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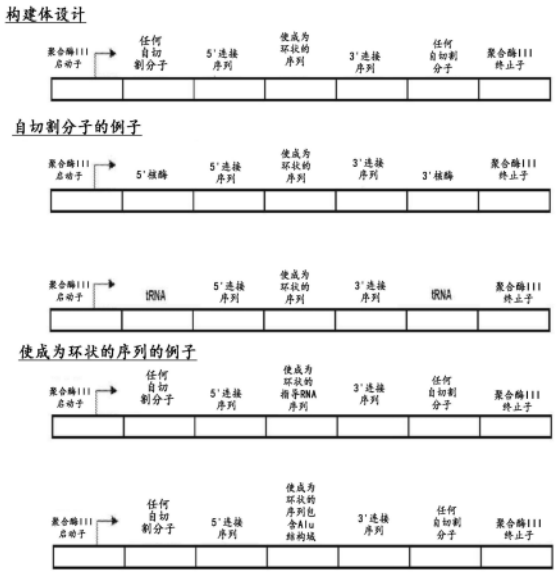
工程化环状指导RNA

(57)摘要

本文公开了经工程化的指导RNA，用于形成经工程化的指导RNA的构建体，所述经工程化的指导RNA的药物组合物，制备所述经工程化的指导RNA的方法，以及通过施用所述经工程化的指导RNA或用于形成所述经工程化的指导RNA的构建体中的一种或多种来治疗或预防受试者的疾病和障碍的方法。



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1.一种用于编辑RNA序列中的核苷酸的经工程化的指导RNA,所述经工程化的指导RNA包含:

RNA编辑实体募集结构域,

其中所述RNA编辑实体募集结构域募集RNA编辑实体,所述RNA编辑实体在与所述经工程化的指导RNA缔合时在所述RNA序列中的核苷酸的碱基上进行化学转化,从而产生经编辑的RNA序列,其中所述经工程化的指导RNA是环状的。

2.根据权利要求1所述的经工程化的指导RNA,其中所述经工程化的指导RNA进一步包含靶向结构域。

3.根据权利要求2所述的经工程化的指导RNA,其中所述靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。

4.根据权利要求2所述的经工程化的指导RNA,其中所述靶向结构域包含长度为至少约100个核苷酸的序列长度。

5.根据权利要求1-4中任一项所述的经工程化的指导RNA,其中所述碱基上的所述化学转化导致所述经编辑的RNA序列的至少部分敲低。

6.根据权利要求5所述的经工程化的指导RNA,其中所述部分敲低包括由所述经编辑的RNA序列表达的蛋白质或其片段的水平降低。

7.根据权利要求6所述的经工程化的指导RNA,其中所述降低的水平为约5%至100%。

8.根据权利要求7所述的经工程化的指导RNA,其中所述降低的水平为约60%至100%。

9.根据权利要求5-8中任一项所述的经工程化的指导RNA,其中与其他方面相同的未经编辑的RNA序列相比,确定所述部分敲低或降低的水平,如在体外测定中所确定的。

10.根据权利要求1-8中任一项所述的经工程化的指导RNA,其中所述化学转化导致有义密码子读作终止密码子。

11.根据权利要求1-8中任一项所述的经工程化的指导RNA,其中所述化学转化导致终止密码子读作有义密码子。

12.根据权利要求1-8中任一项所述的经工程化的指导RNA,其中所述化学转化导致第一有义密码子读作第二有义密码子。

13.根据权利要求1-8中任一项所述的经工程化的指导RNA,其中所述化学转化导致第一终止密码子读作第二终止密码子。

14.根据权利要求1-13中任一项所述的经工程化的指导RNA,其中所述经工程化的指导RNA被配置成形成二级结构,其包括:茎环结构、十字形结构、立足点结构、错配凸起结构或其任何组合。

15.根据权利要求1-14中任一项所述的经工程化的指导RNA,其中所述RNA编辑实体募集结构域包含与以下的至少约20个核酸的至少约80%序列同源性:Alu结构域、APOBEC募集结构域、GluR2结构域或Cas13募集结构域。

16.根据权利要求15所述的经工程化的指导RNA,其中所述RNA编辑实体募集结构域包含与所述Alu结构域的至少约20个核酸的至少约80%序列同源性。

17.根据权利要求16所述的经工程化的指导RNA,其中所述RNA编辑实体募集结构域包含与所述Alu结构域的至少约80%序列同源性。

18.根据权利要求15所述的经工程化的指导RNA,其中所述RNA编辑实体募集结构域包

含与所述APOBEC募集结构域的至少约20个核酸的至少约80％序列同源性。

19.根据权利要求18所述的经工程化的指导RNA，其中所述RNA编辑实体募集结构域包含与所述APOBEC募集结构域的至少约80％序列同源性。

20.根据权利要求15所述的经工程化的指导RNA，其中所述RNA编辑实体募集结构域包括所述Cas13募集结构域，其为Cas13a募集结构域、Cas13b募集结构域、Cas13c募集结构域或Cas13d募集结构域。

21.根据权利要求20所述的经工程化的指导RNA，其中所述RNA编辑实体募集结构域包含与所述Cas13b募集结构域的至少约20个核酸的至少约80％序列同源性。

22.根据权利要求21所述的经工程化的指导RNA，其中所述序列包含与所述Cas13b募集结构域的至少约80％序列同源性。

23.根据权利要求1-22中任一项所述的经工程化的指导RNA，其中所述RNA编辑实体是内源酶。

24.根据权利要求1-22中任一项所述的经工程化的指导RNA，其中所述RNA编辑实体是重组酶。

25.根据权利要求1-24中任一项所述的经工程化的指导RNA，其中所述经工程化的指导RNA包含修饰。

26.根据权利要求25所述的经工程化的指导RNA，其中所述修饰包括糖修饰。

27.根据权利要求25所述的经工程化的指导RNA，其中所述经工程化的指导RNA的核苷酸包含甲基、氟基、甲氧基乙基、乙基、磷酸基团、酰胺基团、酯基团或其任何组合。

28.根据权利要求1-27中任一项所述的经工程化的指导RNA，其中所述经工程化的指导RNA包含蛋白质包被。

29.根据权利要求1-28中任一项所述的经工程化的指导RNA，其中所述经工程化的指导RNA是可遗传编码的。

30.根据权利要求1-29中任一项所述的经工程化的指导RNA，其中所述RNA编辑实体连接到所述经工程化的指导RNA。

31.根据权利要求30所述的经工程化的指导RNA，其中所述经工程化的指导RNA和所述RNA编辑实体之间的连接是直接或间接共价连接。

32.根据权利要求1-31中任一项所述的经工程化的指导RNA，其中所述经工程化的指导RNA在生理pH的水溶液中保留比非环状的可比指导RNA长至少约4倍的半衰期。

33.根据权利要求1-32中任一项所述的经工程化的指导RNA，其中向有需要的受试者给药的所述经工程化的指导RNA的治疗有效量基于重量比率比非环状的可比指导RNA少至少约4倍。

34.一种用于编辑RNA序列中的核苷酸的经工程化的指导RNA，所述经工程化的指导RNA包含：

RNA编辑实体募集结构域，

其中所述RNA编辑实体募集结构域募集RNA编辑实体，所述RNA编辑实体在与所述经工程化的指导RNA缔合时在所述RNA序列中的核苷酸的碱基上进行化学转化，并且

其中所述经工程化的指导RNA不包含能够暴露于溶剂的5'还原羟基、能够暴露于溶剂的3'还原羟基或两者。

35.一种用于编辑RNA序列中的核苷酸的经工程化的指导RNA,所述经工程化的指导RNA包含:

RNA编辑实体募集结构域,

其中所述RNA编辑实体募集结构域募集RNA编辑实体,所述RNA编辑实体在与所述经工程化的指导RNA缔合时在所述RNA序列中的核苷酸的碱基上进行化学转化,从而产生经编辑的RNA序列,

其中所述经工程化的指导RNA包含比天然存在于人类细胞中的mRNA更不易受水解降解影响的二级结构。

36.根据权利要求34或权利要求35所述的经工程化的指导RNA,其中所述经工程化的指导RNA进一步包含靶向结构域。

37.根据权利要求36所述的经工程化的指导RNA,其中所述靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。

38.根据权利要求36所述的经工程化的指导RNA,其中所述靶向结构域包含长度为至少约100个核苷酸的序列长度。

39.根据权利要求34-38中任一项所述的经工程化的指导RNA,其中所述碱基上的所述化学转化导致所述经编辑的RNA序列的至少部分敲低。

40.根据权利要求39所述的经工程化的指导RNA,其中所述至少部分敲低包括由所述经编辑的RNA序列表达的蛋白质或其片段的水平降低。

41.根据权利要求40所述的经工程化的指导RNA,其中所述降低的水平为约5%至100%。

42.根据权利要求41所述的经工程化的指导RNA,其中所述降低的水平为约60%至100%。

43.根据权利要求34-42中任一项所述的经工程化的指导RNA,其中所述化学转化导致有义密码子读作终止密码子。

44.根据权利要求34-42中任一项所述的经工程化的指导RNA,其中所述化学转化导致终止密码子读作有义密码子。

45.根据权利要求34-42中任一项所述的经工程化的指导RNA,其中所述化学转化导致第一有义密码子读作第二有义密码子。

46.根据权利要求1-45中任一项所述的经工程化的指导RNA,其中所述经工程化的指导RNA是经预应变的环状RNA序列。

47.根据权利要求46中任一项所述的经工程化的指导RNA,其中所述经工程化的指导RNA与未经应变的环状RNA序列相比包含降低的熵。

48.一种载体,所述载体包含根据权利要求1-47中任一项所述的经工程化的指导RNA。

49.根据权利要求48所述的载体,其中所述载体包括脂质体、病毒载体、纳米颗粒或其任何组合。

50.根据权利要求49所述的载体,其中所述载体是所述病毒载体,并且其中所述病毒载体是腺相关病毒(AAV)载体。

51.根据权利要求48-50中任一项所述的载体,其中所述载体包含DNA。

52.根据权利要求51所述的载体,其中所述DNA是双链的。

53.一种核酸,所述核酸编码根据权利要求1-47中任一项所述的经工程化的指导RNA。

54.根据权利要求53所述的核酸,其中所述核酸是双链的。

55.一种分离的细胞,所述分离的细胞包含根据权利要求1-47中任一项所述的经工程化的指导RNA、根据权利要求48-52中任一项所述的载体或者根据权利要求53或权利要求54所述的核酸。

56.一种形成环状RNA的方法,所述方法包括:

在包含经工程化的指导RNA的序列的多于一个末端之间直接或间接形成共价连接以形成所述环状RNA,

其中所述经工程化的指导RNA包含:

RNA编辑实体募集结构域,其中所述RNA编辑实体募集结构域募集RNA编辑实体,所述RNA编辑实体在与所述经工程化的指导RNA缔合时在RNA序列中的核苷酸的碱基上进行化学转化,从而产生经编辑的RNA序列。

57.根据权利要求56所述的方法,其中所述方法采用酶来形成所述共价连接。

58.根据权利要求56或权利要求57所述的方法,其中所述酶是连接酶。

59.根据权利要求56-58中任一项所述的方法,其中所述经工程化的指导RNA进一步包含靶向结构域。

60.根据权利要求59所述的方法,其中所述靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。

61.根据权利要求59所述的方法,其中所述靶向结构域包含长度为至少约100个核苷酸的序列长度。

62.根据权利要求56-61中任一项所述的方法,其中所述碱基上的所述化学转化导致所述经编辑的RNA序列的至少部分敲低。

63.根据权利要求62所述的方法,其中所述至少部分敲低包括由所述经编辑的RNA序列表达的蛋白质或其片段的水平降低。

64.根据权利要求63所述的方法,其中所述降低的水平为约5%至100%。

65.根据权利要求64所述的方法,其中所述降低的水平为约60%至100%。

66.根据权利要求63-65中任一项所述的方法,其中与其他方面相同的未经编辑的RNA序列相比,确定所述部分敲低或降低的水平,如在体外测定中所确定的。

67.根据权利要求56-65中任一项所述的方法,其中所述化学转化导致有义密码子读作终止密码子。

68.根据权利要求56-65中任一项所述的方法,其中所述化学转化导致终止密码子读作有义密码子。

69.根据权利要求56-65中任一项所述的方法,其中所述化学转化导致第一有义密码子读作第二有义密码子。

70.一种药物组合物,所述药物组合物包含根据权利要求1-47中任一项所述的经工程化的指导RNA、根据权利要求48-52中任一项所述的载体或者根据权利要求53或权利要求54所述的核酸以及药学上可接受的:赋形剂、稀释剂或载体。

71.根据权利要求69所述的药物组合物,所述药物组合物呈单位剂型。

72.根据权利要求70所述的药物组合物,所述药物组合物进一步包含RNA编辑实体。

73.根据权利要求71所述的药物组合物，其中所述RNA编辑实体是重组RNA编辑实体。

74.根据权利要求70-73中任一项所述的药物组合物，其中所述RNA编辑实体直接或间接连接到所述经工程化的指导RNA。

75.根据权利要求74所述的药物组合物，其中所述RNA编辑实体和所述经工程化的指导RNA之间的连接是共价连接。

76.一种试剂盒，所述试剂盒包含根据权利要求1-47中任一项所述的经工程化的指导RNA、根据权利要求48-52中任一项所述的载体或根据权利要求70-75中任一项所述的药物组合物以及容器。

77.一种制备试剂盒的方法，所述方法包括将根据权利要求1-47中任一项所述的经工程化的指导RNA、根据权利要求48-52中任一项所述的载体或根据权利要求70-75中任一项所述的药物组合物至少部分包装到包装中。

78.一种治疗有需要的受试者的方法，所述方法包括：向所述受试者施用根据权利要求1-47中任一项所述的经工程化的指导RNA、根据权利要求48-52中任一项所述的载体或根据权利要求70-75中任一项所述的药物组合物。

79.根据权利要求78所述的方法，所述方法进一步包括向所述有需要的受试者施用经修饰的转移RNA、RNA编辑实体或其组合。

80.根据权利要求79所述的方法，其中将所述经修饰的转移RNA、所述RNA编辑实体或其组合与所述经工程化的指导RNA、所述载体或所述药物组合物共同施用。

81.根据权利要求79或权利要求80所述的方法，其中所述经修饰的转移RNA、所述RNA编辑实体或其组合直接或间接连接到所述经工程化的指导RNA、所述载体或所述药物组合物。

82.根据权利要求81所述的方法，其中与所述经工程化的指导RNA、所述载体或所述药物组合物的连接是共价连接。

83.根据权利要求78-82中任一项所述的方法，其中所述施用通过静脉内注射、肌内注射、鞘内注射、眶内注射、皮下注射或其任何组合。

84.根据权利要求78-83中任一项所述的方法，所述方法进一步包括向所述受试者施用第二疗法。

85.根据权利要求78-83中任一项所述的方法，其中所述受试者患有或被怀疑患有选自以下的疾病或病症：神经退行性障碍、肌肉障碍、代谢障碍、眼部障碍及其任何组合。

86.根据权利要求85所述的方法，其中所述疾病或病症是阿尔茨海默病、肌营养不良、色素性视网膜炎、帕金森病、疼痛、斯塔加特黄斑营养不良、沙尔科-马里-图思病或雷特综合征。

87.根据权利要求86所述的方法，其中所述疾病或病症是所述肌营养不良，其为迪谢内肌营养不良(DMD)。

88.根据权利要求75-87中任一项所述的方法，其中所述受试者是哺乳动物。

89.根据权利要求88所述的方法，其中所述哺乳动物是人。

90.根据权利要求75-89中任一项所述的方法，其中所述受试者已经通过诊断被诊断患有疾病或病症。

91.一种制备根据权利要求70-75中任一项所述的药物组合物的方法，所述方法包括将所述药物组合物配制成单位剂型。

92.一种制备根据权利要求1-47中任一项所述的经工程化的指导RNA的方法,所述方法包括对所述经工程化的指导RNA进行遗传编码或化学合成所述经工程化的指导RNA。

93.一种制备根据权利要求1-47中任一项所述的经工程化的指导RNA的方法,所述方法包括在所述经工程化的指导RNA的多于一个末端之间直接或间接形成共价连接以形成环状RNA,其中使用自切割实体加工所述经工程化的指导RNA。

94.根据权利要求93所述的方法,其中所述自切割实体是核酶。

95.根据权利要求94所述的方法,其中所述核酶是RNA酶P。

96.根据权利要求93所述的方法,其中所述自切割实体是tRNA。

97.根据权利要求93所述的方法,其中所述自切割实体是适配体或其催化活性片段。

98.根据权利要求93所述的方法,所述方法进一步包括募集酶以在所述经工程化的指导RNA的多于一个末端之间形成共价键。

99.一种制备根据权利要求1-47中任一项所述的经工程化的指导RNA的方法,所述方法包括使用连接元件连接所述经工程化的指导RNA的多于一个末端。

100.根据权利要求99所述的方法,其中所述连接元件采用点击化学来形成环状序列。

101.根据权利要求99所述的方法,其中所述连接元件是基于叠氮化物的连接。

102.一种用于形成环状指导RNA序列的构建体,所述构建体包含:编码以下的核苷酸序列:

(a)用于环化的指导RNA序列,其包含RNA编辑实体募集结构域;

(b)连接序列;和

(c)核酶。

103.根据权利要求102所述的构建体,其中所述经工程化的指导RNA进一步包含靶向结构域。

104.根据权利要求103所述的构建体,其中所述靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。

105.根据权利要求103所述的构建体,其中所述靶向结构域包含长度为至少约100个核苷酸的序列长度。

106.根据权利要求102所述的构建体,其中所述RNA编辑实体募集结构域包括Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13募集结构域或其任何组合。

107.根据权利要求102所述的构建体,其中所述RNA编辑实体募集结构域包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约400个核苷酸的至少约80%序列同源性。

108.根据权利要求107所述的构建体,其中所述RNA编辑实体募集结构域包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约80%序列同源性。

109.根据权利要求102-108中任一项所述的构建体,其中所述指导RNA序列的5'末端或3'末端侧接所述连接序列。

110.根据权利要求109所述的构建体,其中所述连接序列的5'末端或3'末端侧接所述核酶。

111.根据权利要求102-110中任一项所述的构建体,其中所述核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。

112.根据权利要求102-111中任一项所述的构建体,其中所述核苷酸序列包括与表1-

12中的任一个多核苷酸具有至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列同源性的序列。

113.一种用于形成环状RNA序列的构建体，所述构建体包含：编码以下的核苷酸序列：

(a)用于环化的RNA序列；

(b)连接序列；和

(c)tRNA。

114.根据权利要求113所述的构建体，其中所述指导RNA序列的5'末端或3'末端侧接所述连接序列，并且其中所述连接序列的5'末端或3'末端侧接所述tRNA。

115.根据权利要求114所述的构建体，其中所述核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。

116.一种用于形成环状RNA序列的构建体，所述构建体包含：编码以下的核苷酸序列：

(a)用于环化的RNA序列；

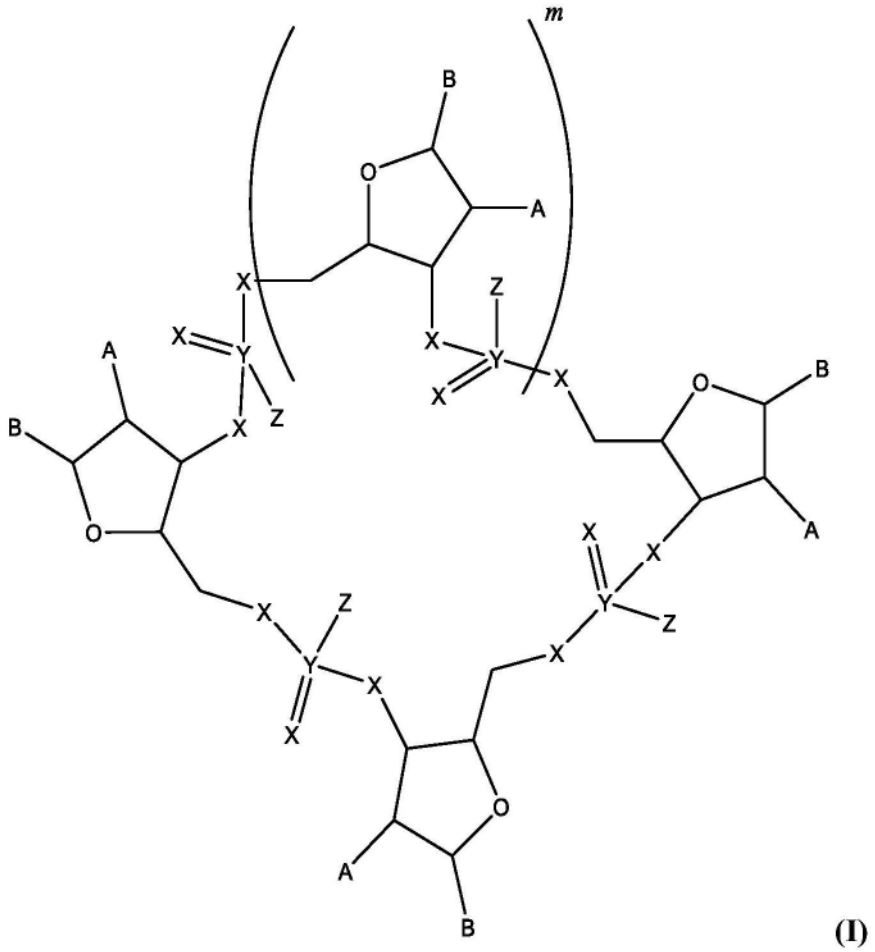
(b)连接序列；和

(c)适配体或其催化活性片段。

117.根据权利要求116所述的构建体，其中所述指导RNA序列的5'末端或3'末端侧接所述连接序列，并且其中所述连接序列的5'末端或3'末端侧接所述适配体或其催化活性片段。

118.根据权利要求117所述的构建体，其中所述核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。

119.一种经工程化的多核苷酸，所述经工程化的多核苷酸包含：与靶RNA至少部分互补的靶向结构域，其中所述经工程化的多核苷酸包含式(I)的结构：



(I)

其中：

每个X是O；

每个Y是P；

每个Z是O或S；

每个A独立地是H、D、卤素、OM、SM、NRM或NRR'；

每个B独立地是尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物；

每个M独立地是无机或有机阳离子、H或D；并且

每个R和R'独立地是H、D、卤素或C_1-C_6烷基；并且

m独立地是0-1,000的整数；

其中所述靶向结构域被配置成与所述靶RNA的编码区至少部分缔合，并且其中所述靶向结构域与所述靶RNA的编码区的缔合促进RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑。

120.根据权利要求119所述的经工程化的多核苷酸，其中在体外测定中确定所述RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑，所述体外测定包括：

(i)将所述靶RNA直接或间接引入原代细胞系中，

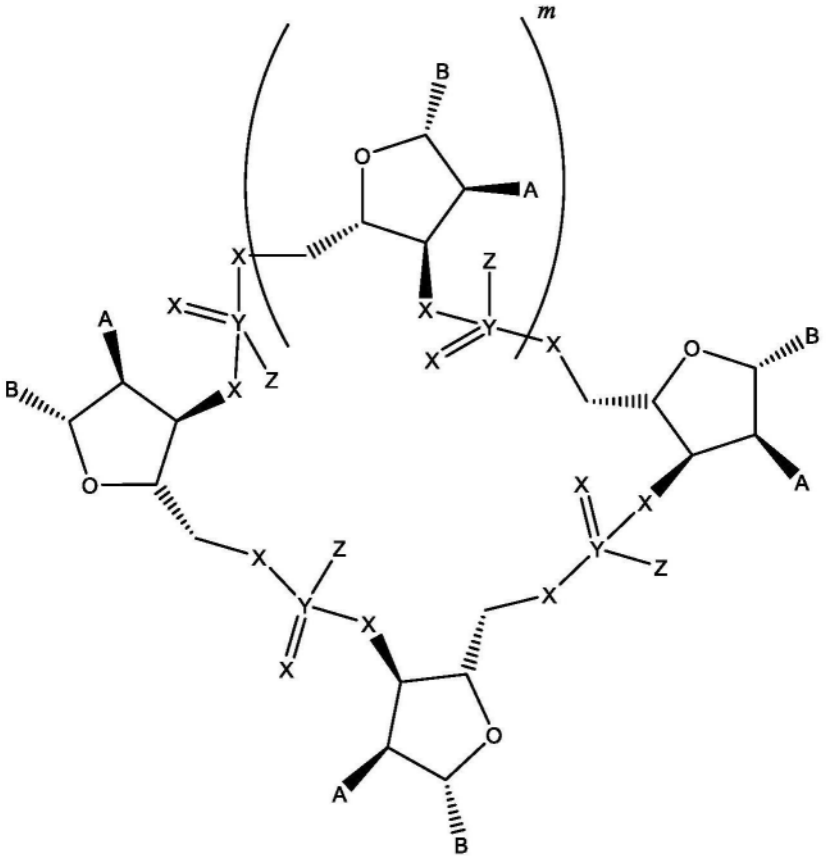
(ii)将所述经工程化的多核苷酸直接或间接引入所述原代细胞系中，以及

(iii)对所述靶RNA测序。

121.根据权利要求119-120中任一项所述的经工程化的多核苷酸，其中每个单元m独立

地呈(D)-或(L)-构型。

122.根据权利要求119-121中任一项所述的经工程化的多核苷酸，其中式(I)是根据式(II)：



(式II)。

123.根据权利要求119-122中任一项所述的经工程化的多核苷酸，其中每个Z是O并且每个R是H。

124.根据权利要求119-123中任一项所述的经工程化的多核苷酸，其中m是约30-600的独立整数。

125.根据权利要求119-124中任一项所述的经工程化的多核苷酸，其中至少部分互补包括所述靶向结构域包含与所述靶RNA的反向互补序列具有至少约80％序列同源性的多核苷酸序列。

126.根据权利要求119-125中任一项所述的经工程化的多核苷酸，其中所述RNA编辑实体包括ADAR蛋白、APOBEC蛋白或两者。

127.根据权利要求119-126中任一项所述的经工程化的多核苷酸，其中所述RNA编辑实体包括ADAR，并且其中ADAR包括ADAR1或ADAR2。

128.根据权利要求119-127中任一项所述的经工程化的多核苷酸，其中碱基的所述编辑将有义密码子转化为终止密码子。

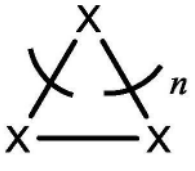
129.根据权利要求119-128中任一项所述的经工程化的多核苷酸，其中碱基的所述编辑将终止密码子转化为有义密码子。

130.根据权利要求119-129中任一项所述的经工程化的多核苷酸，其中碱基的所述编辑将第一有义密码子转化为第二有义密码子。

131.根据权利要求119-130中任一项所述的经工程化的多核苷酸，其中碱基的所述编辑将指定第一氨基酸的有义密码子转化为指定第二氨基酸的第二有义密码子。

132.根据权利要求131所述的经工程化的多核苷酸，其中所述第一氨基酸是蛋白酶切割位点。

133.一种经工程化的多核苷酸，所述经工程化的多核苷酸包含与靶RNA至少部分互补的靶向结构域，其中所述经工程化的多核苷酸包含式(III)的结构：



(III)

其中在所述经工程化的多核苷酸中，每个X是包含独立地为尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物的碱基的核苷酸；

n独立地室0-1,000的整数；并且

其中对于每个连接，每个核苷酸独立地通过磷酸酯、磷酸硫酯、硫代磷酸酯或亚磷酰胺连接而连接到两个相邻核苷酸；并且

其中所述靶向结构域被配置成与所述靶RNA的编码区至少部分缔合，其中所述靶向结构域与所述靶RNA的编码区的缔合促进RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑。

134.根据权利要求133所述的经工程化的多核苷酸，其中在体外测定中确定所述RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑，所述体外测定包括：

(i)将所述靶RNA直接或间接引入原代细胞系中，

(ii)将所述经工程化的多核苷酸直接或间接引入所述原代细胞系中，以及

(iii)对所述靶RNA测序。

135.根据权利要求133或134所述的经工程化的多核苷酸，其中所述RNA编辑实体包括ADAR蛋白、APOBEC蛋白或两者。

136.根据权利要求134-135中任一项所述的经工程化的多核苷酸，其中所述RNA编辑实体包括ADAR，并且其中ADAR包括ADAR1或ADAR2。

137.根据权利要求119-136中任一项所述的经工程化的多核苷酸，其中所述原代细胞系包括神经元细胞、感光细胞、视网膜色素上皮细胞、胶质细胞、成肌细胞、肌管细胞、肝细胞、肺上皮细胞或成纤维细胞。

138.根据权利要求119-137中任一项所述的经工程化的多核苷酸，其中所述经工程化的多核苷酸不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者。

139.根据权利要求138所述的经工程化的多核苷酸，其中每个5'羟基和每个3'羟基独立地通过共价氧磷键键合到磷。

140.根据权利要求139所述的经工程化的多核苷酸，其中所述磷包含在磷酸二酯基团中。

141.根据权利要求119-140中任一项所述的经工程化的多核苷酸，其中所述经工程化的多核苷酸进一步包含RNA编辑实体募集结构域。

142.根据权利要求119-141中任一项所述的经工程化的多核苷酸，其中所述靶向结构域为约20个核苷酸至约150个核苷酸。

143.根据权利要求119-142中任一项所述的经工程化的多核苷酸，其中所述靶RNA包含无义突变。

144.根据权利要求119-143中任一项所述的经工程化的多核苷酸，其中所述靶向结构域包含与所述靶RNA错配的至少单个核苷酸。

145.根据权利要求144所述的经工程化的多核苷酸，其中所述错配核苷酸与互补于所述靶RNA的两个核苷酸相邻，所述错配核苷酸的每侧各一个。

146.根据权利要求119-145中任一项所述的经工程化的多核苷酸，其中所述靶向结构域与在疾病或病症中实施的靶RNA至少部分结合。

147.根据权利要求146所述的经工程化的多核苷酸，所述经工程化的多核苷酸包含所述疾病或病症，其包括雷特综合征、亨廷顿病、帕金森病、阿尔茨海默病、肌营养不良或泰-萨二氏病。

148.根据权利要求119-147中任一项所述的经工程化的多核苷酸，其中相对于缺乏所述编辑的其他方面可比的靶RNA的翻译蛋白，碱基的所述编辑在进行所述碱基编辑的所述靶RNA翻译后导致蛋白质或其片段的水平增加、蛋白质或其片段的长度增加、蛋白质或其片段的功能性增加、蛋白质或其片段的稳定性增加或其任何组合。

149.根据权利要求148所述的经工程化的多核苷酸，其中所述增加的水平为约5％至约100％。

150.根据权利要求148所述的经工程化的多核苷酸，其中所述增加的长度为所述蛋白质或其片段的约5％至约100％。

151.根据权利要求148所述的经工程化的多核苷酸，其中所述增加的稳定性是所述蛋白质或其片段的增加的半衰期。

152.根据权利要求119-151中任一项所述的经工程化的多核苷酸，其中所述经工程化的多核苷酸包含与表1-12中的任一个多核苷酸具有至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列同源性的多核苷酸序列。

153.根据权利要求119-152中任一项所述的经工程化的多核苷酸，其中所述经工程化的多核苷酸包含长度为表1-12中的任一个多核苷酸的序列长度的至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％的多核苷酸序列。

154.根据权利要求119-153中任一项所述的经工程化的多核苷酸，其中所述经工程化的多核苷酸包含与表1-12中的任一个多核苷酸具有至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列同源性和至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列长度的多核苷酸序列。

155.一种包含与靶RNA至少部分互补的靶向结构域的经工程化的指导RNA，其中所述经工程化的指导RNA包含含有共价连接在一起的多个糖和磷酸部分的主链，并且其中所述主链不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者，其中所述靶向结构域被配置成与所述靶RNA的编码区至少部分缔合，其中所述靶向结构域与所述靶RNA的编码区的缔合促进RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑。

156.一种经工程化的指导RNA，所述经工程化的指导RNA包含：与靶RNA至少部分互补的靶向结构域；和RNA编辑实体募集结构域，其中所述RNA编辑实体募集结构域被配置成与RNA编辑实体至少瞬时缔合；其中所述经工程化的指导RNA包含含有共价连接在一起的多个糖

和磷酸部分的主链，并且其中所述主链不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者，其中所述靶向结构域被配置成与所述靶RNA的编码区至少部分缔合，其中所述靶向结构域与所述靶RNA的编码区的缔合促进RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑。

157.根据权利要求155或156所述的经工程化的多核苷酸，其中至少部分互补包括所述靶向结构域包含与所述靶RNA的反向互补序列具有至少约80％、至少约85％、至少约90％、至少约92％或至少约95％序列同源性的多核苷酸序列。

158.根据权利要求155-157中任一项所述的经工程化的多核苷酸，其中在体外测定中确定RNA编辑实体对所述靶RNA的核苷酸的碱基的编辑，所述体外测定包括：

(i)将所述靶RNA转染到原代细胞系中，

(ii)将所述经工程化的多核苷酸转染到原代细胞系中，以及

(iii)对所述靶RNA测序。

工程化环状指导RNA

相关申请的交叉引用

[0001] 本申请根据35 U.S.C.§119(e)要求2019年12月2日提交的美国临时申请号62/942,725和2020年11月11日提交的美国临时申请号63/112,492的优先权,将其公开内容出于所有目的通过引用并入本文。

政府支持声明

[0002] 本发明是在由美国国立卫生研究院授予的资助号R01GM123313、R01CA222826和R01HG009285下在美国政府支持下完成的。美国政府享有本发明的某些权利。

技术领域

[0003] 本公开文本提供了经工程化的指导RNA、其药物组合物、制备经工程化的指导RNA的方法以及通过施用一种或多种经工程化的指导RNA来治疗受试者的方法。

通过引用并入序列表

[0004] 伴随本申请的是名称为“00015-380WO1_SL25”的序列表,创建于2020年12月1日并且具有374,077字节的数据,在IBM-PC的MS-Windows操作系统上进行机器格式化。将序列表出于所有目的通过引用以其整体特此并入。

背景技术

[0005] RNA编辑领域中的一个重要障碍是指导物稳定性。为了成功地募集内源ADAR,adRNA应当存在延长的时间段,但是单链RNA在哺乳动物细胞中具有约30分钟或更短的半衰期。这可能是由于它们对从5’或3’末端降解单链RNA的核酸外切酶的敏感性。

发明内容

[0006] 本公开文本的一个方面提供了用于编辑核苷酸的经工程化的指导RNA。在一些情况下,经工程化的指导RNA可以包含靶向结构域。在一些情况下,经工程化的指导RNA可以包含RNA编辑实体募集结构域。在一些情况下,经工程化的指导RNA可以不包含RNA编辑实体募集结构域。在一些情况下,RNA编辑实体募集结构域可以能够募集在RNA序列中的核苷酸的碱基上进行化学转化从而产生经编辑的RNA序列的RNA编辑实体。在一些情况下,经工程化的指导RNA可以是环状的。在一些情况下,经工程化的指导RNA可以能够形成二级结构,所述二级结构包括茎环结构、十字形结构、立足点结构(toe hold)、错配凸起结构、任何这些中的多于一种或其任何组合。在一些情况下,RNA编辑实体募集结构域可以包含与以下的至少约80%序列同源性:Alu结构域、APOBEC募集结构域或GluR2结构域。在一些情况下,经工程化的指导RNA可以包含多于一个RNA编辑实体募集结构域。在一些情况下,经工程化的指导RNA可以包含Cas13募集结构域。在一些情况下,RNA编辑实体可以是内源酶。在一些情况下,RNA编辑实体可以是重组酶。在一些情况下,经工程化的指导RNA的至少一个碱基可以是经修饰的碱基。在一些情况下,经修饰的碱基可以包含糖修饰。在一些情况下,经工程化的指导RNA可以是可遗传编码的。在一些情况下,当使经工程化的指导RNA与RNA编辑实体和与靶

向结构域的至少一部分互补的靶核酸接触时，经工程化的指导RNA：(i)可以以比非环状的可比核酸高至少约4倍的效率修饰靶核酸的至少一个碱基对；(ii)可以保留比非环状的可比核酸长至少约4倍的半衰期；(iii)与向受试者给药的非环状的可比核酸相比，可以将向受试者给药的经工程化的指导RNA的治疗有效量减少至少约4倍；或(iv)其任何组合。本公开文本的另一个方面提供了载体。在一些情况下，载体可以包含经工程化的指导RNA。在一些情况下，载体可以包括脂质体、病毒载体、纳米颗粒或其任何组合。在一些情况下，载体可以是AAV载体。在一些情况下，载体可以包含DNA。在一些情况下，DNA可以是双链的。本公开文本的另一个方面提供了可以编码经工程化的指导RNA的核酸。在一些情况下，核酸可以是双链的。本公开文本的另一个方面提供了可以包含经工程化的指导RNA的分离的细胞。

[0007] 本公开文本的另一个方面提供了经工程化的指导RNA。经工程化的指导RNA可以包含靶向结构域。在一些情况下，经工程化的指导RNA可以包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，经工程化的指导RNA可以不包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，经工程化的指导RNA可以不包含能够暴露于溶剂的5'还原羟基。本公开文本的另一个方面提供了载体。在一些情况下，载体可以包含经工程化的指导RNA。在一些情况下，载体可以包括脂质体、病毒载体、纳米颗粒或其任何组合。在一些情况下，载体可以是AAV载体。在一些情况下，载体可以包含DNA。在一些情况下，DNA可以是双链的。本公开文本的另一个方面提供了可以编码经工程化的指导RNA的核酸。在一些情况下，核酸可以是双链的。本公开文本的另一个方面提供了可以包含经工程化的指导RNA的分离的细胞。

[0008] 本公开文本的另一个方面提供了经工程化的指导RNA。经工程化的指导RNA可以包含靶向结构域。在一些情况下，经工程化的指导RNA可以包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，经工程化的指导RNA可以不包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，经工程化的指导RNA可以包含比天然存在于人类细胞中的mRNA更不易受水解降解影响的二级结构。本公开文本的另一个方面提供了载体。在一些情况下，载体可以包含经工程化的指导RNA。在一些情况下，载体可以包括脂质体、病毒载体、纳米颗粒或其任何组合。在一些情况下，载体可以是AAV载体。在一些情况下，载体可以包含DNA。在一些情况下，DNA可以是双链的。本公开文本的另一个方面提供了可以编码经工程化的指导RNA的核酸。在一些情况下，核酸可以是双链的。本公开文本的另一个方面提供了可以包含经工程化的指导RNA的分离的细胞。

[0009] 本公开文本的另一个方面提供了形成环状RNA的方法。在一些情况下，所述方法可以包括在经工程化的指导RNA的多于一个末端之间直接或间接形成共价连接以形成环状RNA。经工程化的指导RNA可以包含靶向结构域。在一些情况下，经工程化的指导RNA可以包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，经工程化的指导RNA可以不包含能够募集进行靶核苷酸编辑的RNA编辑实体的募集结构域。在一些情况下，所述方法可以采用酶来形成共价连接。

[0010] 本公开文本的另一个方面提供了包含经工程化的指导RNA或载体的呈单位剂型的药物组合物。在一些情况下，药物组合物可以包含药学上可接受的赋形剂、稀释剂或载体。在一些情况下，药物组合物可以包含经修饰的转移RNA(tRNA)。在一些情况下，经修饰的tRNA可以是正交tRNA。在一些情况下，药物组合物可以包含RNA编辑实体。在一些情况下，

RNA编辑实体可以是重组RNA编辑实体。在一些情况下,RNA编辑实体可以直接或间接连接到经工程化的指导RNA。在一些情况下,RNA编辑实体和经工程化的指导RNA之间的连接可以是共价连接。

[0011] 本公开文本的另一个方面提供了包含本文公开的经工程化的指导RNA、本文公开的载体或本文公开的药物组合物以及容器的试剂盒。

[0012] 本公开文本的另一个方面提供了制备试剂盒的方法,所述试剂盒包含本文公开的经工程化的指导RNA、本文公开的载体或本文公开的药物组合物,并包装成包装。

[0013] 本公开文本的另一个方面提供了治疗受试者的疾病或病症的方法。在一些情况下,所述方法可以包括向受试者施用经工程化的指导RNA、载体或药物组合物。在一些情况下,所述方法可以包括向受试者施用经修饰的转移RNA、RNA编辑实体或其组合。在一些情况下,经修饰的转移RNA、RNA编辑实体或其组合可以与经工程化的指导RNA、载体或药物组合物共同施用。在一些情况下,经修饰的转移RNA、RNA编辑实体或其组合可以直接或间接连接到经工程化的指导RNA、载体或药物组合物。在一些情况下,与经工程化的指导RNA、载体或药物组合物的连接可以是共价连接。在一些情况下,施用可以通过静脉内注射、肌内注射、鞘内注射、眶内注射、皮下注射或其任何组合。在一些情况下,所述方法可以包括向受试者施用第二疗法。在一些情况下,疾病或病症可以选自:神经退行性障碍、肌肉障碍、代谢障碍、眼部障碍及其任何组合。在一些情况下,疾病或病症可以是阿尔茨海默病、肌营养不良、色素性视网膜炎、帕金森病、疼痛、斯塔加特黄斑营养不良(Stargardt macular dystrophy)、沙尔科-马里-图思病或雷特综合征。在一些情况下,受试者可以是哺乳动物。在一些情况下,哺乳动物可以是人。在一些情况下,受试者可能已经通过诊断被诊断患有疾病或病症。

[0014] 本公开文本的另一个方面提供了制备经工程化的指导RNA的方法。在一些情况下,所述方法可以包括对经工程化的指导RNA进行遗传编码或化学合成经工程化的指导RNA。本公开文本的另一个方面提供了制备药物组合物的方法。在一些情况下,所述方法可以包括将药物组合物配制成单位剂型。

[0015] 本公开文本的另一个方面提供了制备经工程化的指导RNA的方法。在一些情况下,所述方法可以包括在经工程化的指导RNA的多于一个末端之间直接或间接形成共价连接以形成环状RNA。在一些情况下,可以使用切割实体加工经工程化的指导RNA。在一些情况下,切割实体可以是核酶。在一些情况下,核酶可以是RNA酶P。在一些情况下,切割实体可以是tRNA。在一些情况下,所述方法可以进一步包括募集酶以在经工程化的指导RNA的多于一个末端之间形成共价键。

[0016] 本公开文本的另一个方面提供了制备经工程化的指导RNA的方法。在一些情况下,所述方法可以包括使用连接元件连接经工程化的指导RNA的多于一个末端。在一些情况下,连接元件可以采用点击化学来形成环状序列。在一些情况下,连接元件可以是基于叠氮化物的连接。

[0017] 本公开文本的另一个方面提供了用于形成环状指导RNA序列的构建体。在一些情况下,构建体可以包含:编码以下的核苷酸序列:(a)用于环化的指导RNA序列;(b)连接序列;和(c)核酶。在一些情况下,用于环化的指导RNA序列可以包含靶向结构域。在一些情况下,用于环化的指导RNA序列可以包含RNA编辑实体募集结构域。在一些情况下,用于环化的

指导RNA序列可以不包含RNA编辑实体募集结构域。在一些情况下,RNA编辑实体募集结构域可以包括Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13募集结构域或其任何组合。在一些情况下,RNA编辑实体募集结构域可以包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约400个核苷酸的至少约80%序列同源性。在一些情况下,RNA编辑实体募集结构域可以包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约80%序列同源性。在一些情况下,指导RNA序列的5'末端或3'末端可以侧接连接序列。在一些情况下,连接序列的5'末端或3'末端可以侧接核酶。在一些情况下,核苷酸序列可以编码至少2种核酶、至少2个连接序列或其组合。

[0018] 本公开文本的另一个方面提供了用于形成环状RNA序列的构建体。在一些情况下,构建体可以包含:编码以下的核苷酸序列:(a)用于环化的RNA序列;(b)连接序列;和(c)tRNA。在一些情况下,指导RNA序列的5'末端或3'末端可以侧接连接序列。在一些情况下,连接序列的5'末端或3'末端可以侧接tRNA。在一些情况下,核苷酸序列可以编码至少2种核酶、至少2个连接序列或其组合。在一些情况下,经工程化的指导RNA可以是经预应变的环状RNA序列。

[0019] 在一些方面,本公开文本提供了用于编辑RNA序列中的核苷酸的经工程化的指导RNA,经工程化的指导RNA包含:RNA编辑实体募集结构域,其中RNA编辑实体募集结构域募集RNA编辑实体,所述RNA编辑实体在与经工程化的指导RNA缔合时在RNA序列中的核苷酸的碱基上进行化学转化,从而产生经编辑的RNA序列,其中经工程化的指导RNA是环状的。在一些实施方案中,经工程化的指导RNA进一步包含靶向结构域。在一些实施方案中,靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。在一些实施方案中,靶向结构域包含长度为至少约100个核苷酸的序列长度。在一些实施方案中,碱基上的化学转化导致经编辑的RNA序列的至少部分敲低。在一些实施方案中,部分敲低包括由经编辑的RNA序列表达的蛋白质或其片段的水平降低。在一些实施方案中,降低的水平为约5%至100%。在一些实施方案中,降低的水平为约60%至100%。在一些实施方案中,化学转化导致有义密码子读作终止密码子。在一些实施方案中,化学转化导致终止密码子读作有义密码子。在一些实施方案中,化学转化导致第一有义密码子读作第二有义密码子。在一些实施方案中,化学转化导致第一终止密码子读作第二终止密码子。在一些实施方案中,经工程化的指导RNA可以被配置成形成二级结构,其包括:茎环结构、十字形结构、立足点结构、错配凸起结构或其任何组合。在一些实施方案中,RNA编辑实体募集结构域包含与以下的至少约20个核酸的至少约80%序列同源性:Alu结构域、APOBEC募集结构域、GluR2结构域或Cas13募集结构域。在一些实施方案中,RNA编辑实体募集结构域包含与Alu结构域的至少约20个核酸的至少约80%序列同源性。在一些实施方案中,RNA编辑实体募集结构域包含与Alu结构域的至少约80%序列同源性。在一些实施方案中,RNA编辑实体募集结构域包含与APOBEC募集结构域的至少约20个核酸的至少约80%序列同源性。在一些实施方案中,RNA编辑实体募集结构域包含与APOBEC募集结构域的至少约80%序列同源性。在一些实施方案中,RNA编辑实体募集结构域包括Cas13募集结构域,其为Cas13a募集结构域、Cas13b募集结构域、Cas13c募集结构域或Cas13d募集结构域。在一些实施方案中,RNA编辑实体募集结构域包含与Cas13b募集结构域的至少约20个核酸的至少约80%序列同源性。在一些实施方案中,序列包含与Cas13b募集结构域的至少约80%序列同源性。在一些实施方案中,RNA编辑实体是内源酶。在一些实施

方案中，RNA编辑实体是重组酶。在一些实施方案中，经工程化的指导RNA包含修饰。在一些实施方案中，修饰包括糖修饰。在一些实施方案中，经工程化的指导RNA的核苷酸包含甲基、氟基、甲氧基乙基、乙基、磷酸基团、酰胺基团、酯基团或其任何组合。在一些实施方案中，经工程化的指导RNA包含蛋白质包被。在一些实施方案中，经工程化的指导RNA是可遗传编码的。在一些实施方案中，RNA编辑实体连接到经工程化的指导RNA。在一些实施方案中，经工程化的指导RNA和RNA编辑实体之间的连接是直接或间接共价连接。在一些实施方案中，经工程化的指导RNA在生理pH的水溶液中保留比非环状的可比指导RNA长至少约4倍的半衰期。在一些实施方案中，向有需要的受试者给药的经工程化的指导RNA的治疗有效量基于重量比率比非环状的可比指导RNA少至少约4倍。

[0020] 在一些方面，本公开文本提供了用于编辑RNA序列中的核苷酸的经工程化的指导RNA，经工程化的指导RNA包含：RNA编辑实体募集结构域，其中RNA编辑实体募集结构域募集RNA编辑实体，所述RNA编辑实体在与经工程化的指导RNA缔合时在RNA序列中的核苷酸的碱基上进行化学转化，并且其中经工程化的指导RNA不包含能够暴露于溶剂的5'还原羟基、能够暴露于溶剂的3'还原羟基或两者。在一些方面，本公开文本提供了用于编辑RNA序列中的核苷酸的经工程化的指导RNA，经工程化的指导RNA包含：RNA编辑实体募集结构域，其中RNA编辑实体募集结构域募集RNA编辑实体，所述RNA编辑实体在与经工程化的指导RNA缔合时在RNA序列中的核苷酸的碱基上进行化学转化，从而产生经编辑的RNA序列，其中经工程化的指导RNA包含比天然存在于人类细胞中的mRNA更不易受水解降解影响的二级结构。在一些实施方案中，经工程化的指导RNA进一步包含靶向结构域。在一些实施方案中，靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。在一些实施方案中，靶向结构域包含长度为至少约100个核苷酸的序列长度。在一些实施方案中，碱基上的化学转化导致经编辑的RNA序列的至少部分敲低。在一些实施方案中，至少部分敲低包括由经编辑的RNA序列表达的蛋白质或其片段的水平降低。在一些实施方案中，降低的水平为约5％至100％。在一些实施方案中，降低的水平为约60％至100％。在一些实施方案中，化学转化导致有义密码子读作终止密码子。在一些实施方案中，化学转化导致终止密码子读作有义密码子。在一些实施方案中，化学转化导致第一有义密码子读作第二有义密码子。在一些实施方案中，经工程化的指导RNA是经预应变的环状RNA序列。在一些实施方案中，经工程化的指导RNA与未经应变的环状RNA序列相比包含降低的熵。

[0021] 在一些方面，本公开文本提供了包含本文所述的任何经工程化的指导RNA的载体。在一些实施方案中，载体包括脂质体、病毒载体、纳米颗粒或其任何组合。在一些实施方案中，载体是病毒载体，并且其中病毒载体是腺相关病毒(AAV)载体。在一些实施方案中，载体包含DNA。在一些实施方案中，DNA是双链的。

[0022] 在一些方面，本公开文本提供了编码本文所述的任何经工程化的指导RNA的核酸。在一些实施方案中，核酸是双链的。

[0023] 在一些方面，本公开文本提供了包含本文所述的任何经工程化的指导RNA、本文所述的任何载体或本文所述的任何核酸的分离的细胞。

[0024] 在一些方面，本公开文本提供了形成环状RNA的方法，所述方法包括：在包含经工程化的指导RNA的序列的多于一个末端之间直接或间接形成共价连接以形成环状RNA，其中经工程化的指导RNA包含：RNA编辑实体募集结构域，其中RNA编辑实体募集结构域募集RNA

编辑实体，所述RNA编辑实体在与经工程化的指导RNA缔合时在RNA序列中的核苷酸的碱基上进行化学转化，从而产生经编辑的RNA序列。在一些实施方案中，所述方法采用酶来形成共价连接。在一些实施方案中，酶是连接酶。在一些实施方案中，经工程化的指导RNA进一步包含靶向结构域。在一些实施方案中，靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。在一些实施方案中，靶向结构域包含长度为至少约100个核苷酸的序列长度。在一些实施方案中，碱基上的化学转化导致经编辑的RNA序列的至少部分敲低。在一些实施方案中，至少部分敲低包括由经编辑的RNA序列表达的蛋白质或其片段的水平降低。在一些实施方案中，降低的水平为约5％至100％。在一些实施方案中，降低的水平为约60％至100％。在一些实施方案中，与其他方面相同的未经编辑的RNA序列相比，可以确定部分敲低或降低的水平，如在体外测定中所确定的。在一些实施方案中，化学转化导致有义密码子读作终止密码子。在一些实施方案中，化学转化导致终止密码子读作有义密码子。在一些实施方案中，化学转化导致第一有义密码子读作第二有义密码子。

[0025] 在一些方面，本公开文本提供了药物组合物，所述药物组合物包含本文所述的任何经工程化的指导RNA、本文所述的任何载体或本文所述的任何核酸，以及药学上可接受的：赋形剂、稀释剂或载体。在一些实施方案中，药物组合物可以呈单位剂型。在一些实施方案中，组合物进一步包含RNA编辑实体。在一些实施方案中，RNA编辑实体是重组RNA编辑实体。在一些实施方案中，RNA编辑实体直接或间接连接到经工程化的指导RNA。在一些实施方案中，RNA编辑实体和经工程化的指导RNA之间的连接是共价连接。

[0026] 在一些方面，本公开文本提供了治疗有需要的受试者的方法，所述方法包括：向受试者施用本文所述的任何经工程化的指导RNA、本文所述的任何载体或本文所述的任何药物组合物。在一些实施方案中，所述方法进一步包括向有需要的受试者施用经修饰的转移RNA、RNA编辑实体或其组合。在一些实施方案中，将经修饰的转移RNA、RNA编辑实体或其组合与经工程化的指导RNA、载体或药物组合物共同施用。在一些实施方案中，经修饰的转移RNA、RNA编辑实体或其组合直接或间接连接到经工程化的指导RNA、载体或药物组合物。在一些实施方案中，与经工程化的指导RNA、载体或药物组合物的连接是共价连接。在一些实施方案中，施用通过静脉内注射、肌内注射、鞘内注射、眶内注射、皮下注射或其任何组合。在一些实施方案中，所述方法进一步包括向受试者施用第二疗法。在一些实施方案中，受试者患有或被怀疑患有选自以下的疾病或病症：神经退行性障碍、肌肉障碍、代谢障碍、眼部障碍及其任何组合。在一些实施方案中，疾病或病症是阿尔茨海默病、肌营养不良、色素性视网膜炎、帕金森病、疼痛、斯塔加特黄斑营养不良、沙尔科-马里-图思病或雷特综合征。在一些实施方案中，疾病或病症是肌营养不良，其为迪谢内肌营养不良(DMD)。在一些实施方案中，受试者是哺乳动物。在一些实施方案中，哺乳动物是人。在一些实施方案中，受试者已经通过诊断被诊断患有疾病或病症。

[0027] 在一些方面，本公开文本提供了制备本文所述的任何药物组合物的方法，所述方法包括将药物组合物配制成单位剂型。

[0028] 在一些方面，本公开文本提供了制备本文所述的任何经工程化的指导RNA的方法，所述方法包括对经工程化的指导RNA进行遗传编码或化学合成经工程化的指导RNA。

[0029] 在一些方面，本公开文本提供了制备本文所述的任何经工程化的指导RNA的方法，所述方法包括在经工程化的指导RNA的多于一个末端之间直接或间接形成共价连接以形成

环状RNA,其中使用自切割实体加工经工程化的指导RNA。在一些实施方案中,自切割实体是核酶。在一些实施方案中,核酶是RNA酶P。在一些实施方案中,自切割实体是tRNA。在一些实施方案中,自切割实体是适配体或其催化活性片段。在一些实施方案中,所述方法进一步包括募集酶以在经工程化的指导RNA的多于一个末端之间形成共价键。

