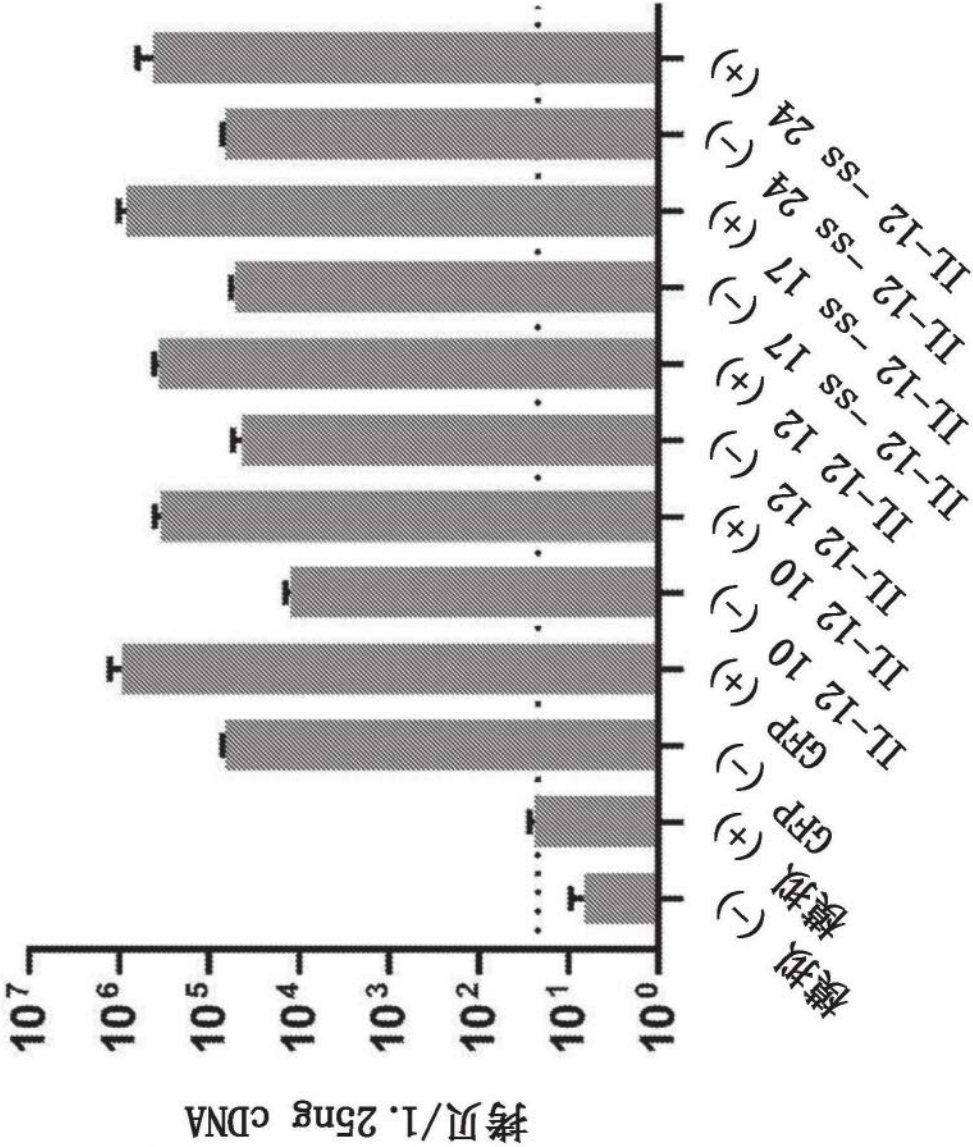


图8B

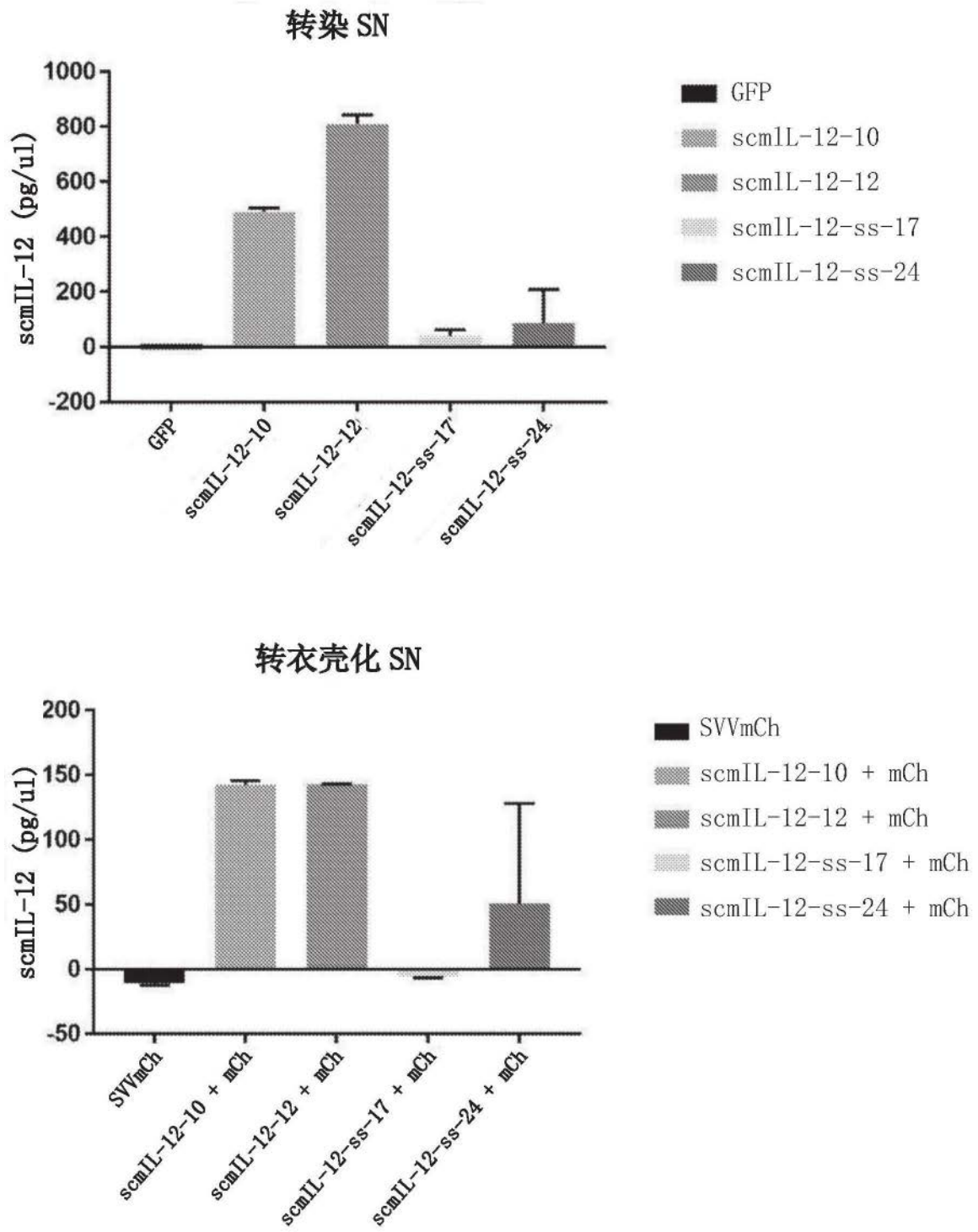


图8C

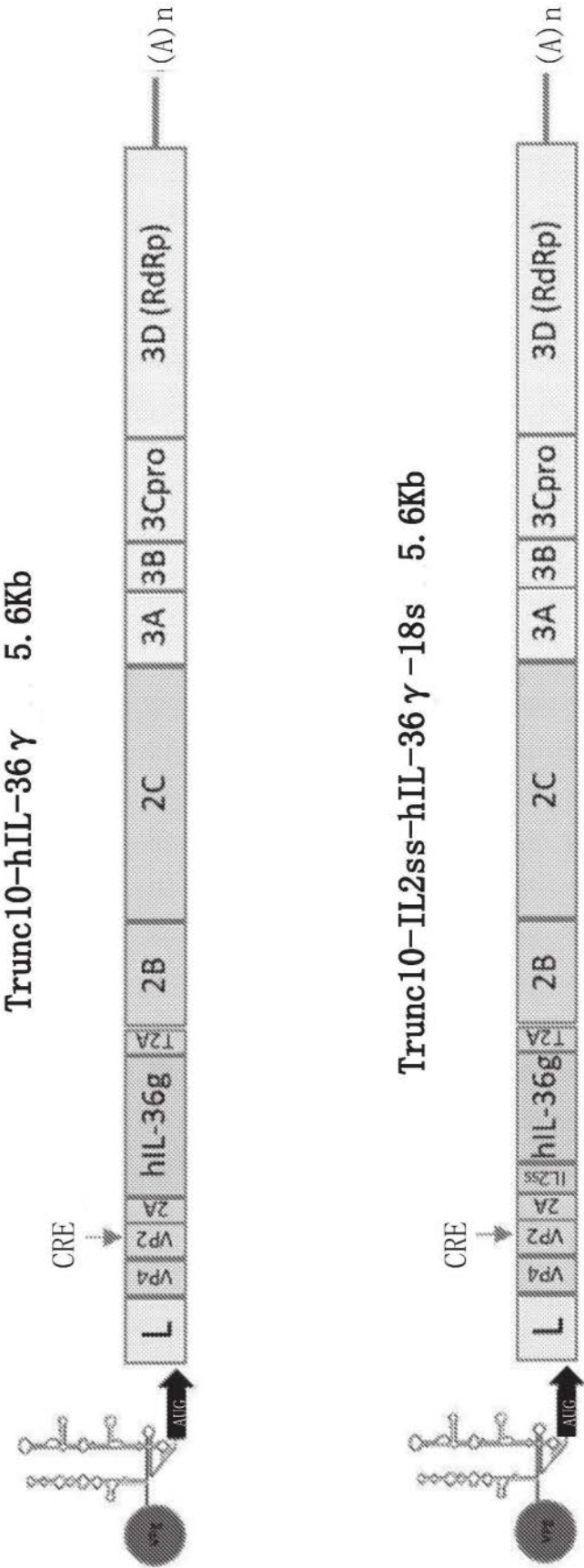


图9A

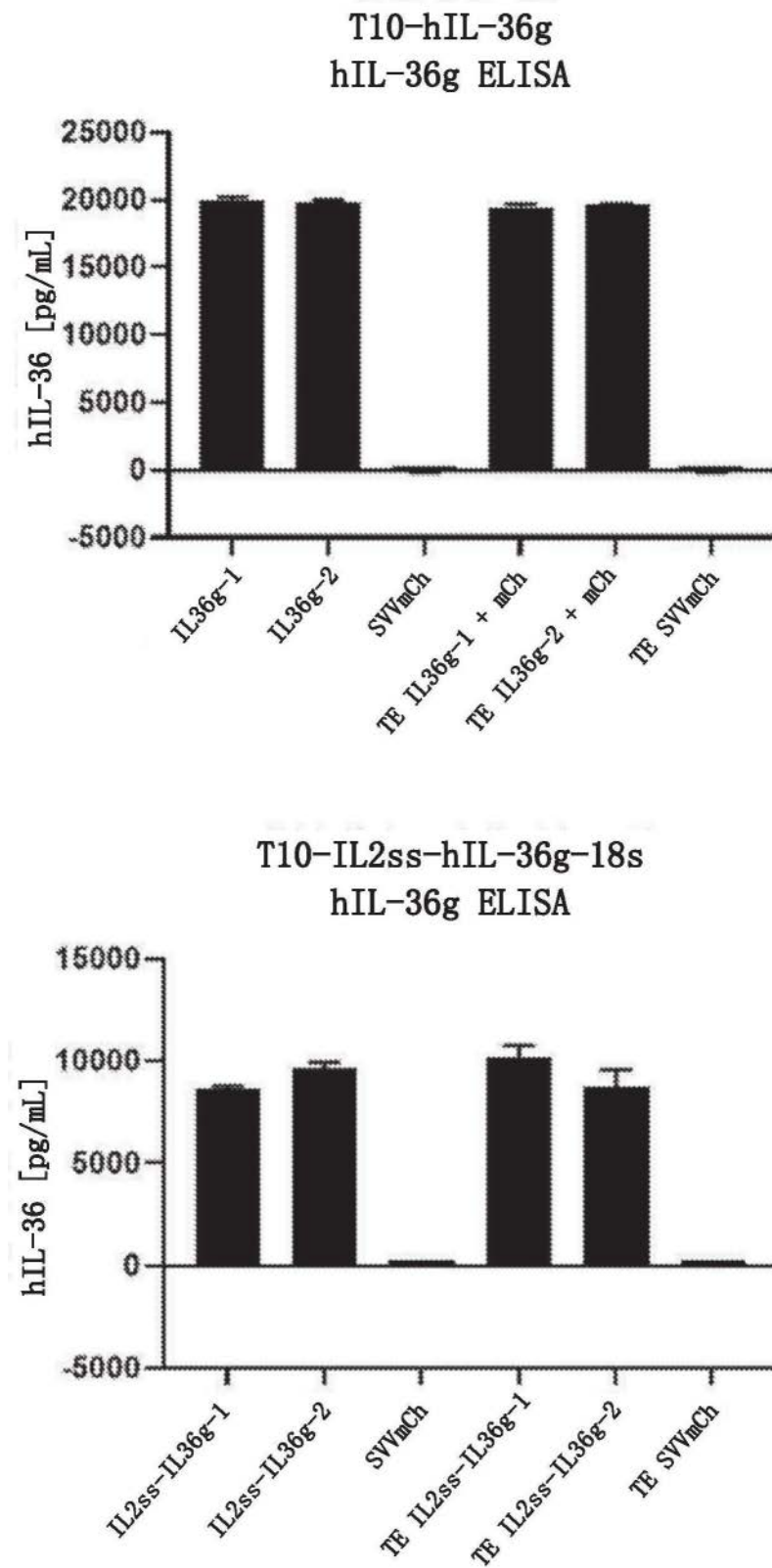


图9B

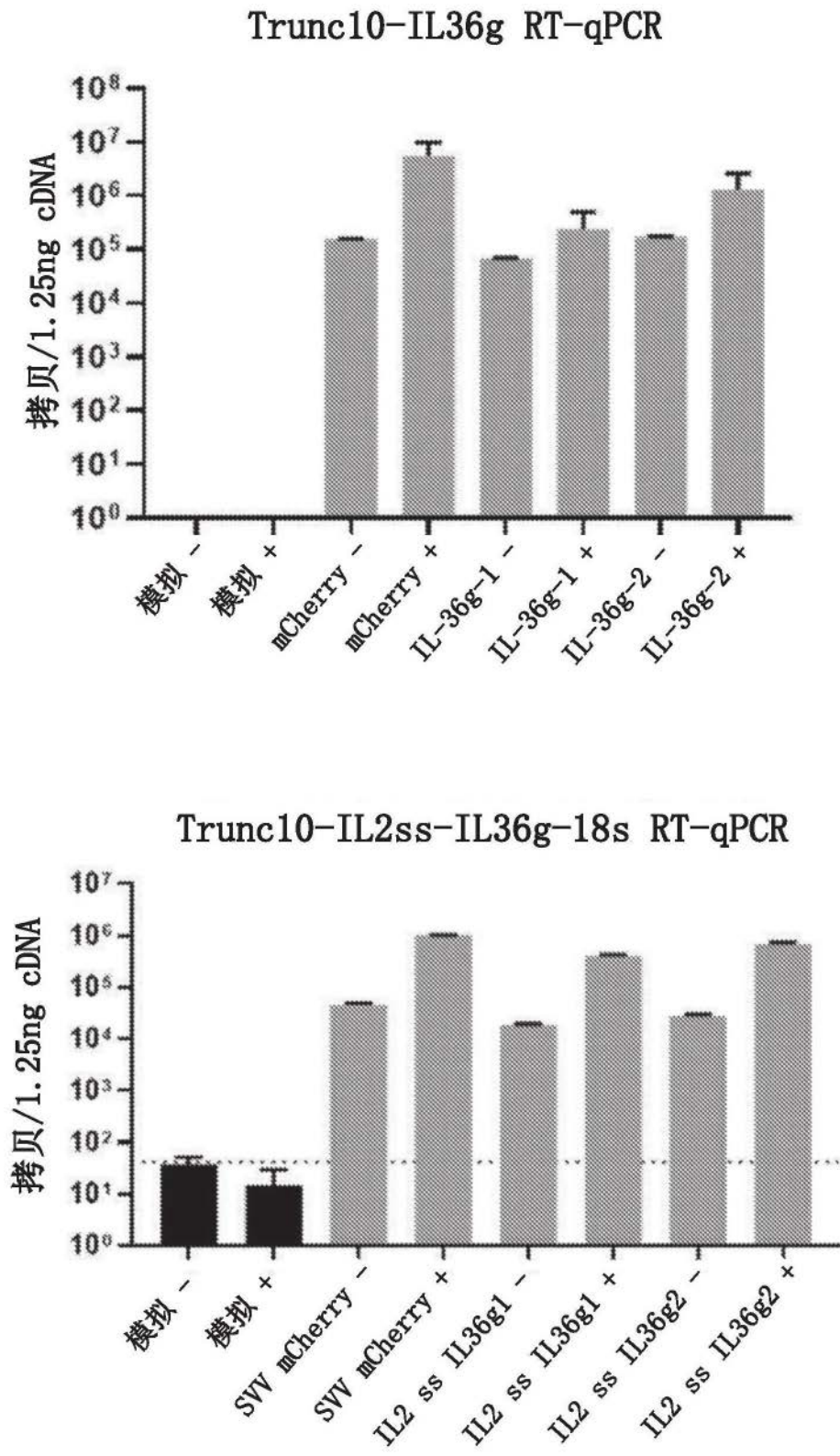


图9C

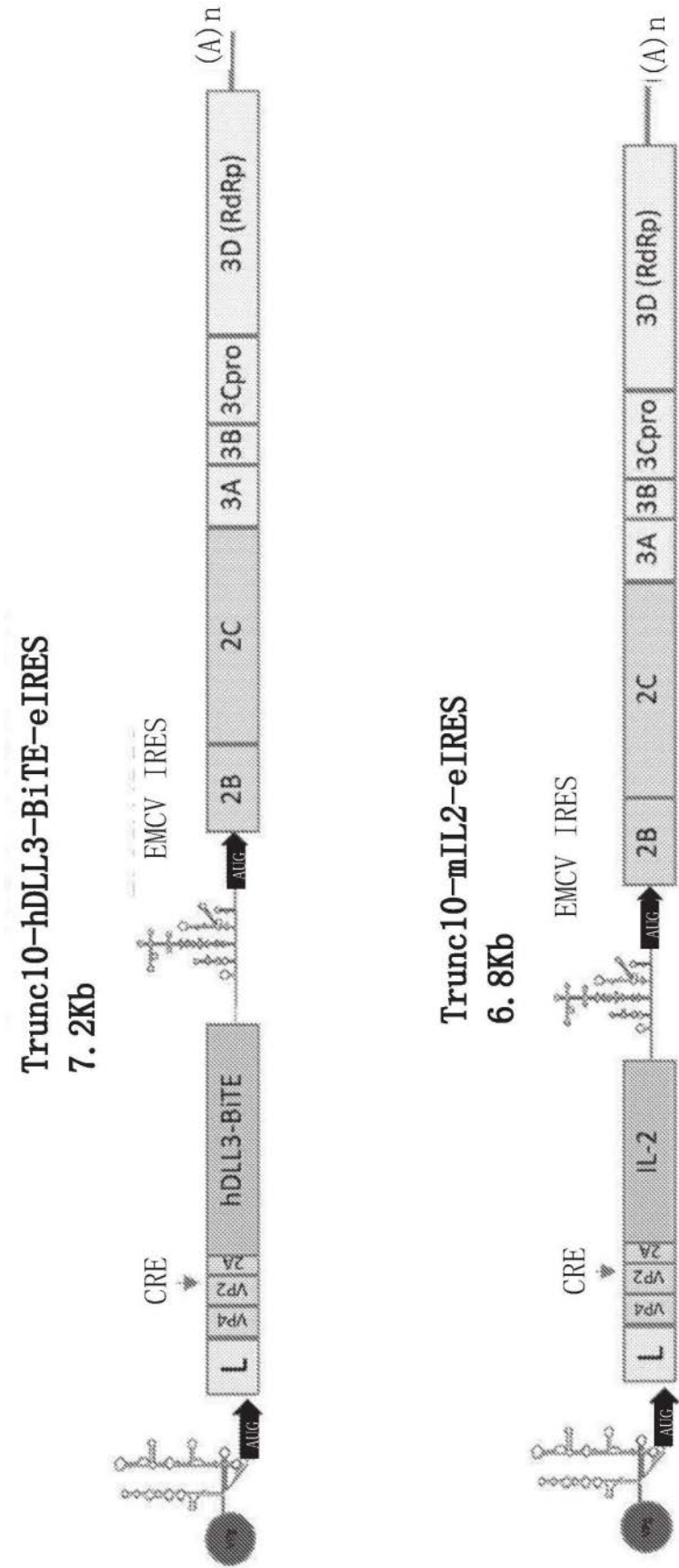


图10A

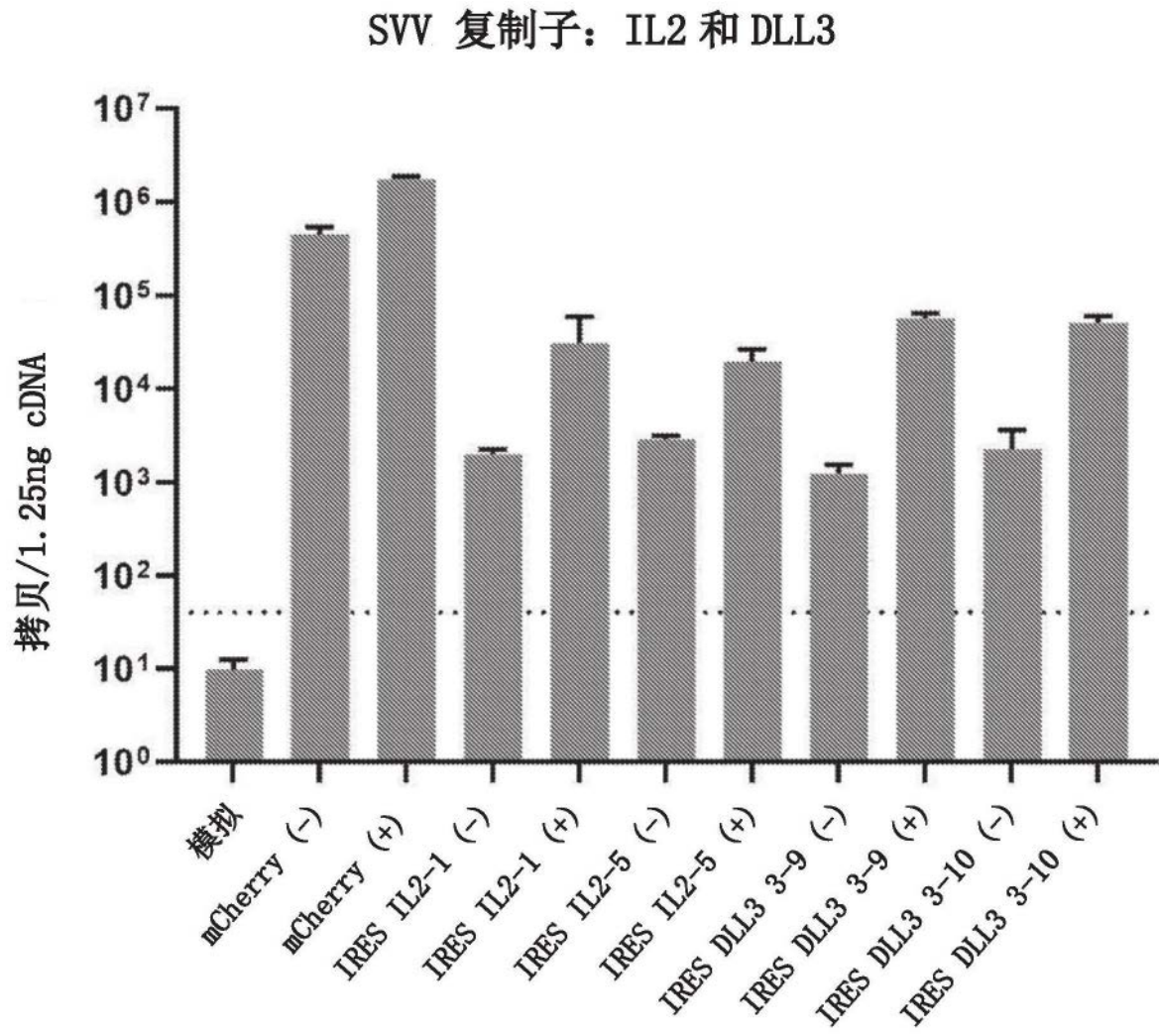


