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(54)发明名称

重组酶突变体

(57)摘要

本文呈现了重组酶以及使用该重组酶的方法和试剂盒,所述重组酶在模式化流动池表面上实现改善的重组酶介导的核酸(如具有单链衔接头区的PCR文库)扩增,从而实现改善的簇扩增。

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1.重组UvsX,其由SEQ ID NO:2的氨基酸序列组成。

2.编码如权利要求1所定义的重组UvsX的核酸分子。

3.扩增靶核酸分子的重组酶聚合酶扩增方法,其包含以下步骤:(a)将权利要求1的重组UvsX与第一和第二核酸引物接触以形成第一和第二核蛋白引物,其中所述核酸引物包含在其3'端的单链区;(b)将所述第一和第二核蛋白引物与所述靶核酸分子接触,从而在所述第一链的第一部分处形成第一双链结构并且在所述第二链的第二部分处形成第二双链结构,从而所述第一核酸引物和所述第二核酸引物的3'端在相同的双链模板核酸分子上彼此相对取向;(c)用一种或多种聚合酶和dNTP延伸所述第一和第二核酸引物的3'端以产生第一和第二双链核酸和核酸的第一和第二置换链;并且(d)通过重复(b)和(c)继续反应,直到达到期望的扩增程度。

4.权利要求3的方法,其中所述靶核酸分子包含双链核酸和/或单链衔接头区。

5.权利要求3的方法,其中在重组酶加载蛋白存在下进行所述方法。

6.权利要求5的方法,其中所述重组酶加载蛋白选自下组:T4 UvsY、大肠杆菌recO、大肠杆菌recR,及其组合。

7.权利要求5的方法,其中在选自下组的单链稳定剂的存在下进行所述方法:gp32、大肠杆菌SSB蛋白、T4 gp32蛋白。

8.权利要求3的方法,其中在选自下组的拥挤剂的存在下进行所述方法:聚乙二醇,聚环氧乙烷,聚苯乙烯,Ficoll,葡聚糖,PVP,和白蛋白,使得所述拥挤剂刺激扩增。

9.权利要求3的方法,其中在扩增位点的阵列上进行所述方法。

10.权利要求9的方法,其中每个扩增位点包含多个用于扩增所述靶核酸的扩增引物。

11.权利要求10的方法,其中所述扩增位点的阵列包含表面上的特征阵列。

12.权利要求11的方法,其中所述特征是不连续的,并且由缺少所述扩增引物的表面的间隙区域分开。

13.权利要求3的方法,其中等温发生所述方法。

14.用于进行重组酶聚合酶反应的试剂盒,其包含:如权利要求1定义的重组UvsX以及如下的一项或多项:

单链DNA结合蛋白;

DNA聚合酶;

dNTP或dNTP和ddNTP的混合物;

拥挤剂;

缓冲剂;

还原剂;

ATP或ATP类似物;

重组酶加载蛋白;和

第一引物。

15.权利要求14的试剂盒,其包含第二引物。

重组酶突变体

[0001] 发明背景

[0002] 重组酶可用于重组酶介导的核酸扩增。例如，重组酶可以促进寡核苷酸靶向DNA靶标，允许通过聚合酶复制DNA。仍然需要具有改善性质的修饰的重组酶。

[0003] 序列表

[0004] 本申请与电子格式的序列表一起提交。该序列表作为一个创建于2014年09月26日，大小为98Kb的，命名为IP1264.TXT的文件提供。序列表的电子格式中的信息通过引用以其整体并入本文。

[0005] 发明概述

[0006] 本文呈现的是用于改善的重组酶介导的核酸扩增的重组酶。令人惊讶地，本发明人已经鉴定出某些改变的重组酶，其在将核酸接种(seeding)至模式化(patterned)流动池表面中具有实质改善的特点。在某些实施方案中，改变的重组酶改善在模式化流动池表面上接种无PCR文库(PCR-free library)(如具有单链衔接头区的PCR文库)，从而实现改善的簇扩增。

[0007] 在某些实施方案中，所述重组酶是重组UvsX，且包含功能上等同于RB49UvsX氨基酸序列中Pro256的位置处的氨基酸取代。野生型RB49 UvsX氨基酸序列如SEQ ID NO:1所示。在某些实施方案中，所述重组UvsX包含氨基酸序列，该氨基酸序列包含与SEQ ID NO:1至少60％、70％、80％、90％、95％、99％相同的氨基酸，并包含在功能上等同于RB49 UvsX氨基酸序列中Pro256的位置处的氨基酸取代突变。在某些实施方案中，取代突变包含突变为带电荷的残基。在某些实施方案中，取代突变包含突变为碱性残基。在某些实施方案中，取代突变包含与RB49 UvsX氨基酸序列中Pro256Lys同源的突变。

[0008] 在一些实施方案中，除以上突变外，重组UvsX还可以包含在功能上等同于RB49 UvsX氨基酸序列中His63的位置处的取代突变。例如，在某些实施方案中，重组UvsX包含与RB49 UvsX氨基酸序列中His63Ser同源的取代突变。

[0009] 在一些实施方案中，除以上任何突变外，重组UvsX还可包含选自下组的突变：在C末端添加一个或多个谷氨酸残基；在C末端添加一个或多个天冬氨酸残基；及其组合。

[0010] 在一些实施方案中，重组UvsX衍生自选自下组的肌病毒科噬菌体：T4、T6、Rb69、Aeh1、KVP40、不动杆菌噬菌体133、气单胞菌噬菌体65、噬蓝藻体P-SSM2、噬蓝藻体PSSM4、噬蓝藻体S-PM2、Rb32、弧菌噬菌体nt-1、Rb16、Rb43，和Rb49。

[0011] 在一些实施方案中，重组UvsX衍生自选自下组的肌病毒科噬菌体：T2、Rb14、气单胞菌噬菌体25、phi-1、噬菌体31、噬菌体44RR2.8t、噬菌体Rb3、和噬菌体LZ2。

[0012] 本文还呈现的是重组UvsX，其包含SEQ ID NO:2和22-35中任一项的氨基酸序列。在某些实施方案中，重组UvsX包括氨基酸序列，所述序列包含与SEQ ID NO:2和22-35至少60％、70％、80％、90％、95％、99％相同的氨基酸，且其包含在功能上等同于RB49 UvsX氨基酸序列中Pro256的位置处的氨基酸取代突变。

[0013] 本文还呈现的是重组UvsX，其包含对包含SEQ ID NO:3-5中任一项的氨基酸序列的半保守域的取代突变(a substitution mutation to the semi-conserved domain

comprising the amino acid sequence of any of SEQ ID NOs:3-5)，其中所述取代突变包含选自下组的突变：在位置7处取代为除Phe、Pro、Asp、Glu或Asn以外的任何残基。在某些实施方案中，重组UvsX包含与重组酶(其包含半保守域，该半保守域包含SEQ ID NO:3-5中任一个的氨基酸序列)至少60％、70％、80％、90％、95％、99％相同的氨基酸，并且其中重组UvsX包含选自下组的取代突变：在位置7处突变为除Phe、Pro、Asp、Glu或Asn以外的任何残基。在某些实施方案中，突变包含突变为带电荷的残基。在某些实施方案中，突变包含突变为碱性残基。在某些实施方案中，突变包含在位置7处取代为Lys。

[0014] 本文还呈现的是重组UvsX，包含对包含SEQ ID NO:6-7中任一项的氨基酸序列的半保守域的取代突变，其中取代突变包含选自下组的突变：在位置12处取代为除Phe、Pro、Asp、Glu或Asn以外的任何残基。在某些实施方案中，重组UvsX包含与重组酶(其包含半保守域，该半保守域包含SEQ ID NO:6-7中任一个的氨基酸序列)至少60％、70％、80％、90％、95％、99％相同的氨基酸，并且其中重组UvsX包含选自下组的突变：在位置12处取代为除Phe、Pro、Asp、Glu或Asn以外的任何残基。在某些实施方案中，突变包含突变为带电荷的残基。在某些实施方案中，突变包含突变为碱性残基。在某些实施方案中，突变包含在位置12取代为Lys。

[0015] 在一些实施方案中，除以上突变外，重组UvsX还可以包含在功能上等同于RB49 UvsX氨基酸序列中His63的位置处的取代突变。例如，在某些实施方案中，重组UvsX包含与在RB49 UvsX氨基酸序列中His63Ser同源的取代突变。

[0016] 在一些实施方案中，除了以上任何突变外，重组UvsX还可以包含选自下组的突变：在C末端添加一个或多个谷氨酸残基；在C末端添加一个或多个天冬氨酸残基；及其组合。

[0017] 在一些实施方案中，重组UvsX衍生自选自下组的肌病毒科噬菌体：T4、T6、Rb69、Aeh1、KVP40、不动杆菌噬菌体133、气单胞菌噬菌体65、噬蓝藻体P-SSM2、噬蓝藻体PSSM4、噬蓝藻体S-PM2、Rb32、弧菌噬菌体nt-1、Rb16、Rb43，和Rb49。

[0018] 在一些实施方案中，重组UvsX衍生自选自下组的肌病毒科噬菌体：T2、Rb14、气单胞菌噬菌体25、phi-1、噬菌体31、噬菌体44RR2.8t、噬菌体Rb3、和噬菌体LZ2。

