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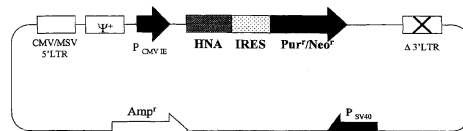
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[54] 发明名称

用于粒细胞抗体检测的谱细胞

[57] 摘要

公开了用于检测抗 - HNA 抗体的谱细胞。所述谱细胞通过在用于检测操作的条件下,以可表达的形式,将编码与抗 - HNA 抗体对应的 HNA 抗原的 DNA 导入细胞来获得,而此细胞在导入 DNA 之前不表现与以下抗体的通过检测操作可检测的应答:抗 - HLA - ABC 抗体、抗 - HLA - DR 抗体、抗 - HLA - DQ 抗体、抗 - HLA - DP 抗体、抗 - HNA - 1 抗体、抗 - HNA - 2a 抗体、抗 - HNA - 3a 抗体、抗 - HNA - 4 抗体、抗 - HNA - 5 抗体和来自健康受试者的血清。通过使用上述谱细胞,对粒细胞抗体的准确和快速检测成为可能。



CMV/MSV 5'LTR: 巨细胞病毒(CMV)I型增强子和小鼠肉瘤病毒(MSV)启动子。
RES: 包装信号
Ψ+: 包装信号
P_CMV III: CMV IE启动子
HNA: HNA-1a, HNA-1b, HNA-2a, CD11b Mart(+), CD11b Mart(-), CD11a Ond(+), CD11a Ond(-), 或 CD18
IRES: 内部核糖体进入位点
Pur/Neo^r: 嘌呤霉素抗性基因或新霉素抗性基因
Δ 3' LTR: 3' MoMuLV LTR(U3缺失)
P_SV40: SV40启动子
Amp^r: 氨基青霉素抗性基因

1. 用于检测抗-HNA 抗体的谱细胞,

所述谱细胞通过以下步骤获得: 将编码与所述抗-HNA 抗体对应的 HNA 抗原的 DNA 导入细胞, 致使所述 DNA 能够在用于检测过程的条件下表达,

其中用于 DNA 导入的细胞在检测过程中不显示与以下抗体的可检测反应: 抗-HLA-ABC 抗体、抗-HLA-DR 抗体、抗-HLA-DQ 抗体、抗-HLA-DP 抗体、抗-HNA-1 抗体、抗-HNA-2a 抗体、抗-HNA-3a 抗体、抗-HNA-4 抗体、抗-HNA-5 抗体和来自正常受试者的血清。

2. 权利要求 1 的谱细胞, 其中用于 DNA 导入的细胞为哺乳动物细胞。

3. 权利要求 2 的谱细胞, 其中所述哺乳动物细胞为非粘附性细胞。

4. 权利要求 3 的谱细胞, 其中所述非粘附性细胞为 K562 细胞。

5. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-1a 抗体, 而与其对应的 HNA 抗原为 HNA-1a 抗原。

6. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-1b 抗体, 而与其对应的 HNA 抗原为 HNA-1b 抗原。

7. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-2a 抗体, 而与其对应的 HNA 抗原为 HNA-2a 抗原。

8. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-4a 抗体, 而与其对应的 HNA 抗原为 HNA-4a 抗原。

9. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-4b 抗体, 而与其对应的 HNA 抗原为 HNA-4b 抗原。

10. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-5a 抗体, 而与其对应的 HNA 抗原为 HNA-5a 抗原。

11. 权利要求 1 的谱细胞, 其中所述抗-HNA 抗体为抗-HNA-5b 抗体, 而与其对应的 HNA 抗原为 HNA-5b 抗原。

12. 权利要求 1 的谱细胞, 其中所述 DNA 被掺入所述细胞的基因组中。

13. 制备用于检测抗-HNA 抗体的谱细胞的方法, 所述方法包括步骤:

提供在检测过程中不显示与以下抗体的可检测反应的细胞: 抗-HLA-ABC 抗体、抗-HLA-DR 抗体、抗-HLA-DQ 抗体、抗-HLA-DP 抗体、抗-HNA-1 抗体、抗-HNA-2a 抗体、抗-HNA-3a 抗体、抗-HNA-4 抗体、抗-HNA-5 抗体和来自正常受试者的血清, 和

将编码与所述抗-HNA 抗体对应的 HNA 抗原的 DNA 导入所述细胞, 以使所述 DNA 能够在用于检测过程的条件下表达。

14. 权利要求 13 的方法, 其中用于 DNA 导入的细胞为哺乳动物细胞。

15. 权利要求 14 的方法, 其中所述哺乳动物细胞为非粘附性细胞。

16. 权利要求 15 的方法, 其中所述非粘附性细胞为 K562 细胞。

17. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-1a 抗体, 而与其对应的 HNA 抗原为 HNA-1a 抗原。

18. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-1b 抗体, 而与其对应的 HNA 抗原为 HNA-1b 抗原。

19. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-2a 抗体, 而与其对应的 HNA 抗原为 HNA-2a 抗原。

20. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-4a 抗体, 而与其对应的 HNA 抗原为 HNA-4a 抗原。

21. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-4b 抗体, 而与其对应的 HNA 抗原为 HNA-4b 抗原。

22. 权利要求 13 的方法, 其中所述抗-HNA 抗体为抗-HNA-5a

抗体，而与其对应的 HNA 抗原为 HNA-5a 抗原。

23. 权利要求 13 的方法，其中所述抗-HNA 抗体为抗-HNA-5b 抗体，而与其对应的 HNA 抗原为 HNA-5b 抗原。

24. 权利要求 13 的方法，其中所述 DNA 被掺入所述细胞的基因组中。

25. 检测试样中的抗-HNA 抗体的方法，所述方法包括步骤：

- (a)提供试样，
- (b)提供权利要求 1-12 中任一项的谱细胞，
- (c)使所述试样与所述谱细胞接触，并检测所述谱细胞与所述抗-HNA 抗体的结合情况。

26. 权利要求 25 的方法，其中所述谱细胞被固定在载体上。

27. 权利要求 25 的方法，其中通过流式细胞术检测所述谱细胞与所述抗-HNA 抗体的结合情况。

28. 用于检测抗-HNA 抗体的试剂，所述试剂包括权利要求 1-12 中任一项的谱细胞。

29. 权利要求 28 的试剂，其中所述谱细胞被固定在载体上。

30. 检测涉及受试者的抗-HNA 抗体疾病的方法，所述方法包括步骤：

- (a)提供得自所述受试者的血清样品，
- (b)提供权利要求 1-12 中任一项的谱细胞，和
- (c)使所述血清样品与所述谱细胞接触，并检测所述谱细胞与所述抗-HNA 抗体的结合情况。

31. 权利要求 30 的方法，其中涉及抗-HNA 抗体的疾病选自：新生儿同种免疫性中性粒细胞减少症、造血干细胞移植之后的同种免疫性中性粒细胞减少症、粒细胞输注不应性、输血相关性急性肺损伤、原发性自身免疫嗜中性粒细胞减少症、继发性自身免疫嗜中性粒细胞减少症和非溶血性输注副作用。

32. 权利要求 30 的方法，其中所述谱细胞被固定在载体上。

33. 权利要求 30 的方法，其中通过流式细胞术检测所述谱细胞

与所述抗-HNA 抗体的结合情况。

34. 用于涉及抗-HNA 抗体的疾病的诊断试剂，所述诊断试剂包括权利要求 1 - 12 中任一项的谱细胞。

35. 权利要求 34 的诊断试剂，其中涉及抗-HNA 抗体的疾病选自：新生儿同种免疫性中性粒细胞减少症、造血干细胞移植之后的同种免疫性中性粒细胞减少症、粒细胞输注不应性、输血相关性急性肺损伤、原发性自身免疫嗜中性粒细胞减少症、继发性自身免疫嗜中性粒细胞减少症和非溶血性输注副作用。

36. 权利要求 34 的诊断试剂，其中将所述谱细胞被固定在载体上。

37. 生产 HNA 抗原的方法，所述方法包括步骤：

培养权利要求 1 - 12 中任一项的谱细胞，和
从培养物中分离所述 HNA 抗原。

用于粒细胞抗体检测的谱细胞

相关申请的引用

[0001]

本专利申请是要求基于日本专利申请第2006-81236号(提交日期: 2006年3月23日)的优先权的申请。日本专利申请第2006-81236号的全部公开内容通过引用结合到本文中。

发明背景

[0002]

发明领域

本发明涉及临床检验领域, 更详细地讲涉及准确和快速检测被认为是引起粒细胞减少(嗜中性粒细胞减少症)和输注副作用原因之一的血清中抗粒细胞抗原的抗体(粒细胞抗体)的方法、以及用于所述方法的谱细胞(panel cell)。

[0003]

背景技术

近年来, 已经在多种临床表现中报道了涉及粒细胞(嗜中性粒细胞)抗原的疾病。涉及同种抗体的疾病包括: 新生儿同种免疫性中性粒细胞减少症、造血干细胞移植之后的同种免疫性中性粒细胞减少症、粒细胞输注不应性、输血相关性急性肺损伤和非溶血性输注副作用等。此外, 涉及自身抗体的疾病包括原发性自身免疫嗜中性粒细胞减少症、继发性自身免疫嗜中性粒细胞减少症等。在这些疾病中, 可观察到抗-人白细胞抗原(HLA)抗体与粒细胞抗体相伴随, 因此需要用于准确而快速地鉴别和鉴定这些抗体的检测方法。

[0004]

粒细胞抗体的检测通常采用: 使用血液粒细胞作为谱细胞(用于

鉴别的细胞), 通过流式细胞术检测粒细胞抗体的方法(GIFT); 使用粒细胞凝集来作为指标的方法(GAT); 使血清和小鼠单克隆抗体与粒细胞反应以确定产生的抗原-抗体复合物的方法(MAIGA); 使用具有粒细胞(或粒细胞提取抗原)固定于其中的平板, 并使平板与样品反应以判断被结合的抗体和抗-人IgG敏感性血细胞(或敏感性珠)的凝集来作为指标的方法(MPHA); 以及方法中的检测步骤涉及使用经标记的抗体来实施MPHA的方法(EIA), 等等。在使用人粒细胞的方法中, 血液取自捐血者, 而粒细胞则从上述血液中分离, 从而获取用于每个检测, 所以与粒细胞抗体的反应随个体而变化。此外, 在用人粒细胞作为谱细胞的方法中, 在流式细胞术等的测量结果中观察到高水平的本底, 本底的水平根据个体的粒细胞而变化, 以致于难以稳定地获得准确的测试结果。因此, 需要开发允许稳定地获得准确测试结果的谱细胞株用于检测粒细胞抗体。

[0005]

迄今, 很多国家包括日本的研究者已经尝试开发谱细胞株用于检测粒细胞抗体。Justus Liebig University的J. Bux 等已经通过将编码这些抗原的基因转染入CHO细胞(中国仓鼠卵巢细胞系), 制备出表达粒细胞抗原HNA-1a、HNA-1b和HNA-SH的谱细胞株(Blood, 第93卷, 第1期, 1999年: 第357-362页)。此外, Hokkaido Red Cross Blood Center的Miyazaki等已经制备出表达HNA-1a和HNA-1b的CHO细胞和COS-7细胞(非洲绿猴肾细胞系)(Japanese Journal of Transfusion Medicine 50, 2, 2004: 第297页)以及表达HNA-2a的293T细胞(人肾细胞系) (Japanese Journal of Transfusion Medicine 51, 2, 2005: 第188页)。

发明概述

[0006]

本发明者已经发现: 通过使用谱细胞, 可准确和快速地检测血清粒细胞抗体, 其中编码HNA抗原的DNA以可表达的形式已被结合

到不对抗-HLA抗体、抗-HNA抗体和来自正常受试者的血清产生应答的细胞中。本发明基于该发现。

[0007]

因此，本发明的目标是提供能够准确和快速检测粒细胞抗体的谱细胞。

[0008]

本发明的谱细胞是用于检测抗-HNA抗体的谱细胞，其通过将编码与所述抗-HNA抗体对应的HNA抗原的DNA导入细胞，致使所述DNA能够在用于检测过程的条件下表达来获得，其中用于DNA导入的细胞在检测过程中不表现与以下抗体发生可检测的反应：抗-HLA-ABC抗体、抗-HLA-DR抗体、抗-HLA-DQ抗体、抗-HLA-DP抗体、抗-HNA-1抗体、抗-HNA-2a抗体、抗-HNA-3a抗体、抗-HNA-4抗体、抗-HNA-5抗体、和来自正常受试者的血清。

[0009]

根据本发明，有可能在本底水平低的粒细胞抗体的检测中稳定地获得准确的测试结果。

附图简述

[0010]

图1显示用于将HNA基因导入细胞的载体结构。

图2显示关于HNA在KY-1a细胞和KY-1b细胞中表达的分析的流式细胞术结果。

图3显示使用KY-1a细胞作为谱细胞，通过流式细胞术对人血清中抗-HNA抗体的检测。

图4显示使用KY-1b细胞作为谱细胞，通过流式细胞术对人血清中抗-HNA抗体的检测。

图5显示关于HNA在KY-2a细胞中表达的分析的流式细胞术结果。

图6显示使用KY-2a细胞作为谱细胞，通过流式细胞术对人血清

中抗-HNA抗体的检测。

图7显示关于HNA在KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞中表达的分析的流式细胞术结果。

图8显示CD11a基因和CD11b基因的多态性。

图9是显示转基因在KY-4a细胞、KY-4b细胞、KY-5a细胞、KY-5b细胞和KY-模拟pn细胞(KY-mock pn cell)中的表达的电泳图。

图10是显示对照基因(G3PDH)在KY-4a细胞、KY-4b细胞、KY-5a细胞、KY-5b细胞和KY-模拟pn细胞中的表达的电泳图。

发明详述

[0011]