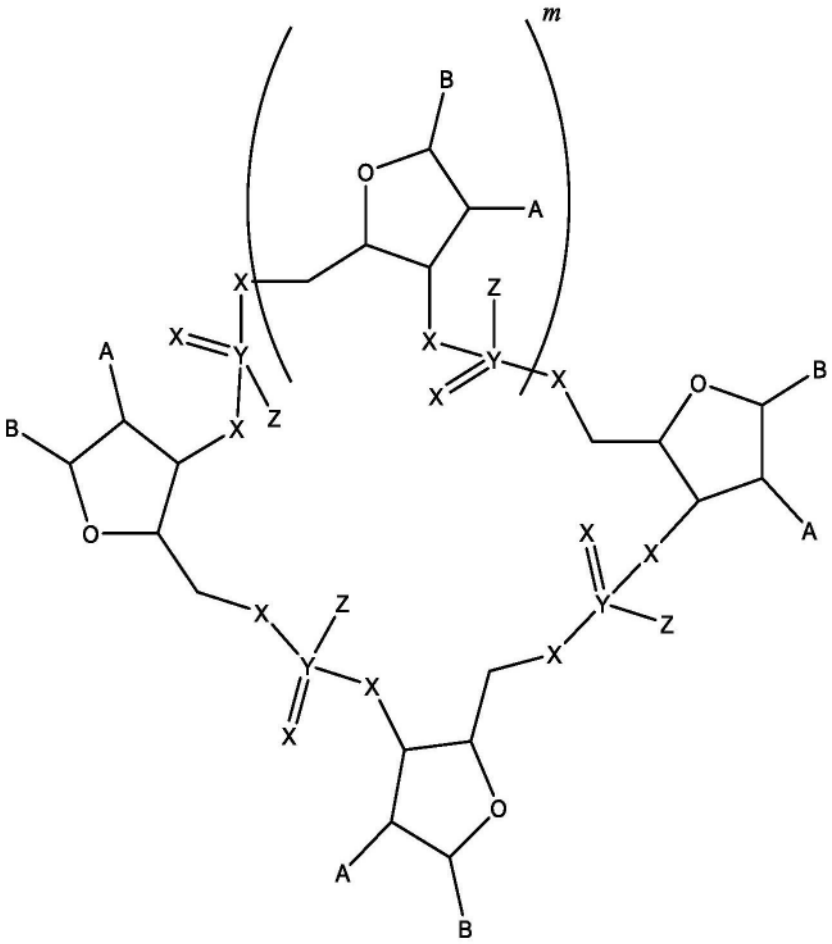
[0030] 在一些方面,本公开文本提供了制备本文所述的任何经工程化的指导RNA的方法,所述方法包括使用连接元件连接经工程化的指导RNA的多于一个末端。在一些实施方案中,连接元件采用点击化学来形成环状序列。在一些实施方案中,连接元件是基于叠氮化物的连接。

[0031] 在一些方面,本公开文本提供了用于形成环状指导RNA序列的构建体,构建体包含:编码以下的核苷酸序列:(a)用于环化的指导RNA序列;(b)连接序列;和(c)核酶。在一些实施方案中,经工程化的指导RNA可以进一步包含RNA编辑实体募集结构域。在一些实施方案中,经工程化的指导RNA可以不包含RNA编辑实体募集结构域。在一些实施方案中,经工程化的指导RNA进一步包含靶向结构域。在一些实施方案中,靶向结构域包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。在一些实施方案中,靶向结构域包含长度为至少约100个核苷酸的序列长度。在一些实施方案中,RNA编辑实体募集结构域包括Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13募集结构域或其任何组合。在一些实施方案中,RNA编辑实体募集结构域包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约400个核苷酸的至少约80%序列同源性。在一些实施方案中,RNA编辑实体募集结构域包含与SEQ ID NO 1418或SEQ ID NO 1419的至少约80%序列同源性。在一些实施方案中,指导RNA序列的5'末端或3'末端侧接连接序列。在一些实施方案中,连接序列的5'末端或3'末端侧接核酶。在一些实施方案中,核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。在一些实施方案中,核苷酸序列包括与表1-12中的任一个多核苷酸具有至少约80%、至少85%、至少90%、至少92%、至少95%、至少97%、至少99%或100%序列同源性的序列。

[0032] 在一些方面,本公开文本提供了用于形成环状RNA序列的构建体,构建体包含:编码以下的核苷酸序列:(a)用于环化的RNA序列;(b)连接序列;和(c)tRNA。在一些实施方案中,指导RNA序列的5'末端或3'末端侧接连接序列,并且其中连接序列的5'末端或3'末端侧接tRNA。在一些实施方案中,核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。

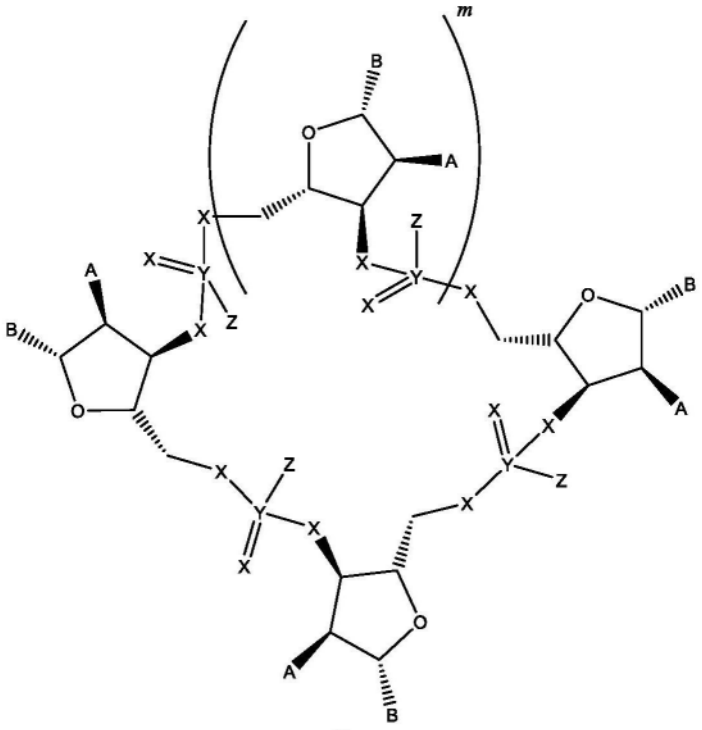
[0033] 在一些方面,本公开文本提供了用于形成环状RNA序列的构建体,构建体包含:编码以下的核苷酸序列:(a)用于环化的RNA序列;(b)连接序列;和(c)适配体或其催化活性片段。在一些实施方案中,指导RNA序列的5'末端或3'末端侧接连接序列,并且其中连接序列的5'末端或3'末端侧接适配体或其催化活性片段。在一些实施方案中,核苷酸序列编码至少2种核酶、至少2个连接序列或其组合。

[0034] 在一些方面,本公开文本提供了经工程化的多核苷酸,所述经工程化的多核苷酸包含:与靶RNA至少部分互补的靶向结构域,其中经工程化的多核苷酸包含式(I)的结构:



式 (I)

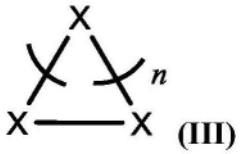
其中:每个X是O;每个Y是P;每个Z是O或S;每个A独立地是H、D、卤素、OM、SM、NRM或NRR';每个B独立地是尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物;每个M独立地是无机或有机阳离子、H或D;并且每个R和R'独立地是H、D、卤素或C_1-C_6烷基;并且m独立地是0-1,000的整数;其中靶向结构域被配置成与靶RNA的编码区至少部分缔合,并且其中靶向结构域与靶RNA的编码区的缔合促进RNA编辑实体对靶RNA的核苷酸的碱基的编辑。在一些实施方案中,在体外测定中确定RNA编辑实体对靶RNA的核苷酸的碱基的编辑,所述体外测定包括:(i)将靶RNA直接或间接引入原代细胞系中,(ii)将经工程化的多核苷酸直接或间接引入原代细胞系中,以及(iii)对靶RNA测序。在一些实施方案中,每个单元m独立地呈(D)-或(L)-构型。在一些实施方案中,式(I)是根据式(II):



(式II)

在一些实施方案中，每个Z是O并且每个R是H。在一些实施方案中，m是约30-600的独立整数。在一些实施方案中，至少部分互补包括所述靶向结构域包含与靶RNA的反向互补序列具有至少约80％序列同源性的多核苷酸序列。在一些实施方案中，RNA编辑实体包括ADAR蛋白、APOBEC蛋白或两者。在一些实施方案中，RNA编辑实体包括ADAR，并且其中ADAR包括ADAR1或ADAR2。在一些实施方案中，碱基的编辑将有义密码子转化为终止密码子。在一些实施方案中，碱基的编辑将终止密码子转化为有义密码子。在一些实施方案中，碱基的编辑将第一有义密码子转化为第二有义密码子。在一些实施方案中，碱基的编辑将指定第一氨基酸的有义密码子转化为指定第二氨基酸的第二有义密码子。在一些实施方案中，第一氨基酸是蛋白酶切割位点。

[0035] 在一些方面，本公开文本提供了包含与靶RNA至少部分互补的靶向结构域的经工程化的多核苷酸；其中经工程化的多核苷酸包含式(III)的结构：



(III)

其中在经工程化的多核苷酸中，每个X是包含独立地为尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物的碱基的核苷酸；n独立地是0-1,000的整数；并且其中对于每个连接，每个核苷酸独立地通过磷酸酯、磷酸硫酯(phosphothioester)、硫代磷酸酯(phosphothioate)或亚磷酰胺连接而连接到两个相邻核苷酸；并且其中靶向结构域被配置成与靶RNA的编码区至少部分缔合，其中靶向结构域与靶RNA的编码区的缔合促进RNA编辑实体对靶RNA的核苷酸的碱基的编辑。在一些实施方案中，在体外测定中确定RNA编辑实体对靶RNA的核苷酸的碱基的编辑，所述体外测定包括：(i)将靶RNA直接或间接引入原代细胞系中，(ii)将经工程化的多核苷酸直接或间接引入原代细

胞系中，以及(iii)对靶RNA测序。在一些实施方案中，RNA编辑实体包括ADAR蛋白、APOBEC蛋白或两者。在一些实施方案中，RNA编辑实体包括ADAR，并且其中ADAR包括ADAR1或ADAR2。在一些实施方案中，原代细胞系包括神经元细胞、感光细胞、视网膜色素上皮细胞、胶质细胞、成肌细胞、肌管细胞、肝细胞、肺上皮细胞或成纤维细胞。在一些实施方案中，经工程化的多核苷酸不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者。在一些实施方案中，每个5'羟基和每个3'羟基独立地通过共价氧磷键键合到磷。在一些实施方案中，磷包含在磷酸二酯基团中。在一些实施方案中，经工程化的多核苷酸进一步包含RNA编辑实体募集结构域。在一些实施方案中，靶向结构域为约20个核苷酸至约150个核苷酸。在一些实施方案中，靶RNA包含无义突变。在一些实施方案中，靶向结构域包含与靶RNA错配的至少单个核苷酸。在一些实施方案中，错配核苷酸与互补于靶RNA的两个核苷酸相邻，错配核苷酸的每侧各一个。在一些实施方案中，靶向结构域与在疾病或病症中实施的靶RNA至少部分结合。在一些实施方案中，疾病或病症包括雷特综合征、亨廷顿病、帕金森病、阿尔茨海默病、肌营养不良或泰-萨二氏病。在一些实施方案中，相对于缺乏编辑的其他方面可比的靶RNA的翻译蛋白，碱基的编辑在进行碱基编辑的靶RNA翻译后导致蛋白质或其片段的水平增加、蛋白质或其片段的长度增加、蛋白质或其片段的功能性增加、蛋白质或其片段的稳定性增加或其任何组合。在一些实施方案中，增加的水平为约5％至约100％。在一些实施方案中，增加的长度为蛋白质或其片段的约5％至约100％。在一些实施方案中，增加的稳定性是蛋白质或其片段的增加的半衰期。在一些实施方案中，经工程化的多核苷酸包含与表1-12中的任一个多核苷酸具有至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列同源性的多核苷酸序列。在一些实施方案中，经工程化的多核苷酸包含长度为表1-12中的任一个多核苷酸的序列长度的至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％的多核苷酸序列。在一些实施方案中，经工程化的多核苷酸包含与表1-12中的任一个多核苷酸具有至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列同源性和至少约80％、至少85％、至少90％、至少92％、至少95％、至少97％、至少99％或100％序列长度的多核苷酸序列。

[0036] 在一些方面，本公开文本提供了包含与靶RNA至少部分互补的靶向结构域的经工程化的指导RNA，其中经工程化的指导RNA包含含有共价连接在一起的多个糖和磷酸部分的主链，并且其中主链不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者，其中靶向结构域被配置成与靶RNA的编码区至少部分缔合，其中靶向结构域与靶RNA的编码区的缔合促进RNA编辑实体对靶RNA的核苷酸的碱基的编辑。

[0037] 在一些方面，本公开文本提供了经工程化的指导RNA，所述经工程化的指导RNA可以包含与靶RNA至少部分互补的靶向结构域。在一些情况下，经工程化的指导RNA可以进一步包含RNA编辑实体募集结构域，其中RNA编辑实体募集结构域被配置成与RNA编辑实体至少瞬时缔合。在一些情况下，经工程化的指导RNA可以不包含RNA编辑实体募集结构域。在一些情况下，经工程化的指导RNA可以包含含有共价连接在一起的多个糖和磷酸部分的主链，并且其中主链不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者，其中靶向结构域被配置成与靶RNA的编码区至少部分缔合，其中靶向结构域与靶RNA的编码区的缔合促进RNA编辑实体对靶RNA的核苷酸的碱基的编辑。在一些实施方案中，至少部分互补包括所述靶向结构域包含与靶RNA的反向互补序列具有至少约80％、至少85％、至少90％、至少92％

或至少95％序列同源性的多核苷酸序列。在一些实施方案中，在体外测定中确定RNA编辑实体对靶RNA的核苷酸的碱基的编辑，所述体外测定包括：(i)将靶RNA转染到原代细胞系中，(ii)将经工程化的多核苷酸转染到原代细胞系中，以及(iii)对靶RNA测序。

[0038] 本公开文本提供了具有以下一般结构的经工程化的环状指导RNA：

-(适配体)-(RNA编辑实体募集结构域)-(RNA靶向结构域)-(任选的RNA编辑实体募集结构域)-(适配体)-。

在一些情况下，经工程化的环状指导RNA可以不(缺乏)包含RNA编辑实体募集结构域。在一个实施方案中，适配体包含适于连接的适配体，使得经工程化的环状指导RNA任一端上的适配体彼此连接，从而形成环状构建体。可以使用内源连接酶或重组提供的连接酶连接适配体。在另一个实施方案中，RNA编辑实体募集结构域可以募集内源RNA编辑实体或者可以募集重组提供的RNA编辑实体。在一个实施方案中，RNA编辑实体募集结构域可以选自Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13结构域和前述任一种的功能片段。在另一个实施方案中，RNA编辑实体募集结构域可以选自APOBEC蛋白(例如，APOBEC1、APOBEC2、APOBEC3A、APOBEC3B、APOBEC3C、APOBEC3E、APOBEC3F、APOBEC3G、APOBEC3H或APOBEC4蛋白)或ADAR蛋白(例如，ADAR1、ADAR2或ADAR3蛋白)。在一个实施方案中，环状指导RNA包含两个RNA编辑实体募集结构域。在一个进一步的实施方案中，两个RNA编辑实体募集结构域侧接RNA靶向结构域(一个在RNA靶向结构域的5'末端，并且一个在3'末端)。在另一个实施方案中，RNA靶向结构域与待编辑的靶RNA序列互补，除了待修饰的碱基。在另一个实施方案中，RNA靶向结构域包括多个错配碱基，其中一个碱基是待化学修饰的靶碱基，而其他碱基是易受超编辑影响的碱基错配。在一个实施方案中，RNA靶向结构域的靶错配碱基对是被靶RNA序列的RNA编辑实体化学修饰的位点。在一个实施方案中，如前述实施方案中所述的经工程化的环状指导RNA由重组多核苷酸编码。在一个进一步的实施方案中，载体可以包含重组多核苷酸。

附图说明

[0039] 将通过参考阐述了利用本公开文本的原理的说明性实施方案的以下具体实施方式和附图获得对本公开文本的某些特征和优点的更好理解，在所述附图中：

[0040] 图1A-C显示了环状指导RNA的示例性构建体设计和制备环状指导RNA的方法。

[0041] 图2显示了只有当形成环状指导RNA时才具有PCR扩增产物的琼脂糖凝胶。含有Alu 100-50指导物的孔显示了扩增产物的条带。

[0042] 图3A显示了Alu-v2环状结构的示例性序列(例如经环化的Alu 60-30R7A指导物和经环化的Alu 100-50R7A指导物)。

[0043] 图3B显示了改进内源ADAR募集的环状adRNA设计。将编辑诱导元件(EIE)或Alu元件经由F30接界添加到环状adRNA中。

[0044] 图4显示了在没有ADAR募集和有ADAR募集两种不同情况下进行RNA编辑以允许核糖体连读从而导致正常萤光素酶表达的萤光素酶测定的示意图。

[0045] 图5显示了靶向mRNA的经预应变的和未经应变的环状adRNA的例子。

[0046] 图6显示了相对光单位的条形图，其指示了各种长度的环状adRNA在添加或不添加外源ADAR酶的情况下通过RNA编辑恢复细胞中萤光素酶活性的能力。

[0047] 图7显示了琼脂糖凝胶中来自各种长度的环状adRNA的扩增条带。用逆转录酶(RT)-PCR扩增adRNA以确认adRNA在细胞中被环化。

[0048] 图8显示了不同构建体的经编辑mRNA百分比的条形图,所述构建体可以在过表达或不过表达ADAR酶的情况下用于环状adRNA构建。另外,图8还显示了具有反义结构域的Alu元件结构的示意图,所述反义结构域包括用于通过ADAR进行RNA编辑的C错配。

[0049] 图9A-E显示了使用本公开文本的构建体获得的各种构建体比较和所得数据。(A)使用各种adRNA设计在RAB7A转录物的3'UTR中实现的RNA编辑效率的比较。值表示平均值+/-SEM(n=3)。(B)adRNA环化的确认。(C)使用各种adRNA设计在转染后2和4天实现的RNA编辑效率。值表示平均值+/-SEM(n=3)。(D)在靶向ADAR1的siRNA存在下评估adRNA对cluc转录物进行RNA编辑的能力。值表示平均值+/-SEM(n=3)。(E)基于siRNA的ADAR1敲低。值表示平均值+/-SEM(n=3)。所有实验都在HEK293FT细胞中进行。

[0050] 图10A-C显示了环状指导RNA的结果和效率。(A)在质粒转染后2天观察到的各种转录物的CDS中的RNA编辑效率。值表示平均值(n=2)。(B)在转染后1天经由IVT环状adRNA和经质粒递送的(经U6转录的)环状adRNA在RAB7A转录物的3'UTR中观察到的RNA编辑效率。值表示平均值+/-SEM(n=3)。(C)IVT adRNA和经质粒递送的(经U6转录的)环状adRNA的环化的确认。值表示平均值+/-SEM(n=3)。

[0051] 图11A-B显示了本公开文本的构建体的编辑效率和表达。(A)经由全身递送包装到AAV8中的经U6转录的环状长反义RNA在小鼠肝脏中的体内RNA编辑效率。值表示平均值+/-SEM(n=3)。(B)环状adRNA的相对表达水平。值表示平均值+/-SEM(n=3)。

[0052] 图12A-C显示了Alu和adRNA设计及其经编辑mRNA活性。(A)Alu元件和从Alu元件工程化的3个adRNA设计的示意图。(B)测定Alu-adRNA募集内源和外源ADAR的能力。值表示平均值+/-SEM(n=3)。(C)用Alu-v2设计评价反义结构域。值表示平均值+/-SEM(n=3)。所有实验都在HEK293FT细胞中进行。

[0053] 图13A-B显示了(A)Alu元件和从Alu元件工程化的3个adRNA设计的示意图。(B)测定Alu-adRNA募集内源和外源ADAR的能力。值表示平均值+/-SEM(n=3)。(c)用Alu-v2设计评价反义结构域。值表示平均值+/-SEM(n=3)。所有实验都在HEK293FT细胞中进行。

[0054] 图14A-B显示了(A)靶位点周围RAB7A cDNA的样品迹线(由大箭头突出显示)。较小的箭头指向脱靶腺苷的编辑。(B)将环状adRNA的线性形式使用T7聚合酶在体外转录,使用LiCl纯化并转染到细胞中,在其中它们通过连接酶环化。

[0055] 图15A-F显示了(A)经由全身递送包装到AAV8中的经U6转录的线性和环状长反义RNA在小鼠肝脏中的体内RNA编辑效率。值表示平均值+/-SEM(n=3)。各组AAV8或PBS注射小鼠中(B)环状adRNA、(C)GFP和(D)人ADAR2的相对表达水平。单独递送adRNA的AAV载体也含有GFP。值表示平均值+/-SEM(n=3)。(E)各组AAV8或PBS注射小鼠中的PCSK9表达水平。值表示平均值+/-SEM(n=3)。(F)描绘了用对应于SI图4a中的图的环状adRNA观察到的超编辑的热图。箭头指示靶腺苷。

[0056] 图16提供了比较用每种长反义adRNA构建体观察到的转录组范围的A至G编辑产量(y轴)与用对照样品观察到的产量(x轴)的2D直方图。每个直方图表示同一组参考位点,其中读数覆盖为至少10,并且在至少一个样品中检测到至少一个推定的编辑事件。当比较处理与对照样品时,突出显示的箱(bin)含有A至G编辑产量具有显著变化的位点。每个图中的

十字指示具有最小调整P值的100个位点。从左上角顺时针，环状100,50;和0,100,50。

[0057] 图17A-D显示了用于减少超编辑的环状adRNA反义设计。底链表示反义结构域，而顶链是靶mRNA。与错配相对指示靶腺苷;(A)产生6-12bp大小的环，与位于此区域内的靶腺苷相距30-40bp。(B)按照以下模式在整个反义结构域中产生单个bp凸起:…-34、-24、-14、-10、0、10、14、24、34…;(C)按照以下模式在整个反义结构域中产生单个bp凸起:…-30、-20、-10、0、10、20、30…;(D)通过相对经超编辑的腺苷定位鸟苷产生凸起。

具体实施方式

[0058] 如本文和所附权利要求书所用，单数形式“一个/一种(a)”、“一个/一种(an)”和“所述(the)”包括复数指代物，除非上下文另外清楚地规定。因此，例如，提及“一个细胞”包括多个此类细胞，并且提及“所述片段”包括提及一个或多个片段及其本领域技术人员已知的等同物，等等。

[0059] 此外，除非另外说明，否则“或”的使用意指“和/或”。类似地，“包含(comprise)”、“包含(comprises)”、“包含(comprising)”、“包括(include)”、“包括(includes)”和“包括(including)”是可互换的，并不旨在是限制性的。

[0060] 应进一步理解，在使用术语“包含”描述各个实施方案的情况下，本领域技术人员将理解，在一些特定情形下，可以可替代地使用语言“基本上由……组成”或“由……组成”来描述实施方案。

[0061] 除非另外定义，否则本文所用的所有技术和科学术语都具有与本公开文本所属领域的普通技术人员通常所理解的相同的含义。尽管许多方法和试剂与本文所述的那些类似或等同，但本文公开了示例性方法和材料。

[0062] 将本文所提到的所有出版物都以全文通过引用并入本文以用于描述和公开可以与本文中的描述结合使用的方法的目的。此外，关于在一个或多个出版物中呈现的与在本公开文本中已经明确地定义的术语类似或相同的任何术语，在所有方面将以如在本公开文本中明确地提供的术语的定义为准。

[0063] 应当理解，本公开文本不限于本文所述的特定方法、方案和试剂等，并且本身可以变化。本文所用的术语仅用于描述特定实施方案或方面的目的，并不旨在限制本公开文本的范围。

[0064] 除了在操作实施例中以外，或者在另外指示的情况下，本文所用的表述成分的量或反应条件的所有数字都应当被理解为在所有情形下都被术语“约”修饰。当用于描述本发明时，与百分比结合的术语“约”意指±1%。如本文所用的术语“约”可以意指在如通过本领域普通技术人员确定的特定值的可接受误差范围内，其可能部分取决于如何测量或确定所述值，例如测量系统的局限性。可替代地，“约”可以意指给定值的加或减20%、加或减10%、加或减5%或者加或减1%的范围。可替代地，特别是关于生物系统或过程，所述术语可以意指在值的一个数量级内、在值的5倍内或在值的2倍内。在本申请和权利要求书中描述特定值的情况下，除非另外说明，否则可以假设术语“约”意指在所述特定值的可接受误差范围内。此外，在提供值的范围和/或子范围的情况下，所述范围和/或子范围可以包括所述范围和/或子范围的端点。在一些情况下，变化可以包括指定量的20%、10%、5%、1%、0.5%或甚至0.1%的量或浓度。

[0065] 对于本文中数字范围的叙述，明确考虑其间具有相同精确度的每个中间数字。例如，对于6-9的范围，除了6和9之外还考虑数字7和8，并且对于范围6.0-7.0，明确考虑数字6.0、6.1、6.2、6.3、6.4、6.5、6.6、6.7、6.8、6.9和7.0。

[0066] 如本文所用的术语“腺嘌呤”、“鸟嘌呤”、“胞嘧啶”、“胸腺嘧啶”、“尿嘧啶”和“次黄嘌呤”(肌苷中的核碱基)是指核碱基本身。

[0067] 术语“腺苷”、“鸟苷”、“胞苷”、“胸苷”、“尿苷”和“肌苷”是指与(脱氧)核糖基糖连接的核碱基。

[0068] 如本文所用的术语“腺相关病毒”或“AAV”是指与此名称相关并属于依赖细小病毒属(dependoparvovirus)细小病毒科(Parvoviridae)的一类病毒的成员。已知此病毒的多种血清型适于基因递送；所有已知的血清型都可以感染来自各种组织类型的细胞。在现有技术中公开了按顺序编号的至少11种血清型。可用于本文公开的目的的非限制性示例性血清型包括11种血清型中的任一种，例如AAV2和AAV8。如本文所用的术语“慢病毒”是指与此名称相关并属于慢病毒属(lentivirus)逆转录病毒科(Retroviridae)的一类病毒的成员。虽然已知一些慢病毒会引起疾病，但已知其他慢病毒适于基因递送。参见例如，Tomás等人(2013)Biochemistry,Genetics and Molecular Biology:“Gene Therapy-Tools and Potential Applications,”ISBN 978-953-51-1014-9,DOI:10.5772/52534。

[0069] 如本文所用的术语“作用于RNA的腺苷脱氨酶”或“ADAR”是指可以将RNA序列中的腺苷(A)转化为肌苷(I)的腺苷脱氨酶。ADAR1和ADAR2是参与体内mRNA编辑的两种示例性ADAR种类。ADAR1的非限制性示例性序列可以在以下参考编号下找到：HGNC：225；Entrez Gene：103；Ensembl：ENSG 00000160710；OMIM：146920；UniProtKB：P55265；和GeneCards：GC01M154554，以及其生物等同物。ADAR2的非限制性示例性序列可以在以下参考编号下找到：HGNC：226；Entrez Gene：104；Ensembl：ENSG00000197381；OMIM：601218；UniProtKB：P78563；和GeneCards：GC21P045073，以及其生物等同物。相关的直向同源物和同源物将容易地使用本领域技术人员可获得的各种序列搜索工具和数据库来鉴定。

[0070] 术语“adRNA”代表ADAR募集RNA，并且可以指代用于指导位点特异性ADAR编辑的正向和反向RNA。在一些情形下，募集ADAR的正向RNA被称为“adRNA”，而募集ADAR的反向RNA被称为“radRNA”。

[0071] 术语“Alu结构域”可以指代从Alu转座元件(“Alu元件”)获得的序列。在一些情况下，Alu元件的长度可以为约300个碱基对。Alu元件通常包含以下结构：十字形-聚A5-TAC-聚A6-十字形-聚A尾，其中两个十字形结构域在核苷酸序列上是类似的。“Alu结构域”可以包含Alu元件的十字形部分。在一些实施方案中，包含十字形结构的两个Alu结构域通过与靶RNA序列互补的序列连接。

[0072] 如本文所用的术语“APOBEC”可以指代属于参与mRNA编辑(即催化C至T编辑，其可以被解释为C至U转换)的进化上保守的胞苷脱氨酶家族的任何蛋白质及其等同物。在一些方面，术语APOBEC可以指代APOBEC1、APOBEC2、APOBEC3A、APOBEC3B、APOBEC3C、APOBEC3E、APOBEC3F、APOBEC3G、APOBEC3H、APOBEC4中的任一种或其各自的等同物。本文提供了包含一个或多个APOBEC结构域的融合蛋白的非限制性示例性序列，所述结构域与ADAR结构域融合或与替代结构域融合以使它们适于在RNA编辑系统中使用。为此，APOBEC可以被认为是ADAR的等同物，尽管通过不同的转换催化编辑。因此，不受理论的约束，据信本文考虑的与基于

ADAR的编辑系统一起使用的所有实施方案都可以适于在基于APOBEC的RNA编辑系统中使用。在一些情况下,APOBEC的使用可以涉及某些修饰,诸如但不限于使用特定的指导RNA或“gRNA”(包括经环化的gRNA)来募集酶。

[0073] 术语“接触”可以意指两种或更多种实体之间的直接或间接结合或相互作用。直接相互作用的例子是结合。间接相互作用的例子是其中一种实体作用于中间分子,所述中间分子又作用于所提及的第二实体。如本文所用的接触包括在溶液中、在固相中、在体外、离体、在细胞中和在体内。在一个实施方案中,接触可以发生在指导RNA和RNA编辑实体之间。体内接触可以被称为施用(administering)或施用(administration)。

[0074] 如本文所用的术语“缺乏”可以指代低于特定药剂的正常(生理学上可接受的)水平。在蛋白质的上下文中,缺乏可以指代低于全长蛋白的正常水平。

[0075] 如本文所用,术语“结构域”是指较大构建体的特定区域,使得所述结构域包含在较大构建体中或者是较大构建体的一部分。关于核酸,结构域可以指代在含有多个编码序列的较大构建体中发现的编码序列。

[0076] 当应用于多核苷酸时,术语“编码”可以指代这样的多核苷酸,如果其处于天然状态或当通过本领域技术人员熟知的方法操作时,它可以被转录和/或翻译以产生多肽和/或其片段的mRNA,则其被称为“编码”所述多肽。反义链是此种核酸的互补序列,并且从反义链中可以推断出编码序列。

[0077] “经工程化的多核苷酸”或“经工程化的指导RNA”可与环状指导RNA互换地使用。经工程化的多核苷酸可以包括DNA或RNA或杂交DNA/RNA构建体的重组多核苷酸。经工程化的多核苷酸可以产生指导RNA,更具体地可以产生环状指导RNA。式I、II和III提供了经工程化的多核苷酸的示例性结构。

[0078] 术语“等同物”或“生物等同物”当指代具有最小同源性同时仍保持所需结构或功能的特定分子、生物材料或细胞材料时可互换地使用。

[0079] 如本文所用,“表达”可以指代多核苷酸被转录成mRNA的过程和/或经转录的mRNA随后被翻译成肽、多肽或蛋白质的过程。如果多核苷酸来源于基因组DNA,则在真核细胞中表达可以包括mRNA的剪接。

[0080] “同源性”或“同一性”或“相似性”可以指代两个肽之间或两个核酸分子之间的序列相似性。可以通过比较每个序列中的位置来确定同源性,所述序列可以出于比较目的进行比对。例如,当所比较序列中的位置由相同的碱基或氨基酸占据时,则分子在该位置处是同源的。序列之间的同源性程度是序列具有的匹配或同源位置的数量的函数。“无关的”或“非同源的”序列与本公开文本的一个序列具有小于40%同一性或可替代地小于25%同一性。

[0081] 同源性可以指代序列与参考序列的百分比(%)同一性。实际上,任何特定序列是否可以与本文所述的任何序列至少50%、60%、70%、80%、85%、90%、92%、95%、96%、97%、98%或99%相同,此种特定肽、多肽或核酸序列可以常规地使用已知的计算机程序如Bestfit程序(威斯康星序列分析包(Wisconsin Sequence Analysis Package),Unix第8版,Genetics Computer Group,University Research Park,575Science Drive,威斯康星州麦迪逊53711)来确定。当使用Bestfit或任何其他序列比对程序来确定特定序列是否与参考序列例如95%相同时,可以这样设置参数使得在参考序列的全长上计算同一性百分比

并且允许同源性空位最多占总参考序列的5%。

[0082] 例如,在一个具体实施方案中,参考序列(查询序列,即本公开文本的序列)和目标序列之间的同一性(也称为全局序列比对)可以使用基于Brutlag等人(Comp.App.Biosci.6:237-245(1990))的算法的FASTDB计算机程序来确定。在一些情况下,在FASTDB氨基酸比对中使用的对同一性进行狭义解释的特定实施方案的参数可以包括:评分方案=PAM(接受突变百分比)0,k元组=2,错配罚分=1,连接罚分=20,随机化组长度=0,截断得分=1,窗口大小=序列长度,空位罚分=5,空位大小罚分=0.05,窗口大小=500或目标序列的长度,以较短者为准。根据此实施方案,如果由于N或C末端缺失而不是因为内部缺失,目标序列比查询序列短,则可以对结果进行手动校正,以在计算全局同一性百分比时考虑FASTDB程序没有考虑目标序列的N和C末端截短的事实。对于相对于查询序列在N和C末端截短的目标序列,可以通过计算查询序列中与相应的目标残基不匹配/对齐的在目标序列的N和C末端侧向的残基的数量作为查询序列总碱基的百分比来校正同一性百分比。残基是否匹配/对齐的确定可以通过FASTDB序列比对的结果来确定。然后可以从由FASTDB程序使用指定参数计算的同一性百分比中减去此百分比,以得到最终同一性百分比得分。此最终同一性百分比得分可以用于此实施方案的目的。在一些情况下,仅考虑与查询序列不匹配/对齐的在目标序列的N和C末端的残基以用于手动调整同一性百分比得分的目的。也就是说,仅考虑在目标序列的最远N和C末端残基之外的查询残基位置用于此手动校正。例如,可以将90个残基的目标序列与100个残基的查询序列比对以确定同一性百分比。缺失发生在目标序列的N末端,因此,FASTDB比对没有显示N末端前10个残基的匹配/对齐。10个未配对残基代表序列的10%(N和C末端不匹配的残基数/查询序列中的残基总数),所以从由FASTDB程序计算的同一性百分比得分中减去10%。如果剩余的90个残基完全匹配,则最终同一性百分比可以是90%。在另一个例子中,将90个残基的目标序列与100个残基的查询序列进行比较。这次缺失是内部缺失,所以在目标序列的N或C末端没有与查询序列不匹配/对齐的残基。在这种情况下,没有对由FASTDB计算的同一性百分比进行手动校正。再次,如FASTDB比对中所显示的,仅对与查询序列不匹配/对齐的在目标序列的N和C末端之外的残基位置进行手动校正。

[0083] “杂交”可以指代一个或多个多核苷酸反应以形成经由核苷酸残基的碱基之间的氢键键合而稳定化的复合物的反应。氢键键合可以通过沃森-克里克碱基配对、Hoogstein结合或以任何其他序列特异性方式发生。复合物可以包含形成双链体结构的两条链、形成多链复合物的三条或更多条链、单条自杂交链或这些的任何组合。杂交反应可以构成更广泛过程(如PC反应的起始或核酶对多核苷酸的酶促切割)中的步骤。

[0084] 严格杂交条件的例子包括:约25℃至约37℃的孵育温度;约6x SSC至约10x SSC的杂交缓冲液浓度;约0%至约25%的甲酰胺浓度;以及约4x SSC至约8x SSC的洗涤溶液。中等杂交条件的例子包括:约40℃至约50℃的孵育温度;约9x SSC至约2x SSC的缓冲液浓度;约30%至约50%的甲酰胺浓度;以及约5x SSC至约2x SSC的洗涤溶液。高严格性条件的例子包括:约55℃至约68℃的孵育温度;约1x SSC至约0.1x SSC的缓冲液浓度;约55%至约75%的甲酰胺浓度;以及约1x SSC、0.1x SSC或去离子水的洗涤溶液。通常,杂交孵育时间是5分钟至24小时,有1个、2个或更多个洗涤步骤,并且洗涤孵育时间是约1、2或15分钟。SSC是0.15M NaCl和15mM柠檬酸盐缓冲液。应理解,可以采用使用其他缓冲液系统的SSC的等同

物。

[0085] 如本文所用的术语“分离的”可以指代基本上不含其他材料的分子或生物制品或细胞材料。在一个方面，术语“分离的”可以指代分别与存在于天然来源中的其他DNA或RNA、或者蛋白质或多肽、或者细胞或细胞器、或者组织或器官分离的核酸(如DNA或RNA)、或者蛋白质或多肽(例如，抗体或其衍生物)、或者细胞或细胞器、或者组织或器官。术语“分离的”还可以指代当通过重组DNA技术产生时基本上不含细胞材料、病毒材料或培养基，或者当化学合成时基本上不含化学前体或其他化学品的核酸或肽。此外，“分离的核酸”意在包括不以片段天然地存在并且不能以天然状态被发现的核酸片段。在一些情况下，术语“分离的”在本文中还用于指代与其他细胞蛋白分离的多肽，并且意在涵盖经纯化的和重组的多肽。在一些情况下，术语“分离的”在本文中还用于指代与其他细胞或组织分离的细胞或组织，并且意在涵盖经培养的和经工程化的细胞或组织。

[0086] “信使RNA”或“mRNA”是从DNA转录，然后加工以除去称为内含子的非编码部分的核酸分子。在一些情况下，所得mRNA被从细胞核(或存在DNA的另一个基因座)中输出并翻译成蛋白质。术语“前体mRNA”可以指代在加工以除去非编码部分之前的链。

[0087] 如本文所用，术语“突变”可以指代编码蛋白质的核酸序列相对于所述蛋白质的共有序列的改变。“错义”突变导致一个密码子取代为另一个密码子；“无义”突变将密码子从编码特定氨基酸的密码子改变为终止密码子。无义突变通常导致蛋白质的截短翻译。“沉默”突变是对所得蛋白质没有影响的突变。如本文所用，术语“点突变”可以指代只影响基因序列中的一个核苷酸的突变。“剪接位点突变”是存在于前体mRNA(在加工以除去内含子之前)中的那些突变，其由于剪接位点的不正确描绘而导致蛋白质的错译并且通常导致截短。突变可以包括单核苷酸变异(SNV)。突变可以包括序列变体、序列变异、序列改变或等位基因变体。参考DNA序列可以从参考数据库获得。突变可能影响功能。突变可能不影响功能。突变可以在DNA水平上在一个或多个核苷酸中发生，在核糖核酸(RNA)水平上在一个或多个核苷酸中发生，在蛋白质水平上在一个或多个氨基酸中发生，或其任何组合。参考序列可以从诸如NCBI参考序列数据库(RefSeq)数据库等的数据库获得。可以构成突变的特定改变可以包括在一个或多个核苷酸或者一个或多个氨基酸中的取代、缺失、插入、倒位或转换。突变可以是点突变。突变可以是融合基因。融合对或融合基因可以由突变(如易位、中间缺失、染色体倒位或其任何组合)产生。突变可以构成重复序列数量的变化，如三倍、四倍或其他倍。例如，突变可以是与给定序列相关的拷贝数的增加或减少(即，拷贝数变异或CNV)。突变可以包括不同等位基因中的两个或更多个序列变化或者一个等位基因中的两个或更多个序列变化。突变可以包括在一个等位基因中的一个位置处的两个不同核苷酸，如嵌合体(mosaic)。突变可以包括在一个等位基因中的一个位置处的两个不同核苷酸，如嵌合体(chimeric)。突变可以存在于恶性组织中。突变的存在或不存在可以指示发生疾病或病症的风险增加。突变的存在或不存在可以指示疾病或病症的存在。突变可以存在于良性组织中。不存在突变可以指示组织或样品是良性的。作为一个替代方案，不存在突变可能不指示组织或样品是良性的。如本文所述的方法可以包括鉴定样品中突变的存在。

[0088] 术语“多核苷酸”和“寡核苷酸”可互换地使用并且是指任何长度的核苷酸(脱氧核糖核苷酸或核糖核苷酸或其类似物或组合)的聚合形式。多核苷酸可以具有任何三维结构并且可以执行任何已知或未知的功能。以下是多核苷酸的非限制性例子：基因或基因片段

(例如,探针、引物、EST或SAGE标签)、外显子、内含子、信使RNA(mRNA)、转移RNA、核糖体RNA、RNAi、核酶、cDNA、重组多核苷酸、分支多核苷酸、质粒、载体、任何序列的分离DNA、任何序列的分离RNA、核酸探针和引物。多核苷酸可以包含经修饰的核苷酸,如经甲基化的核苷酸和核苷酸类似物。在多核苷酸组装之前或之后可以赋予对核苷酸结构的修饰(如果存在的话)。核苷酸的序列可以被非核苷酸组分中断。可以在聚合后进一步修饰多核苷酸,如通过与标记组分缀合。所述术语还可以指代双链和单链分子。除非另外指定或要求,否则本公开文本的作为多核苷酸的任何实施方案都可以涵盖双链形式和已知或预测构成双链形式的两个互补单链形式中的每一个。在一些实施方案中,多核苷酸可以包括RNA和DNA核苷酸。

[0089] 术语“多核苷酸序列”可以是多核苷酸分子的字母表示。此字母表示可以被输入到具有中央处理单元的计算机中的数据库中,并且用于生物信息学应用,如功能基因组学和同源性搜索。在任何字母表示中,本公开文本考虑了RNA和DNA(即,其中“T”被“U”替代或反之亦然)。

[0090] 术语“募集结构域”是指可以结合至或募集一种或多种RNA编辑实体的多核苷酸序列。示例性募集结构域可以是Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13募集结构域或其任何组合。

[0091] 术语“RNA编辑实体”是指可以引起核苷酸的化学修饰以将核苷酸改变为不同核苷酸的生物分子。在一些实施方案中,可以将RNA编辑实体募集到多核苷酸中的特定位点以引起所需位点处核酸序列的改变。RNA编辑实体的例子包括APOBEC蛋白(例如,APOBEC1、APOBEC2、APOBEC3A、APOBEC3B、APOBEC3C、APOBEC3E、APOBEC3F、APOBEC3G、APOBEC3H或APOBEC4蛋白)或ADAR蛋白(例如,ADAR1、ADAR2或ADAR3蛋白)。

[0092] 如本文所用,术语“受试者”是指动物,包括但不限于灵长类动物(例如,人、猴、黑猩猩、大猩猩等)、啮齿类动物(例如,大鼠、小鼠、沙鼠、仓鼠、雪貂等)、兔类动物、猪(swine)(例如,猪(pig)、小型猪)、马、犬、猫等。术语“受试者”和“患者”在本文中可互换地使用。例如,哺乳动物受试者可以指代人类患者。

[0093] “靶向结构域”是指可以与细胞中的靶RNA至少部分互补的多核苷酸序列。靶向结构域通常与靶RNA不是100%相同的,而是在需要化学反应来修饰靶RNA序列的一个或多个位点处具有错配。靶向结构域包括与靶RNA互补的RNA反义序列以及编码(在转录后)与RNA靶序列互补的反义RNA序列的DNA序列。靶向结构域通常与靶RNA序列足够互补以在生物学条件下与靶RNA序列杂交。

[0094] “转移核糖核酸”或“tRNA”是有助于将mRNA翻译成蛋白质的核酸分子。tRNA具有独特的折叠结构,包括三个发夹环;这些环中的一个包含编码反密码子的“茎”部分。反密码子识别mRNA上的相应密码子。每个tRNA“加载有”对应于mRNA密码子的氨基酸;这种“加载”通过tRNA合成酶实现。在tRNA识别对应于其反密码子的密码子后,tRNA将其所加载的氨基酸转移到生长的氨基酸链上,以形成多肽或蛋白质。内源tRNA可以通过内源tRNA合成酶加载。因此,内源tRNA通常加载有典型氨基酸。来源于外部来源的正交tRNA需要相应的正交tRNA合成酶。此类正交tRNA可以加载有典型和非典型氨基酸。在一些实施方案中,tRNA所加载的氨基酸可以被可检测地标记以使得能够在体内检测到。标记技术是本领域已知的,并且包括但不限于点击化学,其中通过正交tRNA/合成酶对添加含叠氮化物/炔烃的非天然氨基酸,因此其可以使用包含炔烃/叠氮化物的荧光团或其他此类分子来检测。

[0095] 如本文所用,术语“转化”和“转染”旨在指代用于将外源核酸引入宿主细胞中的多种本领域公认的技术,包括磷酸钙或氯化钙共沉淀、DEAE-葡聚糖介导的转染、脂质体转染(例如,使用可商购获得的试剂,例如像LIPOFECTIN®(Invitrogen Corp.,加利福尼亚州圣迭戈)、LIPOFECTAMINE®(Invitrogen)、FUGENE®(Roche Applied Science,瑞士巴塞尔)、JETPEI™(Polyplus-transfection Inc.,纽约州纽约)、EFFECTENE®(Qiagen,加利福尼亚州瓦伦西亚)、DREAMFECT™(OZ Biosciences,法国)等)或电穿孔。用于转化或转染宿主细胞的合适方法可以在Sambrook等人(Molecular Cloning:A Laboratory Manual.第2版,Cold Spring harbor Laboratory,Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y.,1989)和其他实验室手册中找到。本文所用的标准重组DNA和分子克隆技术是本领域熟知的,并且描述于Sambrook,J.,Fritsch,E.F.和Maniatis,T.,Molecular Cloning:A Laboratory Manual,第2版;Cold Spring Harbor Laboratory:Cold Spring Harbor,N.Y.,(1989)以及Silhavy,T.J.,Bennan,M.L.和Enquist,L.W.,Experiments with Gene Fusions;Cold Spring Harbor Laboratory:Cold Spring Harbor,N.Y.,(1984);以及Ausubel,F.M.等人,Current Protocols in Molecular Biology,Greene Publishing and Wiley-Interscience(1987)中,将其中的每一个通过引用以其整体特此并入。另外的有用的方法描述于手册中,所述手册包括Advanced Bacterial Genetics(Davis,Roth和Botstein,Cold Spring Harbor Laboratory,1980)、Experiments with Gene Fusions(Silhavy,Berman和Enquist,Cold Spring Harbor Laboratory,1984)、Experiments in Molecular Genetics(Miller,Cold Spring Harbor Laboratory,1972)、Experimental Techniques in Bacterial Genetics(Maloy,Jones and Bartlett,1990)和A Short Course in Bacterial Genetics(Miller,Cold Spring Harbor Laboratory 1992),将其中的每一个通过引用以其整体特此并入。

[0096] 如本文所用,术语“治疗(treat)”、“治疗(treating)”和“治疗(treatment)”是指改善与疾病或障碍相关的症状,包括预防或延迟疾病或障碍症状的发作和/或减轻疾病或障碍的症状的严重程度或频率。

[0097] 如本文所用,在核酸分子(例如经工程化的指导RNA)的上下文中使用的术语“环状”通常可以指代可以表示为一个核苷酸接另一个核苷酸的呈环状2维形式的多核苷酸序列的核酸分子,其中所表示的多核苷酸是环状的。在一些实施方案中,环状核酸分子不包含能够暴露于溶剂的5’还原羟基、3’还原羟基或两者

[0098] 如本文所用,术语“载体”可以指代设计用于在不同宿主之间转移的核酸构建体,包括但不限于质粒、病毒、粘粒、噬菌体、BAC、YAC等。在一些实施方案中,“病毒载体”被定义为重组产生的病毒或病毒颗粒,其包含待体内、离体或体外递送到宿主细胞中的多核苷酸。在一些实施方案中,质粒载体可以由可商购获得的载体制备。在其他实施方案中,根据本领域已知的技术,病毒载体可以由杆状病毒、逆转录病毒、腺病毒、AAV等产生。在一个实施方案中,病毒载体是慢病毒载体。病毒载体的例子包括逆转录病毒载体、腺病毒载体、腺相关病毒载体、甲病毒载体等。基于感染性烟草花叶病毒(TMV)的载体可以用于制造蛋白质,并且已经被报道在烟草叶片中表达格瑞弗森(Griffithsin)(O’Keefe等人(2009)Proc.Nat.Acad.Sci.USA 106(15):6099-6104)。甲病毒载体(如基于塞姆利基森林病毒的载体和基于辛德毕斯病毒的载体)也已经被开发用于在基因疗法和免疫疗法中使用。参见

Schlesinger和Dubensky(1999)Curr.Opin.Biotechnol.5:434-439以及Ying等人(1999)Nat.Med.5(7):823-827。在基因转移由逆转录病毒载体介导的方面,载体构建体可以指代包含逆转录病毒基因组或其部分和目的基因的多核苷酸。关于用于在基因转移中使用的载体的现代方法的进一步细节可以在例如Kotterman等人(2015)Viral Vectors for Gene Therapy:Translational and Clinical Outlook Annual Review of Biomedical Engineering 17中找到。含有多核苷酸可以可操作地连接的启动子和克隆位点的载体是本领域熟知的。此类载体能够在体外或体内转录RNA,并且可从诸如Agilent Technologies(加利福尼亚州圣克拉拉)和Promega Biotech(威斯康星州麦迪逊)等的来源商购获得。在一个方面,启动子是pol III启动子。

[0099] 某些载体能够在它们所引入的宿主细胞中自主复制(例如,具有细菌复制起点的细菌载体和附加型哺乳动物载体)。其他载体(例如,非附加型哺乳动物载体)在被引入宿主细胞中后整合到宿主细胞的基因组中,从而与宿主基因组一起复制。此外,某些载体能够指导与其可操作地连接的基因的表达。此类载体在本文中被称为“表达载体”。一般来说,用于重组DNA技术中的表达载体通常呈质粒形式。在本说明书中,“质粒”和“载体”可以可互换地使用。然而,本公开文本旨在包括发挥同等功能的此类其他形式的表达载体,如病毒载体(例如,复制缺陷型逆转录病毒、腺病毒和腺相关病毒)。通常,载体或质粒含有指导一个或多个相关基因的转录和翻译的序列、选择性标记和允许自主复制或染色体整合的序列。合适的载体包含基因5'的具有转录起始控制的区域和DNA片段3'的控制转录终止的区域。两个控制区都可以来源于对于经转化的宿主细胞而言同源的基因,但应理解,此类控制区也可以来源于对于选择作为生产宿主的物种而言非天然的基因。

[0100] 通常,载体或质粒含有指导基因片段的转录和翻译的序列、选择性标记和允许自主复制或染色体整合的序列。合适的载体包含基因5'的具有转录起始控制的区域和DNA片段3'的控制转录终止的区域。两个控制区都可以来源于对于经转化的宿主细胞而言同源的基因,但应理解,此类控制区也可以来源于对于选择作为生产宿主的物种而言非天然的基因。

[0101] 可用于驱动相关编码区在所需宿主细胞中表达的起始控制区或启动子很多,并且是本领域技术人员所熟悉的。实际上,任何能够驱动这些遗传元件的启动子都适于在本公开文本中使用。终止控制区也可以来源于对于优选宿主而言天然的各种基因。

[0102] 腺苷至肌苷(A至I)RNA编辑是一种由作用于RNA的腺苷脱氨酶(ADAR)酶催化的常见转录后RNA修饰。ADAR编辑双链RNA(dsRNA),主要在非编码区(如Alu重复元件)中,同时还编辑编码区中的少量位点,导致蛋白质功能的主要改变。肌苷和鸟苷之间的结构相似性解释了将经编辑的碱基识别为鸟苷的翻译和剪接机制,从而使ADAR成为改变蛋白质序列的有吸引力的工具。在过去十年中,几项研究已经通过使用经工程化的ADAR募集RNA(adRNA)在体外和体内将ADAR酶募集到靶RNA序列而将它们重新用于位点特异性RNA编辑。然而,几乎所有这些研究都依赖于经外源表达的ADAR酶及其变体。在一些情况下,使用外源酶过表达的主要限制之一是其倾向于在转录组中引入大量脱靶A至I编辑。此问题的一个潜在解决方案是工程化adRNA以使得能够募集在多种不同细胞类型中表达的内源ADAR。最近已经表明,使用长度为100bp的简单长反义RNA足以募集内源ADAR,并且这些长反义RNA是可遗传编码且可化学合成的。使用可遗传编码的长反义RNA以及经化学修饰的反义寡核苷酸使得能够

进行高度转录物特异性RNA编辑。然而，这些方法的效率显著低于在酶过表达情况下看到的效率。另外，经化学修饰的反义寡核苷酸合成起来非常昂贵。相反，可遗传编码的adRNA可以作为DNA递送，并且由细胞自身经由H1、U6或类似启动子转录，或者当通过体外转录合成时作为RNA递送。使用可遗传编码的adRNA可以比经化学修饰的反义寡核苷酸更便宜且更方便。

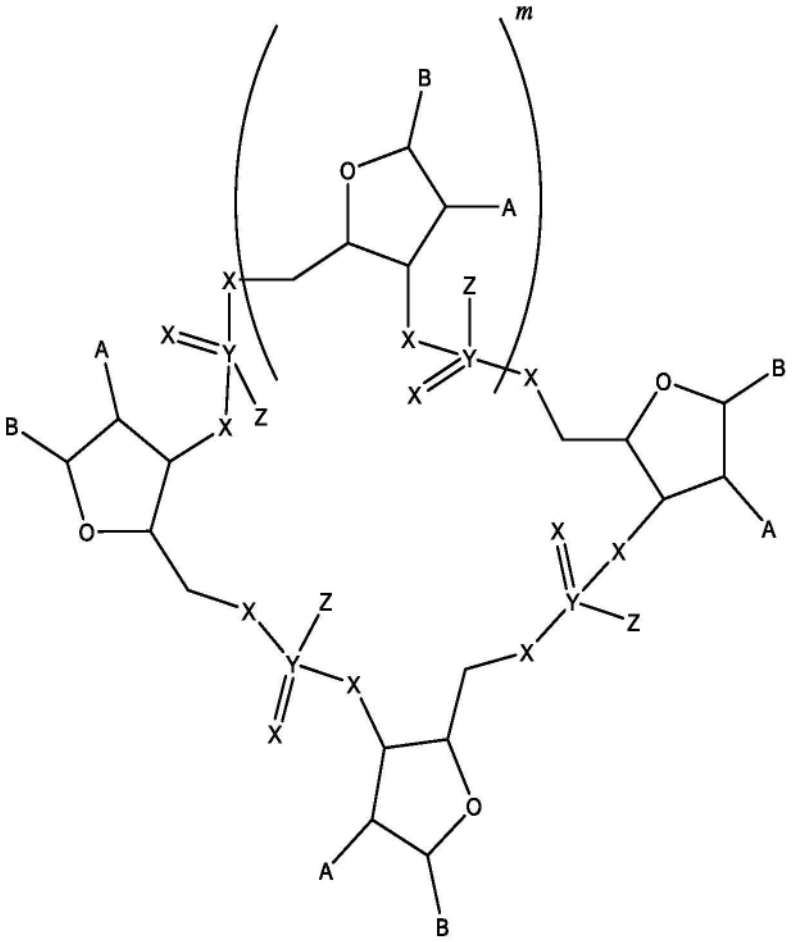
[0103] 在一些情况下，RNA编辑领域中的一个障碍可以是指导物稳定性。为了成功地募集内源ADAR，adRNA可以存在延长的时间段，但是单链RNA在哺乳动物细胞中可能具有约30分钟或更短的半衰期。这可能是由于它们对可以从5'或3'末端降解单链RNA的核酸外切酶的敏感性。可以对指导RNA进行修饰以增加指导物稳定性。如本文所述，形成环状指导RNA可以是增强指导RNA稳定性的一种类型的修饰。环化可以防止指导RNA的暴露末端被降解，并且可以显著增加指导RNA的半衰期，如在体内或体外。在一些情况下，环状指导RNA可以防止一个或多个暴露末端被水解降解。在一些情况下，与非环状的可比指导RNA相比，环状指导RNA可以显著增加指导RNA的半衰期。在一些情况下，与非环状的可比指导RNA相比，形成环状指导RNA可以显著增加指导RNA在体内递送(如递送至受试者)时的半衰期。在一些情况下，与非环状的可比指导RNA相比，形成环状指导RNA可以显著减少向受试者给药的指导RNA的量(如治疗有效量)。在一些情况下，与非环状的可比指导RNA相比，形成环状指导RNA可以显著增强编辑效率，可以显著减少脱靶编辑，或其组合。