[0019] 还呈现的是编码如任何以上实施方案所定义的重组UvsX的核酸分子。本文还呈现的是包含上述核酸分子的表达载体。本文还呈现的是包含上述载体的宿主细胞。

[0020] 还呈现的是扩增靶核酸分子的重组酶聚合酶扩增方法，其包含以下步骤：(a)将任何以上实施方案的重组UvsX与第一和第二核酸引物接触以形成第一和第二核蛋白引物，其中所述核酸引物包含在其3’端的单链区；(b)将所述第一和第二核蛋白引物与所述靶核酸分子接触，从而在所述第一链的第一部分处形成第一双链结构并且在所述第二链的第二部分处形成第二双链结构，从而所述第一核酸引物和所述第二核酸引物的3’端在相同的双链模板核酸分子上彼此相对定向；(c)用一种或多种聚合酶和dNTP延伸所述第一和第二核酸引物的3’端以产生第一和第二双链核酸和核酸的第一和第二置换链；和(d)通过重复(b)和(c)继续反应，直到达到期望的扩增程度。

[0021] 在该方法的某些实施方案中，靶核酸分子包含双链核酸。在某些实施方案中，靶核酸分子包含单链核酸。例如，在一些实施方案中，靶核酸包含单链衔接头区。在某些实施方案中，所述方法在重组酶加载蛋白(loading protein)存在下进行。例如，重组酶加载蛋白可选自下组：T4UvsY、大肠杆菌(E.coli)recO、大肠杆菌recR，及其组合。在某些实施方案

中,所述方法在选自下组的单链稳定剂的存在下进行:gp32、大肠杆菌SSB蛋白、T4gp32蛋白,及其衍生物。在某些实施方案中,所述方法在选自下组的拥挤剂(crowding agent)的存在下进行:聚乙二醇,聚环氧乙烷,聚苯乙烯,Ficoll,葡聚糖,PVP,和白蛋白,使得所述拥挤剂刺激扩增。

[0022] 在某些实施方案中,该方法在扩增位点的阵列上进行。在某些实施方案中,每个扩增位点包含多个用于扩增靶核酸的扩增引物。在某些实施方案中,所述扩增位点的阵列包含表面上的特征阵列。例如,所述特征可以是不连续的并由缺少扩增引物的表面的间隙区域分开。在某些实施方案中,扩增位点的阵列包含溶液中的珠粒或表面上的珠粒。在某些实施方案中,扩增位点的阵列包含乳液。在某些实施方案中,等温发生所述方法。

[0023] 还呈现的是用于进行重组酶聚合酶反应的试剂盒。在某些实施方案中,试剂盒可以包含如上述任何实施方案中所定义的重组UvsX,以及如下一种或多种:单链DNA结合蛋白;DNA聚合酶;dNTP或dNTP和ddNTP的混合物;拥挤剂;缓冲液;还原剂;ATP或ATP类似物;重组酶加载蛋白;第一引物和任选地第二引物。

[0024] 一个或多个实施方案的细节在附图和下面的描述中阐述。其他特征、目的和优点将从说明书和附图,以及权利要求书中变得显而易见。

[0025] 附图简述

[0026] 图1是示意图,其示出了来自以下的UvsX氨基酸序列的比对:肠杆菌噬菌体T4(T4)(SEQ ID NO:8)、肠杆菌噬菌体T6(T6)(SEQ ID NO:9)、不动杆菌噬菌体133(Phage133)(SEQ ID NO:10)、肠杆菌噬菌体RB69(Rb69)(SEQ ID NO:11)、气单胞菌噬菌体Aeh1(Aeh1)(SEQ ID NO:12)、气单胞菌噬菌体65(Ae65)(SEQ ID NO:13)、弧菌噬菌体KVP40(Kvp40)(SEQ ID NO:14)、肠杆菌噬菌体RB43(Rb43)(SEQ ID NO:15)、原绿球菌(Prochlorococcus)噬菌体P-SSM2(PSSM2)(SEQ ID NO:16),和原绿球菌噬菌体P-SSM4(PSSM4)(SEQ ID NO:17),如在US 2009/0029421的并入材料中阐述。突出显示了位置上和功能上等同于RB49 UvsX氨基酸序列中Pro256的残基,并由三角形符号表示。

[0027] 图2是示意图,其示出了来自肠杆菌噬菌体RB49(RB49)(SEQ ID NO:1)和肠杆菌噬菌体T4(T4)(SEQ ID NO:8)的UvsX氨基酸序列的比对。突出显示了位置上和/或功能上等同于RB49 UvsX氨基酸序列中Pro256的残基,并由三角形符号表示。

[0028] 图3A示出了使用T4UvsX制剂接种到模式化流动池上的无PCR文库的簇图像的截图。

[0029] 图3B示出了使用包含RB49 P256K重组酶的液体制剂接种到模式化流动池上的无PCR文库的簇图像的截图。

[0030] 图4A示出了使用T4UvsX制剂接种到模式化流动池上的单链(ssDNA)无PCR文库的簇图像的截图。

[0031] 图4B示出了使用包含RB49 P256K重组酶的液体制剂接种到模式化流动池上的单链无PCR文库的簇图像的截图。

[0032] 发明详述

[0033] 本文呈现的是用于改善的重组酶介导的核酸扩增的重组酶。令人惊讶地,本发明人已经鉴定出某些改变的重组酶,其在将核酸接种至模式化流动池表面上中具有实质改善的特点。

[0034] 如下文更详细地描述的，令人惊讶地，发明人发现，对重组酶中一个或多个残基的一个或多个突变导致在模式化流动池表面上接种DNA文库(如例如具有单链衔接头区的PCR文库)中的深刻的改进，给出改善的簇扩增。

[0035] 在某些实施方案中，取代突变包含突变为具有带电荷的侧链的残基。例如，在一些实施方案中，带电荷的氨基酸是带正电荷的氨基酸残基。术语“带正电荷的氨基酸残基”指侧链pKa值大于7的亲水性氨基酸，即碱性氨基酸。由于与水合氢离子(hydronium ion)缔合，碱性氨基酸通常在生理pH下具有带正电荷的侧链。天然发生的(遗传编码的)碱性氨基酸包括赖氨酸(Lys,K)、精氨酸(Arg,R)和组氨酸(His,H)，而非天然(非遗传编码的，或非标准)碱性氨基酸包括例如鸟氨酸、2,3,-二氨基丙酸、2,4-二氨基丁酸、2,5,6-三氨基己酸、2-氨基-4-胍酸丁酸，和高精氨酸。术语“带负电荷的氨基酸”指天然或非天然氨基酸(不论手性)，其除了C末端羧基外包含至少一个额外的带负电荷的基团，如羧基、磷酸根(phosphate)，膦酸根(phosphonate)，磺酸根(sulfonate)等。

[0036] 本文还呈现的是包含对重组UvsX的半保守域的取代突变的重组UvsX。如本文所用，术语“半保守域”指重组UvsX中在各种物种间完全保守的，或者至少部分保守的部分。已经令人惊讶地发现半保守域中一个或多个残基的突变影响重组酶活性(特别是在单链模板核酸存在下)；导致在重组酶介导的扩增反应中接种和/或扩增的增强。如下面的实施例部分所述，这些突变的重组酶在模式化细胞池表面上接种无PCR文库(如具有单链衔接头区的PCR文库)中具有改善的性能，导致改善的簇扩增。

[0037] 在一些实施方案中，半保守域包含具有SEQ ID NO:3-7中任一个所示序列的氨基酸。SEQ ID NO:3-7对应于各种物种中半保守域中的残基。SEQ ID NO:3对应于T4UvsX氨基酸序列的残基251-258，其在本文中如SEQ ID NO:8所示。在图1和图2中示出了在半保守域中显示各种物种间的保守的比对。图1中示出的UvsX序列获得自Genbank数据库登录号NP_049656(T4)，YP_004300647(噬菌体133)；NP_861734(RB69)；NP_943894.1(Aeh1)；YP_004300858(Ae65)；NP_899256(KVP40)；YP_239013(RB43)；YP_214417(P-SSM2)；YP_214708(P-SSM4)；以及来自US公开号2009/0029421(T6)。图2是示意图，其示出了来自肠杆菌噬菌体RB49(RB49)(SEQ ID NO:1)和肠杆菌噬菌体T4(T4)(SEQ ID NO:8)的UvsX氨基酸序列的比对。突出显示了位置上和/或功能上等同于RB49 UvsX氨基酸序列中Pro256的残基，并由三角形符号表示。图2中所示的UvsX序列获得自Genbank数据库登录号NP_891595(RB49)和NP_049656(T4)。

[0038] 令人惊讶地，发现对半保守域中一个或多个残基的突变增加了重组酶的活性，特别是在单链模板核酸存在下，导致重组酶介导的扩增反应中的接种和/或扩增的增强。如下面的实施例部分所述，这些突变的重组酶在模式化细胞池表面接种无PCR文库(如具有单链衔接头区的PCR文库)中具有改善的性能，导致改善的簇扩增。例如，在一些本文呈现的重组UvsX的实施方案中，取代突变包含在SEQ ID NO:3-5中任一个的位置7处突变为除Phe、Pro、Asp、Glu或Asn以外的任何残基取代。在某些实施方案中，重组UvsX包含SEQ ID NO:3-5中任一个的位置7处突变为Lys。在一些本文呈现的重组UvsX的实施方案中，取代突变包含在SEQ ID NO:6-7中任一个的位置12处突变为除Phe、Pro、Asp、Glu或Asn以外的任何残基。在某些实施方案中，重组UvsX包含SEQ ID NO:6-7中任一个的位置12处突变为Lys。