在本发明中经过基因转移的细胞是在检测过程中不表现与以下抗体发生可检测反应的细胞：抗-HLA-ABC抗体、抗-HLA-DR抗体、抗-HLA-DQ抗体、抗-HLA-DP抗体、抗-HNA-1抗体、抗-HNA-2a抗体、抗-HNA-3a抗体、抗-HNA-4抗体、抗-HNA-5抗体、和来自正常受试者的血清。用于本文的短语“在检测过程中不表现可检测的反应”意指在用于检测抗-HNA抗体的过程中细胞不表现与各别的抗体或血清的反应，或表现低于检测限的反应。通过检测与上述抗体和血清的反应活性，可确定满足这样的定义的细胞。这样的细胞优选选自哺乳动物细胞，更优选选自非粘附性细胞。满足这样的定义的细胞包括中幼粒细胞性白血病细胞(myelocytic leukemia cell)、K562细胞(ATCC编号CCL-243, Cell Bank in Riken Bioresource Center的RCB编号：RCB0027)。

[0012]

本发明的谱细胞通过将编码与被检测的抗-HNA抗体对应的HNA抗原的DNA导入上述细胞致使所述DNA能够在用于检测过程的条件下表达来制备。

[0013]

人粒细胞抗原包括：分别与抗-HNA-1a抗体、抗-HNA-1b抗体、

抗-HNA-1SH抗体、抗-HNA-2a抗体、抗-HNA-3a抗体、抗-HNA-4a抗体、和抗-HNA-5a抗体对应的HNA-1a抗原、HNA-1b抗原、HNA-1SH抗原、HNA-2a抗原、HNA-3a抗原、HNA-4a抗原、和HNA-5a抗原，且根据待检测的抗体来选择。也有可能使用人粒细胞抗原，例如与抗-HNA-4b抗体或抗-HNA-5b抗体对应的HNA-4b抗原或HNA-5b抗原。

[0014]

在本发明的优选实施方案中，待检测的抗-HNA抗体是抗-HNA-1a抗体，而与其对应的HNA抗原是HNA-1a抗原。作为编码HNA-1a抗原的DNA，HNA-1a抗原基因的基因组DNA或cDNA可以优选使用。HNA-1a抗原基因的cDNA包括含SEQ ID NO: 1所代表的核苷酸序列的DNA，所述核苷酸序列编码SEQ ID NO: 2所代表的氨基酸序列。例如使用基于在SEQ ID NO: 1中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-1a抗原基因的cDNA。

[0015]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-1b抗体，而与其对应的HNA抗原是HNA-1b抗原。作为编码HNA-1b抗原的DNA，HNA-1b抗原基因的基因组DNA或cDNA可以优选使用。HNA-1b抗原基因的cDNA包括含SEQ ID NO: 3所代表的核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 4所代表的氨基酸序列。例如使用基于在SEQ ID NO: 3中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-1b抗原基因的cDNA。

[0016]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-2a抗体，而与其对应的HNA抗原是HNA-2a抗原。作为编码HNA-2a抗原的DNA，HNA-2a抗原基因的基因组DNA或cDNA可以优选使用。HNA-2a抗原基因的cDNA包括含SEQ ID NO: 5所代表的

核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 6所代表的氨基酸序列。例如使用基于在SEQ ID NO: 5中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-2a抗原基因的cDNA。

[0017]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-4a抗体，而与其对应的HNA抗原是HNA-4a抗原。HNA-4a抗原是CD11bMart(+)抗原和CD18抗原的复合体。作为编码HNA-4a抗原的DNA，CD11bMart(+)抗原基因和CD18抗原基因的基因组DNA或cDNA可以优选使用。CD11bMart(+)抗原基因的cDNA包括含SEQ ID NO: 7所代表的核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 8所代表的氨基酸序列。CD18抗原基因的cDNA的核苷酸序列和CD18抗原的氨基酸序列分别由SEQ ID NO: 15和16代表。例如使用基于在SEQ ID NO: 7和15中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-4a抗原基因的cDNA。

[0018]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-4b抗体，而与其对应的HNA抗原是HNA-4b抗原。HNA-4b抗原是CD11bMart(-)抗原和CD18抗原的复合体。作为编码HNA-4b抗原的DNA，CD11bMart(-)抗原基因和CD18抗原基因的基因组DNA或cDNA可以优选使用。CD11bMart(-)抗原基因的cDNA包括含SEQ ID NO: 9所代表的核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 10所代表的氨基酸序列。CD18抗原基因的cDNA的核苷酸序列和CD18抗原的氨基酸序列分别由SEQ ID NO: 15和16代表。例如使用基于在SEQ ID NO: 9和15中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-4b抗原基因的cDNA。

[0019]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-5a抗体，而与其对应的HNA抗原是HNA-5a抗原。HNA-5a抗原是CD11aOnd(+)抗原和CD18抗原的复合体。作为编码HNA-5a抗原的DNA，CD11aOnd(+)抗原基因和CD18抗原基因的基因组DNA或cDNA可以优选使用。CD11aOnd(+)抗原基因的cDNA包括含SEQ ID NO: 11所代表的核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 12所代表的氨基酸序列。CD18抗原基因的cDNA的核苷酸序列和CD18抗原的氨基酸序列分别由SEQ ID NO: 15和16代表。例如使用基于在SEQ ID NO: 11和15中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-5a抗原基因的cDNA。

[0020]

在本发明的另一优选实施方案中，待检测的抗-HNA抗体是抗-HNA-5b抗体，而与其对应的HNA抗原是HNA-5b抗原。HNA-5b抗原是CD11aOnd(-)抗原和CD18抗原的复合体。作为编码HNA-5b抗原的DNA，CD11aOnd(-)抗原基因和CD18抗原基因的基因组DNA或cDNA可以优选使用。CD11aOnd(-)抗原基因的cDNA包括含SEQ ID NO: 13所代表的核苷酸序列的DNA，该核苷酸序列编码SEQ ID NO: 14所代表的氨基酸序列。CD18抗原基因的cDNA的核苷酸序列和CD18抗原的氨基酸序列分别由SEQ ID NO: 15和16代表。例如使用基于在SEQ ID NO: 13和15中5'-末端和3'-末端部分的序列而设计的引物，并使用从表达抗原的细胞中获得的作为模板的mRNA，通过RT-PCR可以扩增出HNA-5b抗原基因的cDNA。

[0021]

用于将DNA导入细胞以使所述DNA能够表达的方法可以依照本领域所熟知的标准技术来实施。例如，可将目标DNA掺入具有在细胞内起作用的启动子的载体中，然后用因此而获得的表达载体转化细胞。作为启动子，可以使用任何种类的启动子如组成型启动子、诱导型启动子等，优选使用在哺乳动物细胞中表现强活性的CMV(巨

细胞病毒)启动子。作为载体,可以使用能在细胞内表达DNA的多种表达载体。在本发明中,特别地,优选将编码HNA抗原的DNA掺入细胞的基因组中,因此为了该目的适当地使用了腺伴随病毒载体和反转录病毒载体。例如,可将抗药基因(如嘌呤霉素抗性基因)通过IRES基因而被连接至所述DNA下游的片段掺入反转录病毒载体中。产生的重组病毒形式的载体可以用于感染细胞,从而可以使DNA导入细胞,以使所述DNA能够表达。根据该方法,通过使用反转录病毒载体,目标基因被安全地导入细胞的染色体中,并且进一步通过IRES基因,目标基因在药物的存在下存活的细胞内安全地表达。

[0022]

本发明的谱细胞可用于检测试样中的抗-HNA抗体。因此,本发明也提供检测试样中抗-HNA抗体的方法,该方法包括步骤:(a)提供试样,(b)提供权利要求1-12中任一项的谱细胞,和(c)使所述试样与所述谱细胞接触,并检测所述谱细胞与所述抗-HNA抗体的结合情况。作为试样,宜用含抗体的样品尤其是血样或血清样品。

[0023]

谱细胞与抗-HNA抗体的结合情况可通过本领域所熟知的方法来检测,所述方法包括:例如,使用流式细胞术的方法(GIFT);使用粒细胞凝集作为指标的方法(GAT);通过使血清和小鼠单克隆抗体与粒细胞反应,并确定所产生的抗原-抗体复合物的方法(MAIGA);通过使用具有粒细胞(或粒细胞提取抗原)固定于其中的平板,并使平板与样品反应,以判断被结合的抗体和抗-人IgG敏感性血细胞(或敏感性珠)的凝集来作为指标的方法(MPHA);以及方法中的检测步骤涉及通过使用经标记的抗体实施MPHA的方法(EIA)等。优选通过流式细胞术来检测谱细胞与抗-HNA抗体的结合情况。

[0024]

在上述的检测抗-HNA抗体的方法中,可以以载体固定形式来使用本发明的谱细胞。载体优选包括热塑性树脂例如聚苯乙烯的平板和珠、并且也可以使用硝酸纤维素滤膜及尼龙滤膜、玻璃纤维、玻

璃珠、磁珠、有机聚合物珠、微生物、血细胞、和细胞膜碎片等。有机聚合物珠包括：例如天然聚合物颗粒如不溶性琼脂糖、纤维素和不溶性葡聚糖、和热塑性合成树脂珠如聚苯乙烯。除聚苯乙烯之外，热塑性合成树脂还包括聚乙烯、聚丙烯、丙烯腈/苯乙烯树脂、丙烯腈/丁二烯/苯乙烯树脂、甲基丙烯酸酯树脂、和氯乙烯等。

[0025]

可以通过无预处理的混合，通过物理化学的修饰，或通过使用结合剂，通过物理化学的键(结合)如共价键、离子键、范德华力、氢键、金属键、机械结合和磁性结合或生物结合如抗原-抗体结合、受体-配体结合、酶-底物结合和核酸的互补结合，使细胞固定到载体上。

[0026]

在检测抗-HNA抗体的方法中，本发明的谱细胞用作检测抗-HNA抗体的试剂。因此，本发明也提供用于检测抗-HNA抗体的试剂，该试剂包含本发明的谱细胞。在本发明的试剂中，所述谱细胞可以是固定在上述载体上的谱细胞。

[0027]

此外，已知抗-HNA抗体与疾病相关。因此，本发明也提供检测或诊断在受试者尤其是人类受试者中涉及抗-HNA抗体的疾病的方法，该方法包括步骤：(a)提供得自所述受试者的血清样品，(b)提供本发明的谱细胞，和(c)使所述血清样品与所述谱细胞接触，并检测所述谱细胞与所述抗-HNA抗体的结合情况。谱细胞与抗-HNA抗体结合情况的检测如上文所述。涉及抗-HNA抗体的疾病包括：新生儿同种免疫性中性粒细胞减少症、造血干细胞移植之后的同种免疫性中性粒细胞减少症、粒细胞输注不应性、输血相关性急性肺损伤、原发性自身免疫嗜中性粒细胞减少症、继发性自身免疫嗜中性粒细胞减少症和非溶血性输注副作用。此外，上述本发明的试剂用作检测或诊断这些疾病的试剂。

[0028]

此外，本发明的谱细胞可以用于生产多种HNA抗原。因此，本发明也提供制备HNA抗原的方法，该方法包括步骤：培养本发明的谱细胞，和从该培养物中分离HNA抗原。

[0029]

如上所述，本发明的谱细胞可以用于检测试样中的抗-HNA抗体和用于诊断在受试者尤其是人类受试者中涉及抗-HNA抗体的疾病。因此，本发明也提供本发明的谱细胞用于检测试样中的抗-HNA抗体的用途，和根据本发明的谱细胞在生产用于检测抗-HNA抗体的试剂中的用途。另外，本发明提供本发明的谱细胞在生产用于诊断涉及在受试者尤其是人类受试者中的抗-HNA抗体的疾病的试剂中的用途。

实施例

[0030]

通过实施例更详细地描述本发明，但本发明的范围不限于这些实施例。

[0031]

参考实施例1：细胞的选择

为了选择用于生产谱细胞的细胞株，六种非粘附性细胞(K562细胞、Jurkat细胞、THP-1细胞、Namalwa细胞、CMK细胞和L细胞)以及五种粘附性细胞(Hela细胞、293T细胞、COS-7细胞、3T3细胞和CHO细胞)经过了以下的试验。首先，用流式细胞术测定每种细胞与三个健康人血清(正常血清)的反应性，以检查在每种细胞中本底水平的增加。其次，使用抗体标记如荧光素(FITC)和藻红蛋白(PE)作为指示，用流式细胞术测定每种细胞与抗-HLA抗体(抗-HLA-ABC抗体和抗-HLA-DR抗体)或抗-HNA抗体(抗-HNA-1抗体、抗-HNA-2a抗体、抗-HNA-3a抗体、抗-HNA-4抗体和抗-HNA-5抗体)的反应性，以检查在每种细胞中本底水平的增加。同样，对于K562细胞，检查了它与抗-HLA-DR抗体、抗-HLA-DQ抗体和抗-HLA-DP抗体的混合物的反

应性。在以上试验中，使用抗-HNA-3a血清检查了细胞与抗-HNA-3a抗体的反应性，并通过使用每种单克隆抗体检查了细胞与其它抗体的反应性。结果显示于表1中。

[0032]