[0104] 与非环状指导RNA相比，环状指导RNA可以提供各种益处。与非环状的可比指导RNA相比，环状指导物可以提供更大的稳定性、改进的RNA编辑实体(如内源RNA编辑酶)的募集、更长的半衰期或其任何组合。环状指导RNA可以提供一种或多种这些改进的特性，并且与包含被设计为改进指导物稳定性的其他类型修饰(如化学修饰或糖添加)的指导RNA相比，可以保留遗传编码能力。环状指导RNA可以能够被遗传编码，能够通过载体递送，并且保留改进的稳定性。在一些情况下，可以对所编码的经工程化的指导RNA进行密码子优化。

[0105] 经工程化的指导RNA可以是环状的。经工程化的指导RNA可以不包含能够暴露于溶剂的5'还原羟基。经工程化的指导RNA可以不包含能够暴露于溶剂的5'还原羟基、3'还原羟基或两者。经工程化的指导RNA可能比天然存在于人类细胞中的mRNA更不易受水解降解影响。经工程化的指导RNA可以是环状的，并且还可以保留与非环状的基本上类似的经工程化的指导RNA基本上类似的二级结构。经工程化的指导RNA可以包含募集结构域、靶向结构域或两者。经工程化的指导RNA可以募集RNA编辑实体(如酶)，以编辑RNA序列的碱基。经工程化的环状指导RNA可以是经预应变的。经工程化的环状指导RNA可以包含降低水平的熵。

[0106] 经工程化的环状指导RNA可以包含募集结构域，如RNA编辑实体募集结构域，其可以募集RNA编辑实体以在RNA序列中的碱基上进行化学转化。募集结构域可以募集内源RNA编辑实体或外源RNA编辑实体。在一些方面，经工程化的环状指导RNA可以不包含单独的募集结构域。RNA编辑实体可以是酶，如内源酶或重组酶。酶可以对碱基进行编辑。经工程化的环状指导RNA还可以包含靶向结构域。

[0107] 经工程化的多核苷酸可以包含式(I)的结构：



式 (I)

在一些情况下,每个X可以独立地是O、S或NR;每个Y可以独立地是P或S;每个Z可以独立地是OM、SM或NRM;每个A可以独立地是H、D、卤素、OM、SM、NRM或NRR';每个B可以独立地是尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物;每个M可以独立地是无机或有机阳离子、H或D;并且每个R和R'可以独立地是H、D、卤素或C_1-C_6烷基;并且m可以是1-1,000的任何整数。在一些情况下,m可以是约:5至约250、100至约500、400至约800、600至约1200、800至约2000、1500至约4000或约300至约10000的独立整数。在一些情形下,每个X可以是O。在一些情形下,每个Z可以独立地是O或S。在一些情形下,每个Y可以是P。在一些情况下,经工程化的多核苷酸可以是环状的。在一些情况下,经工程化的多核苷酸可以是指导多核苷酸,如经工程化的指导RNA。在一些情况下,靶向结构域可以被配置成与靶RNA的编码区至少部分缔合。在一些情况下,靶向结构域可以与靶RNA至少部分互补。在一些情况下,至少部分互补可以包含靶向结构域,所述靶向结构域可以包含与靶RNA的反向互补序列具有至少约80%序列同源性的多核苷酸序列。在一些情形下,至少部分互补可以包含靶向结构域,其包含与靶RNA的反向互补序列具有至少约70%、至少约80%或至少约90%序列同源性的多核苷酸序列。在一些情况下,靶向结构域可以与可以在疾病或病症中实施的靶RNA至少部分结合。靶向结构域和靶RNA的缔合可以促进RNA编辑实体(如ADAR1、ADAR2、APOBEC或其组合)对碱基的编辑。在一些情况下,经工程化的多核苷酸可以进一步包含RNA编辑实体募集结构域。在一些情况下,碱基的编辑可以是碱基的化学转化。在一些实施方案中,靶RNA可以包含无义突变、错义突变或两者。在一些情况下,靶向结构域可以包含可以与

靶RNA错配的至少单个核苷酸。在一些情形下,靶向结构域上的错配核苷酸可以与可以互补于靶RNA的两个核苷酸相邻,错配核苷酸的每侧各一个。在一些情况下,可以在体外测定中通过将靶RNA和被设计为靶向靶RNA的经工程化的多核苷酸转染到同一细胞中来确定RNA编辑。可以对靶RNA测序以鉴定通过经工程化的多核苷酸进行的编辑。在一些情况下,将靶RNA转染到原代细胞系中可以包括将编码靶RNA的质粒转染到原代细胞系中。在一些情形下,将经工程化的多核苷酸转染到原代细胞系中可以包括将编码经工程化的多核苷酸的质粒转染到原代细胞系中。在一些情况下,可以通过以下方式来确定靶RNA的RNA编辑百分比:在用指导RNA或经工程化的多核苷酸转染后的不同时间点(例如24小时、48小时、96小时)将靶RNA逆转录成cDNA,然后使用Sanger测序来确定靶RNA的RNA编辑百分比。在一些情况下,可以在测序前通过聚合酶链式反应扩增cDNA。可以分析来自Sanger测序的Sanger迹线以评估指导RNA的编辑效率。在一些情况下,细胞可以是原代细胞。在一些情况下,原代细胞或细胞可以是神经元、感光细胞(例如S视锥细胞、L视锥细胞、M视锥细胞、视杆细胞)、视网膜色素上皮细胞、胶质细胞(例如星形胶质细胞、少突胶质细胞、小胶质细胞)、肌细胞(例如成肌细胞、肌管)、肝细胞、肺上皮细胞或成纤维细胞(例如真皮成纤维细胞)。在一些情况下,细胞可以是水平细胞、神经节细胞或双极细胞。在一些情况下,细胞系可以是哺乳动物细胞系,如HEK293T、NCI-60、MCF-7、HL-60、RD、分化的LHCN、未分化的LHCN、Saos-2、CHO或HeLa细胞。在一些情况下,细胞系可以是昆虫细胞系,如Sf9。

[0108] 经工程化的多核苷酸(如经工程化的指导多核苷酸)可以包含式(III)的结构:

(III)

在一些情况下,每个X可以是包含碱基的核苷酸,所述碱基可以独立地是尿嘧啶、胸腺嘧啶、腺嘌呤、胞嘧啶、鸟嘌呤、任何这些的盐或任何这些的衍生物;并且n可以独立地是0-1,000的整数。在一些情况下,n可以独立地是约:5至约250、100至约500、400至约800、600至约1200、800至约2000、1500至约4000或约300至约10000的整数。在一些情况下,对于每个连接,每个核苷酸可以独立地通过磷酸酯、磷酸硫酯、硫代磷酸酯或亚磷酰胺连接而连接到两个相邻核苷酸。在一些情况下,靶向结构域可以被配置成与靶RNA的编码区至少部分缔合。在一些情况下,靶向结构域可以与可以在疾病或病症中牵涉的靶RNA至少部分结合。在一些情况下,靶向结构域可以被配置成与靶RNA的编码区至少部分缔合。靶向结构域和靶RNA的缔合可以促进RNA编辑实体(如ADAR1、ADAR2、APOBEC或其任何组合)对碱基的编辑。在一些情况下,碱基的编辑可以是碱基的化学转化。在一些实施方案中,靶RNA可以包含无义突变、错义突变或两者。在一些情况下,靶向结构域可以包含可以与靶RNA错配的至少单个核苷酸。在一些情形下,靶向结构域上的错配核苷酸可以与可以互补于靶RNA的两个核苷酸相邻,错配核苷酸的每侧各一个。在一些情况下,可以通过如本文所述的体外测定来确定编辑。在一些情况下,经工程化的多核苷酸可以进一步包含RNA编辑实体募集结构域。

[0109] 在一些实施方案中,化学转化(如通过RNA编辑实体进行的化学转化)可以包括碱基的编辑。在一些实施方案中,相对于缺乏化学转化的其他方面可比的靶RNA,化学转化(如碱基的编辑)在进行化学转化的靶RNA翻译后可以导致蛋白质或其片段的水平增加。在一些

情况下，增加的水平可以为约：5％至约100％、10％至约50％、25％至约75％或约40％至约90％。在一些实施方案中，相对于缺乏化学转化的其他方面可比的靶RNA，化学转化在进行化学转化的靶RNA翻译后可以导致蛋白质或其片段的水平降低。在一些情况下，降低的水平可以为约：5％至约99％、10％至约50％、25％至约75％或约40％至约90％。在一些实施方案中，相对于缺乏编辑的其他方面可比的靶RNA的翻译蛋白，化学转化在进行碱基编辑的靶RNA翻译后可以导致蛋白质或其片段的长度增加、蛋白质或其片段的功能性增加、蛋白质或其片段的稳定性增加或其任何组合。在一些情况下，增加的长度可以为约：5％至约100％、2％至约10％、10％至约25％、25％至约50％、40％至约80％或约75％至约150％。在一些情况下，蛋白质或其片段的增加的长度可以超过100％。在一些情况下，增加的稳定性可以是蛋白质或其片段的增加的半衰期。在一些情况下，增加的半衰期可以比缺乏编辑的其他方面可比的靶RNA的翻译蛋白大至少约：2x、3x、4x、5x、6x、7x、8x、9x或10x。在一些情况下，增加的功能性可以包含这样的蛋白质或其片段(如酶)，其可以增加反应速度，增加V_{max}或两者。在一些情况下，增加的功能性可以包含由进行碱基编辑的靶RNA编码的蛋白质(例如酶)或其片段，其与缺乏编辑的其他方面可比的靶RNA的翻译蛋白相比包含更低的活化能。

[0110] 在一些实施方案中，经工程化的多核苷酸可以不包含(缺乏)能够暴露于溶剂的5’还原羟基、3’还原羟基或两者。在一些情况下，每个5’羟基和每个3’羟基可以独立地通过共价氧磷键键合到磷。在一些情形下，磷可以包含在磷酸二酯基团中。

[0111] 在一些实施方案中，经工程化的多核苷酸可以包含手性。在一些实施方案中，可以为手性的任何中心原子可以独立地呈R或S构型。在一些情况下，手性可以包含分子中可以键合到四种不同类型的原子或原子链的原子。在一些情形下，经工程化的多核苷酸(如指导RNA)可以是单一非对映异构体或者可以主要是一种非对映异构体。在一些情形下，经工程化的多核苷酸可以具有约：51％至约100％、51％至约60％、60％至约75％、70％至约90％或约80％至约99％的非对映体过量。非对映体过量可以是用于手性物质的纯度的量度。在一些情况下，它可以反映样品含有量大于另一种非对映异构体的一种非对映异构体的程度。在一些情况下，单一纯非对映异构体可以具有100％的非对映体过量。具有70％的一种非对映异构体和30％的另一种非对映异构体的样品可以具有40％(70％-30％)的非对映体过量。

[0112] 经工程化的多核苷酸(例如经工程化的指导RNA)可以包含可以与靶RNA至少部分互补的靶向结构域。在一些情况下，经工程化的指导RNA可以包含主链，其包含共价连接在一起的多个糖和磷酸部分。在一些情况下，主链可以不包含(缺乏)能够暴露于溶剂的5’还原羟基、3’还原羟基或两者。在一些情况下，经工程化的指导RNA可以具有RNA编辑实体募集结构域。RNA编辑实体募集结构域可以被配置成与RNA编辑实体(例如像ADAR1或ADAR2)相互作用。在一些情况下，经工程化的指导RNA可以不具有(缺乏)RNA编辑实体募集结构域。

[0113] 碱基上的化学转化可以包括编辑靶向RNA序列的一个或多个碱基。碱基上的化学转化可以将有义密码子编辑为终止密码子，将终止密码子编辑为有义密码子，将第一有义密码子编辑为第二有义密码子，或者将第一终止密码子编辑为第二终止密码子。在一些情况下，化学转化可以将指定第一氨基酸的有义密码子转化为指定第二氨基酸的第二有义密码子。在一些情况下，第一氨基酸可以是蛋白酶切割位点。

[0114] 在一些情形下，多核苷酸序列可以与本文所述的序列具有约：70％、71％、72％、

73%、74%、75%、76%、77%、78%、79%、80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或100%序列同源性。在一些情形下，可以将本文所叙述的任何序列的长度截短至原始序列的约：30%、35%、40%、45%、50%、55%、60%、65%、70%、71%、72%、73%、74%、75%、76%、77%、78%、79%、80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%或98%。

[0115] 在一些情形下，靶向结构域可以具有长度为约：20个核苷酸至约1,000个核苷酸、10个核苷酸至约100个核苷酸、50个核苷酸至约500个核苷酸或约400个核苷酸至约1000个核苷酸的序列长度。在一些情形下，经工程化的多核苷酸或用于形成经工程化的多核苷酸的构建体的靶向结构域可以包含与SEQ ID NO:1-1417中的任一个多核苷酸(还参见表1-12)具有至少约：70%、75%、80%、85%、90%或95%同源性的多核苷酸序列。在一些情形下，表1-12中的序列可以至少部分编码经工程化的多核苷酸或用于形成经工程化的多核苷酸的构建体的靶向结构域。在一些情形下，在表1-12中，多核苷酸中的T(胸腺嘧啶)可以被U(尿嘧啶)取代。在一些情形下，在表1-12中，多核苷酸中的所有T可以都被U取代。在一些情形下，用于形成经工程化的多核苷酸的构建体或经工程化的多核苷酸的靶向结构域可以包含与表1-12中的任一个多核苷酸具有至少约：70%、75%、80%、85%、90%或95%序列长度的多核苷酸序列。在一些情形下，用于形成经工程化的多核苷酸的构建体或经工程化的多核苷酸的靶向结构域可以包含与表1-12中的任一个多核苷酸具有至少约：70%、75%、80%、85%、90%或95%序列长度的多核苷酸序列以及与表1-12中的任一个的多核苷酸具有至少约：70%、75%、80%、85%、90%或95%同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表1中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表2中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表3中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表4中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表5中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表6中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表7中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表8中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表9中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表10中的多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表11中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。在一些情形下，经工程化的多核苷酸可以包含与表12中的任一个多核苷酸具有至少约80%序列同源性的多核苷酸序列。

[0116] 表1(将认识到，下面的序列可以是RNA或DNA(除非甲基化另外明确指示，否则T可以是U或反之亦然)。例如，可以从载体表达DNA序列以产生RNA)

SEQ ID NO.	序列5' -> 3
1	G*G*G*C*A*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T
2	G*G*C*A*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C
3	G*C*A*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C*C
4	C*A*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C*C*A
5	A*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C*C*A*A
6	C*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C*C*A*A*A
7	mG*mG*mG*mC*mA*C*A*A*G*G*G*C*A*C*A*G*A*C*T*T
8	mG*mG*mC*mA*mC*A*A*G*G*G*C*A*C*A*G*A*C*T*T*C
9	mG*mC*mA*mU*mA*A*G*G*G*C*A*C*A*G*A*C*T*T*C*C
10	mC*mA*mC*mA*mA*G*G*G*C*A*C*A*G*A*C*T*T*C*C*A
11	mA*mC*mA*mA*mG*G*G*C*A*C*A*G*A*C*T*T*C*C*A*A
12	mC*mA*mA*mG*mG*G*C*A*C*A*G*A*C*T*T*C*C*A*A*A
13	mG*mG*mG*mC*mA*C*A*A*G*G*G*C*A*C*A*mG*mA*mC*mU*mU
14	mG*mG*mC*mA*mC*A*A*G*G*G*C*A*C*A*G*mA*mC*mU*mU*mC
15	mG*mC*mA*mC*mA*A*G*G*G*C*A*C*A*G*A*mC*mU*mU*mC*mC
16	mC*mA*mU*mA*mA*G*G*G*C*A*C*A*G*A*C*mU*mU*mC*mC*mA
17	mA*mC*mA*mA*mG*G*G*C*A*C*A*G*A*C*T*mU*mC*mC*mA*mA
18	mC*mA*mA*mG*mG*G*C*A*C*A*G*A*C*T*T*mC*mC*mA*mA*mA
19	mG*mC*mA*mC*mA*mA*mG*mG*G*C*A*C*A*G*A*mC*mU*mU*mC*mC
20	mC*mA*mC*mA*mA*mG*mG*G*C*A*C*A*G*A*mC*mU*mU*mC*mC*mA
21	mA*mC*mA*mA*mG*mG*G*C*A*C*A*G*A*mC*mU*mU*mC*mC*mA*mA
22	mC*mA*mA*mG*mG*G*C*A*C*A*G*A*mC*mU*mU*mC*mC*mA*mA*mA
23	mGmCmAmCmAmAmGmG*G*C*A*C*A*G*A*mCmUmUmCmC
24	mCmAmCmAmAmGmG*G*C*A*C*A*G*A*mCmUmUmCmCmA
25	mAmCmAmAmGmG*G*C*A*C*A*G*A*mCmUmUmCmCmAmA
26	mCmAmAmGmG*G*C*A*C*A*G*A*mCmUmUmCmCmAmAmA
27	mGmGmGmCmA*C*A*A*G*G*G*C*A*C*A*mGmAmCmUmU
28	mGmGmCmAmC*A*A*G*G*G*C*A*C*A*G*mAmCmUmUmC
29	mGmCmAmCmA*A*G*G*G*C*A*C*A*G*A*mCmUmUmCmC
30	mCmAmCmAmA*G*G*G*C*A*C*A*G*A*C*mUmUmCmCmA
31	mAmCmAmAmG*G*G*C*A*C*A*G*A*C*T*mUmCmCmAmA
32	mCmAmAmGmG*G*C*A*C*A*G*A*C*T*T*mCmCmAmAmA
33	G*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST
34	G*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
35	G*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC
36	C*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA
37	A*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA
38	C*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA
39	mG*SmG*SmC*SmA*SmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*SmC*SmU*SmU*SmC
40	mG*RmG*RmC*RmA*RmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*RmC*RmU*RmU*RmC
41	mGmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmUmC

42	mG*SmG*SmC*SmA*SmC*SmA*SmA*SmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
43	mG*RmG*RmC*RmA*RmU*RmA*RmA*RmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
44	mGmGmCmAmCmAmAmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
45	mG*RmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*RmC
46	mG*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SmC
47	G*SC*SA*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA
48	C*SA*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC
49	A*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST
50	A*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG
51	A*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG*SG
52	G*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG*SG*SC
53	mG*mG*mC*mA*mC*A*A*G*G*G*C*A*C*A*G*mA*mC*mU*BrdU*mC
54	mG*mG*mC*mA*mC*A*A*G*G*G*C*A*C*A*G*mA*mC*BrdU*BrdU*mC
55	G*G*G*C*A*C*A*A*G*G*G*C*d2AP*C*A*G*A*C*T*T
56	G*G*C*A*C*A*A*G*G*G*C*d2AP*C*A*G*A*C*T*T*C
57	G*C*A*C*A*A*G*G*G*C*d2AP*C*A*G*A*C*T*T*C*C
58	G*G*G*C*A*C*A*A*G*G*G*C*dDAP*C*A*G*A*C*T*T
59	G*G*C*A*C*A*A*G*G*G*C*dDAP*C*A*G*A*C*T*T*C
60	G*C*A*C*A*A*G*G*G*C*dDAP*C*A*G*A*C*T*T*C*C
61	G*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SC
62	G*mGmCmAmC*A*A*G*G*G*C*A*C*A*G*mAmCmUmU*C
63	mG*mGmCmAmC*A*A*G*G*G*C*A*C*A*G*mAmCmUmU*mC
64	Geo*Geom5CeoAeom5Ceo*A*A*G*G*G*C*A*C*A*G*Aeom5CeoTeoTeo*m5Ceo
65	G*A*G*C*A*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A
66	A*G*C*A*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C
67	G*C*A*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C*A
68	C*A*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C*A*A
69	A*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C*A*A*C
70	G*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C*A*A*C*C
71	mG*mA*mG*mC*mA*G*C*T*G*C*A*A*C*C*T*G*G*C*A*A
72	mA*mG*mC*mA*mG*C*T*G*C*A*A*C*C*T*G*G*C*A*A*C
73	mG*mC*mA*mG*mC*T*G*C*A*A*C*C*T*G*G*C*A*A*C*A
74	mC*mA*mG*mC*mU*G*C*A*A*C*C*T*G*G*C*A*A*C*A*A
75	mA*mG*mC*mU*mG*C*A*A*C*C*T*G*G*C*A*A*C*A*A*C
76	mG*mC*mU*mG*mC*A*A*C*C*T*G*G*C*A*A*C*A*A*C*C
77	mG*mA*mG*mC*mA*G*C*T*G*C*A*A*C*C*T*mG*mG*mC*mA*mA
78	mA*mG*mC*mA*mG*C*T*G*C*A*A*C*C*T*G*mG*mC*mA*mA*mC
79	mG*mC*mA*mG*mC*T*G*C*A*A*C*C*T*G*G*mC*mA*mA*mC*mA
80	mC*mA*mG*mC*mU*G*C*A*A*C*C*T*G*G*C*mA*mA*mC*mA*mA
81	mA*mG*mC*mU*mG*C*A*A*C*C*T*G*G*C*A*mA*mC*mA*mA*mC
82	mG*mC*mU*mG*mG*A*A*C*C*T*G*G*C*A*A*mC*mA*mA*mC*mC
83	mG*mA*mG*mC*mA*mG*mC*T*G*C*A*A*C*C*mU*mG*mG*mC*mA*mA
84	mGmAmGmCmAmGmC*T*G*C*A*A*C*C*mUmGmGmCmAmA
85	mA*mG*mC*mA*mG*mC*T*G*C*A*A*C*C*T*G*mG*mC*mA*mA*mC
86	mAmGmCmAmGmC*T*G*C*A*A*C*C*T*G*mGmCmAmAmC
87	mG*mG*mA*mG*mC*T*G*C*A*A*C*C*mG*mG*mG*mC*mA*mA*mC*mA
88	mGmCmAmGmC*T*G*C*A*A*C*C*mUmGmGmCmAmAmCmA

89	mGmAmGmCmA*G*C*T*G*C*A*A*C*C*T*mGmGmCmAmA
90	mAmGmCmAmG*C*T*G*C*A*A*C*C*T*G*mGmCmAmAmC
91	mGmCmAmGmC*T*G*C*A*A*C*C*T*G*G*mCmAmAmCmA
92	mCmAmGmCmU*G*C*A*A*C*C*T*G*G*C*mAmAmCmAmA
93	mAmGmCmUmG*C*A*A*C*C*T*G*G*C*A*mAmCmAmAmC
94	mGmCmUmGmC*A*A*C*C*T*G*G*C*A*A*mCmAmAmCmC
95	G*SA*SG*SC*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA
96	A*SG*SC*SA*SG*SC*Sr4SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC
97	G*SC*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA
98	C*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA
99	A*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA*SC
100	G*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA*SC*SC
101	G*G*G*C*C*A*A*C*A*G*C*C*A*G*C*C*T*G*C*A
102	G*G*C*C*A*A*C*A*G*C*C*A*G*C*C*T*G*C*A*G
103	G*C*C*A*A*C*A*G*C*C*A*G*C*C*T*G*T*A*G*G
104	C*C*A*A*C*A*G*C*C*A*G*C*C*T*G*C*A*G*G*A
105	C*A*A*C*A*G*C*C*A*G*C*C*T*G*C*A*G*G*A*G
106	A*A*C*A*G*C*T*A*G*C*C*T*G*C*A*G*G*A*G*G
107	mG*mG*mG*mC*mC*A*A*C*A*G*C*C*A*G*C*C*T*G*C*A
108	mG*mG*mC*mC*mA*A*C*A*G*C*C*A*G*C*C*T*G*C*A*G
109	mG*mC*mC*mA*mA*C*A*G*C*C*A*G*C*C*T*G*C*A*G*G
110	mC*mC*mA*mA*mC*A*G*C*C*A*G*C*C*T*G*C*A*G*G*A
111	mC*mA*mA*mC*mA*G*C*C*A*G*C*C*T*G*C*A*G*G*A*G
112	mA*mA*mC*mA*mG*T*C*A*G*C*C*T*G*C*A*G*G*A*G*G
113	mG*mG*mG*mC*mC*A*A*C*A*G*C*C*A*G*C*mC*mU*mG*mC*mA
114	mG*mG*mC*mC*mA*A*C*A*G*C*C*A*G*C*C*mU*mG*mC*mA*mG
115	mG*mC*mC*mA*mA*C*A*G*C*C*A*G*C*C*T*mG*mU*mA*mG*mG
116	mC*mC*mA*mA*mC*A*G*C*C*A*G*C*C*T*G*mC*mA*mG*mG*mA
117	mC*mA*mA*mU*mA*G*C*C*A*G*C*C*T*G*C*mA*mG*mG*mA*mG
118	mA*mA*mC*mA*mG*C*C*A*G*C*C*T*G*C*A*mG*mG*mA*mG*mG
119	mG*mG*mG*mC*mC*mA*mA*C*A*G*C*C*A*G*mC*mC*mU*mG*mC*mA
120	mGmGmGmCmCmAmA*C*A*G*C*C*A*G*mCmCmUmGmCmA
121	mG*mG*mC*mC*mA*mA*C*A*G*C*C*A*G*C*C*mU*mG*mC*mA*mG
122	mGmGmCmCmAmA*C*A*G*C*C*A*G*C*C*mUmGmCmAmG
123	mG*mC*mC*mA*mA*C*A*G*C*C*A*G*mC*mC*mU*mG*mC*mA*mG*mG
124	mGmCmCmAmA*C*A*G*C*C*A*G*mCmCmUmGmCmAmGmG
125	mGmGmGmCmC*A*A*C*A*G*C*C*A*G*C*mCmUmGmCmA
126	mGmGmCmCmA*A*C*A*G*C*C*A*G*C*C*mUmGmCmAmG
127	mGmCmCmAmA*C*A*G*C*C*A*G*C*C*T*mGmCmAmGmG
128	mCmCmAmAmC*A*G*C*C*A*G*C*C*T*G*mCmAmGmGmA
129	mCmAmAmCmA*G*C*C*A*G*C*C*T*G*C*mAmGmGmAmG
130	mAmAmCmAmG*C*C*A*G*C*C*T*G*C*A*mGmGmAmGmG
131	G*SG*SG*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA
132	G*SG*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG
133	G*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG
134	C*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA
135	C*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA*SG
136	A*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA*SG*SG
137	A*T*T*A*A*T*A*A*A*T*T*G*T*C*A*T*C*A*C*C

138	A*ST*ST*SA*SA*ST*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
139	A*ST*ST*SA*SA*ST*SA*SA*SA*ST*ST*SG*ST*SC*SA*RT*SC*SA*SC*SC
140	mA*SmU*SmU*SmA*SmA*SmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmC*SmA*SmC*SmC
141	mA*RmU*RmU*RmA*RmA*RmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmC*RmA*RmC*RmC
142	mA*SmU*SmU*SmA*SmA*SmU*SmA*SmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
143	mA*RmU*RmU*RmA*RmA*RmU*RmA*RmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
144	mAmUmUmAmAmUmAmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
145	mAmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmCmC
146	mA*SmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*SmC
147	mA*RmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*RmC
148	A*SmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*SC
149	A*mUmUmAmAmU*A*A*A*T*T*G*T*C*A*T*mCmAmC*C
150	T*G*T*C*A*T*C*A*C*C*A*G*A*A*A*mA*mA*mG*mU*mC
151	mU*T*G*T*C*A*T*C*A*C*C*A*G*A*A*mA*mA*mA*mG*mU
152	T*T*G*T*C*A*T*C*A*C*C*A*G*A*A*mA*mA*mA*mG*mU
153	mA*mU*T*G*T*C*A*T*C*A*C*C*A*G*A*mA*mA*mA*mA*mG
154	mA*T*T*G*T*C*A*T*C*A*C*C*A*G*A*mA*mA*mA*mA*mG
155	mA*mA*mU*T*G*T*C*A*T*C*A*C*C*A*G*mA*mA*mA*mA*mA
156	mA*mA*T*T*G*T*C*A*T*C*A*C*C*A*G*mA*mA*mA*mA*mA
157	mA*mA*mA*T*T*G*T*C*A*T*C*A*C*C*A*mG*mA*mA*mA*mA
158	mA*mA*mA*mU*T*G*T*C*A*T*C*A*C*C*A*mG*mA*mA*mA*mA
159	mil*mA*mA*mA*mU*T*G*T*C*A*T*C*A*C*C*A*mG*mA*mA*mA
160	mil*mA*mA*mA*mU*T*G*T*C*A*T*C*A*C*C*mA*mG*mA*mA*mA
161	mA*mU*mA*mA*mA*T*T*G*T*C*A*T*C*A*C*C*mA*mG*mA*mA
162	mA*mU*mA*mA*mA*T*T*G*T*C*A*T*C*A*C*mC*mA*mG*mA*mA
163	mA*mA*mU*mA*mA*A*T*T*G*T*C*A*T*C*A*C*C*mA*mG*mA
164	mA*mA*mU*mA*mA*A*T*T*G*T*C*A*T*C*A*C*mC*mA*mG*mA
165	mA*mA*mU*mA*mA*A*T*T*G*T*C*A*T*C*A*mC*mC*mA*mG*mA
166	mU*mA*mA*mU*mA*A*A*T*T*G*T*C*A*T*C*A*C*C*mA*mG
167	mU*mA*mA*mU*mA*A*A*T*T*G*T*C*A*T*C*A*C*mC*mA*mG
168	mU*mA*mA*mU*mA*A*A*T*T*G*T*C*A*T*C*A*mC*mC*mA*mG
169	mU*mA*mA*mU*mA*A*A*T*T*G*T*C*A*T*C*mA*mC*mC*mA*mG
170	mU*mU*mA*mA*mU*A*A*A*T*T*G*T*C*A*T*C*A*C*C*mA
171	mU*mU*mA*mA*mU*A*A*A*T*T*G*T*C*A*T*C*A*C*mC*mA
172	mU*mU*mA*mA*mU*A*A*A*T*T*G*T*C*A*T*C*A*mC*mC*mA
173	mU*mU*mA*mA*mU*A*A*A*T*T*G*T*C*A*T*C*mA*mC*mC*mA
174	mA*mU*mU*mA*mA*T*A*A*A*T*T*G*T*C*A*T*C*A*C*C
175	mA*mU*mU*mA*mA*T*A*A*A*T*T*G*T*C*A*T*C*A*C*mC
176	mA*mU*mU*mA*mA*T*A*A*A*T*T*G*T*C*A*T*C*A*mC*mC
177	mA*mU*mU*mA*mA*T*A*A*A*T*T*G*T*C*A*T*C*mA*mC*mC
178	mU*mA*mU*mU*mA*A*T*A*A*A*T*T*G*T*C*A*T*C*A*C
179	mU*mA*mU*mU*mA*A*T*A*A*A*T*T*G*T*C*A*T*C*A*mC
180	mU*mA*mU*mU*mA*A*T*A*A*A*T*T*G*T*C*A*T*C*mA*mC
181	mC*mU*mA*mU*mU*A*A*T*A*A*A*T*T*G*T*C*A*T*C*A
182	mC*mU*mA*mU*mU*A*A*T*A*A*A*T*T*G*T*C*A*T*C*mA
183	mA*mC*mU*mA*mU*T*A*A*T*A*A*A*T*T*G*T*C*A*T*C

184	T*G*T*C*A*T*C*A*C*C*A*G*A*A*A*mAmAmGmU*mC
185	mU*T*G*T*C*A*T*C*A*C*C*A*G*A*A*mAmAmAmG*mU
186	T*T*G*T*C*A*T*C*A*C*C*A*G*A*A*mAmAmAmG*mU
187	mA*mU*T*G*T*C*A*T*C*A*C*C*A*G*A*mAmAmAmA*mG
188	mA*T*T*G*T*C*A*T*C*A*C*C*A*G*A*mAmAmAmA*mG
189	mA*mAmU*T*G*T*C*A*T*C*A*C*C*A*G*mAmAmAmA*mA
190	mA*mA*T*T*G*T*C*A*T*C*A*C*C*A*G*mAmAmAmA*mA
191	mA*mAmA*T*T*G*T*C*A*T*C*A*C*C*A*mGmAmAmA*mA
192	mA*mAmAmU*T*G*T*C*A*T*C*A*C*C*A*mGmAmAmA*mA
193	mU*mAmAmAmU*T*G*T*C*A*T*C*A*C*C*A*mGmAmA*mA
194	mU*mAmAmAmU*T*G*T*C*A*T*C*A*C*C*mAmGmAmA*mA
195	mA*mUmAmAmA*T*T*G*T*C*A*T*C*A*C*C*mAmGmA*mA
196	mA*mUmAmAmA*T*T*G*T*C*A*T*C*A*C*mCmAmGmA*mA
197	mA*mAmUmAmA*A*T*T*G*T*C*A*T*C*A*C*C*mAmG*mA
198	mA*mAmUmAmA*A*T*T*G*T*C*A*T*C*A*C*mCmAmG*mA
199	mA*mAmUmAmA*A*T*T*G*T*C*A*T*C*A*mCmCmAmG*mA
200	mU*mAmAmUmA*A*A*T*T*G*T*C*A*T*C*A*C*C*mA*mG
201	mU*mAmAmUmA*A*A*T*T*G*T*C*A*T*C*A*C*mCmA*mG
202	mU*mAmAmUmA*A*A*T*T*G*T*C*A*T*C*A*mCmCmA*mG
203	mU*mAmAmUmA*A*A*T*T*G*T*C*A*T*C*mAmCmCmA*mG
204	mU*mUmAmAmU*A*A*A*T*T*G*T*C*A*T*C*A*C*C*mA
205	mU*mUmAmAmU*A*A*A*T*T*G*T*C*A*T*C*A*C*mC*mA
206	mU*mUmAmAmU*A*A*A*T*T*G*T*C*A*T*C*A*mCmC*mA
207	mU*mUmAmAmU*A*A*A*T*T*G*T*C*A*T*C*mAmCmC*mA
208	mA*mUmUmAmA*T*A*A*A*T*T*G*T*C*A*T*C*A*C*C
209	mA*mUmUmAmA*T*A*A*A*T*T*G*T*C*A*T*C*A*C*mC
210	mA*mUmUmAmA*T*A*A*A*T*T*G*T*C*A*T*C*A*mC*mC
211	mA*mUmUmAmA*T*A*A*A*T*T*G*T*C*A*T*C*mAmC*mC
212	mU*mAmUmUmA*A*T*A*A*A*T*T*G*T*C*A*T*C*A*C
213	mU*mAmUmUmA*A*T*A*A*A*T*T*G*T*C*A*T*C*A*mC
214	mU*mAmUmUmA*A*T*A*A*A*T*T*G*T*C*A*T*C*mA*mC
215	mC*mUmAmUmU*A*A*T*A*A*A*T*T*G*T*C*A*T*C*A
216	mC*mUmAmUmU*A*A*T*A*A*A*T*T*G*T*C*A*T*C*mA
217	mA*mCmUmAmU*T*A*A*T*A*A*A*T*T*G*T*C*A*T*C
218	G*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST
219	G*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*S T*SC
220	G*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*S T*ST*SC*SC
221	C*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA
222	A*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA
223	C*SA*SA*SG*SG*SC*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA
224	mG*SmG* SmC* SmA*SmC*SA* SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*SmC*SmU*SmU*SmC
225	mG*RmG*RmC*RmA*RmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*RmC*RmU*RmU*RmC
226	mGmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmUmC
227	mG*SmG*SmC*SmA*SmC*SmA*SmA*SmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
228	mG*RmG*RmC*RmA*RmC*RmA*RmA*RmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC
229	mGmGmCmAmCmAmAmG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC

230	mG*RmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*RmC
231	mG*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SmC
232	G*SC*SA*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA
233	C*SA*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC
234	A*SG*SG*SG*SC*SA*SC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST
235	A*SA*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG
236	A*SG*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG*SG
237	G*SG*SG*SC*SA*SC*RA*SG*SA*SC*ST*ST*SC*SC*SA*SA*SA*SG*SG*SC
238	G*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SC
239	G*SG*SG*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA
240	G*SG*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG
241	G*SC*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG
242	C*SC*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA
243	C*SA*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA*SG
244	A*SA*SC*SA*SG*SC*RC*SA*SG*SC*SC*ST*SG*SC*SA*SG*SG*SA*SG*SG
245	G*SA*SG*SC*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA
246	A*SG*SC*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC
247	G*SC*SA*SG*SC*ST*SG*SC*SA*RS*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA
248	C*SA*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA
249	A*SG*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA*SC
250	G*SC*ST*SG*SC*SA*RA*SC*SC*ST*SG*SG*SC*SA*SA*SC*SA*SA*SC*SC
251	A*T*T*A*A*T*A*A*A*T*T*G*T*C*A*T*C*A*C*C
252	A*ST*ST*SA*SA*ST*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
253	A*ST*ST*SA*SA*ST*SA*SA*SA*ST*ST*SG*ST*SC*SA*RT*SC*SA*SC*SC
254	mA*SmU*SmU*SmA*SmA*SmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmC*SmA*SmC*SmC
255	mA*RmU*RmU*RmA*RmA*RmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmC*RmA*RmC*RmC
256	mA*SmU*SmU*SmA*S mA*S mU*SmA*SmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
257	mA*RmU*RmU*RmA*RmA*RmU *RmA*RmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
258	mAmUmUmAmAmUmAmA*SA*ST*ST*SG*ST*SC*RA*ST*SC*SA*SC*SC
259	mAmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmCmC
260	mA*SmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*SmC
261	mA*RmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*RmC
262	A*SmUmUmAmAmU*SA*SA*SA*ST*ST*SG*ST*SC*RA*ST*SmCmAmC*SC

[0117] 在表1中;“*”表示立体无规硫代磷酸酯连接;“*S”表示Sp硫代磷酸酯连接;“*R”表示Rp硫代磷酸酯连接;所有非标记连接都是天然磷酸连接;在碱基前的“m”表示2’-OMe;“d2AP”表示2-氨基嘌呤;“dDAP”表示2,6-二氨基嘌呤;在碱基后面的“eo”表示2′-MOE;并且“BrdU”表示溴脱氧尿苷。

[0118] 表2

SEQ ID NO.	序列5' -> 3
263	m5C*m5C*G*T*m5C*G*m5C*m5C*m5C*T*T*m5C*A*G*m5C*A*m5C*G*m5C*A
264	m5C*Sm5C*SG*ST*Sm5C*SG*Sm5C*Sm5C*Sm5C*ST*ST*Sm5C*RA*SG*Sm5C*SA*Sm5C*SG*Sm5C*SA
265	m5Ceo*m5Ceo*Geo*Teo*m5Ceo*G*m5C*m5C*m5C*T*T*m5C*A*G*m5C*Aeo*m5Ceo*Geo*m

	5Ceo*Aeo
266	m5Ceo*Sm5Ceo*SGeo*STeo*Sm5Ceo*SG*Sm5C*Sm5C*Sm5C*ST*ST*Sm5C*SA*SG*Sm5C*SAeo* Sm5Ceo*SGeo*Sm5Ceo*SAeo
267	m5Ceo*Sm5Ceo*SGeo*STeo*Sm5Ceo*SG*Sm5C*Sm5C*Sm5C*ST*ST*Sm5C*RA*SG*Sm5C*SAeo* Sm5Ceo*SGeo*Sm5Ceo*SAeo
268	m5Ceo*Rm5Ceo*RGeo*RTeo*Rm5Ceo*RG*Sm5C*Sm5C*Sm5C*5T*ST*Sm5C*RA*SG*Sm5C*SAeo* Rm5Ceo*RGeo*Rm5Ceo*RAeo
269	Geo*Teo*m5Ceo*m5Ceo*m5Ceo*T*G*A*A*G*A*T*G*T*m5C*Aeo*Aeo*Teo*Geo*m5Ceo
270	Geo*RTeo*Rm5Ceo*Rm5Ceo*Rm5Ceo*RT*RG*RA*RA*RG*RA*RT*RG*RT*Rm5C*RAeo*RAeo*RTeo* RGeo*Rm5Ceo
271	Geo*STeo*Sm5Ceo*Sm5Ceo*Sm5Ceo*ST*SG*SA*SA*SG*SA*ST*SG*ST*Sm5C*SAeo*SAeo*STeo* SGeo*Sm5Ceo
272	Geo*RTeo*Rm5Ceo*Rm5Ceo*Rm5Ceo*RT*SG*SA*SA*SG*SA*ST*SG*ST*Sm5C*SAeo*RAeo*RTeo* RGeo*Rm5Ceo
273	Geo*STeo*Sm5Ceo*Sm5Ceo*Sm5Ceo*ST*RG*RA*RA*RG*RA*RT*RG*RT*Rm5C*RAeo*SAeo*STeo* SGeo*Sm5Ceo
274	mG*mG*mC*mA*mC*A*A*G*G*G*C*A*C*A*G*mA*mC*mU*mU*mC
275	mG*SmG*SmC*SmA*SmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*SmC*SmU*SmU*SmC
276	mG*RmG*RmC*RmA*RmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmA*RmC*RmU*RmU*RmC
277	mGmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmUmC
278	mG*RmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*RmC
279	mG*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SmC
280	G*SmGmCmAmC*SA*SA*SG*SG*SG*SC*SA*SC*RA*SG*SmAmCmUmU*SC
281	G*mGmCmAmC*A*A*G*G*G*C*A*C*A*G*mAmCmUmU*C
282	mG*mGmCmAmC*A*A*G*G*G*C*A*C*A*G*mAmCmUmU*mC
283	Geo*Geom5CeoAeom5Ceo*A*A*G*G*G*C*A*C*A*G*Aeom5CeoTeoTeo*m5Ceo
284	mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU
285	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SmA*SmU*SmU*SmU* SmC*SmU
286	mU*RmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*RmU*RmU* RmC*RmU
287	mU*SmC*RmA*SmA*RmG*SmG*RmA*SmA*RmG*SmA*RmU*SmG*RmG*SmC*RmA*SmU*RmU*SmU* RmC*SmU
288	mU*RmC*RmA*RmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SmA*SmU*SmU*RmU* RmC*RmU
289	mU*SmC*SmA*SmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*mG*RmC*RmA*RmU*RmU*SmU* SmC*SmU
290	mU*RmC*RmA*RmA*RmG*RmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmA*RmU*RmU*RmU* RmC*RmU
291	mU*SmC*SmA*SmA*SmG*SmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmA*SmU*SmU*SmU* SmC*SmU
292	mU*RmC*RmA*RmA*SmG*SmG*RmA*RmA*SmG*RmA*RmU*RmG*SmG*RmC*RmA*SmU

	*SmU*RmU* RmC*RmU
293	mU*SmC*SmA*SmA*RmG*RmG*SmA*SmA*RmG*SmA*SmU*SmG*RmG*SmC*SmA*RmU*RmU*SmU* SmC*SmU
294	mU*SmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*RmU*RmU* RmC*SmU
295	mU*RmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SmA*SmU*SmU*SmU* SmC*RmU
296	mU*SmC*RmA*SmA*SmG*RmG*RmA*SmA*SmG*RmA*SmU*SmG*RmG*RmC*RmA*SmU*SmU*SmU* SmC*RmU
297	mU*RmC*SmA*RmA*RmG*SmG*SmA*RmA*RmG*SmA*RmU*RmG*SmG*SmC*SmA*RmU*RmU*RmU* RmC*SmU
298	mU*SmC*SmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*SmG*RmG*RmC*SmA*RmU*SmU*SmU* SmC*SmU
299	mU*RmC*RmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*RmG*SmG*SmC*RmA*SmU*RmU*RmU* RmC*RmU
300	T*C*A*A*G*G*A*A*G*A*T*G*G*C*A*T*T*T*C*T
301	mUmCmAmAmGmGmAmAmGmAmUmGmGmCmAmUmUmUmCmU
302	T*RC*RA*RA*RG*RG*RA*RA*RG*RA*RT*RG*RG*RC*RA*RT*RT*RT*RC*RT
303	T*SC*SA*SA*SG*SG*SA*SA*SG*SA*ST*SG*SG*SC*SA*ST*ST*ST*SC*ST
304	T*SC*SA*SA*SG*SmGmAmAmGmAmUmGmGmCA*ST*ST*ST*SC*ST
305	mUmCmAmAG*SG*SA*SmAG*SA*ST*SG*SmGC*SA*ST*SmUmUmCmU
306	T*SmCA*SmAG*SmGA*SmAG*SmAT*SmGG*SmCA*SmUT*SmUC*SmU
307	mUC*SmAA*SmGG*SmAA*SmGA*SmUG*SmGC*SmAT*SmUT*SmCmU
308	T*SC*SmAmAG*SG*SmAmAG*SA*ST*SmGmGC*SA*SmUmUT*SC*SmU
309	T*SC*SA*SmAmGmGA*SA*SmGmAmUG*SG*SmCmAmUT*ST*SC*SmU
310	T*SC*SA*SA*SmGmGmAmAG*SA*ST*SmGmGmCmAT*ST*ST*SC*SmU
311	T*SC*SA*SmAG*SG*SA*SmAG*SA*ST*SmGG*SC*SA*SmUT*ST*SC*SmU
312	mUmCmAmAG*SG*SA*SA*SG*SmAmUmGmGmCA*ST*ST*ST*SC*SmU
313	T*SC*SmAmAmGmGmAmAmGmAT*SmGmGC*SmAT*ST*ST*SC*SmU
314	T*C*A*A*G*mGmAmAmGmAmUmGmGmCA*T*T*T*C*T
315	mUmCmAmAG*G*A*mAG*A*T*G*mGC*A*T*mUmUmCmU
316	T*mCA*mAG*mGA*mAG*mAT*mGG*mCA*mUT*mUC*mU
317	mUC*mAA*mGG*mAA*mGA*mUG*mGC*mAT*mUT*mCmU
318	T*C*mAmAG*G*mAmAG*A*T*mGmGC*A*mUmUT*C* mU
319	T*C*A*mAmGmGA*A*mGmAmUG*G*mCmAmUT*T*C*mU
320	T*C*A*A*mGmGmAmAG*A*T*mGmGmCmAT*T*T*C*mU
321	T*C*A*mAG*G*A*mAG*A*T*mGG*C*A*mUT*T*C* mU
322	mUmCmAmAG*G*A*A*G*mAmUmGmGmCA*T*T*T*C*mU
323	T*C*mAmAmGmGmAmAmGmAT*mGmGC*mAT*T*T*C*mU
324	fU*fC*fA*fA*fG*fG*fA*fA*fG*fA*fU*fG*fG* fC*fA*fU*fU*fU*fC*fU
325	fU*fC*mA*mA*mG*mG*mA*mA*mG*mA*fU*mG*mG* fC*mA*fU*fU*fU*fC*fU

326	mU*mC*fA*fA*fG*fG*fA*fA*fG*fA*mU*fG*fG* mC*fA*mU*mU*mU*mC*mU
327	mU*fC*mA*fA*mG*fG*mA*fA*mG*fA*mU*fG*mG* fC*mA*fU*mU*fU*mC*fU
328	mU*mC*mA*mA*mG*mG*fA*fA*fG*fA*fU*fG*fG* fC*mA*mU*mU*mU*mC*mU
329	fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG* mC*fA*fU*fU*fU*fC*fU
330	mU*fC*mA*mA*fG*fG*mA*mA*fG*mA*mU*fG*fG* fC*mA*mU*mU*mU*fC*mU
331	fU*mC*fA*fA*mG*mG*fA*fA*mG*fA*fU*mG*mG* mC*fA*fU*fU*fU*mC*fU
332	mUmCmAmAmGmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmAmUmUmUmCmU
333	mUmCmAmAmGmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmAmUmUmUmCmU
334	mU*SmCmAmAmGmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmAmUmUmUmC*SmU
335	mU*RmCmAmAmGmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmAmUmUmUmC*RmU
336	mU*RmCmAmAmGmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmAmUmUmUmC*RmU
337	mU*SmCmAmAmGmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmAmUmUmUmC*SmU
338	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmA*SmU*SmU*SmU*SmC*SmU
339	mU*SmC*RmA*SmA*SmG*RmG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RmA*SmU*SmU*RmU*SmC*SmU
340	mU*RmC*SmA*RmA*RmG*SmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmA*RmU*RmU*SmU*RmC*RmU
341	mUmCmAmAmGmG*SmA*SmAmG*SmA*SmUmG*SmG*SmCmAmUmUmUmCmU
342	mU*SmCmAmAmGmG*SmA*SmAmG*SmA*SmUmG*SmG*SmCmAmUmUmUmC*SmU
343	mU*SmCmAmAmGmGmAmAmGmAmUmGmGmCmAmUmUmUmC*SmU
344	mU*SmC*SmAmAmGmGmAmAmGmAmU*SmGmGmC*SmAmU*SmU*SmU*SmC*SmU
345	mU*SmC*SmA*SmA*SmG*SmGmAmAmGmAmUmGmGmCmA*SmU*SmU*SmU*SmC*SmU
346	mU*RmC*RmA*RmA*RmG*RmGmAmAmGmAmUmGmGmCmA*RmU*RmU*RmU*RmC*RmU
347	mU*SmC*SmA*SmA*SmG*SmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RA*SmU*SmU*SmU*SmC*SmU
348	mU*RmC*RmA*RmA*RmG*RmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SmA*RmU*RmU*RmU*RmC*RmU
349	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*RmG*RmG*RmC*RA*RmU*RmU*RmU*RmC*RmU
350	mU*RmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*SmG*SmG*SmC*SmA*SmU*SmU*SmU*SmC*SmU
351	mU*RmC*RmA*RmA*RmG*SmG*SmA*RmA*SmG*SmA*RmU*SmG*SmG*RmC*RmA*RmU*RmU*RmU*RmC*RmU
352	mU*RmC*RmA*RmA*RmG*RmG*RmA*SmA*SmG*RmA*SmU*SmG*RmG*SmC*SmA*RmU*RmU*RmU*RmC*RmU
353	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SfA*SfU*SfG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
354	fU*RfC*RfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RfU*RfG*RfG*RfC*RfA*RfU*RfU*RfU*RfC*RfU

355	fU*RfC*RfA*RfA*RfG*RfG*SfA*SfA*RfG*SfA*SfU*RfG*SfG*SfC*RfA*RfU*RfU*RfU*RfC*RfU
356	fU*SfC*RfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RfU*RfG*RfG*RfC*RfA*RfU*RfU*RfU*RfC*SfU
357	fU*SfC*SfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RfU*SfG*RfG*RfC*SfA*RfU*SfU*SfU*SfC*SfU
358	fU*SfC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SfU*SmG*SmG*SfC*SmA*SfU*SfU*SfU*SfC*SfU
359	fU*RfC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RfU*RmG*RmG*RfC*RmA*RfU*RfU*RfU*RfC*RfU
360	fU*RfC*RmA*RmA*RmG*RmG*SmA*SmA*RmG*SmA*SfU*RmG*SmG*SfC*RmA*RfU*RfU*RfU*RfC*RfU
361	fU*SfC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RfU*RmG*RmG*RfC*RmA*RfU*RfU*RfU*RfC*SfU
362	fU*SfC*SmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RfU*SmG*RmG*RfC*SmA*RfU*SfU*SfU*SfC*SfU
363	mU*SmC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SfA*SmU*SfG*SfG*SmC*SfA*SmU*SmU*SmU*SmC*SmU
364	mU*RmC*RfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RmU*RfG*RfG*RmC*RfA*RmU*RmU*RmU*RmC*RmU
365	mU*RmC*RfA*RfA*RfG*RfG*SfA*SfA*RfG*SfA*SmU*RfG*SfG*SmC*RfA*RmU*RmU*RmU*RmC*RmU
366	mU*SmC*RfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RmU*RfG*RfG*RmC*RfA*RmU*RmU*RmU*RmC*SmU
367	mU*SmC*SfA*RfA*RfG*RfG*RfA*RfA*RfG*RfA*RmU*SfG*RfG*RmC*SfA*RmU*SmU*SmU*SmC*SmU
368	mU*SfC*SmA*SfA*SmG*SfG*SmA*SfA*SmG*SfA*SmU*SfG*SmG*SfC*SmA*SfU*SmU*SfU*SmC*SfU
369	mU*RfC*RmA*RfA*RmG*RfG*RmA*RfA*RmG*RfA*RmU*RfG*RmG*RfC*RmA*RfU*RmU*RfU*RmC*RfU
370	mU*RfC*RmA*RfA*RmG*RfG*SmA*SfA*RmG*SfA*SmU*RfG*SmG*SfC*RmA*RfU*RmU*RfU*RmC*RfU
371	mU*SfC*RmA*RfA*RmG*RfG*RmA*RfA*RmG*RfA*RmU*RfG*RmG*RfC*RmA*RfU*RmU*RfU*RmC*SfU
372	mU*SfC*SmA*RfA*RmG*RfG*RmA*RfA*RmG*RfA*RmU*SfG*RmG*RfC*SmA*RfU*SmU*SfU*SmC*SfU
373	mU*SmC*SmA*SmA*SmG*SmG*SfA*SfA*SfG*SfA*SfU*SfG*SfG*SfC*SmA*SmU*SmU*SmU*SmC*SmU
374	mU*RmC*RmA*RmA*RmG*RmG*RfA*RfA*RfG*RfA*RfU*RfG*RfG*RfC*RmA*RmU*RmU*RmU*RmC*RmU
375	mU*RmC*RmA*RmA*RmG*RmG*SfA*SfA*RfG*SfA*SfU*RfG*SfG*SfC*RmA*RmU*RmU*RmU*RmC*RmU
376	mU*SmC*RmA*RmA*RmG*RmG*RfA*RfA*RfG*RfA*RfU*RfG*RfG*RfC*RmA*RmU*RmU*RmU*RmC*SmU
377	mU*SmC*SmA*RmA*RmG*RmG*RfA*RfA*RfG*RfA*RfU*SfG*RfG*RfC*SmA*RmU*SmU*SmU*SmC*SmU