[0039] 在一些实施方案中，重组酶是UvsX蛋白。任何噬菌体重组酶可以用于本文呈现的

实施方案中，包括例如噬菌体重组酶，如衍生自肌病毒科噬菌体的UvsX或UvsX样重组酶，如例如T4、T6、Rb69、Aeh1、KVP40、不动杆菌噬菌体133、气单胞菌噬菌体65、噬蓝藻体P-SSM2、噬蓝藻体PSSM4、噬蓝藻体S-PM2、Rb32、弧菌噬菌体nt-1、Rb16、Rb43，和Rb49。在某些实施方案中，重组酶是衍生自肌病毒科噬菌体的UvsX或UvsX样重组酶，如例如T2、Rb14、气单胞菌噬菌体25、phi-1、噬菌体31、噬菌体44RR2.8t、噬菌体Rb3、和噬菌体LZ2。对于本领域技术人员来说显而易见的是，其他重组酶蛋白可以用于本文呈现的实施方案中。如下面更详细描述的，可以使用许多本领域已知的方法(如例如BLAST比对)通过与UvsX的同源性来鉴定适合的重组酶蛋白。

[0040] “功能等同”意指对照重组酶(在使用完全不同重组酶的研究的情况下)将包含被认为在酶中具有相同的功能作用的其他重组酶的氨基酸位置处发生的氨基酸取代。作为一个例子，T4UvsX中位置257从苯丙氨酸到赖氨酸(F257K)的突变将与RB49 UvsX中位置256从脯氨酸到赖氨酸(P256K)的取代是功能等同的。

[0041] 通常在两种或更多种不同重组酶中的功能等同取代突变发生在重组酶的氨基酸序列中的同源氨基酸位置。因此，本文使用术语“功能等同”也包含与给定突变“位置上等同”或“同源”的突变，而不考虑突变氨基酸的特定功能是否已知。可以基于序列比对和/或分子建模(modelling)来鉴定两个或更多个不同重组酶的氨基酸序列中的位置等同或同源的氨基酸残基。图1中列出了鉴定位置等同和/或功能等同残基的序列比对的实例，所述图1列出了来自以下的UvsX氨基酸序列的比对：肠杆菌噬菌体T4(T4)(SEQ ID NO:8)、肠杆菌噬菌体T6(T6)(SEQ ID NO:9)、不动杆菌噬菌体133(噬菌体133)(SEQ ID NO:10)、肠杆菌噬菌体RB69(Rb69)(SEQ ID NO:11)、气单胞菌噬菌体Aeh1(Aeh1)(SEQ ID NO:12)、气单胞菌噬菌体65(Ae65)(SEQ ID NO:13)、弧菌噬菌体KVP40(Kvp40)(SEQ ID NO:14)、肠杆菌噬菌体RB43(Rb43)(SEQ ID NO:15)、原绿球菌噬菌体P-SSM2(PSSM2)(SEQ ID NO:16)，和原绿球菌噬菌体P-SSM4(PSSM4)(SEQ ID NO:17)，如也在US 2009/0029421的并入材料中阐述。图1所示的UvsX序列获自Genbank数据库登录号NP_049656(T4)，YP_004300647(噬菌体133)；NP_861734(RB69)；NP_943894.1(Aeh1)；YP_004300858(Ae65)；NP_899256(KVP40)；YP_239013(RB43)；YP_214417(P-SSM2)；YP_214708(P-SSM4)；以及来自US公开号2009/0029421(T6)。

[0042] 图2是示意图，其示出了来自肠杆菌噬菌体RB49(RB49)(SEQ ID NO:1)和肠杆菌噬菌体T4(T4)(SEQ ID NO:8)的UvsX氨基酸序列的比对。突出显示了位置上和/或功能上等同于RB49 UvsX氨基酸序列中Pro256的残基，并由三角形符号表示。示于图2的UvsX序列获得自Genbank数据库登录号NP_891595(RB49)和NP_049656(T4)。

[0043] 位置上等同和/或功能上等同的残基可以通过将那些序列与参考序列(例如T4和RB49)的序列进行比对来对任何数量的其他UvsX序列中的一个或多个测定。作为非限制性的示例，来自聚球藻(Synechococcus)噬菌体S-PM2、肠杆菌噬菌体RB32、弧菌噬菌体nt-1、肠杆菌噬菌体RB16的UvsX序列如SEQ ID NOs:18-21所列，并获得自Genbank数据库登录号YP_195169.1;YP_802982.1;YP_008125207.1;YP_003858336.1，其可以与参考UvsX序列如T4UvsX(SEQ ID NO:8)和RB49 UvsX(SEQ ID NO:1)比对，并且鉴定了位置上等同和/或功能上等同的残基。例如，示于下表的残基被鉴定为与RB49 UvsX氨基酸序列中Pro256在位置上等同和/或功能上等同。本领域技术人员将容易理解，其他UvsX蛋白的位置上等同和/或功能上等同的位置可以按照以下类似的方法来确定。

[0044]

噬菌体物种	SEQ ID NO:	位置上等同和/或功能上等同的位置
T4	8	Phe257
T6	9	Phe259
不动杆菌噬菌体133	10	Pro257
Rb69	11	Pro258
Aeh1	12	Pro269
气单胞菌噬菌体65	13	Asp266
KVP40	14	Pro267
Rb43	15	Pro259

[0045]

噬蓝藻体P-SSM2	16	Gln261
噬蓝藻体PSSM4	17	Glu264
噬蓝藻体S-PM2	18	Glu264
Rb32	19	Phe259
弧菌噬菌体nt-1	20	Pro267
Rb16	21	Pro259

[0046] 上文描述的重组UvsX蛋白可以包含已知增强重组酶活性、稳定性或任何其它所需性质的一个或多个方面的其它取代突变。例如，在一些实施方案中，除了上述任何突变之外，重组UvsX还可包含与RB49 UvsX氨基酸序列中His63功能上等同的位置的取代突变，如本领域已知并以US 2009/0029421的披露为例，其通过引用以其整体并入。例如，在某些实施方案中，重组UvsX包含与RB49 UvsX氨基酸序列中His63Ser同源的取代突变。

[0047] 在一些实施方案中，除了以上任何突变之外，与野生型重组酶相比，重组UvsX可包含额外的取代、缺失和/或添加突变。可以在位置的一个或多个处进行多种取代突变中的任一种，如本领域已知并以2009/0029421的并入材料示例。例如，在一些实施方案中，除以上突变外，重组UvsX还可包含选自下组的突变：在C末端添加一个或多个谷氨酸残基；在C末端添加一个或多个天冬氨酸残基；及其组合。

[0048] 使重组酶突变

[0049] 在本公开中任选使用各种类型的诱变，例如修饰重组酶以产生变体，如根据重组酶模型和模型预测，或使用随机或半随机突变方法。通常，任何可用的诱变程序可用于制备重组酶突变体。此类诱变程序任选地包括对突变体核酸和多肽选择感兴趣的一种或多种活性(如，在固体支持物上的增强的接种和/或扩增)。可以使用的程序包括但不限于：定点诱变(site-directed point mutagenesis)、随机点诱变、体外或体内同源重组(DNA改组和组合重叠PCR)、使用含尿嘧啶的模板进行诱变、寡核苷酸指导的诱变(oligonucleotide-

directed mutagenesis)、硫代磷酸酯修饰的DNA诱变、使用有缺口的双链体DNA进行诱变、点错配修复、使用修复缺陷宿主菌株的诱变、限制性选择和限制性纯化、缺失诱变、全基因合成诱变(mutagenesis by total gene synthesis)、简并PCR、双链断裂修复,以及技术人员已知的许多其他方法。用于突变的起始重组酶可以是本文所述的任何一种,包括可用重组酶突变体,如那些在例如US 2009/0029421中鉴定的,其通过引用以其整体并入本文。

[0050] 任选地,诱变可以通过来自天然存在的重组酶分子,或已知改变的或突变的重组酶(如使用如先前参考文献中所述的现有突变体重组酶)的已知信息,如序列、序列比对、物理特性、晶体结构和/或等引导,如上所述。然而,在另一类实施方案中,修饰可以是基本上随机的(如作为经典或"家族"DNA改组,例如参见Crameri et al.(1998)"DNA shuffling of a family of genes from diverse species accelerates directed evolution" Nature 391:288-291)。

[0051] 关于突变形式(formats)的额外信息可参见:Sambrook等人,Molecular Cloning--A Laboratory Manual(3rd Ed.),Vol.1-3,Cold Spring Harbor Laboratory,Cold Spring Harbor,N.Y.,2000("Sambrook");Current Protocols in Molecular Biology,F.M.Ausubel等人,eds.,Current Protocols,a joint venture between Greene Publishing Associates,Inc.and John Wiley&Sons,Inc.,(通过2011补入)("Ausubel"))和PCR Protocols A Guide to Methods and Applications(Innis等人编)Academic Press Inc.San Diego,Calif.(1990)("Innis")。以下引用的出版物和参考文献提供了关于突变形式的额外细节:Arnold,Protein engineering for unusual environments,Current Opinion in Biotechnology4:450-455(1993);Bass等人,Mutant Trp repressors with new DNA-binding specificities,Science 242:240-245(1988);Bordo and Argos(1991)Suggestions for"Safe"Residue Substitutions in Site-directed Mutagenesis 217:721-729;Botstein&Shortle,Strategies and applications of in vitro mutagenesis,Science229:1193-1201(1985);Carter等人,Improved oligonucleotide site-directed mutagenesis using M13vectors,Nucl.Acids Res.13:4431-4443(1985);Carter,Site-directed mutagenesis,Biochem.J.237:1-7(1986);Carter,Improved oligonucleotide-directed mutagenesis using M13vectors,Methods in Enzymol.154:382-403(1987);Dale等人,Oligonucleotide-directed random mutagenesis using the phosphorothioate method,Methods Mol.Biol.57:369-374(1996);Eghtedarzadeh&Henikoff,Use of oligonucleotides to generate large deletions,Nucl.Acids Res.14:5115(1986);Fritz等人,Oligonucleotide-directed construction of mutations:a gapped duplex DNA procedure without enzymatic reactions in vitro,Nucl.Acids Res.16:6987-6999(1988);Grundstrom等人,Oligonucleotide-directed mutagenesis by microscale`shot-gun`gene synthesis,Nucl.Acids Res.13:3305-3316(1985);Hayes(2002)Combining Computational and Experimental Screening for rapid Optimization of Protein Properties PNAS99(25)15926-15931;Kunkel,The efficiency of oligonucleotide directed mutagenesis,in Nucleic Acids&Molecular Biology(Eckstein,F.and Lilley,D.M.J.eds.,Springer Verlag,Berlin))(1987);Kunkel,Rapid and efficient site-