表 1: 候选的待转导细胞在与健康人血清的反应性以及 HLA 表达和 HNA 表达方面的比较。

	非粘附性细胞系										粘附性细胞系			
	K562	Jurkat	THP-1	Namalwa	CMK	L-细胞	Hela	293T	Cos7	3T3				
	0/3	0/3	0/3	0/3	0/3	3/3	1/3	2/3	0/3	2/3				
正常血清 ^{#1}	0/3	0/3	0/3	0/3	0/3	3/3	1/3	2/3	0/3	2/3	2/3 微弱			
HLA ^{#2}	ABC	-	+	+	+	-	+	+	+	-	-			
	DR	-	-	+	-	+	-	-	+	-	-			
	DR、DQ、DP	-	NT	NT	NT	NT	NT	NT	NT	NT	NT			
HNA	1 ^{#3}	-	-	-	-	-	-	-	-	-	±微弱			
	2a ^{#4}	-	-	-	-	-	-	-	-	-	-			
	3a ^{#5}	-	NT	NT	NT	NT	NT	NT	NT	NT	NT			
	4 ^{#6}	-	-	-	+	-	-	-	+	-	-			
	5 ^{#6}	-	+	+	+	-	-	-	-	-	-			

1 使用与三种正常人血清孵育后的 FITC-抗-人 IgG, 由间接免疫荧光光测试法测定。
2 使用 FITC-抗-HLA-ABC 抗体、PE-抗-HLA-DR 抗体、以及 PE-抗-HLA-DQ 抗体和 PE-抗-HLA-DP 抗体的混合物, 由直接免疫荧光光测试法测定。
3 使用 FITC-TAG-1、FITC-TAG-2 和 TAG-3, 由直接免疫荧光光测试法测定。
4 使用 FITC-TAG-4, 由直接免疫荧光光测试法测定。
5 使用与 HNA-3a-活性血清孵育后的 FITC-抗-人 IgG, 由间接免疫荧光光测试法测定。
6 使用 PE-抗-HLA-4 抗体(抗-Mac-1 抗体)和 FITC-抗-HNA5 抗体(抗-LFA1 抗体), 由直接免疫荧光光测试法测定。

[0033]

如表1所示, L细胞、Hela细胞、293T细胞、3T3细胞和CHO细胞表现了与正常血清的高反应性。在另一方面, 五种非粘附性细胞(K562细胞、Jurkat细胞、THP-1细胞、Namalwa细胞和CMK细胞)和一种粘附性细胞(COS-7细胞)表现与正常血清几乎无反应性。此外, 在与正常血清没有反应性的细胞当中, K562细胞显示与抗-HLA抗体或抗-HNA抗体均无反应性。因此, 选择K562细胞作为导入HNA基因的细胞。

[0034]

实施例1: 分别表达HNA-1a、HNA-1b和HNA-2a抗原的细胞的制备

分别从得自具有HNA-1a/a、HNA-1b/b或HNA-2a/a基因型的健康受试者的外周单核细胞中, 制备HNA-1a抗原、HNA-1b抗原和HNA-2a抗原中的每种cDNA。具体地讲, 从上述每种细胞中提取总RNA, 以通过RT-PCR合成cDNA。将因此获得的cDNA克隆入到可市购的质粒pCR2.1-TOPO(Invitrogen, Carlsbad, CA)中, 以确定HNA-1a基因、HNA-1b基因或HNA-2a基因的DNA序列。HNA-1a的cDNA序列和氨基酸序列列于SEQ ID NO: 1和SEQ ID NO: 2中。HNA-1b的cDNA序列和氨基酸序列列于SEQ ID NO: 3和SEQ ID NO: 4中。HNA-2a的cDNA序列和氨基酸序列列于SEQ ID NO: 5和SEQ ID NO: 6中。

[0035]

接下来, 将每种cDNA亚克隆在可市购的反转录病毒载体pQCXIP (Becton Dickinson, SanJose, CA)的BamHI位点和NotI位点之间。将含HNA-1a、HNA-1b和HNA-2a的cDNA的载体分别命名为pQCXIP-1a、pQCXIP-1b和pQCXIP-2a。这些载体的结构显示于图1中。

[0036]

接着, 使用Lipofetamine Plus试剂(Invitrogen)并依照其标准方案, 将pQCXIP-1a、pQCXIP-1b或pQCXIP-2a以及pVSV-G (Becton Dickinson)转染入gp-293T包装细胞株(Becton Dickinson)中。与此相关

的是，也按类似步骤制备其中仅导入了不含HNA基因的pQCXIP质粒的另一株细胞。

[0037]

将此经转染的gp-293T细胞培养48小时，以加到含 10^5 颗粒/ml的重组病毒颗粒的上清液中。将悬浮于0.9ml用于侵染的培养基(含10%FBS的RPMI1640培养基，补充1,5-二甲基-1,5-二氮十一亚甲基聚甲溴化物(Polybrene)至终浓度为 $8\mu\text{g/ml}$)中的 1×10^6 个K562细胞添加到0.1ml上清液中，培养混合物2小时，用R10培养基(含10%FBS的RPMI1640培养基)洗两次，然后在R10培养基中培养2天。随后，通过有限稀释法，克隆其中的经重组病毒侵染的嘌呤霉素抗性细胞，以给予分别表达HNA-1a、HNA-1b和HNA-2a的KY-1a细胞、KY-1b细胞和KY-2a细胞以及其中仅转染了载体的KY-模拟细胞。

[0038]

实施例2：分别表达HNA-4a、HNA-4b、HNA-5a和HNA-5b抗原的细胞的制备

分别从得自具有HNA-4a/a、HNA-4b/b、HNA-5a/a或HNA-5b/b基因型的健康受试者的外周单核细胞，制备HNA-4a抗原、HNA-4b抗原、HNA-5a抗原和HNA-5b抗原中的每种cDNA。具体地讲，从每种细胞中提取总RNA，以通过RT-PCR合成cDNA。将因此获得的cDNA克隆入可市购的质粒pCR2.1-TOPO(Invitrogen, Carlsbad, CA)中，以确定以下基因的DNA序列：CD11bMart(+)基因(决定HNA-4a的多态性)、CD11bMart(-)基因(决定HNA-4b的多态性)、CD11aOnd(+)基因(决定HNA-5a的多态性)、CD11aOnd(-)基因(决定HNA-5b的多态性)和CD18基因(通常在HNA-4和HNA-5中表达)。分别将CD11bMart(+)的cDNA序列和氨基酸序列列于SEQ ID NO: 7和SEQ ID NO: 8中。分别将CD11bMart(-)的cDNA序列和氨基酸序列列于SEQ ID NO: 9和SEQ ID NO: 10中。分别将CD11aOnd(+)的cDNA序列和氨基酸序列列于SEQ ID NO: 11和SEQ ID NO: 12中。分别将CD11aOnd(-)的cDNA序

列和氨基酸序列列于SEQ ID NO: 13和SEQ ID NO: 14中。分别将CD18的cDNA序列和氨基酸序列列于SEQ ID NO: 15和SEQ ID NO: 16中。

[0039]

接着将CD11bMart(+)、CD11bMart(-)、CD11aOnd(+)和CD11aOnd(-)中的每种cDNA亚克隆到pQCXIP的PacI位点和NotI位点之间。分别将这些载体命名为pQCXIP-CD11bMart(+)、pQCXIP-CD11bMart(-)、pQCXIP-CD11aOnd(+)和pQCXIP-CD11aOnd(-)。另外,将CD18的cDNA亚克隆到可市购的反转录病毒载体pQCXIN(与pQCXIP不同的是嘌呤霉素抗性基因已被新霉素抗性基因置换,Becton Dickinson, San Jose, CA)的PacI位点和NotI位点之间,将此载体命名为pQCXIN-CD18。这些载体的结构显示于图1中。

[0040]

接着,使用Lipofetamine Plus试剂(Invitrogen)并依照其标准方案,将pQCXIP-CD11bMart(+)、pQCXIP-CD11bMart(-)、pQCXIP-CD11aOnd(+)或pQCXIP-CD11aOnd(-)以及pQCXIN-CD18和pVSV-G(Becton Dickinson)转染入gp-293T包装细胞株(Becton Dickinson)中。与此相关的是,也按类似步骤制备其中仅导入了不含HNA基因的pQCXIP或pQCXIN的另一株细胞。

[0041]

将此经转染的gp-293T细胞培养48小时,以加到含 10^5 颗粒/ml的重组病毒颗粒的上清液中。将已转染了pQCXIN-CD18的gp-293T细胞培养物的0.1ml上清液、以及悬浮于0.8ml用于侵染的培养基(含10%FBS的RPMI1640培养基,补充聚凝胺至终浓度为 $8\mu\text{g/ml}$)中的 1×10^6 个K562细胞,依次添加到0.1ml已转染了pQCXIP-CD11bMart(+)、pQCXIP-CD11bMart(-)、pQCXIP-CD11aOnd(+)或pQCXIP-CD11aOnd(-)的gp-293T细胞培养物的0.1ml上清液中,培养混合物2小时,用R10培养基(含10%FBS的RPMI1640培养基)洗两次,然后在R10培养基中培养2天。随后,通过有限稀释法,克隆其中经重组病

毒侵染的嘌呤霉素抗性细胞和新霉素抗性细胞，以给予分别表达HNA-4a、HNA-4b、HNA-5a和HNA-5b的KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞。也制备了其中仅转染了载体(pQCXIP和pQCXIN)的KY-模拟pn。

[0042]

实施例3：流式细胞术分析(FCM)

(1)HNA在KY-1a细胞和KY-1b细胞中表达的检测

使KY-1a细胞、KY-1b细胞和KY-模拟细胞与经荧光素(FITC)标记的FITC-TAG1(针对HNA-1a抗原的单克隆抗体)或FITC-TAG2(针对HNA-1b抗原的单克隆抗体)在4℃下孵育15分钟。然后，通过流式细胞术(FCM)检测每种细胞与每种抗体的结合情况。结果显示于图2。

[0043]

在图2中所示的各个分图中，显示了使用左侧所示抗体而获得的峰图和使用具有相同同种型的小鼠IgG作为对照而获得的峰图。当这两个峰图不完全重叠时，左侧的峰图为使用小鼠IgG而获得的峰图。图2说明：其中导入了HNA-1a基因的KY-1a细胞仅与抗-HNA-1a抗体反应，并因此特异性地表达HNA-1a抗原。也显示：其中导入了HNA-1b基因的KY-1b细胞仅与抗-HNA-1b抗体反应，并因此特异性地表达HNA-1b抗原。在作为对照的KY-模拟细胞中未观察到非特异性反应。

[0044]

(2)使用KY-1a细胞和KY-1b细胞作为谱细胞检测人血清中的抗-HNA抗体

通过流式细胞术(FCM)检测KY-1a细胞、KY-1b细胞和KY-模拟细胞与10个抗-HNA抗体阳性血清和20个正常血清的反应性。结果显示，这些细胞均不与这些血清反应。

[0045]

接着，通过流式细胞术(FCM)检测KY-1a细胞、KY-1b细胞和KY-模拟细胞与2个含抗-HNA-1a抗体的血清(抗-HNA-1a血清)或3个

含抗-HNA-1b抗体的血清(三个血清中之一也包含抗-HNA I类抗体)(抗-HNA-1b血清)的反应性。结果显示于图3和图4。

[0046]

图3说明了关于KY-1a细胞的结果。在图3所示的各个分图中,显示了使用KY-1a细胞而获得的峰图和使用KY-模拟细胞而获得的峰图。当这两个峰图不完全重叠时,左侧的峰图为使用KY-模拟细胞而获得的峰图。图3说明KY-1a细胞仅与抗-HNA-1a血清反应,并且反应强度取决于血清中抗-HNA-1a抗体的浓度。

[0047]

图4说明了关于KY-1b细胞的结果。在图4中所示的各个分图中,显示了使用KY-1b细胞而获得的峰图和使用KY-模拟细胞作为对照而获得的峰图。当这两个峰图不完全重叠时,左侧的峰图为使用KY-模拟细胞而获得的峰图。图4说明KY-1b细胞仅与抗-HNA-1b血清反应,并且反应强度取决于血清中抗-HNA-1b抗体的浓度。

[0048]

(3)HNA在KY-2a细胞中表达的检测

使KY-2a细胞与经荧光素(FITC)标记的FITC-TAG1、FITC-TAG2、FITC-TAG3(针对HNA-1抗原的单克隆抗体)、FITC-TAG4(针对HNA-2a抗原的单克隆抗体)在4℃下孵育15分钟。然后,通过流式细胞术(FCM)检测KY-2a细胞与每种抗体的结合情况。结果显示于图5。

[0049]

在图5中所示的各个分图中,显示了使用栏上所示的抗体而获得的峰图和使用具有相同同种型的小鼠IgG作为对照而获得的峰图。当这两个峰图不完全重叠时,左侧的峰图为使用小鼠IgG获得的峰图。图5说明:其中导入了HNA-2a基因的KY-2a细胞仅与抗-HNA-2a抗体反应,并因此特异性地表达HNA-2a抗原。

[0050]

(4)使用KY-2a细胞作为谱细胞检测人血清中的抗-HNA抗体

通过流式细胞术(FCM)检测KY-2a细胞与10个抗-HLA抗体阳性血清和20个正常血清的反应性。结果显示, KY-2a细胞均不与这些血清反应。

[0051]

接着, 通过流式细胞术(FCM)检测KY-2a细胞和KY-模拟细胞与2个抗-HNA-1a血清、3个抗-HNA-1b血清、或2个含抗-HNA-2a抗体的血清(抗-HNA-2a血清)的反应性。结果显示于图6。