378	fU*SfC*SfA*SfA*SfG*SfG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SfA*SfU*SfU*SfU*SfC*SfU
379	fU*RfC*RfA*RfA*RfG*RfG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RfA*RfU*RfU*RfU*RfC*RfU
380	fU*RfC*RfA*RfA*RfG*RfG*SmA*SmA*RmG*SmA*SmU*RmG*SmG*SmC*RfA*RfU*RfU*RfU*RfC*RfU
381	fU*SfC*RfA*RfA*RfG*RfG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RfA*RfU*RfU*RfU*RfC*SfU
382	fU*SfC*SfA*RfA*RfG*RfG*RmA*RmA*RmG*RmA*RmU*SmG*RmG*RmC*SfA*RfU*SfU*SfU*SfC*SfU
383	mU*SfC*SmA*SmA*SfG*SfG*SmA*SmA*SfG*SmA*SmU*SfG*SfG*SfC*SmA*SmU*SmU*SmU*SfC*SmU
384	mU*RfC*RmA*RmA*RfG*RfG*RmA*RmA*RfG*RmA*RmU*RfG*RfG*RfC*RmA*RmU*RmU*RmU*RfC*RmU
385	mU*RfC*RmA*RmA*RfG*RfG*SmA*SmA*RfG*SmA*SmU*RfG*SfG*SfC*RmA*RmU*RmU*RmU*RfC*RmU
386	mU*SfC*RmA*RmA*RfG*RfG*RmA*RmA*RfG*RmA*RmU*RfG*RfG*RfC*RmA*RmU*RmU*RmU*RfC*SmU
387	mU*SfC*SmA*RmA*RfG*RfG*RmA*RmA*RfG*RmA*RmU*SfG*RfG*RfC*SmA*RmU*SmU*SmU*SfC*SmU
388	fU*SmC*SfA*SfA*SmG*SmG*SfA*SfA*SmG*SfA*SfU*SmG*SmG*SmC*SfA*SfU*SfU*SfU*SmC*SfU
389	fU*RmC*RfA*RfA*RmG*RmG*RfA*RfA*RmG*RfA*RfU*RmG*RmG*RmC*RfA*RfU*RfU*RfU*RmC*RfU
390	fU*RmC*RfA*RfA*RmG*RmG*SfA*SfA*RmG*SfA*SfU*RmG*SmG*SmC*RfA*RfU*RfU*RfU*RmC*RfU
391	fU*SmC*RfA*RfA*RmG*RmG*RfA*RfA*RmG*RfA*RfU*RmG*RmG*RmC*RfA*RfU*RfU*RfU*RmC*SfU
392	fU*SmC*SfA*RfA*RmG*RmG*RfA*RfA*RmG*RfA*RfU*SmG*RmG*RmC*SfA*RfU*SfU*SfU*SmC*SfU
393	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SmA*SmU*SmU*SmU*SmC*SmU
394	mU*mC*mA*mA*mG*mG*mA*mA*mG *mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
395	mG*mG*mC*mC*mA*mA*mA*mC*mC *mU*mC*mG*mG*mC*mU*mU*mA*m C*mC*mU
396	mC*mU*mC*mC*mA*mA*mC*mA*mU *mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU* mC*mU*mA*mG
397	mA*mC*mC*mA*mG*mA*mG*mU*mA *mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*mG*mG*mA*mG
398	mC*mA*mC*mC*mA*mG*mA*mG*mU *mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*mG*mG*mA
399	mU*mC*mA*mC*mC*mA*mG*mA*mG *mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*mG*mG
400	mG*mU*mC*mA*mC*mC*mA*mG*mA *mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*mG
401	mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG

402	mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU
403	mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC
404	mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU
405	mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG
406	mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC
407	mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA
408	mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA
409	mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU
410	mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG
411	mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA
412	mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG
413	mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA
414	mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC
415	mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC
416	mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA
417	mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG
418	mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU
419	mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG
420	mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU
421	mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU
422	mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG
423	mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG
424	mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC

425	mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA
426	mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC
427	mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC
428	mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA
429	mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA
430	mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG
431	mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA
432	mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU
433	mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU
434	mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC
435	mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU
436	mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU
437	mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC
438	mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA
439	mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA
440	mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG
441	mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG
442	mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU
443	mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG
444	mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA
445	mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU
446	mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU
447	mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA

448	mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG
449	mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU
450	mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG
451	mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG
452	mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU
453	mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA
454	mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC
455	mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA
456	mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA
457	mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC
458	mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC
459	mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU
460	mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG
461	mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA
462	mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG
463	mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA
464	mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU*mG
465	mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC*mU
466	mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU*mC
467	mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA'mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*mU
468	mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA
469	mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA
470	mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA

471	mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG
472	mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU
473	mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mC*mG*mG*mU
474	mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mC*mG*mG
475	mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC*mG
476	mC*mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*mC*mC*mC
477	mA*mA*mA*mG*mC*mC*mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA
478	mG*mA*mA*mA*mG*mC*mC*mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC
479	mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU*mG*mU*mG*mA*mU
480	mG*mG*mU*mC*mA*mC*mC*mC*mA *mC*mC*mA*mU*mC*mA*mC*mC*mC*mA*mU*mC*mU*mG*mU*mG*mA
481	mA*mA*mG*mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU*mG*mU
482	mC*mA*mA*mG*mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU*mG
483	mU*mC*mA*mA*mG*mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU
484	mC*mU*mC*mA*mA*mG*mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC
485	mC*mU*mU*mG*mA*mU*mC*mA*mA*mG*mC*mA*mG*mA*mG*mA*mA*mA*mG*mC*mC*mA*mG*mU*mC
486	mA*mU*mA*mA*mC*mU*mU*mG*mA*mU*mC*mA*mA*mG*mC*mA*mG*mA*mG*mA*mA*mG*mC*mC
487	mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*mG*m G*mA*mG
488	mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*mA*m G*mG*mA
489	mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*mU*m A*mG*mG
490	mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*mC*mU*mG*mA*mG*m U*mA*mG
491	mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*mU*m C*mU*mG
492	mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*mG*m U*mC*mU
493	mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*mA*m G*mU*mC
494	mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*mC*m A*mG*mU
495	mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*mA*mA*m C*mA*mG
496	mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*mU*m A*mA*mC
497	mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*mG*m U*mA*mA
498	mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*mA*m G*mU*mA

499	mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*mG*m A*mG*mU
500	mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*mA*m G*mA*mG
501	mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*mC*m A*mG*mA
502	mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*mC*m C*mA*mG
503	mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*mA*m C*mC*mA
504	mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*mC*m A*mC*mC
505	mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*mU*m C*mA*mC
506	mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*mG*mU*mG*m U*mC*mA
507	mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*mU*m G*mU*mG
508	mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*mU*m U*mG*mU
509	mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*mG*m U*mU*mG
510	mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*mG*m G*mU*mU
511	mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*mA*m G*mG*mU
512	mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*mC*m A*mG*mG
513	mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*mC*mA*m C*mA*mG
514	mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*mC*m C*mA*mC
515	mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*mA*m C*mC*mA
516	mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*mA*m A*mC*mC
517	mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*mU*m A*mA*mC
518	mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*mG*m U*mA*mA
519	mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*mU*mA*m G*mU*mA
520	mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*mU*m U*mA*mG
521	mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*mC*m U*mU*mA
522	mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*mC*m C*mU*mU
523	mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*mU*m C*mC*mU
524	mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*mG*mU*mU*m U*mC*mC
525	mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*mA*m G*mU*mU
526	mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*mG*mG*mC*m A*mG*mU
527	mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*mA*mG*mA*mU*m G*mG*mC
528	mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*mU*mG*mG*m A*mG*mA
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530	mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU*mA*mG*mU*mU*m U*mG*mG
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533	mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*m U*mA*mG
534	mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*m C*mU*mA
535	mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
536	mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*m A*mU*mU

537	mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*m G*mC*mA
538	mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*m U*mG*mG
539	mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*mA*mG*mG*mA*mA*m G*mA*mU
540	mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*mA*m A*mG*mG
541	mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*mC*mA*mU*mC*m A*mA*mG
542	mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*mA*m C*mA*mU
543	mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*mC*mC*mA*m A*mC*mA
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546	mU*mG*mC*mC*mA*mG*mA*mG*mC*mA*mG*mG*mU*mA*mC*mC*mU*m C*mC*mA
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550	mU*mU*mG*mA*mA*mA*mU*mC*mU*mG*mC*mC*mA*mG*mA*mG*mC*m A*mG*mG
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555	mU*mC*mC*mA*mA*mG*mC*mC*mC*mG*mG*mU*mU*mG*mA*mA*mA*m U*mC*mU
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566	mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*mC*mC*mA*mA*mG*m C*mC*mC
567	mC*mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*mU*m C*mC*mA
568	mC*mC*mA*mG*mU*mC*mG*mG*mU*mA*mA*mG*mU*mU*mC*mU*mG*m U*mC*mC
569	mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU*mG*mU*m G*mA*mU
570	mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*mU*mG*m U*mG*mA
571	mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*mC*m U*mG*mU
572	mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*mU*m C* mU*mG
573	mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*mC*m U*mC*mU
574	mG*mG*mU*mC*mA*mC*mC*mC*mA*mC*mC*mA*mU*mC*mA*mC*mC*m C*mU*mC

575	mU*mC*mA*mA*mG*mC*mA*mG*mA*mG*mA*mA*mA*mG*mC*mC*mA*m G*mU*mC
576	mU*mU*mG*mA*mU*mC*mA*mA*mG*mC*mA*mG*mA*mG*mA*mA*mA*m G*mC*mC
577	mC*mA*mA*mA*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*m C*mU*mA*mG*mU*mU*mU*mG
578	mG*mC*mA*mA*mA*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
579	fG*fC*fA*fA*fA*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*f U*fC*fU
580	fU*fC*fA*fA*fG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*fU*fU*f U*fC*fU
581	fU*fC*fA*fA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*fU*f U*fC*fU
582	fU*fC*fA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*f U*fC*fU
583	fU*fC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*fC*fU
584	fU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*fU
585	fU*fC*fA*fA*fG*fGmA*mA*mG*mA*mU*mG*mG*mCfA*fU*fU*fU* fC*fU
586	fU*fC*fA*fA*fGfGmA*mA*mG*mA*mU*mG*mG*mCfAfU*fU*fU*fC *fU
587	fU*fC*fA*fAfGfGmA*mA*mG*mA*mU*mG*mG*mCfAfUfU*fU*fC*f U
588	fU*fC*fAfAfGfGmA*mA*mG*mA*mU*mG*mG*mCfAfUfUfU*fC*fU
589	fU*fCfAfAfGfGmA*mA*mG*mA*mU*mG*mG*mCfAfUfUfUfC*fU
590	fUfCfAfAfGfGmA*mA*mG*mA*mU*mG*mG*mCfAfUfUfUfCfU
591	fU*fC*fA*fA*fG*fG*fA*fA*fG*fA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
592	mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*fU*fG*fG*fC*fA*fU*fU*f U*fC*fU
593	fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
594	mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*f U*fC*fU
595	mU*RmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*R mC*RmA*RmU*RmU*RmU*RmC*RmU
596	mU*SmC*RmA*SmA*RmG*SmG*RmA*SmA*RmG*SmA*RmU*SmG*RmG*S mC*RmA*SmU*RmU*SmU*RmC*SmU
597	mU*RmC*RmA*RmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*S mC*SmA*SmU*SmU*RmU*RmC*RmU
598	mU*SmC*SmA*SmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU *RmU*SmU*SmC*SmU
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600	mU*SmC*SmA*SmA*SmG*SmG*RmA*RmA*SmG*RmA*RmU*SmG*RmG*RmC*SmA*SmU* SmU*SmU*SmC*SmU
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602	mU*SmC*SmA*SmA*RmG*RmG*SmA*SmA*RmG*SmA*SmU*SmG*RmG*SmC*SmA*RmU* RmU*SmU*SmC*SmU
603	mU*SmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*Rm U*RmU*RmU*RmC*SmU
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605	mU*SmC*RmA*SmA*SmG*RmG*RmA*SmA*SmG*RmA*SmU*SmG*RmG*RmC*RmA*SmU* SmU*SmU*SmC*RmU

606	mU*RmC*SmA*RmA*RmG*SmG*SmA*RmA*RmG*SmA*RmU*RmG*SmG*SmC*SmA*RmU*RmU*RmU*RmC*SmU
607	mU*SmC*SmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*SmG*RmG*RmC*SmA*RmU*SmU*SmU*SmC*SmU
608	mU*RmC*RmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*SmU*RmG*SmG*SmC*RmA*SmU*RmU*RmU*RmC*RmU
609	fG*fG*fC*fC*fA*fA*fA*fC*fC*fU*fC*fG*fG*fC*fU*fU*fA*fC*fC*fU
610	mG*mG*fC*fC*mA*mA*mA*fC*fC*fU*fC*mG*mG*fC*fU*fU*mA*fC*fC*fU
611	fG*fG*mC*mC*fA*fA*fA*mC*mC*mU*mC*fG*fG*mC*mU*mU*fA*mC*mC*mU
612	mG*fG*mC*fC*mA*fA*mA*fC*mC*fU*mC*fG*mG*fC*mU*fU*mA*fC*mC*fU
613	mG*mG*mC*mC*mA*mA*fA*fC*fC*fU*fC*fG*fG*fC*mU*mU*mA*mC*mC*mU
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615	fG*fG*fC*fC*mA*mA*mA*fC*fC*mU*fC*fG*fG*fC*mU*mU*mA*fC*fC*mU
616	mG*mG*mC*mC*fA*fA*fA*mC*mC*fU*mC*mG*mG*mC*fU*fU*fA*mC*mC*fU
617	fU*fC*fA*fA*fG*fG*fA*fA*fG*fA*fU*fG*fG*fC*fA*fU*fU*fU*fC*fU
618	fU*fC*mA*mA*mG*mG*mA*mA*mG*mA*fU*mG*mG*fC*mA*fU*fU*fU*fC*fU
619	mU*mC*fA*fA*fG*fG*fA*fA*fG*fA*mU*fG*fG*mC*fA*mU*mU*mU*mC*mU
620	mU*fC*mA*fA*mG*tG*mA*fA*mG*fA*mU*fG*mG*fC*mA*fU*mU*fU*mC*fU
621	mU*mC*mA*mA*mG*mG*fA*fA*fG*fA*fU*fG*fG*fC*mA*mU*mU*mU*mC*mU
622	fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*fU*fC*fU
623	mU*fC*mA*mA*fG*fG*mA*mA*fG*mA*mU*fG*fG*fC*mA*mU*mU*mU*fC*mU
624	fU*mC*fA*fA*mG*mG*fA*fA*mG*fA*fU*mG*mG*mC*fA*fU*fU*fU*mC*fU
625	G*G*C*C*A*A*A*C*C*T*C*G*G*C*T*T*A*C*C*T
626	mGmGmCmCmAmAmAmCmCmUmCmGmGmCmUmUmAmCmCmU
627	G*RG*RC*RC*RA*RA*RA*RC*RC*RT*RC*RG*RG*RC*RT*RT*RA*RC*RC*RT
628	G*SG*SC*SC*SA*SA*SA*SC*SC*ST*SC*SG*SG*SC*ST*ST*SA*SC*SC*ST
629	G*SG*SC*SC*SA*SmAmAmCmCmUmCmGmGmCT*ST*SA*SC*SC*ST
630	mGmGmCmCA*SA*SA*SmCC*ST*SC*SG*SmGC*ST*ST*SmAmCmCmU
631	G*SmGC*SmCA*SmAA*SmCC*SmUC*SmGG*SmCT*SmUA*SmCC*SmU
632	mGG*SmCC*SmAA*SmAC*SmCT*SmCG*SmGC*SmUT*SmAC*SmCmU
633	G*SG*SmCmCA*SA*SmAmCC*ST*SC*SmGmGC*ST*SmUmAC*SC*SmU
634	G*SG*SC*SmCmAmAA*SC*SmCmUmCG*SG*SmCmUmUA*SC*SC*SmU
635	G*SG*SC*SC*SmAmAmAmCC*ST*S C*SmGmGmCmUT*SA*SC*SC*SmU
636	G*SG*SC*SmCA*SA*SA*SmCC*ST *SC*SmGG*SC*ST*SmUA*SC*SC* SmU
637	mGmGmCmCA*SA*SA*SC*SC*SmUm CmGmGmCT*ST*SA*SC*SC*SmU
638	G*G*C*C*A*mAmAmCmCmUmCmGmG mCT*T*A*C*C*T
639	mGmGmCmCA*A*A*mCC*T*C*G*mG C*T*T*mAmCmCmU
640	G*mGC*mCA*mAA*mCC*mUC*mGG* mCT*mUA*mCC*mU
641	mGG*mCC*mAA*mAC*mCT*mCG*mG C*mUT*mAC*mCmU

642	G*G*mCmCA*A*mAmCmCT*C*mGmG C*T*mUmAC*C*mU
643	G*G*C*mCmAmAA*C*mCmUmCG*G* mCmUmUA*C*C*mU
644	G*G*C*C*mAmAmAmCC*T*C*mGmG mCmUT*A*C*C*mU
645	G*G*C*mCA*A*A*mCC*T*C*mGG* C*T*mUA*C*C*mU
646	mGmGmCmCA*A*A*C*C*mUmCmGmG mCT*T*A*C*C*mU
647	G*G*mCmCmAmAmAmCmCmUC*mGmG C*mUT*A*C*C*mU
648	mG*mG*mC*mC*mA*mAmAmCmCmUm CmGmGmCmU*mU*mA*mC*mC*mU
649	mGmGmCmCmA*mA*mA*mCmC*mU*m C*mG*mGmC*mU*mU*mAmCmCmU
650	mG*mGmC*mCmA*mAmA*mCmC*mUm C*mGmG*mCmU*mUmA*mCmC*mU
651	mGmG*mCmC*mAmA*mAmC*mCmU*m CmG*mGmC*mUmU*mAmC*mCmU
652	mG*mG*mCmCmA*mA*mAmCmCmU*m C*mGmGmC*mU*mUmAmC*mC*mU
653	mG*mG*mC*mCmAmAmA*mC*mCmUm CmG*mG*mCmUmUmA*mC*mC*mU
654	mG*mG*mC*mC*mAmAmAmCmC*mU* mC*mGmGmCmUmU*mA*mC*mC*mU
655	mG*mG*mC*mCmA*mA*mA*mCmC*mU*mC*mGmG*mC*mU*mUmA*mC*mC *mU
656	mGmGmCmCmA*mA*mA*mC*mC*mUmCmGmGmCmU*mU*mA*mC*mC*mU
657	mG*mG*mCmCmAmAmAmCmCmUmC*m GmGmC*mUmU*mA*mC*mC*mU
658	LOOl*mG*mG*mC*mC*mA*mA*mA*mC*mC*mU*mC*mG*mG*mC*mU*mU *mA*mC*mC*mU
659	LOOl*mG*mG*mC*mC*mA*mA*mA*mC*mC*mU*mC*mG*mG*mC*mU*mU *mA*mC*mC*mU*mG*mA*mA*mA*m G*SG*SmCmCmAmAmAmCmCmUC*Sm
660	G*SG*SmCmCmAmAmAmCmCmUC*SmGmGC*SmUT*SA*SC*SC*SmU
661	T*C*A*A*G*G*A*A*G*A*T*G*G* C*A*T*T*T*C*T
662	mUmCmAmAmGmGmAmAmGmAmUmGmG mCmAmUmUmUmCmU
663	T*RC*RA*RA*RG*RG*RA*RA*RG* RA*RT*RG*RG*RC*RA*RT*RT*RT *RC*RT
664	T*SC*SA*SA*SG*SG*SA*SA*SG* SA*ST*SG*SG*SC*SA*ST*ST*ST *SC*ST
665	T*SC*SA*SA*SG*SmGmAmAmGmAmUmGmGmCA*ST*ST*ST*SC*ST
666	mUmCmAmAG*SG*SA*SmAG*SA*ST*SG*SmGC*SA*ST*SmUmUmCmU
667	T*SmCA*SmAG*SmGA*SmAG*SmAT*SmGG*SmCA*SmUT*SmUC*SmU
668	mUC*SmAA*SmGG*SmAA*SmGA*SmUG*SmGC*SmAT*SmUT*SmCmU
669	T*SC*SmAmAG*SG*SmAmAG*SA*ST*SmGmGC*SA*SmUmUT*SC*SmU
670	T*SC*SA*SmAmGmGA*SA*SmGmAmUG*SG*SmCmAmUT*ST*SC*SmU
671	T*SC*SA*SA*SmGmGmAmAG*SA*ST*SmGmGmCmAT*ST*ST*SC*SmU
672	T*SC*SA*SmAG*SG*SA*SmAG*SA*ST*SmGG*SC*SA*SmUT*ST*SC* SmU
673	mUmCmAmAG*SG*SA*SA*SG*SmAm UmGmGmCA*ST*ST*ST*SC*SmU
674	T*SC*SmAmAmGmGmAmAmGmAT*Sm GmGC*SmAT*ST*ST*SC*SmU
675	T*C*A*A*G*mGmAmAmGmAmUmGmG mCA*T*T*T*C*T
676	mUmCmAmAG*G*A*mAG*A*T*G*mGC*A*T*mUmUmCmU
677	T*mCA*mAG*mGA*mAG*mAT*mGG*mCA*mUT*mUC*mU
678	mUC*mAA*mGG*mAA*mGA*mUG*mGC*mAT*mUT*mCmU

679	T*C*mAmAG*G*mAmAG*A*T*mGmGC*A*mUmUT*C*mU
680	T*C*A*mAmGmGA*A*mGmAmUG*G*mCmAmUT*T*C*mU
681	T*C*A*A*mGmGmAmAG*A*T*mGmG mCmAT*T*T*C*mU
682	T*C*A*mAG*G*A*mAG*A*T*mGG*C*A*mUT*T*C*mU
683	mUmCmAmAG*G*A*A*G*mAmUmGmGmCA*T*T*T*C*mU
684	T*C*mAmAmGmGmAmAmGmAT*mGmGC*mAT*T*T*C*mU
685	mU*mC*mA*mA*mG*mGmAmAmGmAmUmGmGmCmA*mU*mU*mU*mC*mU
686	mUmCmAmAmG*mG*mA*mAmG*mA*mU*mG*mGmC*mA*mU*mUmUmCmU
687	mU*mCmA*mAmG*mGmA*mAmG*mAmU*mGmG*mCmA*mUmU*mUmC*mU
688	mUmC*mAmA*mGmG*mAmA*mGmA*mUmG*mGmC*mAmU*mUmU*mCmU
689	mU*mC*mAmAmG*mG*mAmAmG*mA*mU*mGmGmC*mA*mUmUmU*mC*mU
690	mU*mC*mA*mAmGmGmA*mA*mGmAmUmG*mG*mCmAmUmU*mU*mC*mU
691	mU*mC*mA*mA*mGmGmAmAmG*mA*mU*mGmGmCmAmU*mU*mU*mC*mU
692	mU*mC*mA*mAmG*mG*mA*mAmG*mA*mU*mGmG*mC*mA*mUmU*mU*mC *mU
693	mUmCmAmAmG*mG*mA*mA*mG*mAmUmGmGmCmA*mU*mU*mU*mC*mU
694	mU*mC*mAmAmGmGmAmAmGmAmU*mGmGmC*mAmU*mU*mU*mC*mU
695	rArGrArArArUrGrCrCrArUrCrU rUrCrCrUrUrGrA
696	mU*SmC*SmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*RmU*RmU*SmC*SmU
697	mU*SmC*SmA*SmA*SmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*SmU*SmU*SmC*SmU
698	mU*SmC*SmA*SmA*SmG*SmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*SmU*SmU*SmU*SmC*SmU
699	mU*SmCmAmAmGmGmAmAmGmAmUmG mGmCmAmUmUmUmC*SmU
700	mU*SmC*SmAmAmGmGmAmAmGmAmU mGmGmCmAmUmUmU*SmC*SmU
701	mU*SmC*SmA*SmAmGmGmAmAmGmA mUmGmGmCmAmUmU*SmU*SmC*SmU
702	mU*SmC*SmA*SmA*SmGmGmAmAmG mAmUmGmGmCmAmU*SmU*SmU*SmC *SmU
703	mU*SmC*SmA*SmA*SmG*SmGmAmA mGmAmUmGmGmCmA*SmU*SmU*SmU *SmC*SmU
704	mU*mCmAmAmGmGmAmAmGmAmUmGm GmCmAmUmUmUmC*mU
705	mU*mC*mAmAmGmGmAmAmGmAmUmG mGmCmAmUmUmU*mC*mU
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707	mU*mC*mA*mA*mGmGmAmAmGmAmU mGmGmCmAmU*mU*mU*mC*mU
708	mU*mC*mA*mA*mG*mGmAmAmGmAm UmGmGmCmA*mU*mU*mU*mC*mU
709	fU*fC*fA*fA*fG*fG*mAmAmGmAmUmGmGmC*fA*fU*fU*fU*fC*fU
710	fU*fC*fA*fA*fG*mGmAmAmGmAmUmGmGmCmA*fU*fU*fU*fC*fU
711	fU*fC*fA*fA*mGmGmAmAmGmAmUmGmGmCmAmU*fU*fU*fC*fU
712	fU*fC*fA*mAmGmGmAmAmGmAmUmGmGmCmAmUmU*fU*fC*fU
713	fU*fC*mAmAmGmGmAmAmGmAmUmGmGmCmAmUmUmU*fC*fU
714	fU*mCmAmAmGmGmAmAmGmAmUmGmGmCmAmUmUmUmC*fU

715	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAmUmGmGmC*SfA*SfU*SfU*SfU*SfC *SfU
716	fU*SfC*SfA*SfA*SfG*SmGmAmA mGmAmUmGmGmCmA*SfU*SfU*SfU *SfC*SfU
717	fU*SfC*SfA*SfA*SmGmGmAmAmG mAmUmGmGmCmAmU*SfU*SfU*SfC *SfU
718	fU*SfC*SfA*SmAmGmGmAmAmGmA mUmGmGmCmAmUmU*SfU*SfC*SfU
719	fU*SfC*SmAmAmGmGmAmAmGmAmU mGmGmCmAmUmUmU*SfC*SfU
720	fU* SmCmAmAmGmGmAmAmGmAmUmG mGmCmAmUmUmUmC*SfU
721	fU*SfC*SfA*SfA*SfG*SfG*SmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*SfA*SfU*SfU*Sf U*SfC*SfU
722	fU*SfC*SfA*SfA*SfG*SmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*SfU*SfU* SfU*SfC*SfU
723	fU*SfC*SfA*SfA*SmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*Sf U*SfU*SfC*SfU
724	fU*SfC*SfA*SmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU*R mU*SfU*SfC*SfU
725	fU*SfC*SmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU* RmU*RmU*SfC*SfU
726	fU*SmC*RmA*RmA*RmG*RmG*RmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*RmA*RmU *RmU*RmU*RmC*SfU
727	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*RmG*RmA*RmU*RmG*RmG*SfC*SfA*SfU*SfU*SfU*Sf C*SfU
728	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmG*RmA*RmU*RmG*SfG*SfC*SfA*SfU*SfU*SfU*SfC *SfU
729	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmA*RmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*S fU
730	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfAmGmAmUmGmG*SfC*SfA*SfU*SfU*SfU*SfC *SfU
731	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAmUmG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
732	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU *SfU*SfC*SfU
733	fU*SfC*SfA*SfA*StG*SfG*SfA*mA*mG*mA*mU*mG*mG*fC*SfA*SfU*SfU*SfU*SfC*SfU
734	mU*SmC*SmA*SmA*SmG*SmG*SmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*SmA*SmU* SmU*SmU*SmC*SmU
735	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*RmG*RmA*RmU*RmG*RmG*SmC*SmA*SmU* SmU*SmU*SmC*SmU
736	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*RmA*RmU*RmG*SmG*SmC*SmA*SmU* SmU*SmU*SmC*SmU
737	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmA*RmU*SmG*SmG*SmC*SmA*SmU*S mU*SmU*SmC*SmU
738	mU*SmC*SmA*SmA*SmG*SmG*SmA *mA*mG*mA*mU*mG*mG*mC*SmA* SmU*SmU*SmU*SmC*SmU
739	LOOl*mU*mC*mA*mA*mG*mG*mA* mA*mG*mA*mU*mG*mG*mC*mA*mU *mU*mU*mC*mU
740	Mod013L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
741	Mod014L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU

742	Mod005L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
743	Mod015L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
744	Mod016L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
745	Mod017L001*mU*mC*mA*mA*mG* mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
746	Mod018L001*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
747	Mod019L001*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
748	Mod006L001*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
749	Mod020L001*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC *mA*mU*mU*mU*mC*mU
750	Mod021*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA* mU*mU*mU*mC*mU
751	mU*mC*mA*mA*mG*mG*mAmAmGmAmUmGmGmC*mA*mU*mU*mU*mC*mU
752	mU*mC*mA*mA*mG*mG*mA*mAmGmAmUmGmG*mC*mA*mU*mU*mU*mC*mU
753	mU*mC*mA*mA*mG*mG*mA*mA*mGmAmUmG*mG*mC*mA*mU*mU*mU*mC*mU
754	mU*mC*mA*mA*mG*mG*mA*mA*mG*mAmU*mG*mG*mC*mA*mU*mU*mU*mC*mU
755	mU*SmC*SmA*SmA*SmG*SmG*SmAmAmGmAmUmGmGmC*SmA*SmU*SmU*SmU*SmC*S mU
756	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmAmGmAmUmGmG*SmC*SmA*SmU*SmU*SmU*S mC*SmU
757	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmGmAmUmG*SmG*SmC*SmA*SmU*SmU*Sm U*SmC*SmU
758	mU*SmC*SmA*SmA*SmG*SmG*SmA*SmA*SmG*SmAmU*SmG*SmG*SmC*SmA*SmU*Sm U*SmU*SmC*SmU
759	fU*fC*fA*fA*fG*fG*fA*mAmGmAmUmGmG*fC*fA*fU*fU*fU*fU* fU
760	fU*fC*fA*fA*fG*fG*fA*fA*mGmAmUmG*fG*fC*fA*fU*fU*fU*f C*fU
761	fU*fC*fA*fA*fG*fG*fA*fA*fG*mAmU*fG*fG*fC*fA*fU*fU*fU*fC*fU
762	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmA*RmUmGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
763	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmG*RmA*RmU*RmGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
764	fU*SfC*SfA*SfA*SfG*SfG*SmAmA*RmG*RmA*RmU*RmG*RmGmC*SfA*SfU*SfU*SfU*SfC *SfU
765	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAfU*SmGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
766	fU*SfC*SfA*SfA*SmG*SmG*SfAfAmGmAfU*SmGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
767	fU*SfC*SfA*SfA*SfG*SfG*SmA*RmA*RmGmAmUmG*RmG*RmC*SfA*SfU*SfU*SfU*SfC*S fU
768	fU*SfC*SfA*SfA*SfG*SfG*SmA*RmAmGmAmUmGmG*RmC*SfA*SfU*SfU*SfU*SfC*SfU
769	fU*SfC*SfA*SfA*SfG*SfG*SmA*SmA*SmGmAmUmG*SmG*SmC*SfA*SfU*SfU*SfU*SfC*Sf U

770	fU*SfC*SfA*SfA*SfG*SfG*SmA*SmAmGmAmUmGmG*SmC*SfA*SfU*SfU*SfU*SfC*SfU
771	fU*SfC*SfA*SfA*SfG*SfG*SmA*SmA*SmG*SmA*SmU*SmG*SmG*SmC*SfA*SfU*SfU*SfU*SfC*SfU
772	fU*SfC*SfA*SfA*SfG*SfG*SmA*RmA*RmG*RmA*RfU*SmG*RmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
773	fU*SfC*SfA*SfA*SmG*SmG*SfA*RfA*RmG*RmA*RfU*SmG*RmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
774	fU*SfC*SfA*SfA*SfG*SfG*SfA*SmAmGmAmUmGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
775	fU*SfC*SfA*SfA*SfG*SfG*SfA*SmA*RmG*RmA*RmU*RmG*RmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
776	mU*SmC*SmA*SfA*SfG*SfG*SmA*RmA*RmG*RmA*RmU*RmG*RmG*RmC*SfA*SfU*SfU*SmU*SmC*SmU
777	mU*SmC*SmA*SfA*SfG*SfG*SfA*SmA*RmG*RmA*RmU*RmG*RmG*SfC*SfA*SfU*SfU*SmU*SmC*SmU
778	mU*SmC*SmA*SfA*SfG*SfG*SfA*SfA*SmG*RmA*RmU*RmG*SfG*SfC*SfA*SfU*SfU*SmU*SmC*SmU
779	mU*SmC*SmA*SfA*SfG*SfG*SfA*SfA*SfG*SmA*RmU*StG*SfG*SfC*SfA*SfU*SfU*SmU*SmC*SmU
780	mU*SmC*SmA*SfA*SfG*SfG*SfA*SfA*SmGmAmUmG*SfG*SfC*SfA*SfU*SfU*SmU*SmC*SmU
781	mU*SmC*SmA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SmU*SmC*SmU
782	fU*fC*fA*fA*fG*fG*fA*fA*mG*mA*mU*mG*mG*fC*fA*fU*fU*fU*fC*fU
783	fU*fC*fA*fA*fG*fC*fA*fA*mG *mA*mU*mG*fG*fC*fA*fU*fU*f U*fC*fU
784	fU*fC*fA*fA*fG*fG*fA*fA*fG *mA*mU*fG*fc*fA*fU*fU*fU*f C*fU
785	fU*fC*fA*fA*fG*fG*fA*mA*mG *mA*mU*mG*mG*fC*fA*fU*fU*f U*fC*fU
786	mU*mC*mA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*mU*mC*mU
787	mU*mC*mA*fA*fG*fG*fA*mA*mG *mA*mU*mG*mG*fC*fA*fU*fU*m U*mC*mU
788	mU*mC*mA*fA*fG*fG*fA*fA*mG *mA*mU*mG*fG*fC*fA*fU*fU*m U*mC*mU
789	mU*mC*mA*fA*fG*fG*fA*fA*fC *mA*mU*fG*fG*fC*fA*fU*fU*m U*mC*mU
790	mU*mC*mA*fA*fG*fG*fA*fA*mG mAmUmG*fG*fC*fA*fU*fU*mU*m C*mU
791	mU*mC*mA*fA*fG*fG*fA*fA*fG*mAmU*fG*fG*fC*fA*fU*fU*mU *mC*mU
792	Mod024L001*mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU
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794	fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*BrdU*mG*mG*mC*fA*fU*fU *fU*fC*fU
795	fU*fC*fA*fA*fG*fG*fA*fA*fG *mA*BrdU*fG*fC*fC*fA*fU*fU *fU*fC*fU
796	mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*BrdU*mG*mG*mC*mA*mU*mU*mU*mC*mU
797	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmABrdUmG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
798	fU*fC*fA*fA*fG*fG*fA*fA*mGmABrdUmG*fG*fC*fA*fC*fU*fU *fC*fU
799	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmABrdUmGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
800	fU*fC*fA*fA*fG*fG*mAmAmGmABrdUmGmGmC*fA*fU*fU*fU*fC* fU

801	LOOl*fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAmUmGmGmC*SfA*SfU*SfU*SfU *SfC*SfU
802	Mod015L001*fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAmUmGmGmC*SfA*SfU*SfU*SfU*SfC *SfU
803	Mod006L001*fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAmUmGmGmC*SfA*SfU*SfU*SfU*SfC *SfU
804	LOOl*fU*SfC*SfA*SfA*SfG*Sf G*SfA*SfA*SmGmAmUmG*SfG*SfC*SfA*SfU *SfU*SfU*SfC*SfU
805	Mod015L001*fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAmUmG*SfG*SfC*SfA *SfU*SfU*SfU*Sf C*SfU
806	Mod006L001*fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAmUmG*SfG*SfC*SfA *SfU*SfU*SfU*Sf C*SfU
807	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAmUmGmG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
808	LOOl*fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*fU*fC *fU
809	Mod015L001*fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU *fU*fC*fU
810	Mod006L001*fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*fU*fC*fU
811	Mod020L001*fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*fU*fC*fU
812	Mod019L001*fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*mU*mG*mG*mC*fA*fU*fU*fU*fC*fU
813	LOOl*fU*fC*fA*fA*fG*fG*fA* fA*mGmAmUmG*fG*fC*fA*fU*fU *fU*fC*fU
814	Mod015L001*fU*fC*fA*fA*fG*fG*fA*fA*mGmAmUmG*fG*fC*fA*fU*fU*fU*fC*fU
815	Mod006L001*fU*fC*fA*fA*fG*fG*fA*fA*mGmAmUmG*fG*fC*fA*fU*fU*fU*fC*fU
816	Mod020L001*fU*ft*fA*fA*fG*fG*fA*fA*mGmAmUmG*fG*fC*fA *fU*fU*fU*fC*fU
817	Mod019L001*fU*ft*fA*fA*fG*fG*fA*fA*mGmAmUmG*fG*fC*fA *fU*fU*fU*fC*fU
818	fU*fC*fA*fA*fG*fG*mAmAmGmA*mUmGmGmC*fA*fU*fU*fU*fC*f U
819	fU*fC*fA*fA*fG*fG*mAmAmG*mA*mU*mGmGmC*fA*fU*fU*fU*fC *fU
820	fU*fC*fA*fA*fG*fG*mAmA*mG*mA*mU*mG*mGmC*fA*fU*fU*fU* fC*fU
821	fU*fC*fA*fA*fG*fG*mA*mA*mGmAmUmG*mG*mC*fA*fU*fU*fU*f C*fU
822	fU*fC*fA*fA*fG*fG*mA*mAmGmAmUmGmG*mC*fA*fU*fU*fU*fC* fU
823	fU*fC*fA*fA*fG*fG*mA*mA*mGmAmUmG*mG*mC*fA*fU*fU*fU*f C*fU
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826	fU*fC*fA*fA*fG*fG*mA*mA*mG*mA*fU*mG*mG*fC*fA*fU*fU*f U*fC*fU
827	fU*fC*fA*fA*mG*mG*fAfAmGmAfU*mGmG*fC*fA*fU*fU*fU*fC* fU
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832	fU*fC*fA*fA*mG*mG*mA*mA*mGmAfUmG*mG*fC*fA*fU*fU*fU*f C*fU
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834	fU*fC*fA*fA*mG*mG*mA*mA*mG*mA*fU*mG*mG*fC*fA*fU*fU*f U*fC*fU
835	fU*fC*fA*fA*mG*mG*fAfAmGmA*fU*mGmG*fC*fA*fU*fU*fU*fC *fU

836	fU*fC*fA*fA*mG*mG*fA*fA*mG*mA*fU*mG*mG*fC*fA*fU*fU*f U*fC*fU
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840	fU*fC*fA*fA*mG*mG*mA*mA*mGmAfU*mGmG*fC*fA*fU*fU*fU*f C*fU
841	fU*SfC*SfA*SfA*SfG*SfG*SmAmAmGmAmU:mGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
842	fU*SfC*SfA*SfA*SfG*SfG*SmAmA:mGmAmUmG:mGmC*SfA*SfU*SfU*SfU*SfC*SfU
843	fU*SfC*SfA*SfA*SfG*SfG*SmA:mAmG:mAmUmGmG:mC*SfA*SfU*SfU*SfU*SfC *SfU
844	fU*SfC*SfA*SfA*SfG*SfG*SmA:mAmGmAmU:mGmG:mC*SfA*SfU*SfU*SfU*SfC *SfU
845	fU*SfC*SfA*SfA*fG:fG:mAmAmGmAmU:mGmGmC*SfA*SfU*SfU*S fU*SfC*SfU
846	fU*SfC*SfA*SfA*mG:mG:mAmAmGmAmU:mGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
847	fU*SfC*SfA*SfA*SfG*SfG*SfA*SmAmGmAmU:mGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
848	fU*SfC*SfA*SfA*fG:fG:fA*SmAmGmAmU:mGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
849	fU*SfC*SfA*SfA*mG:mG:fA*Sm AmGmAmU:mGmG*SfC*SfA*SfU*SfU*SfU*SfC *SfU
850	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAmU:mG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
851	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmG:mA:mU:mG*SfG*SPC*SfA*SfU*SfU*SfU*SfC*SfU
852	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmG:mAmU:mG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
853	fU*SfC*SfA*SfA*fG:fG:fA*SfA*SmGmAmU:mG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
854	fU*SfC*SfA*SfA*mG:mG:fA*SfA*SmGmAmU:mG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
855	Mod015L001mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU *mC*mU
856	Mod019L001mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU *mC*mU
857	Mod020L001mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU *mC*mU
858	Mod015L001:mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
859	Mod019L001:mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
860	Mod020L001:mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*m U*mC*mU
861	fU*SfC*SfA*SfA*SfG:fG:mAmAmGmAmU:mGmGmC*SfA*SfU*SfU* SfU*SfC*SfU
862	fU*SfC*SfA*SfA*SmG:mG:mAmAmGmAmU:mGmGmC*SfA*SfU*SfU*SfU*SfC*SfU
863	fU*SfC*SfA*SfA*SfG:fG:fA*SmAmGmAmU:mGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
864	fU*SfC*SfA*SfA*SmG:mG:fA*SmAmGmAmU:mGmG*StC*SfA*SfU*SfU*SfU*SfC *SfU
865	fU*SfC*SfA*SfA*SfG:fG:fA*SfA*SmGmAmU:mG*SPG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
866	fU*SPC*SfA*SfA*SmG:mG:fA*SfA*SmGmAmU:mG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
867	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmUmG*SfG*SfC*SfA*SfU*SfU*SfU*SPC*SfU
868	fU*fC*fA*fA*fG*fG*fA*fA*fG*mAmUmG*fG*fC*fA*fU*fU*fU* fC*fU
869	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfA*SmUfG*SmGfC*SfA*SfU*SfU*SfU*SfC*SfU

870	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGfA*SmUPG*SmG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
871	LOO1mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU
872	LOO1fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*S fU
873	Mod013L001mU*mC*mA*mA*mG*mG*mA*mA*mG*mA*mU*mG*mG*mC*mA*mU*mU*mU*mC*mU
874	Mod013L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
875	Mod014L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
876	Mod005L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
877	Mod015L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
878	Mod020L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
879	Mod027L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*SfU*SfU*SfU *SfC*SfU
880	Mod029L001fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAmU*SfG*SfG*SfC*SfA*sfU*SfU*SfU *SfC*SfU
881	fU*SfC*SfA*SfA*SfG*SfGfA*SmAfG*SmAfU*SmGfGfC*SfA*SfU*SfU*SfU*SfC*SfU
882	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfAfG*SmAfU*SmG*SmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
883	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAfU*SmG*SfG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
884	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SmGmAfU*SmGmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
885	fU*SfC*SfA*SfA*SfG*SfG*SfA*SfA*SfG*SmAfU*SmGfG*SfC*SU*SfC*SfU
886	fU*SfC*SfA*SfA*SfG*mAmAmGm AfU*SmGmG*SfC*SfA*SfU*SfU* SfU*SfC*SfU
887	fU*SfC*SfA*SfA*SfG*SfG*SmA*SmA*SmG*SmA*SfU*SmG*SmG*SfC*SfA*SfU*SfU*SfU*SfC*SfU
888	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfA*SfUfG*SmGfC*SfA*SfU*SfU*SfU*SfC*SfU
889	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfA*SfUmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
890	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
891	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
892	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfAfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
893	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmAfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
894	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfA*SfU*SmGmGfC*SfAfU*SfU*SfU*SfC*SfU
895	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfAfU*SfU*SfU*SfC*SfU
896	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfAfU*SmGmGfC*SmA*SfU*SfU*SfU*SfC*SfU
897	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmAfU*SmGmGfC*SmA*SfU*SfU*SfU*SfC*SfU
898	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfAfU*SmGmGfC*SmAfU*SfU*SfU*SfC*SfU
899	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmAfU*SmGmGfC*SmAfU*SfU*SfU*SfC*SfU
900	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGfAfU*SmGmGfC*SfAfU*SfU*SfU*SfC*SfU

901	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmAfU*SmGmGfC*SfAfU*SfU*SfU*SfC*SfU
902	fU*fC*fA*fA*fG*fG*mAfA*mGf A*mUfG*mGfC*fA*fU*fU*fU*fC *fU
903	Mod030fU*fC*fA*fA*fG*fG*mA fA*mGfA*mUfG*mGfC*fA*fU*fU *fU*fC*fU
904	Mod031fU*fC*fA*fA*fG*fG*mA fA*mGfA*mUfG*mGfC*fA*fU*fU *fU*fC*fU
905	Mod032fU*fC*fA*fA*fG*fG*mA fA*mGfA*mUfG*mGfC*fA*fU*fU *fU*fC*fU
906	Mod033fU*fC*fA*fA*fG*fG*mA fA*mGfA*mUfG*mGfC*fA*fU*fU *fU*fC*fU
907	Mod013L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
908	Mod005L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
909	Mod015L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
910	Mod020L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
911	Mod027L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
912	Mod029L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
913	Mod030fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
914	Mod032fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
915	Mod033fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
916	Mod020L001*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*
917	Mod005L001*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
918	Mod014L001fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
919	Mod030*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
920	Mod032*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
921	Mod033*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
922	Mod033*fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
923	Mod020L001fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
924	Mod020L001*fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
925	LOOl*fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*S fU
926	LOOlfU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*Sf U
927	rGrCrCrArArCrUrGrGrGrArGrCrUrGrGrArGrCrGrCrArCrCrArArCrCrArG

928	LOOl*fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
929	LOOlfU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
930	Mod015L001*fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
931	Mod015L001fU*fC*fA*fA*fG*fG*mAfA*mGfA*mUfG*mGfC*fA*fU*fU*fU*fC*fU
932	fC*fC*fU*fU*fC*fC*mCfU*GmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
933	LOOlfC*fC*fU*fU*fC*fC*mCfU*GmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
934	Mod020L001fC*fC*fU*fU*fC*fC*mCfU*GmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
935	fC*fC*fU*fU*fC*fC*mCfU*mGmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
936	LOOlfC*fC*fU*fU*fC*fC*mCfU*mGmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
937	Mod020L001fC*fC*fU*fU*fC*fC*mCfU*mGmAfA*mGmGfU*fU*fC*fC*fU*fC*fC
938	Mod015L001*fU*SPC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU *SfC*SfU
939	Mod015L001*SfU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*Sf U*SfC *SfU
940	L001*SfU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU* SfU*SfC*
941	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC
942	fU*SfC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*S fU*SfU*SfU
943	fC*SfA*SfA*SfG*SfG*SmAfA*SmGmA*SfU*SmGmGfC*SfA*SfU*SfU*SfU*SfC*SfU
944	Mod020L001mG*mG*mC*mC*mA*mASmA*mC*mC*mU*mC*mG*mG*mC* mU*mU*mA*mC*mC*mU
945	Mod015L001mG*mG*mC*mC*mA*mA*mA*mC*mC*mU*mC*mG*mG*mC* mU*mU*mA*mC*mC*mU
946	fU*fU*fC*fU*fG*fU*mA*mA*mG*mG*mU*mU*mU*mU*fU*fA*fU*f G*fU*fG
947	fA*fU*fU*fU*rC*fU*mG*mU*mA*mA*mG*mG*mU*mU*fU*fU*fU*f A*fU*fG
948	fC*fC*fA*fU*fU*fU*mC*mU*mG*mU*mA*mA*mG*mG*fU*fU*fU*f U*fU*fA
949	fA*fU*fC*fC*fA*fU*mU*mU*mC*mU*mG*mU*mA*mA*fG*fG*fU*f U*fU*fU
950	fC*fA*fU*fC*fC*fA*mU*mU*mU*mC*mU*mG*mU*mA*fA*fG*fG*f U*fU*fU
951	fC*fC*fA*fU*fC*fC*mA*mU*mU*mU*mC*mU*mG*mU*fA*fA*fG*f G*fU*fU
952	fG*fC*fC*fA*fU*fC*mC*mA*mU*mU*mU*mC*mU*mG*fU*fA*fA*f G*fG*fU
953	fA*fG*fC*fC*fA*fU*mC*mC*mA*mU*mU*mU*mC*mU*fG*fU*fA*f A*fG*fG
954	fC*fA*fG*fC*fC*fA*mU*mC*mC*mA*mU*mU*mU*mC*fU*fG*fU*f A*fA*fG
955	fU*fC*fA*fG*fC*fC*mA*mU*mC*mC*mA*mU*mU*mU*fC*fU*fG*f U*fA*fA
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959	fA*fA*fC*fU*fU*fC*mA*mG*mC*mC*mA*mU*mC*mC*fA*fU*fU*f U*fC*fU
960	fC*fA*fA*fC*fU*fU*mC*mA*mG*mC*mC*mA*mU*mC*fC*fA*fU*f U*fU*fC
961	fU*fC*fA*fA*fC*fU*mU*mC*mA*mG*mC*mC*mA*mU*fC*fC*fA*f U*fU*fU
962	fC*fC*fA*fG*fG*fG*mC*mA*mG*mG*mC*mC*mA*mU*fU*fC*fC*f U*fC*fU
963	fC*fC*fC*fA*fG*fG*mG*mC*mA*mG*mG*mC*mC*mA*fU*fU*fC*f C*fU*fC

964	fC*fC*fC*fC*fA*fG*mG*mG*mC*mA*mG*mG*mC*mC*fA*fU*fU*f C*fC*fU
965	fC*fC*fC*fC*fC*fA*mG*mG*mG*mC*mA*mG*mG*mC*fC*fA*fU*f U*fC*fC
966	fU*fC*fc*fC*fC*fC*mA*mG*mG*mG*mC*mA*mG*mG*fC*fC*fA*f U*fU*fC
967	fA*fU*fC*fC*fC*fC*mC*mA*mG*mG*mG*mC*mA*mG*fG*fC*fC*f A*fU*fU
968	fC*fA*fU*fC*fC*fC*mC*mC*mA*mG*mG*mG*mC*mA*fG*fG*fC*f C*fA*fU
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970	fA*fG*fC*fA*fU*fC*mC*mC*mC*mC*mA*mG*mG*mG*fC*fA*fG*f G*fC*fC
971	fC*fA*fG*fC*fA*fU*mC*mC*mC*mC*mC*mA*mG*mG*fG*fC*fA*f G*fG*fC
972	fU*fC*fA*fG*fC*fA*mU*mC*mC*mC*mC*mC*mA*mG*fG*fG*fC*f A*fG*fG
973	fU*fU*fC*fA*fG*fC*mA*mU*mC*mC*mC*mC*mC*mA*fG*fG*fG*f C*fA*fG
974	fU*fU*fU*fC*fA*fG*mC*mA*mU*mC*mC*mC*mC*mC*fA*fG*fG*f G*fC*fA
975	fA*fU*fU*fU*fC*fA*mG*mC*mA*mU*mC*mC*mC*mC*fC*fA*fG*f G*fG*fC
976	fG*fA*fU*fU*fU*fC*mA*mG*mC*mA*mU*mC*mC*mC*fC*fC*fA*f G*fG*fG
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978	fA*fG*fG*fA*fU*fU*mU*mC*mA*mG*mC*mA*mU*mC*fC*fC*fC*f C*fA*fG
979	fC*fA*fG*fG*fA*fU*mU*mU*mC*mA*mG*mC*mA*mU*fC*fC*fC*f C*fC*fA
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985	fU*fU*fU*fU*fU*fU*mC*mA*mG*mG*mA*mU*mU*mU*fC*fA*fG*f C*fA*fU
986	fG*fU*fU*fU*fU*fU*mU*mC*mA*mG*mG*mA*mU*mU*fU*fC*fA*f G*fC*fA
987	fU*fG*fU*fU*fU*fU*mU*mU*mC*mA*mG*mG*mA*mU*fU*fU*fC*f A*fG*fC
988	fC*fU*fG*fU*fU*fU*mU*mU*mU*mC*mA*mG*mG*mA*fU*fU*fU*f C*fA*fG
989	fG*fC*fU*fG*fU*fU*mU*mU*mU*mU*mC*mA*mG*mG*fA*fU*fU*f U*fC*fA
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991	fG*fA*fG*fC*fU*fG*mU*mU*mU*mU*mU*mU*mC*mA*fG*fG*fA*f U*fU*fU
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993	fU*fU*fG*fA*fG*fC*mU*mG*mU*mU*mU*mU*mU*mU*fC*fA*fG*f G*fA*fU
994	fU*fU*fU*fG*fA*fG*mC*mU*mG*mU*mU*mU*mU*mU*fU*fC*fA*f G*fG*fA
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997	fC*fA*fU*fU*fG*fU*mU*mU*mG*mA*mG*mC*mU*mG*fU*fU*fU*f U*fU*fU
998	fG*fC*fA*fU*fU*fG*mU*mU*mU*mG*mA*mG*mC*mU*fG*fU*fU*f U*fU*fU
999	fU*fG*fC*fA*fU*fU*mG*mU*mU*mU*mG*mA*mG*mC*fU*fG*fU*f U*fU*fU
1000	fC*fU*fG*fC*fA*fU*mU*mG*mU*mU*mU*mG*mA*mG*fC*fU*fG*f U*fU*fU
100	fU*fC*fU*fG*fC*fA*mU*mU*mG*mU*mU*mU*mG*mA*fG*fC*fU*f G*fU*fU

1	
1002	fC*fU*fC*fU*fG*fC*mA*mU*mU*mG*mU*mU*mU*mG*fA*fG*fC*f U*fG*fU
1003	fA*fC*fU*fC*fU*fG*mC*mA*mU*mU*mG*mU*mU*mU*fG*fA*fG*f C*fU*fG
1004	fU*fA*fC*fU*fC*fU*mG*mC*mA*mU*mU*mG*mU*mU*fU*fG*fA*f G*fC*fU
1005	fU*fU*fA*fC*fU*fC*mU*mG*mC*mA*mU*mU*mG*mU*fU*fU*fG*f A*fG*fC
1006	fC*fU*fU*fA*fC*fU*mC*mU*mG*mC*mA*mU*mU*mG*fU*fU*fU*f G*fA*fG
1007	fU*fC*fU*fU*fA*fC*mU*mC*mU*mG*mC*mA*mU*mU*fG*fU*fU*f U*fG*fA
1008	fA*fU*fC*fU*fU*fA*mC*mU*mC*mU*mG*mC*mA*mU*fU*fG*fU*f U*fU*fG
1009	fA*fA*fU*fC*fU*fU*mA*mC*mU*mC*mU*mG*mC*mA*fU*fU*fG*f U*fU*fU
1010	fC*fA*fA*fA*fU*fC*mU*mU*mA*mC*mU*mC*mU*mG*fC*fA*fU*f U*fG*fU
1011	fG*fA*fU*fA*fC*fA*mA*mA*mU*mC*mU*mU*mA*mC*fU*fC*fU*f G*fC*fA
1012	Geo*Geo*Geo*Teo*m5Ceo*A*G*C*T*G*C*C*A*A*T*Geo*m5Ceo* Teo*Aeo*Geo
1013	Mod030Geo*Geo*Geo*Teo*m5Ceo*A*G*C*T*G*C*C*A*A*T*Geo*m5Ceo*Teo*Aeo*Geo
1014	Mod031Geo*Geo*Geo*Teo*m5Ceo*A*G*C*T*G*C*C*A*A*T*Geo*m5Ceo*Teo*Aeo*Geo
1015	Mod032Geo*Geo*Geo*Teo*m5Ceo*A*G*C*T*G*C*C*A*A*T*Geo*m5Ceo*Teo*Aeo*Geo
1016	Mod033Geo*Geo*Geo*Teo*m5Ceo*A*G*C*T*G*C*C*A*A*T*Geo*m5Ceo*Teo*Aeo*Geo