图10B

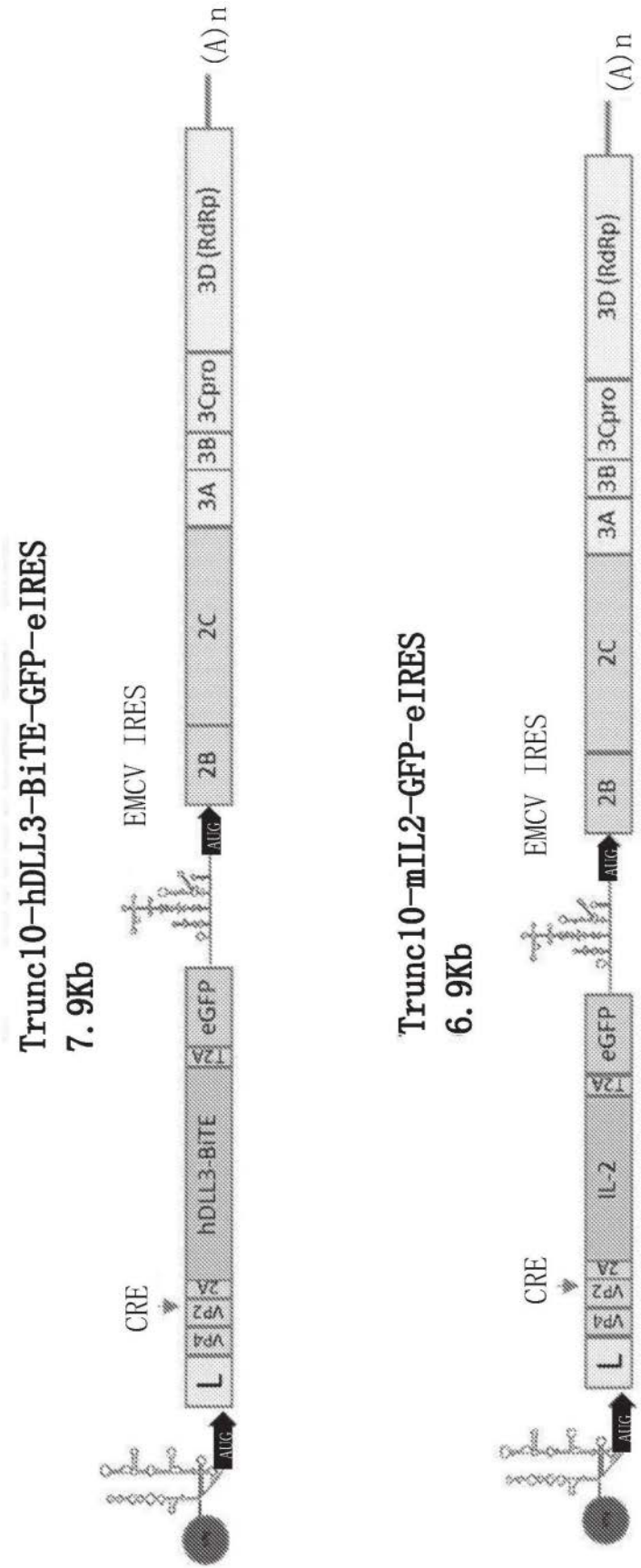


图11A

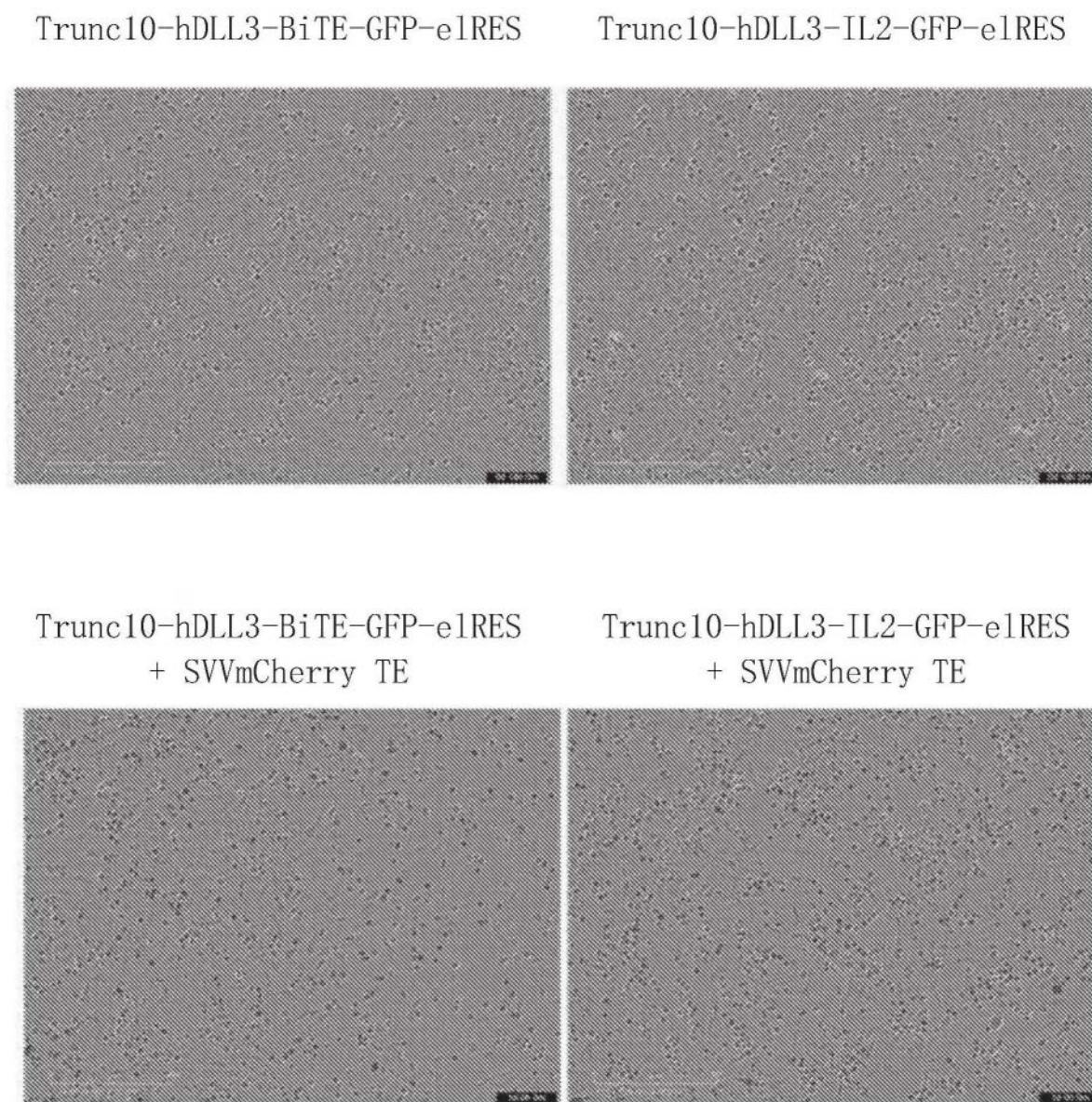


图11B

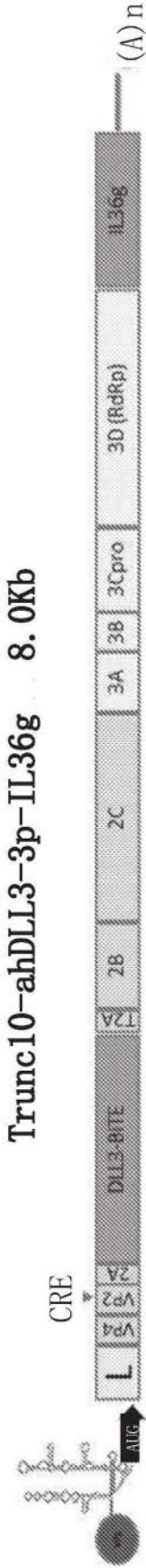


图12A

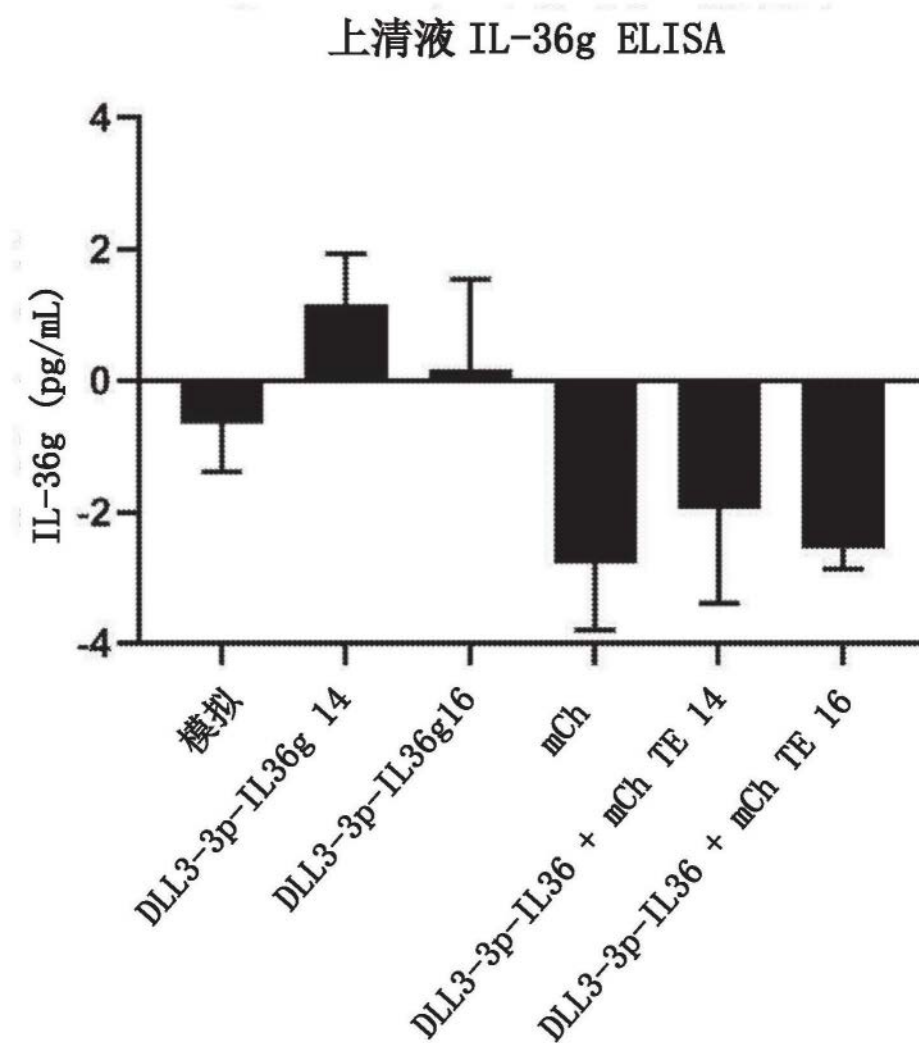


图12B

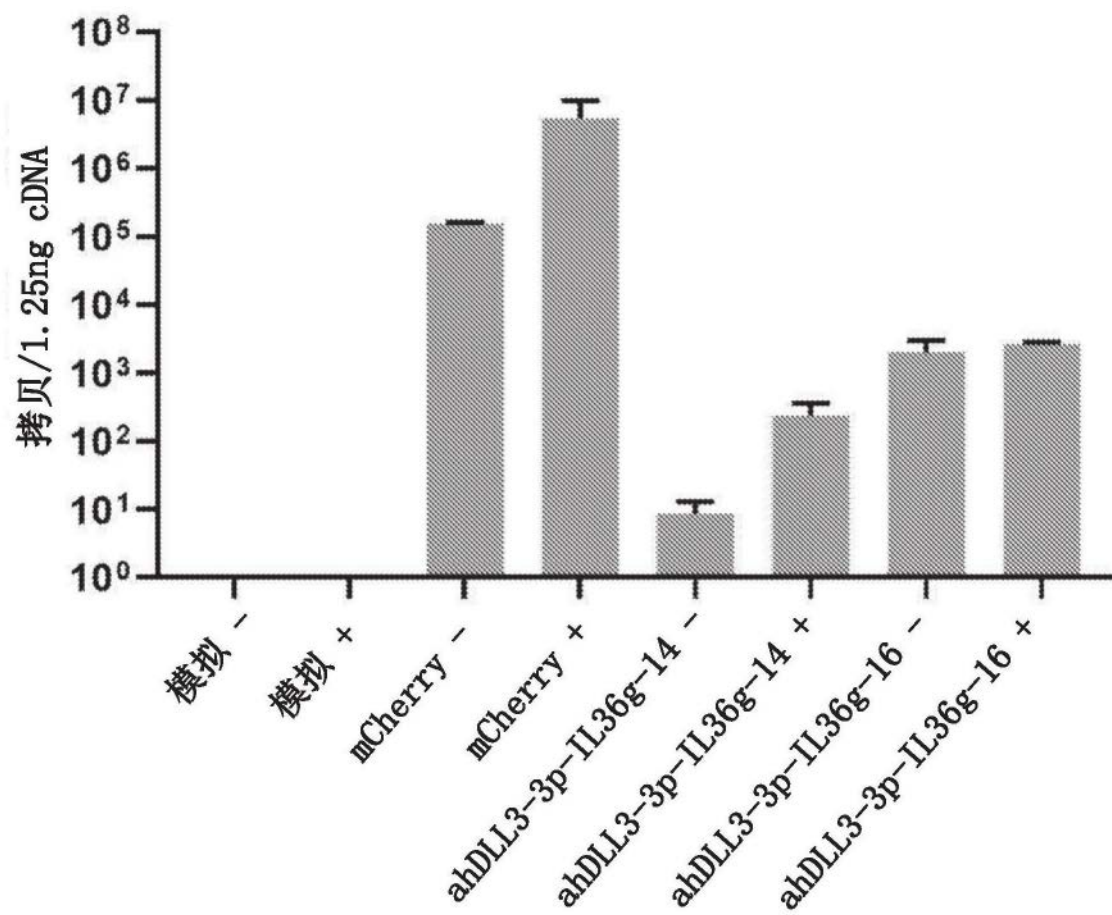


图12C

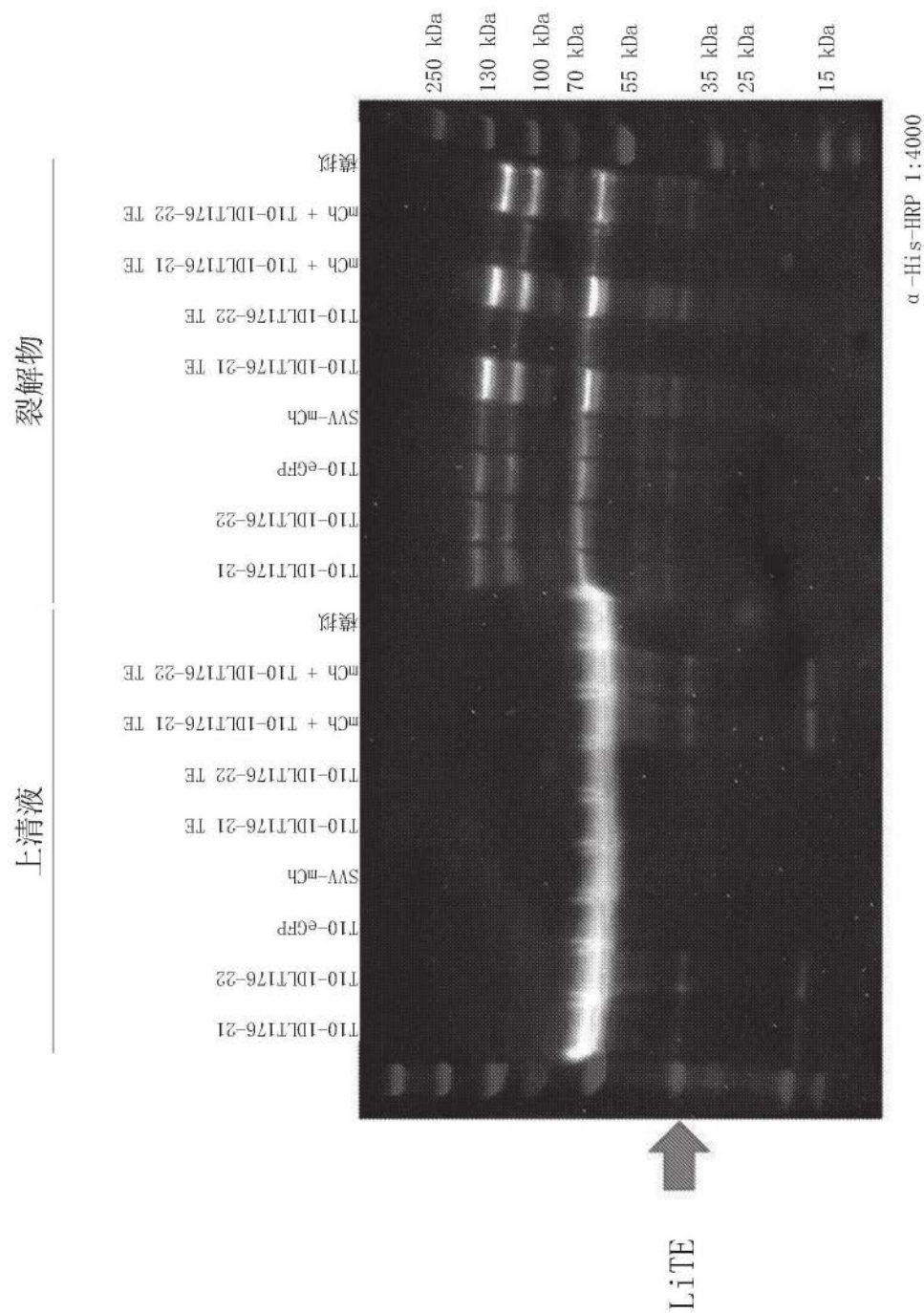


图13A