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[0052] 制备和分离重组的重组酶

[0053] 通常,编码如本文呈现的重组酶的核酸可通过以下方法制备:克隆、重组、体外合成、体外扩增和/或其他可用方法。多种重组方法可用于表达编码本文呈现的重组酶的表达载体。制备重组核酸、表达和分离表达产物的方法是公知的并描述于现有技术中。本文描述了多个示例性的突变和突变的组合,以及用于设计所期望突变的策略。

[0054] 突变、重组和体外核酸操作方法(包括克隆、表达、PCR等)的其他有用参考文献包括:Berger and Kimmel,Guide to Molecular Cloning Techniques,Methods in Enzymology volume 152Academic Press,Inc.,San Diego,Calif.(Berger);Kaufman等人(2003)Handbook of Molecular and Cellular Methods in Biology and Medicine Second Edition Ceske(编)CRC Press(Kaufman);和The Nucleic Acid Protocols Handbook Ralph Rapley(编)(2000)Cold Spring Harbor,Humana Press Inc(Rapley);Chen等人(编)PCR Cloning Protocols,Second Edition(Methods in Molecular Biology,volume 192)Humana Press;和在Viljoen等人(2005)Molecular Diagnostic PCR Handbook Springer,ISBN 1402034032。

[0055] 此外,商业上可获得用于从细胞纯化质粒和其他相关核酸的多种试剂盒(例如参见EasyPrep.TM.,FlexiPrep.TM.两者来自Pharmacia Biotech;来自Stratagene的StrataClean.TM.;和来自Qiagen的QIAprep.TM.)。可进一步操作任何分离的和/或纯化的核酸以产生其他核酸,用于转染细胞、整合入相关载体以感染生物体用于表达和/或等等。典型的克隆载体含有转录和翻译终止子、转录和翻译起始序列,以及可用于调节特定靶核酸表达的启动子。载体任选地包含通用表达盒,该表达盒包含至少一个独立终止子序列、允许盒在真核生物,或原核生物,或两者中复制的序列(如穿梭载体),和用于原核和真核系统两者的选择标记物。载体适用于原核生物,真核生物或两者的复制和整合。

[0056] 其他有用的参考文献(例如用于分离和培养细胞(例如用于后续核酸分离))包括Freshney(1994)Culture of Animal Cells,a Manual of Basic Technique,third edition,Wiley-Liss,New York及其所引用的参考文献;Payne et al.(1992)Plant Cell and Tissue Culture in Liquid Systems John Wiley&Sons,Inc.New York,N.Y.;Gamborg and Phillips(编)(1995)Plant Cell,Tissue and Organ Culture;Fundamental Methods Springer Lab Manual,Springer-Verlag(Berlin Heidelberg New York)以及Atlas and Parks(编)The Handbook of Microbiological Media(1993)CRC Press,Boca

Raton,Fla。

[0057] 编码本文公开的重组重组酶的核酸也是本文所呈现的实施方案的特征。特定的氨基酸可以由多个密码子编码,并且某些翻译系统(例如原核或真核细胞)通常表现出密码子偏好,例如不同的生物体往往偏好编码相同氨基酸的几个同义密码子之一。因此,本文呈现的核酸可任选地“密码子优化”,这意味着合成核酸以包括密码子,该密码子为用于表达表达重组酶的特定翻译系统所偏好。例如,当需要在细菌细胞(或甚至是特定的细菌菌株)中表达重组酶时,可以合成核酸以包括在该细菌细胞的基因组中最常见的密码子,用于有效表达重组酶。当希望在真核细胞中表达重组酶时,可以采用类似的策略,例如核酸可以包括真核细胞所偏好的密码子。

[0058] 已知多种蛋白分离和检测方法,并且所述方法可用于分离重组酶(例如从表达本文呈现的重组的重组酶的重组细胞培养物中分离)。多种分离和检测蛋白的方法在本领域中是公知的,包括,如下中列出的那些方法:R.Scopes,Protein Purification,Springer-Verlag,N.Y.(1982);Deutscher,Methods in Enzymology Vol.182:Guide to Protein Purification,Academic Press,Inc.N.Y.(1990);Sandana(1997)Bioseparation of Proteins,Academic Press,Inc.;Bollag等人(1996)Protein Methods,2.sup.nd Edition Wiley-Liss,NY;Walker(1996)The Protein Protocols Handbook Humana Press,NJ,Harris and Angal(1990)Protein Purification Applications:A Practical Approach IRL Press at Oxford,Oxford,England;Harris and Angal Protein Purification Methods:A Practical Approach IRL Press at Oxford,Oxford,England;Scopes(1993)Protein Purification:Principles and Practice 3.sup.rd Edition Springer Verlag,NY;Janson and Ryden(1998)Protein Purification:Principles,High Resolution Methods and Applications,Second Edition Wiley-VCH,NY;以及Walker(1998)Protein Protocols on CD-ROM Humana Press,NJ;以及其中所引用的参考文献。关于蛋白质纯化和检测方法的其他细节可以在Satinder Ahuja编,Handbook of Bioseparations,Academic Press(2000)中找到。

[0059] 使用方法

[0060] 本文呈现的改变的重组酶可用于重组酶介导的扩增程序,如重组酶聚合酶扩增(RPA)技术。简单来说,可以通过使靶核酸与重组酶和对靶核酸分子特异性的单链核酸引物接触来引发RPA。然后,可以通过聚合酶,如在dNTP的存在下能够链置换以产生双链靶核酸分子和核酸分子的置换链的聚合酶延长杂交的引物。进一步扩增可以通过重组酶介导的引物靶向至核酸分子的置换链以及引物的延伸以产生双链核酸分子来实现。可通过将上述组分与例如重组酶加载因子(recombinase-loading factors)、特异性链置换聚合酶以及强健的(robust)能量再生系统的组合调控RPA程序。可以容易地适用于与本公开的重组UvsX蛋白一起使用的示例性RPA程序、系统和组分记载于例如US专利号8,071,308;7,399,590,7,485,428,7,270,981,8,030,000,7,666,598,7,763,427,8,017,399,8,062,850,和7,435,561,其各自通过引用并入本文。

[0061] 在一些实施方案中,可以使用动力学排除扩增(kinetic exclusion amplification)(KEA)(其也称为排除扩增(ExAmp))来进行等温扩增。可以使用利用动力学排除的方法制备本公开的核酸文库。当过程以足够快的速率发生以有效地排除另一种事件

或过程发生时，可以发生动力学排除。举例来说，制备核酸阵列，其中将来自溶液的靶核酸随机接种到阵列的位点，并在扩增过程中产生靶核酸的拷贝，以对每个接种位点填充容量(capacity)。根据本公开的动力学排除方法，接种和扩增步骤可以在扩增速率超过接种速率的条件下同时进行。因此，在已经由第一靶核酸接种的位点制备拷贝的相对较快的速率将有效地将第二核酸排除在接种扩增位点外。动力学排除扩增方法可以如US申请公开No.2013/0338042公开内容中详细描述的那样进行，其通过引用以其整体并入本文。

[0062] 在一些实施方案中，扩增的靶核酸是完全双链的。在一些实施方案中，扩增的靶核酸包含双链核酸的区域，并且还包含具有单链核酸的区域。在某些实施方案中，靶核酸包含一个或多个叉状衔接头，其在文库片段的每个末端具有约5,10,15,20,25,30,35,40或超过约40个碱基的单链序列的区域。叉状衔接头的设计和使用更为详细地描述于美国专利号7,742,463和8,563,748的公开中，其通过引用以其整体并入本文。

[0063] 动力学排除可以利用用于制备靶核酸的第一拷贝的相对缓慢的速率对用于制备靶核酸或第一拷贝的后续拷贝的相对快的速率。在上一段的例子中，动力学排除由于以下而发生：靶核酸接种的相对缓慢的速率(例如，相对缓慢的扩散或转运)对发生扩增以填充具有核酸种子的拷贝的位点的相对快速速率。在另一个示例性的实施方案中，动力学排除可以由于以下而发生：已经接种位点的靶序列的第一拷贝的形成延迟(例如延迟或缓慢活化)对制备后续拷贝以填充位点的相对快速速率。在该实例中，单个位点可能已经接种了几种不同的靶核酸(例如，几个靶核酸可以在扩增前在每个位点存在)。然而，可以随机激活用于任何给定靶核酸的第一拷贝形成，使得第一拷贝形成的平均速率相较于生成随后拷贝的速率而言是相对缓慢的。在这种情况下，尽管单个位点可能已经接种了几种不同的靶核酸，动力学排除将仅允许扩增那些靶核酸之一。更为具体地，一旦第一靶核酸已经被激活用于扩增，所述位点将用其拷贝迅速填充容量，从而防止在该位点产生第二靶核酸的拷贝。