[0119] 在表2中;“*”表示立体无规硫代磷酸酯连接;“*S”表示Sp硫代磷酸酯连接;“*R”表示Rp硫代磷酸酯连接;所有非标记连接都是天然磷酸连接;在碱基前的“m”表示2′-OMe;并且在碱基后面的“eo”表示2′-MOE。F表示氟化核苷。L001表示C6 PO(磷酸二酯)或PS(硫代磷酸酯)接头。Mod分别表示与核酸附接的修饰:月桂酸(Lauric)(在Mod013中)、肉豆蔻酸(Myristic)(在Mod014中)、棕榈酸(Palmitic)(在Mod005中)、硬脂酸(Stearic)(在Mod015中)、油酸(Oleic)(在Mod016中)、亚油酸(Linoleic)(在Mod017中)、α-亚麻酸(alpha-Linoleinc)(在Mod018中)、γ-亚麻酸(gamma-Linolenic)(在Mod019中)、DHA(在Mod006中)、喇叭藻酸(Turbinaric)(在Mod020中)、二亚油酸(Dilinoleic)(在Mod021中)、TriGlcNAc(在Mod024中)、三α甘露糖(TrialphaMannose)(在Mod026中)、单磺酰胺(MonoSulfonamide)(在Mod 027中)、三磺酰胺(TriSulfonamide)(在Mod029中)、月桂酸(Lauric)(在Mod030中)、肉豆蔻酸(Myristic)(在Mod031中)、棕榈酸(Palmitic)(在Mod032中)和硬脂酸(Stearic)(在Mod033中):月桂酸(Lauric acid)(对于Mod013)、肉豆蔻酸(Myristic acid)(对于Mod014)、棕榈酸(Palmitic acid)(对于Mod005)、硬脂酸(Stearic acid)(对于Mod015)、油酸(Oleic acid)(对于Mod016)、亚油酸(Linoleic acid)(对于Mod017)、α-亚麻酸(alpha-Linolenic acid)(对于Mod018)、γ-亚麻酸(gamma-Linolenic

acid)(对于Mod019)、二十二碳六烯酸(docosahexaenoic acid)(对于Mod006)、喇叭藻酸(Turbinaric acid)(对于Mod020)、二亚油基醇(alcohol for Dilinoleyl)(对于Mod021)、TriGlcNAc酸(acid for TriGlcNAc)(对于Mod024)、三α甘露糖酸(acid for TrialphaMannose)(对于Mod026)、单磺酰胺酸(acid for MonoSulfonamide)(对于Mod027)、三磺酰胺酸(acid for TriSulfonamide)(对于Mod029)、月桂醇(Lauryl alcohol)(对于Mod030)、肉豆蔻醇(Myristyl alcohol)(对于Mod031)、棕榈醇(Palmityl alcohol)(对于Mod032)和硬脂醇(Stearyl alcohol)(对于Mod033),通过酰胺基团、C6氨基接头、磷酸二酯连接(PO)和/或硫代磷酸酯连接(PS)缀合到寡核苷酸链。

[0120] 表3

SEQ ID NO.	序列5' -> 3
1017	GUGGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCACACUGAGCAAUGCcGUAGUCAG*C*A*A*U
1018	GUGGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCACGUACUGAGCAAUGCcGUAGUCAGCAA*U*C*U*U
1019	GGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCACUGAGCAAUGCcGUAGUCAG*C*A*A*U
1020	GGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCGUACUGAGCAAUGCcGUAGUCAGCAA*U*C*U*U
1021	cgcgcgttttcgcgcgGCUGAACCACUGCAC
1022	cgcgcgttttcgcgcgGAGAUACUCACAAUU
1023	cgcgcgttttcgcgcgCGUUGACCUCCACUC
1024	rGrGrArArUrArGrUrArUrArArCrArArUrArUrgrcrurararArUrGrUrUrGrUrUrArUrArGrUrArUrCrCrCmC*mA*mG*mU*mCmCmCmUmUmUmCrUrCrGmUmCmGmAmUmGmG*mU*mC*mA*mG
1025	mG*mG*mA*mA*mU*mA*mG*mU*mA*mU*mA*mA*mC*mA*mA*mU*mA*mU*mG*mC*mU*mA*mA*mA*mU*mG*mU*mU*mG*mU*mU*mA*mU*mA*mG*mU*mA*mU*mC*mC*mCmC*mA*mG*mU*mCmCmCmUmUmUmCrUrCrGmUmCmGmAmUmGmG*mU*mC*mA*mG
1026	未经修饰的GUGUUGGCCAUGGAACAUAUAACAAUAUgcuaaAUGUUGUUAUA
1027	2'OMe- PS UAUAACAAUAUgcuaaAUGUUGUUAUAGUGUUGGCCAUGGAACA
1028	2'Ome- PS GUGUUGGCCAUGGAACAUAUAACAAUAUgcuaaAUGUUGUUAUA
1029	未经修饰的GUGUUGGCCAUGGAACAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAU
1030	未经修饰的GGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCGUGUUGGCCAUGGAACA
1031	未经修饰的GUGUUGGCCAUGGAACAGGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCC
1032	2'OMe-PSGGAAUAGUAUAACAAUAUgcuaaAUGUUGUUAUAGUAUCCCGUGUUGGCCAUGGAACA

[0121] 在表3中;“R”表示无修饰;“m”表示2′O-Me,“PS”表示硫代磷酸酯连接,并且“*”表示硫代磷酸酯连接。

[0122] 表4

SEQ ID NO.	序列5' -> 3	碱基修饰
1033	u*c*a*g*ucccuuucUCGucgauggucagc*a*c*a*g	
1034	u*c*a*g*ucccuuucuCGucgauggucagc*a*c*a*g	
1035	u*c*a*g*ucccuuucuCGUcgauggucagc*a*c*a*g	
1036	u*c*a*g*ucccuuucucgucgauggucagc*a*c*a*g	

1037	u*c*a*g*ucccuuucU*CGucgauggucagc*a*c*a*g	
1038	u*c*a*g*ucccuuuc[TCG]ucgauggucagc*a*c*a*g	
1039	u*c*a*g*ucccuuuc(ucg)ucgauggucagc*a*c*a*g	
1040	u*c*a*g*ucccuuuc{U}C{G}ucgauggucagc*a*c*a*g	
1041	u*c*a*g*ucccuuuc{U}X{G}ucgauggucagc*a*c*a*g	X：5-甲基胞苷
1042	u*c*a*g*ucccuuucUCZucgauggucagc*a*c*a*g	Z：肌苷
1043	u*c*a*g*ucccuuucUXZucgauggucagc*a*c*a*g	X：5-甲基胞苷， Z：肌苷
1044	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-甲基胞苷， Z：肌苷
1045	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-甲基胞苷， Z：肌苷
1046	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：5-甲基尿苷，X：5-甲基胞苷， Z：肌苷
1047	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：噻吩并尿苷， X：5-甲基胞苷， Z：肌苷
1048	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：2,6-二氨基嘌呤， X：5-甲基胞苷， Z：肌苷
1049	u*c*a*g*ucccuuucUXZucgauggucagc*a*c*a*g	X：吡咯并胞苷，Z：肌苷
1050	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：吡咯并胞苷，Z：肌苷
1051	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：噻吩并尿苷， X：吡咯并胞苷，Z：肌苷
1052	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷，X：5-甲基胞苷， Z：噻吩并鸟苷
1053	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：吡咯并胞苷，Z：噻吩并鸟苷
1054	u*c*a*g*ucccuuucU'C'Gvucgauggucagc*a*c*a*g	
1055	u*c*a*g*ucccuuucU"C"G"ucgauggucagc*a*c*a*g	
1056	u*c*a*g*ucccuuucUACAGAucgauggucagc*a*c*a*g	
1057	u*c*a*g*ucccuuucU#C#G#ucgauggucagc*a*c*a*g	
1058	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：5-甲氧基尿苷， X：5-甲基胞苷， Z：肌苷
1059	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：二氢尿苷，X：5-甲基胞苷， Z：肌苷
1060	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-羟基甲基胞苷， Z：肌苷
1061	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷，

		X：5-甲基胞苷， Z：7-甲基鸟苷
1062	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-甲基胞苷， Z：7-脱氮鸟苷
1063	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-甲基胞苷， Z：8-氮杂-7-脱氮鸟苷
1064	u*c*a*g*ucccuuucYXZucgauggucagc*a*c*a*g	Y：假尿苷， X：5-甲基胞苷， Z：7-氨基甲基-7-脱氮鸟苷
1065	c*c*u*g*cgacacuucggcCCAgagcugcucc*u*c*a*u	
1066	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：7-甲基腺苷
1067	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：8-甲基腺苷
1068	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：3-脱氮腺苷
1069	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：7-脱氮腺苷
1070	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：8-叠氮基腺苷
1071	c*c*u*g*cgacacuucggcXXYgagcugcucc*u*c*a*u	X：5-甲基胞苷， Y：肌苷
1072	c*a*u*u*gaagaagauaagagaaaguacugagaaguguuggCCAuggaacag*g*u*a*g	
1073	c*a*u*u*gaagaagauaagagaaaguacugagaaguguuggCCZuggaacag*g*u*a*g	Z：2-氨基嘌呤
1074	c*a*u*u*gaagaagauaagagaaaguacugagaaguguugg[C]C[A]uggaacag*g*u*a*g	
1075	g*a*c*u*gagguacuccuuagagaaaggug[CCA]cuucuuggcaa*a*g*g*a	
1076	g*u*a*g*gcaugggaggaaaaggugCCAcuucuuggcaa*a*g*g*a	
1077	c*u*g*u*ccaacacagccccagccuuugagaccucugcCCAgaguuguu*c*u*c*c	
1078	c*u*g*u*ccaacacagccccagccuuugagaccucuguCC[A]gaguuguu*c*u*c*c idT	
1079	c*u*g*u*ccaacacagccccagccuuugagaccucugucC[A]gaguuguu*c*u*c*c idT	
1080	c*u*g*u*ccaacacagccccagccuuugagaccucuguXC[A]gaguuguu*c*u*c*c idT	X：5-甲基胞苷
1081	c*u*g*u*ccaacacagccccagccuuugagaccucugucC[X]gaguuguu*c*u*c*c idT	X：脱氧2-氨基嘌呤
1082	c*u*g*u*ccaacacagccccagccuuugagaccucugucC[A]gaauuguu*c*u*c*c idT	
1083	c*u*g*u*ccaacacagccccagccuuugagaccucugucC[AGA]guuguu*c*u*c*c idT	
1084	c*u*g*u*ccaacacagccccagccuuugagaccucuguc*C*[A]*G*A*guuguu*c*u*c*c idT	
1085	c*u*g*u*ccaacacagccccagccuuugagaccucuguc*C*[A]*gaguuguu*c*u*c*c idT	
1086	c*u*g*u*ccaacacagccccagccuuugagaccucug*u*C*C*A*g*aguuguu*c*u*c*c idT	
1087	c*u*g*u*ccaacacagccccagccuuugagaccucuguc(caga)guuguu*c*u*c*c	
1088	c*u*g*u*ccaacacagccccagccuuugagaccucugu[CCA]gaguuguu*c*u*c*c	
1089	c*u*g*u*c*c*a*a*c*a*c*a*gccccagccuuugagaccucugu[CCA]gaguuguu*c*u*c*c	
1090	c*u*g*u*ccaacacagccc*c*a*g*c*c*u*u*u*g*a*gaccucugu[CCA]gaguuguu*c*u*c*c	
1091	c*u*g*u*c*c*a*a*c*a*c*a*gccc*c*a*g*c*c*u*u*u*g*a*gaccucugu[CCA]gaguuguu*c*u*c*c	
1092	c*u*g*u*ccaacacagccccagccuuugagaccucuguc[CA]gaguuguu*c*u*c*c	
1093	c*u*g*u*ccaacacagccccagccuuugagaccucugu[C)(c)[A]gaguuguu*c*u*c*c	
1094	c*u*g*u*ccaacacagccccagccuuugagaccucugu[C*C*A*]gaguuguu*c*u*c*c	

1095	c*u*g*u*ccaacacagccccagccuuugagaccucugu[CCA]gaguuguu*c*u*c*c idT
1096	a*c*a*c*a*G*cuc*c*a*g*c*c*u*u*u*G*A*gaccu*c*u*g*cCCAGaguu*g*u*u*c*u*c*c
1097	c*a*c*a*gccccagccuuugagaccucugu[CCA]gaguuguu*c*u*c*c
1098	c*a*c*a*g*c*c*c*c*a*g*c*c*u*u*u*g*agaccucugu[CCA]gaguuguu*c*u*c*c
1099	c*a*c*a*gccc*c*a*g*c*c*u*u*u*g*a*gaccucugcc*[C*A]*gaauuguu*c*u*c*c
1100	g*a*c*u*gagguacuccauagggaaaggcacC[A]cuucuuggcaa*a*g*g*a
1101	g*a*c*u*gagguacuccauagggaaaggcacC[ACU]ucuuggcaa*a*g*g*a
1102	g*a*c*u*gagguacuccauagggaaaggcacC[A]<cu>ucuuggcaa*a*g*g*a

[0123] 在表4中，具体的YXZ碱基修饰在第三列中提及。小写字母核苷酸是RNA且2'-O-甲基修饰的。大写字母核苷酸是RNA，除了加括号的[NNN]核苷酸是DNA。描绘为(nnn)的小写字母核苷酸是2'-氟RNA修饰的核苷酸。描述为<nnn>的小写字母核苷酸是2'-NH2 RNA修饰的核苷酸。描绘为{N}的核苷酸是解锁核酸(UNA)。“idT”指示3'反向T修饰，其增强对降解的抗性并且还阻止AON的3'末端在PCR扩增期间延伸。“*”表示硫代磷酸酯连接；“'”＝3'-亚甲基膦酸酯连接；“″”表示5'-亚甲基膦酸酯连接；“Λ”表示3'-氨基磷酸酯连接；并且“#”表示2'-5'磷酸二酯连接。

[0124] 表5

SEQ ID NO.	序列5' -> 3
1103	g*a*c*u*gagguacuccuuagagaaaggugCCAcuucuuggcaa*a*g*g*a-
1104	mC*mA*mU*mU*mGmAmAmGmAmAmGmAmUmAmAmGmAmGmAmAmAmGmUmAmC mUmGmAmGmAmAmGmUmGmUmUmGmGCCAmUmGmGmAmAmCmAmG*mG*mU*mA *mG
1105	cauugaagaa gauaagagaa aguacugaga aguguuggcc auggaacagg uag

[0125] 在表5中；RNA用A、C、G或U描绘；DNA用dA、dC、dG或dT描绘；2'-Ome用mA、mC、mG或mU描绘；PMO(二氨基磷酸酯吗啉代寡聚物)用pA、pC、pG或pT描绘；并且硫代磷酸酯用“*”描绘。

[0126] 表6

SEQ ID NO.	序列5' -> 3
1106	GUGGAUAGUAUAACAAUAUGCUMAAUGUUGUUAUAGUAUCCCAC
1107	GUGGASSSGSASASCAAUAUGCUMAAUGUUGSUSUSGSSSCCCAC
1108	GUGGAASAGSASAACAAUAUGCUMAAUGUUGUUSUSGUSUCCCAC
1109	GUGGASASUAUAACAAUAUGCUMAAUGUUGUUAUAGYAYCCCAC
1110	GUGGASSSGSSSSSSSSUAUGCUMAAUGSSSSSSSSGSSSCCCAC
1111	GUGGAASSGSASASCAAUAUGCUMAAUGUUGSUSUSGSSU CCCAC
1112	GUGGSAUAGUAUAACAAUAUGCUMAAUGUUGUUAUAGUAUCCCAC
1113	ACGCAACCAAGUCAUA
1114	GCAAUGCCAUCACCUC
1115	AGGGGUCCACAUGGCA
1116	GGCUCCCCAGGCCCCU
1117	UGCCGUCCACCAGGAU
1118	CAGAUUCCAGGUGGGA
1119	UCCCUGCCAGAAUAGA
1120	CUCCGCCCACCAAAUG
1121	CCCAAACCACAACAGA
1122	ACCCACCCACCCAGGU
1123	CUGCCGCCAGCUGGAU

1124	AGGGAACCAGACAGUU

[0127] 在表6中；“S”可以是G或C，“Y”可以是C或T；并且“M”可以是A或C。

[0128] 表7

SEQ ID NO.	序列5’->3
1125	U*U*C*A*C*U*UcAG*U*G*U*As*Us*Gs*Cs*C*
1126	U*U*C*A*C*U*UcAG*U*G*U*As*Us*Gs*Cs*C*
1127	A*C*C*U*C*C*AcUC*A*G*U*Gs*Us*Gs*As*U*
1128	U*U*U*C*C*U*CcAC*U*G*U*Us*Gs*Cs*As*A*
1129	U*G*U*G*U*A*UcUU*G*C*U*Gs*Us*Gs*As*G*
1130	G*A*G*G*U*C*CcUG*G*G*G*Gs*Cs*Gs*Cs*U*
1131	G*A*U*C*U*U*CcUG*A*U*G*Gs*Cs*Cs*As*C*
1132	A*G*C*C*A*C*AcAC*U*C*C*Gs*Us*Cs*As*G*
1133	G*A*U*U*U*U*CcUG*A*U*A*Gs*Cs*Us*As*C*
1134	G*G*C*C*A*C*AcAU*U*C*U*Gs*Us*Cs*As*G*
1135	G*A*U*C*U*U*CcUG*A*U*G*Gs*Cs*Cs*As*C*
1136	G*G*C*C*A*C*AcAC*U*C*C*Gs*Us*Cs*As*G*
1137	G*A*U*U*U*U*CcUG*A*U*A*Gs*Cs*As*As*C*
1138	G*G*C*U*A*C*GcAC*U*C*U*Gs*Us*Cs*As*A*
1139	A*G*G*C*C*G*CcGU*C*G*U*Gs*Gs*Cs*Gs*G*
1140	C*C*G*C*U*C*CcUCcU C*A*G*C*Cs*Cs*Gs*Us*C*
1141	A*C*G*C*C*A*CcAG*C*U*C*Cs*As*As*Cs*U*
1142	G*U*C*U*C*A*CcAA*U*U*G*Cs*Us*Cs*Us*C*
1143	G*A*A*A*U*A*CcAU*C*A*G*As*Us*Us*Us*G*
1144	A*A*U*U*A*G*CcUU*C*U*G*Gs*Cs*Cs*As*U*
1145	G*A*U*C*A*G*CcUC*C*U*G*Gs*Cs*Cs*As*U*
1146	G*A*U*C*A*G*CcUU*C*U*G*Gs*Cs*Cs*As*U*
1147	G*A*U*C*A*G*CcUU*C*U*G*Gs*Cs*Cs*As*U*
1148	*A*C*U*G*C*CcAG*G*C*A*Us*Cs*As*Gs*C*
1149	C*A*C*U*G*C*CcGG*G*C*A*Us*Cs*As*Gs*C*
1150	U*C*C*G*C*C*CcGA*U*C*C*As*Cs*Gs*As*U*
1151	C*C*U*U*U*C*UcGU*C*G*A*Us*Gs*Gs*Us*C*
1152	C*C*U*U*U*C*U*cGU*C*G*A*Us*Gs*Gs*Us*C*
1153	C*U*U*G*A*U*AcAU*C*C*A*Gs*Us*Us*Cs*C*
1154	U*U*U*C*A*G*GcAU*U*U*C*Cs*Us*Cs*Cs*G*
1155	C*U*U*C*A*G*GcAU*G*G*G*Gs*Cs*As*Gs*C*
1156	A*G*G*A*A*C*AcAA*C*C*U*Us*Us*Gs*Us*C*
1157	U*U*U*C*A*C*AcAU*C*C*A*Us*Cs*As*As*C*
1158	C*U*U*C*A*C*GcAU*C*C*A*Us*Cs*As*As*C*
1159	U*G*G*G*A*C*AcAA*C*C*C*Cs*Us*Gs*Cs*C*

1160	C*G*A*C*U*C*CcUC*U*G*G*As*Us*Gs*Us*U*
1161	C*G*A*C*U*C*UcUC*U*G*G*As*Us*Gs*Us*U*

[0129] 在表7中;N_a和N_b可以形成错配,在一些情况下,其中N_a是腺苷并且N_b是胞苷;N_c和N_d形成错配,在一些情况下,其中N_c和N_d是鸟苷;“Gs”是包含硫代磷酸酯基团的鸟苷;“Gs1”是包含硫代磷酸酯基团的LNA鸟苷;并且其中星号(*)指示在2碳原子处的核苷酸的修饰,在一些情况下用2'-氢(2'-脱氧)、2'-O-甲基、2'-O-甲氧基乙基或2'-氟修饰;“A”是腺苷核苷酸或其变体,在一些情况下是腺苷核糖核苷酸、腺苷脱氧核苷酸、经修饰的腺苷核糖核苷酸或经修饰的腺苷脱氧核苷酸;“C”是胞苷核苷酸或其变体,例如胞苷核糖核苷酸、胞苷脱氧核苷酸、经修饰的胞苷核糖核苷酸或经修饰的胞苷脱氧核苷酸;“G”是鸟苷核苷酸或其变体,例如鸟苷核糖核苷酸、鸟苷脱氧核苷酸、经修饰的鸟苷核糖核苷酸或经修饰的鸟苷脱氧核苷酸;“U”是尿苷核苷酸或其变体,例如尿苷核糖核苷酸、尿苷脱氧核苷酸、经修饰的尿苷核糖核苷酸或经修饰的尿苷脱氧核苷酸;“A”、“C”、“G”或“U”是核苷酸,在一些情况下是如上定义的核糖核苷酸或脱氧核苷酸,其进一步包含硫代磷酸酯基团;其中星号(*)指示在2'碳原子处的前述核苷酸的化学修饰,例如用2'-氢(2'-脱氧)、2'-O-甲基、2'-O-甲氧基乙基或2'-氟修饰;并且其中小写字母c指示对应于靶序列中待编辑的核苷酸(例如腺苷或胞苷,例如腺苷)的位置,并且其中c表示胞苷核苷酸或其变体、脱氧胞苷核苷酸或其变体、或无碱基位点。

[0130] 表8

SEQ ID NO.	序列5' -> 3
1162	(GUGGAAUAGUAUAACAAUAUGCUAAAUGUUGUUAUAGUAUCCCACGUGCAGCCAGCCGUCCUCUAGAGGGCCCUGAAGAGGGCCC)
1163	(GUGGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCCACGUGCAGCCAGCCGUCCUCUAGAGGGCCCUGAAGAGGGCCC)
1164	(GUGGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACCACGUGCAGCCAGCCGUCCUCUAGAGGGCCCUGAAGAGGGCCC)
1165	[GCAAUG](CCA)[UCAC][C*][U][C][C*][C]
1166	(GGUGAAUAGUAUAACAAUAUGCUAAAUGUUGUUAUAGUAUCCACC)[GCAAUG](CCA)[UCAC][C][U*][C*][C*][C]
1167	(GGUGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCACC)[GCAAUG](CCA)[UCAC][C][U*][C*][C*][C]
1168	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACC)[GCAAUG](CCA)[UCAC][C*][U*][C][C][C]
1169	[AGGGGU](CCA)[CAUG][G][C*][A][A][C]
1170	(GGUGAAUAGUAUAACAAUAUGCUAAAUGUUGUUAUAGUAUCCACC)[AGGGGU](CCA)[CAUG][G*][C*][A][A][C]
1171	(GGUGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCACC)[AGGGGU](CCA)[CAUG][G*][C*][A*][A*][C]
1172	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACC)[AGGGGU](CCA)[CAUG][G*][C*][A*][A*][C]
1173	[G*][G*][U](G)[U][C](GAGAAGAGGAGAA)[C](AA)[U]
1174	[GGGGUG](CCA)[AGCA][G*][U*][U*][G*][G]
1175	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACC)[GGGGUG](CCA)[AGCA][G*][U*][U*][G][G]
1176	[GGGGUG](CCA)[AGCA][G][U*][U*][G*][G]
1177	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACC)[GUUUUU](CCA)[GACG][G*][C*][A*][G*][G]
1178	[G]*[G]*[U](G)[U][C](GAGAAGAGGAGAA)[C](AA)[U]
1179	[G]*[G]*[U](GUCGAGAAGAGGAGAACAAUAUGCUA
1180	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACC)[CCUUUC](UCG)[UCGA][U*][G*][G*][U*][C]
1181	(CAUGGCCCCAGCAGCUUCAGUC)[C]{C}[UUUC](UCG)
1182	[G*][G*][U](G)[U][C](GAGAAGAGGAGAA)[C](AA)[U](A)[U](G)[C][U](AAA)[U](G)[U][U](G)[U][U][C][U][U][C][C][U][C}[GACACCCAUGGCCCCAGCAGCUUCAGUC)[C]{C}[UUUC](UCG)[UCGA]{T*}[G*][G*]{T*}[C]
1183	[G*][G*][U](G)[U][C](GAGAAGAGGAGAA)[C](AA)[U](A)[U](G)[C][U](AAA)[U](G)[U][U](G)[U][U][C][U][C](G)[U][C][U][C][C][U][C](GACACCCAUGGCCCCAGCAGCUUCAGUC)[C]{C}[UUUCU](CG)[UCGA]{T*}[G*][G*]{T*}[C]
1184	[G*][G*][U](G)[U][C](GAGAAGAGGAGAA)[C](AA)[U]
1185	(GGUGAAUAGUAUAACAAUAUGCUAAAUGUUGUUAUAGUAUCCACCAGGGGUCCACAUGGCAAC)

1186	(GGUGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCACCAGGGGUCCACAUGGCAAC)
1187	(GGUGUCGAGAAGAGGAGAACAAUAUGCUAAAUGUUGUUCUCGUCUCCUCGACACCAGGGGUCCACAUGGCAAC)
1188	(GGACCAACUGCUUGGCACCCCUGGCCAAGGUCAUCCAUGACAACUUUGGUAUCGUGGAAGGACC)
1189	(GGGAACUGGAUCUAUCAAGACUGAGUUGAUUUCUGUGUCUGAAGUGUAAGUGAACACAGAA)
1190	(GGACCATCGACGAGAAAGGGACTGAAGCTGCTGGGGCCATGTTTTTAGAGGCCATACCCAT)

[0131] 在表8中;括号中的碱基例如“(N)”描绘了RNA碱基;方括号中的字母例如“[N]”描绘了2'-OMe RNA碱基;“*”描绘了硫代磷酸酯连接;大括号中的碱基例如“{N}”描绘了LNA碱基;“c”是在对应于靶序列中待编辑的核苷酸(在一些情况下是例如腺苷或胞苷,在一些情况下是例如腺苷)的位置处的胞苷核苷酸或其变体、脱氧胞苷核苷酸或其变体、或无碱基位点。

[0132] 表9

SEQ ID NO.	序列5' -> 3
1191	*UsCsAUUAAACG**CCA**GAGUCsCsGsGsA*
1192	*UsCsUGAAUAAU**CCA**GGAAAsAsGsCsA*
1193	*UsAsUAGGGGUG**CCA**AGCAGsUsUsGsG*
1194	*UsAsUGGUUUUU**CCA**GACGGsCsAsGsG*
1195	*GsGsUGCAGAUU**CCA**GGUGGsGsAsCsG*
1196	*AsCsAGACUUGG**CCA**CUGAGsUsGsGsG*
1197	*UsAsUGUGUCGG**CCA**CGGAAsCsAsGsG*
1198	*AsAsUAAGGGGU**CCA**CAUGGsCsAsAsC*
1199	*UsCsGAGCAAUG**CCA**UCACCsUsCsCsC*
1200	*UsAsUUUCCCUG**CCA**GAAUAsGsAsUsG*
1201	*GsAsUGCUCCAA**CCA**CCACAsAsGsUsU*
1202	*CsGsUCUCUUGC**CCA**CGCCAsCsCsAsG*
1203	*GsUsCUCUUGAU**ACA**UCCAGsUsUsCsC*
1204	*CsAsCAUGGGAU**UCC**CAUUGsAsUsGsA*
1205	*UsAsUCGACCAA**ACC**CGUUGsAsCsUsC*
1206	*CsAsCGUCAUGA**GCC**CUUCCsAsCsGsA*
1207	*AsAsCGAGGGAU**CCC**GCUCCsUsGsGsA*
1208	*GsAsAGAGGCUG**UCG**UCAUAsCsUsUsC*
1209	*CsAsAGAGGUCA**ACG**AAGGGsGsUsCsA*
1210	*AsAsCGCCAGGG**GCG**CUAAGsCsAsGsU*
1211	*UsAsCGCAUGGA**CCG**UGGUCsAsUsGsA*
1212	*UsAsCAUGACCC**UCU**UGGCUsCsCsCsC*
1213	*GsAsCUAGCCAA**ACU**CGUUGsUsCsAsU*
1214	*AsGsUCGCCACA**GCU**UCCCGsGsAsGsG*
1215	*UsGsUAUAUCCA**CCU**UACCAsGsAsGsU*
1216	*AsGsGAGGGGUC**UCA**CUCCUsUsGsGsA*
1217	*CsUsAGGCAACA**ACA**UCCACsUsUsUsA*
1218	*CsCsGAGCGCCA**GCA**GAGGCsAsGsGsG*
1219	*UsAsUGGUUUUU**CCA**GACGGsCsAsGsG*
1220	*GsAsAGAGGCUGU**CG**UCAUAsCsUsUsC*
1221	*GsAsAGAGGCUGU**CG**UCAUAsCsUsUsC*
1222	*UsAsCAUGACCCU**CU** UGGCUsCsCsCsC*

1223	*UsAsCAUGACCCU**CU** UGGCUsCsCsCsC*
1224	*AsGsUCGCCACA**GC**UUCCCGsGsAsGsG*
1225	*AsGsUCGCCACA**GC**UUCCCGsGsAsGsG*
1226	*AsGsGAGGGGUCU**CA**CUCCUsUsGsGsA*
1227	*AsGsGAGGGGUC**UCA**CUCCUsUsGsGsA*

[0133] 在表9中;以粗体突出显示的核苷酸是未经修饰的并且与三联体相对放置,其中靶腺苷位于中间。以斜体突出显示的核苷酸用2'-O-甲基化修饰,2'-氟化核苷酸被灰视。主链含有末端硫代磷酸酯连接,如用"s"指示。5'末端的前三个核苷酸与mRNA底物不互补,而是用作gRNA和SNAP标签之间的接头序列。

[0134] 表10

SEQ ID NO.	序列5' -> 3
1228	TAATCTAGGAAAACTGAGAACAGAGGCCCTGAAAAAGGGCCAAA TTCTTCCACCC

[0135] 表11

SEQ ID NO.	序列5' -> 3
1229	AAACCGAGGGAUCAUAGGGGACUGAAUCCACCAUUCUUCUCCCAAUCCCUGCAA CUCCUUCUUCCCCUGC
1230	UGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGG CGCUGCCUCCUCCGCC
1231	UCUCAGUCCAAUGUAUGGUCCGAGCACAAGCUCUAAUCAAAGUCCGCGGGUGUA GACCGGUUGCCAUAGGA
1232	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1233	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCAAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1234	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCUAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1235	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCGAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1236	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUGCAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1237	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUUCAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1238	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUACAGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1239	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCUGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1240	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUGCUGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1241	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUUCUGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1242	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUACUGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1243	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCCGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1244	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUGCCGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1245	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUUCCGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1246	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUACCGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1247	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCGGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG

1248	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUGCUGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1249	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUUCGGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1250	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUACGGCAUCGCGAGCAGGCGC UGCCUCCUCCGCCGCUG
1251	ACUGGCAGAGCCCUCCAGCAUCGCGAGCAGG
1252	GCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCC
1253	ACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCU GCCUCCUCCGCCGCUG
1254	ACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCG AGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGC
1255	GCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUG GCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCC GCCGCUGCCUCCUCCGCCCUGCUCGCCGUCCAGCUCGACCAGGAUGGGCACCACC CCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGC AGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCCUGCAG CUUGUACA
1256	UCGCCGUCCAGCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCU UGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCU GCCUCCUCCGCCGCUGCCUCCUCCGCCCUGCAGCUUGUACA
1257	GCCGUUUACGUCGCCGUCCAGCUCGACCAGGAUGGGCACCACCCCGGUGAACAG CUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCU CCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCU CGUCCAU
1258	UGAACUUGUGGCCGUUUACGUCGCCGUCCAGCUCGACCAGGAUGGGCACCACCC CGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGC AGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCCUGCAG CUUGUACAGCUCGUCCAUGCCGCCGGUG
1259	CCGGACACGCUGAACUUGUGGCCGUUUACGUCGCCGUCCAGCUCGACCAGGAUG GGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGC AUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCC GCCCUGCAGCUUGUACAGCUCGUCCAUGCCGCCGGUGGAGUGGCGGC
1260	GCGACCGGGGAUCUCCACAGAUUCUUCCGGC
1261	GCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCU
1262	CCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUG UAUACCUUCUGCUGCCU
1263	GUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUC UUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGC
1264	CACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUC CACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGCUGCCUCCUC C
1265	CCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGA CCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGC CGCUGCCUCCUCCGCCGCUGCCU
1266	UCCAGCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCA CGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGC CUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCCU
1267	CGGCGACGUAUCCAGCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUC GCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUA CCUUCUGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCCUGC AGCUUGUA
1268	UGUGGCCGUUUACGUCGCCGUCCAGCUCGACCAGGAUGGGCACCACCCCGGUGA ACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCC GGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUCC UCCGCCCUGCAGCUUGUACAGCUCGUCC
1269	ACGCUGAACUUGUGGCCGUUUACGUCGCCGUCCAGCUCGACCAGGAUGGGCACC ACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCAC

	AGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGCUGCCUCCUCCGC CGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCAUGCCGCCGG
1270	CAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCUGCCUC CUCCGCCCUGCAGCUU
1271	CCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCGCCGCU GCCUCCUCCGCCCUGC
1272	CAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCUCCUCCG CCGCUGCCUCCUCCGC
1273	ACUGGCAGAGCCCUCCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCUGCCU CCUCCGCCGCUGCCUCC
1274	UGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCGCU GCCUCCUCCGCCGCUG
1275	GCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUCCUCCG CCGCUGCCUCCUCCGC
1276	UCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGGCGCUGCCUC CUCCGCCGCUGCCUCC
1277	GGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCA GGCGCUGCCUCCUCCGC
1278	ACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCG AGCAGGCGCUGCCUCC
1279	GCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCA UCGCGAGCAGGCGCUG
1280	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC CAGCAUCGCGAGCAGG
1281	ACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGA GCCCUCCAGCAUCGCGA
1282	GCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUG GCAGAGCCCUCCAGCAU
1283	GUCCAGCUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUC ACUGGCAGAGCCCUCC
1284	CACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGCUGCCUCCUC CGCCGCUGCCUCCUCC
1285	AUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCCGCUGCC UCCUCCGCCGCUGCCU
1286	CGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCUCCGCC GCUGCCUCCUCCGCCGC
1287	GCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGCCUCCU CCGCCGCUGCCUCCUCC
1288	CGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCUGCUGC CUCCUCCGCCGCUGCCU
1289	GCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUACCUUCU GCUGCCUCCUCCGCCGC
1290	CCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCGGCGUGUAUAC CUUCUGCUGCCUCCUCC
1291	CAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUCUUCCG GCGUGUAUACCUUCUGC
1292	GUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACAGAUUC UUCCGGCGUGUAUACCU
1293	CCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUCCACA GAUUCUUCCGGCGUGUA
1294	CACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGGGAUCUC CACAGAUUCUUCCGGC
1295	AUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGACCGGG GAUCUCCACAGAUUCUU
1296	CCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGUGGCGA CCGGGGAUCUCCACAGA
1297	CUCGACCAGGAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACGGU GGCGACCGGGGAUCUCC

1298	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC CAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1299	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1300	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UCAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1301	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU ACAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1302	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC CGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1303	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GCGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1304	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UCGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1305	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU ACGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1306	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC CUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1307	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GCUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1308	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU ACUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1309	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UCUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1310	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC CCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1311	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GCCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1312	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UCCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1313	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU ACCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1314	UACCGCUACAGCCACGCUGAUUUCAGCUAUACCUGCCCGGUAUAAAGGGACGUU CACACCGCGAUGUUCUCUGCUGGGGAAUUGCGCGAUAUUCAGGAUUAAAAGAAG UGC
1315	ACUACAGUUGCUCCGAUAUUUAGGCUACGUCAAUAGGCACUAACUUAUUGGCGC UGGUGAACGGACUUCCUCUCGAGUACCAGAAGAUGACUACAAAACUCCUUUCCA UUGCGAGUAUCGGAGUCUGGCUCAGUUUGGCCAGGGAGGCACU
1316	CGGAAGAGGGUGGGGCCGCGGUGGCCAGGGAGCCGGCGCCGCCACGCGCGG
1317	CAGCUGAGGCCGGAAGAGGGUGGGGCCGCGGUGGCCAGGGAGCCGGCGCCGCCA CGCGCGGGUGGGGGGGA
1318	GGAGGCGAAAGCAGCCCGGACAGCUGAGGCCGGAAGAGGGUGGGGCCGCGGUGG

	CCAGGGAGCCGGCGCCGCCACGCGCGGGUGGGGGGGACUGGGGUUGCUCGCGGGCUC
1319	GAGGCGCAGCAUCCACAGGCGGAGGCGAAAGCAGCCCGGACAGCUGAGGCCGGAAGAGGGUGGGGCCGCGGUGGCCAGGGAGCCGGCGCCGCCACGCGCGGGUGGGGGGGACUGGGGUUGCUCGCGGGCUCCGGGCGGGCGGCGGGCGCCG
1320	UCUUGCCUACGCCACCAGCUCCAACCACCACAAGUUUAUAUUCAGUCAUUU
1321	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUUGCCUACGCCACCAGCUCCAACCACCACAAGUUUAUAUUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGGAGC
1322	AUCAUAUUCGUCCACAAAAUGAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUUGCCUACGCCACCAGCUCCAACCACCACAAGUUUAUAUUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGGAGCCGCUGAGCCUCUGGCCCCGC
1323	UCGGCAUGGUAUGAAGUACUUCGUCCAGGAGCUGGAGGGCCCGGUGUAAGU
1324	GGGUCUGCAAUCGGCAUGGUAUGAAGUACUUCGUCCAGGAGCUGGAGGGCCCGGUGUAAGUGAAUUUCAAU
1325	GACCUCAGUCUAAAGGUUGUGGGUCUGCAAUCGGCAUGGUAUGAAGUACUUCGUCCAGGAGCUGGAGGGCCCGGUGUAAGUGAAUUUCAAUCCAGCAAGGUGUUUCUUUGA
1326	UAAGGGCCCCAACGGUAAAAGACCUCAGUCUAAAGGUUGUGGGUCUGCAAUCGGCAUGGUAUGAAGUACUUCGUCCAGGAGCUGGAGGGCCCGGUGUAAGUGAAUUUCAAUCCAGCAAGGUGUUUCUUUGAUGCUCUGUCUUGGGUAAUCC
1327	UGGGGGGUUCGGCUGCCGACAUCAGCAAUUGCUCUGCCACCAUCUCAGCCC
1328	AGCAGGGCCGUGGGGGGUUCGGCUGCCGACAUCAGCAAUUGCUCUGCCACCAUCUCAGCCCAUCCUCCGAA
1329	AGUAGAAGGCCAAGAGCCACAGCAGGGCCGUGGGGGGUUCGGCUGCCGACAUCAGCAAUUGCUCUGCCACCAUCUCAGCCCAUCCUCCGAAGUGAAUGAACAGGAACCAGC
1330	CCUCCCAUCACGGGGGCCGUAGUAGAAGGCCAAGAGCCACAGCAGGGCCGUGGGGGGGUUCGGCUGCCGACAUCAGCAAUUGCUCUGCCACCAUCUCAGCCCAUCCUCCGAAGUGAAUGAACAGGAACCAGCUCUCAAAGGGACCUCCGCAG
1331	GCCAAACACCACATGCTTGCCATCTAGCCAGGCTGTCTTGACTGTCGTGATGAAGAACTGGGAGCCGTTGGTGTCCTTGCCTGCGTTGGCCATGCTCACCCAGCCAGGCCCGTAGTGCTTCAGTTTGAAGTTCTCATCGGGGAAGCGCTCA
1332	GGGAGTGGGTCCGCTCCACCAGATGCCAGCACCGGGGCCAGTGCAGCTCAGAGCCCTGTGGCGGACTACAGGGCCCGCACAGACGGTCACTCAAAGAAAGATGTCCCTGTGCCCTACTCCTTGGCGATGGCAAAGGGCTTCTCCACCTCGA
1333	TGCATTTTGTAAAATAGATACTAGCAGATTGTCCCAAGATGTGTACAGCTCATTCTCACAGCCCAGCGAGGGCACCTACTCCACAAATGCGTGGCCACAGGTCATCACCTGTCCTGTGGCCCTGGCGAGCCTGATCCCTCACGCCGGGCAC
1334	GCTCATTCTCACAGCCCAGCGAGGGCACTTACTCCACAAATGCGTGGCCACAGGTCATCACCTGTCCTGTGGCCCCGGCGAGCCTGATCCCTCACGCCGGGCACCCACACGGCCTGCGTGCCTTCTAGACTTGAGTTCGCAGCTCTTTAAG
1335	TCGGCCGGGCCCTGGGGGCGGTGGGCGCTGGCCAGGACGCCCACCGTGTGGTTGCTGTCCAGGACGGTCCCGGCCCGCGACACTTCGGCCCAGAGCTGCTCCTCATCCAGCAGCGCCAGCAGCCCCATGGCCGTGAGCACCGGCTTGCGCA
1336	UGACCAGUCUUAAGAUCUUUCUUGACCUGCACCAUAAGAACUUCUCCAAAGGUACCAAAAUACUCUUUCAGGUCCUGUUCGGUUGUUUUCCAUGGGAGACCCAACACUAUU
1337	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCAU
1338	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUGGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCAU
1339	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUUGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCAU

1340	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1341	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1342	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GGGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1343	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UGGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1344	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1345	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1346	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1347	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1348	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1349	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1350	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GGCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1351	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UGCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1352	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1353	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1354	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1355	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1356	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1357	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1358	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1359	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC

	GCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1360	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1361	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU GGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1362	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU UGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1363	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCU AGUGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUC CAU
1364	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GAGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1365	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GCGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCCA U
1366	GAUGGGCACCACCCCGGUGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUC GGGCAUCGCGAGCAGGCGCUGCCUCCUCCGCCCUGCAGCUUGUACAGCUCGUCC AU
1367	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCGUGCCGACGCCACCAGCUCCAA CCACCACAAGUGGAGAGUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGG AGC
1368	GAUUCUGAAUUAGCUGGAUCGUCAAGGCACUCGGGCCGACGCCACCAGCUCCAA CCACCACAAGUGGAGAGUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCGGGG AGC
1369	GGGAGCAGCCUCUGGCAUUCUGGGAGCUUCAUCUGGACCUGGGUCUUCAGUGAA CCAUUGUUCAAUAUCGUCCGGGGACAGCAUCAAAUCAUCCAUUGCUUGGGACGG CAA
1370	GGGAGCAGCCUCUGGCAUUCUGGGAGCUUCAUCUGGACCUGGGUCUUCAGUGAA CCAUUGUUCAAGAUCGUCCGGGGACAGCAUCAAAUCAUCCAUUGCUUGGGACGG CAA
1371	GGGAGCAGCCUCUGGCAGUCGGGGAGCUUCAUCUGGACCUGGGUCUUCAGUGAA CCAUUGUUCAAGAUCGUCCGGGGACAGCAUCAAAUCAUCCAGUGCUUGGGACGG CAA
1372	CAUAUUACAGAAUACCUUGAUAGCAUCCAAUUUGCAUCCUUGGUUAGGGUCAAC CCAGUAUUCUCCACUCUUGAGUUCAGGAUGGCAGAAUUUCAGGUCUCUGCAGUU UCU
1373	GUGAAGAUAAGCCAGUCCUCUAGUAACAGAAUGAGCAAGACGGCAAGAGCUUAC CCAGUCACUUGUGUGGAGACUUAAAUACUUGCAUAAAGAUCCAUUGGGAUAGU ACUC
1374	GUGAACGUCAAACUGUCGGACCAAUAUGGCAGAAUCUUCUCUCAUCUCAACUUU CCAUAUCCGUAUCAUGGAAUCAUAGCAUCCUGUAACUACUAGCUCUCUUACAGC UGG
1375	GCCAAUGAUCUCGUGAGUUAUCUCAGCAGUGUGAGCCAUCAGGGUGAUGACAUC CCAGGCGAUCGUGUGGCCUCCAGGAGCCCAGAGCAGGAAGUUGAGGAGAAGGUG CCU
1376	CAAGACGGUGAACCACUCCAUGGUCUUCUUGUCGGCUUUCUGCACUGUGUACCC CCAGAGCUCCGUGUUGCCGACAUCCUGGGGUGGCUUCCACUCCAGAGCCACAUU AAG
1377	AGGAUUCUCUUUUGAAGUAUUGCUCCCCCAGUGGAUUGGGUGGCUCCAUUCACU CCAAUGCUGAGCACUUCCACAGAGUGGGUUAAAGCGGCUCCGAACACGAAACGU GUA
1378	GACGCCCACCGUGUGGUUGCUGUCCAGGACGGUCCCGGCCUGCGACACUUCGGC CCAGAGCUGCUCCUCAUCCAGCAGCGCCAGCAGCCCCAUGGCCGUGAGCACCGGC

	UU
1379	GACGCCCACCGUGUGGUUGCUGUCCAGGACGGUCCCGGCCUGCGACACUUCGGC CCAGAGCUGCUCCUCAUCUGCGGGGCGGGGGGGGGCCGUCGCCGCGUGGGGUCG UUG
1380	GGGTGATGGGTGCTGGCCAGGACACCCACTGTATGATTGCTGTCCAACACAGCCCC AGCCTTTGAGACCTCTGCCCAGAGTTGTTCTCCATCCAACAGGGCCATGAGCCCCA TGACTGTGAGTACTGGCTTTCGCAGCAACTGCACATGGG
1381	ACTACAGTTGCTCCGATATTTAGGCTACGTCAATAGGCACTAACTTATTGGCGCTG GTGAACGGACTTCCTCTCGAGTACCAGAAGATGACTACAAAACTCCTTTCCATTGC GAGTATCGGAGTCTGGCTCAGTTTGGCCAGGGAGGCACT
1382	CTGCAGGGCGGAGGAGGCAGCGGCGGAGGAGGCAGCGGCGGAGGAGGCAGCAGA AGGTATACACGCCGGAAGAATCTGTAGAGATCCCCGGTCGCCACC
1383	CTGCAGGGCGGAGGAGGCAGCGGCGGAGGAGGCAGCGGCGGAGGAGGCAGCGCC TGCTCGCGATGCTAGAGGGCTCTGCCA
1384	CTGCAGGGCGGAGGAGGCAGCGCCTGCTCGCGATGCTAGAGGGCTCTGCCA
1385	AAACCGAGGGAUCAUAGGGGACUGAAUCCACCAUUCUUCUCCCAAUCCCUGCAA CUCCUUCUUCCCCUGC
1386	ATGGACGAGCTGTACAAGCTGCAGGGCGGAGGAGGCAGCGCCTGCTCGCGATGCT ATAGGGCTCTGCCAGTGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCAT C
1387	UAGCUGUAUCGUCAAGGCACUCUUGCCUACGCCACCAGCUCCAACCACCACAAG UUUAUAUUCAGUCAUUUUCAGCAGGCCUCUCUCCCGC
1388	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUUGCCUACGCCACCAGCUCCAA CUACCACAAGUUUAUAUUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGG AGC
1389	UCCACAAAAUGAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUUGCCUACGCCA CCAGCUCCAACUACCACAAGUUUAUAUUCAGUCAUUUUCAGCAGGCCUCUCUCC CGCACCUGGGAGCCGCUGAGCCU
1390	AUCAUAUUCGUCCACAAAAUGAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUU GCCUACGCCACCAGCUCCAACCACCACAAGUUUAUAUUCAGUCAUUUUCAGCAG GCCUCUCUCCCGCACCUGGGAGCCGCUGAGCCUCUGGCCCCGC
1391	CUAUUGUUGGAUCAUAUUCGUCCACAAAAUGAUUCUGAAUUAGCUGUAUCGUCA AGGCACUCUUGCCUACGCCACCAGCUCCAACCACCACAAGUUUAUAUUCAGUCA UUUUCAGCAGGCCUCUCUCCCGCACCUGGGAGCCGCUGAGCCUCUGGCCCCGCCG CCGCCUUC
1392	UAGGAAUCCUCUAUUGUUGGAUCAUAUUCGUCCACAAAAUGAUUCUGAAUUAGC UGUAUCGUCAAGGCACUCUUGCCUACGCCACCAGCUCCAACCACCACAAGUUUA UAUUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGGAGCCGCUGAGCCUC UGGCCCCGCCGCCGCCUUCAGUGCCUGCG
1393	GAGGCGCAGCAUCCACAGGCGGAGGCGAAAGCAGCCCGGACAGCUGAGGCCGGA AGAGGGUGGGGCCGCGGUGGCCAGGGAGCCGGCGCCGCCACGCGCGGGUGGGGG GGACUGGGGUUGCUCGCGGGCUCCGGGCGGGCGGCGGGCGCCG
1394	UCCUGUAGCUAAGGCCACAAAAUUAUCCACUGUUUUUGGAACAGUCUUUCCGAA GAGACCAAAGAUCACCCGGCCCACAUCUUCAUCUCCAAUUCGUAGGUCAAAAUA CACCUUGACGGUGACUUUGGGCCCCUUCUUCUUCUCAUCGGCC
1395	GCCCUGGAUCAUGAAGUCCUUGAUUACACGAUGGAAUUUGCUGUUUUUGUAGCC AAAUCCUUUCUCUCCUGUAGCCAAGGCCACAAAAUUAUCCACUGUUUUUGGAAC AGUCUUUCCGAAGAGACCAAAGAUCACCCGGCCUACAUCUUCA
1396	GCGCAAGUUAGGUUUUGUCAAGAAAGGGUGUAACGCAACCAAGUCAUAGUCCGC CUAGAAGCAUUUGCGGUG
1397	GCCAUGCCAAUCUCAUCUUGUUUUCUGCGCAAGUUAGGUUUUGUCAAGAAAGGG UGUAACGCAACCAAGUCAUAGUCCGCCUAGAAGCAUUUGCGGUGGACGAUGGAG GGGCCGGACUCGUCAUACUCCUG
1398	GGACUUCCUGUAACAACGCAUCUCAUAUUUGGAAUGACCAUUAAAAAAACAACA AUGUGCAAUCAAAGUC
1399	CAAGGUGCGGCUCCGGCCCCUCCCCUCUUCAAGGGGUCCACAUGGCAACUGUGA GGAGGGGAGAUUCAGUG
1400	UAGCUGUAUCGUCAAGGCACUCGUGCCGACGCCACCAGCUCCAACCACCACAAG

	GGGAGAGUCAGUCAGGGUCAGCAGGCCUCUCUCCCGC
1401	UAGCUGUAUCGUCAAGGCACUCUUGCCGACGCCACCAGCUCCAACCACCACAAG UGUAUAGUCAGUCAUUUUCAGCAGGCCUCUCUCCCGC
1402	UAGCUGGAUCGUCAAGGCACUCGUGCCGACGCCACCAGCUCCAACCACCACAAG GGGAGAGGCAGUCAGGGUCAGCAGGCCUCUCUCCCGC
1403	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCUUGCCGACGCCACCAGCUCCAA CCACCACAAGUGUAUAGUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGG AGC
1404	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCGUGCCGACGCCACCAGCUCCAA CCACCACAAGUGGAGAGUCAGUCAUUUUCAGCAGGCCUCUCUCCCGCACCUGGG AGC
1405	GAUUCUGAAUUAGCUGUAUCGUCAAGGCACUCGUGCCGACGCCACCAGCUCCAA CCACCACAAGGGGAGAGUCAGUCAGGGUCAGCAGGCCUCUCUCCCGCACCUGGG AGC
1406	GCUCCCCGGUGCGGGAGAGAGGCCUGCUGACCCUGACUGCCUCUCCCCUUGUGG UGGUUGGAGCUGGUGGCGUCGGCACGAGUGCCUUGACGAUCCAGCUAAUUCAGA AUC
1407	GCAGAGCCUCCAGC
1408	CUCACUGGCAGAGCCUCCAGC
1409	CCCUUGCUCACUGGCAGAGCCUCCAGC
1410	CUCUCGCCCUUGCUCACUGGCAGAGCCUCCAGC
1411	CUCUCGCCCUUGCUCACUGGCAGAGCCUCCAGCAUCGC
1412	UGAACAGCUCUCGCCCUUGCUCACUGGCAGAGCCUCCAGCAUCGC
1413	UGAACAGCUCCUCGCCCUUGCUCACUGGCAGAGCCCUCCAGCAUCGCGAGCAGG CGCUGCCUCCUCCGCC

[0136] 表12

SEQ ID NO.	序列5'->3
1414	ACAAAUGGGGACGAGGGGGGCGGGGCGGCC
1415	CGGAGAGCAGAGAGGGAGCG
1416	AAAAAAAAAAGATCTTGAAACTGTTTTAAGGTTGGCCGATCTTAAAAAA
1417	UCAUAAUCAAUUUAUUAUUUUCUUUUAUUUUAUUCACAUAAUUUUGUUUUU

[0137] 碱基上的化学转化可以导致经编辑的RNA序列的至少部分敲低。化学转化可以导致经编辑的RNA序列的基本上完全敲低。化学转化可以导致经编辑的RNA序列的部分敲低，其足以赋予接受经工程化的多核苷酸(例如，经工程化的环状指导RNA)的受试者治疗效果。经编辑的RNA序列的至少部分敲低可以导致所表达的蛋白质或其蛋白质片段的水平降低。降低的水平可以为约5％至100％。降低的水平可以为约10％至100％。降低的水平可以为约15％至100％。降低的水平可以为约20％至100％。降低的水平可以为约25％至100％。降低的水平可以为约30％至100％。降低的水平可以为约40％至100％。降低的水平可以为约50％至100％。降低的水平可以为约60％至100％。降低的水平可以为约70％至100％。降低的水平可以为约80％至100％。

[0138] 经工程化的多核苷酸(例如，经工程化的环状指导RNA)可以包含用于靶向核酸序列中的特定序列区或碱基以供RNA编辑实体进行化学转化的靶向结构域。经工程化的多核苷酸还可以包含募集结构域。靶向结构域可以包含可以比反义RNA、短发夹RNA、siRNA、miRNA或snoRNA更长的序列长度。靶向结构域可以包含足以使经工程化的指导RNA形成二级结构的序列长度。在一些情况下，碱基可以指代核苷酸。在一些情况下，核苷酸可以指代碱基。靶向结构域可以包含长度为约20个核苷酸至约1,000个核苷酸的序列长度。靶向结构域可以包含长度为约50个核苷酸至约1,000个核苷酸的序列长度。靶向结构域可以包含长度

为约100个核苷酸至约1,000个核苷酸的序列长度。靶向结构域可以包含长度为约200个核苷酸至约1,000个核苷酸的序列长度。靶向结构域可以包含长度为约500个核苷酸至约1,000个核苷酸的序列长度。靶向结构域可以包含长度为至少约:50、60、70、80、90、100、110、120、130、140、150、160、170、180、190、200个核苷酸的序列长度。

[0139] 经工程化的指导RNA的至少一部分(如靶向结构域、募集结构域或两者)可以包含二级结构。二级结构可以包括茎环结构、十字形结构、立足点结构、错配凸起结构、任何这些中的多于一种或其任何组合。尽管被环化,但经工程化的环状指导RNA与未被环化的基本上类似的经工程化的指导RNA相比,可以保留基本上类似的二级结构。