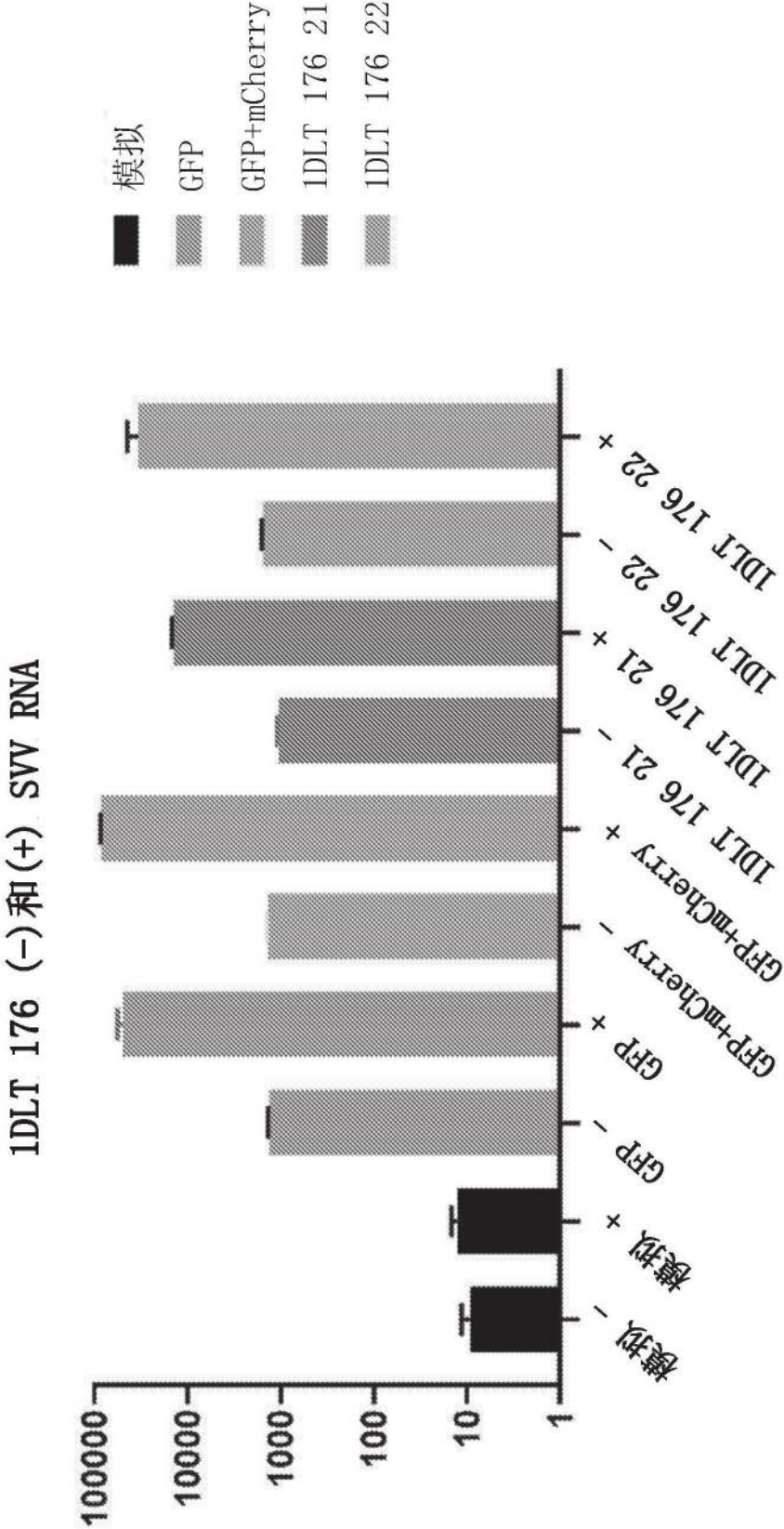


图13B

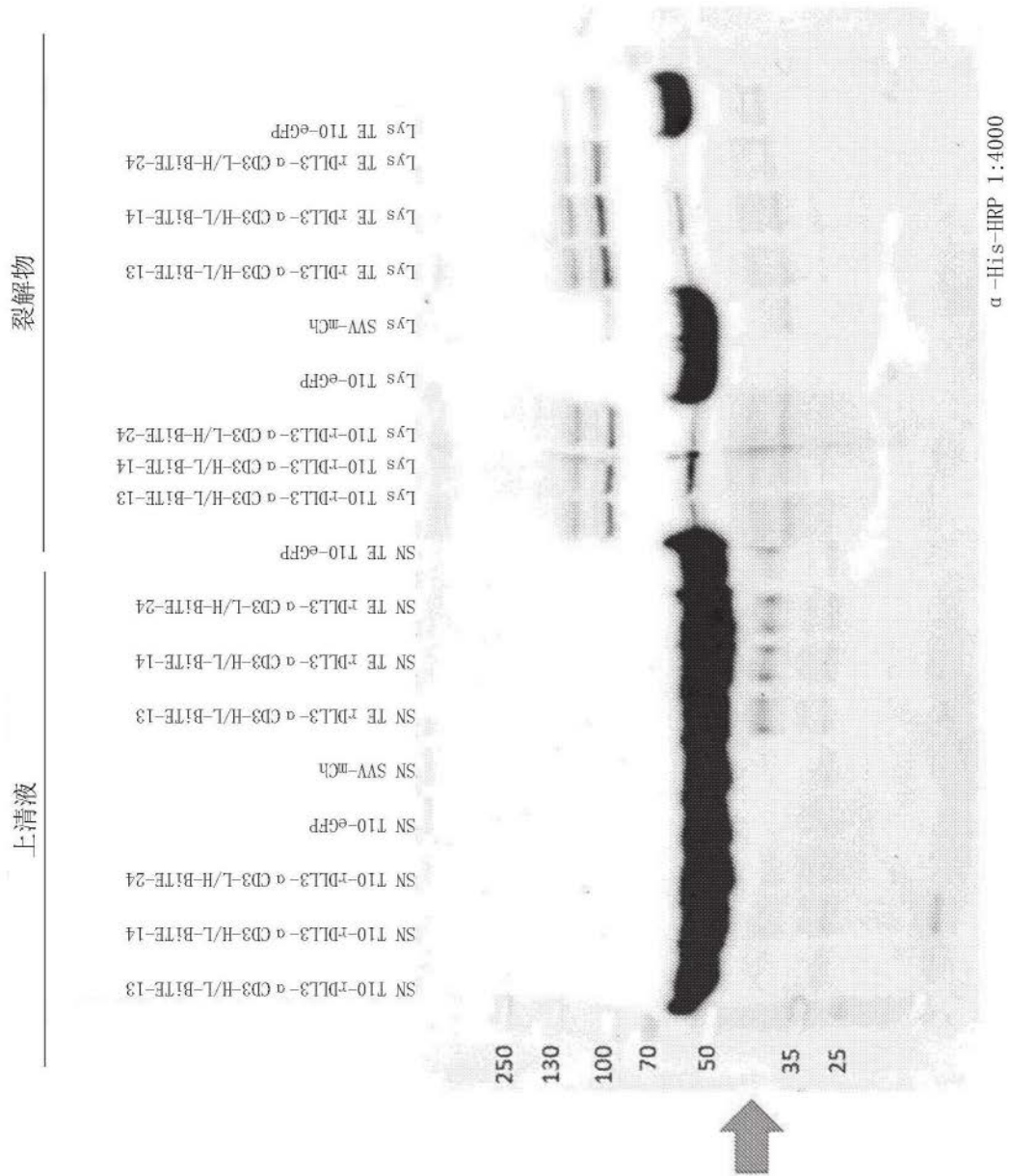


图14A

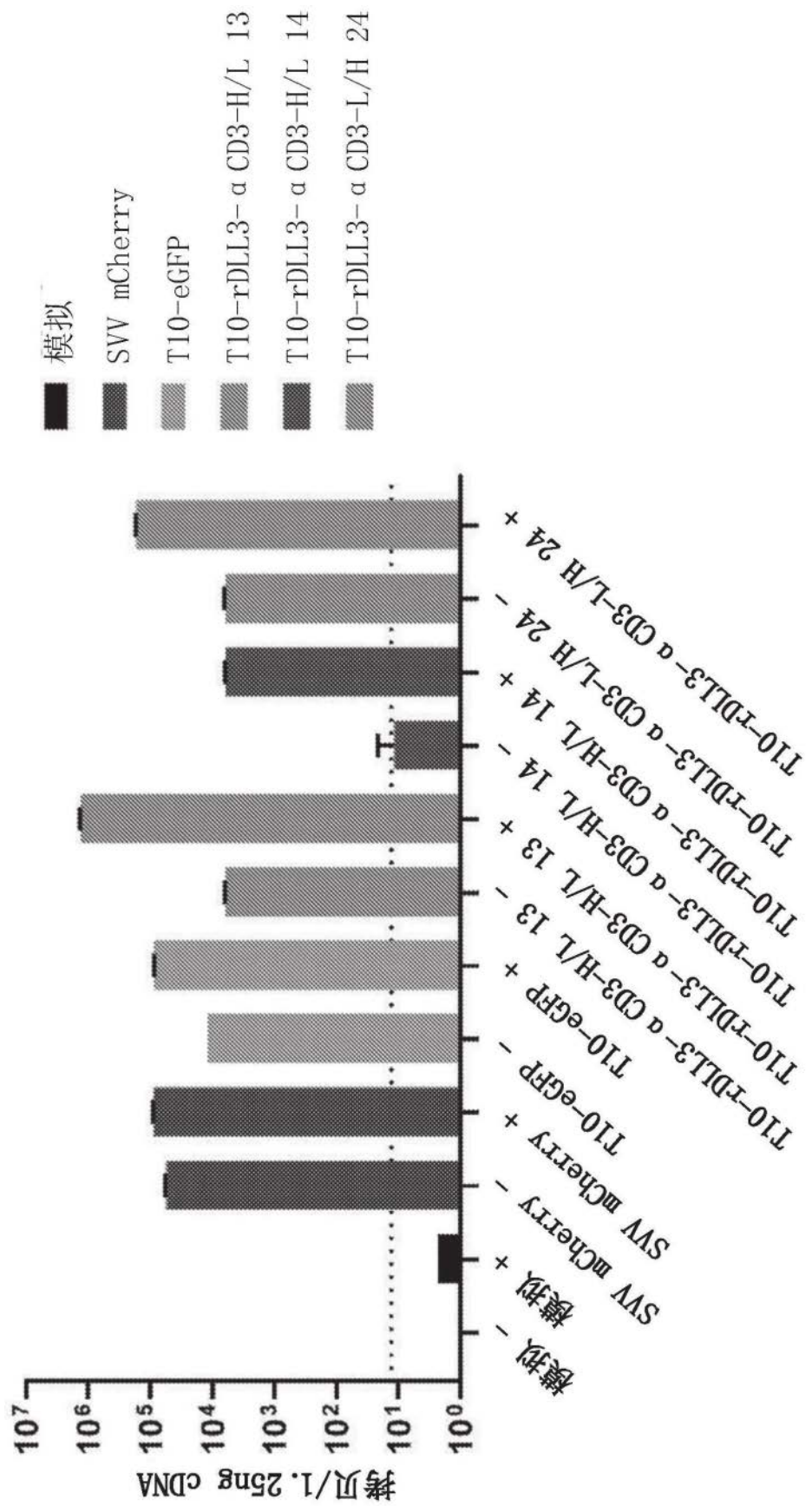


图14B



图15A

CXCL10 ELISA

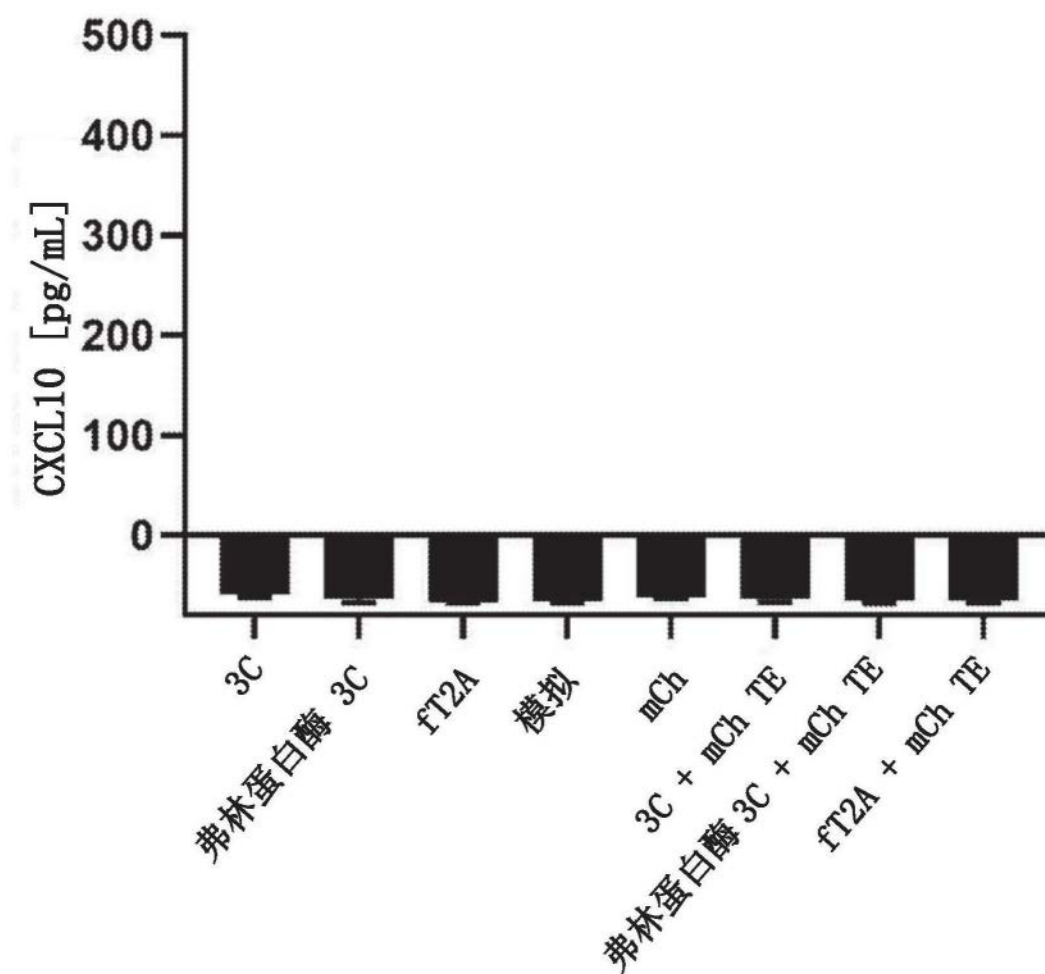


图15B

SVV 复制子 RT-qPCR

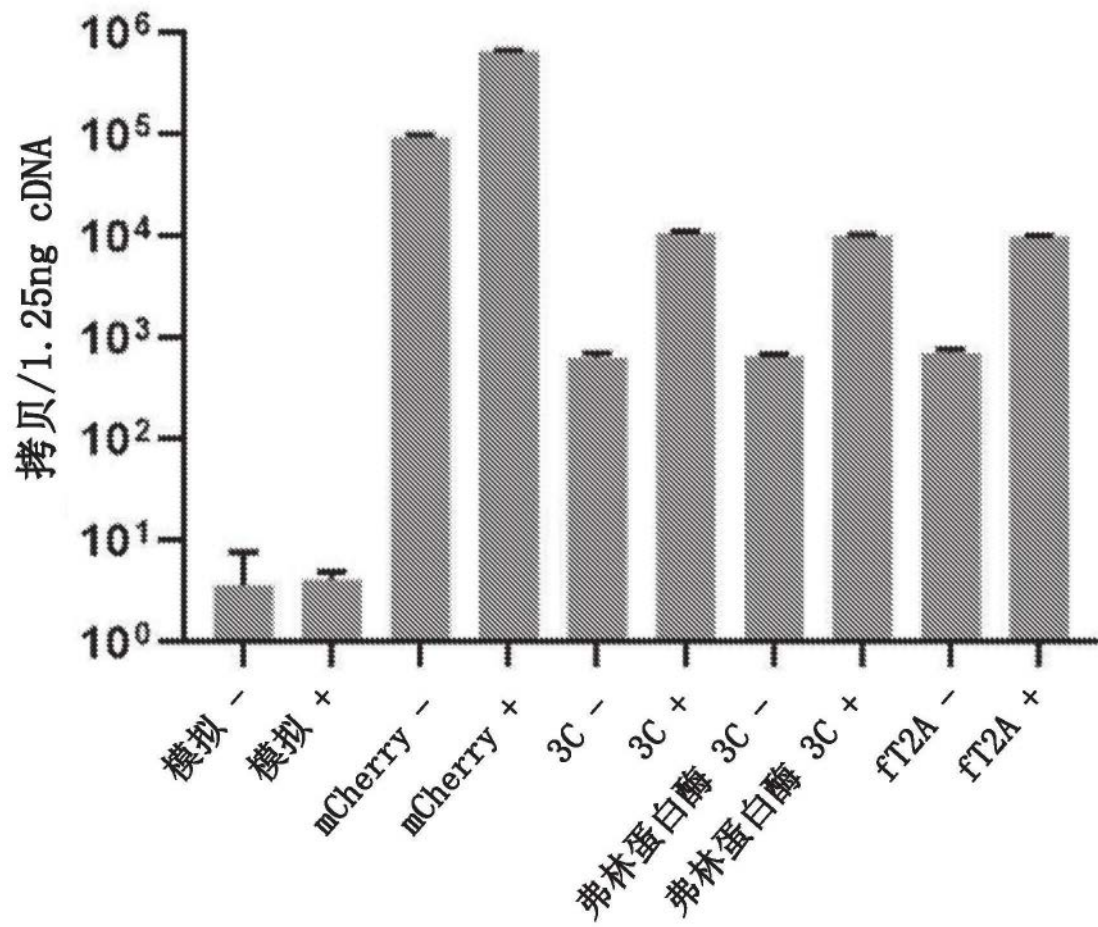


图15C

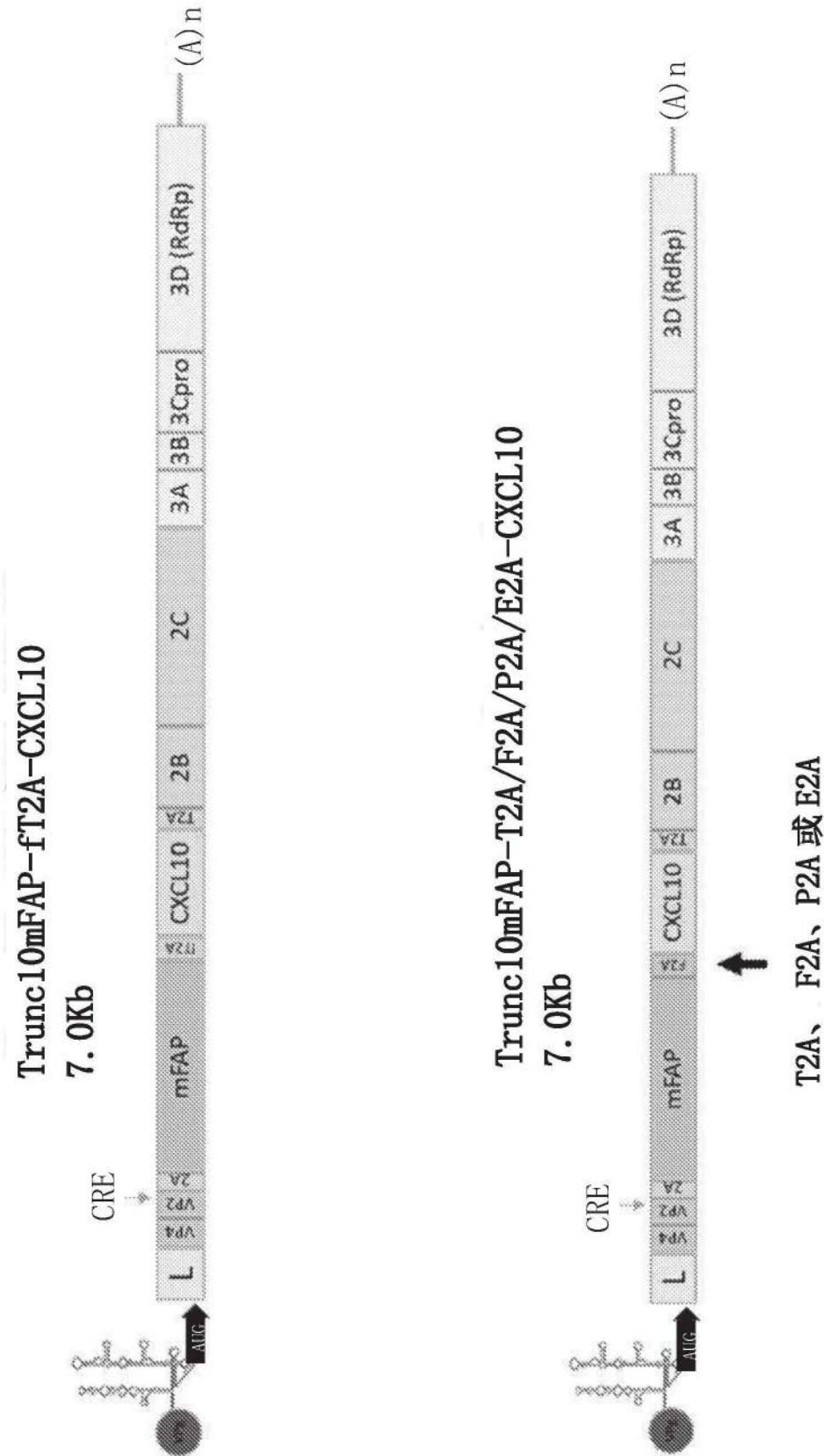