[0064] 扩增试剂可以包括促进扩增子形成，并且在某些情况下增加扩增子形成的速率的其它成分。重组酶(如例如UvsX)可以通过允许重复入侵/延伸来促进扩增子形成。更为具体地，重组酶可以促进聚合酶对靶核酸的侵入和通过聚合酶使用靶核酸作为扩增子形成的模板延伸引物。该过程可以作为锁式反应重复，其中从每轮入侵/延伸产生的扩增子在随后的一轮中充当模板。由于不需要变性循环(如经由加热或化学变性)，过程可以比标准PCR更为快速发生。因此，可以等温进行重组酶促进的扩增。通常期望在重组酶促进的扩增试剂中包括ATP或其他核苷酸(或在一些情况下为其不可水解的类似物)以促进扩增。重组酶和单链结合(SSB)蛋白的混合物特别有用，因为SSB可进一步促进扩增。用于重组酶促进的扩增的示例性的配制剂包括那些市售的配制剂，如TwistDx的TwistAmp试剂盒(Cambridge,UK)。重组酶促进扩增试剂的有用组分以及反应条件列于US5,223,414和US 7,399,590中，每个通过引用并入本文。

[0065] 序列比对、同一性和同源性

[0066] 术语“相同的”或“百分比同一性”，在两个或更多个核酸或多肽序列的语境中，是指在为了最大对应性而比较和比对时，相同的两个或更多个序列或亚序列或者具有相同的氨基酸残基或核苷酸的规定百分比，如使用下文描述的序列比较算法之一(或技术人员可用的其他算法)或通过视觉检查测量的。

[0067] 短语“实质上相同”，在两个核酸或多肽(如编码重组酶的DNA或重组酶的氨基酸序

列)的语境中,是指为了最大对应性而比较和比对时具有至少60%,约80%、约90-95%、约98%、约99%或更多的核苷酸或氨基酸残基同一性的两个或更多个序列或亚序列,如使用序列比较算法或通过视觉检查测量。通常认为所述"实质性相同"序列是"同源的",而不参考实际的祖先。优选地,"实质性同一性"存在于长度为至少大约50个残基的序列的区域里,更优选地在至少大约100个残基的区域里,以及最优选地,该序列在至少大约150个残基里或在要比较的序列的全长里实质上相同。

[0068] 当蛋白质和/或蛋白质序列天然地或人工地衍生自共同的祖先蛋白质或蛋白质序列时,它们是"同源的"。类似地,当核酸和/或核酸序列天然地或人工地衍生自共同的祖先核酸或核酸序列时,它们是同源的。同源性通常由两个或更多个核酸或蛋白质(或其序列)之间的序列相似度推断。可用于建立同源性的序列之间相似度的精确百分比随讨论的核酸和蛋白质而变化,但常规地使用超过50,100,150或更多残基至少25%的序列相似度建立同源性。较高水平的序列相似度(如30%,40%,50%,60%,70%,80%,90%,95%,或99%或更高)也可用于建立同源性。用于确定序列相似度百分比的方法(如使用默认参数的BLASTP和BLASTN)在本文中描述并且是通常可获得的。

[0069] 对于序列比对和同源性确定,通常一个序列作用为比较测试序列的参考序列。当使用序列比较算法时,测试和参考序列被输入到计算机中,指定子序列坐标(如果必要),并且指定序列算法程序参数。然后,序列比较算法基于指定的程序参数来计算测试序列相对于参考序列的百分比序列同一性。

[0070] 可以进行用于比较的最佳序列比对,例如通过Smith&Waterman,Adv.Appl.Math.2:482(1981)的局部同源性算法,通过Needleman&Wunsch,J.Mol.Biol.48:443(1970)的同源比对算法,通过Pearson&Lipman,Proc.Nat'l.Acad.Sci.USA 85:2444(1988)的寻找相似度方法,对这些算法的计算机化实现(在Wisconsin Genetics软件包中的GAP,BESTFIT,FASTA,和TFASTA,Genetics Computer Group,575Science Dr.,Madison,Wis.),或通过视觉检查(一般参见Current Protocols in Molecular Biology,Ausubel等人编,Current Protocols,a joint venture between Greene Publishing Associates,Inc.and John Wiley&Sons,Inc.,到2004年补充)。

[0071] 适合于测定百分比序列同一性和序列相似度的算法的一个实例为BLAST算法,其描述于Altschul等人,J.Mol.Biol.215:403-410(1990)中。进行BLAST分析的软件可通过National Center for Biotechnology Information公开获得。这个算法包括首先通过鉴定询问序列中的W长度的短词来鉴定高得分序列对(HSP),所述询问序列当与数据库序列中相同长度的词比对时匹配或满足正值阈值得分T。T是指临近词得分阈值(Altschul等人,如上)。这些最初的临近词命中作用为启动搜索以寻找更长的包含它们的HSP。词命中然后在两个方向上沿着每个序列延伸,远到可增加累积比对得分。对于核苷酸序列,累积得分以M参数(一对匹配残基的奖励得分;总是大于0)和N(不匹配残基的惩罚得分;总是小于0)来计算。对于氨基酸序列,用得分矩阵来计算累计得分。当下述情况时停止每个方向上的词命中的延伸:累积比对得分从其所达到的最大值下降数量X;由于一个或多个负得分残基比对的积累,累积得分到达零或以下;或者,达到任何一个序列的末端。BLAST算法参数W,T和X决定了比对的敏感性和速度。BLASTN程序(对核苷酸序列来说)使用词长度(W)为11,期望值(E)为10,截留为100,M=5,N=-4,以及对两条链的比较作为默认。对于氨基酸序列,BLASTP程

序使用词长度(W)为3,期望值(E)为10以及BLOSUM62得分矩阵作为默认(参见Henikoff& Henikoff(1989)Proc.Natl.Acad.Sci.USA 89:10915)。

[0072] 除了计算序列同一性百分比,BLAST算法也进行两个序列间相似度的统计学分析(参见例如,Karlin&Altschul,Proc.Nat'l.Acad.Sci.USA 90:5873-5787(1993))。BLAST算法所提供的相似度的一种测量为最小总概率(smallest sum probability)(p(N)),其提供了两个核苷酸或氨基酸序列之间的匹配偶然发生的概率的指示。例如,当测试核酸与参考核酸的比较中的最小总概率小于大约0.1,更优选地小于大约0.01,最优选地小于大约0.001时,此核酸被认为是与参考序列相似。

[0073] 编码改变的重组酶的核酸

[0074] 本文还呈现的是编码本文呈现的改变的重组酶的核酸分子。对于任意给定的改变的重组酶(其是已知氨基酸序列以及优选地还有编码重组酶的野生型核苷酸序列的重组酶的突变形式),可以根据分子生物学的基本原理获得编码突变体的核苷酸序列。例如,鉴于编码RB49 UvsX重组酶的野生型核苷酸序列是已知的,可以使用标准遗传密码推断编码具有一个或多个氨基酸取代的任何给定的突变型RB49 UvsX的核苷酸序列。类似地,可以容易地衍生核苷酸序列,用于其他重组酶的突变体形式,如例如T4、T6、Rb69、Aeh1、KVP40、不动杆菌噬菌体133、气单胞菌噬菌体65、噬蓝藻体P-SSM2、噬蓝藻体PSSM4、噬蓝藻体S-PM2、Rb32、弧菌噬菌体nt-1、Rb16、Rb43、T2、Rb14、气单胞菌噬菌体25、phi-1、噬菌体31、噬菌体44RR2.8t,噬菌体Rb3,和噬菌体LZ2等。然后可以使用本领域已知的标准分子生物学技术构建具有所需核苷酸序列的核酸分子。

[0075] 根据本文呈现的实施方式,定义的核酸不仅包括相同的核酸,而且还包括任何次要的碱基变异,包括特别是在由于保守氨基酸取代中的简并密码子而导致同义密码子的情况下的取代(规定相同氨基酸残基的不同密码子)。术语"核酸序列"也包括与关于碱基变异给出的任何单链序列的互补序列。

[0076] 有利地,本文所述的核酸也可以被包括在合适的表达载体中以在合适的宿主中表达从其编码的重组酶蛋白。将克隆的DNA掺入合适的表达载体中用于随后转化所述细胞并随后选择转化的细胞是本领域技术人员熟知的,如提供于Sambrook等人(1989),Molecular cloning:A Laboratory Manual,Cold Spring Harbor Laboratory中,其以其整体通过引用并入。

[0077] 此类表达载体包括下述载体,其具有可操作地连接于调节序列的根据本文呈现的实施方案的核酸,所述调节序列能够实现所述DNA片段的表达,如启动子区域。术语"可操作地连接"是指并列位置,其中所描述的组件处于允许它们以其预期方式发挥作用的关系中。可以将此类载体转化到合适的宿主细胞中以提供根据本文呈现的实施方案的蛋白质表达。

[0078] 核酸分子可以编码成熟蛋白或具有原序列(prosequence)的蛋白,包括编码在前蛋白上的前导序列的,所述前蛋白然后由宿主细胞切割以形成成熟蛋白。载体可以是(例如)提供有复制起点,以及任选地用于表达所述核苷酸的启动子和任选地启动子的调节子的质粒、病毒或噬菌体。载体可以含有一个或多个选择性标记物,如例如抗生素抗性基因。

[0079] 表达所需的调控元件包括启动子序列以结合RNA聚合酶并以引导适当水平的转录起始以及还包括用于核糖体结合的翻译起始序列。例如,细菌表达载体可以包括启动子,如lac启动子和用于翻译起始,Shine-Dalgarno序列,以及起始密码子AUG。类似地,真核表达

载体可以包括对于RNA聚合酶II的异源或同源启动子、下游聚腺苷酸化信号、启动密码子AUG,和用于核糖体分离的终止密码子。此类载体可以商业获得或由本领域公知的方法描述的序列组装。

[0080] 可以通过在载体中包含增强子序列来优化由高等真核生物的编码重组酶的DNA的转录。增强子是作用于启动子以提高转录水平的DNA的顺式作用元件。除了可选择的标记物之外,载体通常还包括复制起点。