[0140] 在一些实施方案中,经工程化的多核苷酸可以包含或产生与待修饰的靶mRNA序列互补的反义RNA序列,除了在靶序列的所需化学修饰的位点处的错配。在一些实施方案中,反义RNA序列可以是经环化的。在另一个实施方案中,反义RNA序列相对于靶RNA序列可以任选地包含在具有可超编辑腺苷核苷酸的位置处的另外的错配。在仍另一个实施方案中,任选的错配可以包含与靶RNA序列中的"A"相对的"G",而靶RNA中的靶向"A"与错配"C"相对。在仍另一个实施方案中,经环化的反义指导RNA可以在待化学修饰的腺苷处包含错配,以及与位于30-40个碱基对的区域内的靶向腺苷相隔30-40个碱基对产生的6-12个碱基对的多个环。在仍另一个实施方案中,经环化的反义指导RNA包含多个凸起,所述凸起是通过相对靶RNA链中的经超编辑的腺苷定位鸟苷错配而产生的。在一些实施方案中,按照-34、-24、-14、-10、0、10、14、24、34等的模式产生凸起,其中0是所需化学修饰的位点。在一些实施方案中,按照-30、-20、-10、0、10、20、30等的模式产生凸起,其中0是所需化学修饰的位点。在图17中提供了前述的示意性表示。

[0141] 经工程化的指导RNA可以包含一个或多个修饰。修饰可以包括经修饰的碱基。修饰可以包括糖修饰,如将葡萄糖或其他基于糖的部分添加到经工程化的指导RNA的一个或多个碱基上。修饰可以包括在经工程化的指导RNA的至少一部分上的蛋白质包被。经工程化的指导RNA的一个或多个核苷酸可以包含甲基、氟基、甲氧基乙基、乙基、磷酸基团、酰胺基团、酯基团或其任何组合。与没有修饰的基本上类似的经工程化的指导RNA相比,修饰可以增加经工程化的指导RNA的稳定性或半衰期。

[0142] 在一些情况下,递送至细胞或受试者的经工程化的指导RNA可以募集RNA编辑实体,如内源RNA编辑实体。在一些情况下,经工程化的指导RNA可以与RNA编辑实体共同递送。在一些情况下,与非环状的指导RNA相比,环状指导RNA可以募集更大量的RNA编辑实体。在一些情况下,经工程化的指导RNA可以被配置成募集足够量的内源RNA编辑实体以进行编辑,如将经工程化的指导RNA递送至可以包含少量内源RNA编辑酶的组织位置。在一些情况下,经工程化的指导RNA可以与RNA编辑实体共同递送。在一些情况下,可以将RNA编辑实体单独递送至细胞或受试者。在一些情况下,经工程化的指导RNA可以与RNA编辑实体缔合或直接连接,并且可以将经缔合或经直接连接的组合物递送至细胞或受试者。

[0143] 本公开文本的指导RNA可以不包含(缺乏)易受水解降解影响的末端。在一些情况下,本公开文本的指导RNA可以包含比天然存在于细胞中的mRNA更不易受水解降解影响的二级结构。本公开文本的指导RNA可以不包含(缺乏)能够暴露于溶剂的还原羟基,如5'还原羟基或3'羟基。在一些情况下,5'羟基、3'羟基或两者可以通过磷-氧键连接。在一些实施方案中,5'羟基、3'羟基或两者可以被修饰成具有含磷部分的磷酸酯。本公开文本的指导RNA

可以不包含(缺乏)暴露末端。本公开文本的指导RNA可以不包含(缺乏)5'末端和3'末端。本公开文本的指导RNA可以保留二级结构,不管指导物是否可以是环状的。例如,环状指导RNA可以包含二级结构,所述二级结构是茎环结构、十字形结构、立足点结构、错配凸起结构、任何这些中的多于一种或其任何组合。环状指导RNA可以包含基本上线性的二级结构。环状指导RNA可以包含经修饰以改进RNA编辑实体的募集的二级结构或部分模拟能够募集RNA编辑实体的天然结构的二级结构。

[0144] 在一些情况下,环状指导RNA可以包含比非环状的可比指导RNA大至少约:2x、3x、4x、5x、6x、7x、8x、9x或10x的半衰期。环状指导RNA的半衰期可以比非环状的可比指导RNA大约2x至约5x。递送至细胞或受试者的环状指导RNA的半衰期可以比非环状的可比指导RNA大约3x至约6x。

[0145] 递送至细胞或受试者的环状指导RNA在细胞或受试者中可以包含至少约:40分钟、50分钟、60分钟、1.5小时、2小时、4小时、6小时、8小时、10小时、12小时、16小时、18小时、20小时、24小时、1.25天、1.5天、2天、3天、4天、5天、6天、7天、10天、14天或更长时间的半衰期。递送至细胞或受试者的环状指导RNA的半衰期可以为约1小时至约6小时。递送至细胞或受试者的环状指导RNA的半衰期可以为约1小时至约24小时。递送至细胞或受试者的环状指导RNA的半衰期可以为约1小时至约2天。递送至细胞或受试者的环状指导RNA的半衰期可以为约6小时至约24小时。递送至细胞或受试者的环状指导RNA的半衰期可以为约6小时至约5天。

[0146] 在一些实施方案中,经工程化的指导RNA可以被配置成在细胞中经历环化。用于形成环状RNA序列的构建体可以包含编码以下的核苷酸序列:(a)用于环化的指导RNA序列,其包含(i)RNA编辑实体募集结构域、(ii)连接序列;以及(b)核酶或其催化活性片段。在一些情况下,核苷酸序列可以编码两个或更多个连接序列。在一些情况下,核苷酸序列可以编码两种或更多种核酶。两个或更多个连接序列可以不同。两种或更多种核酶可以不同。指导RNA序列的5'末端、3'末端或两者可以侧接连接序列。连接序列的5'末端或3'末端可以侧接核酶或其催化活性片段。

[0147] 用于形成环状RNA序列的构建体可以包含编码以下的核苷酸序列:(a)用于环化的RNA序列,(b)连接序列,和(c)tRNA、适配体或其催化活性片段。在一些情况下,核苷酸序列可以编码两个连接序列。在一些情况下,核苷酸序列可以编码两种自切割实体(如两种tRNA、两种适配体或组合)。核苷酸序列可以编码两个不同的连接序列。核苷酸序列可以编码两种不同的自切割实体,如两种不同的tRNA、两种不同的适配体或组合。指导RNA序列的5'末端、3'末端或两者可以侧接连接序列。连接序列的5'末端或3'末端可以侧接tRNA、适配体或其他自切割实体。

[0148] 可以通过在RNA序列的多于一个末端(如5'末端和3'末端)之间形成连接(如共价连接)而直接或间接形成环状RNA。RNA序列可以包含经工程化的指导RNA(如募集结构域、靶向结构域或两者)。可以通过采用酶(如连接酶)形成连接。在一些情况下,酶可以是酶的生物活性片段。酶可以被募集到RNA序列以形成连接。可以通过使用连接元件连接RNA序列的多于一个末端形成环状RNA。连接元件可以采用点击化学来形成环状RNA。连接元件可以是基于叠氮化物的连接。可以通过对环状RNA进行遗传编码或化学合成环状RNA来形成环状RNA。可以通过采用自切割实体形成环状RNA,所述自切割实体诸如核酶、tRNA、适配体、任何

这些的催化活性片段或其任何组合。自切割核酶可以包括RNA酶P。

[0149] 指导物可以是环状指导物。参考图3A-B，显示了具有环状构建体的序列的几个例子。对于每个示例性序列，显示了P3核酶的元件、Alu元件、反义指导物、靶C错配、P1核酶。例如，环状指导物可以包含Alu结构域，如图3中所示的Alu 60-30R7A指导物。环状指导物可以包含Alu结构域，如图3中所示的Alu 100-50R7A指导物。在一些情况下，在如本文所述的任何方法中利用的环状指导物或指导物可以包含与图3的序列的至少一部分具有至少约：70％、75％、80％、85％、90％、95％、98％、99％或更高序列同源性的序列。

[0150] 可以采用一种或多种方法来实现形成环状序列(如环状RNA或环状DNA)。在图1A-C中显示了几种方法。第一种方法可以包括工程化经遗传编码的环状adRNA或apRNA，如图1A-B所示。构建体可以被设计为自动催化加工环状RNA。构建体可以编码使成为环状的序列，如指导RNA序列。指导RNA可以包括靶向结构域和RNA编辑实体募集结构域。RNA编辑实体募集结构域可以包括Alu结构域、APOBEC募集结构域、GluR2结构域、Cas13募集结构域或其任何组合。构建体可以编码至少一个连接序列，在一些情况下编码两个连接序列。构建体可以编码至少一种自切割分子，在一些情况下编码两种自切割分子。自切割分子可以包括核酶、tRNA或任何其他自切割分子。在一些情况下，自切割分子可以是tRNA。在一些情况下，使成为环状的序列的5'末端或3'末端中的至少一个可以侧接连接序列，如连接酶(如内源连接酶)识别的序列。在一些情况下，连接序列的5'末端或3'末端中的至少一个可以侧接编码自切割分子的序列。示例构建体显示为图1B的元件100。聚合酶III转录101产生从所编码的构建体转录的RNA序列，通常使用H1、U6或7SK启动子。然后此RNA序列可以被自动催化自切割102，以将自切割部分103(过程的副产物)与使成为环状的序列104(前体环状RNA)分离。在自切割后，使成为环状的序列可以侧接5'末端具有OH基团且3'末端具有2',3'-环状磷酸基团的连接序列。连接酶(如内源连接酶)可以识别连接序列并连接5'和3'末端105，这可以导致环状RNA的形成106。此构建体设计可以编码任何自切割分子，如核酶、tRNA或其他。此构建体设计可以编码使成为环状的任何序列，如用于治疗性递送的RNA，如miR、RNAi、RNA酶H、siRNA、指导RNA(包括CRISPR指导物)或其他。此构建体设计可以编码任何连接酶识别的任何连接序列，以连接线性构建体的末端以形成环状序列。连接酶可以是内源连接酶。连接酶可以与构建体共同递送。构建体设计可以被设计为通过特异性连接酶或多种连接酶连接。所述方法可以包括形成经预应变的环状adRNA，如图5所示。

[0151] 形成环状RNA的另一种方法可以包括工程化经化学合成的环状adRNA或apRNA，如图1C所示。在这种情况下，线性寡核苷酸的化学环化可以使用溴化氰或碳二亚胺交联剂1-乙基-3-(3-二甲基氨基丙基)碳二亚胺与桥接模板一起实现，如107所示。在其他情况下，可以通过T4连接酶进行环状DNA或RNA寡核苷酸的酶促合成。这些酶可以环化线性序列末端的反应性3'-羟基(OH)和5'-磷酸(PO4)基团，如108所示。构建体设计可以包括形成经预应变的环状adRNA，如图5所示。所述方法可以包括形成经预应变的环状adRNA，如图5所示。

[0152] 合适的自切割分子可以包括核酶。核酶可以包括RNA酶P、rRNA(如肽基转移酶23S rRNA)、引导酶(Leadzyme)、I组内含子核酶、II组内含子核酶、GIR1分支核酶、glmS核酶、发夹核酶(hairpin ribozyme)、锤头状核酶(Hammerhead ribozyme)、HDV核酶、绕线核酶(Twister ribozyme)、绕线姐妹核酶(Twister sister ribozyme)、VS核酶、手枪核酶(Pistol ribozyme)、手斧核酶(Hatchet ribozyme)、类病毒或其任何组合。

[0153] 合适的连接酶(或合成酶)可以包括形成共价键的连接酶。共价键可以包括碳-氧键、碳-硫键、碳-氮键、碳-碳键、磷酸酯键或其任何组合。

[0154] 构建环状RNA序列(如指导物)的途径可以开始于tRNA剪接核酸内切酶与特异性识别序列结合并在经切割的末端产生5'羟基和2'-3'环状磷酸。这些经切割的末端可以通过连接酶如内源连接酶(例如,普遍表达的RNA连接酶RtcB)连接在一起。采用此策略的优点可以是不需要另外的酶。可以表达含有侧接自切割分子(如核酶)的目的RNA的RNA转录物。添加编码核酶的序列可以产生自催化RNA。在一些情况下,核酶可以是P3绕线(Twister)和P1绕线,它们可以经历自发自催化切割。所得RNA可以含有5'和3'末端,它们然后可以通过连接酶(如普遍表达的内源RNA连接酶RtcB)连接。增加adRNA的稳定性可能对体内研究具有显著影响,因为编辑依赖于长期表达。所述方法可以包括形成经预应变的环状adRNA,如图5所示。

[0155] 本公开文本的一个方面提供了用于RNA编辑的经工程化的指导RNA、包含经工程化的指导RNA的载体、组合物和药物组合物。以上或如本文所述的任一种可以被配置用于A(腺苷)至I(肌苷)编辑、C(胞嘧啶)至T(胸腺嘧啶)编辑或其组合。在一些情况下,A至I编辑可以被解释为或解读为C至U突变。在一些情况下,A至I编辑可以被解释为或解读为A至G突变。如本文所述的经工程化的指导RNA、包含经工程化的指导RNA的载体、组合物和药物组合物可以提供与天然系统相比增强的编辑效率、减少的脱靶编辑、增强的稳定性或体内半衰期或者其任何组合。

[0156] 本公开文本的一个方面提供了载体。载体可以包含具有编码以下的多核苷酸序列的核酸:(i)RNA编辑实体募集结构域,(ii)与靶RNA的至少一部分互补的靶向结构域,(iii)任选地结构域(i)和/或(ii)中的多于一种,或(iv)其任何组合。在一些情况下,可以将载体施用给受试者,如有需要的受试者。在一些情况下,可以将载体作为药物组合物的一部分施用给受试者,如有需要的受试者。在一些情况下,多核苷酸序列编码环状指导RNA。

[0157] 本公开文本的一个方面提供了非天然存在的RNA。非天然存在的RNA可以包含(i)RNA编辑实体募集结构域,(ii)与靶RNA的至少一部分互补的靶向结构域,(iii)任选地结构域(i)和/或(ii)中的多于一种,或(iv)其任何组合。在一些情况下,非天然存在的RNA是环状的。在一些情况下,非天然存在的RNA不包含(缺乏)暴露末端或单链末端。在一些情况下,可以将非天然存在的RNA施用给受试者,如有需要的受试者。在一些情况下,可以将非天然存在的RNA作为药物组合物的一部分施用给受试者,如有需要的受试者。在一些情况下,可以将非天然存在的RNA配制在载体中以供施用。载体可以包括病毒载体、脂质体、纳米颗粒或其任何组合。在一些情况下,非天然存在的RNA可以包含具有修饰(如化学修饰)的至少一个碱基、至少一个糖、任一种中的多于一个或其组合。

[0158] 经工程化的指导RNA可以包含一个或多个结构域,如1、2、3、4、5个或更多个结构域。在一些情况下,经工程化的指导RNA可以包含募集结构域、靶向结构域、任一种中的多于一个或其组合。在一些情况下,经工程化的指导RNA可以包含靶向结构域和募集结构域。在一些情况下,经工程化的指导RNA可以包含一个靶向结构域和两个募集结构域。

[0159] 结构域可以形成二维形状或二级结构。例如,靶向结构域、募集结构域或其组合可以形成二级结构,所述二级结构可以包括线性区域、十字形结构或其部分、立足点结构、茎环结构或其任何组合。结构域本身可以形成基本上线性的二维结构。结构域可以形成二级

结构,所述二级结构可以包括十字形结构。结构域可以形成二级结构,所述二级结构可以包括茎环结构。结构域可以形成二级结构,所述二级结构可以包括立足点结构。

[0160] 在一些情况下,靶向结构域可以与募集结构域相邻定位,包括紧邻或相邻但被多个核苷酸(例如,1、2、3、4、5、6、7、8、9、10、15、20、25、30个或更多个核苷酸)分开。在一些情况下,靶向结构域可以侧接两个募集结构域。在一些情况下,两个或更多个募集结构域可以彼此相邻。

[0161] 与可以形成不同二维形状或二级结构的核酸相比,结构域的二维形状或二级结构可以影响编辑效率、脱靶效应或其组合。因此,本公开文本的一个方面包括修饰核酸,使得可以有利地设计二维形状以增强编辑效率并降低脱靶效应。对包含天然存在的募集结构域的序列的修饰也可以增强编辑效率并降低脱靶效应。因此,本公开文本的一个方面包括修饰核酸,使得可以有利地设计序列(如合成序列)以增强编辑效率并降低脱靶效应。修饰可以包括改变结构域的长度(如延长长度)、改变导致二级结构改变的天然序列、添加化学修饰或其任何组合。如本文所述的核酸可以提供这些优点。修饰可以包括提供呈环状形式的指导RNA。修饰可以包括形成环状指导RNA以除去一个或多个暴露末端或者一个或多个单链末端。指导RNA的环化可以允许指导RNA保留二级结构,如茎环结构或十字形结构。

[0162] 在一些情况下,募集结构域可以包含与Alu结构域的至少约:15、20、25、30或35个核酸的至少约:80%、85%、90%或95%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与Alu结构域编码序列的至少约80%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与Alu结构域编码序列的至少约85%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与Alu结构域编码序列的至少约90%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与Alu结构域编码序列的至少约95%序列同源性。在一些情况下,Alu结构域编码序列可以是非天然存在的序列。在一些情况下,Alu结构域编码序列可以包含经修饰的部分。在一些情况下,Alu结构域编码序列可以包含天然存在的Alu结构域序列的一部分。

[0163] 在一些情况下,募集结构域可以包含与APOBEC募集结构域的至少约:15、20、25、30或35个核酸的至少约:80%、85%、90%或95%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与APOBEC募集结构域编码序列的至少约80%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与APOBEC募集结构域编码序列的至少约85%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与APOBEC募集结构域编码序列的至少约90%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与APOBEC募集结构域编码序列的至少约95%序列同源性。在一些情况下,APOBEC募集结构域编码序列可以是非天然存在的序列。在一些情况下,APOBEC募集结构域编码序列可以包含经修饰的部分。在一些情况下,APOBEC募集结构域编码序列可以包含天然存在的APOBEC募集结构域序列的一部分。

[0164] 在一些情况下,募集结构域可以包含与GluR2结构域的至少约:15、20、25、30或35个核酸的至少约:80%、85%、90%或95%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与GluR2结构域编码序列的至少约80%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与GluR2结构域编码序列的至少约85%序列同源性。在一些情况下,募集结构域的至少一部分可以包含与GluR2结构域编码序列的至少约90%序列同源性。

在一些情况下，募集结构域的至少一部分可以包含与GluR2结构域编码序列的至少约95%序列同源性。在一些情况下，GluR2结构域编码序列可以是非天然存在的序列。在一些情况下，GluR2结构域编码序列可以包含经修饰的部分。在一些情况下，GluR2结构域编码序列可以包含天然存在的GluR2结构域序列的一部分。

[0165] 在一些情况下，募集结构域可以包含与Cas13募集结构域的至少约：15、20、25、30或35个核酸的至少约：80％、85％、90％或95％序列同源性。Cas13募集结构域可以是Cas13a募集结构域、Cas13b募集结构域、Cas13c募集结构域或Cas13d募集结构域。在一些情况下，募集结构域的至少一部分可以包含与Cas13募集结构域编码序列的至少约80％序列同源性。在一些情况下，募集结构域的至少一部分可以包含与Cas13募集结构域编码序列的至少约85％序列同源性。在一些情况下，募集结构域的至少一部分可以包含与Cas13募集结构域编码序列的至少约90％序列同源性。在一些情况下，募集结构域的至少一部分可以包含与Cas13募集结构域编码序列的至少约95％序列同源性。在一些情况下，Cas13募集结构域编码序列可以是非天然存在的序列。在一些情况下，Cas13募集结构域编码序列可以包含经修饰的部分。在一些情况下，Cas13募集结构域编码序列可以包含天然存在的Cas13募集结构域序列的一部分。

[0166] 在一些情况下，募集结构域的至少一部分可以包含与募集ADAR、募集APOBEC或其组合的编码序列的至少约80％序列同一性。

[0167] 在一些情况下，经工程化的多核苷酸可以编码至少一个RNA编辑实体募集结构域。在一些情况下，经工程化的多核苷酸可以编码与靶RNA的至少一部分互补的RNA。在一些情况下，经工程化的多核苷酸可以编码募集结构域和靶向结构域。在一些情况下，经工程化的多核苷酸可以编码环状指导RNA。在一些情况下，经工程化的多核苷酸可以编码募集结构域并且核酸可以编码靶向结构域。靶RNA的部分可以包含单个核苷酸碱基。靶RNA的部分可以包含多个碱基。靶RNA的部分可以包含约：2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、100、200、300、400、500、600、700、800、900、1000个或更多个碱基对。在一些情况下，靶RNA可以包含约1bp至约10bp。在一些情况下，靶RNA可以包含约10bp至约100bp。在一些情况下，靶RNA可以包含约10bp至约500bp。在一些情况下，靶RNA可以包含约10bp至约1000bp。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约200bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约150bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约250bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约275bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约300bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约400bp的连续序列。包含靶向结构域和募集结构域的经工程化的多核苷酸可以包含长度为至少约500bp的连续序列。

[0168] 载体可以用于递送经工程化的多核苷酸。载体可以包含DNA，如双链DNA或单链DNA。载体可以包含RNA。在一些情况下，RNA可以包含一个或多个碱基修饰。载体可以包括重组载体。在一些情况下，载体可以是从天然存在的载体修饰的载体。载体可以包含非天然存在的载体的至少一部分。可以利用任何载体。在一些情况下，载体可以包括病毒载体、脂质体、纳米颗粒、外来体、细胞外囊泡或其任何组合。在一些情况下，病毒载体可以包括腺病毒

载体、腺相关病毒载体(AAV)、慢病毒载体、逆转录病毒载体、任何这些的一部分或其任何组合。在一些情况下,纳米颗粒载体可以包括基于聚合物的纳米颗粒、基于氨基脂的纳米颗粒、金属纳米颗粒(如基于金的纳米颗粒)、任何这些的一部分或其任何组合。在一些情况下,载体可以包括AAV载体。载体可以被修饰以包括经修饰的VP1蛋白(如经修饰以包括VP1蛋白的AAV载体)。AAV可以包含血清型,如AAV1血清型、AAV2血清型、AAV3血清型、AAV4血清型、AAV5血清型、AAV6血清型、AAV7血清型、AAV8血清型、AAV9血清型、任何这些的衍生物或其任何组合。

[0169] 包含指导RNA的经工程化的多核苷酸的施用可以在整个治疗过程中以一个剂量连续或间歇进行。确定最有效的施用方式和剂量的方法是本领域技术人员已知的,并且可以随用于疗法的组合物、疗法的目的、所治疗的靶细胞和所治疗的受试者而变化。可以用由治疗医师选择的剂量水平和模式来进行单次或多次施用。合适的剂量配制品和施用药剂的方法是本领域已知的。还可以确定施用途径,并且确定最有效的施用途径的方法是本领域技术人员已知的,并且可以随用于治疗的组合物、治疗目的、所治疗的受试者的健康状况或疾病阶段和靶细胞或组织而变化。施用途径的非限制性例子包括口服施用、经鼻施用、注射和局部应用。

[0170] 施用可以指代可以用于使得能够将化合物或组合物(如DNA构建体、病毒载体或其他)递送至所需生物作用位点的方法。这些方法可以包括将(如洗剂、乳膏、软膏)局部施用到表面(如皮肤)的外表面。这些方法可以包括肠胃外施用(包括静脉内、皮下、鞘内、腹膜内、肌内、血管内或输注)、口服施用、吸入施用、十二指肠内施用和直肠施用。在一些情形下,受试者可以在没有监督的情况下施用组合物。在一些情形下,受试者可以在医疗专业人员(例如,医师、护士、助理医师、护工、临终关怀工作者等)的监督下施用组合物。在一些情况下,医疗专业人员可以施用组合物。在一些情况下,美容专业人员可以施用组合物。

[0171] 本文公开的组合物的施用或应用可以进行至少约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、63、64、65、66、67、68、69、70、71、72、73、74、75、76、77、78、79、80、81、82、83、84、85、86、87、88、89、90、91、92、93、94、95、96、97、98、99或100天连续或不连续天数的治疗持续时间。在一些情况下,治疗持续时间可以为约1至约30天、约2至约30天、约3至约30天、约4至约30天、约5至约30天、约6至约30天、约7至约30天、约8至约30天、约9至约30天、约10至约30天、约11至约30天、约12至约30天、约13至约30天、约14至约30天、约15至约30天、约16至约30天、约17至约30天、约18至约30天、约19至约30天、约20至约30天、约21至约30天、约22至约30天、约23至约30天、约24至约30天、约25至约30天、约26至约30天、约27至约30天、约28至约30天或约29至约30天。

[0172] 本文公开的组合物的施用或应用可以每天进行至少1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或24次。在一些情况下,本文公开的组合物的施用或应用可以每周进行至少1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20或21次。在一些情况下,本文公开的组合物的施用或应用可以每月进行至少1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、

60、61、62、63、64、65、66、67、68、69、70、71、72、73、74、75、76、77、78、79、80、81、82、83、84、85、86、87、88、89或90次。

[0173] 在一些情况下，组合物可以作为单剂量或分开剂量施用或应用。在一些情况下，本文所述的组合物可以在第一时间点和第二时间点施用。在一些情况下，可以这样施用组合物，使得第一次施用先于另一次而施用，施用时间的差异为1小时、2小时、4小时、8小时、12小时、16小时、20小时、1天、2天、4天、7天、2周、4周、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、1年或更长时间。

[0174] 与基本上可比的线性RNA序列相比，环状RNA序列的体外半衰期可以长至少约：1x、1.5x、2x、2.5x、3x、3.5x、4x、5x、10x、20x或更多。与基本上可比的线性RNA序列相比，环状RNA序列的体内半衰期可以长至少约：1x、1.5x、2x、2.5x、3x、3.5x、4x、5x、10x、20x或更多。与向有需要的受试者施用的包含基本上可比的线性RNA序列的组合物相比，向有需要的受试者施用的包含环状RNA序列的组合物的剂量可以小至少约：1x、1.5x、2x、2.5x、3x、3.5x、4x、5x、10x或20x。与作为两次或更多次治疗给予的包含基本上可比的线性RNA序列的组合物相比，向有需要的受试者施用的包含环状RNA序列的组合物可以作为单次治疗给予。

[0175] 组合物可以包含活性剂(例如，本公开文本的经工程化的指导RNA)、化合物或组合物与天然存在的或非天然存在的载体、惰性(例如，可检测试剂或标记)或活性物质(如佐剂、稀释剂、粘合剂、稳定剂、缓冲液、盐、亲脂性溶剂、防腐剂、佐剂等)的组合，并且包括药学上可接受的载体。载体还包括药物赋形剂和添加剂蛋白质、肽、氨基酸、脂质和碳水化合物(例如，糖，包括单糖、二寡糖、三寡糖、四寡糖以及寡糖；经衍生化的糖，如糖醇、醛糖酸(aldolic acid)、经酯化的糖等；以及多糖或糖聚合物)，其可以单独或组合存在，包括单独或组合按重量或体积计1％-99.99％。示例性蛋白质赋形剂包括血清白蛋白如人血清白蛋白(HSA)、重组人白蛋白(rHA)、明胶、酪蛋白等。也可以在缓冲容量中发挥功能的代表性氨基酸/抗体组分包括丙氨酸、精氨酸、甘氨酸、精氨酸、甜菜碱、组氨酸、谷氨酸、天冬氨酸、半胱氨酸、赖氨酸、亮氨酸、异亮氨酸、缬氨酸、甲硫氨酸、苯丙氨酸、阿斯巴甜等。碳水化合物赋形剂也旨在在本技术的范围内，其例子包括但不限于单糖，如果糖、麦芽糖、半乳糖、葡萄糖、D-甘露糖、山梨糖等；二糖，如乳糖、蔗糖、海藻糖、纤维二糖等；多糖，如棉子糖、松三糖、麦芽糖糊精、葡聚糖、淀粉等；以及糖醇，如甘露糖醇、木糖醇、麦芽糖醇、乳糖醇、木糖醇山梨糖醇(葡萄糖醇)和肌醇。

[0176] 在一些实施方案中，试剂盒可以包含指导RNA。在一些情形下，试剂盒可以包含经工程化的多核苷酸、经工程化的指导RNA、用于形成环状指导RNA序列的构建体、包含经工程化的多核苷酸的载体、经工程化的多核苷酸的核酸、药物组合物和容器。在一些情况下，容器可以是无菌的。在一些情形下，容器可以是塑料、玻璃、金属或其任何组合。在一些情况下，试剂盒可以包含使用说明书，如向有需要的受试者施用的说明书。在一些实施方案中，制备试剂盒的方法可以包括将本文所述的多核苷酸添加到容器中。

[0177] 药物组合物可以包含第一活性成分。第一活性成分可以包含如本文所述的载体或经工程化的指导RNA。可以将药物组合物配制成单位剂型。药物组合物可以包含药学上可接受的赋形剂、稀释剂或载体。药物组合物可以包含第二、第三或第四活性成分。

[0178] 在一些实施方案中，药物组合物可以以毫克(mg)、毫克每公斤(mg/kg)、拷贝数或分子数配制。

[0179] 本文所述的组合物可以包含赋形剂。赋形剂可以包括冷冻保护剂，如DMSO、甘油、聚乙烯吡咯烷酮(PVP)或其任何组合。赋形剂可以包括冷冻保护剂，如蔗糖、海藻糖、淀粉、任何这些的盐、任何这些的衍生物或其任何组合。赋形剂可以包括pH剂(以使组合物的组分的氧化或降解最小化)、稳定剂(以防止组合物的组分的改性或降解)、缓冲剂(以增强温度稳定性)、增溶剂(以增加蛋白质溶解度)或其任何组合。赋形剂可以包括表面活性剂、糖、氨基酸、抗氧化剂、盐、非离子表面活性剂、增溶剂、甘油三酯、醇或其任何组合。赋形剂可以包括碳酸钠、乙酸盐、柠檬酸盐、磷酸盐、聚乙二醇(PEG)、人血清白蛋白(HSA)、山梨糖醇、蔗糖、海藻糖、聚山梨醇酯80、磷酸钠、蔗糖、磷酸二钠、甘露糖醇、聚山梨醇酯20、组氨酸、柠檬酸盐、白蛋白、氢氧化钠、甘氨酸、柠檬酸钠、海藻糖、精氨酸、乙酸钠、乙酸盐、HCl、依地酸二钠、卵磷脂、甘油、黄原胶橡胶、大豆异黄酮、聚山梨醇酯80、乙醇、水、替普瑞酮或其任何组合。赋形剂可以是在Handbook of Pharmaceutical Excipients,American Pharmaceutical Association(1986)中描述的赋形剂。

[0180] 合适的赋形剂的非限制性例子可以包括缓冲剂、防腐剂、稳定剂、粘合剂、压实剂、润滑剂、螯合剂、分散增强剂、崩解剂、调味剂、甜味剂、着色剂。

[0181] 在一些情况下，赋形剂可以是缓冲剂。合适的缓冲剂的非限制性例子可以包括柠檬酸钠、碳酸镁、碳酸氢镁、碳酸钙和碳酸氢钙。作为缓冲剂，碳酸氢钠、碳酸氢钾、氢氧化镁、乳酸镁、葡糖酸镁、氢氧化铝、柠檬酸钠、酒石酸钠、乙酸钠、碳酸钠、聚磷酸钠、聚磷酸钾、焦磷酸钠、焦磷酸钾、磷酸氢二钠、磷酸氢二钾、磷酸三钠、磷酸三钾、偏磷酸钾、氧化镁、氢氧化镁、碳酸镁、硅酸镁、乙酸钙、甘油磷酸钙、氯化钙、氢氧化钙和其他钙盐或其组合可以用于药物配制品中。

[0182] 在一些情况下，赋形剂可以包括防腐剂。合适的防腐剂的非限制性例子可以包括抗氧化剂，如α-生育酚和抗坏血酸盐；以及抗微生物剂，如对羟基苯甲酸酯、氯丁醇和苯酚。抗氧化剂可以进一步包括但不限于EDTA、柠檬酸、抗坏血酸、丁基羟基甲苯(BHT)、丁基羟基茴香醚(BHA)、亚硫酸钠、对氨基苯甲酸、谷胱甘肽、没食子酸丙酯、半胱氨酸、甲硫氨酸、乙醇和N-乙酰基半胱氨酸。在一些情形下，防腐剂可以包括有效霉素A、TL-3、原钒酸钠、氟化钠、N-a-甲苯磺酰基-Phe-氯甲基酮、N-a-甲苯磺酰基-Lys-氯甲基酮、抑肽酶、苯甲基磺酰氟、二异丙基氟磷酸、激酶抑制剂、磷酸酶抑制剂、半胱天冬酶抑制剂、颗粒酶抑制剂、细胞粘附抑制剂、细胞分裂抑制剂、细胞周期抑制剂、脂质信号传导抑制剂、蛋白酶抑制剂、还原剂、烷化剂、抗微生物剂、氧化酶抑制剂或其他抑制剂。

[0183] 在一些情况下，药物配制品可以包含粘合剂作为赋形剂。合适的粘合剂的非限制性例子可以包括淀粉、预胶化淀粉、明胶、聚乙烯吡咯烷酮、纤维素、甲基纤维素、羧甲基纤维素钠、乙基纤维素、聚丙烯酰胺、聚乙烯噁唑烷酮、聚乙烯醇、C12-C18脂肪酸醇、聚乙二醇、多元醇、糖、寡糖及其组合。

[0184] 可以用于药物配制品中的粘合剂可以选自淀粉，如马铃薯淀粉、玉米淀粉、小麦淀粉；糖，如蔗糖、葡萄糖、右旋糖、乳糖、麦芽糖糊精；天然和合成树胶；明胶；纤维素衍生物，如微晶纤维素、羟丙基纤维素、羟乙基纤维素、羟丙基甲基纤维素、羧甲基纤维素、甲基纤维素、乙基纤维素；聚乙烯吡咯烷酮(聚维酮)；聚乙二醇(PEG)；蜡；碳酸钙；磷酸钙；醇，如山梨糖醇、木糖醇、甘露糖醇；和水；或其组合。

[0185] 在一些情况下，药物配制品可以包含润滑剂作为赋形剂。合适的润滑剂的非限制

性例子可以包括硬脂酸镁、硬脂酸钙、硬脂酸锌、氢化植物油、sterotex、聚氧乙烯单硬脂酸酯、滑石、聚乙二醇、苯甲酸钠、十二烷基硫酸钠、十二烷基硫酸镁和轻质矿物油。可以用于药物配制品中的润滑剂可以选自金属硬脂酸盐(如硬脂酸镁、硬脂酸钙、硬脂酸铝)、脂肪酸酯(如硬脂酰富马酸钠)、脂肪酸(如硬脂酸)、脂肪醇、山蒈酸甘油酯、矿物油、石蜡、氢化植物油、亮氨酸、聚乙二醇(PEG)、金属十二烷基硫酸盐(如十二烷基硫酸钠、十二烷基硫酸镁)、氯化钠、苯甲酸钠、乙酸钠和滑石或其组合。

[0186] 在一些情况下,药物配制品可以包含分散增强剂作为赋形剂。合适的分散剂的非限制性例子可以包括淀粉、海藻酸、聚乙烯吡咯烷酮、瓜尔胶、高岭土、膨润土、经纯化的木纤维素、乙醇酸淀粉钠、同晶硅酸盐和作为高HLB乳化剂表面活性剂的微晶纤维素。

[0187] 在一些情况下,药物配制品可以包含崩解剂作为赋形剂。在一些情况下,崩解剂可以是非泡腾崩解剂。合适的非泡腾崩解剂的非限制性例子可以包括淀粉,如玉米淀粉、马铃薯淀粉、其预胶化和改性淀粉;甜味剂;粘土,如膨润土;微晶纤维素;海藻酸盐;乙醇酸淀粉钠;树胶,如琼脂、瓜尔胶、刺槐豆胶、刺梧桐胶、果胶和黄芪胶。在一些情况下,崩解剂可以是泡腾崩解剂。合适的泡腾崩解剂的非限制性例子可以包括碳酸氢钠与柠檬酸的组合以及碳酸氢钠与酒石酸的组合。

[0188] 在一些情况下,赋形剂可以包括调味剂。掺入外层中的调味剂可以选自合成调味油和调味芳香剂;天然油;来自植物、叶、花和果实的提取物;及其组合。在一些情况下,调味剂可以选自肉桂油;冬青油;薄荷油;三叶草油;干草油;茴香油;桉树;香草;柑橘油,如柠檬油、橙油、葡萄和葡萄柚油;以及水果香精,包括苹果、桃、梨、草莓、覆盆子、樱桃、李子、菠萝和杏。

[0189] 在一些情况下,赋形剂可以包括甜味剂。合适的甜味剂的非限制性例子可以包括葡萄糖(玉米糖浆)、右旋糖、转化糖、果糖及其混合物(当不用作载体时);糖精及其各种盐,如钠盐;二肽甜味剂,如阿斯巴甜;二氢查耳酮化合物、甘草甜素;甜叶菊(Stevia Rebaudiana)(甜菊苷);蔗糖的氯代衍生物,如三氯蔗糖;和糖醇,如山梨糖醇、甘露糖醇、木糖醇(sylitol)等。

[0190] 受试者、宿主、个体和患者在本文中可以可互换地用于指代任何真核生物或原核生物。在一些情况下,受试者可以指代动物,如哺乳动物。可以向哺乳动物施用如本文所述的载体、经工程化的指导RNA、细胞或组合物。哺乳动物的非限制性例子包括人、非人灵长类动物(例如,猿、长臂猿、黑猩猩、猩猩、猴、猕猴等)、家畜(例如,狗和猫)、农场动物(例如,马、牛、山羊、绵羊、猪)和实验动物(例如,小鼠、大鼠、兔、豚鼠)。在一些实施方案中,哺乳动物是人。哺乳动物可以是任何年龄或处于任何发育阶段(例如,成人、青少年、儿童、婴儿或子宫中的哺乳动物)。哺乳动物可以是雄性或雌性。哺乳动物可以是怀孕的雌性。在一些实施方案中,受试者是人。在一些实施方案中,受试者患有或被怀疑患有癌症或肿瘤性障碍。在其他实施方案中,受试者患有或被怀疑患有与异常蛋白质表达相关的疾病或障碍。在一些情况下,人可以大于约:1日龄至约10月龄、约9月龄至约24月龄、约1岁至约8岁、约5岁至约25岁、约20岁至约50岁、约1岁至约130岁或约30岁至约100岁。人可以大于约:1、2、5、10、20、30、40、50、60、70、80、90、100、110或120岁。人可以小于约:1、2、5、10、20、30、40、50、60、70、80、90、100、110、120或130岁。

[0191] 疾病或病症可以包括神经退行性疾病、肌肉障碍、代谢障碍、眼部障碍或其任何组

合。疾病或病症可以包括囊性纤维化、白化病、α-1-抗胰蛋白酶缺乏症、阿尔茨海默病、肌萎缩侧索硬化、哮喘、β-地中海贫血、Cadasil综合征、沙尔科-马里-图思病、慢性阻塞性肺病(COPD)、远端型脊肌萎缩症(DSMA)、迪谢内/贝克肌营养不良、营养不良性大疱性表皮松解症、大疱性表皮松解症、法布里病、因子V Leiden相关障碍、家族性腺瘤性息肉病、半乳糖血症、戈谢病、葡萄糖-6-磷酸脱氢酶、血友病、遗传性血色病、亨特综合征、亨廷顿病、赫尔勒综合征、炎性肠病(IBD)、遗传性多凝集综合征、莱伯先天性黑蒙、莱施-奈恩综合征、林奇综合征、马方综合征、粘多糖贮积症、肌营养不良、I型和II型肌强直性营养不良、神经纤维瘤病、A、B和C型尼曼-皮克病、NY-eso1相关癌症、帕金森病、波伊茨-耶格综合征、苯丙酮尿症、庞贝症、原发性睫状体疾病、凝血酶原突变相关障碍(如凝血酶原G20210A突变)、肺动脉高压、色素性视网膜炎、桑德霍夫病、重症联合免疫缺陷综合征(SCID)、镰状细胞性贫血、脊肌萎缩症、斯塔加特病(Stargardt's Disease)、泰-萨二氏病、厄舍综合征、X连锁免疫缺陷、各种形式的癌症(例如BRCA1和2连锁的乳腺癌和卵巢癌)。疾病或病症可以包括肌营养不良、鸟氨酸氨甲酰基转移酶缺乏症、色素性视网膜炎、乳腺癌、卵巢癌、阿尔茨海默病、疼痛、斯塔加特黄斑营养不良、沙尔科-马里-图思病、雷特综合征或其任何组合。组合物的施用可以足以:(a)相对于施用前基因的表达降低基因的表达;(b)编辑受试者(如有需要的受试者)中的至少一个点突变;(c)编辑受试者中的至少一个终止密码子以产生终止密码子的连读;(d)在受试者中产生外显子跳跃;或(e)其任何组合。疾病或病症可以包括肌营养不良。肌营养不良可以包括肌强直性肌营养不良、迪谢内肌营养不良、贝克肌营养不良、肢带型肌营养不良、面肩肱型肌营养不良、先天性肌营养不良、眼咽型肌营养不良、远端型肌营养不良、埃默里-德赖弗斯肌营养不良或其任何组合。疾病或病症可以包括疼痛,如慢性疼痛。疼痛可以包括神经性疼痛、伤害性疼痛或其组合。伤害性疼痛可以包括内脏疼痛、躯体疼痛或其组合。

实施例

[0192] 实施例1-通过改进ADAR1向靶标的募集或通过使得adRNA能够具有更长的持久性或使用两者的组合,可以使经由内源ADAR的RNA编辑过程更有效。由于Alu元件是ADAR1的已知底物,因此假设工程化携带Alu结构域的adRNA可能改进ADAR1向靶标的募集。因此,通过小心地将反义结构域定位在Alu共有序列中的不同位置并测定在HE293FT细胞中RAB7A转录物的3'UTR中的腺苷处的编辑来产生三种形式的Alu adRNA(图9A、12A-B)。另外,测试不同长度的反义结构域(图12C)。在长反义adRNA上添加Alu结构域没有显著提高经由内源ADAR进行RNA编辑的效率(图9A);然而,Alu-v2adRNA在募集过表达的ADAR1-150(ADAR1的IFN诱导型同种型)方面是高度有效的(图12B-C)。

[0193] 未经修饰的RNA通常具有短的半衰期。本公开文本提供了使得adRNA能够具有更长的持久性的方法和组合物,测试已经显示提高siRNA稳定性的U6+27盒。向长反义adRNA中添加U6+27导致RAB7A转录物编辑的轻微改进(图9A)。进一步地,已知环状RNA在细胞中持续数天的持续时间,因此质疑是否可以产生用于募集内源ADAR的环状adRNA。研究着眼于哺乳动物细胞中经U6转录的环状RNA(图13A)。产生具有不同反义长度的环状adRNA,并且测定它们修复海萤(cypridina)萤光素酶(cluc)转录物中过早终止密码子的能力(图13B)。通过设计仅选择性扩增经环化的RNA的引物,经RT-PCR确认HEK293FT细胞中adRNA的环化(图9B)。使用反义长度为100bp和200bp的环状adRNA,在转染后2天观察到RAB7A转录物的35%-38%编

辑,比长反义adRNA效率提高3.5倍,并且比Alu adRNA和U6+27adRNA提高2倍(图9A)。另外,使用环状adRNA也观察到转染后4天RNA编辑的显著水平的持久性,此时经由线性形式进行编辑几乎不存在(图9C)。在乱序和ADAR1 siRNA存在下进行萤光素酶测定。在靶向ADAR1的siRNA存在下证明萤光素酶活性的显著下降,从而确认经由递送长反义adRNA及其环状变体进行RNA编辑由于内源ADAR1的募集而发生(图9D、9E)。然而,使用具有长反义结构域的环状adRNA的一个问题是在靶标侧翼的腺苷中看到的超编辑(图14A)。使用靶标侧翼的经超编辑的腺苷处的错配来解决这个问题。

[0194] 为了确认结果的普遍性,具有200bp反义长度的环状和线性adRNA用于编辑HEK 293FT细胞中三种转录物(GAPDH、ALDOA和DAXX)的编码序列(CDS)中的腺苷(图10A)。环状adRNA在编辑GAPDH和ALDOA转录物方面更好,而对于DAXX,在转染后2天未观察到线性和环状构建体之间的差异。进一步地,测试经体外转录的(IVT)环状adRNA使得能够进行RNA编辑的能力,所述环状adRNA以线性形式递送至细胞,但是在细胞中经历环化(图14B)。在转染后一天内,与经由质粒递送看到的25%相比,使用IVT adRNA观察到RAB7A转录物的接近40%编辑(图10B)。还经由qPCR确认IVT adRNA和经质粒递送的adRNA在细胞中的环化(图10C)。

[0195] 比较线性和环状adRNA在编辑小鼠中内源转录物方面的效率。将靶向PCSK9转录物的3'UTR中的腺苷的U6+27线性和环状adRNA包装到已知具有高肝向性的AAV8中。作为阳性对照,使用已经包装U6+27adRNA以及ADAR2酶的第三种AAV。注射后2周,收获小鼠肝脏,并且显示出经由募集内源ADAR对PCSK9转录物中靶位点的6%-7%编辑,相比之下在U6+27adRNA情况下看到<1%或在过表达的ADAR2存在下经由U6+27adRNA看到2%-3%(图10A)。进行qPCR以确认环状adRNA和其他经AAV递送的构建体的表达(图15B-D)。另外,经AAV递送的线性和环状长反义adRNA不显著改变小鼠肝脏中PCSK9的表达水平(图15E)。然而,使用环状adRNA,在位于靶标上游6bp处的PCSK9转录物中的非靶腺苷处观察到同等高水平的编辑(图15F)。假设可以通过增加环状adRNA的表达来提高RNA编辑的效率。因此,测试携带经由hU6和mU6启动子表达的环状adRNA的两个拷贝的AAV载体,所述启动子都被克隆在CMV启动子驱动的mCherry的下游。另外,据信长反义RNA保持与目的转录物结合,从而阻止经编辑的mRNA的有效逆转录。为了克服这个问题,在cDNA合成之前,使用有义RNA来捕获长反义RNA,从而释放靶mRNA用于逆转录。使用对cDNA合成方案进行轻微改变的此载体,在注射后两周内,观察到PCSK9基因座的35%-40%编辑(图11A)。另外,观察到环状adRNA的稳健表达,其比所使用的原始载体高约3倍。(图11B和15B)。

[0196] 因为本公开文本的组合物和方法在体内实现了35%-40%的内源靶标,所以此方法为潜在的基因疗法打开了大门,所述基因疗法可以用于有效地修复G至A点突变或过早终止密码子。尽管针对递送环状adRNA的先天免疫反应需要进一步评估,但基于AAV的基因疗法已经用于临床,并且由于此方法不需要递送外源效应蛋白,因此此方法可能具有巨大的治疗潜力。

[0197] 实施例2-受试者将被诊断患有疾病。受试者将被开具药物组合物的给药方案。药物组合物将包含经工程化的环状指导RNA或编码经工程化的环状指导RNA的重组多核苷酸。经工程化的环状指导RNA将包含靶向结构域和能够募集进行核苷酸编辑的RNA编辑实体的RNA编辑实体募集结构域。药物组合物将通过注射施用给受试者。经工程化的环状指导RNA的给药方案的频率将比通过注射接受非环状的可比经工程化的指导RNA的受试者低2x。给

药方案将包含治疗疾病的有效量。

[0198] 实施例3-将通过获得经工程化的指导RNA形成经工程化的环状指导RNA。经工程化的指导RNA将包含靶向结构域和能够募集进行核苷酸编辑的RNA编辑实体的RNA编辑实体募集结构域，而另一种构建体将包含靶向结构域但将不包含单独的RNA编辑实体募集结构域。适配体将被添加到经工程化的指导RNA的每个末端。连接酶将与经工程化的指导RNA的每个末端的适配体接触以在适配体之间形成共价连接，从而形成经工程化的环状指导RNA。与非环状的可比经工程化的指导RNA的二级结构相比，经工程化的环状指导RNA将基本上保留二级结构。

[0199] 实施例4-受试者将被诊断患有疾病。受试者将被开具药物组合物的给药方案。药物组合物将包含经工程化的环状指导RNA或编码经工程化的环状指导RNA的重组多核苷酸。经工程化的环状指导RNA将包含靶向结构域。药物组合物将通过注射与重组RNA编辑酶共同施用给受试者。给药方案将包含治疗疾病的有效量。

[0200] 实施例5-在此实施例中，将一个或多个核酶结构域添加到指导物设计上以确定指导物是否发生环化。通过以下方式在体外测试指导物：用lipofectamine转染293FT并过表达ADAR酶或使用平衡质粒来确定adRNA募集内源ADAR的能力。引物被设计为仅在发生环化时进行扩增。当使用引物时，如果发生环化，则发生扩增。参考图2，凝胶显示出Alu-v2-100-50指导物的环化。

[0201] 实施例6-由于环化可能需要更长的指导物，因此将针对RAB7A和CLuc基因座测试各种更长的指导物。这些指导物的长度将为100、200、300、400、500和600bp，其中C错配被设计为跨越靶标A定位。将针对在pCAG启动子下含有具有过早TAG终止密码子的萤光素酶基因的CLuc报告质粒测试这些指导物。当ADAR将TAG中的靶标A转化为I(读作G)时，核糖体完全翻译了蛋白质，如图4所图示。将转染细胞，并且在48小时后将通过萤光素酶报告基因测定进行可视化。来自细胞的光读出将指示萤光素酶活性的恢复。参考图4，第一种情况证明了这样的实施例，其中核糖体将到达萤光素酶基因中的过早TAG终止密码子，并且将终止翻译，产生截短的无功能萤光素酶。在第二种情况下，ADAR将被adRNA募集到这样的位点，在此处它将TAG终止密码子编辑为色氨酸的TGG密码子，这将允许核糖体连读，从而将导致正常的萤光素酶表达。此种系统将允许评价adRNA对ADAR的适当募集。当将检测到萤光素酶表达时，将已经发生adRNA对ADAR的募集。当将未检测到萤光素酶表达时，ADAR募集将尚未发生。

[0202] 实施例7-采用环状adRNA进行治疗性施用的优点：当前polIII转录物的半衰期可能是几分钟或更短，但是环状adRNA的寿命可能异常长-可以可作为经化学合成的寡核苷酸递送，并且可以不需要对受试者重复施用。采用环状adRNA进行治疗性施用的挑战可以包括：环状RNA可能能够与靶RNA杂交，并且核酸可能彼此缠绕，所以由于拓扑约束，环状adRNA可能需要进行预应变。如图5所示，方法(1)显示了经预应变的环状adRNA。如图5所示，方法(2)显示了大的环状adRNA，其在拓扑学上可能更灵活。图6和图7中的数据对应于图5中的方法(2)的构建体。可以使用U6+27启动子与仅U6。可以使用Alu-adRNA和长adRNA作为经工程化的环状adRNA的支架。对于环状构建体设计，可以采用U6+27启动子。对于环状构建体设计，Alu-adRNA或长adRNA可以用作在其上工程化环状adRNA的支架。

[0203] 实施例8-环状adRNA可能影响RNA编辑：测试了范围从100-600的各种长度的环状adRNA(对于构建体的长度，参见图6的x轴，即600_300或500_250，第一个数字指示环状

adRNA的长度，下划线后的数字指示错配的靶核苷酸的位置)在用海萤萤光素酶(cluc W85X)报告基因转染的细胞中恢复萤光素酶活性的能力。相对光单位指示在y轴上，并且较高的值指示萤光素酶活性的恢复。此实验是在存在adRNA或添加外源酶ADAR1-p110、ADAR1-p150和ADAR2的情况下进行的。在图6中显示了结果。

[0204] 实施例9-在图7中显示了adRNA在细胞中被环化的确认。简言之，从用携带不同长度的线性反义结构域(即，如图7中每个泳道的顶部所示的100_50、200_100、300_150)的质粒转染的细胞中提取RNA，所述线性反义结构域侧接环化结构域。将所提取的RNA转化为cDNA，随后使用被设计为确认环化的引物进行PCR;如果线性RNA是模板，引物将不会产生扩增子。用GluR2 adRNA或编码经环化的变体的质粒转染的细胞用作阴性对照。在图7中显示了结果。

[0205] 实施例10-除了长adRNA(例如，0-100-50、0-200-100等)之外，Alu-adRNA也可以用作用于环状adRNA构建的支架。用编码各种环状adRNA的质粒转染细胞。在靶RNA通过逆转录酶转化为cDNA后通过Sanger测序确定靶RNA(RAB7A)的RNA编辑百分比。分析Sanger迹线以评估编辑效率。在图8所示的数据中，长Alu-v2-100-50指导物在没有ADAR酶过表达的细胞中显示出改进的编辑。ADAR1p150的过表达导致Alu构建体的编辑速率显著更高，而线性100-50指导物的编辑速率类似。ADAR1p150可能优先结合Z-RNA，这是由于其较短同种型ADAR1p110缺乏的额外ds-RNA结合结构域。具有高GC含量的Alu元件可以形成Z-DNA和Z-RNA，有助于ADAR1p150的募集。

[0206] 虽然在本文中已经显示和描述了本发明的优选实施方案，但对于本领域技术人员而言应明显的是，此类实施方案仅通过举例的方式来提供。在不背离本发明的情况下，本领域技术人员现在应想到许多改变、变化和替换。应当理解的是，本文所述的本发明的实施方案的各种替代方案都可以用于实践本发明。以下权利要求旨在限定本发明的范围，并且由此覆盖这些权利要求及其等同物范围内的方法和结构。

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<210> 1000

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<210> 1003

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<210> 1004

<211> 20

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<210> 1011

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<210> 1013

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<210> 1014

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<210> 1015

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<210> 1016

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<210> 1017

<211> 70

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agucagcaau 70

<210> 1018

<211> 75

<212> RNA

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guagucagca aucuu 75

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agcaau 66
<210> 1020
<211> 71
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ucagcaaucu u 71
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ggucag 66
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ggucag 66
<210> 1026
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<212> RNA
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<210> 1028
<211> 44
<212> RNA
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<210> 1029
<211> 52
<212> RNA
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<210> 1030
<211> 58
<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1030

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<210> 1031

<211> 58

<212> RNA

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<210> 1032

<211> 58

<212> RNA

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<210> 1033

<211> 31

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1034

<211> 31

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1035

<211> 31

<212> RNA

<213> Artificial Sequence

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<210> 1036

<211> 31

<212> RNA

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1037

<211> 31

<212> RNA

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<210> 1038

<211> 31

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<223> Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

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<210> 1039

<211> 31

<212> RNA

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1039

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<210> 1040

<211> 31

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1041

<211> 31

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1042

<211> 31

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<213> Artificial Sequence

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<222> (15)..(15)

<223> Inosine

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<223> 2,6-diamino purine

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oligonucleotide
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oligonucleotide

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oligonucleotide

<400> 1055

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<210> 1056

<211> 34

<212> RNA

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1057

<211> 31

<212> RNA

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<210> 1058

<211> 31

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<210> 1059

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oligonucleotide
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oligonucleotide
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oligonucleotide
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<400> 1087
cuguccaaca cagccccagc cuuugagacc ucuguccaga guuguucucc 50
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oligonucleotide

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oligonucleotide

<400> 1114

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<210> 1115

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oligonucleotide

<400> 1127

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<210> 1128

<211> 17

<212> RNA

<213> Artificial Sequence

<220>

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<210> 1129

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<210> 1130

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<220>

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<210> 1131

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<210> 1145
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<210> 1146
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gaucagcuuc uggccau 17
<210> 1148
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ccuuucuguc gaugguc 17
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oligonucleotide