[0052]

在图6所示的各个分图中, 显示了使用KY-2a细胞而获得的峰图和使用KY-模拟细胞作为对照而获得的峰图。当这两个峰图不完全重叠时, 左侧的峰图为使用KY-模拟细胞而获得的峰图。图6说明KY-2a细胞仅与抗-HNA-2a血清反应, 并且反应强度取决于血清中抗-HNA-2a抗体的浓度。

[0053]

(5)HNA在KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞中表达的检测

使KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞与经异氰酸荧光素(FITC)标记的FITC-CD11a抗体(针对HNA-5抗原的单克隆抗体)或FITC-CD11b抗体(针对HNA-4抗原的单克隆抗体)以及与经藻红蛋白(PE)标记的CD18抗体(HNA-4抗原为CD11b和CD18的复合体, 而HNA-5抗原为CD11a和CD18的复合体。CD18抗体为针对HNA-4抗原和HNA-5抗原共有的CD-18的单克隆抗体)在4℃温育15分钟。然后, 通过流式细胞术(FCM)检测每种细胞与每种抗体的结合情况。结果显示于图7。

[0054]

在图7中所示的各个分图中, 显示了使用左侧所示抗体而获得的直方图和使用具有相同同种型的小鼠IgG作为对照而获得的直方图。当这两个直方图不完全重叠时, 左侧的直方图为使用小鼠IgG而获得的直方图。图7说明: 其中导入了HNA-4a基因的KY-4a细胞或其中导

入了HNA-4b基因的KY-4b细胞仅与抗-HNA-4抗体(CD11b)反应, 并因此特异性地表达HNA-4a或HNA-4b抗原。也显示了: 其中导入了HNA-5a基因的KY-5a细胞或其中导入了HNA-5b基因的KY-5b细胞仅与抗-HNA-5抗体(CD11a)反应, 并因此特异性地表达HNA-5a或HNA-5b抗原。也通过CD18抗体证实了HNA-4抗原和HNA-5抗原共有的CD18分子的表达。

[0055]

实施例4: 抗原在KY-1a细胞、KY-1b细胞和KY-2a细胞中表达的稳定性

检查基因在实施例1中所制备的KY-1a细胞、KY-1b细胞和KY-2a细胞中表达(抗原表达)的稳定性。具体地讲, 使上述三种细胞在用嘌呤霉素补充至终浓度为0.5 μ g/ml的R10培养基中培养, 使用针对抗原的单克隆抗体(FITC-TAG1、FITC-TAG2和FITC-TAG4), 通过流式细胞术(FCM), 测定抗原在这些细胞中表达与时间的关系。在制备后的0、1、3和6个月, 观察到在KY-1a和KY-1b细胞中的抗原表达无变化的高稳定性。同样地, KY-2a细胞直到制备后的3个月还稳定表达抗原。

[0056]

实施例5: 通过RT-PCR证实转基因在KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞中表达

通过RT-PCR检查转基因在实施例2中所制备的KY-4a细胞、KY-4b细胞、KY-5a细胞和KY-5b细胞中的表达情况。具体地讲, 从每种细胞中提取总RNA, 以通过RT-PCR合成cDNA, 用特异性引物扩增包含决定HNA-4(在CD11b抗原上存在)或HNA-5(在CD11a抗原上存在)多态性的位点的核苷酸序列, 以通过观察限制性酶消化所获得的裂解谱(fragmentation pattern), 来检查多态性所致的核苷酸序列差异。

[0057]

如图8所示, 编码HNA-4抗原(CD11b)的基因展示了具有两个限制酶AciI的限制位点的HNA-4a基因和只有一个同样的限制位点的

HNA-4b基因的多态性。编码HNA-5抗原(CD11a)的基因展示了具有两个限制酶Bsp1286I的限制位点的HNA-5a基因和只有一个同样的限制位点的HNA-5b基因的多态性。通过限制酶消化在各细胞中由RT-PCR所扩增的产物,并使其电泳。结果显示于图9。

[0058]

如图9所示,用特异性地扩增作为模板的cDNA中的多态性位点的引物来进行PCR,所述cDNA合成自导入了HNA-4a或HNA-4b基因的KY-4a或KY-4b细胞。结果显示,可观察到特异性扩增产物(CD11b、RT+、酶-)。在用KY-模拟pn的cDNA的PCR中未观察到这些扩增产物。此外,当用限制酶AciI消化扩增产物时,在导入了HNA-4a基因的KY-4a细胞中观察到对应于272 bp、208 bp和124 bp的三个条带(2个限制位点),而在KY-4b细胞中观察到对应于480 bp和124 bp的两个条带(1个限制位点)。这表明:HNA-4a和HNA-4b基因的mRNA分别在KY-4a和KY-4b细胞中特异性地表达。也用KY-5a和KY-5b细胞进行了相似的检查,并分别观察到HNA-5a和HNA-5b基因的mRNA的特异性表达。此外,通过检查G3PDH的表达量证实:细胞之间的总RNA量(cDNA量)没有差异(图10)。

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<120> 用于粒细胞抗体检测的谱细胞

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 85 90 95
 Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
 100 105 110
 Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
 115 120 125
 His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
 130 135 140
 Gly Lys Asp Arg Lys Tyr Phe His His Asn Ser Asp Phe His Ile Pro
 145 150 155 160
 Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
 165 170 175
 Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
 180 185 190
 Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Ser Pro Pro Gly Tyr Gln
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 Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
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 Leu Tyr Phe Ser Val Lys Thr Asn Ile
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Leu Ala Leu	Leu Gly Phe	Ile Leu Pro	Leu Pro Gly	Val Gln Ala	Leu										
10				15				20							
ctc tgc cag	ttt ggg aca	gtt cag cat	gtg tgg aag	gtg tcc gac	ctg										149
Leu Cys Gln	Phe Gly Thr	Val Gln His	Val Trp Lys	Val Ser Asp	Leu										
25				30				35							
ccc cgg caa	tgg acc cct	aag aac acc	agc tgc gac	agc ggc ttg	ggg										197
Pro Arg Gln	Trp Thr Pro	Lys Asn Thr	Ser Cys Asp	Ser Gly Leu	Gly										
40				45				50							
tgc cag gac	acg ttg atg	ctc att gag	agc gga ccc	caa gtg agc	ctg										245
Cys Gln Asp	Thr Leu Met	Leu Ile Glu	Ser Gly Pro	Gln Val Ser	Leu										
55				60				65				70			
gtg ctc tcc	aag ggc tgc	acg gag gcc	aag gac cag	gag ccc cgc	gtc										293
Val Leu Ser	Lys Gly Cys	Thr Glu Ala	Lys Asp Gln	Glu Pro Arg	Val										
75				80				85							
act gag cac	cgg atg ggc	ccc ggc ctc	tcc ctg atc	tcc tac acc	ttc										341
Thr Glu His	Arg Met Gly	Pro Gly Leu	Ser Leu Ile	Ser Tyr Thr	Phe										
90				95				100							
gtg tgc cgc	cag gag gac	ttc tgc aac	aac ctc gtt	aac tcc ctc	cgc										389
Val Cys Arg	Gln Glu Asp	Phe Cys Asn	Asn Leu Val	Asn Ser Leu	Pro										
105				110				115							
ctt tgg gcc	cca cag ccc	cca gca gac	cca gga tcc	ttg agg tgc	cca										437
Leu Trp Ala	Pro Gln Pro	Pro Ala Asp	Pro Gly Ser	Leu Arg Cys	Pro										
120				125				130							
gtc tgc ttg	tct atg gaa	ggc tgt ctg	gag ggg aca	aca gaa gag	atc										485
Val Cys Leu	Ser Met Glu	Gly Cys Leu	Glu Gly Thr	Thr Glu Glu	Ile										
135				140				145				150			
tgc ccc aag	ggg acc aca	cac tgt tat	gat ggc ctc	ctc agg ctc	agg										533
Cys Pro Lys	Gly Thr Thr	His Cys Tyr	Asp Gly Leu	Leu Arg Leu	Arg										
155				160				165							
gga gga ggc	atc ttc tcc	aat ctg aga	gtc cag gga	tgc atg ccc	cag										581
Gly Gly Gly	Ile Phe Ser	Asn Leu Arg	Val Gln Gly	Cys Met Pro	Gln										
170				175				180							
cca ggt tgc	aac ctg ctc	aat ggg aca	cag gaa att	ggg ccc gtg	ggt										629
Pro Gly Cys	Asn Leu Leu	Asn Gly Thr	Gln Glu Ile	Gly Pro Val	Gly										

185	190	195	
atg act gag aac tgc aat agg aaa gat ttt ctg acc tgt cat cgg ggg Met Thr Glu Asn Cys Asn Arg Lys Asp Phe Leu Thr Cys His Arg Gly 200	205	210	677
acc acc att atg aca cac gga aac ttg gct caa gaa ccc act gat tgg Thr Thr Ile Met Thr His Gly Asn Leu Ala Gln Glu Pro Thr Asp Trp 215	220	225	725
acc aca tcg aat acc gag atg tgc gag gtg ggg cag gtg tgt cag gag Thr Thr Ser Asn Thr Glu Met Cys Glu Val Gly Gln Val Cys Gln Glu 235	240	245	773
acg ctg ctg ctc ata gat gta gga ctc aca tca acc ctg gtg ggg aca Thr Leu Leu Leu Ile Asp Val Gly Leu Thr Ser Thr Leu Val Gly Thr 250	255	260	821
aaa ggc tgc agc act gtt ggg gct caa aat tcc cag aag acc acc atc Lys Gly Cys Ser Thr Val Gly Ala Gln Asn Ser Gln Lys Thr Thr Ile 265	270	275	869
cac tca gcc cct cct ggg gtg ctt gtg gcc tcc tat acc cac ttc tgc His Ser Ala Pro Pro Gly Val Leu Val Ala Ser Tyr Thr His Phe Cys 280	285	290	917
tcc tcg gac ctg tgc aat agt gcc agc agc agc agc gtt ctg ctg aac Ser Ser Asp Leu Cys Asn Ser Ala Ser Ser Ser Ser Val Leu Leu Asn 295	300	305	965
tcc ctc cct cct caa gct gcc cct gtc cca gga gac cgg cag tgt cct Ser Leu Pro Pro Gln Ala Ala Pro Val Pro Gly Asp Arg Gln Cys Pro 315	320	325	1013
acc tgt gtg cag ccc ctt gga acc tgt tca agt ggc tcc ccc cga atg Thr Cys Val Gln Pro Leu Gly Thr Cys Ser Ser Gly Ser Pro Arg Met 330	335	340	1061
acc tgc ccc agg ggc gcc act cat tgt tat gat ggg tac att cat ctc Thr Cys Pro Arg Gly Ala Thr His Cys Tyr Asp Gly Tyr Ile His Leu 345	350	355	1109
tca gga ggt ggg ctg tcc acc aaa atg agc att cag ggc tgc gtg gcc Ser Gly Gly Gly Leu Ser Thr Lys Met Ser Ile Gln Gly Cys Val Ala 360	365	370	1157
caa cct tcc agc ttc ttg ttg aac cac acc aga caa atc ggg atc ttc Gln Pro Ser Ser Phe Leu Leu Asn His Thr Arg Gln Ile Gly Ile Phe 375	380	385	1205
		390	

tct gcg cgt gag aag cgt gat gtg cag cct cct gcc tct cag cat gag 1253
 Ser Ala Arg Glu Lys Arg Asp Val Gln Pro Pro Ala Ser Gln His Glu
 395 400 405

gga ggt ggg gct gag ggc ctg gag tct ctc act tgg ggg gtg ggg ctg 1301
 Gly Gly Gly Ala Glu Gly Leu Glu Ser Leu Thr Trp Gly Val Gly Leu
 410 415 420

gca ctg gcc cca gcg ctg tgg tgg gga gtg gtt tgc cct tcc tgc 1346
 Ala Leu Ala Pro Ala Leu Trp Trp Gly Val Val Cys Pro Ser Cys
 425 430 435

taactctatt acccccacga ttcttcaccg ctgctgacca cccacactca acctccctct 1406

gacctcataa cctaattggcc ttggacacca gattctttcc cattctgtcc atgaatcatc 1466

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gcatccggac ttgccctatg ggagagggga cgctggagga rtggctgcat gtatctgata 1586

atacagaccc tgtcctttca aaaaaaaaaa aaaaaaaaaa aaaa 1630

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Trp Lys Val Ser Asp Leu Pro Arg Gln Trp Thr Pro Lys Asn Thr Ser
 35 40 45