实施例

[0081] 实施例1

[0082] 本实施例提供了在模式化流动池表面接种无PCR文库用于改善的簇扩增的方法。在一个实施方案中,本发明的方法使用接种制剂,其包括包含上述突变的UvsX,例如包含Pro256Lys的RB49 UvsX(如本文中意以SEQ ID NO:2所示,本文称为"RB49 P256K")。令人惊讶地发现,使用其进行的重组酶介导的扩增实质性改善了将具有单链衔接头区的PCR文库接种到模式化流动池表面上。在另一个实施方案中,本发明的方法使用接种制剂,其包括相对高浓度的DNA聚合酶(例如eBsu聚合酶)与RB49 P256K重组酶的组合。

[0083] 为了评估RB49 P256K制剂在将无PCR文库接种到模式化流动池表面上的功效,使用TruSeq®DNA无PCR样本制备物试剂盒(Illumina,Inc.)生成无PCR文库。使用TruSeq®文库制备试剂盒生成的无PCR文库具有叉状衔接头,其在文库片段的每个末端带有约40个碱基的单链序列的区域。

[0084] 图3A示出了使用含T4UvsX重组酶(如本文中以SEQ ID NO:8所示,本文称为"T4UvsX")的标准制剂接种到模式化流动池上的无PCR文库的簇图像的截图100。图3B示出了使用包含RB49 P256K重组酶的液体制剂接种到模式化流动池上的无PCR文库的簇图像的截图150。在该实施例中,将T4UvsX制剂或RB49 P256K制剂与文库混合至100pM终浓度,冲到流动池上,并在cBot上于38℃下孵育。在1小时的孵育期后,将温度降至20℃并且用HT2洗涤缓冲液(Illumina)洗涤流动池。用0.1M Tris/0.1M抗坏血酸钠中的SYBR®Green(Life Technologies)的1:5,000稀释液对簇染色,并且在荧光显微镜上成像。参见图3A,通过用标准制剂(如T4UvsX)将无PCR文库接种到模式化流动池所生成的簇浓度是相对稀疏的。参见图3B,通过使用包含RB49 P256K重组酶的制剂将无PCR文库接种到模式化流动池所生成的簇浓度是显著改善的。

[0085] 图4A示出了使用标准T4UvsX制剂接种到模式化流动池上的单链(ssDNA)无PCR文库的簇图像的截图200。图4B示出了使用包含RB49 P256K重组酶的液体制剂接种到模式化流动池上的单链无PCR文库的簇图像的截图250。在该实施例中,使用NaOH变性双链无PCR文库并随后在50pM的浓度下接种到模式化流动池上。参见图4A,通过用标准制剂(如T4UvsX)将ssDNA,无PCR文库接种到模式化流动池上所生成的簇浓度是相对稀疏的。参见图4B,通过使用包含RB49 P256K重组酶的制剂将ssDNA无PCR文库接种到模式化流动池上所生成的簇浓度是显著改善的。

[0086] 实施例2

[0087] 使用RB49 P256K突变体的改善的扩增

[0088] 本实施例描述了本文所述的具有和不具有P256K突变的重组酶之间的扩增性能的

比较。为了本实施例的目的，“对照”RB49 UvsX(如SEQ ID NO:1所示)还包含H63S突变。通过进一步突变该对照以在位置256处携带Lys残基而产生P256K突变体，如SEQ ID NO:2所示。

[0089] 如上文实施例1所述，在cBot上使用对照或P256K突变体进行模式化流动池上的无PCR文库的成簇(Clustering)。然后，在HiSeq装置(Illumina,Inc.)上进行测序，并且分析测序结果以确定通常在以前的测序数据中呈现较差的多个区域的可呼叫性(callability)。

[0090] 可呼叫性是正确呼叫单核苷酸多态性(SNP)的位点的分数的测量。理想情况下，此值为1(即100％)，意味着在特定类型区域(即高GC等)内的100％位点，正确呼叫SNP。覆盖率是具有覆盖率>n的位点分数的测量，其中n通常是30x(即人类基因组的标准覆盖率)。fosmid启动子是一组100个基因启动子，其在先前的测序数据中被鉴定为呈现较差的。将启动子克隆入fosmid载体中。高GC区域可以定义为具有至少100bp的区域，其中GC含量等于或超过75％(N50(G+C≥0.75)100N50)。大量GC的区域可以定义为具有至少100bp的GC，其中GC含量等于或大于85％(N50(G+C≥0.85)100N50)。低GC区域可以定义为至少100bp的区域，其中GC含量等于或小于40％(N50(G+C≥0.40)100N50)。高AT区可以被定义为具有至少100bp的区域，其中AT含量等于或超过75％(N50(A+T≥0.75)100N50)，下采样至约50k区域。可以将大量AT的区域定义为具有至少100bp的区域，其中AT含量等于或大于85％(N50(A+T≥0.85)100N50)，下采样至约50k区域。AT二核苷酸重复区可以被定义为包括长的ATAT重复延伸的区域。

[0091] 对于对照与P256K突变体的可呼叫性比较表明与对照相比，P256K突变体在fosmid启动子区域、高GC、大量GC、低GC、高AT、大量AT，和AT二核苷酸重复区的一个或多个中显示了出乎预料的且显著的改善。

[0092] 实施例3

[0093] 使用具有与P256K同源的突变的突变体的改善扩增

[0094] 对于其他重组酶，重复上文在实施例2中所述的性能比较。在本实施例中，通过修饰野生型重组酶以包含与RB49中的H63S同源的突变来产生“对照”重组酶，如在下表的“对照”栏列出。通过进一步修饰对照以携带与RB49中P256K同源的突变来产生“P256K同系物”突变体，如在下表的“P256K同系物”栏列出。

[0095] 例如，对于T6UvsX，通过修饰野生型T6UvsX(SEQ ID NO:9)以携带H66S突变来生成对照。进一步修饰P256K同系物以携带H66S和F259K突变两者。

[0096]

WT主链	WT主链SEQ ID NO:	对照	P256K同系物
T4	8	64S	64S F257K
T6	9	H66S	H66S F259K
不动杆菌噬菌体133	10	H64S	H64S P257K
Rb69	11	H64S	H64S P258K
Aeh1	12	H76S	H76S P269K
气单胞菌噬菌体65	13	H73S	H73S D266K
KVP40	14	H64S	H64S P267K
Rb43	15	H66S	H66S P259K
噬蓝藻体P-SSM2	16	T62S	T62S Q261K
噬蓝藻体PSSM4	17	T65S	T65S E264K
噬蓝藻体S-PM2	18	T65S	T65S E264K
Rb32	19	H66S	H66S F259K
弧菌噬菌体nt-1	20	H64S	H64S P267K

[0097]

Rb16	21	H66S	H66S P259K

[0098] 使用对照或P256K突变体，如上文实施例1所述在cBot进行模式化流动池上的无PCR文库的成簇(Clustering)。然后，在HiSeq仪(Illumina,Inc.)上进行测序，并且如实施例2中所述分析测序结果，以确定通常在先前测序数据中较差呈现的多种区域的可呼叫性。

[0099] 对于对照与P256K同系物突变体的可呼叫性的比较表明与对照相比，P256K同系物突变体在fosmid启动子区域、高GC、大量GC、低GC、高AT、大量AT，和AT二核苷酸重复区的一个或多个中显示出乎预料的且显著的改善。

[0100] 在本申请中，已经引用了各种出版物，专利和/或专利申请。这些出版物的全部内容通过引用并入本申请中。

[0101] 术语“包括”旨在是开放式的，不仅包括列举的元件，而且还包括任何另外的元件。

[0102] 已经描述了许多实施方案。然而，应当理解，可以进行各种修改。因此，其它实施方案在所附权利要求书的范围内。

[0001] 序列表

[0002] <110> 伊卢米纳剑桥有限公司

[0003] KELLINGER, MATTHEW

[0004] BOUTELL, JONATHAN

[0005] <120> 重组酶突变体

[0006] <130> IP-1264-PRV

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[0019] 35 40 45

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[0076] 85 90 95

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[0090] 195 200 205

[0091] Gly Gly Thr Gly Ala Met Tyr Ser Ala Asn Glu Val Phe Ile Ile Gly

[0092] 210 215 220

[0093] Arg Arg Gln Gln Lys Glu Gly Thr Glu Ile Thr Gly Tyr Asp Phe Ile

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[0109] Asp Met Leu Ala

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[0205] Arg Thr Lys Ile Pro Met Met Asn Ile Ala Leu Ser Gly Glu Ile Thr

[0206] 35 40 45

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[0208] 50 55 60

[0209] Phe Lys Ser Asn Phe Gly Leu Thr Met Val Ser Ser Tyr Met Arg Gln

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[0211] Tyr Pro Asp Ala Val Cys Leu Phe Tyr Asp Ser Glu Phe Gly Ile Thr

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[0226] 195 200 205

[0227] Gly Gly Gly Thr Gly Pro Met Tyr Ser Ala Asp Thr Val Phe Ile Ile

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[0245] Asp Glu Leu Ile Asn Ser Lys Val Glu Lys Phe Lys Ser Pro Glu Ser

[0246] 355 360 365

[0247] Lys Ser Lys Ser Ala Ala Asp Leu Glu Thr Asp Leu Glu Gln Leu Ser

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[0249] Asp Met Glu Glu Phe Asn Glu

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[0252] <211> 393

[0253] <212> PRT

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[0258] Lys Met Thr Ala Glu Leu Thr Thr Ser Lys Phe Phe Asn Glu Lys Asp

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[0262] Ile Asp Gly Gly Met Gln Ser Gly Leu Thr Ile Phe Ala Gly Pro Ser