<400> 1153

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<210> 1155

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<210> 1156

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<210> 1158
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cuucacgauc caucaac 17
<210> 1159
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<210> 1161
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cucuagaggg cccugaagag ggccc 85
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<212> RNA
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<400> 1163
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cucuagaggg cccugaagag ggccc 85
<210> 1164
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<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
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gccagccguc cucuagaggg cccugaagag ggccc 95
<210> 1165
<211> 18
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<400> 1165
gcaaugccau caccuccc 18
<210> 1166
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<212> RNA

<213> Artificial Sequence
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ccc 63
<210> 1167
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<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide
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ggugaagagg agaacaauau gcuaaauguu guucucgucu ccaccgcaau gccaucaccu 60
ccc 63
<210> 1168
<211> 73
<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1168
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gccaucaccu ccc 73
<210> 1169
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<400> 1169
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ggugaauagu auaacaauau gcuaaauguu guuauaguau ccaccagggg uccacauggc 60
aac 63
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aac 63
<210> 1172
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
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uccacauggc aac 73
<210> 1173
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<213> Artificial Sequence
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<400> 1173
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<210> 1174
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<213> Artificial Sequence
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<210> 1175
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gccaagcagu ugg 73
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uccagacggc agg 73
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<210> 1179
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cucgucgaug guc 73
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oligonucleotide
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<223> Description of Combined DNA/RNA Molecule: Synthetic
oligonucleotide
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agcagcuuca gucccuuucu cgucgatggt c 91
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oligonucleotide
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<223> Description of Combined DNA/RNA Molecule: Synthetic
oligonucleotide
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ggugucgaga agaggagaac aauaugcuaa auguuguucu cgucuccucg acacccaugg 60
ccccagcagc uucagucccu uucucgucga tggtc 95
<210> 1184
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oligonucleotide
<400> 1184
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<210> 1185
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oligonucleotide
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aac 63

<210> 1186
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aac 63
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uccacauggc aac 73
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gacc 64
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oligonucleotide
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t 61
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oligonucleotide
<400> 1191
ucauuaaacg ccagaguccg ga 22
<210> 1192
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oligonucleotide
<400> 1192
ucugaauaau ccaggaaaag ca 22
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oligonucleotide
<400> 1193
uauaggggug ccaagcaguu gg 22
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cacgucauga gcccuuccac ga 22
<210> 1207

<211> 22
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aacgagggau cccgcuccug ga 22
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<210> 1209
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<210> 1210
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<210> 1211
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<210> 1213
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gacuagccaa acucguuguc au 22
<210> 1214
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<210> 1215
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<400> 1215
uguauaucca ccuuaccaga gu 22
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<210> 1217
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cuaggcaaca acauccacuu ua 22
<210> 1218
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ccgagcgcca gcagaggcag gg 22
<210> 1219
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<212> RNA
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<210> 1220

<211> 22
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gaagaggcug ucgucauacu uc 22
<210> 1221
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1221
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<210> 1222
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<400> 1222
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<210> 1223
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<210> 1224
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<400> 1224
agucgccaca gcuucccgga gg 22
<210> 1225
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<400> 1225
agucgccaca gcuucccgga gg 22
<210> 1226
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1226
aggagggguc ucacuccuug ga 22
<210> 1227
<211> 22
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1227
aggagggguc ucacuccuug ga 22
<210> 1228
<211> 55
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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1228
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<210> 1229
<211> 70
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aaaccgaggg aucauagggg acugaaucca ccauucuucu cccaaucccu gcaacuccuu 60
cuucccugc 70
<210> 1230
<211> 70
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
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ugaacagcuc cucgcccuug cucacuggca gagcccucca gcaucgcgag caggcgcugc 60
cuccuccgcc 70
<210> 1231
<211> 71
<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1231
ucucagucca auguaugguc cgagcacaag cucuaaucaa aguccgcggg uguagaccgg 60
uugccauagg a 71
<210> 1232
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1232
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cuccgccgcu g 71
<210> 1233
<211> 71
<212> RNA
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide
<400> 1233
acagcuccuc gcccuugcuc acuggcagag cccucaagca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1234
<211> 71
<212> RNA
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide
<400> 1234
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cuccgccgcu g 71
<210> 1235
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide
<400> 1235
acagcuccuc gcccuugcuc acuggcagag cccucgagca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1236
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic

oligonucleotide

<400> 1236

acagcuccuc gcccuugcuc acuggcagag cccugcagca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1237

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

oligonucleotide

<400> 1237

acagcuccuc gcccuugcuc acuggcagag cccuucagca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1238

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

oligonucleotide

<400> 1238

acagcuccuc gcccuugcuc acuggcagag cccuacagca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1239

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

oligonucleotide

<400> 1239

acagcuccuc gcccuugcuc acuggcagag cccuccugca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1240

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1240

acagcuccuc gcccuugcuc acuggcagag cccugcugca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1241

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1241

acagcuccuc gcccuugcuc acuggcagag cccuucugca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1242

<211> 71

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1242

acagcuccuc gcccuugcuc acuggcagag cccuacugca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1243

<211> 71

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1243

acagcuccuc gcccuugcuc acuggcagag cccucccgca ucgcgagcag gcgcugccuc 60

cuccgccgcu g 71

<210> 1244

<211> 71

<212> RNA

<213> Artificial Sequence

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<400> 1244
acagcuccuc gcccuugcuc acuggcagag cccugccgca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1245
<211> 71
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<400> 1245
acagcuccuc gcccuugcuc acuggcagag cccuuccgca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1246
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<212> RNA
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<400> 1246
acagcuccuc gcccuugcuc acuggcagag cccuaccgca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1247
<211> 71
<212> RNA
<213> Artificial Sequence
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<400> 1247
acagcuccuc gcccuugcuc acuggcagag cccuccggca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1248
<211> 71
<212> RNA

<213> Artificial Sequence
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<400> 1248
acagcuccuc gcccuugcuc acuggcagag cccugcugca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1249
<211> 71
<212> RNA
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<400> 1249
acagcuccuc gcccuugcuc acuggcagag cccuucggca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1250
<211> 71
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1250
acagcuccuc gcccuugcuc acuggcagag cccuacggca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1251
<211> 31
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1251
acuggcagag cccuccagca ucgcgagcag g 31
<210> 1252
<211> 51
<212> RNA

<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1252
gcccuugcuc acuggcagag cccuccagca ucgcgagcag gcgcugccuc c 51
<210> 1253
<211> 71
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1253
acagcuccuc gcccuugcuc acuggcagag cccuccagca ucgcgagcag gcgcugccuc 60
cuccgccgcu g 71
<210> 1254
<211> 91
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1254
accccgguga acagcuccuc gcccuugcuc acuggcagag cccuccagca ucgcgagcag 60
gcgcugccuc cuccgccgcu gccuccuccg c 91
<210> 1255
<211> 282
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1255
gcucgaccag gaugggcacc accccgguga acagcuccuc gcccuugcuc acuggcagag 60
cccuccagca ucgcgagcag gcgcugccuc cuccgccgcu gccuccuccg ccgcugccuc 120
cuccgcccug cucgccgucc agcucgacca ggaugggcac caccccggug aacagcuccu 180
cgcccuugcu cacuggcaga gcccuccagc aucgcgagca ggcgcugccu ccuccgccgc 240
ugccuccucc gccgcugccu ccuccgcccu gcagcuugua ca 282

<210> 1256
<211> 151
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1256
ucgccgucca gcucgaccag gaugggcacc accccgguga acagcuccuc gcccuugcuc 60
acuggcagag cccuccagca ucgcgagcag gcgcugccuc cuccgccgcu gccuccuccg 120
ccgcugccuc cuccgcccug cagcuuguac a 151
<210> 1257
<211> 171
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1257
gccguuuacg ucgccgucca gcucgaccag gaugggcacc accccgguga acagcuccuc 60
gcccuugcuc acuggcagag cccuccagca ucgcgagcag gcgcugccuc cuccgccgcu 120
gccuccuccg ccgcugccuc cuccgcccug cagcuuguac agcucgucca u 171
<210> 1258
<211> 191
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1258
ugaacuugug gccguuuacg ucgccgucca gcucgaccag gaugggcacc accccgguga 60
acagcuccuc gcccuugcuc acuggcagag cccuccagca ucgcgagcag gcgcugccuc 120
cuccgccgcu gccuccuccg ccgcugccuc cuccgcccug cagcuuguac agcucgucca 180
ugccgccggu g 191
<210> 1259
<211> 211
<212> RNA
<213> Artificial Sequence
<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1259

ccggacacgc ugaacuugug gccguuuacg ucgccgucca gcucgaccag gaugggcacc 60

accccgguga acagcuccuc gcccuugcuc acuggcagag cccuccagca ucgcgagcag 120

gcgcugccuc cuccgccgcu gccuccuccg ccgcugccuc cuccgcccug cagcuuguac 180

agcucgucca ugccgccggu ggaguggcgg c 211

<210> 1260

<211> 31

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1260

gcgaccgggg aucuccacag auucuuccgg c 31

<210> 1261

<211> 51

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1261

gcucacggug gcgaccgggg aucuccacag auucuuccgg cguguauacc u 51

<210> 1262

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1262

ccucgcccuu gcucacggug gcgaccgggg aucuccacag auucuuccgg cguguauacc 60

uucugcugcc u 71

<210> 1263

<211> 91

<212> RNA

<213> Artificial Sequence

<220>
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<400> 1263
gugaacagcu ccucgcccuu gcucacggug gcgaccgggg aucuccacag auucuuccgg 60
cguguauacc uucugcugcc uccuccgccg c 91
<210> 1264
<211> 111
<212> RNA
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1264
caccaccccg gugaacagcu ccucgcccuu gcucacggug gcgaccgggg aucuccacag 60
auucuuccgg cguguauacc uucugcugcc uccuccgccg cugccuccuc c 111
<210> 1265
<211> 131
<212> RNA
<213> Artificial Sequence
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<400> 1265
ccaggauggg caccaccccg gugaacagcu ccucgcccuu gcucacggug gcgaccgggg 60
aucuccacag auucuuccgg cguguauacc uucugcugcc uccuccgccg cugccuccuc 120
cgccgcugcc u 131
<210> 1266
<211> 151
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1266
uccagcucga ccaggauggg caccaccccg gugaacagcu ccucgcccuu gcucacggug 60
gcgaccgggg aucuccacag auucuuccgg cguguauacc uucugcugcc uccuccgccg 120
cugccuccuc cgccgcugcc uccuccgccc u 151
<210> 1267

<211> 171
<212> RNA
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<400> 1267
cggcgacgua uccagcucga ccaggauggg caccaccccg gugaacagcu ccucgcccuu 60
gcucacggug gcgaccgggg aucuccacag auucuuccgg cguguauacc uucugcugcc 120
uccuccgccg cugccuccuc cgccgcugcc uccuccgccc ugcagcuugu a 171
<210> 1268
<211> 191
<212> RNA
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<400> 1268
uguggccguu uacgucgccg uccagcucga ccaggauggg caccaccccg gugaacagcu 60
ccucgcccuu gcucacggug gcgaccgggg aucuccacag auucuuccgg cguguauacc 120
uucugcugcc uccuccgccg cugccuccuc cgccgcugcc uccuccgccc ugcagcuugu 180
acagcucguc c 191
<210> 1269
<211> 211
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1269
acgcugaacu uguggccguu uacgucgccg uccagcucga ccaggauggg caccaccccg 60
gugaacagcu ccucgcccuu gcucacggug gcgaccgggg aucuccacag auucuuccgg 120
cguguauacc uucugcugcc uccuccgccg cugccuccuc cgccgcugcc uccuccgccc 180
ugcagcuugu acagcucguc caugccgccg g 211
<210> 1270
<211> 71
<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1270

cagcaucgcg agcaggcgcu gccuccuccg ccgcugccuc cuccgccgcu gccuccuccg 60

cccugcagcu u 71

<210> 1271

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1271

cccuccagca ucgcgagcag gcgcugccuc cuccgccgcu gccuccuccg ccgcugccuc 60

cuccgcccug c 71

<210> 1272

<211> 71

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1272

cagagcccuc cagcaucgcg agcaggcgcu gccuccuccg ccgcugccuc cuccgccgcu 60

gccuccuccg c 71

<210> 1273

<211> 72

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1273

acuggcagag cccucccagc aucgcgagca ggcgcugccu ccuccgccgc ugccuccucc 60

gccgcugccu cc 72

<210> 1274

<211> 71

<212> RNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1274
ugcucacugg cagagcccuc cagcaucgcg agcaggcgcu gccuccuccg ccgcugccuc 60
cuccgccgcu g 71
<210> 1275
<211> 71
<212> RNA
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<400> 1275
gcccuugcuc acuggcagag cccuccagca ucgcgagcag gcgcugccuc cuccgccgcu 60
gccuccuccg c 71
<210> 1276
<211> 71
<212> RNA
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<400> 1276
uccucgcccu ugcucacugg cagagcccuc cagcaucgcg agcaggcgcu gccuccuccg 60
ccgcugccuc c 71
<210> 1277
<211> 71
<212> RNA
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<400> 1277
ggugaacagc uccucgcccu ugcucacugg cagagcccuc cagcaucgcg agcaggcgcu 60
gccuccuccg c 71
<210> 1278
<211> 71
<212> RNA

<213> Artificial Sequence
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<400> 1278
accccgguga acagcuccuc gcccuugcuc acuggcagag cccuccagca ucgcgagcag 60
gcgcugccuc c 71
<210> 1279
<211> 71
<212> RNA
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<400> 1279
gcaccacccc ggugaacagc uccucgcccu ugcucacugg cagagcccuc cagcaucgcg 60
agcaggcgcu g 71
<210> 1280
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1280
gaugggcacc accccgguga acagcuccuc gcccuugcuc acuggcagag cccuccagca 60
ucgcgagcag g 71
<210> 1281
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1281
accaggaugg gcaccacccc ggugaacagc uccucgcccu ugcucacugg cagagcccuc 60
cagcaucgcg a 71
<210> 1282
<211> 71

<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1282
gcucgaccag gaugggcacc accccgguga acagcuccuc gcccuugcuc acuggcagag 60
cccuccagca u 71
<210> 1283
<211> 71
<212> RNA
<213> Artificial Sequence
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<400> 1283
guccagcucg accaggaugg gcaccacccc ggugaacagc uccucgcccu ugcucacugg 60
cagagcccuc c 71
<210> 1284
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1284
cacagauucu uccggcgugu auaccuucug cugccuccuc cgccgcugcc uccuccgccg 60
cugccuccuc c 71
<210> 1285
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1285
aucuccacag auucuuccgg cguguauacc uucugcugcc uccuccgccg cugccuccuc 60
cgccgcugcc u 71
<210> 1286

<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1286
cggggaucuc cacagauucu uccggcgugu auaccuucug cugccuccuc cgccgcugcc 60
uccuccgccg c 71
<210> 1287
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1287
gcgaccgggg aucuccacag auucuuccgg cguguauacc uucugcugcc uccuccgccg 60
cugccuccuc c 71
<210> 1288
<211> 71
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1288
cgguggcgac cggggaucuc cacagauucu uccggcgugu auaccuucug cugccuccuc 60
cgccgcugcc u 71
<210> 1289
<211> 71
<212> RNA
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1289
gcucacggug gcgaccgggg aucuccacag auucuuccgg cguguauacc uucugcugcc 60
uccuccgccg c 71

<210> 1290
<211> 71
<212> RNA
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cugccuccuc c 71
<210> 1291
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1291
cagcuccucg cccuugcuca cgguggcgac cggggaucuc cacagauucu uccggcgugu 60
auaccuucug c 71
<210> 1292
<211> 71
<212> RNA
<213> Artificial Sequence
<220>
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<400> 1292
gugaacagcu ccucgcccuu gcucacggug gcgaccgggg aucuccacag auucuuccgg 60
cguguauacc u 71
<210> 1293
<211> 71
<212> RNA
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ccccggugaa cagcuccucg cccuugcuca cgguggcgac cggggaucuc cacagauucu 60

uccggcgugu a 71
<210> 1294
<211> 71
<212> RNA
<213> Artificial Sequence
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auucuuccgg c 71
<210> 1295
<211> 71
<212> RNA
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cacagauucu u 71
<210> 1296
<211> 71
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ccaggauggg caccaccccg gugaacagcu ccucgcccuu gcucacggug gcgaccgggg 60
aucuccacag a 71
<210> 1297
<211> 71
<212> RNA
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<400> 1297

cucgaccagg augggcacca ccccggugaa cagcuccucg cccuugcuca cgguggcgac 60
cggggaucuc c 71
<210> 1298
<211> 111
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1299
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<211> 111
<212> RNA
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1301
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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<213> Artificial Sequence
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polynucleotide
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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polynucleotide
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<210> 1304
<211> 111
<212> RNA
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polynucleotide
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 1305

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1306

<211> 111

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

polynucleotide

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1307

<211> 111

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 1307

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1308

<211> 111

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 1308

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1309

<211> 111

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1309

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1310

<211> 111

<212> RNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic polynucleotide

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1311

<211> 111

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1311

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1312

<211> 111

<212> RNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1312

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1313

<211> 111

<212> RNA

<213> Artificial Sequence

<220>
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<400> 1313
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1314
<211> 111
<212> RNA
<213> Artificial Sequence
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gcgauguucu cugcugggga auugcgcgau auucaggauu aaaagaagug c 111
<210> 1315
<211> 151
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
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acuacaguug cuccgauauu uaggcuacgu caauaggcac uaacuuauug gcgcugguga 60
acggacuucc ucucgaguac cagaagauga cuacaaaacu ccuuuccauu gcgaguaucg 120
gagucuggcu caguuuggcc agggaggcac u 151
<210> 1316
<211> 51
<212> RNA
<213> Artificial Sequence
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<400> 1316
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<210> 1317
<211> 71
<212> RNA

<213> Artificial Sequence
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<400> 1317
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ggugggggg a 71
<210> 1318
<211> 111
<212> RNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1318
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agccggcgcc gccacgcgcg ggugggggg acuggguug cucgcgggcu c 111
<210> 1319
<211> 151
<212> RNA
<213> Artificial Sequence
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<400> 1319
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uggggccgcg guggccaggg agccggcgcc gccacgcgcg ggugggggg acuggguug 120
cucgcgggcu ccgggcgggc ggcgggcgcc g 151
<210> 1320
<211> 51
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1320
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<210> 1321
<211> 111

<212> RNA
<213> Artificial Sequence
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gauucugaau uagcuguauc gucaaggcac ucuugccuac gccaccagcu ccaaccacca 60
caaguuuaua uucagucauu uucagcaggc cucucucccg caccugggag c 111
<210> 1322
<211> 151
<212> RNA
<213> Artificial Sequence
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<400> 1322
aucauauucg uccacaaaau gauucugaau uagcuguauc gucaaggcac ucuugccuac 60
gccaccagcu ccaaccacca caaguuuaua uucagucauu uucagcaggc cucucucccg 120
caccugggag ccgcugagcc ucuggccccg c 151
<210> 1323
<211> 51
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<400> 1323
ucggcauggu augaaguacu ucguccagga gcuggagggc ccgguguaag u 51
<210> 1324
<211> 71
<212> RNA
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<400> 1324
gggucugcaa ucggcauggu augaaguacu ucguccagga gcuggagggc ccgguguaag 60
ugaauuucaa u 71
<210> 1325

<211> 111
<212> RNA
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gcuggagggc ccgguguaag ugaauuucaa uccagcaagg uguuucuuug a 111
<210> 1326
<211> 151
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1326
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augaaguacu ucguccagga gcuggagggc ccgguguaag ugaauuucaa uccagcaagg 120
uguuucuuug augcucuguc uuggguaauc c 151
<210> 1327
<211> 51
<212> RNA
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<400> 1327
ugggggguuc ggcugccgac aucagcaauu gcucugccac caucucagcc c 51
<210> 1328
<211> 71
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic oligonucleotide
<400> 1328
agcagggccg ugggggguuc ggcugccgac aucagcaauu gcucugccac caucucagcc 60
cauccuccga a 71

<210> 1329
<211> 111
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1329
aguagaaggc caagagccac agcagggccg ugggggguuc ggcugccgac aucagcaauu 60
gcucugccac caucucagcc cauccuccga agugaaugaa caggaaccag c 111
<210> 1330
<211> 151
<212> RNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1330
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ggcugccgac aucagcaauu gcucugccac caucucagcc cauccuccga agugaaugaa 120
caggaaccag cucucaaagg gaccuccgca g 151
<210> 1331
<211> 151
<212> DNA
<213> Artificial Sequence
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<400> 1331
gccaaacacc acatgcttgc catctagcca ggctgtcttg actgtcgtga tgaagaactg 60
ggagccgttg gtgtccttgc ctgcgttggc catgctcacc cagccaggcc cgtagtgctt 120
cagtttgaag ttctcatcgg ggaagcgctc a 151
<210> 1332
<211> 151
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1332
gggagtgggt ccgctccacc agatgccagc accggggcca gtgcagctca gagccctgtg 60
gcggactaca gggcccgcac agacggtcac tcaaagaaag atgtccctgt gccctactcc 120
ttggcgatgg caaagggctt ctccacctcg a 151
<210> 1333
<211> 151
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
<400> 1333
tgcattttgt aaaatagata ctagcagatt gtcccaagat gtgtacagct cattctcaca 60
gcccagcgag ggcacctact ccacaaatgc gtggccacag gtcatcacct gtcctgtggc 120
cctggcgagc ctgatccctc acgccgggca c 151
<210> 1334
<211> 151
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Synthetic polynucleotide
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gctcattctc acagcccagc gagggcactt actccacaaa tgcgtggcca caggtcatca 60
cctgtcctgt ggccccggcg agcctgatcc ctcacgccgg gcacccacac ggcctgcgtg 120
ccttctagac ttgagttcgc agctctttaa g 151
<210> 1335
<211> 151
<212> DNA
<213> Artificial Sequence
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<400> 1335
tcggccgggc cctgggggcg gtgggcgctg gccaggacgc ccaccgtgtg gttgctgtcc 60
aggacggtcc cggcccgcga cacttcggcc cagagctgct cctcatccag cagcgccagc 120
agccccatgg ccgtgagcac cggcttgcgc a 151
<210> 1336
<211> 111

<212> RNA
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ugaccagucu uaagaucuuu cuugaccugc accauaagaa cuucuccaaa gguaccaaaa 60
uacucuuuca gguccuguuc gguuguuuuc caugggagac ccaacacuau u 111
<210> 1337
<211> 111
<212> RNA
<213> Artificial Sequence
<220>
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<400> 1337
gaugggcacc accccgguga acagcuccuc gcccuugcuc acuggcagag cccucgagca 60
ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1338
<211> 111
<212> RNA
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<400> 1338
gaugggcacc accccgguga acagcuccuc gcccuugcuc acuggcagag cccuggagca 60
ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1339
<211> 111
<212> RNA
<213> Artificial Sequence
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1340

<211> 111
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1341
<211> 111
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1342
<211> 111
<212> RNA
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1343
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<400> 1343
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1344
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<212> RNA
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1345
<211> 111
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1346
<211> 111
<212> RNA
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1348

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<212> RNA

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1349

<211> 111

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<400> 1349

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1350

<211> 111

<212> RNA

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<223> Description of Artificial Sequence: Synthetic polynucleotide

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

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<400> 1351

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1354
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
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<210> 1356
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polynucleotide
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<210> 1357
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<212> RNA
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polynucleotide
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1358
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<212> RNA
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polynucleotide
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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111
<210> 1359
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polynucleotide

<400> 1359

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1360

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

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<223> Description of Artificial Sequence: Synthetic

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ucgcgagcag gcgcugccuc cuccgcccug cagcuuguac agcucgucca u 111

<210> 1362

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 1362

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<211> 111

<212> RNA

<213> Artificial Sequence

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<210> 1365

<211> 111

<212> RNA

<213> Artificial Sequence

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caaguggaga gucagucauu uucagcaggc cucucucccg caccggggag c 111
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<211> 111
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cugagcacuu ccacagagug gguuaaagcg gcuccgaaca cgaaacgugu a 111
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<212> RNA
<213> Artificial Sequence
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cugcuccuca uccagcagcg ccagcagccc cauggccgug agcaccggcu u 111
<210> 1379

<211> 111
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cugcuccuca ucugcggggc gggggggggc cgucgccgcg uggggucguu g 111
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agtactggct ttcgcagcaa ctgcacatgg g 151
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<211> 151
<212> DNA
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acggacttcc tctcgagtac cagaagatga ctacaaaact cctttccatt gcgagtatcg 120
gagtctggct cagtttggcc agggaggcac t 151
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<400> 1382

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cuucccugc 70
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uucagucauu uucagcaggc cucucucccg c 91
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polynucleotide
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caaguuuaua uucagucauu uucagcaggc cucucucccg caccugggag c 111
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polynucleotide
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ccgcugagcc u 131
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polynucleotide

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ucuugccuac gccaccagcu ccaaccacca caaguuuaua uucagucauu uucagcaggc 120

cucucucccg caccugggag ccgcugagcc ucuggccccg ccgccgccuu c 171

<210> 1392

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gucaaggcac ucuugccuac gccaccagcu ccaaccacca caaguuuaua uucagucauu 120

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cagugccugc g 191

<210> 1393

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<212> RNA

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ucauacuccu g 131
<210> 1398
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aaucaaaguc 70
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gagauucagu g 71
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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 1411

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oligonucleotide
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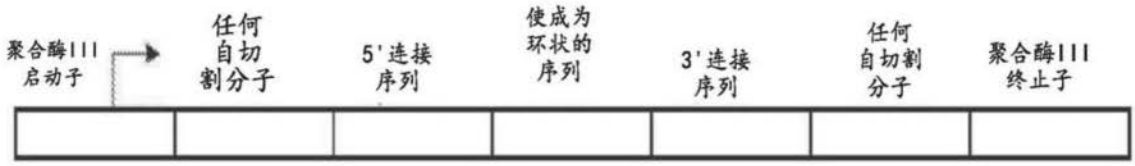
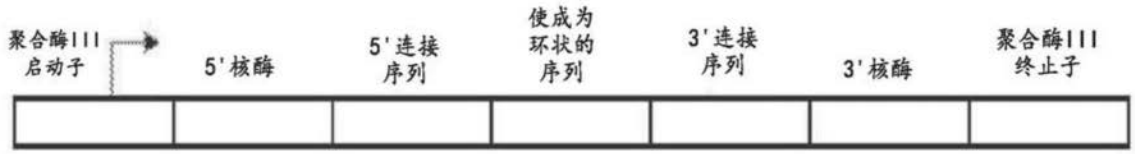
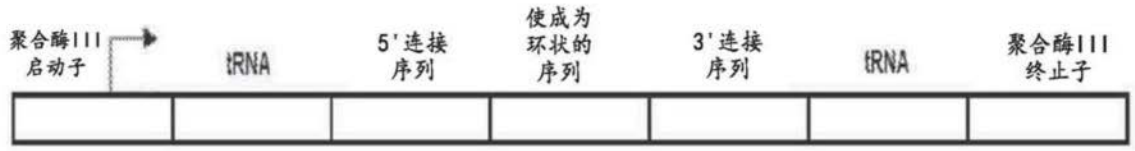
构建体设计



自切割分子的例子





使成为环状的序列的例子

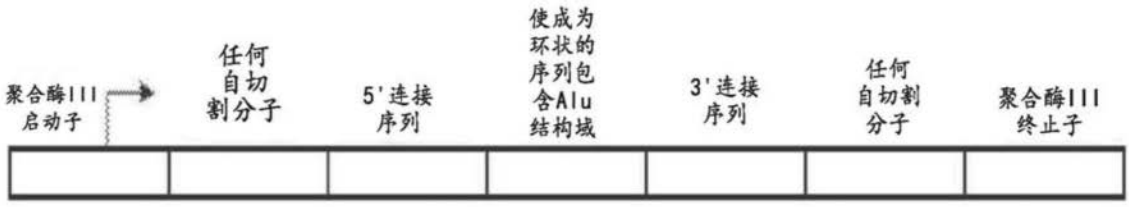


FIG.1A

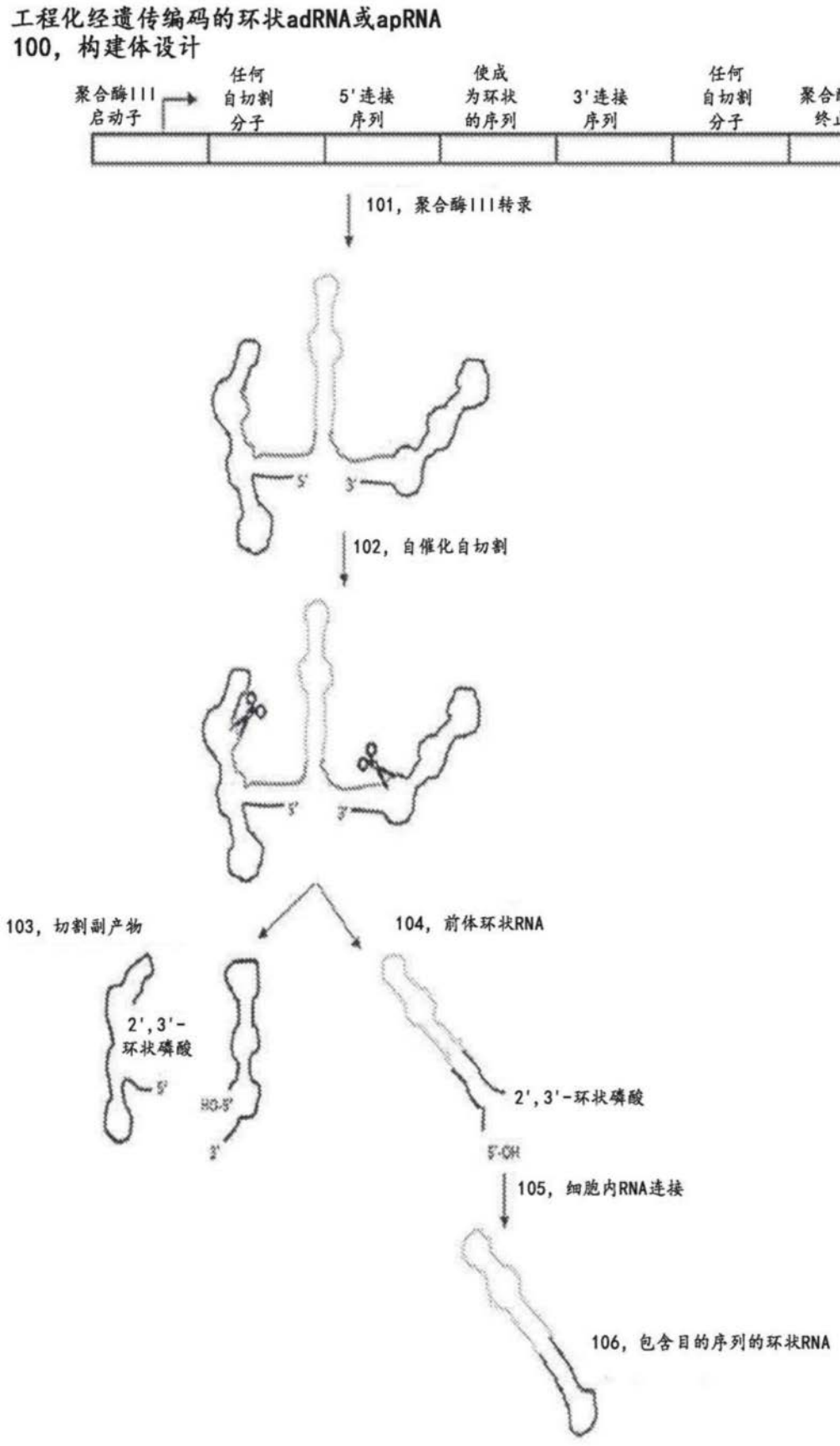
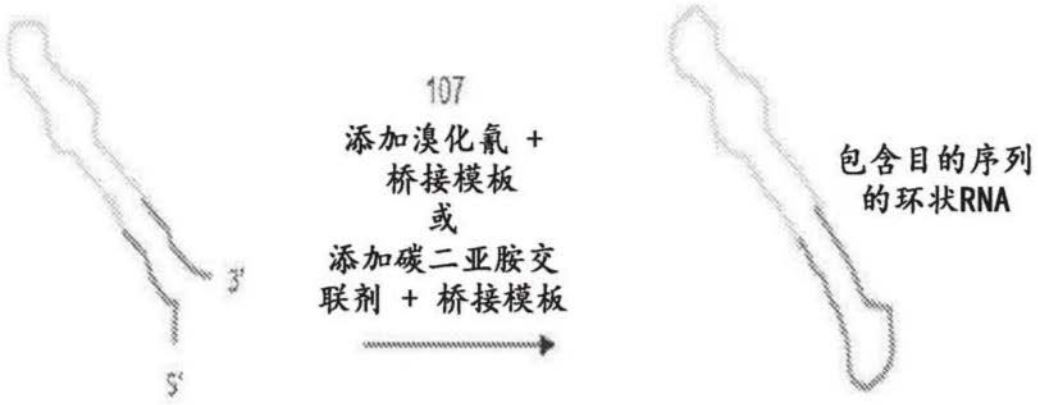

工程化经遗传编码的环状adRNA或apRNA
100，构建体设计
聚合酶III启动子
任何自切割分子
5'连接序列
使成为环状的序列
3'连接序列
任何自切割分子
聚合酶III终止子
101，聚合酶III转录
5'
3'
102，自催化自切割
103，切割副产物
104，前体环状RNA
2',3'-环状磷酸
5'
HO-5'
3'
2',3'-环状磷酸
5'-OH
105，细胞内RNA连接
106，包含目的序列的环状RNA

FIG.1B

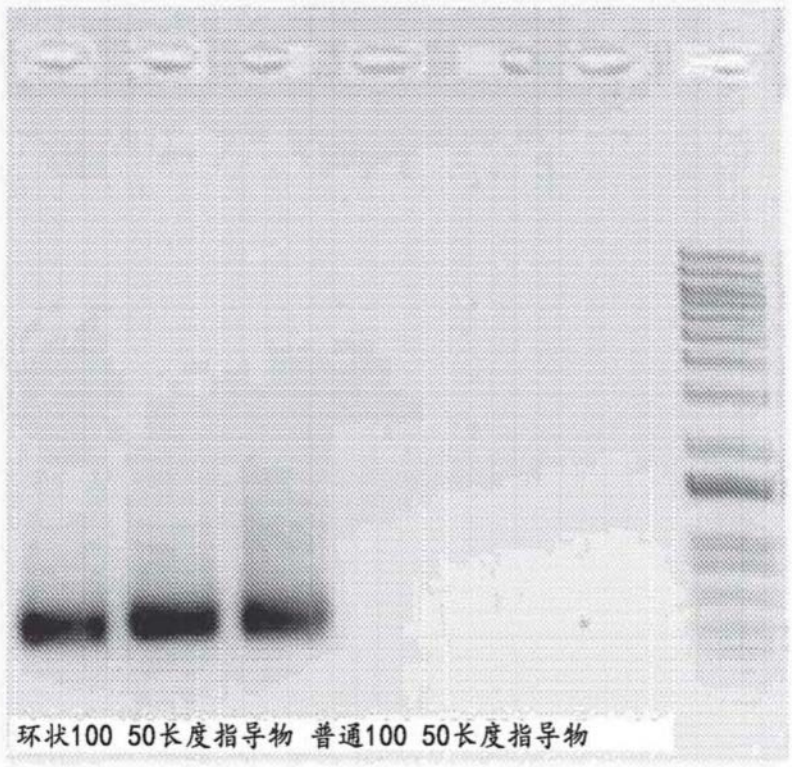
工程化经化学合成的环状adRNA或apRNA

可以使用溴化氰或碳二亚胺交联剂1-乙基-3-(3-二甲基氨基丙基)碳二亚胺与桥接模板一起实现线性寡核苷酸的化学环化。



环状DNA或RNA寡核苷酸的酶促合成可以通过T4连接酶进行。这些酶可以环化反应性3'-OH和5'PO4基团。

FIG.1C



上图：凝胶显示出Alu 100_50指导物的环化

FIG.2

Alu-v2经环化的构建体的序列：

P3核酶

Alu元件

反义指导物

靶C错配

P1核酶

SEQ. ID NO 1418

经环化的Alu 60-30 R7A指导物：

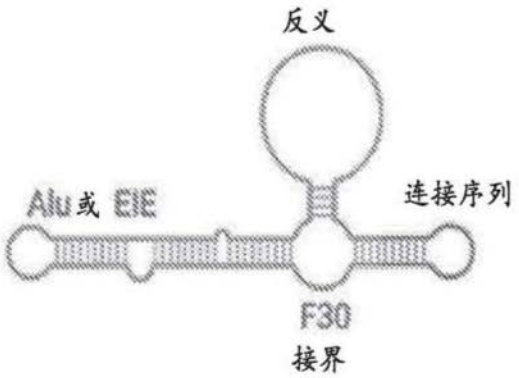
CTTGTGGAAAGGACGAAACACCGCCATCAGTCGCCGGTCCCAAGCCCGGATAAAATGGGAGGGGGCGGGA
AACCGCCTAACCATGCCGACTGATGGCAGAAAAAAAAAAGGCCGGGCGCGGTGGCTCACGCCTGTAATCC
CAGCACTTTGGGAGGCCGAGGCGGGGAGATTGCTTGAGCCCAGGAGTTCGAGACCAGCCTGGGCAACATA
GCGAGACCCCGTCTCTCTTGTGTCTACTGTACAGAATACTGCCGCCAGCTGGATTTCCCAATTCTGAGTA
ACACAGCCGGGCGTGGTGGCGCGCGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGGATCGCTT
GAGCCCAGGAGTTCGAGGCTGCAGTGAGCTATGATCGCGCCACTGCACTCCAGCCTGGGCGACAGAGCGA
GACCCTGTCTCAAAAAAAAAAACTGCCATCAGTCGGCGTGGACTGTAGAACACTGCCAATGCCGGTCCCAA
GCCCGGATAAAAGTGGAGGGTACAGTCCACGC

SEQ. ID NO 1419

经环化的Alu 100-50 R7A指导物：

CTTGTGGAAAGGACGAAACACCGCCATCAGTCGCCGGTCCCAAGCCCGGATAAAATGGGAGGGGGCGGGA
AACCGCCTAACCATGCCGACTGATGGCAGAAAAAAAAAAGGCCGGGCGCGGTGGCTCACGCCTGTAATCC
CAGCACTTTGGGAGGCCGAGGCGGGGAGATTGCTTGAGCCCAGGAGTTCGAGACCAGCCTGGGCAACATA
GCGAGACCCCGTCTCTGATAAAAGGCGTACATAATTCTTGTGTCTACTGTACAGAATACTGCCGCCAGCT
GGATTTCCCAATTCTGAGTAACACTCTGCAATCCAAACAGGGTTCAGCCGGGCGTGGTGGCGCGCGCCTG
TAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGGATCGCTTGAGCCCAGGAGTTCGAGGCTGCAGTGAGC
TATGATCGCGCCACTGCACTCCAGCCTGGGCGACAGAGCGAGACCCTGTCTCAAAAAAAAAAACTGCCATC
AGTCGGCGTGGACTGTAGAACACTGCCAATGCCGGTCCCAAGCCCGGATAAAAGTGGAGGGTACAGTCCA
CGC

FIG.3A



所使用的Alu元件的序列 (SEQ ID NO:1420):

ggctgggcgcagtggctcatgcctgtaatcccagcacttcgggaggccgagtgggggtggctcacctgaggtca
ggagttcgagaccatcctggccaacatggtgaaaccccatctctactaaaaatgcaaaaaattagccaggtgt
ggtggtgggcacctgtaatctcagctactcgggaggatgaggcaggaaaatcgcttaaacccaggaggtggag
gttgcagttgagctgagatcgtgccattgcactccagcctgggcaacaagagcaaaactccatctcaaaaaaa
aaaaaaacaaaaaaacagtgtttcctccaagctgcccatgagacaggcaggacaaggattcttttatatattt
atacacacacacacacacacacacacacgcacgtttatatatatttttggtagagataggatcttgccatgtt
gcctggactagcctcaaactgggctcaagtgatcctcccacatctgcctctaagtagctaggactacaggctc
acaccaccacaccgggctaattgttaaaaatttttttttgtagagacagggtctccctatgttgcccaggctgg
tattgaactcctggcccctagggattctcccatctaagcttcccaaagtgtcgggattacaggtgtggccact
gcacagggccag

GABRA3 EIE的序列(SEQ ID NO:1421):

gaagcaaaggaagggctgagaagcacttcctgagagatctgtattgggaccagaagtgagtagcctgtagccc
gcaggaactcagcagggctatgttctattcactgggggtcatcaatacaattctcaactggagtgcttcttggt
aatctggccttaactagtcac

GluA2 EIE的序列(SEQ ID NO:1422):

ggttggtcactcacctgcttcaactttgtgcaatttaggtctcaagtggatattcatggtgtctatgaattca
ctataaagatgtcagcagctgccgaccatttgtccaagcaaatttaagatgcttagaaggcaaattcttaccg
tcggcgtaagcctgtgaaatacctgaacaatgttccttgaatgttgatcatgtgtttcccctggtgaaatcata
tacaccatggagaggctataaaatgcagaaggttcctatcattccatgcctgc

Cyfip2 EIE的序列(SEQ ID NO:1423):

gatgcaggtggattcccacagtgccaggaggggaatggcttgagtgctctgagccctttggcatcagcccctta
gctaccaggctctaaagggctcagagcacagccacaccccctgtcctgctctgcggtgactccccctccc

FIG.3B

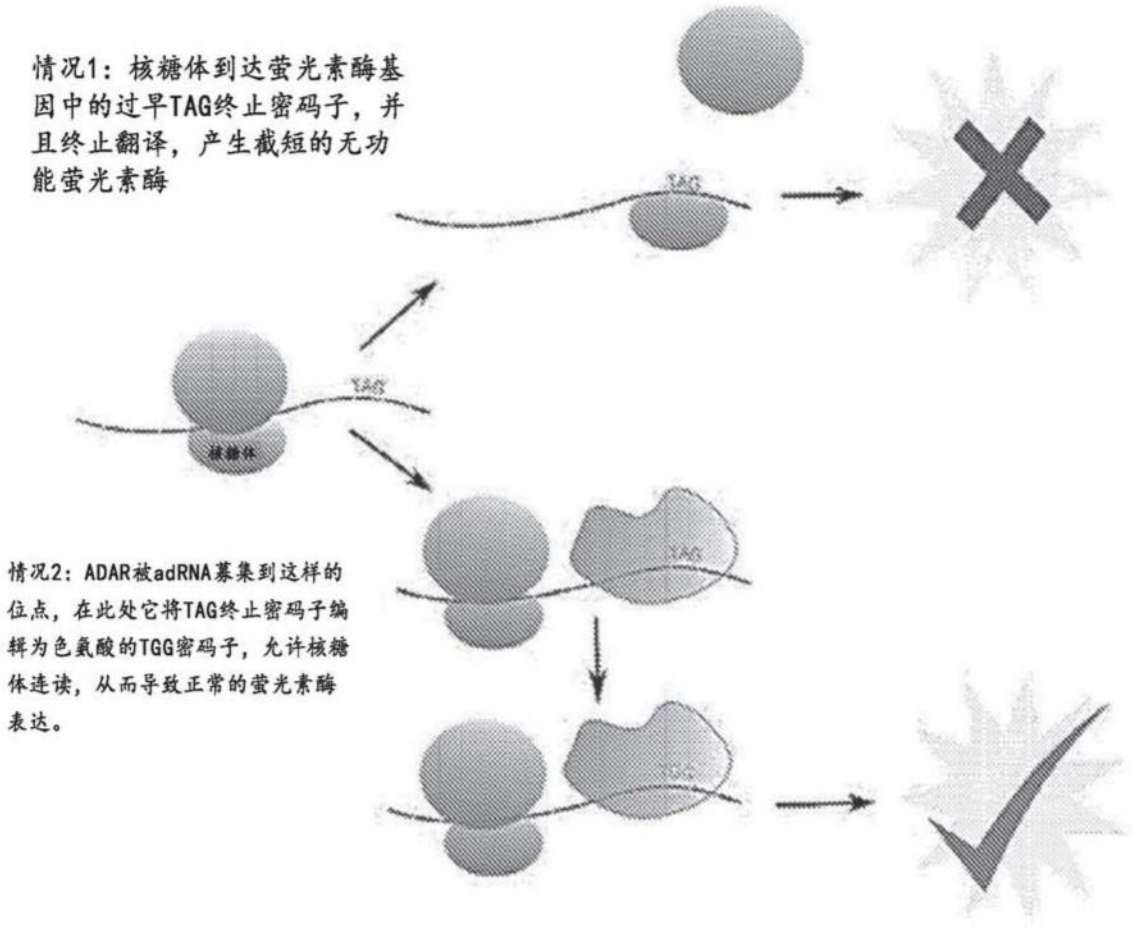

情况1：核糖体到达萤光素酶基因中的过早TAG终止密码子，并且终止翻译，产生截短的无功能萤光素酶
TAG
TAG
核糖体
情况2：ADAR被adRNA募集到这样的位点，在此处它将TAG终止密码子编辑为色氨酸的TGG密码子，允许核糖体连读，从而导致正常的萤光素酶表达。
TAG
TGG

FIG.4

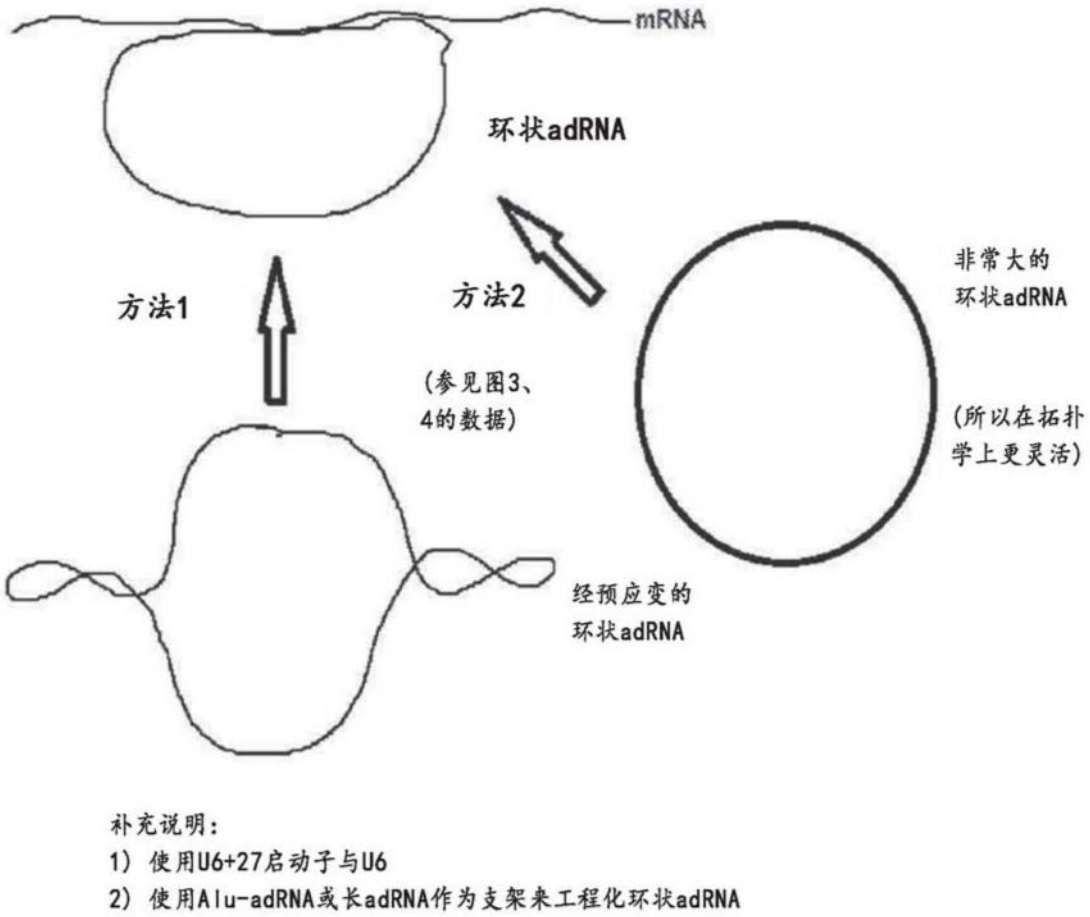

mRNA
环状adRNA
方法1
方法2
(参见图3、
4的数据)
非常大的
环状adRNA
(所以在拓扑
学上更灵活)
经预应变的
环状adRNA
补充说明:
1) 使用U6+27启动子与U6
2) 使用Alu-adRNA或长adRNA作为支架来工程化环状adRNA

FIG.5

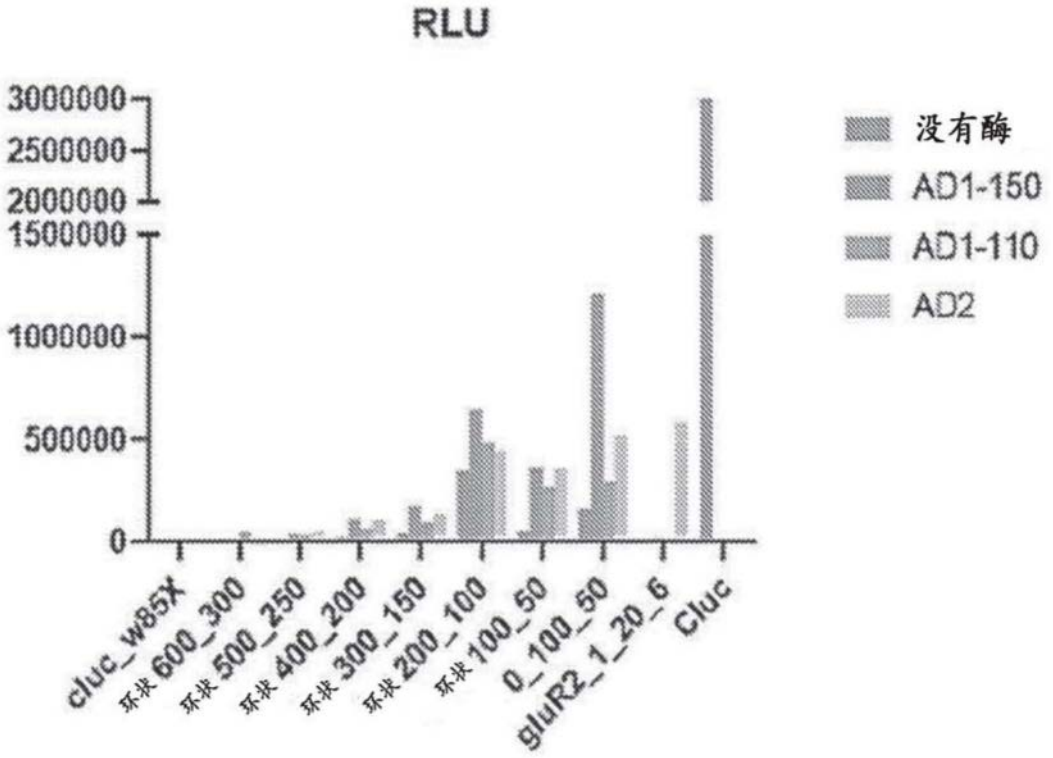

RLU
3000000
2500000
2000000
1500000
1000000
500000
0
没有酶
AD1-150
AD1-110
AD2
cluc_w85X
环状600_300
环状500_250
环状400_200
环状300_150
环状200_100
环状100_50
0_100_50
gluR2_1_20_6
Cluc

FIG.6

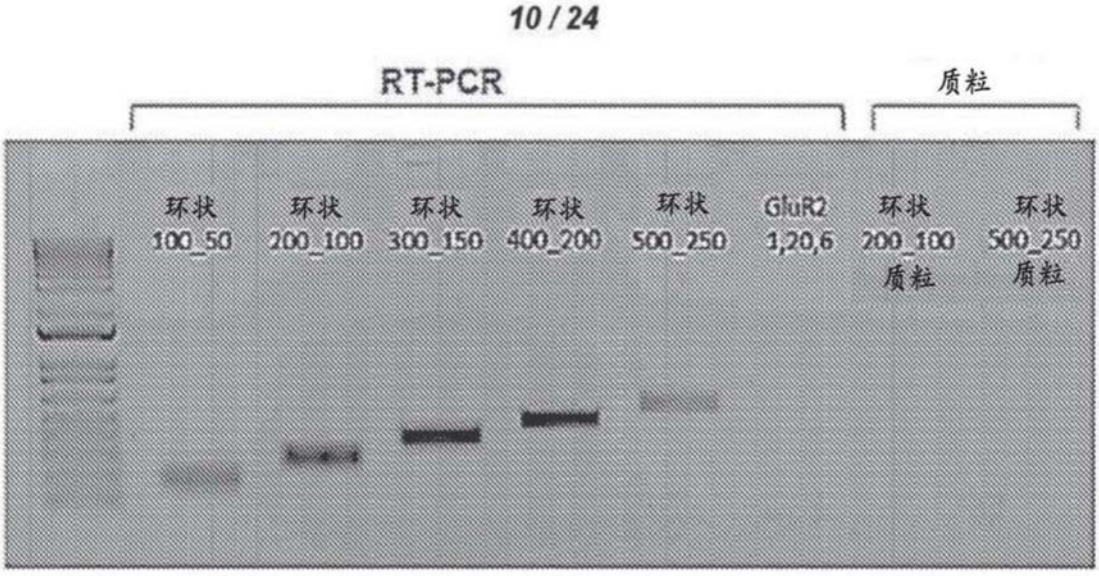
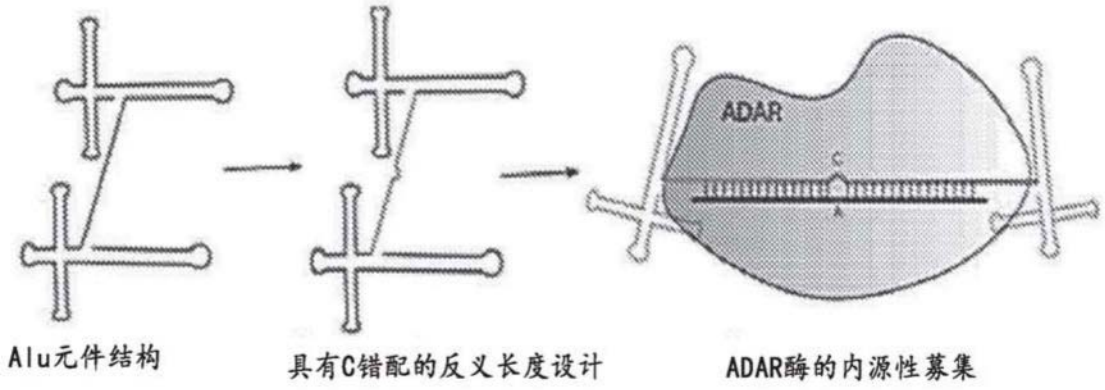

10 / 24
RT-PCR
质粒
环状 100_50
环状 200_100
环状 300_150
环状 400_200
环状 500_250
GluR2 1,20,6
环状 200_100 质粒
环状 500_250 质粒