图16A

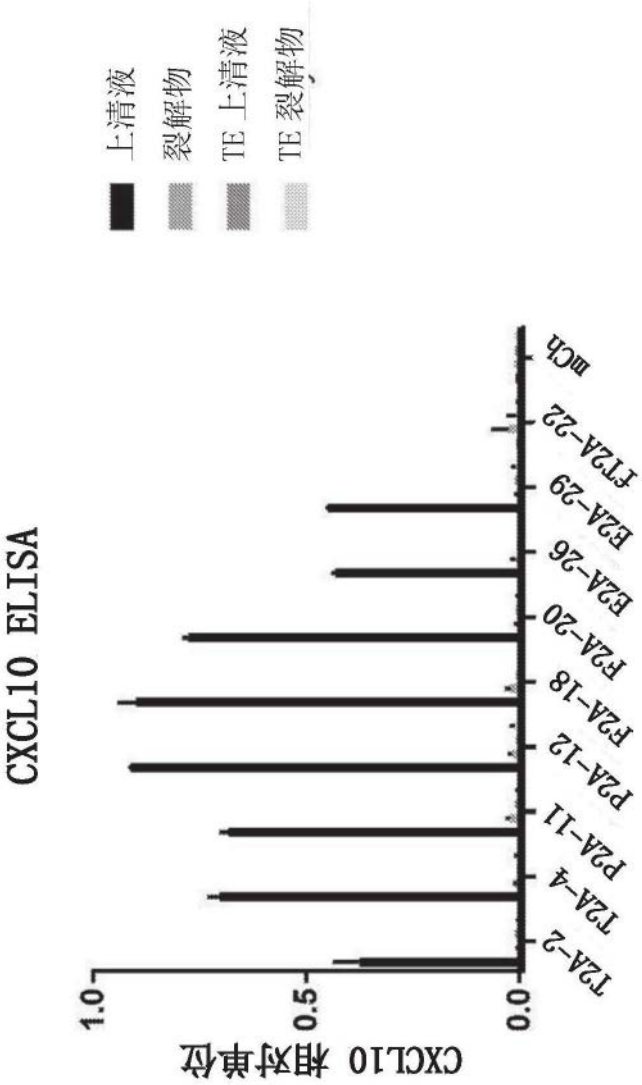


图16B

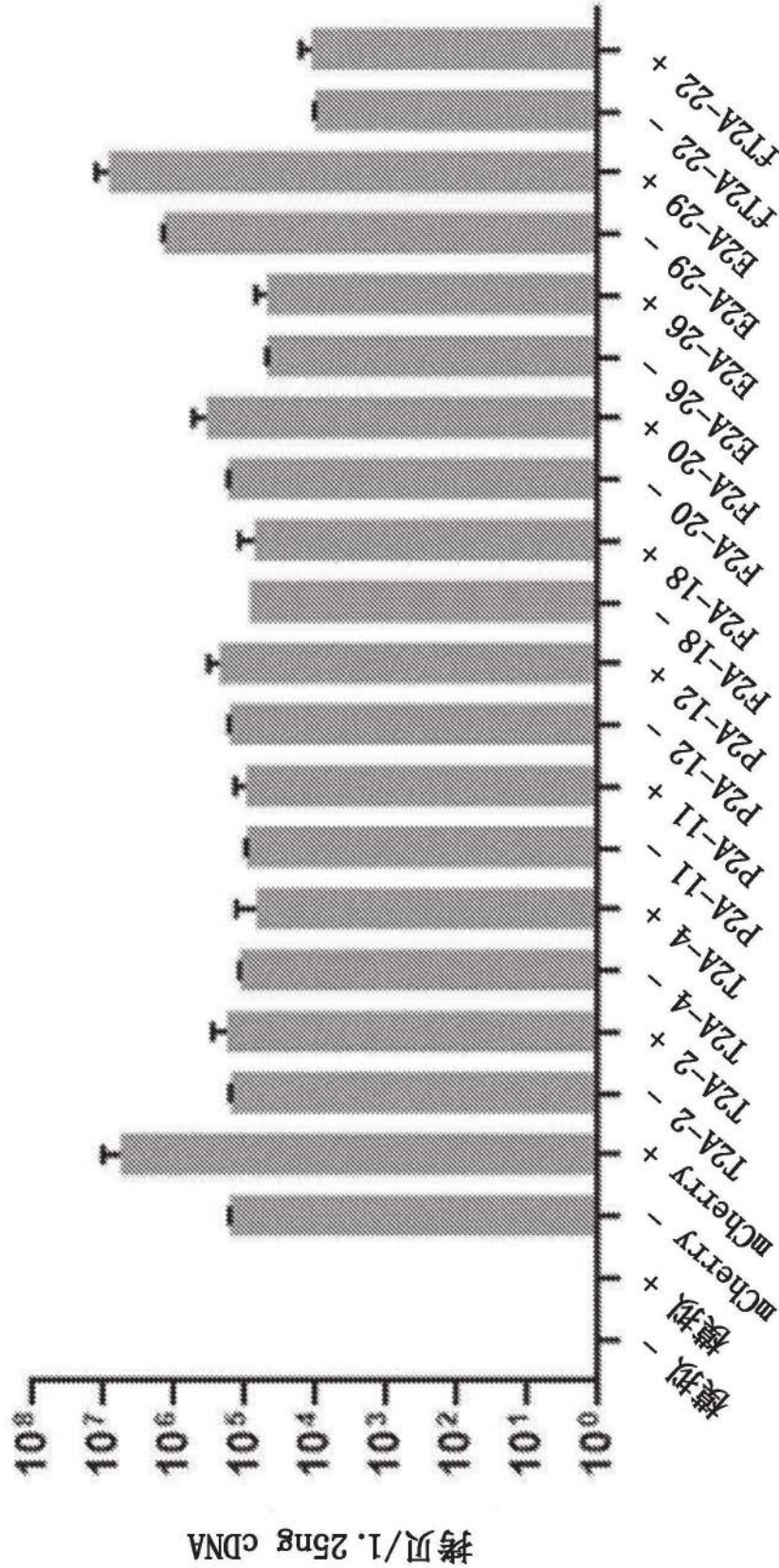


图16C

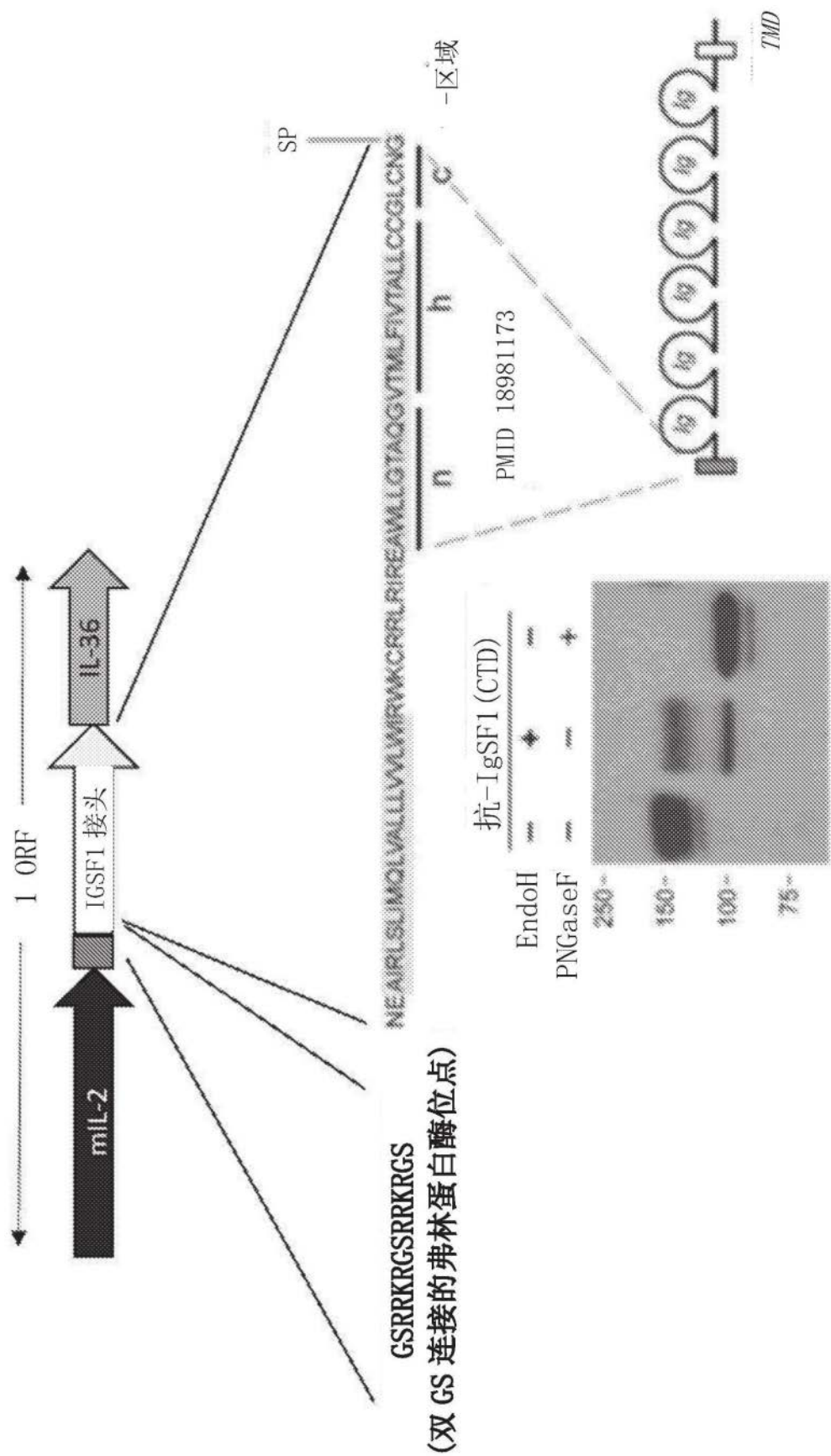


图17A

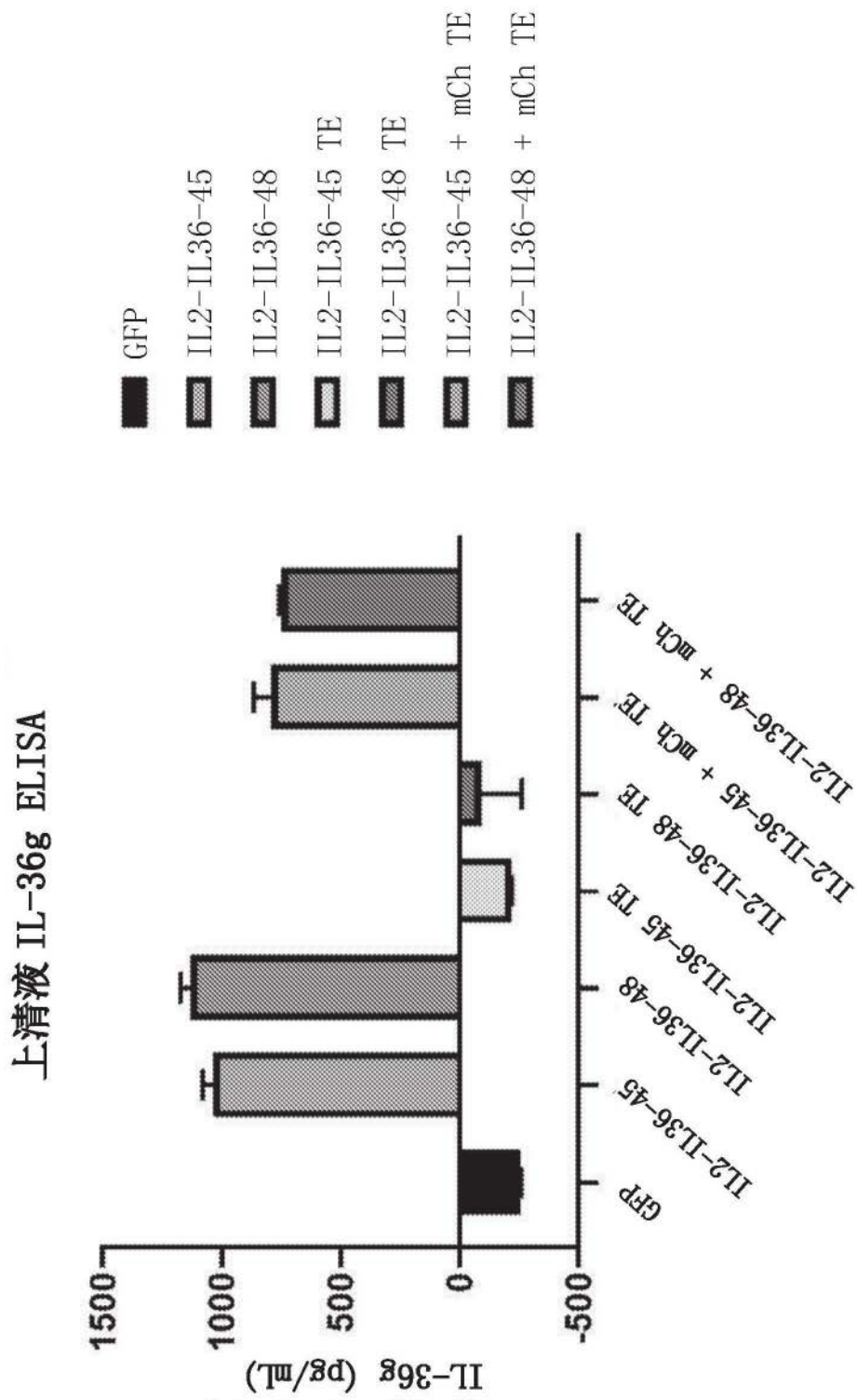


图17B

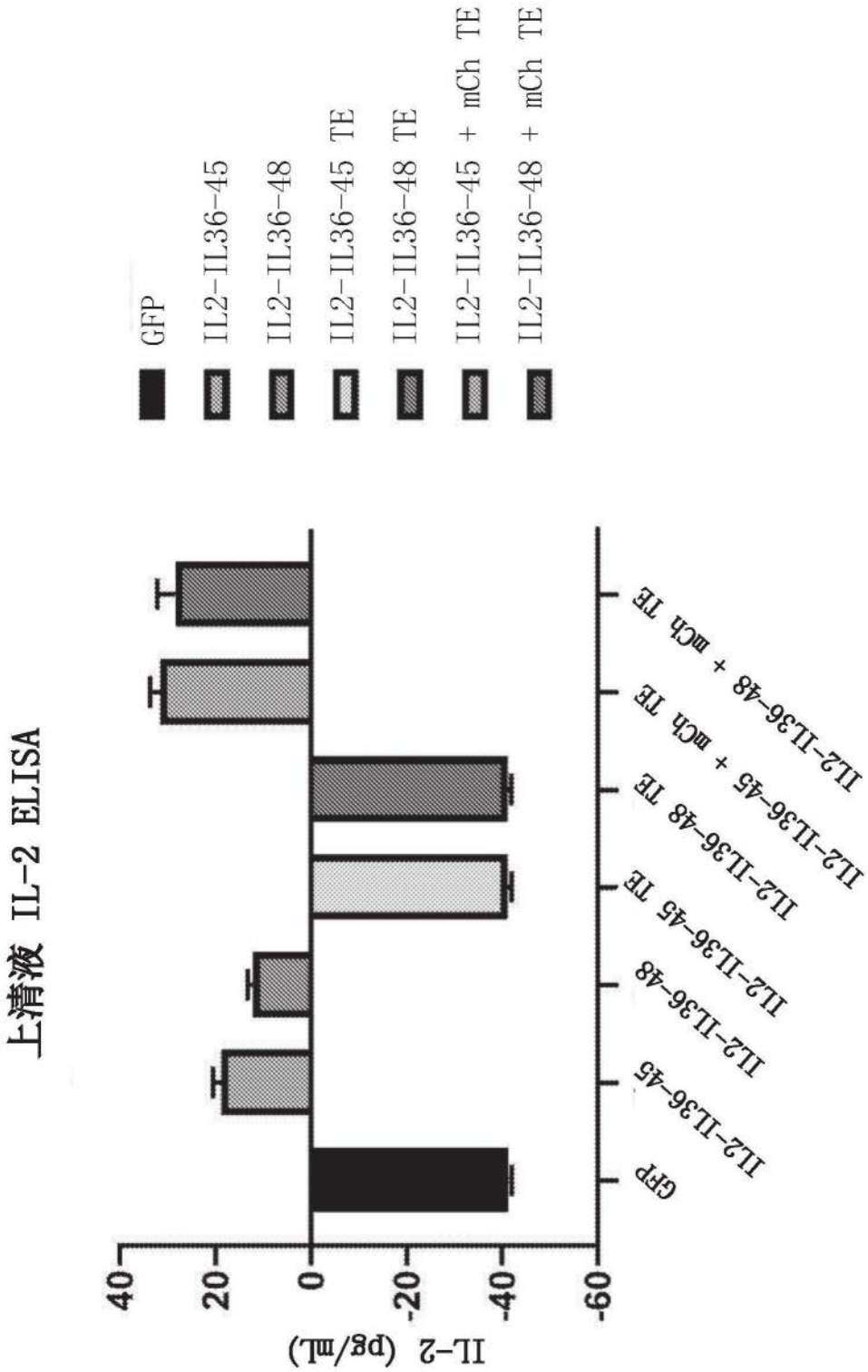


图17C

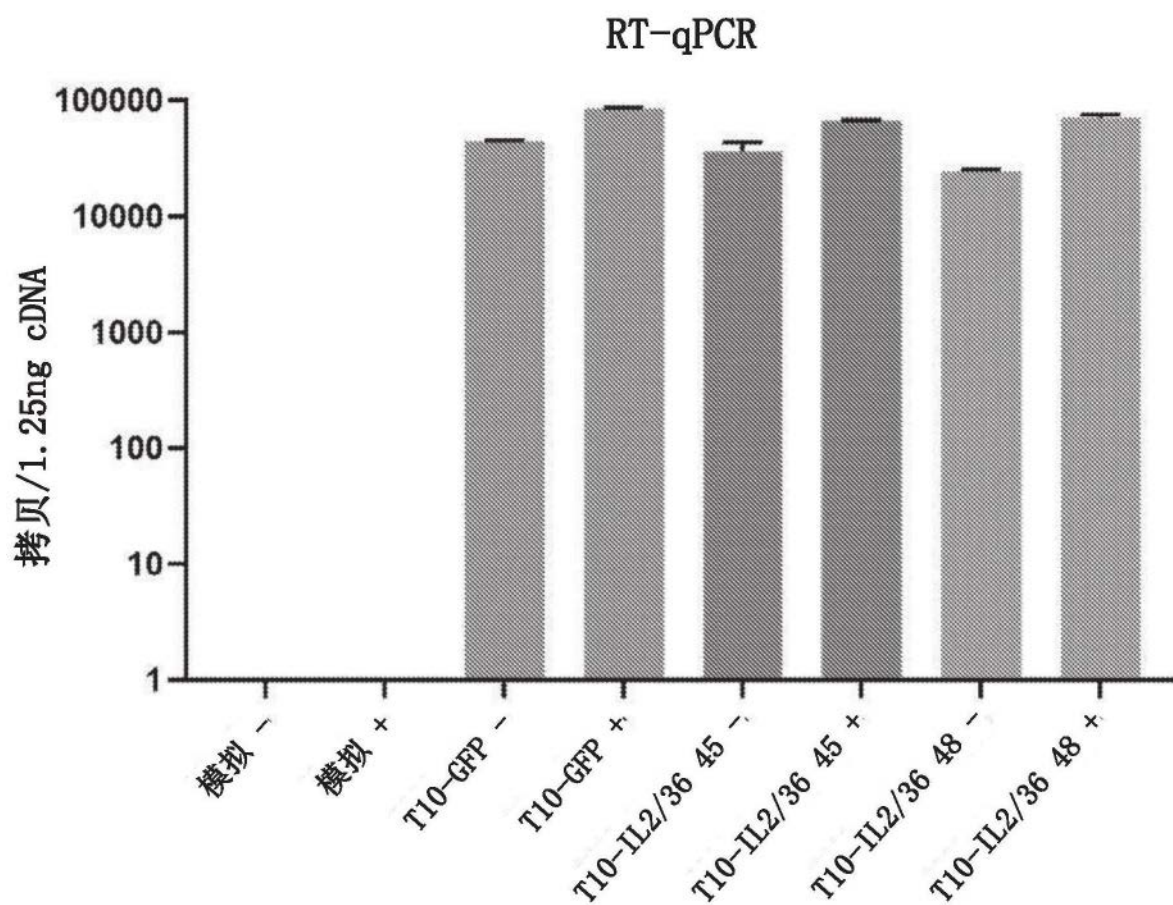


图17D