Cys Asp Ser Gly Leu Gly Cys Gln Asp Thr Leu Met Leu Ile Glu Ser
 50 55 60

Gly Pro Gln Val Ser Leu Val Leu Ser Lys Gly Cys Thr Glu Ala Lys
 65 70 75 80

Asp Gln Glu Pro Arg Val Thr Glu His Arg Met Gly Pro Gly Leu Ser
 85 90 95

Leu Ile Ser Tyr Thr Phe Val Cys Arg Gln Glu Asp Phe Cys Asn Asn

100	105	110
Leu Val Asn Ser Leu Pro Leu Trp Ala Pro Gln Pro Pro Ala Asp Pro		
115	120	125
Gly Ser Leu Arg Cys Pro Val Cys Leu Ser Met Glu Gly Cys Leu Glu		
130	135	140
Gly Thr Thr Glu Glu Ile Cys Pro Lys Gly Thr Thr His Cys Tyr Asp		
145	150	155
Gly Leu Leu Arg Leu Arg Gly Gly Gly Ile Phe Ser Asn Leu Arg Val		
165	170	175
Gln Gly Cys Met Pro Gln Pro Gly Cys Asn Leu Leu Asn Gly Thr Gln		
180	185	190
Glu Ile Gly Pro Val Gly Met Thr Glu Asn Cys Asn Arg Lys Asp Phe		
195	200	205
Leu Thr Cys His Arg Gly Thr Thr Ile Met Thr His Gly Asn Leu Ala		
210	215	220
Gln Glu Pro Thr Asp Trp Thr Thr Ser Asn Thr Glu Met Cys Glu Val		
225	230	235
Gly Gln Val Cys Gln Glu Thr Leu Leu Leu Ile Asp Val Gly Leu Thr		
245	250	255
Ser Thr Leu Val Gly Thr Lys Gly Cys Ser Thr Val Gly Ala Gln Asn		
260	265	270
Ser Gln Lys Thr Thr Ile His Ser Ala Pro Pro Gly Val Leu Val Ala		
275	280	285
Ser Tyr Thr His Phe Cys Ser Ser Asp Leu Cys Asn Ser Ala Ser Ser		
290	295	300
Ser Ser Val Leu Leu Asn Ser Leu Pro Pro Gln Ala Ala Pro Val Pro		
305	310	315
Gly Asp Arg Gln Cys Pro Thr Cys Val Gln Pro Leu Gly Thr Cys Ser		
325	330	335
Ser Gly Ser Pro Arg Met Thr Cys Pro Arg Gly Ala Thr His Cys Tyr		
340	345	350
Asp Gly Tyr Ile His Leu Ser Gly Gly Gly Leu Ser Thr Lys Met Ser		
355	360	365

Ile Gln Gly Cys Val Ala Gln Pro Ser Ser Phe Leu Leu Asn His Thr
370 375 380

Arg Gln Ile Gly Ile Phe Ser Ala Arg Glu Lys Arg Asp Val Gln Pro
385 390 395 400

Pro Ala Ser Gln His Glu Gly Gly Gly Ala Glu Gly Leu Glu Ser Leu
405 410 415

Thr Trp Gly Val Gly Leu Ala Leu Ala Pro Ala Leu Trp Trp Gly Val
420 425 430

Val Cys Pro Ser Cys
435

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Met Lys Asp Ser Cys Ile Thr
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gtg atg gcc atg gcg ctg ctg tct ggg ttc ttt ttc ttc gcg ccg gcc 162
Val Met Ala Met Ala Leu Leu Ser Gly Phe Phe Phe Phe Ala Pro Ala
10 15 20

tgc agc tac aac ctg gac gtg cgg ggc gcg cgg agc ttc tcc cca ccg 210
Ser Ser Tyr Asn Leu Asp Val Arg Gly Ala Arg Ser Phe Ser Pro Pro
25 30 35

cgc gcc ggg agg cac ttt gga tac cgc gtc ctg cag gtc gga aac ggg 258
Arg Ala Gly Arg His Phe Gly Tyr Arg Val Leu Gln Val Gly Asn Gly
40 45 50 55

gtc atc gtg gga gct cca ggg gag ggg aac agc aca gga agc etc tat 306
Val Ile Val Gly Ala Pro Gly Glu Gly Asn Ser Thr Gly Ser Leu Tyr
60 65 70

cag tgc cag tcg ggc aca gga cac tgc ctg cca gtc acc ctg aga ggt Gln Cys Gln Ser Gly Thr Gly His Cys Leu Pro Val Thr Leu Arg Gly 75 80 85	354
tcc aac tat acc tcc aag tac ttg gga atg acc ttg gca aca gac ccc Ser Asn Tyr Thr Ser Lys Tyr Leu Gly Met Thr Leu Ala Thr Asp Pro 90 95 100	402
aca gat gga agc att ttg gcc tgt gac cct ggg ctg tct cga acg tgt Thr Asp Gly Ser Ile Leu Ala Cys Asp Pro Gly Leu Ser Arg Thr Cys 105 110 115	450
gac cag aac acc tat ctg agt ggc ctg tgt tac ctc ttc cgc cag aat Asp Gln Asn Thr Tyr Leu Ser Gly Leu Cys Tyr Leu Phe Arg Gln Asn 120 125 130 135	498
ctg cag ggt ccc atg ctg cag ggg cgc cct ggt ttt cag gaa tgt atc Leu Gln Gly Pro Met Leu Gln Gly Arg Pro Gly Phe Gln Glu Cys Ile 140 145 150	546
aag ggc aac gta gac ctg gta ttt ctg ttt gat ggt tcg atg agc ttg Lys Gly Asn Val Asp Leu Val Phe Leu Phe Asp Gly Ser Met Ser Leu 155 160 165	594
cag cca gat gaa ttt cag aaa att ctg gac ttc atg aag gat gtg atg Gln Pro Asp Glu Phe Gln Lys Ile Leu Asp Phe Met Lys Asp Val Met 170 175 180	642
aag aaa ctc agc aac act tcg tac cag ttt gct gct gtt cag ttt tcc Lys Lys Leu Ser Asn Thr Ser Tyr Gln Phe Ala Ala Val Gln Phe Ser 185 190 195	690
aca agc tac aaa aca gaa ttt gat ttc tca gat tat gtt aaa cgg aag Thr Ser Tyr Lys Thr Glu Phe Asp Phe Ser Asp Tyr Val Lys Arg Lys 200 205 210 215	738
gac cct gat gct ctg ctg aag cat gta aag cac atg ttg ctg ttg acc Asp Pro Asp Ala Leu Leu Lys His Val Lys His Met Leu Leu Leu Thr 220 225 230	786
aat acc ttt ggt gcc atc aat tat gtc gcg aca gag gtg ttc cgg gag Asn Thr Phe Gly Ala Ile Asn Tyr Val Ala Thr Glu Val Phe Arg Glu 235 240 245	834
gag ctg ggg gcc cgg cca gat gcc acc aaa gtg ctt atc atc atc acg Glu Leu Gly Ala Arg Pro Asp Ala Thr Lys Val Leu Ile Ile Ile Thr 250 255 260	882

gat ggg gag gcc act gac agt ggc aac atc gat gcg gcc aaa gac atc Asp Gly Glu Ala Thr Asp Ser Gly Asn Ile Asp Ala Ala Lys Asp Ile 265 270 275	930
atc cgc tac atc atc ggg att gga aag cat ttt cag acc aag gag agt Ile Arg Tyr Ile Ile Gly Ile Gly Lys His Phe Gln Thr Lys Glu Ser 280 285 290 295	978
cag gag acc ctc cac aaa ttt gca tca aaa ccc gcg agc gag ttt gtg Gln Glu Thr Leu His Lys Phe Ala Ser Lys Pro Ala Ser Glu Phe Val 300 305 310	1026
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cag aag aag atc tat gtc att gag ggc aca agc aaa cag gac ctg act Gln Lys Lys Ile Tyr Val Ile Glu Gly Thr Ser Lys Gln Asp Leu Thr 330 335 340	1122
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Ile Gly Ser Tyr Phe Gly Gly Glu Leu Cys Gly Val Asp Val Asp Gln	
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gat ggg gag aca gag ctg ctg ctg att ggt gcc cca ctg ttc tat ggg	1554
Asp Gly Glu Thr Glu Leu Leu Leu Ile Gly Ala Pro Leu Phe Tyr Gly	
475 480 485	
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Glu Gln Arg Gly Gly Arg Val Phe Ile Tyr Gln Arg Arg Gln Leu Gly	
490 495 500	
ttt gaa gaa gtc tca gag ctg cag ggg gac ccc ggc tac cca ctc ggg	1650
Phe Glu Glu Val Ser Glu Leu Gln Gly Asp Pro Gly Tyr Pro Leu Gly	
505 510 515	
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Arg Phe Gly Glu Ala Ile Thr Ala Leu Thr Asp Ile Asn Gly Asp Gly	
520 525 530 535	
ctg gta gac gtg gct gtg ggg gcc cct ctg gag gag cag ggg gct gtg	1746
Leu Val Asp Val Ala Val Gly Ala Pro Leu Glu Glu Gln Gly Ala Val	
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Tyr Ile Phe Asn Gly Arg His Gly Gly Leu Ser Pro Gln Pro Ser Gln	
555 560 565	
cgg ata gaa ggg acc caa gtg ctc tca gga att cag tgg ttt gga cgc	1842
Arg Ile Glu Gly Thr Gln Val Leu Ser Gly Ile Gln Trp Phe Gly Arg	
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Ser Ile His Gly Val Lys Asp Leu Glu Gly Asp Gly Leu Ala Asp Val	
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Ala Val Gly Ala Glu Ser Gln Met Ile Val Leu Ser Ser Arg Pro Val	
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Val Asp Met Val Thr Leu Met Ser Phe Ser Pro Ala Glu Ile Pro Val	
620 625 630	
cat gaa gtg gag tgc tcc tat tca acc agt aac aag atg aaa gaa gga	2034
His Glu Val Glu Cys Ser Tyr Ser Thr Ser Asn Lys Met Lys Glu Gly	
635 640 645	
gtt aat atc aca atc tgt ttc cag atc aag tct ctc atc ccc cag ttc	2082
Val Asn Ile Thr Ile Cys Phe Gln Ile Lys Ser Leu Ile Pro Gln Phe	

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caa ggc cgc ctg gtt gcc aat ctc act tac act ctg cag ctg gat ggc Gln Gly Arg Leu Val Ala Asn Leu Thr Tyr Thr Leu Gln Leu Asp Gly 665	670	675	2130
cac cgg acc aga aga cgg ggg ttg ttc cca gga ggg aga cat gaa ctc His Arg Thr Arg Arg Arg Gly Leu Phe Pro Gly Gly Arg His Glu Leu 680	685	690	2178
aga agg aat ata gct gtc acc acc agc atg tca tgc act gac ttc tca Arg Arg Asn Ile Ala Val Thr Thr Ser Met Ser Cys Thr Asp Phe Ser 700	705	710	2226
ttt cat ttc ccg gta tgt gtt caa gac ctc atc tcc ccc atc aat gtt Phe His Phe Pro Val Cys Val Gln Asp Leu Ile Ser Pro Ile Asn Val 715	720	725	2274
tcc ctg aat ttc tct ctt tgg gag gag gaa ggg aca ccg agg gac caa Ser Leu Asn Phe Ser Leu Trp Glu Glu Glu Gly Thr Pro Arg Asp Gln 730	735	740	2322
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gcc ctg cgt cta act gct ttt gcc agc ctc tct gtg gag ctg agc ctg Ala Leu Arg Leu Thr Ala Phe Ala Ser Leu Ser Val Glu Leu Ser Leu 795	800	805	2514
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ccc ccg gga ctc tcc ttc cgc aag gtg gag atg ctg aag ccc cat agc Pro Pro Gly Leu Ser Phe Arg Lys Val Glu Met Leu Lys Pro His Ser 825	830	835	2610
cag ata cct gtg agc tgc gag gag ctt cct gaa gag tcc agg ctt ctg Gln Ile Pro Val Ser Cys Glu Glu Leu Pro Glu Glu Ser Arg Leu Leu 840	845	850	2658
		855	

tcc agg gca tta tct tgc aat gtg agc tct ccc atc ttc aaa gca ggc Ser Arg Ala Leu Ser Cys Asn Val Ser Ser Pro Ile Phe Lys Ala Gly 860 865 870	2706
cac tcg gtt gct ctg cag atg atg ttt aat aca ctg gta aac agc tcc His Ser Val Ala Leu Gln Met Met Phe Asn Thr Leu Val Asn Ser Ser 875 880 885	2754
tgg ggg gac tcg gtt gaa ttg cac gcc aat gtg acc tgt aac aat gag Trp Gly Asp Ser Val Glu Leu His Ala Asn Val Thr Cys Asn Asn Glu 890 895 900	2802
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ctg tac ccc atc aac atc ctc atc cag gac caa gaa gac tcc aca ctc Leu Tyr Pro Ile Asn Ile Leu Ile Gln Asp Gln Glu Asp Ser Thr Leu 920 925 930 935	2898
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acc ctg gag gct gtg gtt ggg gtg cca cag cct ccc agc gag ggg ccc Thr Leu Glu Ala Val Val Gly Val Pro Gln Pro Pro Ser Glu Gly Pro 970 975 980	3042
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aac agc agc aag cat ttc cac ctc tat ggc agc aac gcc tcc ctg Asn Ser Ser Lys His Phe His Leu Tyr Gly Ser Asn Ala Ser Leu 1060 1065 1070	3315
gcc cag gtt gtc atg aag gtt gac gtg gtg tat gag aag cag atg Ala Gln Val Val Met Lys Val Asp Val Val Tyr Glu Lys Gln Met 1075 1080 1085	3360
ctc tac ctc tac gtg ctg agc ggc atc ggg ggg ctg ctg ctg ctg Leu Tyr Leu Tyr Val Leu Ser Gly Ile Gly Gly Leu Leu Leu Leu 1090 1095 1100	3405
ctg ctc att ttc ata gtg ctg tac aag gtt ggt ttc ttc aaa cgg Leu Leu Ile Phe Ile Val Leu Tyr Lys Val Gly Phe Phe Lys Arg 1105 1110 1115	3450
aac ctg aag gag aag atg gag gct ggc agg ggt gtc ccg aat gga Asn Leu Lys Glu Lys Met Glu Ala Gly Arg Gly Val Pro Asn Gly 1120 1125 1130	3495
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agt ggt ggt ggc aag gac tgagtccagg cctgtgaggt gcagagtgcc Ser Gly Gly Gly Lys Asp 1165 1170	3633
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Val Leu Gln Val Gly Asn Gly Val Ile Val Gly Ala Pro Gly Glu Gly
50 55 60