[0263] 50 55 60

[0264] Lys His Phe Lys Ser Asn Met Ser Leu Thr Met Val Ala Ala Tyr Leu

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[0268] Ile Thr Pro Ala Tyr Leu Arg Ser Met Gly Val Asp Pro Glu Arg Val

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[0271] 115 120 125

[0272] Asn Gln Leu Glu Ala Ile Glu Arg Gly Glu Lys Val Ile Val Phe Ile

[0273] 130 135 140

[0274] Asp Ser Ile Gly Asn Met Ala Ser Lys Lys Glu Thr Glu Asp Ala Leu

[0275] 145 150 155 160

[0276] Asn Glu Lys Ser Val Ala Asp Met Thr Arg Ala Lys Ser Leu Lys Ser

[0277] 165 170 175

[0278] Leu Phe Arg Ile Val Thr Pro Tyr Phe Ser Ile Lys Asn Ile Pro Cys

[0279] 180 185 190

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[0283] 210 215 220

[0284] Ile Ile Gly Lys Arg Gln Ile Lys Asp Gly Ser Asp Leu Gln Gly Tyr

[0285] 225 230 235 240

[0286] Gln Phe Val Leu Asn Val Glu Lys Ser Arg Thr Val Lys Glu Lys Ser

[0287] 245 250 255

[0288] Lys Phe Phe Ile Asp Val Lys Phe Asp Gly Gly Ile Asp Pro Tyr Ser

[0289] 260 265 270

[0290] Gly Leu Leu Asp Met Ala Leu Glu Leu Gly Phe Val Val Lys Pro Lys

[0291] 275 280 285

[0292] Asn Gly Trp Tyr Ala Arg Glu Phe Leu Asp Glu Glu Thr Gly Glu Met

[0293] 290 295 300

[0294] Ile Arg Glu Glu Lys Ser Trp Arg Ala Lys Asp Thr Asn Cys Thr Thr

[0295] 305 310 315 320

[0296] Phe Trp Gly Pro Leu Phe Lys His Gln Pro Phe Arg Asp Ala Ile Lys

[0297] 325 330 335

[0298] Arg Ala Tyr Gln Leu Gly Ala Ile Asp Ser Asn Glu Ile Val Glu Ala

[0299] 340 345 350

[0300] Glu Val Asp Glu Leu Ile Asn Ser Lys Val Glu Lys Phe Lys Ser Pro

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[0302] Glu Ser Lys Ser Lys Ser Ala Ala Asp Leu Glu Thr Asp Leu Glu Gln

[0303] 370 375 380

[0304] Leu Ser Asp Met Glu Glu Phe Asn Glu

[0305] 385 390

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[0308] <212> PRT

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[0315] Arg Thr Arg Ile Pro Met Leu Asn Ile Ala Ile Ser Gly Ala Leu Asn

[0316] 35 40 45

[0317] Gly Gly Met Gln Ser Gly Leu Thr Ile Phe Ala Gly Pro Ser Lys His

[0318] 50 55 60

[0319] Phe Lys Ser Asn Met Gly Leu Thr Met Val Ala Ala Tyr Met Lys Ala

[0320] 65 70 75 80

[0321] Phe Pro Asp Ala Val Cys Met Phe Tyr Asp Ser Glu Phe Gly Ile Thr

[0322] 85 90 95

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[1279] Ile Gln Cys Glu Ser Val Glu Arg Met Lys Phe Glu Met Ala Asn Gln
[1280] 115 120 125
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[1284] 145 150 155 160
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[1286] 165 170 175

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[1289] Phe Thr Met Leu Asp Ile Pro Cys Ile Ala Ile Asn His Thr Tyr Gln
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[1292] 210 215 220
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[1295] Asp Gly Lys Asp Ile Ile Gly Tyr His Phe Ile Met Asn Ile Glu Lys
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[1298] 260 265 270
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[1305] Ala Lys Glu Thr Gln Thr Ile Ser Phe Trp Lys Asp Ile Ile Asn Ser
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[1334] Asp Ser Val Gly Asn Thr Ala Ser Lys Lys Glu Leu Ala Asp Ala Leu
[1335] 145 150 155 160
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[1337] 165 170 175
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[1341] 195 200 205
[1342] Val Ile Ser Gly Gly Thr Gly Leu Met Tyr Ser Ala Asp Thr Ala Ile
[1343] 210 215 220
[1344] Ile Leu Gly Lys Gln Gln Val Lys Glu Gly Thr Glu Val Val Gly Tyr
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[1348] Lys Phe Lys Leu His Val Thr Tyr Glu Gly Gly Ile Ser Met Tyr Ser
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[1358] Asp Lys Tyr Arg Ile Pro Asp Lys Glu Ile Thr Asp Gly Ala Ala Leu
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[1379] Thr Tyr Phe Ser Leu Ala Val Val Lys Asn Phe Leu Asp Asn Asn Pro

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[1381] Asp Gly Tyr Cys Leu Tyr Phe Asp Thr Glu Ala Ala Val Asn Lys Gly

[1382] 85 90 95

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[1384] 100 105 110

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[1386] 115 120 125

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[1391] Leu Asp Asp Lys Gln Val Arg Asp Met Thr Lys Ser Gln Leu Val Lys

[1392] 165 170 175

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[1394] 180 185 190

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[1396] 195 200 205

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[1443] 195 200 205
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[1451] 260 265 270
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[1482] 130 135 140

[1483] Met Phe Val Leu Asp Ser Leu Gly Met Leu Ala Thr Lys Lys Glu Val

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[1488] 180 185 190

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[1490] 195 200 205

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[1494] 225 230 235 240

[1495] Asp Leu Val Gly Asn Ile Ile Lys Cys Glu Ala Lys Lys Ser Arg Leu

[1496] 245 250 255

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[1506] 325 330 335

[1507] Ala Ser Asp Asp Gly Glu Asp

[1508] 340

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[1519] 35 40 45

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[1525] 85 90 95

[1526] Ile Thr Pro Ala Tyr Leu Arg Ser Met Gly Val Asp Pro Glu Arg Val

[1527] 100 105 110

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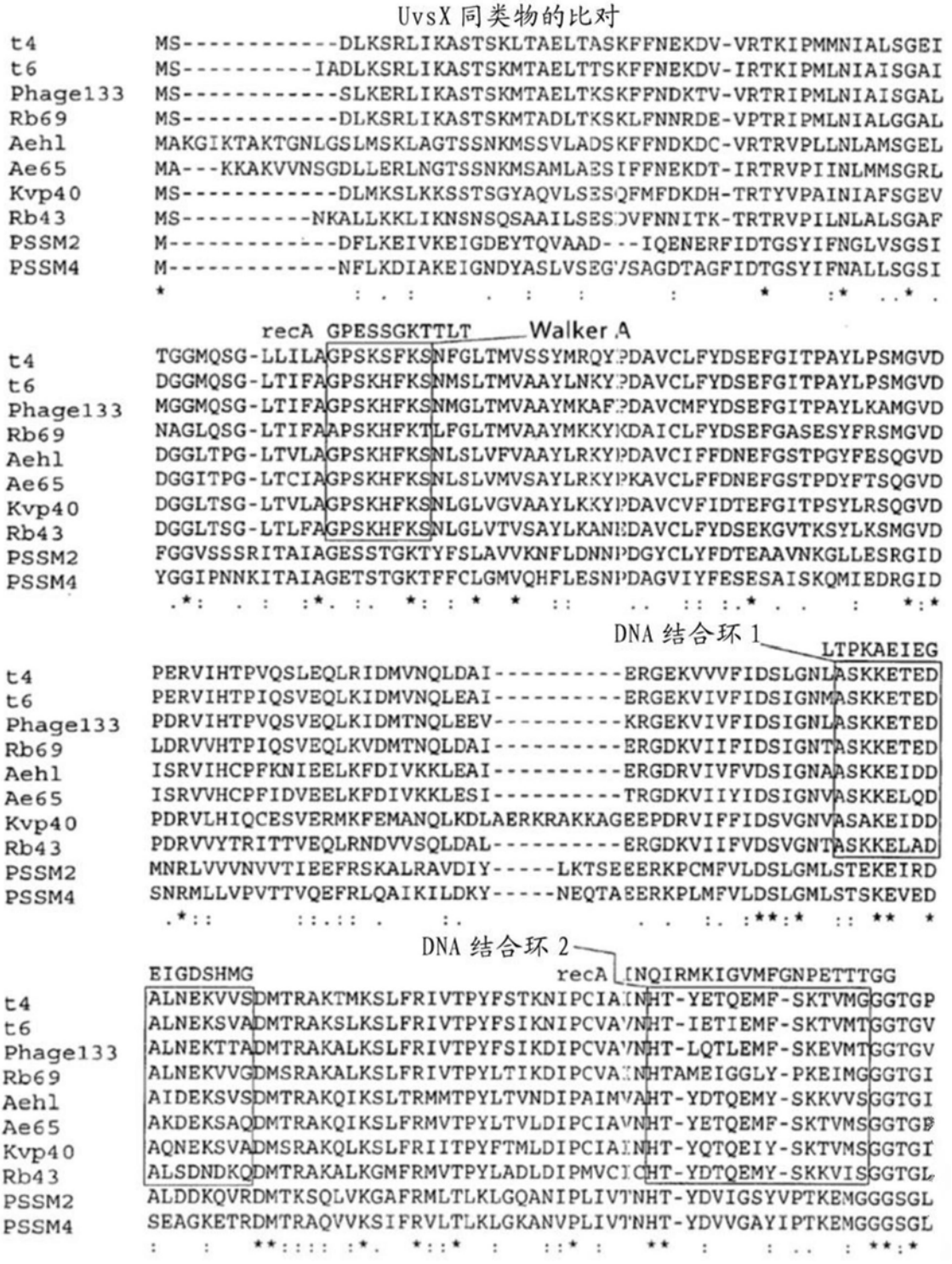
UvsX 同类物的比对
recA GPESSGKTTLT
Walker A
DNA 结合环 1
LTPKAEIEG
DNA 结合环 2
recA
t4
t6
Phage133
Rb69
Aehl
Ae65
Kvp40
Rb43
PSSM2
PSSM4