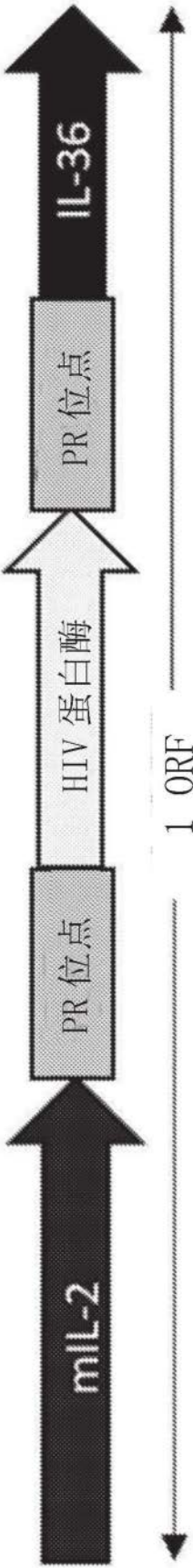


图18A

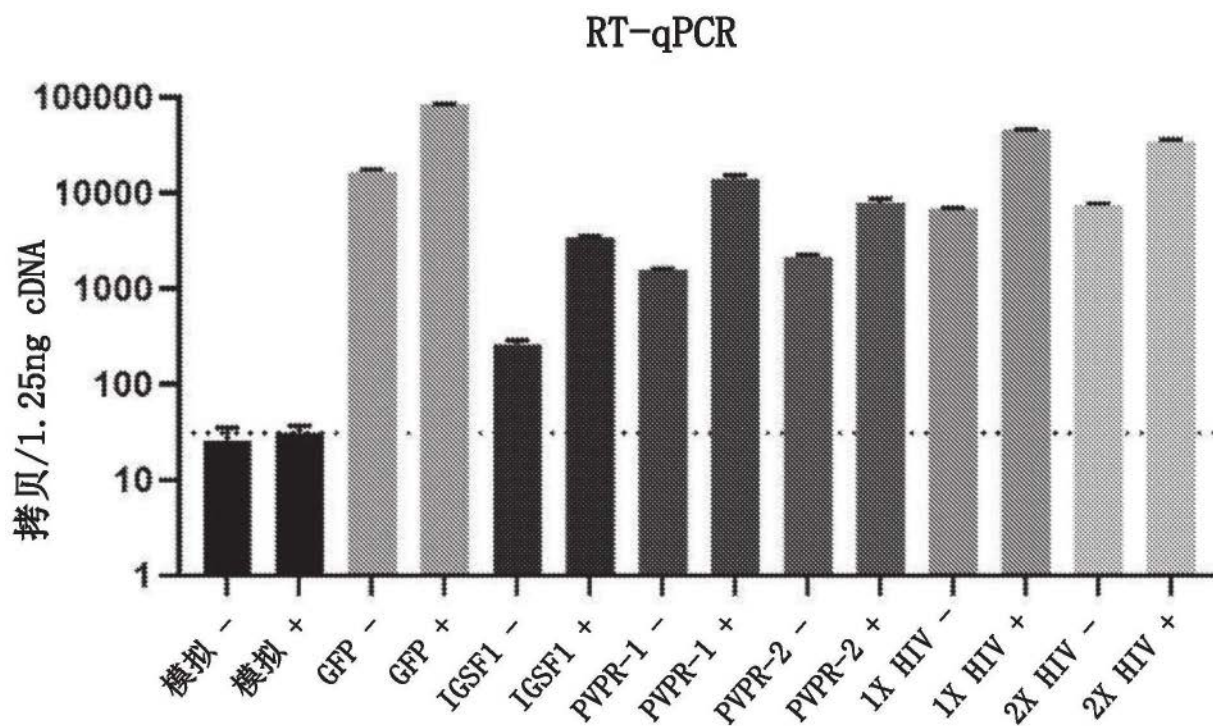


图18B

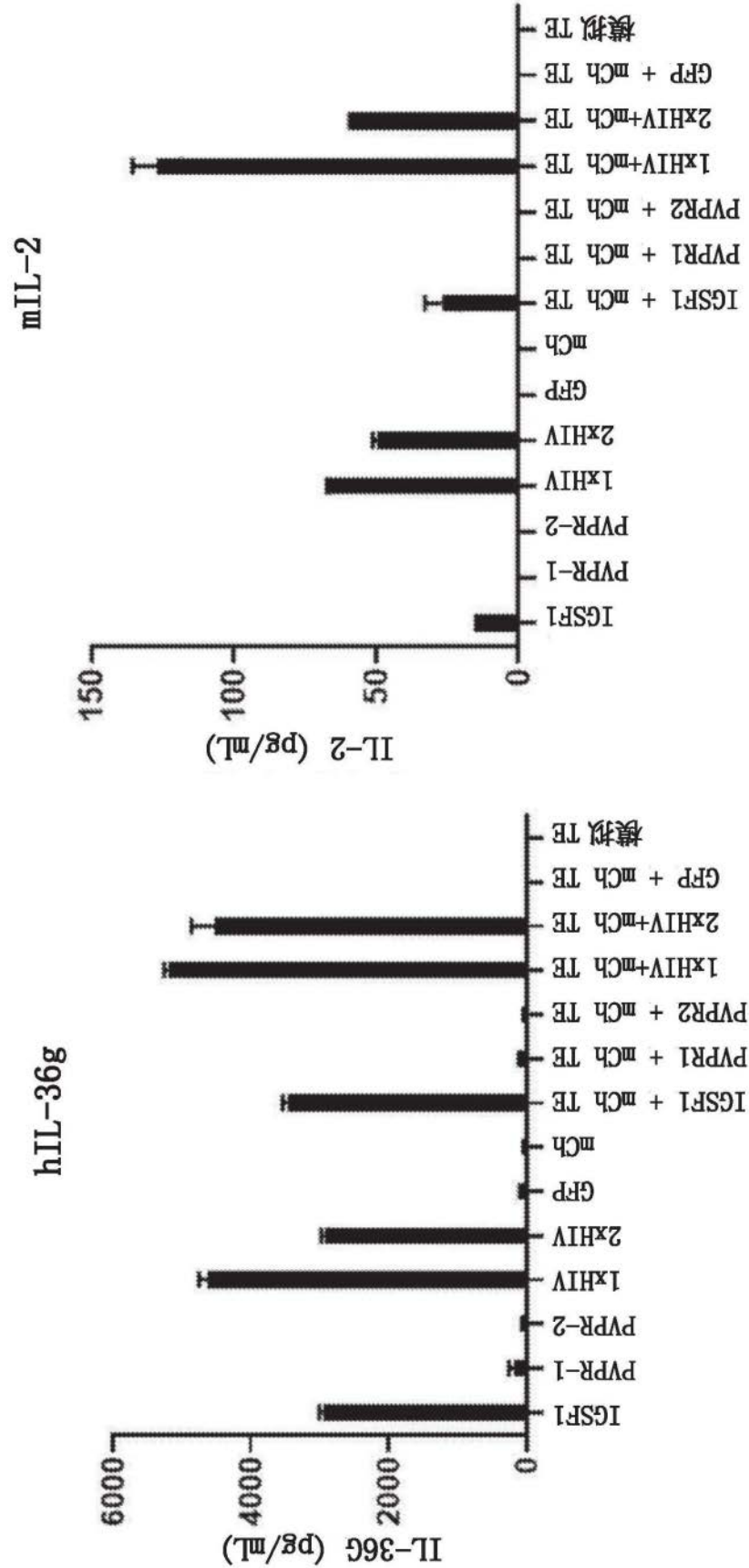


图18C

Trunc10-BiTE-1xHIVPR-hIL36g
7.6Kb



图19A

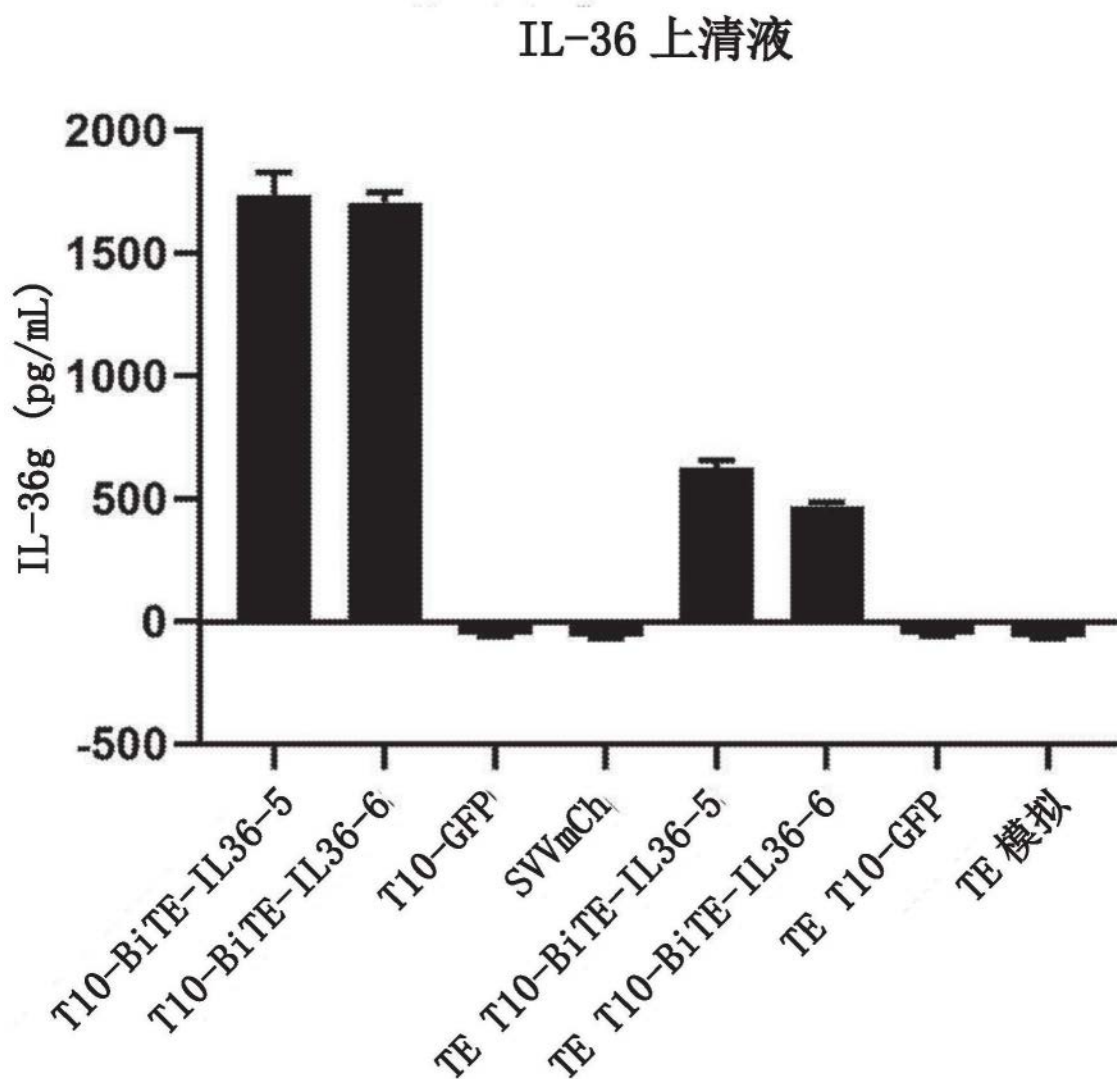


图19B

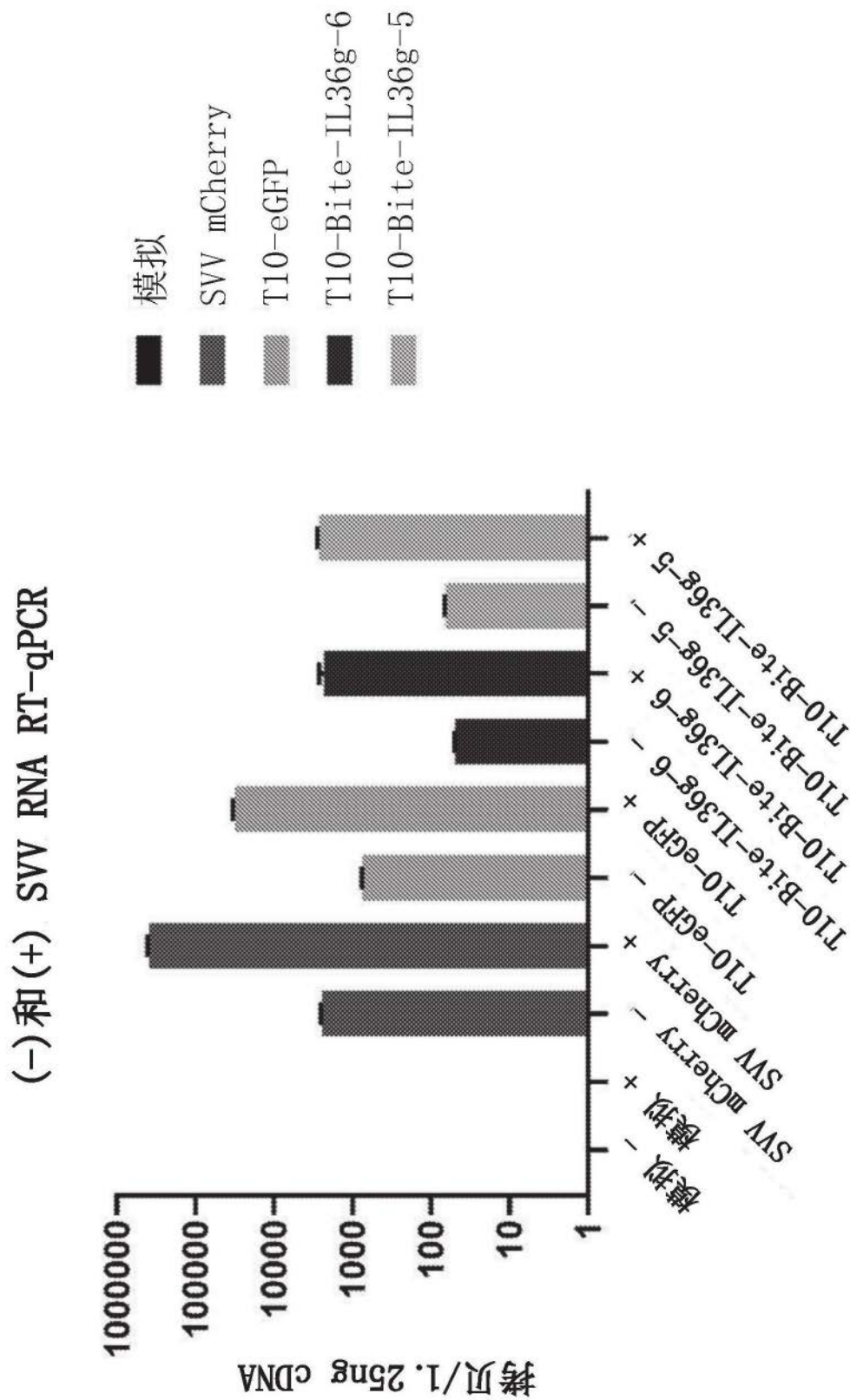


图19C

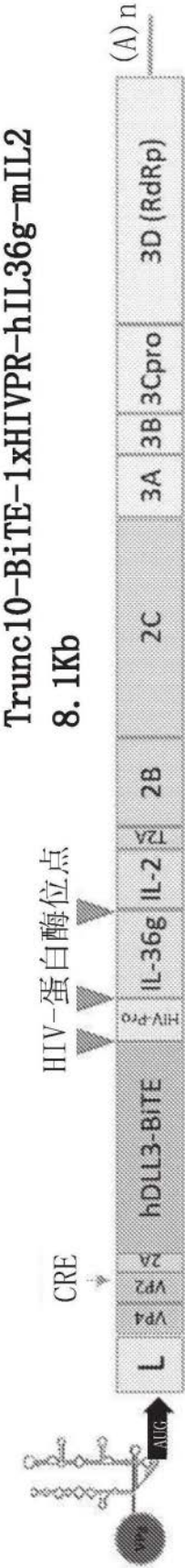