FIG.7


ADAR
C
A
Alu元件结构
具有C错配的反义长度设计
ADAR酶的内源性募集

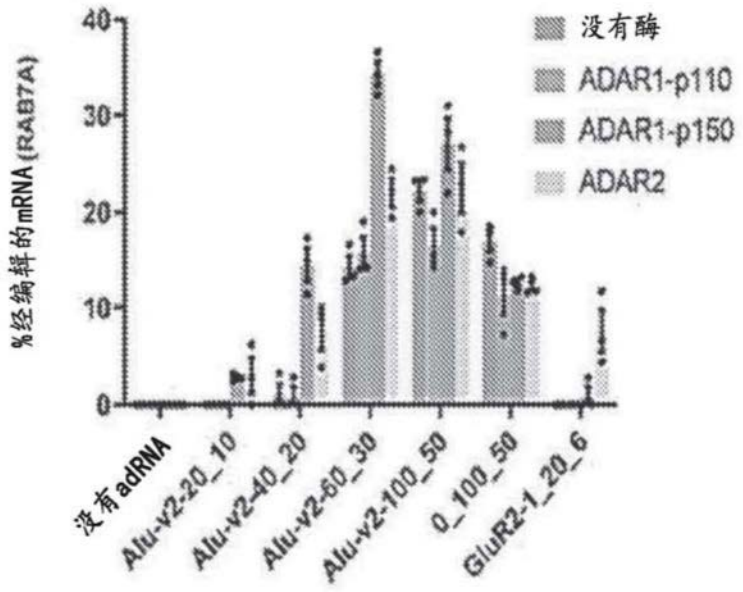

%经编辑的mRNA (RAB7A)
40
30
20
10
0
没有酶
ADAR1-p110
ADAR1-p150
ADAR2
没有adRNA
Alu-v2-20_10
Alu-v2-40_20
Alu-v2-60_30
Alu-v2-100_50
0_100_50
GluR2-1_20_6

FIG.8

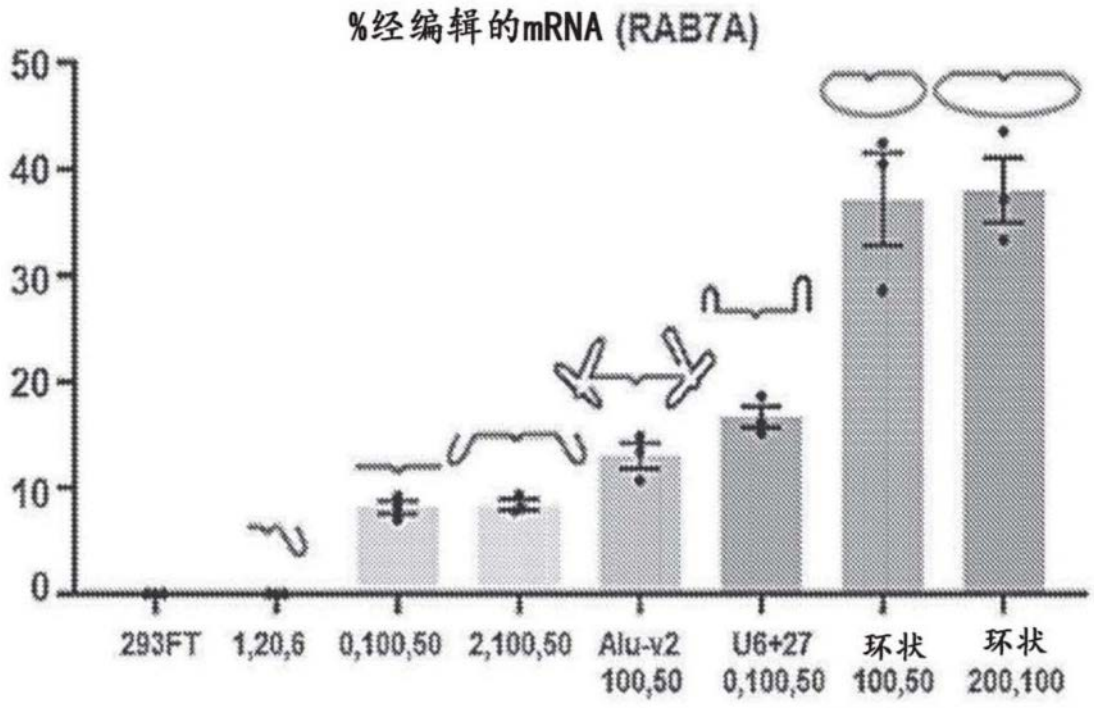

%经编辑的mRNA (RAB7A)
50
40
30
20
10
0
293FT
1,20,6
0,100,50
2,100,50
Alu-v2
100,50
U6+27
0,100,50
环状
100,50
环状
200,100

FIG.9A

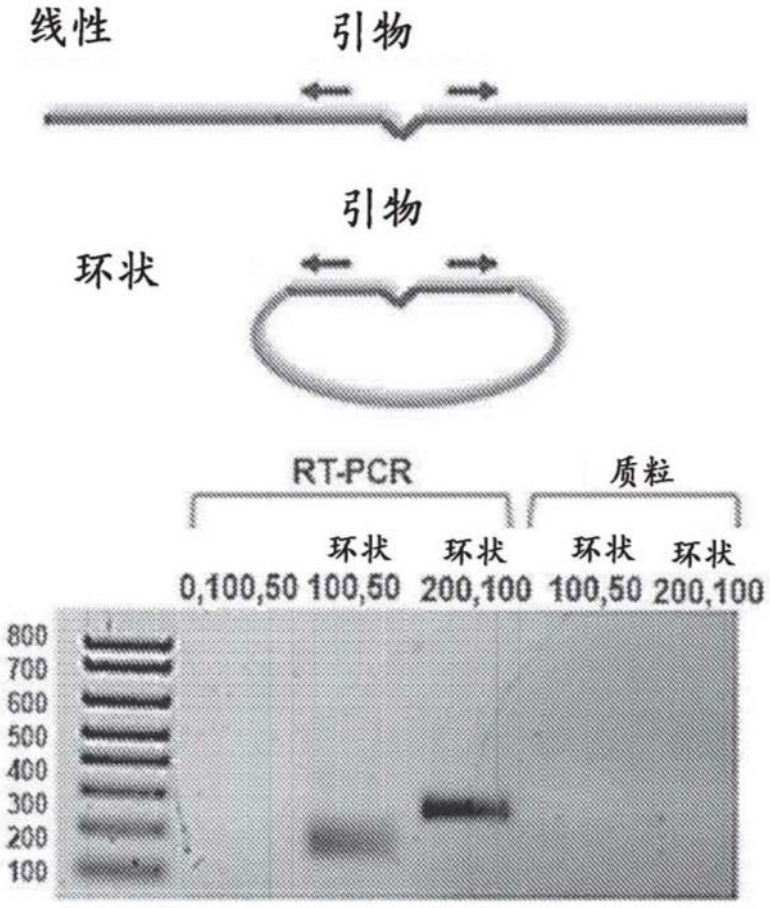

线性
引物
引物
环状
RT-PCR
质粒
环状
环状
环状
环状
0,100,50
100,50
200,100
100,50
200,100
800
700
600
500
400
300
200
100

FIG.9B

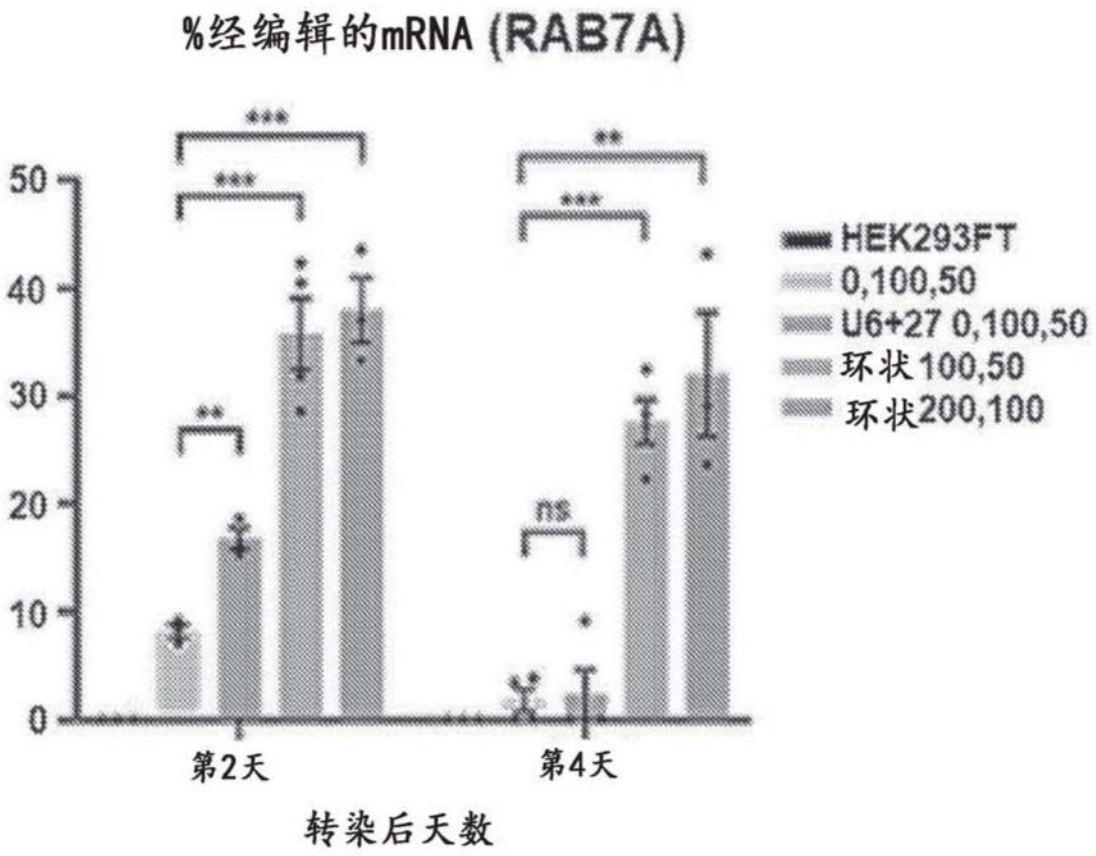

%经编辑的mRNA (RAB7A)
50
40
30
20
10
0
***
***
**
**
***
ns
HEK293FT
0,100,50
U6+27 0,100,50
环状100,50
环状200,100
第2天
第4天
转染后天数

FIG.9C

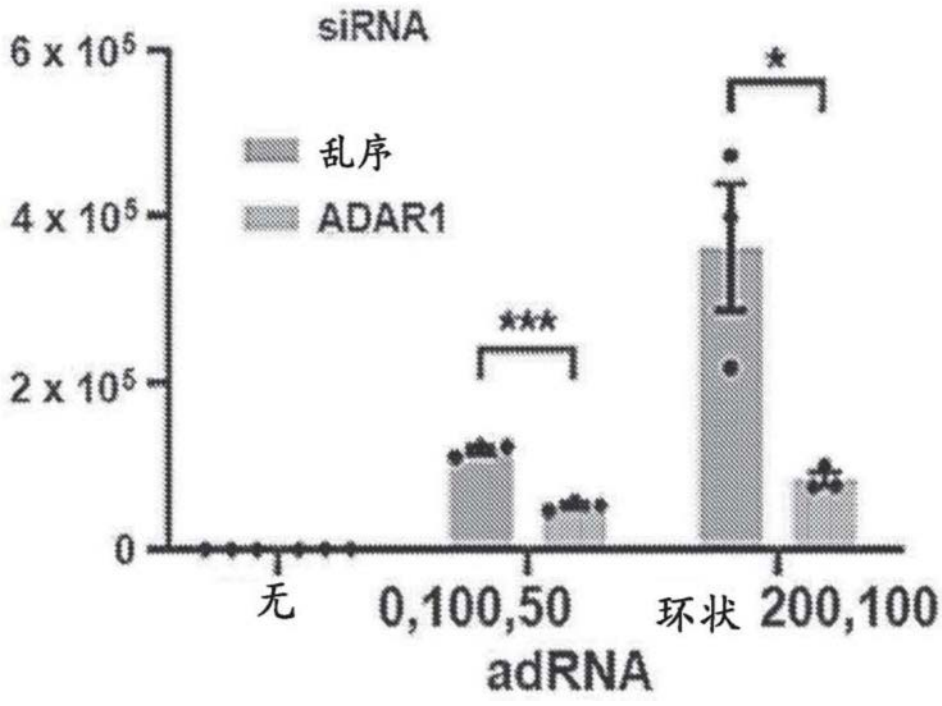

siRNA
6 x 10^5
4 x 10^5
2 x 10^5
0
乱序
ADAR1
***
*
无
0,100,50
环状 200,100
adRNA

FIG.9D

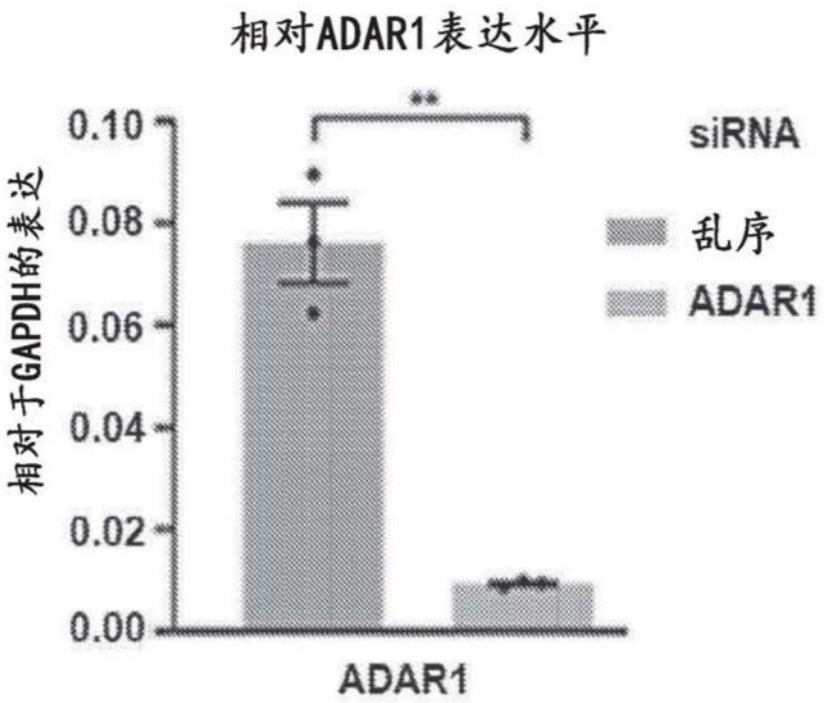


FIG.9E

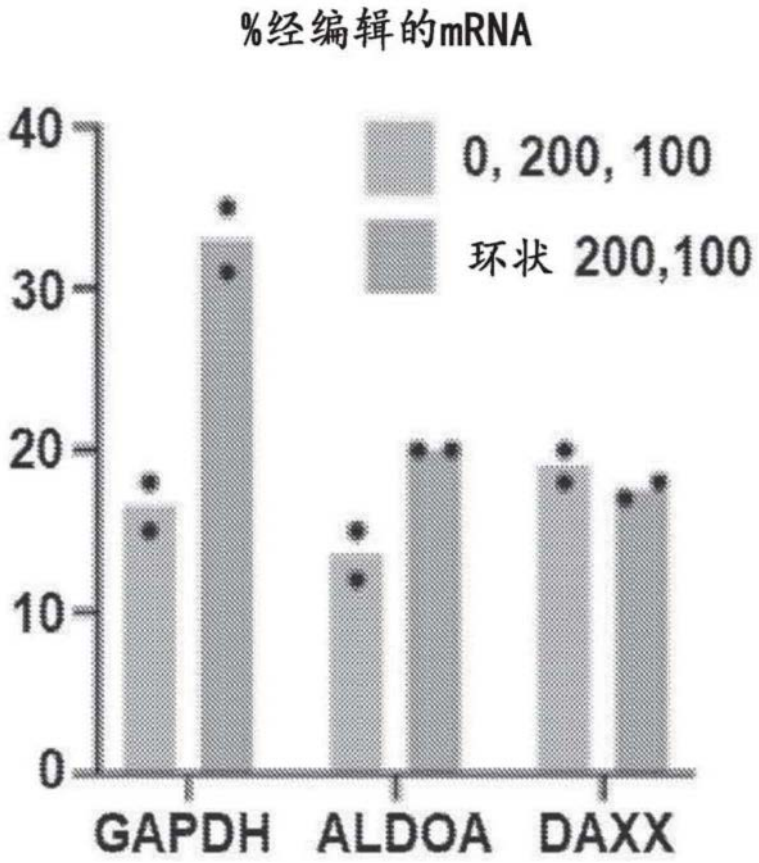


FIG.10A

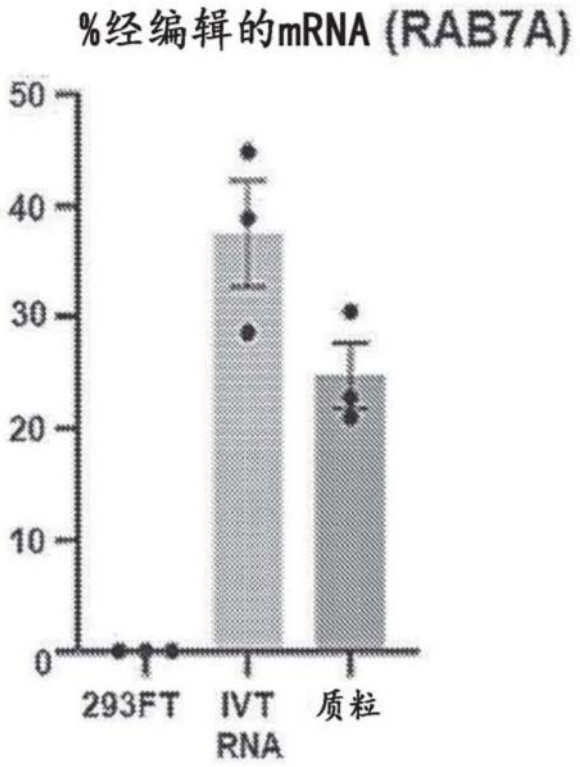


FIG.10B

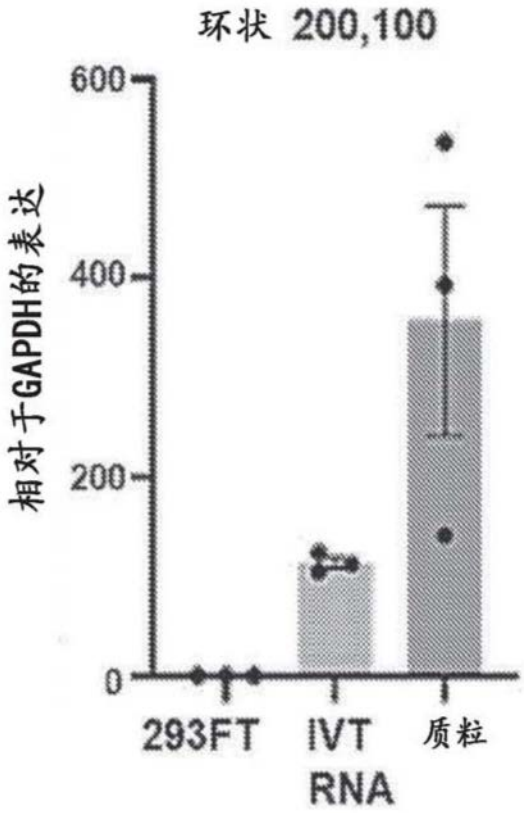


FIG.10C

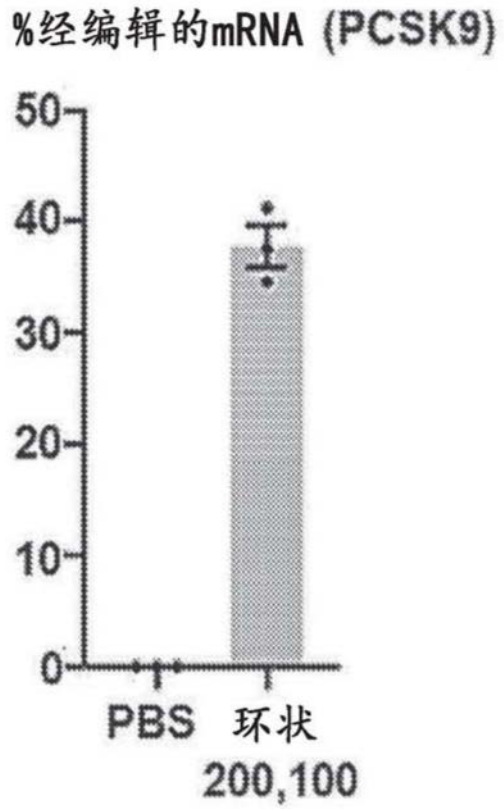


FIG.11A

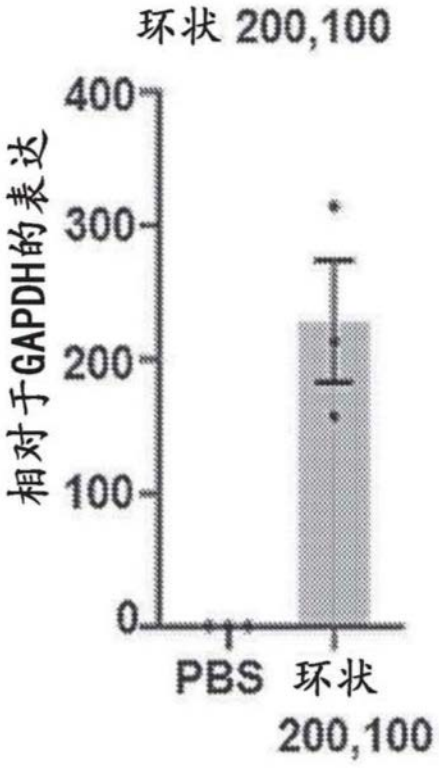


FIG.11B

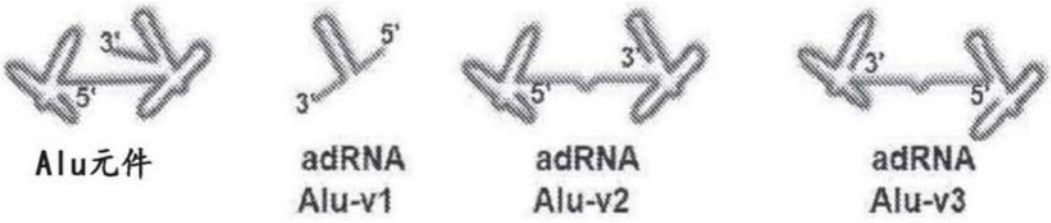


FIG.12A

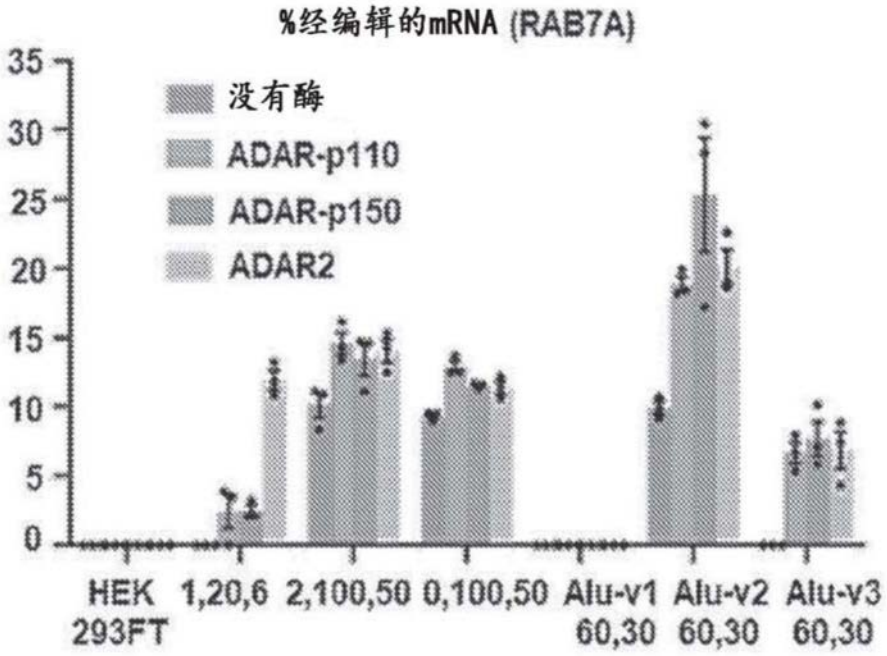


FIG.12B

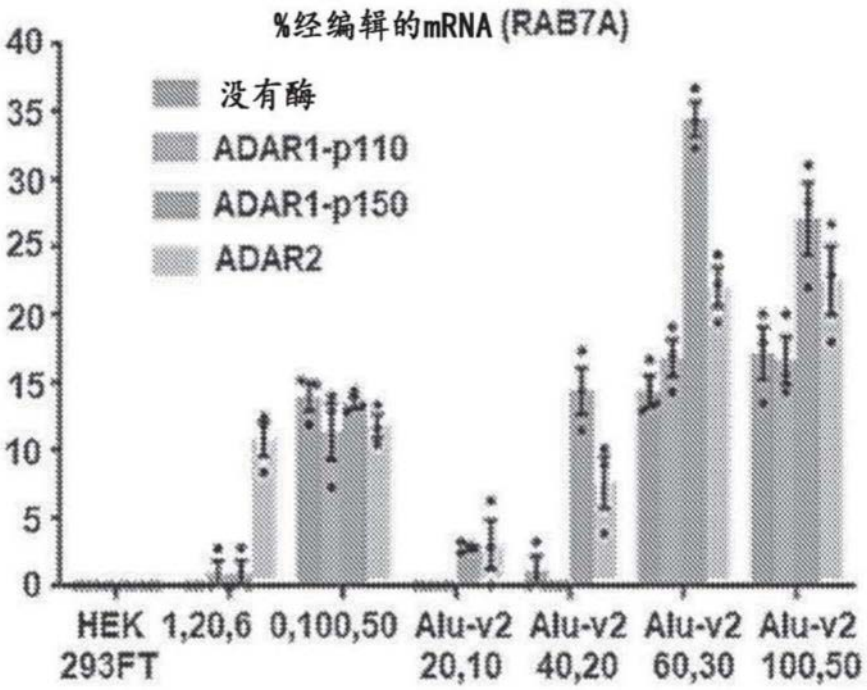

%经编辑的mRNA (RAB7A)
40
35
30
25
20
15
10
5
0
没有酶
ADAR1-p110
ADAR1-p150
ADAR2
HEK 293FT
1,20,6
0,100,50
Alu-v2 20,10
Alu-v2 40,20
Alu-v2 60,30
Alu-v2 100,50

FIG.12C

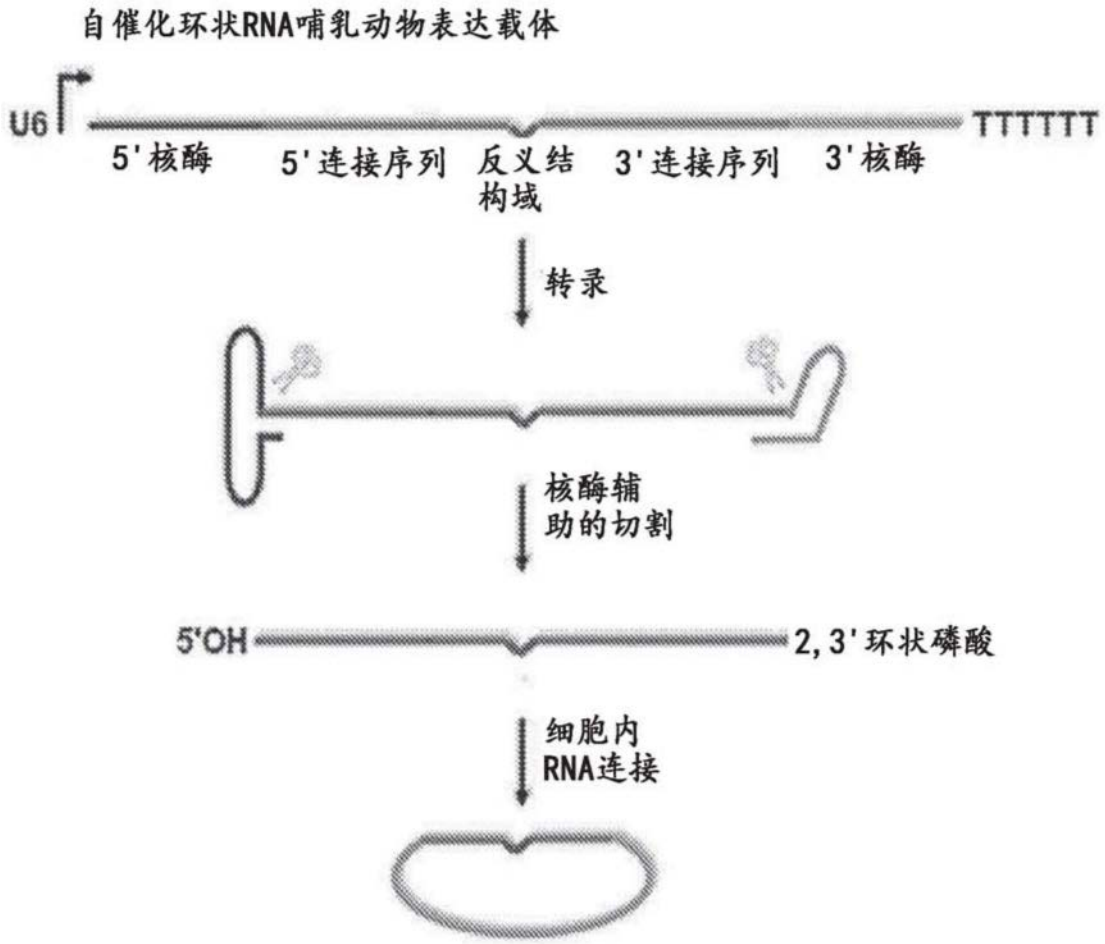


FIG.13A

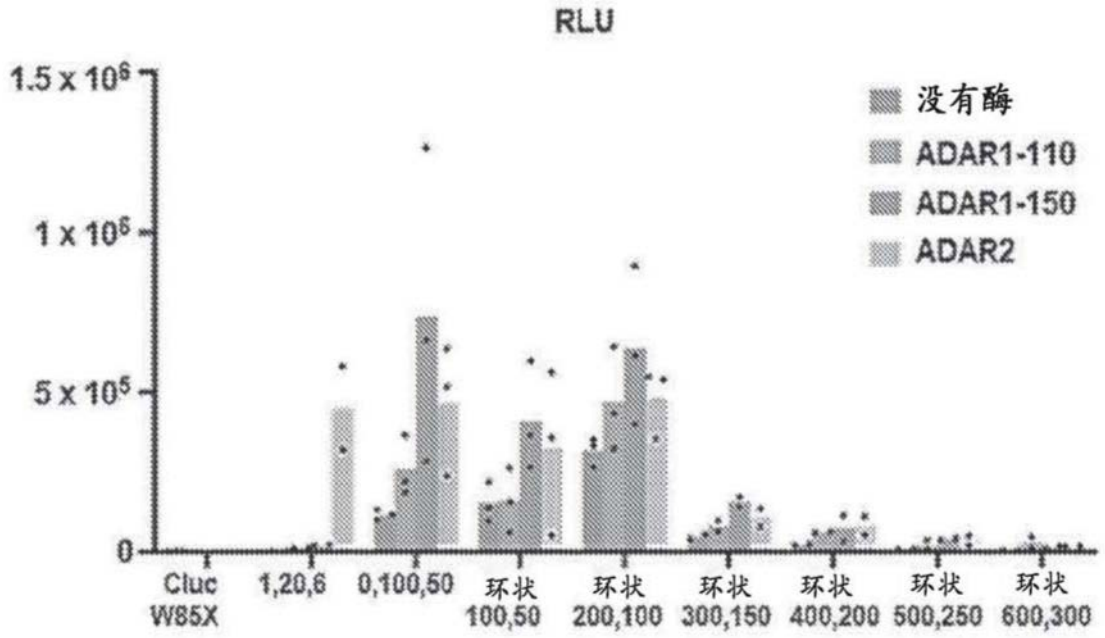


FIG.13B

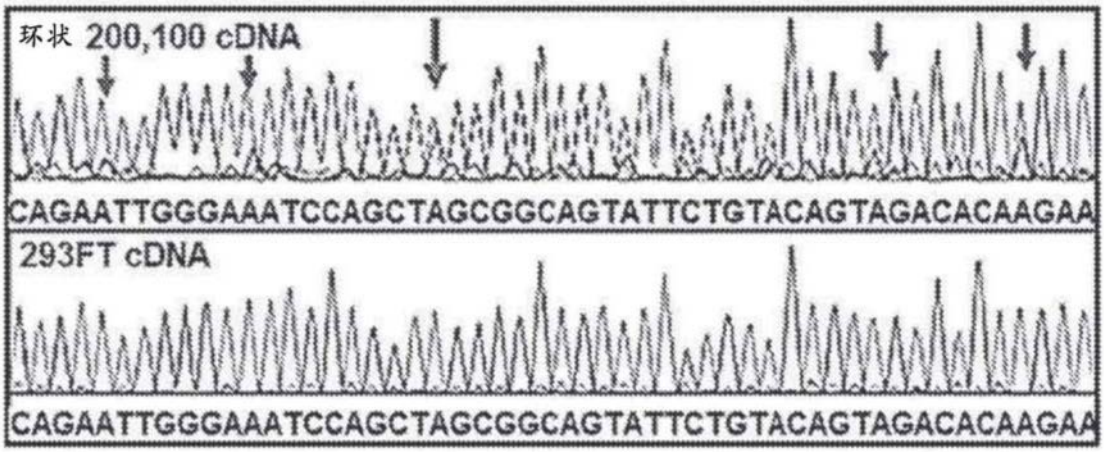


FIG.14A

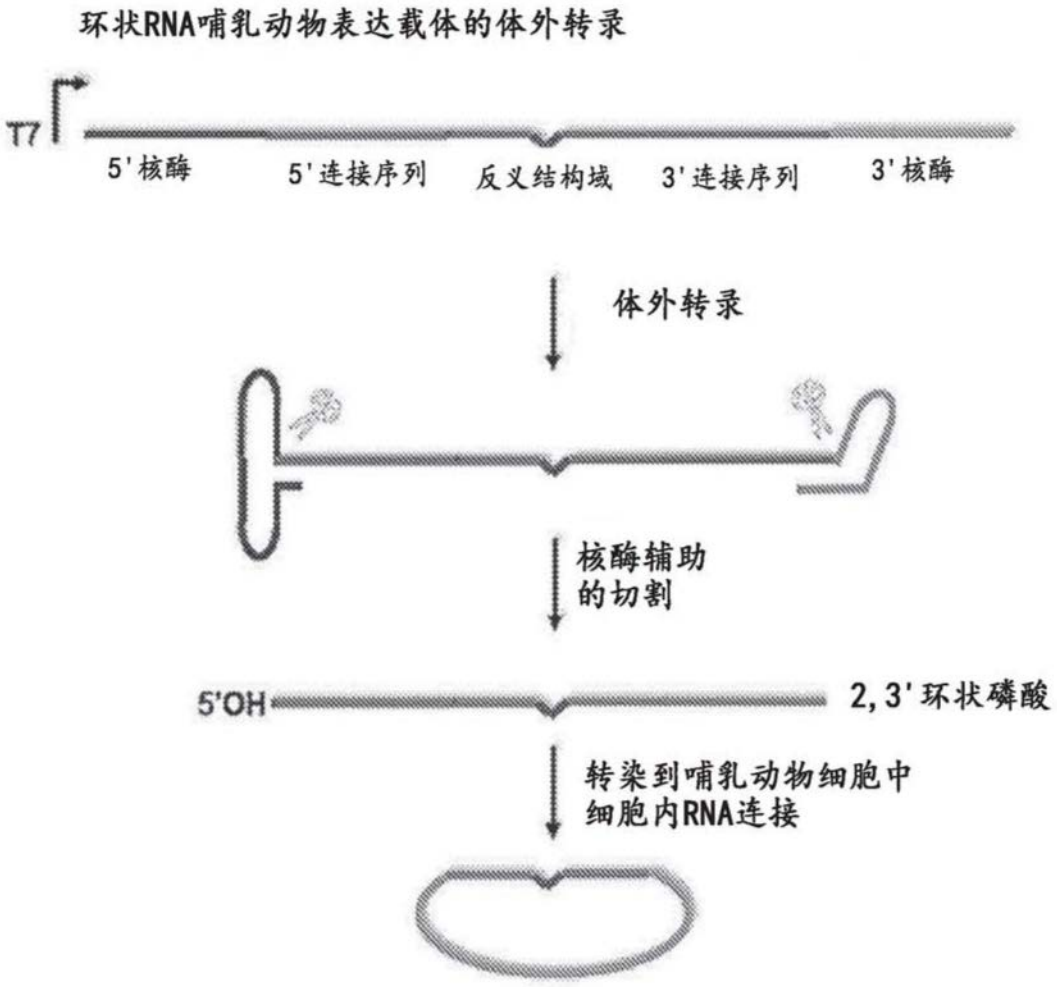


FIG.14B

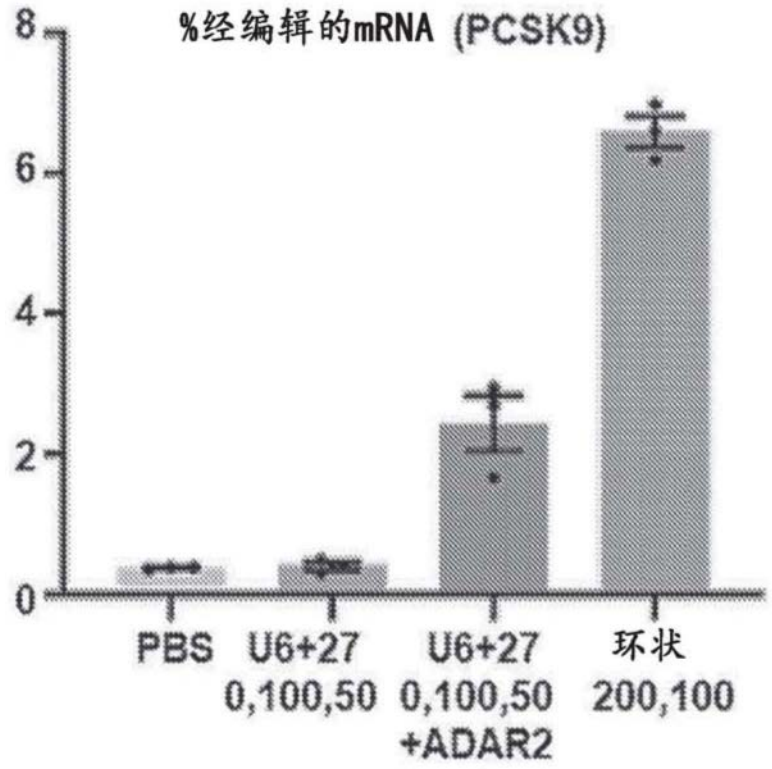


FIG.15A

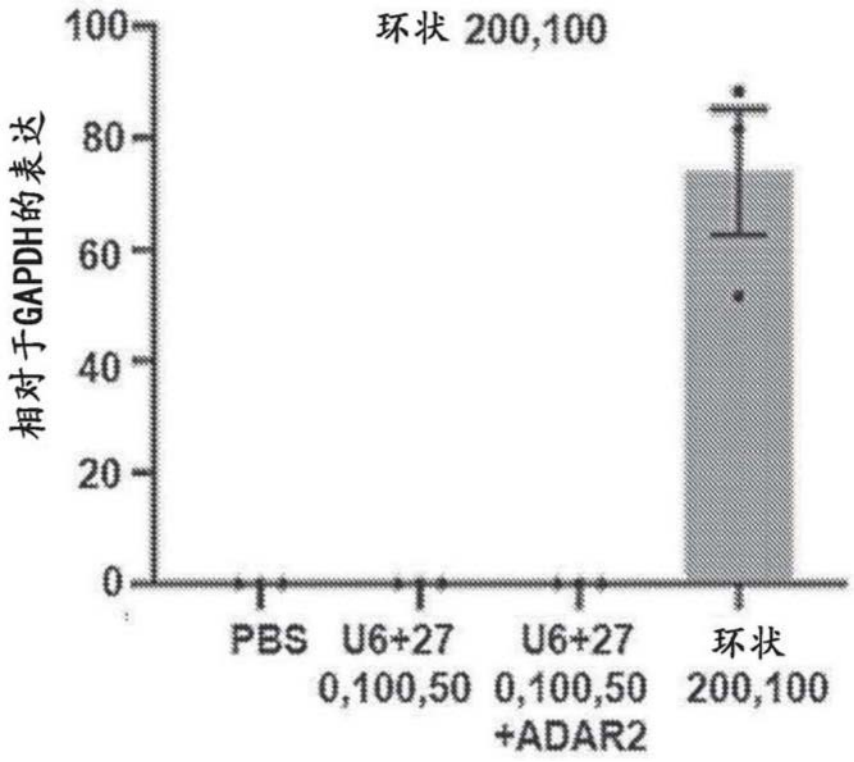


FIG.15B

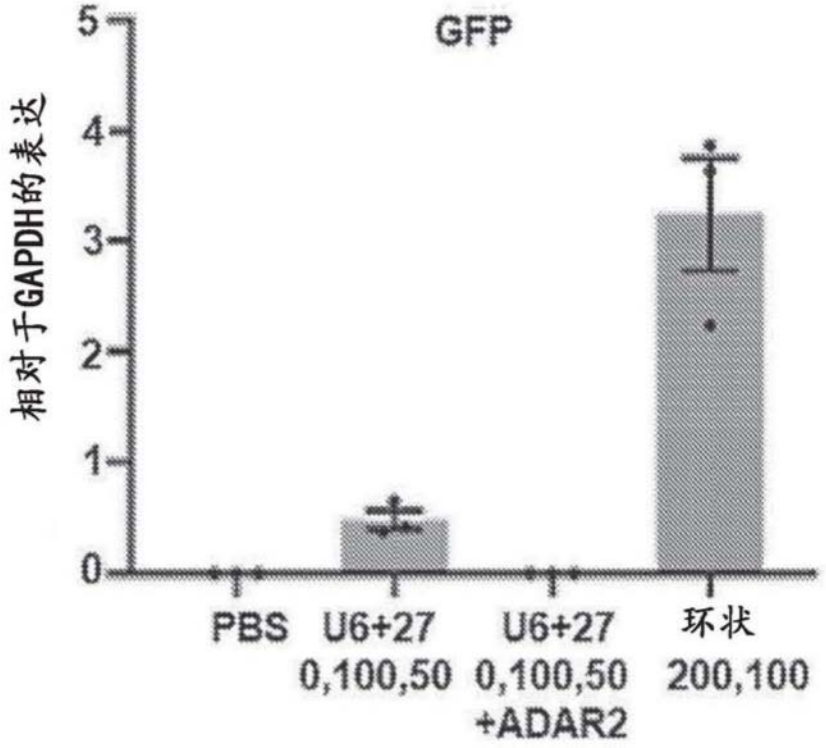


FIG.15C

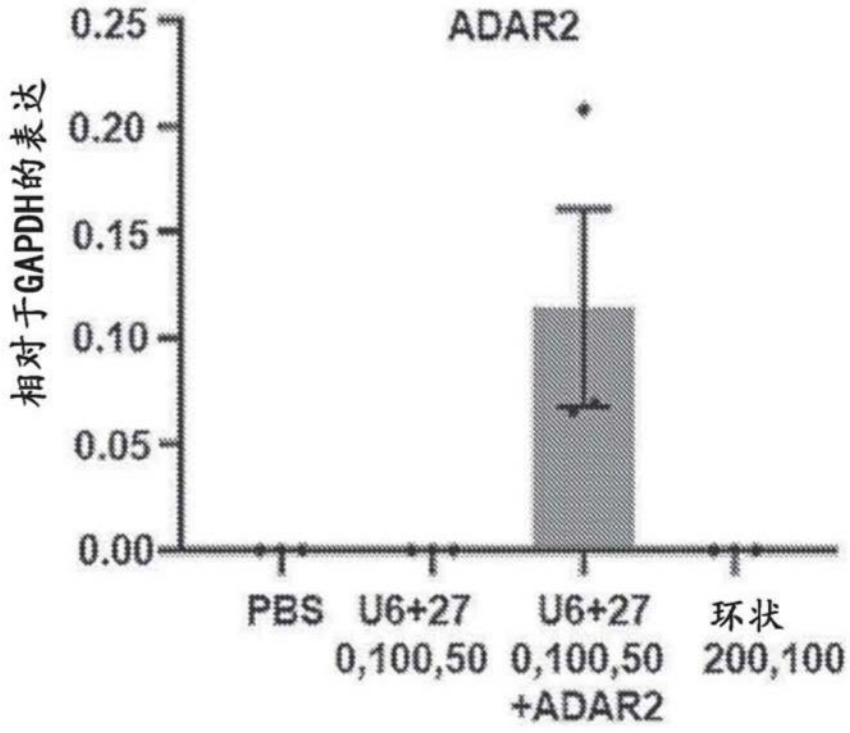


FIG.15D

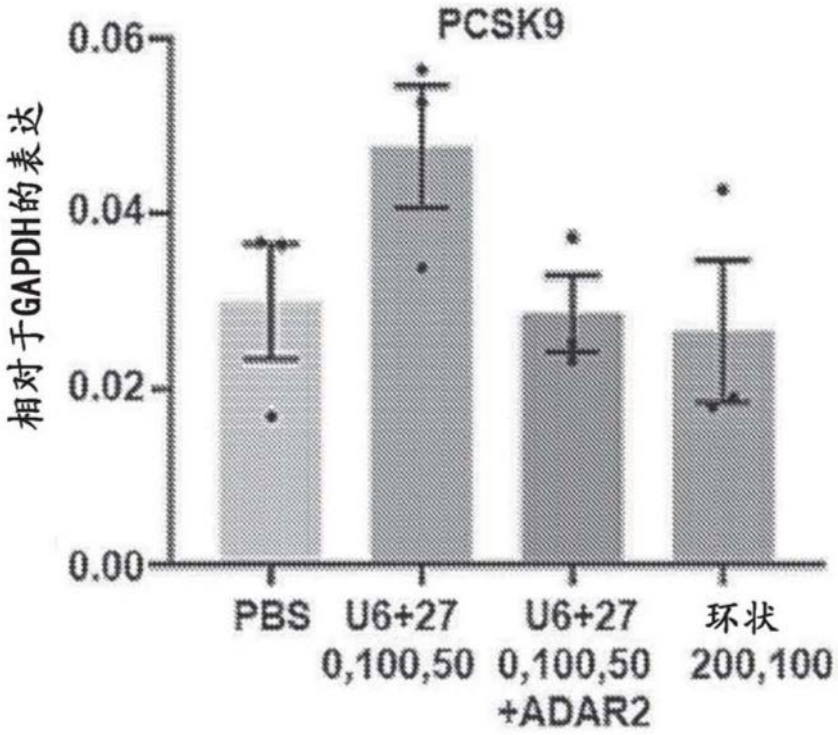


FIG.15E

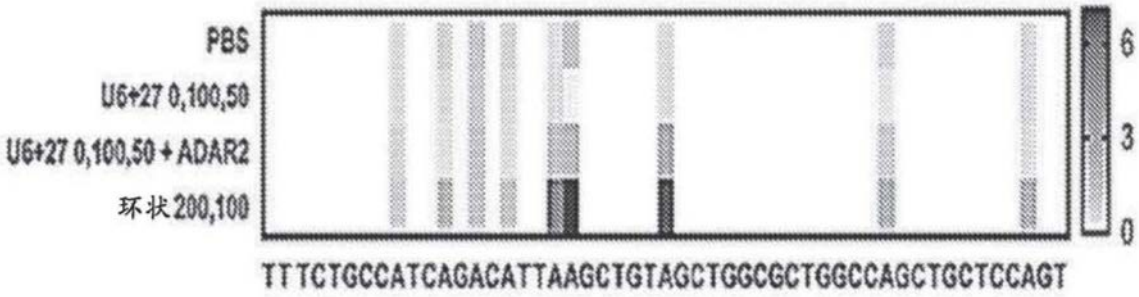


FIG.15F

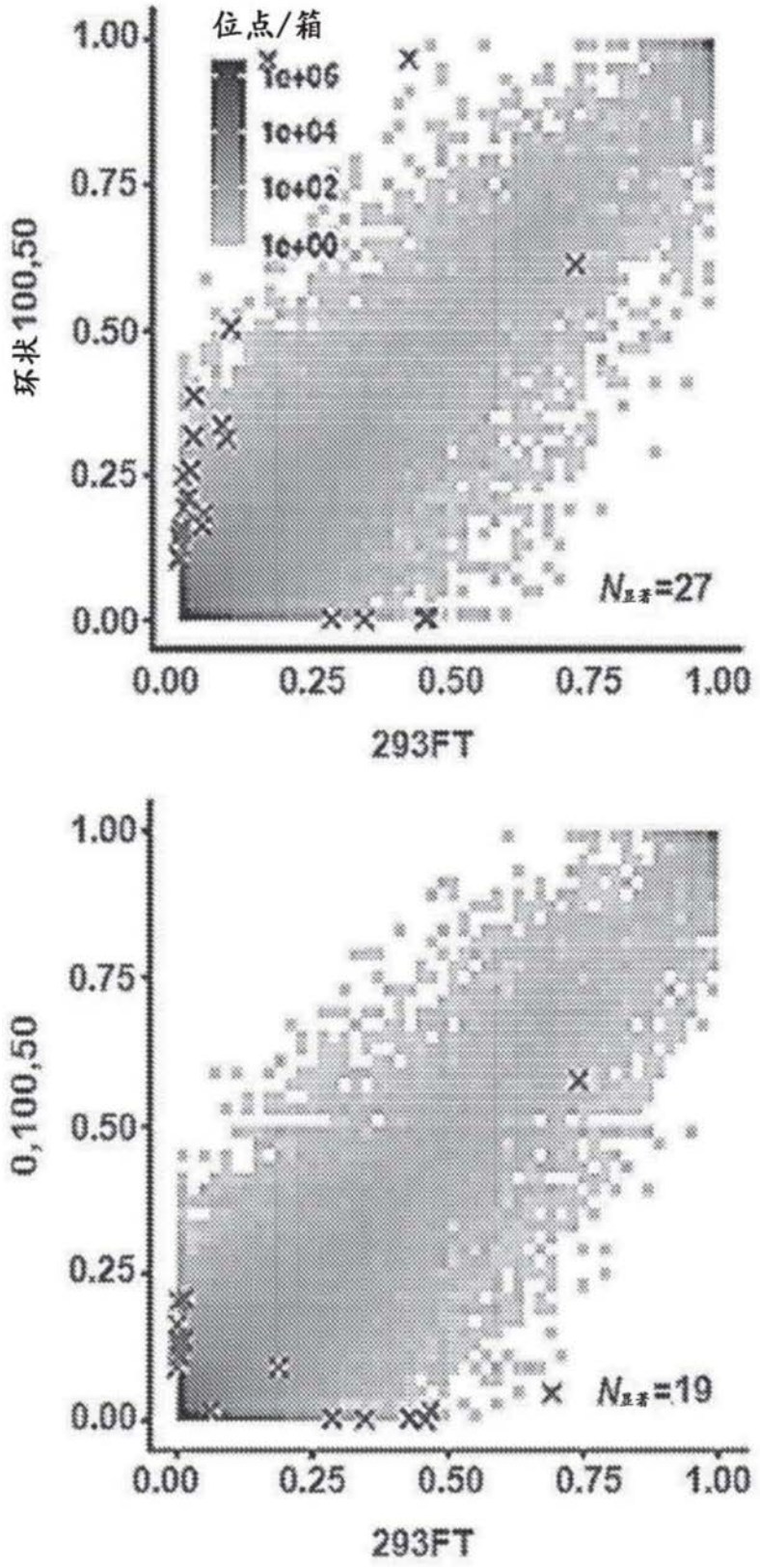

位点/箱
1e+06
1e+04
1e+02
1e+00
环状100,50
1.00
0.75
0.50
0.25
0.00
N总者=27
0.00
0.25
0.50
0.75
1.00
293FT
0,100,50
N总者=19

FIG.16

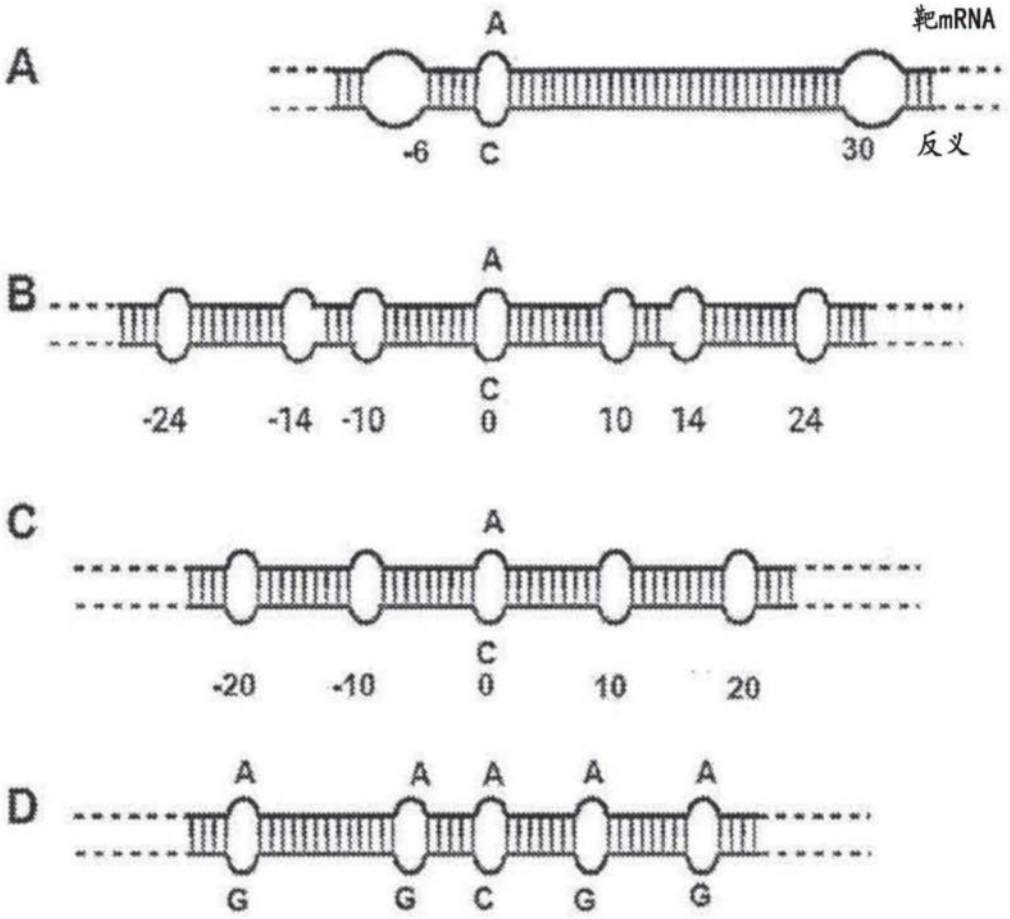

A
A
靶mRNA
-6
C
30
反义
B
A
C
-24
-14
-10
0
10
14
24
C
A
C
-20
-10
0
10
20
D
A
A
A
A
A
G
G
C
G
G

FIG.17A-D