Asn Ser Thr Gly Ser Leu Tyr Gln Cys Gln Ser Gly Thr Gly His Cys
65 70 75 80

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Gly Ile Gln Trp Phe Gly Arg Ser Ile His Gly Val Lys Asp Leu Glu
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Gly Asp Gly Leu Ala Asp Val Ala Val Gly Ala Glu Ser Gln Met Ile
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Val Leu Ser Ser Arg Pro Val Val Asp Met Val Thr Leu Met Ser Phe
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Ser Pro Ala Glu Ile Pro Val His Glu Val Glu Cys Ser Tyr Ser Thr

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Lys Ser Leu Ile Pro Gln Phe Gln Gly Arg Leu Val Ala Asn Leu Thr			
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Tyr Thr Leu Gln Leu Asp Gly His Arg Thr Arg Arg Arg Gly Leu Phe			
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Pro Gly Gly Arg His Glu Leu Arg Arg Asn Ile Ala Val Thr Thr Ser			
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Ile Leu Arg Pro Ser Leu His Ser Glu Thr Trp Glu Ile Pro Phe Glu			
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Val Gln Leu Asp Leu His Phe Pro Pro Gly Leu Ser Phe Arg Lys Val			
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Ser Pro Ile Phe Lys Ala Gly His Ser Val Ala Leu Gln Met Met Phe			
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Leu Thr Ala Leu Thr Leu Cys His Gly Phe Asn Leu Asp Thr Glu Asn
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Gln Leu Gln Gly Ser Arg Val Val Val Gly Ala Pro Gln Glu Ile Val
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Ala Ala Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr Gly
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Ser Cys Glu Pro Ile Arg Leu Gln Val Pro Val Glu Ala Val Asn Met
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tcc ctg ggc ctg tcc ctg gca gcc acc acc agc ccc cct cag ctg ctg 402
Ser Leu Gly Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu Leu
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gcc tgt ggt ccc acc gtg cac cag act tgc agt gag aac acg tat gtg 450

Ala Cys Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr Val	
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Lys Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro Gln	
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Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp Ile	
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Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp Phe Arg	
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Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys Lys Ser	
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Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile His	
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Ser Arg Gln Glu Leu Asn Thr Ile Ala Ser Lys Pro Pro Arg Asp His	

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Glu	Asn	Asn	Met	Pro	Arg	Thr	Asn	Lys	Thr	Glu	Phe	Gln	Leu	Glu	Leu	
905						910						915				
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Pro	Val	Lys	Tyr	Ala	Val	Tyr	Met	Val	Val	Thr	Ser	His	Gly	Val	Ser	
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Gln	His	Gln	Tyr	Gln	Val	Ser	Asn	Leu	Gly	Gln	Arg	Ser	Leu	Pro	Ile	
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Ser	Leu	Val	Phe	Leu	Val	Pro	Val	Arg	Leu	Asn	Gln	Thr	Val	Ile	Trp	
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Ile	Gln	Cys	Asp	Ile	Pro	Phe	Phe	Gly	Ile	Gln	Glu	Glu	Phe	Asn		
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Ser	His	Asn	His	Leu	Leu	Ile	Val	Ser	Thr	Ala	Glu	Ile	Leu	Phe		
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Asn	Asp	Ser	Val	Phe	Thr	Leu	Leu	Pro	Gly	Gln	Gly	Ala	Phe	Val		

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Leu Ala Leu Ile Thr Ala	Ala Leu Tyr Lys Leu	Gly Phe Phe Lys	
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Arg Gln Tyr Lys Asp Met	Met Ser Glu Gly Gly	Pro Pro Gly Ala	
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Glu Pro Gln			
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50 55 60			

Gln Cys Asp Tyr Ser Thr Gly Ser Cys Glu Pro Ile Arg Leu Gln Val			
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Pro Val Glu Ala Val Asn Met Ser Leu Gly Leu Ser Leu Ala Ala Thr			
	85	90	95
Thr Ser Pro Pro Gln Leu Leu Ala Cys Gly Pro Thr Val His Gln Thr			
	100	105	110
Cys Ser Glu Asn Thr Tyr Val Lys Gly Leu Cys Phe Leu Phe Gly Ser			
	115	120	125
Asn Leu Arg Gln Gln Pro Gln Lys Phe Pro Glu Ala Leu Arg Gly Cys			
	130	135	140
Pro Gln Glu Asp Ser Asp Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser			
145	150	155	160
Ile Ile Pro His Asp Phe Arg Arg Met Lys Glu Phe Val Ser Thr Val			
	165	170	175
Met Glu Gln Leu Lys Lys Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr			
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Ser Glu Glu Phe Arg Ile His Phe Thr Phe Lys Glu Phe Gln Asn Asn			
	195	200	205
Pro Asn Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly Arg			
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Thr His Thr Ala Thr Gly Ile Arg Lys Val Val Arg Glu Leu Phe Asn			
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Ile Thr Asn Gly Ala Arg Lys Asn Ala Phe Lys Ile Leu Val Val Ile			
	245	250	255
Thr Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly Tyr Glu Asp Val Ile			
	260	265	270
Pro Glu Ala Asp Arg Glu Gly Val Ile Arg Tyr Val Ile Gly Val Gly			
	275	280	285
Asp Ala Phe Arg Ser Glu Lys Ser Arg Gln Glu Leu Asn Thr Ile Ala			
	290	295	300
Ser Lys Pro Pro Arg Asp His Val Phe Gln Val Asn Asn Phe Glu Ala			
305	310	315	320
Leu Lys Thr Ile Gln Asn Gln Leu Arg Glu Lys Ile Phe Ala Ile Glu			

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Gly Thr Gln Thr Gly Ser Ser Ser Ser Phe Glu His Glu Met Ser Gln		
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Glu Gly Phe Ser Ala Ala Ile Thr Ser Asn Gly Pro Leu Leu Ser Thr		
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Val Gly Ser Tyr Asp Trp Ala Gly Gly Val Phe Leu Tyr Thr Ser Lys		
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Glu Lys Ser Thr Phe Ile Asn Met Thr Arg Val Asp Ser Asp Met Asn		
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Asp Ala Tyr Leu Gly Tyr Ala Ala Ala Ile Ile Leu Arg Asn Arg Val		
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Gln Ser Leu Val Leu Gly Ala Pro Arg Tyr Gln His Ile Gly Leu Val		
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Gln Gly Gln Pro Trp Gly Arg Phe Gly Ala Ala Leu Thr Val Leu Gly		
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Ser Pro Arg Leu Gln Tyr Phe Gly Gln Ser Leu Ser Gly Gly Gln Asp		
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Val Val Thr Tyr Asp Leu Ala Leu Asp Ser Gly Arg Pro His Ser Arg
675 680 685

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Leu Gly Leu Thr Gln Thr Cys Glu Thr Leu Lys Leu Gln Leu Pro Asn
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725 730 735

Leu Val Gly Thr Pro Leu Ser Ala Phe Gly Asn Leu Arg Pro Val Leu
740 745 750

Ala Glu Asp Ala Gln Arg Leu Phe Thr Ala Leu Phe Pro Phe Glu Lys
755 760 765

Asn Cys Gly Asn Asp Asn Ile Cys Gln Asp Asp Leu Ser Ile Thr Phe
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Ser Phe Met Ser Leu Asp Cys Leu Val Val Gly Gly Pro Arg Glu Phe
785 790 795 800

Asn Val Thr Val Thr Val Arg Asn Asp Gly Glu Asp Ser Tyr Arg Thr
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Ile Thr Phe Asp Val Asp Ser Lys Ala Ser Leu Gly Asn Lys Leu Leu
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Val Thr Ser His Gly Val Ser Thr Lys Tyr Leu Asn Phe Thr Ala Ser
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Glu Asn Thr Ser Arg Val Met Gln His Gln Tyr Gln Val Ser Asn Leu
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Gly Gln Arg Ser Leu Pro Ile Ser Leu Val Phe Leu Val Pro Val Arg
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Tyr Gln Cys Asp Tyr Ser Thr Gly Ser Cys Glu Pro Ile His Leu Gln		
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Cys Ser Glu Asn Thr Tyr Val Lys Gly Leu Cys Phe Leu Phe Gly Ser
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Pro Gln Glu Asp Ser Asp Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser
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Ser Glu Glu Phe Arg Ile His Phe Thr Phe Lys Glu Phe Gln Asn Asn
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Pro Asn Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly Arg
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Ser Lys Pro Pro Arg Asp His Val Phe Gln Val Asn Asn Phe Glu Ala

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Ala Met Phe Arg Gln Asn Thr Gly Met Trp Glu Ser Asn Ala Asn Val			
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Asp Val Asp Ser Asn Gly Ser Thr Asp Leu Val Leu Ile Gly Ala Pro			
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Pro Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Val Leu Tyr Gly Glu			
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			75					80					85			
cag	gaa	gac	cac	aat	ggg	ggc	cag	aag	cag	ctg	tcc	cca	caa	aaa	gtg	402
Gln	Glu	Asp	His	Asn	Gly	Gly	Gln	Lys	Gln	Leu	Ser	Pro	Gln	Lys	Val	
			90				95					100				
acg	ctt	tac	ctg	cga	cca	ggc	cag	gca	gca	gcg	ttc	aac	gtg	acc	ttc	450
Thr	Leu	Tyr	Leu	Arg	Pro	Gly	Gln	Ala	Ala	Ala	Phe	Asn	Val	Thr	Phe	
			105				110					115				
cgg	cgg	gcc	aag	ggc	tac	ccc	atc	gac	ctg	tac	tat	ctg	atg	gac	ctc	498
Arg	Arg	Ala	Lys	Gly	Tyr	Pro	Ile	Asp	Leu	Tyr	Tyr	Leu	Met	Asp	Leu	
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tcc	tac	tcc	atg	ctt	gat	gac	ctc	agg	aat	gtc	aag	aag	cta	ggt	ggc	546
Ser	Tyr	Ser	Met	Leu	Asp	Asp	Leu	Arg	Asn	Val	Lys	Lys	Leu	Gly	Gly	
						140									150	
gac	ctg	ctc	cgg	gcc	ctc	aac	gag	atc	acc	gag	tcc	ggc	cgc	att	ggc	594
Asp	Leu	Leu	Arg	Ala	Leu	Asn	Glu	Ile	Thr	Glu	Ser	Gly	Arg	Ile	Gly	
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ttc	ggg	tcc	ttc	gtg	gac	aag	acc	gtg	ctg	cgg	ttc	gtg	aac	acg	cac	642
Phe	Gly	Ser	Phe	Val	Asp	Lys	Thr	Val	Leu	Pro	Phe	Val	Asn	Thr	His	
						170									180	
cct	gat	aag	ctg	cga	aac	cca	tgc	ccc	aac	aag	gag	aaa	gag	tgc	cag	690
Pro	Asp	Lys	Leu	Arg	Asn	Pro	Cys	Pro	Asn	Lys	Glu	Lys	Glu	Cys	Gln	
						185									195	
ccc	ccg	ttt	gcc	ttc	agg	cac	gtg	ctg	aag	ctg	acc	aac	aac	tcc	aac	738
Pro	Pro	Phe	Ala	Phe	Arg	His	Val	Leu	Lys	Leu	Thr	Asn	Asn	Ser	Asn	
						200									215	
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Gln	Phe	Gln	Thr	Glu	Val	Gly	Lys	Gln	Leu	Ile	Ser	Gly	Asn	Leu	Asp	
						220									230	
gca	ccc	gag	ggt	ggg	ctg	gac	gcc	atg	atg	cag	gtc	gcc	gcc	tgc	ccg	834
Ala	Pro	Glu	Gly	Gly	Leu	Asp	Ala	Met	Met	Gln	Val	Ala	Ala	Cys	Pro	
						235									245	
gag	gaa	atc	ggc	tgg	cgc	aac	gtc	acg	cgg	ctg	ctg	gtg	ttt	gcc	act	882
Glu	Glu	Ile	Gly	Trp	Arg	Asn	Val	Thr	Arg	Leu	Leu	Val	Phe	Ala	Thr	
						250									260	
gat	gac	ggc	ttc	cat	ttc	gcg	ggc	gac	ggg	aag	ctg	ggc	gcc	atc	ctg	930
Asp	Asp	Gly	Phe	His	Phe	Ala	Gly	Asp	Gly	Lys	Leu	Gly	Ala	Ile	Leu	