图20A

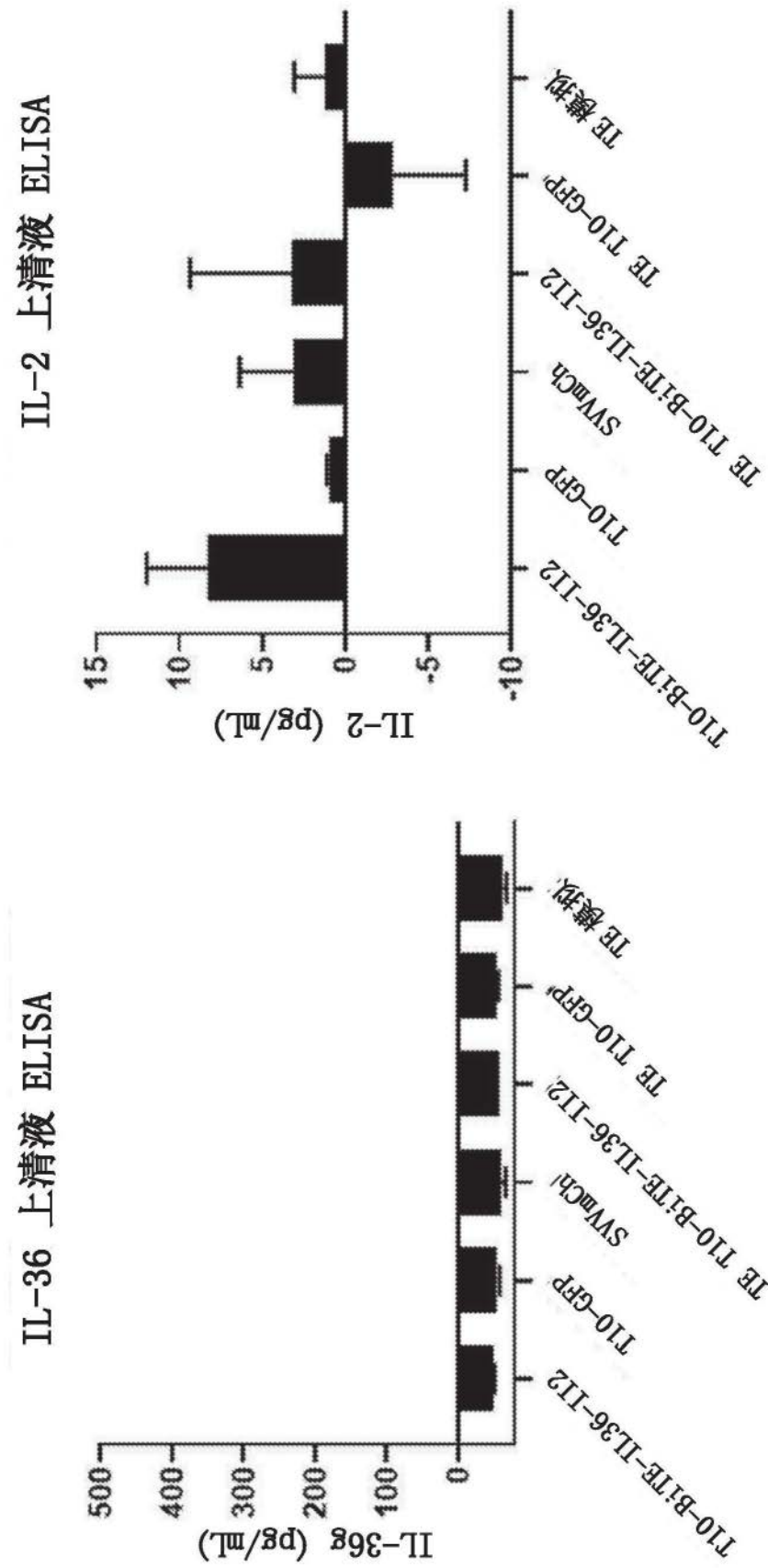


图20B

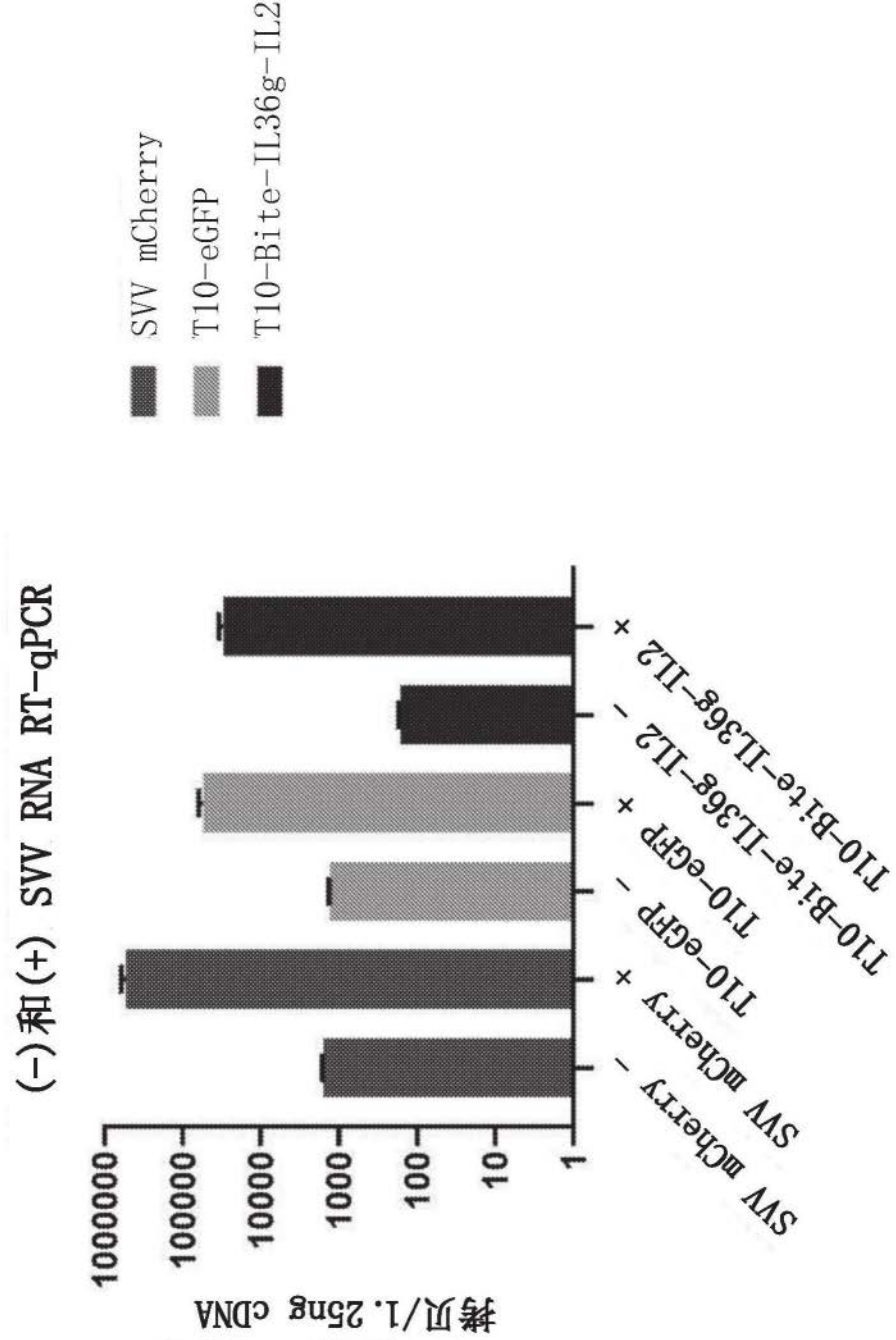


图20C

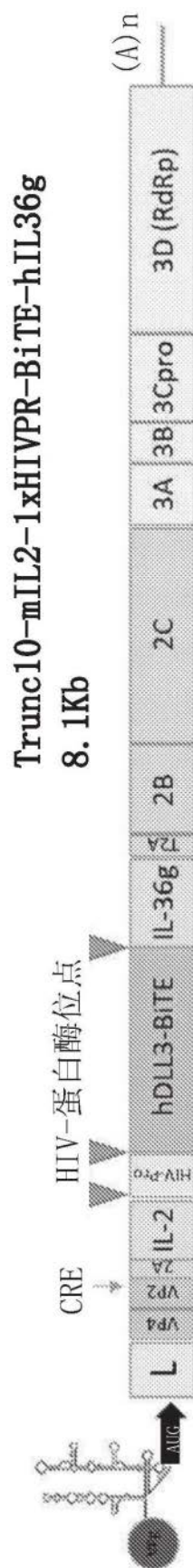


图21A

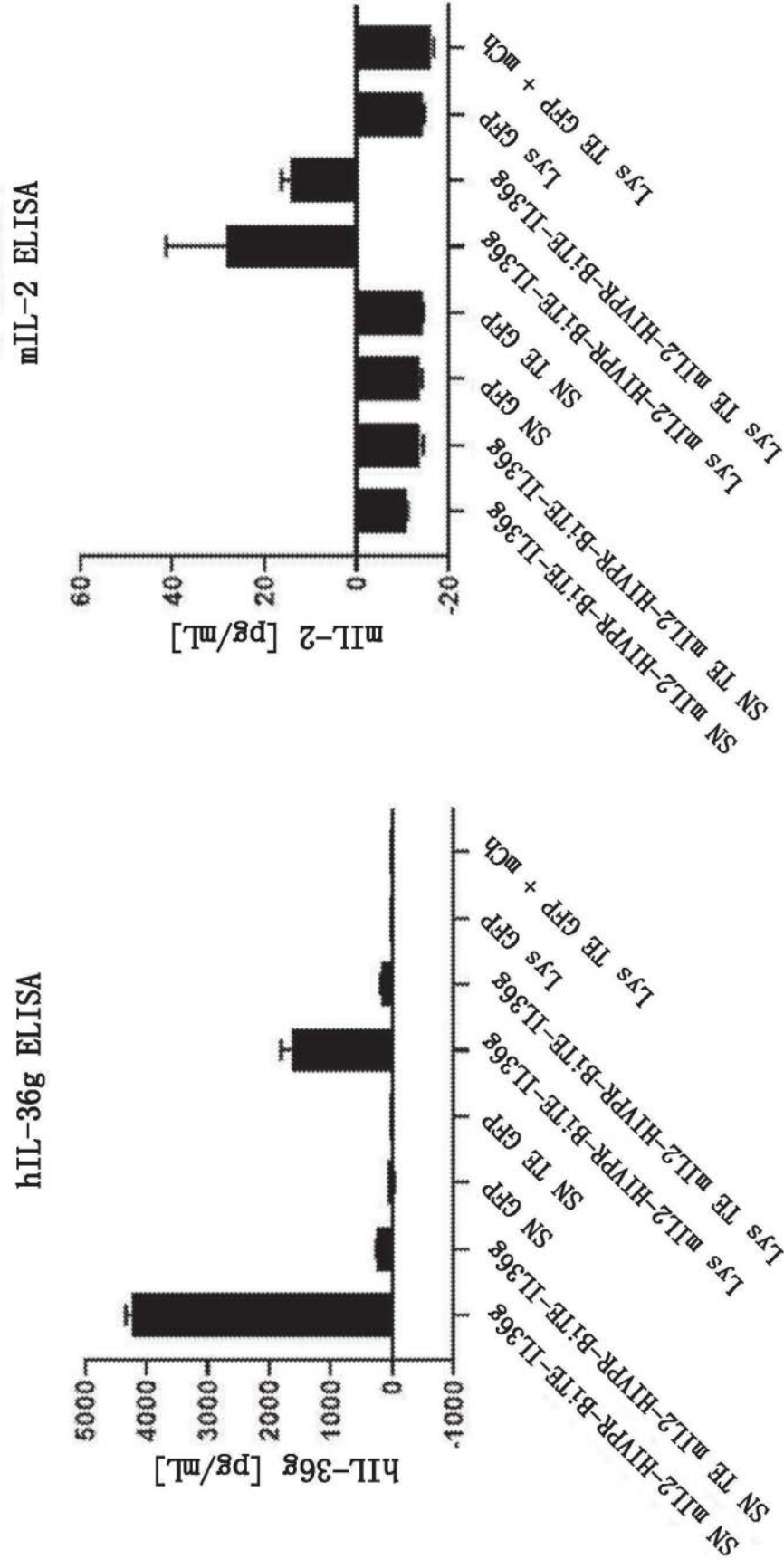


图21B

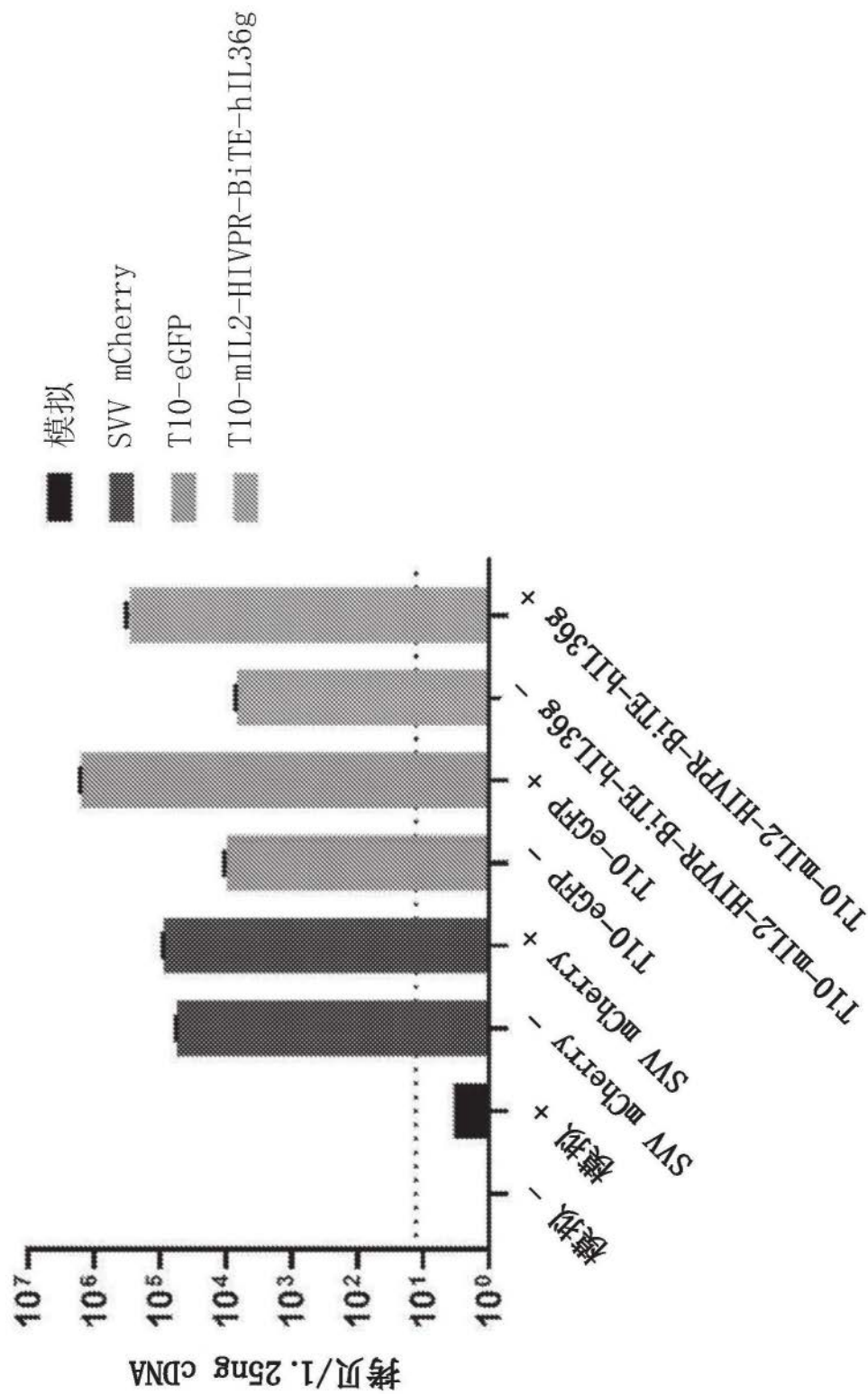


图21C

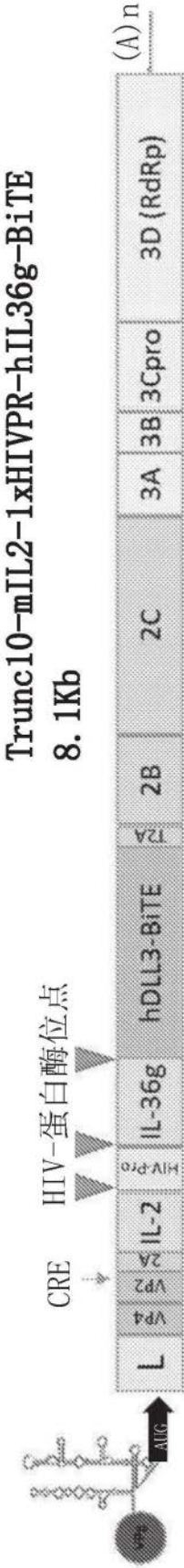


图22A