图1A


UvsX 同类物的比对
t4 MYSADTVFIIGKRQIKDGSDLQGYQFVLNVEKSRTVKEKSKFFIDVKFD-GGIDPYSGLL
t6 MYSADTVFIIGKRQIKDGSDLQGYQFVLNVEKSRTVKEKSKFFIDVKFD-GGIDPYSGLL
Phage133 MYSADTVFFIGKRQVKDGTELAGYEFILKAEKSRMVKEKSVFFITVKFD-GGIDPYSGLL
Rb69 LYSANTVFFISKRQVKEGTELTGYDFTLKAEKSRTVKEKSTFFITVNFD-GGIDPFSGLL
Aeh1 TYSSDTVIIIGRQQEKDGKELLGYNFVLNMEKSRFVKEQSKLFLEVTFQ-GGINTYSGML
Ae65 MYSADTVIILGKQQDKDGKELLGYNFVMNAEKSRAIKEKSKLLLMVSFE-GGINTYSGLL
Kvp40 MYSADTVIILGKQQEKDGKDIIGYHFIMNIEKSRFVKEKMKVFLTVTYE-NGIDPFSGLL
Rb43 MYSADTAIILGKQQVKEGTEVVGYDFIMNIEKSRFVKEKSKFFLHVTYE-GGISMYSGLL
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PSSM4 KYAASTIVYLSKKKEKNGKEVVGNIIKCKTAKSRLTKENSDVETRLYYD-RGLDRYYGLL
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GVKRIYCLGQLD-ESELFGEVDSLFD----------
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IAKEHFSYGTN----------
AAAKEFRYGN----------
NE------
NE------
ED------
DE------
DELFANLD

图1B

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T4      MSDLKSRLIKASTSKLTAELTASKFFNEKDVVRTKIPMMNIALSGEITGGMQSGLLILAGPSKSFK  66

RB49    SNMGLTCVSAYMKQNPDAACLFFDSEFGITSAYLESMGVDPDRVVHVPIKNIEELKFEIM  125
T4      SNFGLTMVSSYMRQYPDAVCLFYDSEFGITPAYLRSMGVDPERVIHTPVQSLEQLRIDMV  126

RB49    NQLEQITREDKVIIFIDSIGNLASKKEVEDAINEKSAQDMTRAKALKGLFRMVTPYLTMN  185
T4      NQLDAIERGEKVVVFIDSLGNLASKKETEDALNEKVVSDMTRAKTMKSLFRIVTPYFSTK  186

RB49    DIPCIAINHTYETQEMFSKTVMSGGTGAMYSANEVFIIGRRQQKEGTEITGYDFILNAEK  245
T4      NIPCIAINHTYETQEMFSKTVMGGGTGPMYSADTVFIIGKRQIKDGSDLQGYQFVLNVEK  246

RB49    SRTVKEKSKFPISVTFSGGIDPYSGLLELAVELGWVVKPSNGWYSRSILNTETGEMETEE  305
T4      SRTVKEKSKFFIDVKFDGGIDPYSGLLDMALELGFVVKPKNGWYAREFLDEETGEMIREE  306

RB49    RKFRAKETNSIEFWKPLLTNDKFNEAINDHYKLGQVISDEAVDKEIEDML  355
T4      KSWRAKDTNCTTFWGPLFKHQPFRDAIKRAYQLGAIDSNEIVEAEVDELI  356
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图2

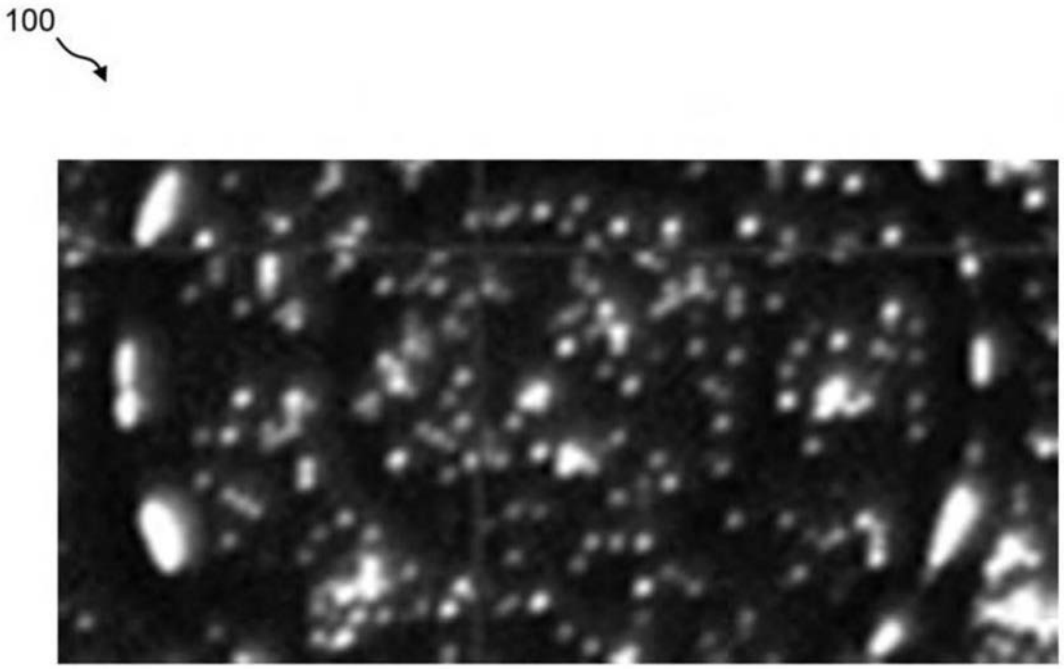

图3A

图3B

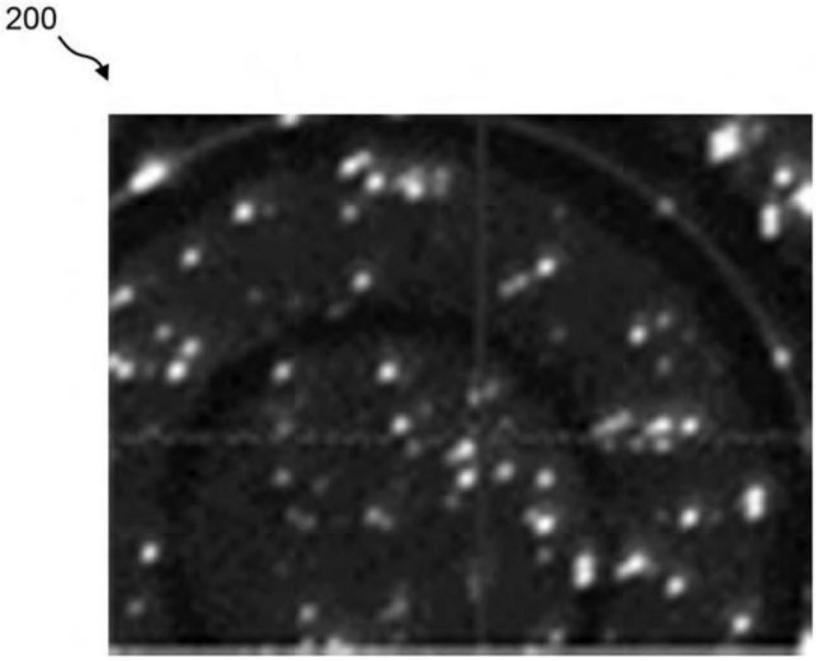

图4A

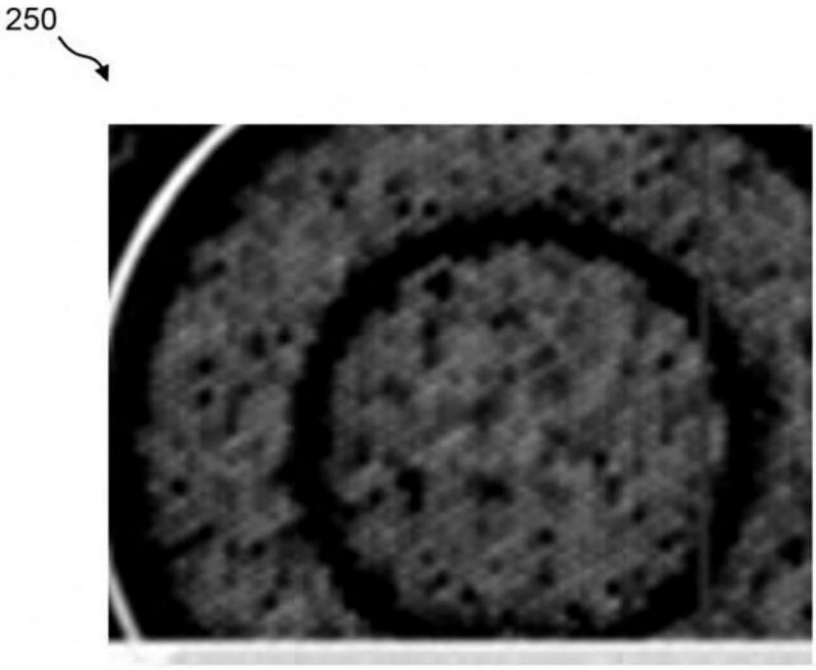

图4B