265	270	275	
acc ccc aac gac ggc cgc tgt cac ctg gag gac aac ttg tac aag agg			978
Thr Pro Asn Asp Gly Arg Cys His Leu Glu Asp Asn Leu Tyr Lys Arg			
280	285	290	295
agc aac gaa ttc gac tac cca tcg gtg ggc cag ctg gcg cac aag ctg			1026
Ser Asn Glu Phe Asp Tyr Pro Ser Val Gly Gln Leu Ala His Lys Leu			
300	305	310	
gct gaa aac aac atc cag ccc atc ttc gcg gtg acc agt agg atg gtg			1074
Ala Glu Asn Asn Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met Val			
315	320	325	
aag acc tac gag aaa ctc acc gag atc atc ccc aag tca gcc gtg ggg			1122
Lys Thr Tyr Glu Lys Leu Thr Glu Ile Ile Pro Lys Ser Ala Val Gly			
330	335	340	
gag ctg tct gag gac tcc agc aat gtg gtc cat ctc att aag aat gct			1170
Glu Leu Ser Glu Asp Ser Ser Asn Val Val His Leu Ile Lys Asn Ala			
345	350	355	
tac aat aaa ctc tcc tcc agg gtc ttc ctg gat cac aac gcc ctc ccc			1218
Tyr Asn Lys Leu Ser Ser Arg Val Phe Leu Asp His Asn Ala Leu Pro			
360	365	370	375
gac acc ctg aaa gtc acc tac gac tcc ttc tgc agc aat gga gtg acg			1266
Asp Thr Leu Lys Val Thr Tyr Asp Ser Phe Cys Ser Asn Gly Val Thr			
380	385	390	
cac agg aac cag ccc aga ggt gac tgt gat ggc gtg cag atc aat gtc			1314
His Arg Asn Gln Pro Arg Gly Asp Cys Asp Gly Val Gln Ile Asn Val			
395	400	405	
ccg atc acc ttc cag gtg aag gtc acg gcc aca gag tgc atc cag gag			1362
Pro Ile Thr Phe Gln Val Lys Val Thr Ala Thr Glu Cys Ile Gln Glu			
410	415	420	
cag tcg ttt gtc atc cgg gcg ctg ggc ttc acg gac ata gtg acc gtg			1410
Gln Ser Phe Val Ile Arg Ala Leu Gly Phe Thr Asp Ile Val Thr Val			
425	430	435	
cag gtt ctt ccc cag tgt gag tgc cgg tgc cgg gac cag agc aga gac			1458
Gln Val Leu Pro Gln Cys Glu Cys Arg Cys Arg Asp Gln Ser Arg Asp			
440	445	450	455
cgc agc ctc tgc cat ggc aag ggc ttc ttg gag tgc ggc atc tgc agg			1506
Arg Ser Leu Cys His Gly Lys Gly Phe Leu Glu Cys Gly Ile Cys Arg			
460	465	470	

tgt gac act ggc tac att ggg aaa aac tgt gag tgc cag aca cag ggc Cys Asp Thr Gly Tyr Ile Gly Lys Asn Cys Glu Cys Gln Thr Gln Gly 475 480 485	1554
cgg agc agc cag gag ctg gaa gga agc tgc cgg aag gac aac aac tcc Arg Ser Ser Gln Glu Leu Glu Gly Ser Cys Arg Lys Asp Asn Asn Ser 490 495 500	1602
atc atc tgc tca ggg ctg ggg gac tgt gtc tgc ggg cag tgc ctg tgc Ile Ile Cys Ser Gly Leu Gly Asp Cys Val Cys Gly Gln Cys Leu Cys 505 510 515	1650
cac acc agc gac gtc ccc ggc aag ctg ata tac ggg cag tac tgc gag His Thr Ser Asp Val Pro Gly Lys Leu Ile Tyr Gly Gln Tyr Cys Glu 520 525 530 535	1698
tgt gac acc atc aac tgt gag cgc tac aac ggc cag gtc tgc ggc ggc Cys Asp Thr Ile Asn Cys Glu Arg Tyr Asn Gly Gln Val Cys Gly Gly 540 545 550	1746
ccg ggg agg ggg ctc tgc ttc tgc ggg aag tgc cgc tgc cac ccg ggc Pro Gly Arg Gly Leu Cys Phe Cys Gly Lys Cys Arg Cys His Pro Gly 555 560 565	1794
ttt gag ggc tca gcg tgc cag tgc gag agg acc act gag ggc tgc ctg Phe Glu Gly Ser Ala Cys Gln Cys Glu Arg Thr Thr Glu Gly Cys Leu 570 575 580	1842
aac ccg cgg cgt gtt gag tgt agt ggt cgt ggc cgg tgc cgc tgc aac Asn Pro Arg Arg Val Glu Cys Ser Gly Arg Gly Arg Cys Arg Cys Asn 585 590 595	1890
gta tgc gag tgc cat tca ggc tac cag ctg cct ctg tgc cag gag tgc Val Cys Glu Cys His Ser Gly Tyr Gln Leu Pro Leu Cys Gln Glu Cys 600 605 610 615	1938
ccc ggc tgc ccc tca ccc tgt ggc aag tac atc tcc tgc gcc gag tgc Pro Gly Cys Pro Ser Pro Cys Gly Lys Tyr Ile Ser Cys Ala Glu Cys 620 625 630	1986
ctg aag ttc gaa aag ggc ccc ttt ggg aag aac tgc agc gcg gcg tgt Leu Lys Phe Glu Lys Gly Pro Phe Gly Lys Asn Cys Ser Ala Ala Cys 635 640 645	2034
ccg ggc ctg cag ctg tcg aac aac ccc gtg aag ggc agg acc tgc aag Pro Gly Leu Gln Leu Ser Asn Asn Pro Val Lys Gly Arg Thr Cys Lys 650 655 660	2082

gag agg gac tca gag ggc tgc tgg gtg gcc tac acg ctg gag cag cag Glu Arg Asp Ser Glu Gly Cys Trp Val Ala Tyr Thr Leu Glu Gln Gln 665 670 675	2130
gac ggg atg gac cgc tac ctc atc tat gtg gat gag agc cga gag tgt Asp Gly Met Asp Arg Tyr Leu Ile Tyr Val Asp Glu Ser Arg Glu Cys 680 685 690 695	2178
gtg gca ggc ccc aac atc gcc gcc atc gtc ggg ggc acc gtg gca ggc Val Ala Gly Pro Asn Ile Ala Ala Ile Val Gly Gly Thr Val Ala Gly 700 705 710	2226
atc gtg ctg atc ggc att ctc ctg ctg gtc atc tgg aag gct ctg atc Ile Val Leu Ile Gly Ile Leu Leu Leu Val Ile Trp Lys Ala Leu Ile 715 720 725	2274
cac ctg agc gac ctc cgg gag tac agg cgc ttt gag aag gag aag ctc His Leu Ser Asp Leu Arg Glu Tyr Arg Arg Phe Glu Lys Glu Lys Leu 730 735 740	2322
aag tcc cag tgg aac aat gat aat ccc ctt ttc aag agc gcc acc acg Lys Ser Gln Trp Asn Asn Asp Asn Pro Leu Phe Lys Ser Ala Thr Thr 745 750 755	2370
acg gtc atg aac ccc aag ttt gct gag agt taggagcact tggatgaagac Thr Val Met Asn Pro Lys Phe Ala Glu Ser 760 765	2420
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tacaaagtgg ttgatctaga gggcccgcgg ttcgaaggta agcctatccc taaccctctc	2540
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aacacggaag	2610

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 Leu Gly Cys Val Leu Ser Gln Glu Cys Thr Lys Phe Lys Val Ser Ser
 20 25 30

Cys Arg Glu Cys Ile Glu Ser Gly Pro Gly Cys Thr Trp Cys Gln Lys
 35 40 45

Leu Asn Phe Thr Gly Pro Gly Asp Pro Asp Ser Ile Arg Cys Asp Thr
 50 55 60

Arg Pro Gln Leu Leu Met Arg Gly Cys Ala Ala Asp Asp Ile Met Asp
 65 70 75 80

Pro Thr Ser Leu Ala Glu Thr Gln Glu Asp His Asn Gly Gly Gln Lys
 85 90 95

Gln Leu Ser Pro Gln Lys Val Thr Leu Tyr Leu Arg Pro Gly Gln Ala
 100 105 110

Ala Ala Phe Asn Val Thr Phe Arg Arg Ala Lys Gly Tyr Pro Ile Asp
 115 120 125

Leu Tyr Tyr Leu Met Asp Leu Ser Tyr Ser Met Leu Asp Asp Leu Arg
 130 135 140

Asn Val Lys Lys Leu Gly Gly Asp Leu Leu Arg Ala Leu Asn Glu Ile
 145 150 155 160

Thr Glu Ser Gly Arg Ile Gly Phe Gly Ser Phe Val Asp Lys Thr Val
 165 170 175

Leu Pro Phe Val Asn Thr His Pro Asp Lys Leu Arg Asn Pro Cys Pro
 180 185 190

Asn Lys Glu Lys Glu Cys Gln Pro Pro Phe Ala Phe Arg His Val Leu
 195 200 205

Lys Leu Thr Asn Asn Ser Asn Gln Phe Gln Thr Glu Val Gly Lys Gln
 210 215 220

Leu Ile Ser Gly Asn Leu Asp Ala Pro Glu Gly Gly Leu Asp Ala Met
 225 230 235 240

Met Gln Val Ala Ala Cys Pro Glu Glu Ile Gly Trp Arg Asn Val Thr
 245 250 255

Arg Leu Leu Val Phe Ala Thr Asp Asp Gly Phe His Phe Ala Gly Asp
 260 265 270

Gly Lys Leu Gly Ala Ile Leu Thr Pro Asn Asp Gly Arg Cys His Leu
 275 280 285

Glu Asp Asn Leu Tyr Lys Arg Ser Asn Glu Phe Asp Tyr Pro Ser Val

290	295	300	
Gly Gln Leu Ala His Lys Leu Ala Glu Asn Asn Ile Gln Pro Ile Phe			
305	310	315	320
Ala Val Thr Ser Arg Met Val Lys Thr Tyr Glu Lys Leu Thr Glu Ile			
	325	330	335
Ile Pro Lys Ser Ala Val Gly Glu Leu Ser Glu Asp Ser Ser Asn Val			
	340	345	350
Val His Leu Ile Lys Asn Ala Tyr Asn Lys Leu Ser Ser Arg Val Phe			
	355	360	365
Leu Asp His Asn Ala Leu Pro Asp Thr Leu Lys Val Thr Tyr Asp Ser			
	370	375	380
Phe Cys Ser Asn Gly Val Thr His Arg Asn Gln Pro Arg Gly Asp Cys			
385	390	395	400
Asp Gly Val Gln Ile Asn Val Pro Ile Thr Phe Gln Val Lys Val Thr			
	405	410	415
Ala Thr Glu Cys Ile Gln Glu Gln Ser Phe Val Ile Arg Ala Leu Gly			
	420	425	430
Phe Thr Asp Ile Val Thr Val Gln Val Leu Pro Gln Cys Glu Cys Arg			
	435	440	445
Cys Arg Asp Gln Ser Arg Asp Arg Ser Leu Cys His Gly Lys Gly Phe			
	450	455	460
Leu Glu Cys Gly Ile Cys Arg Cys Asp Thr Gly Tyr Ile Gly Lys Asn			
465	470	475	480
Cys Glu Cys Gln Thr Gln Gly Arg Ser Ser Gln Glu Leu Glu Gly Ser			
	485	490	495
Cys Arg Lys Asp Asn Asn Ser Ile Ile Cys Ser Gly Leu Gly Asp Cys			
	500	505	510
Val Cys Gly Gln Cys Leu Cys His Thr Ser Asp Val Pro Gly Lys Leu			
	515	520	525
Ile Tyr Gly Gln Tyr Cys Glu Cys Asp Thr Ile Asn Cys Glu Arg Tyr			
	530	535	540
Asn Gly Gln Val Cys Gly Gly Pro Gly Arg Gly Leu Cys Phe Cys Gly			
545	550	555	560

Lys Cys Arg Cys His Pro Gly Phe Glu Gly Ser Ala Cys Gln Cys Glu
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Arg Thr Thr Glu Gly Cys Leu Asn Pro Arg Arg Val Glu Cys Ser Gly
 580 585 590

Arg Gly Arg Cys Arg Cys Asn Val Cys Glu Cys His Ser Gly Tyr Gln
 595 600 605

Leu Pro Leu Cys Gln Glu Cys Pro Gly Cys Pro Ser Pro Cys Gly Lys
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Tyr Ile Ser Cys Ala Glu Cys Leu Lys Phe Glu Lys Gly Pro Phe Gly
 625 630 635 640

Lys Asn Cys Ser Ala Ala Cys Pro Gly Leu Gln Leu Ser Asn Asn Pro
 645 650 655

Val Lys Gly Arg Thr Cys Lys Glu Arg Asp Ser Glu Gly Cys Trp Val
 660 665 670

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Val Asp Glu Ser Arg Glu Cys Val Ala Gly Pro Asn Ile Ala Ala Ile
 690 695 700

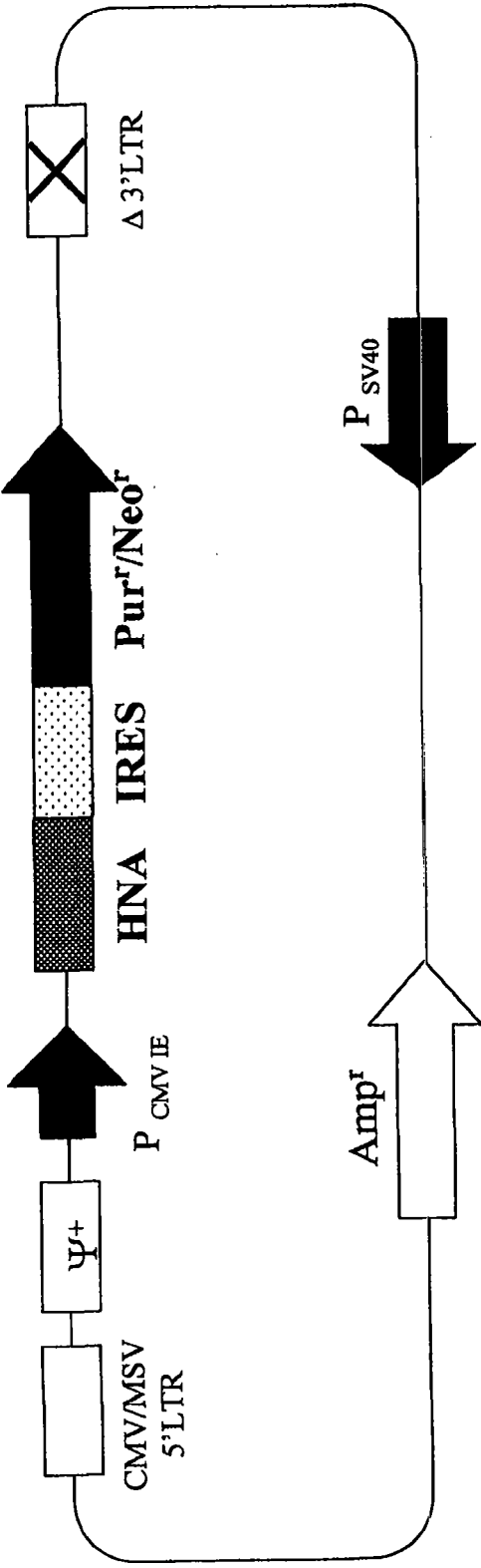
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Arg Phe Glu Lys Glu Lys Leu Lys Ser Gln Trp Asn Asn Asp Asn Pro
 740 745 750