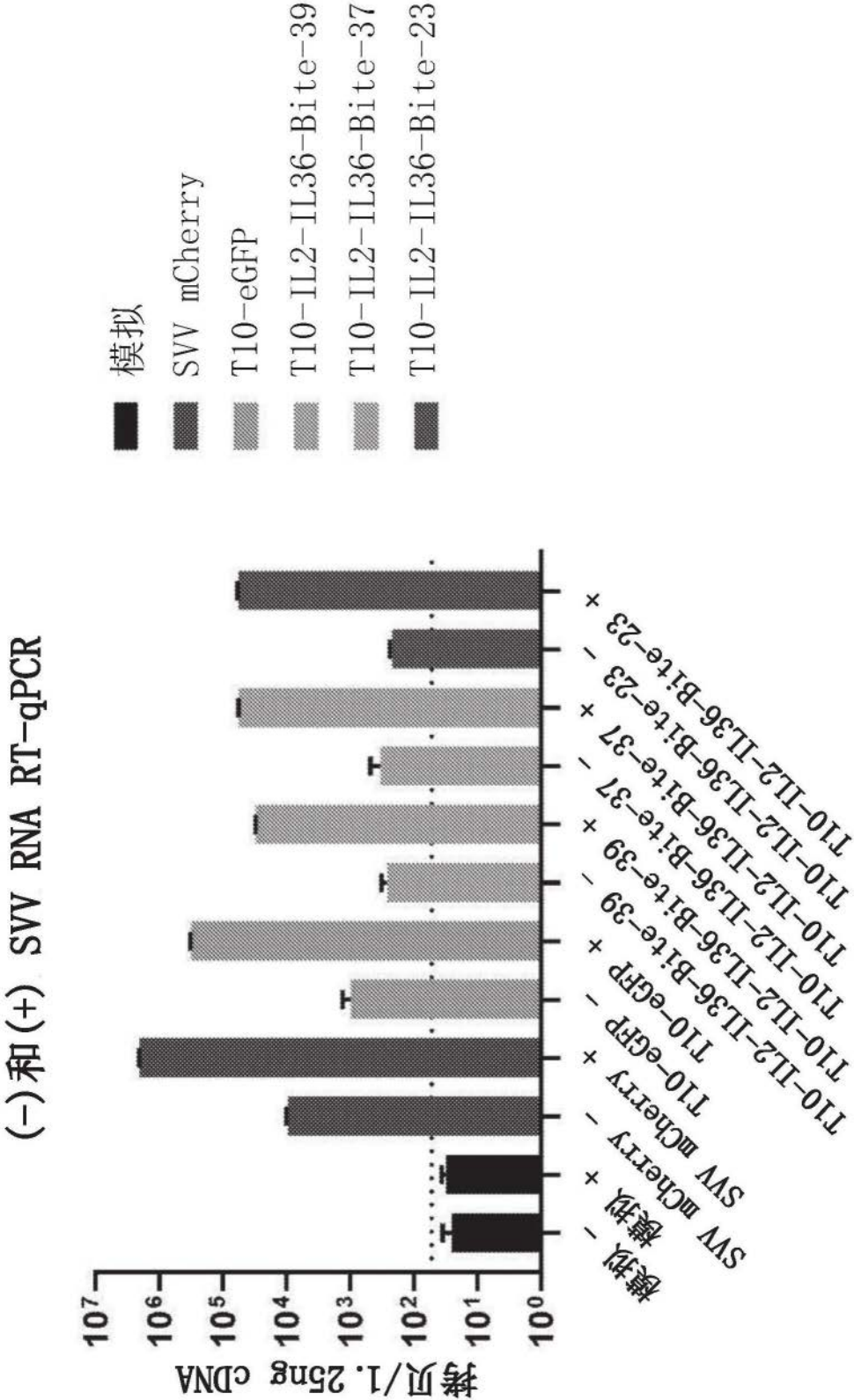


图22B

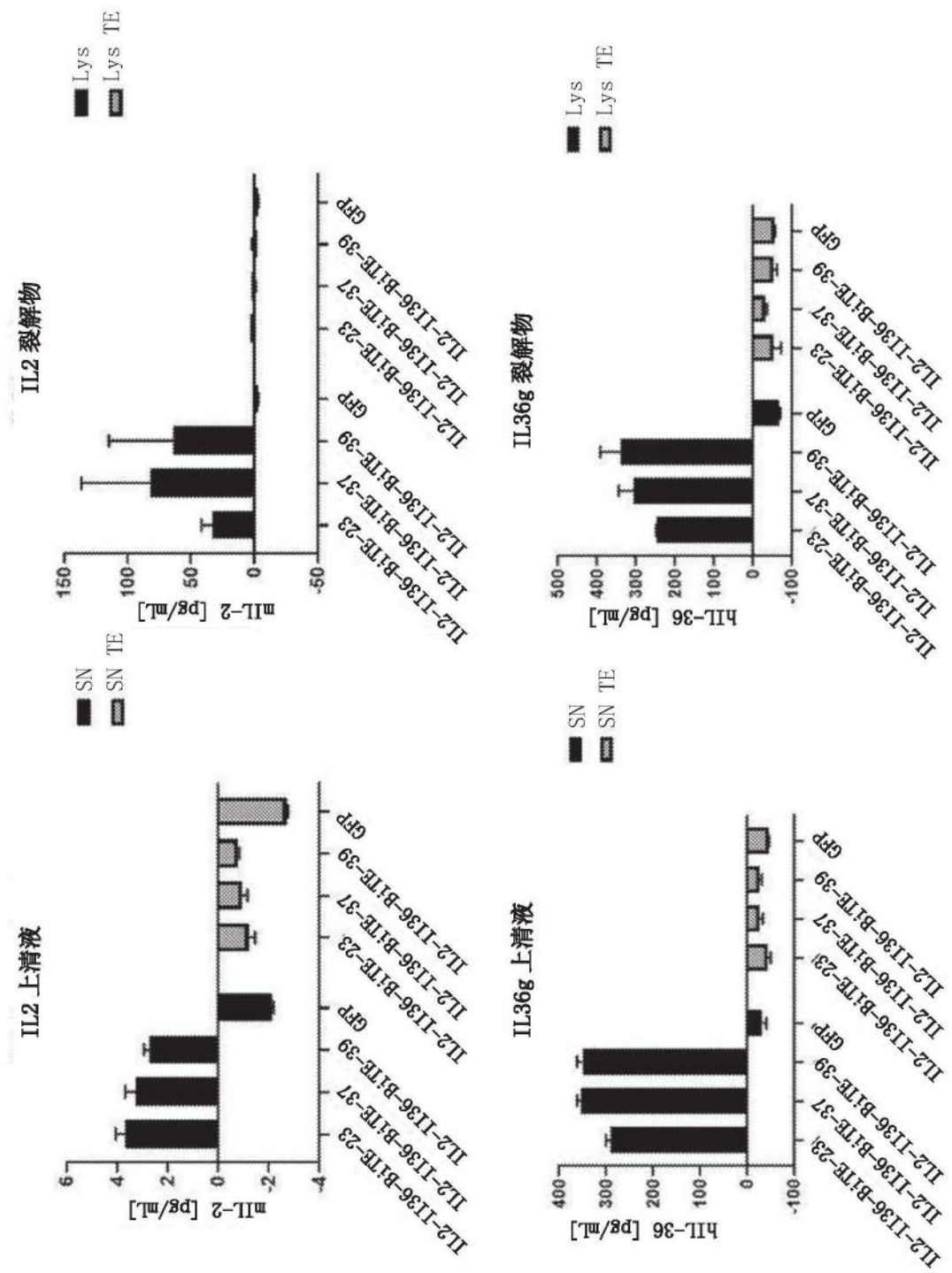


图22C

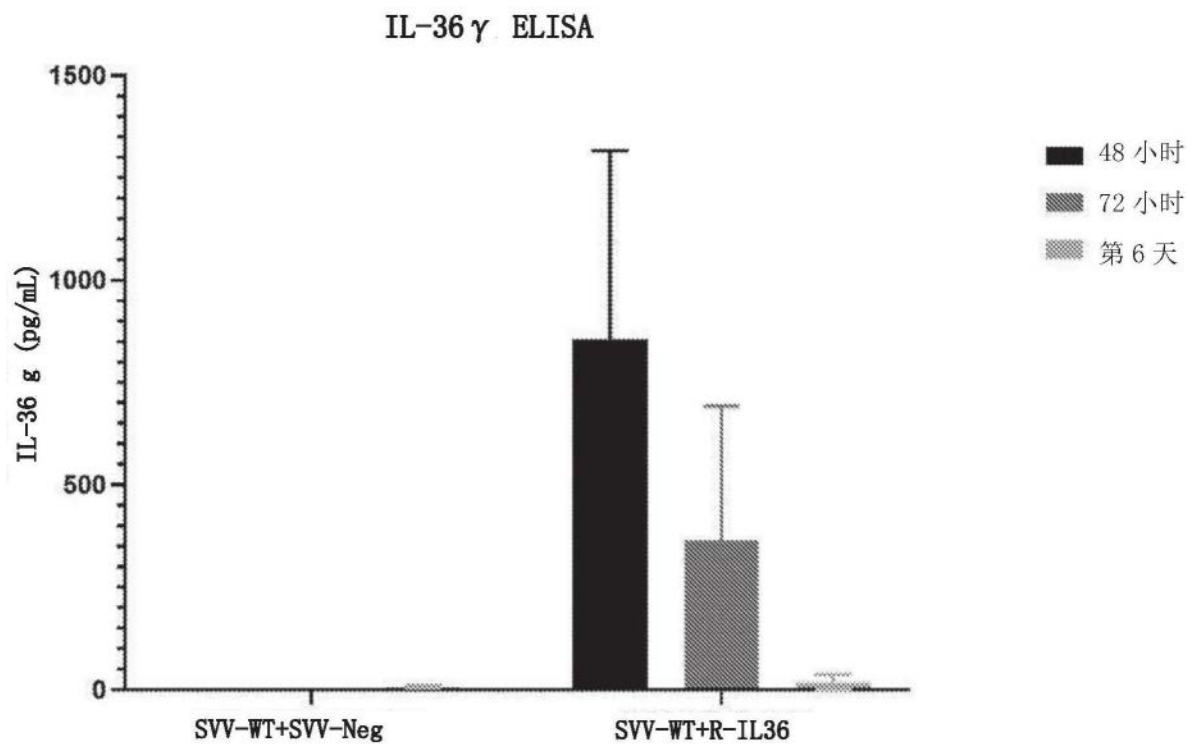


图23A

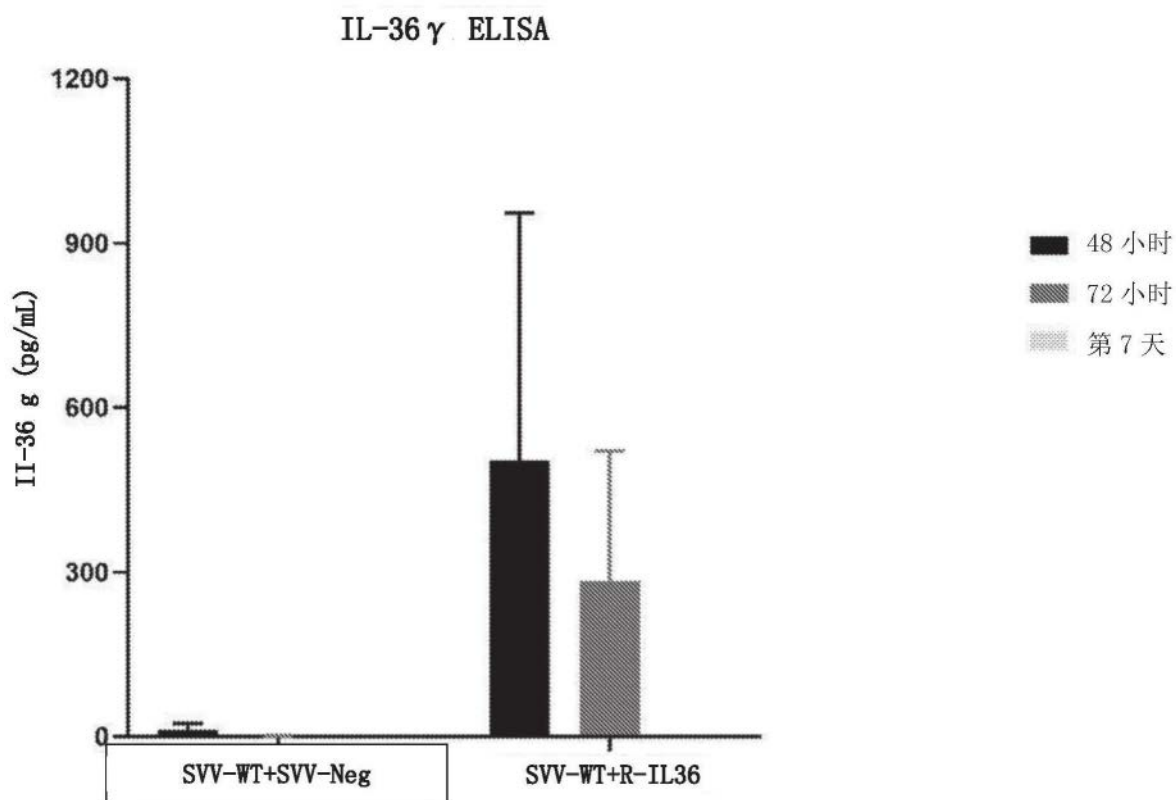


图23B

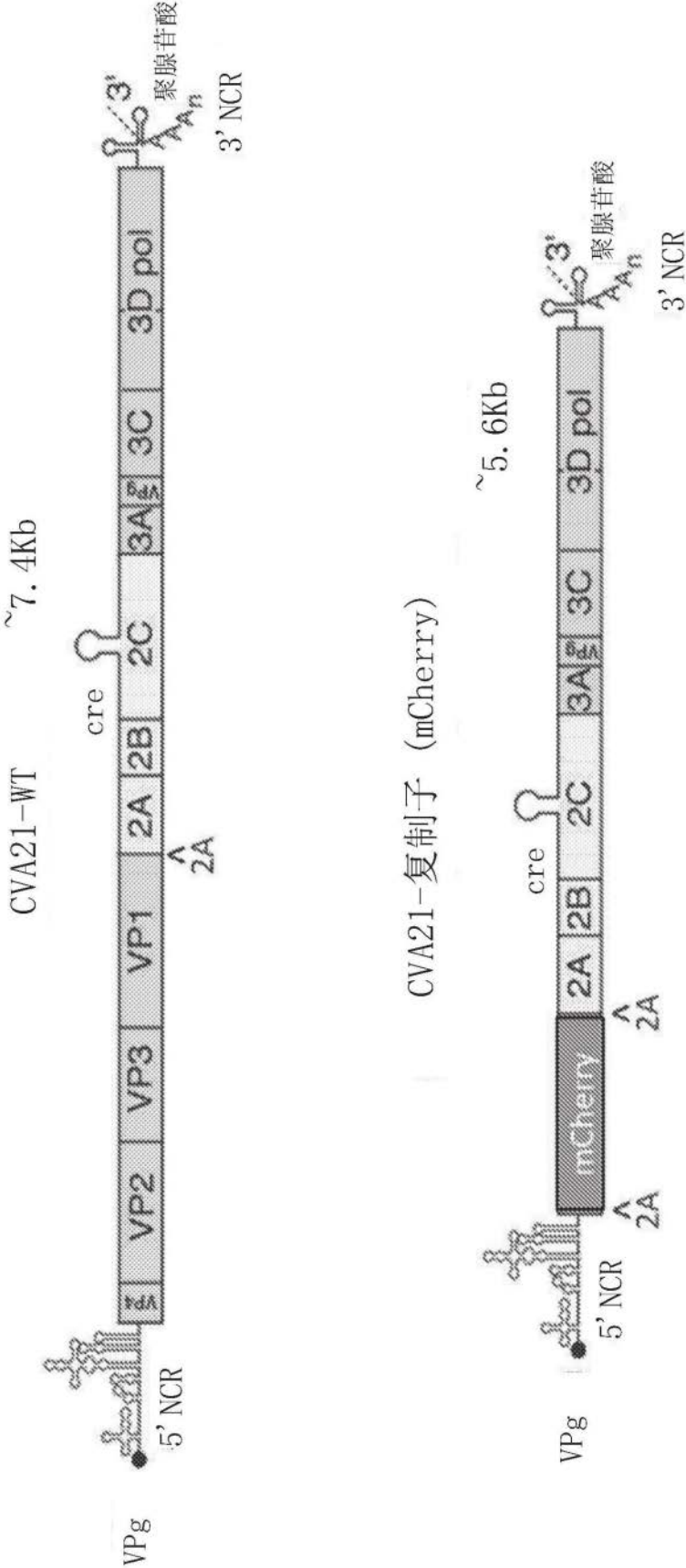


图24

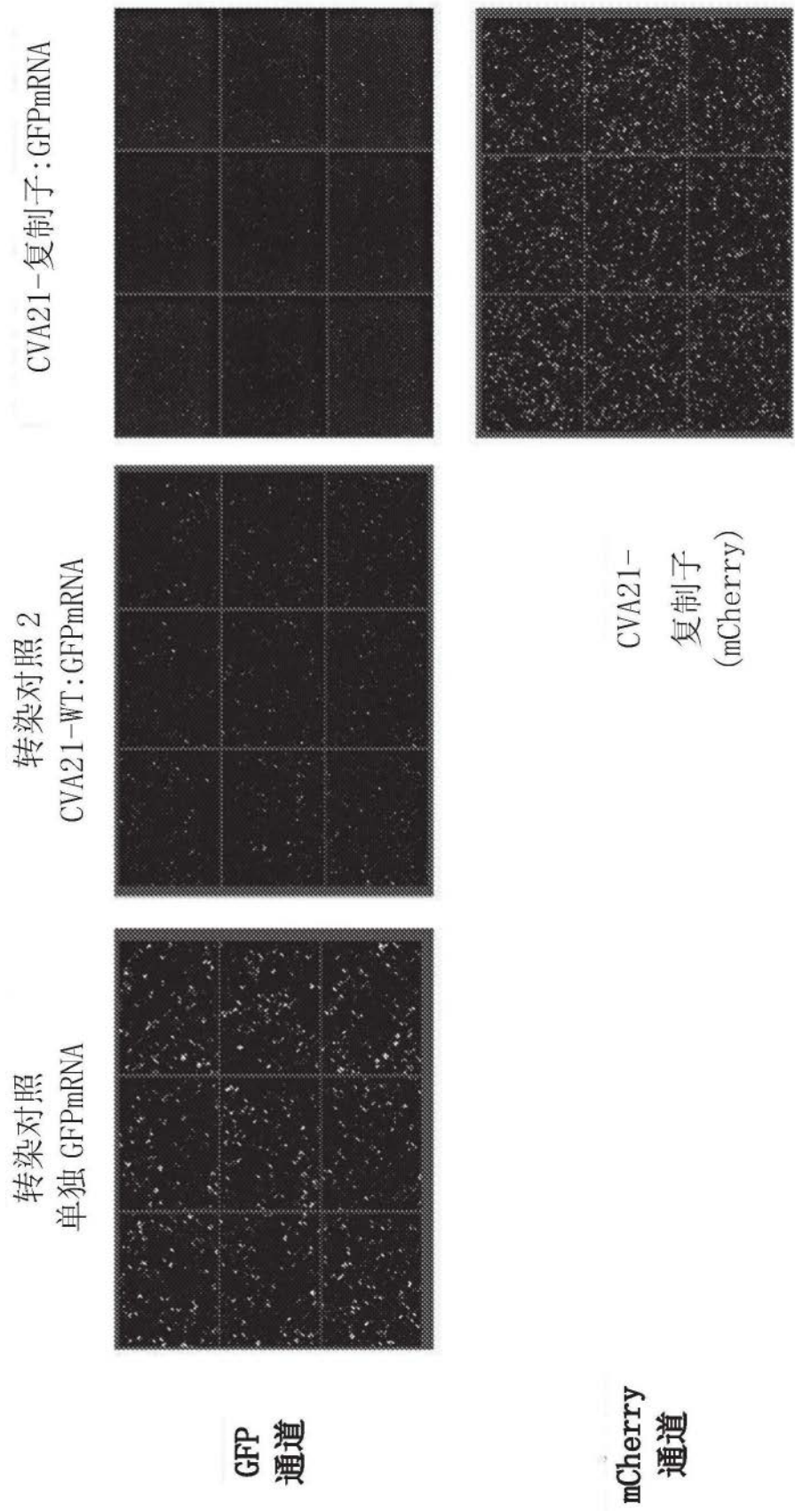
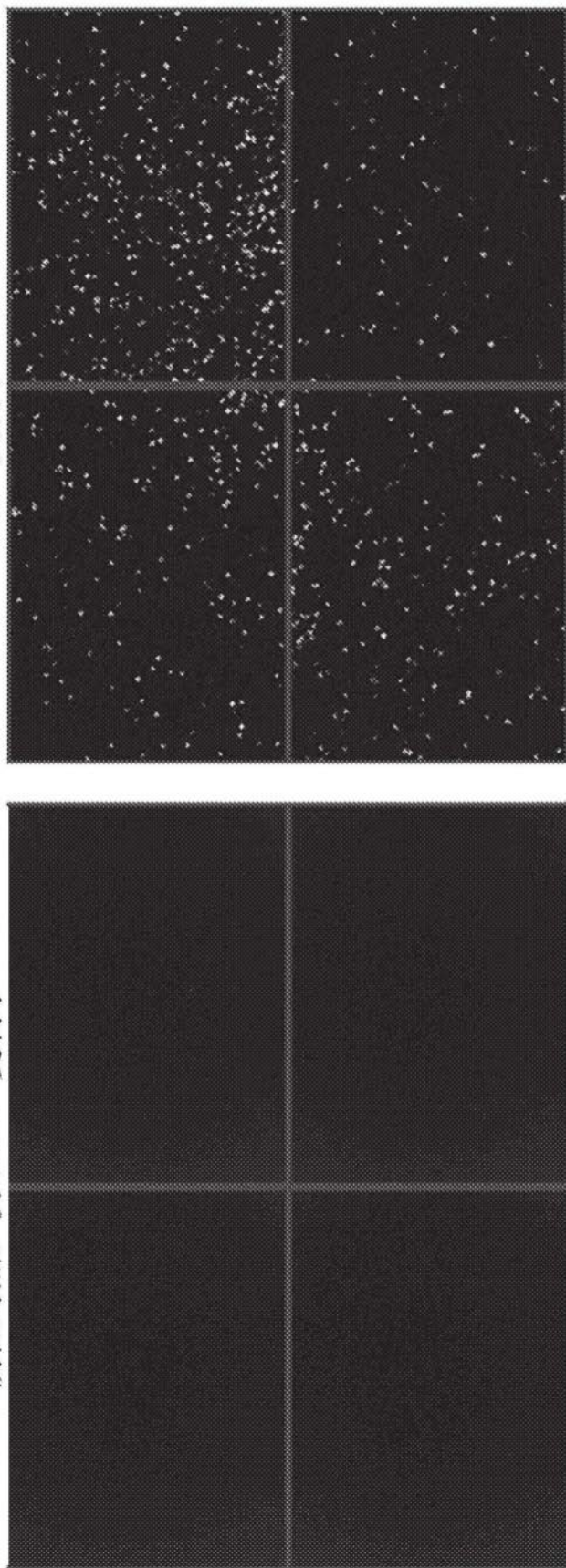


图25A

用转染上清液感染后 24 小时

阴性对照：仅 CVA21-复制子

CVA21-复制子:CVA21-WT



(显示了 mCherry 信号)

图25B

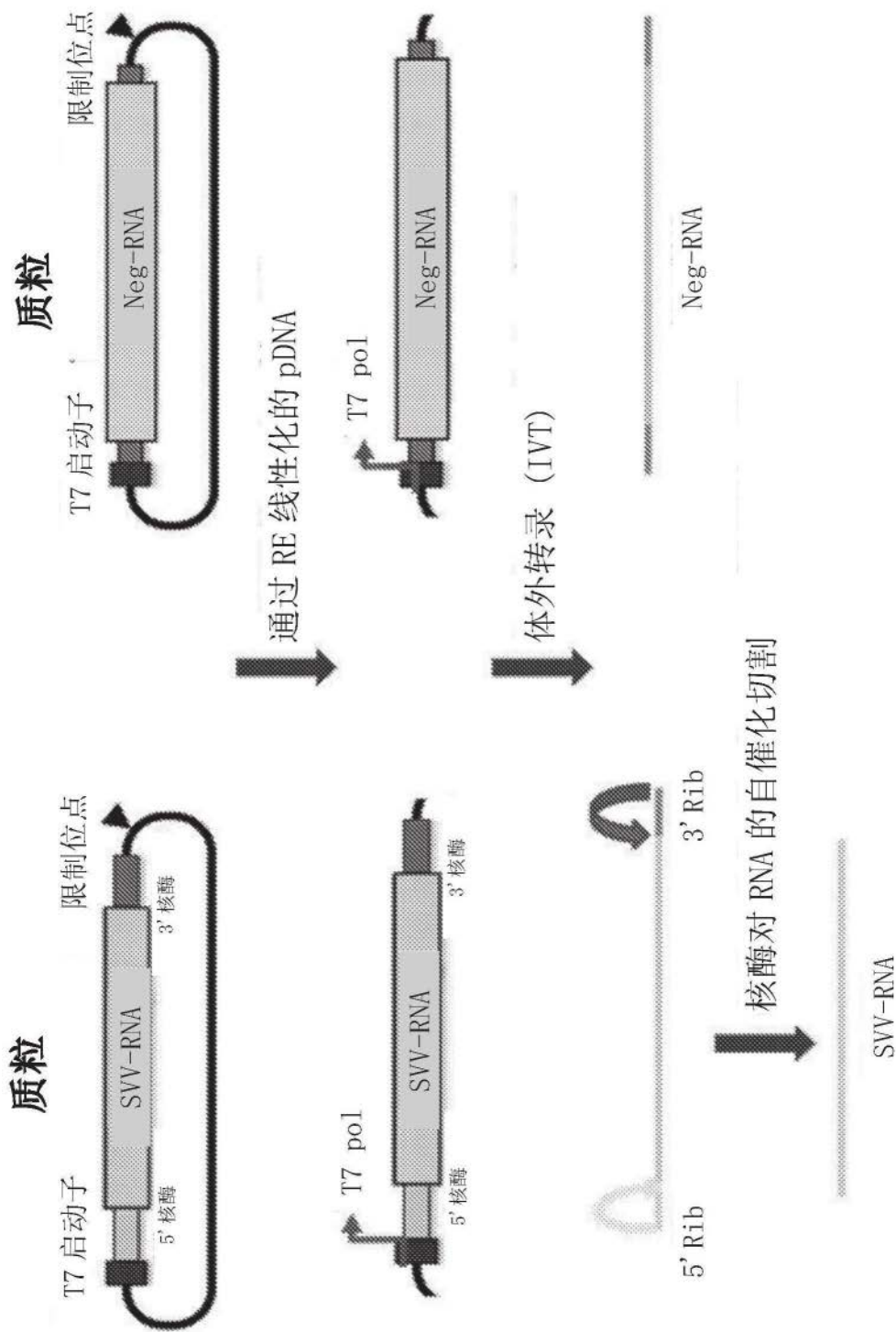


图26

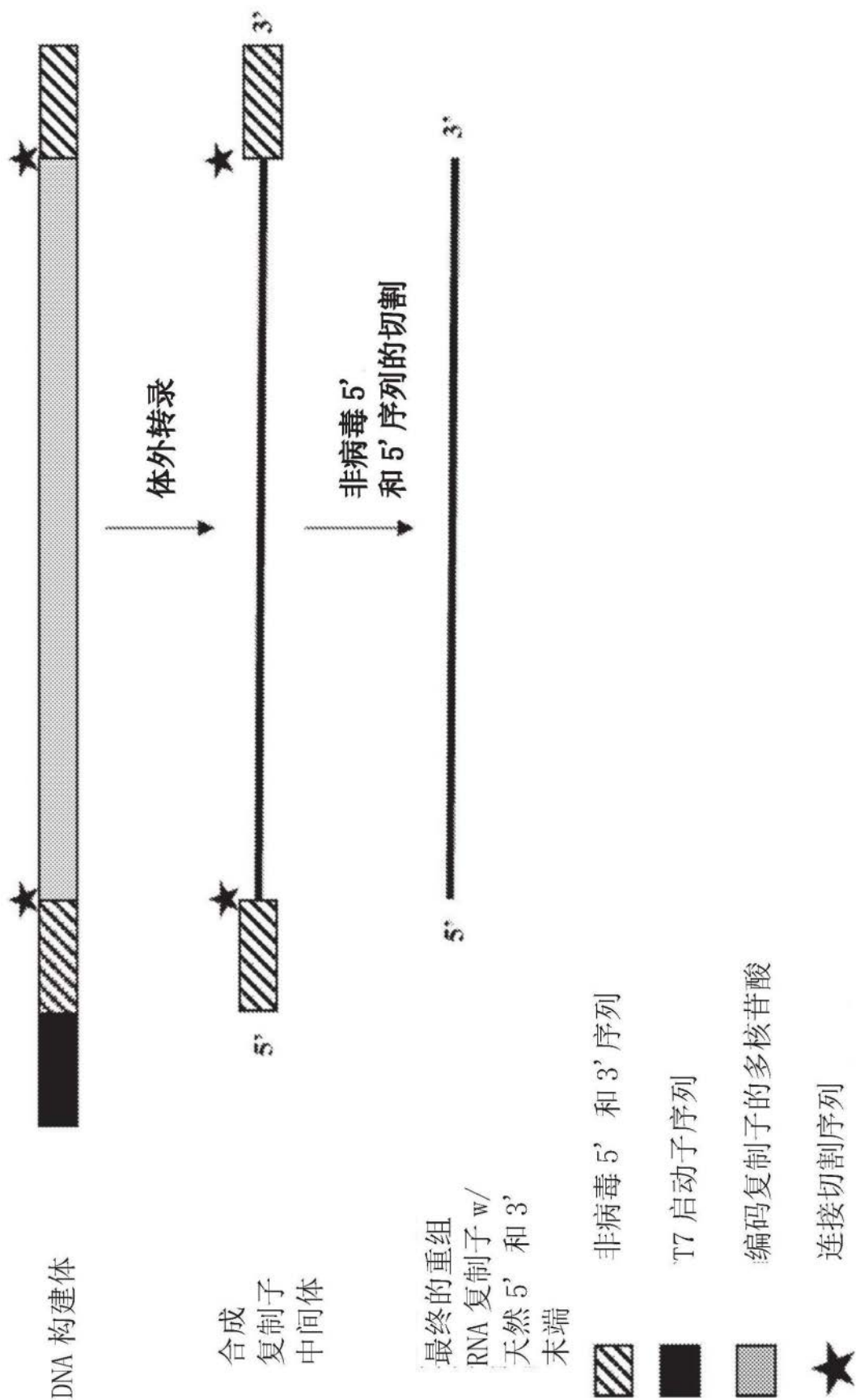


图27

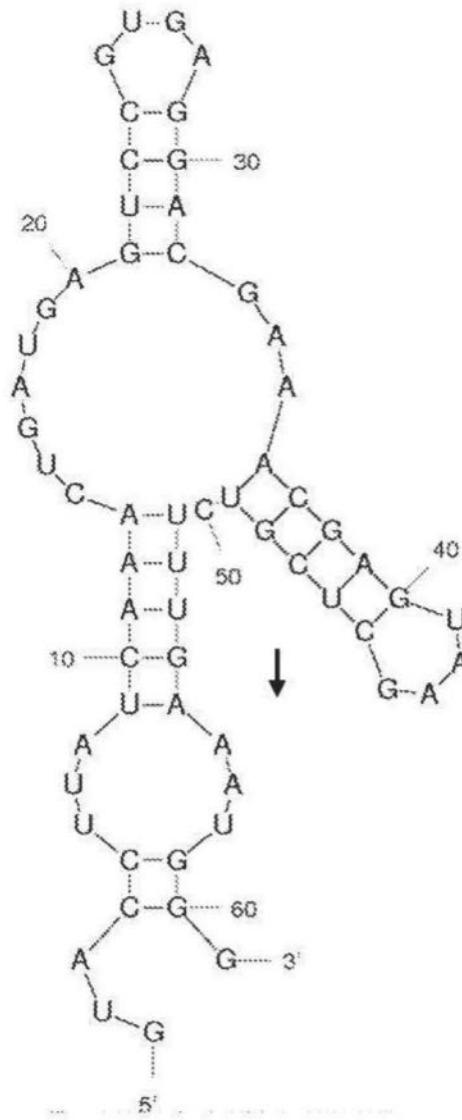


图28A

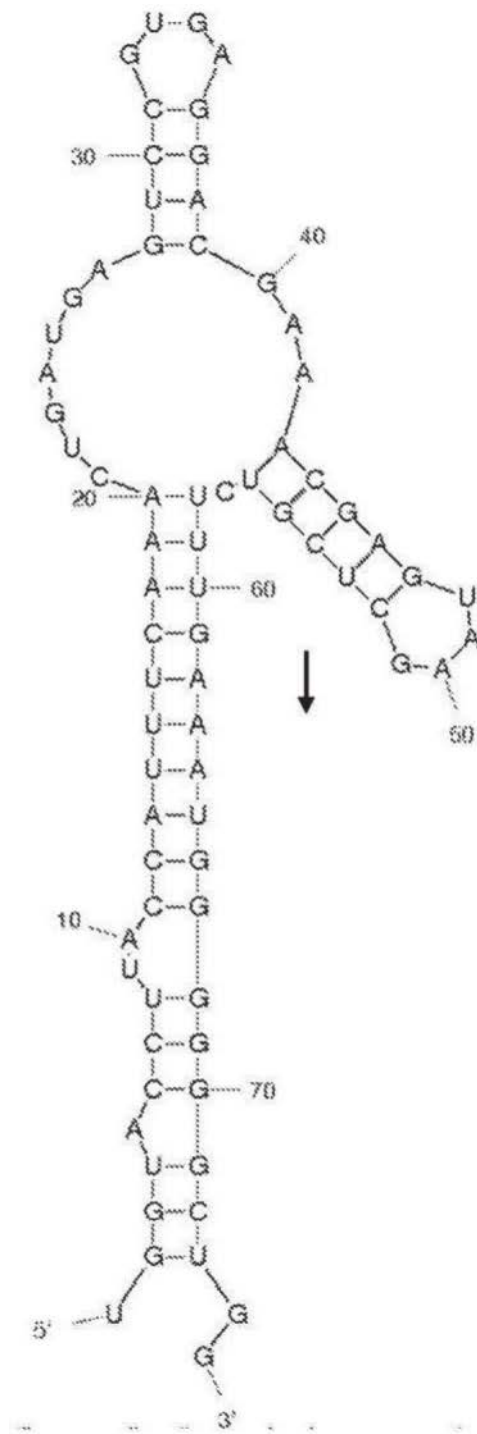


图28B

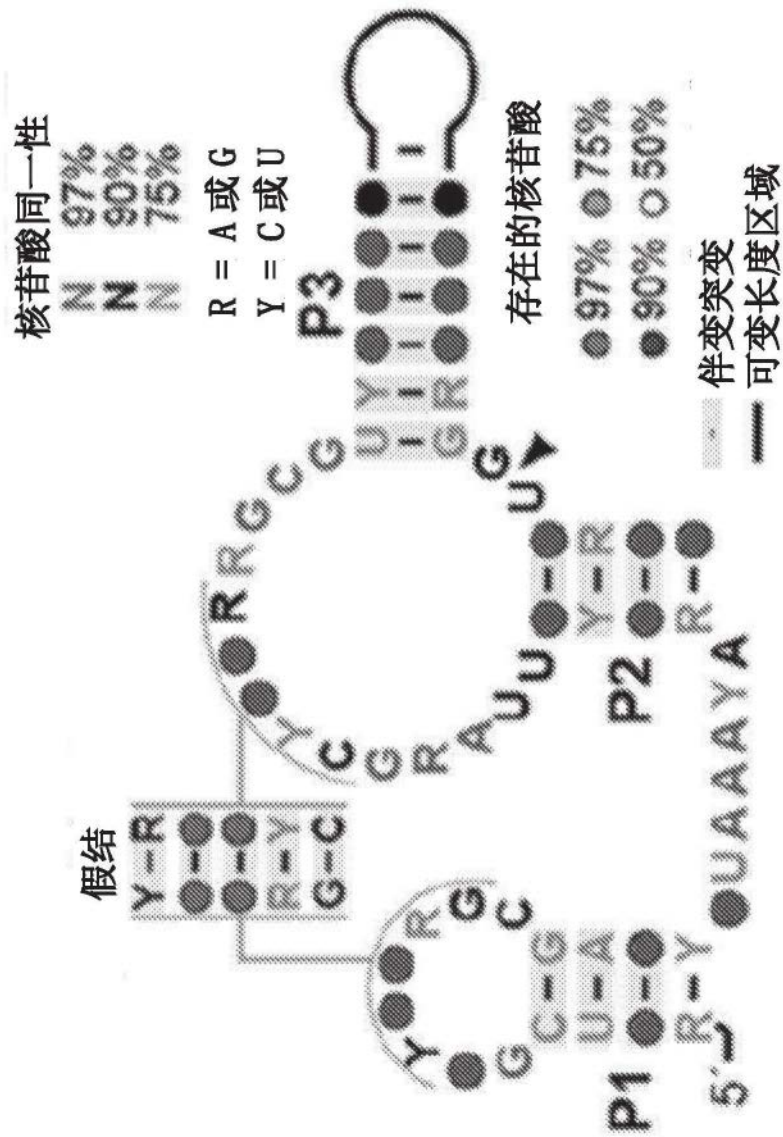


图29A

PMID: 22454536

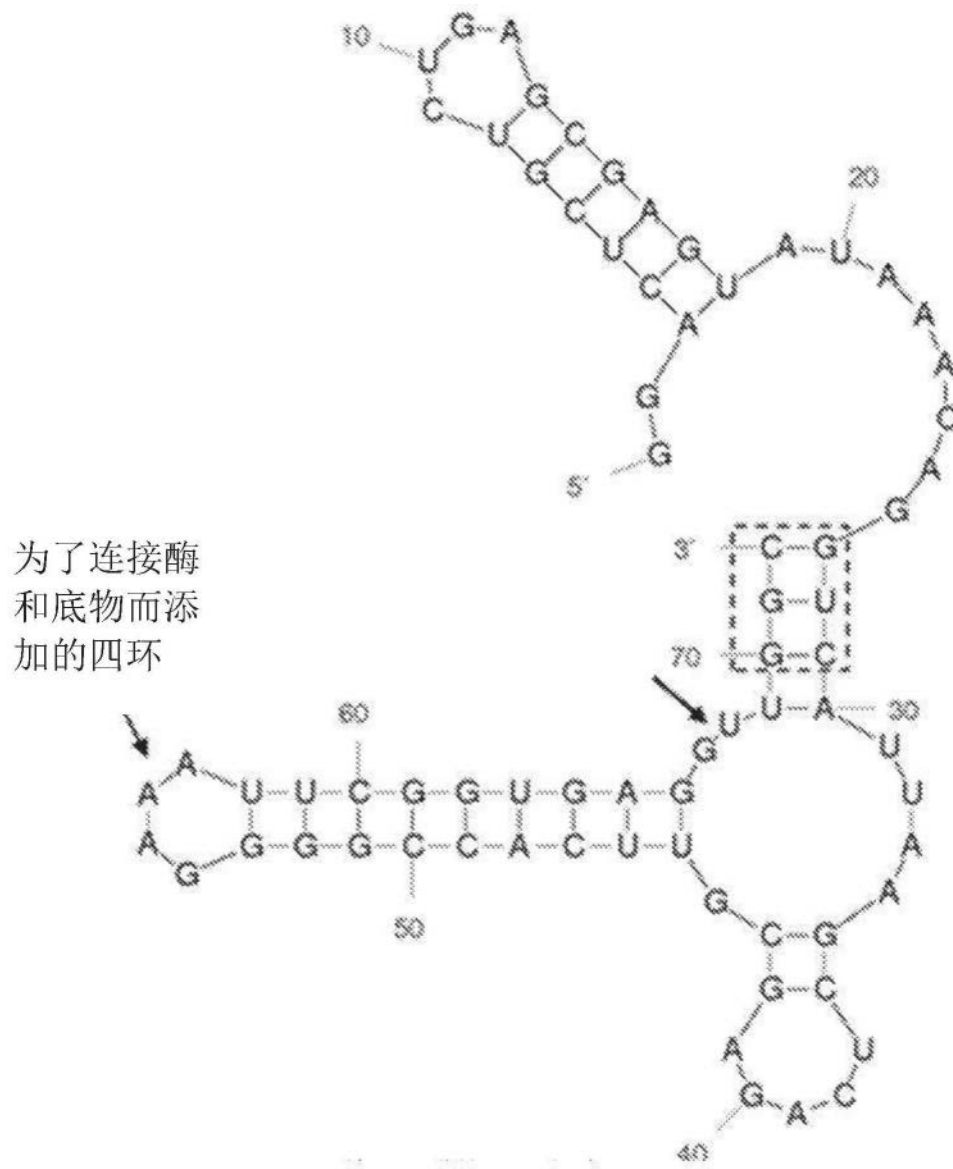


图29B