Leu Phe Lys Ser Ala Thr Thr Thr Val Met Asn Pro Lys Phe Ala Glu
 755 760 765

Ser



CMV/MSV 5'LTR: 巨细胞病毒(CMV)1型增强子和小鼠肉瘤病毒(MSV)启动子, R区

- ψ⁺ : 延长的包装信号
- P_{CMV IE} : CMV IE启动子
- HNA : HNA-1a、HNA-1b、HNA-2a、CD11b Mart(+), CD11bMart(-), CD11aOnd(+), CD11aOnd(-), 或CD18
- IRES : 内部核糖体进入位点
- Pur⁺/Neo⁺ : 嘌呤霉素抗性基因或新霉素抗性基因
- Δ3' LTR : 3' MoMuLV LTR(U3缺失)
- P_{SV40} : SV40启动子
- Amp⁺ : 氨苄青霉素抗性基因

图1

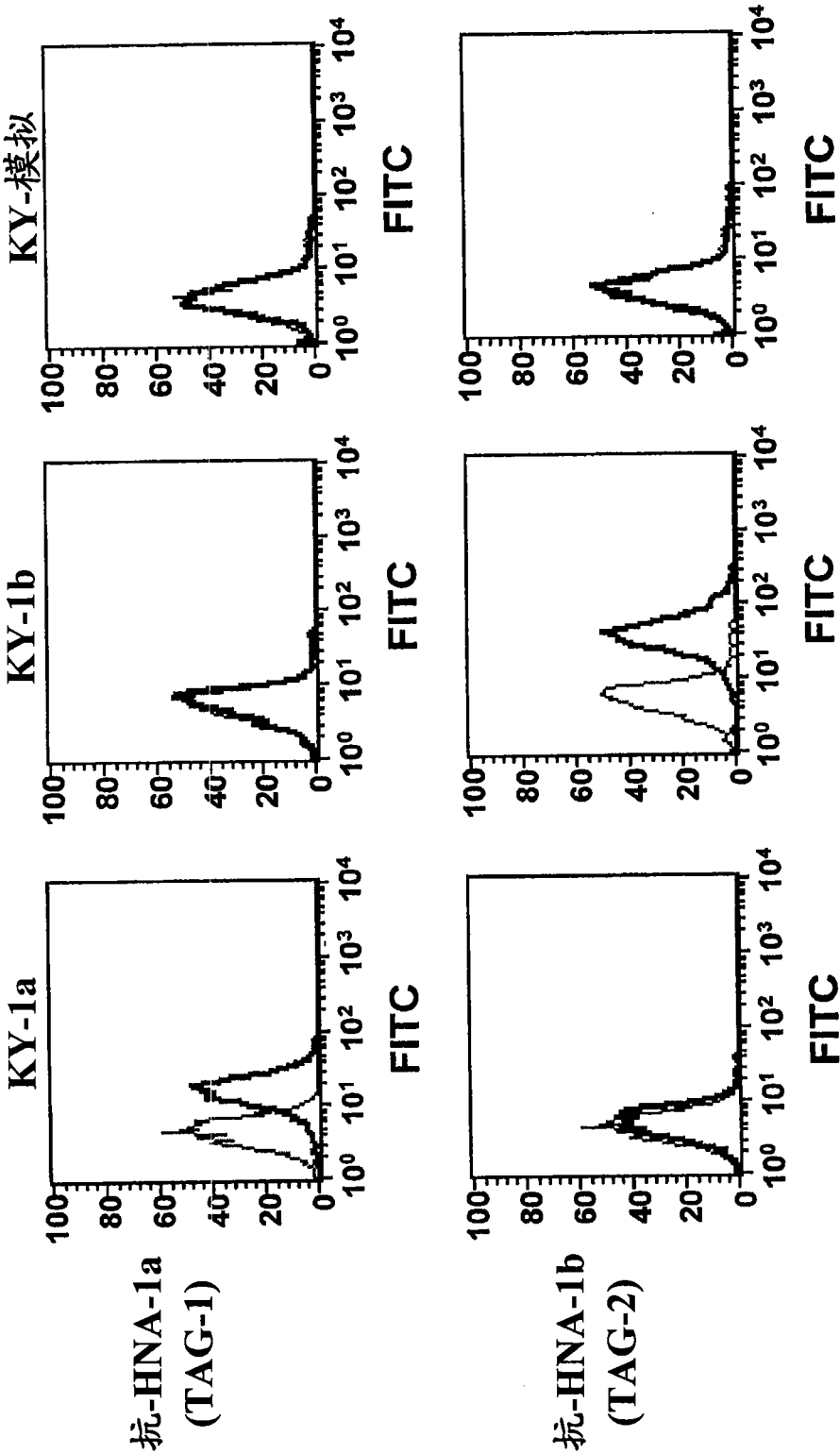


图2

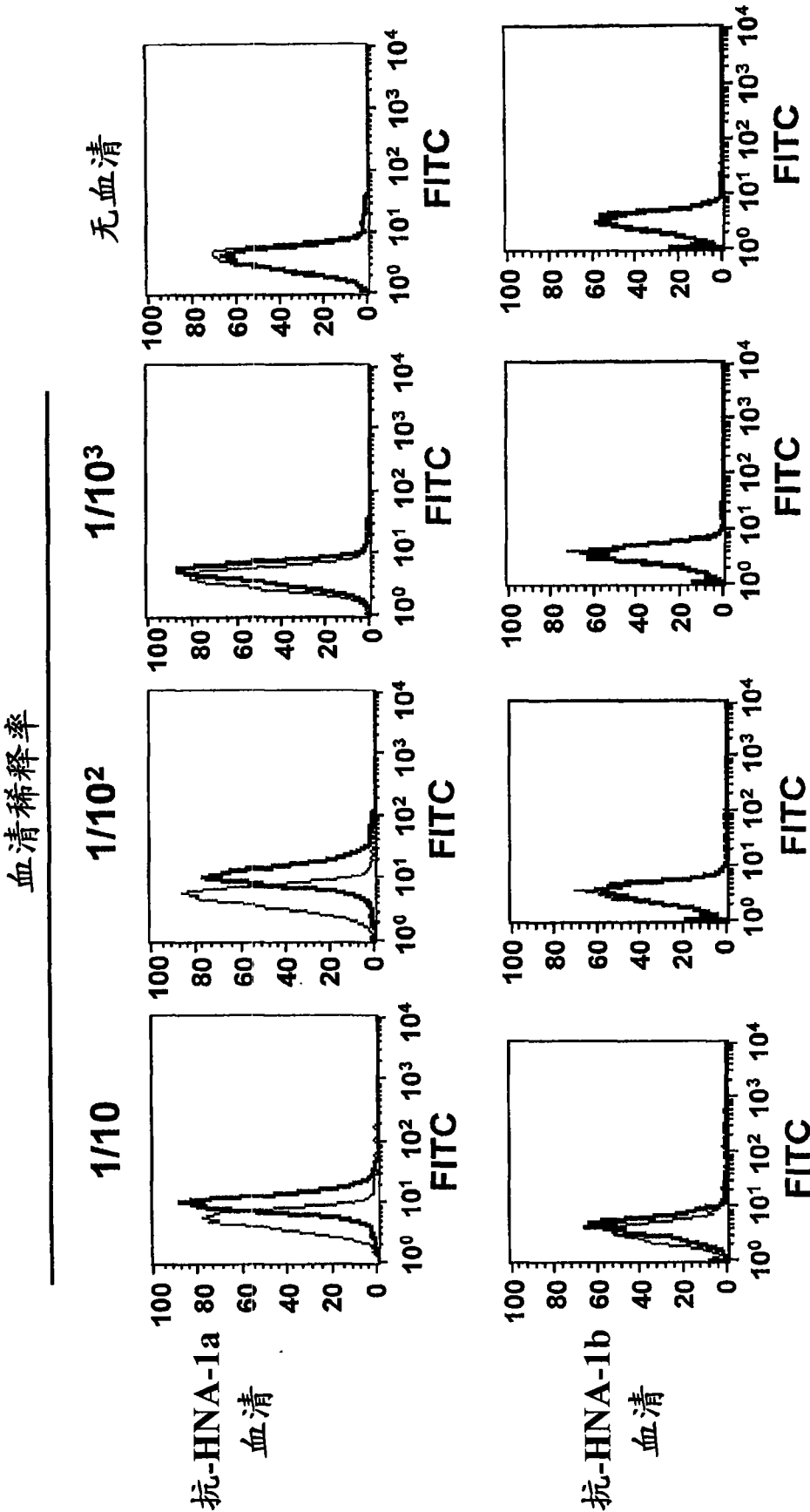


图3

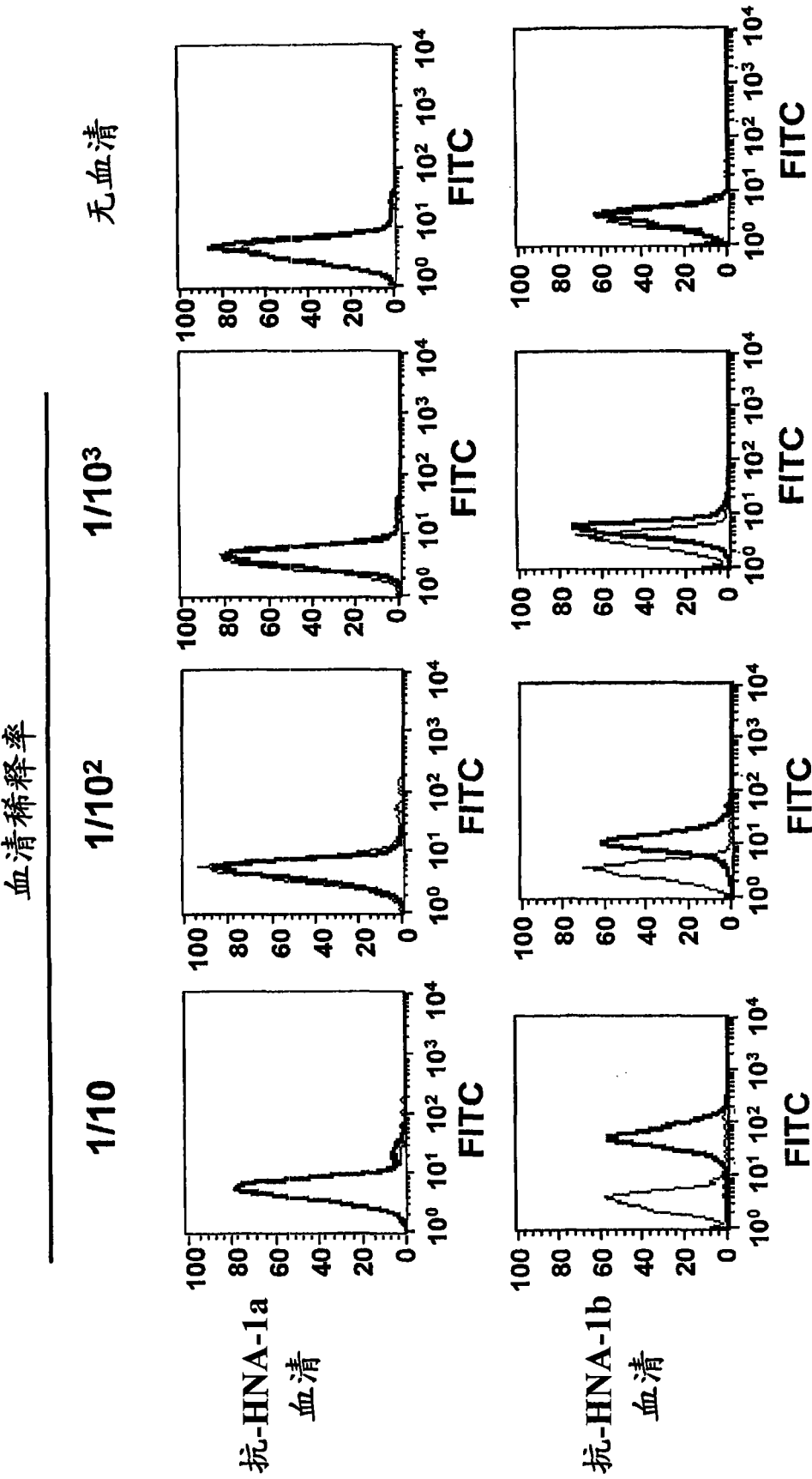


图4

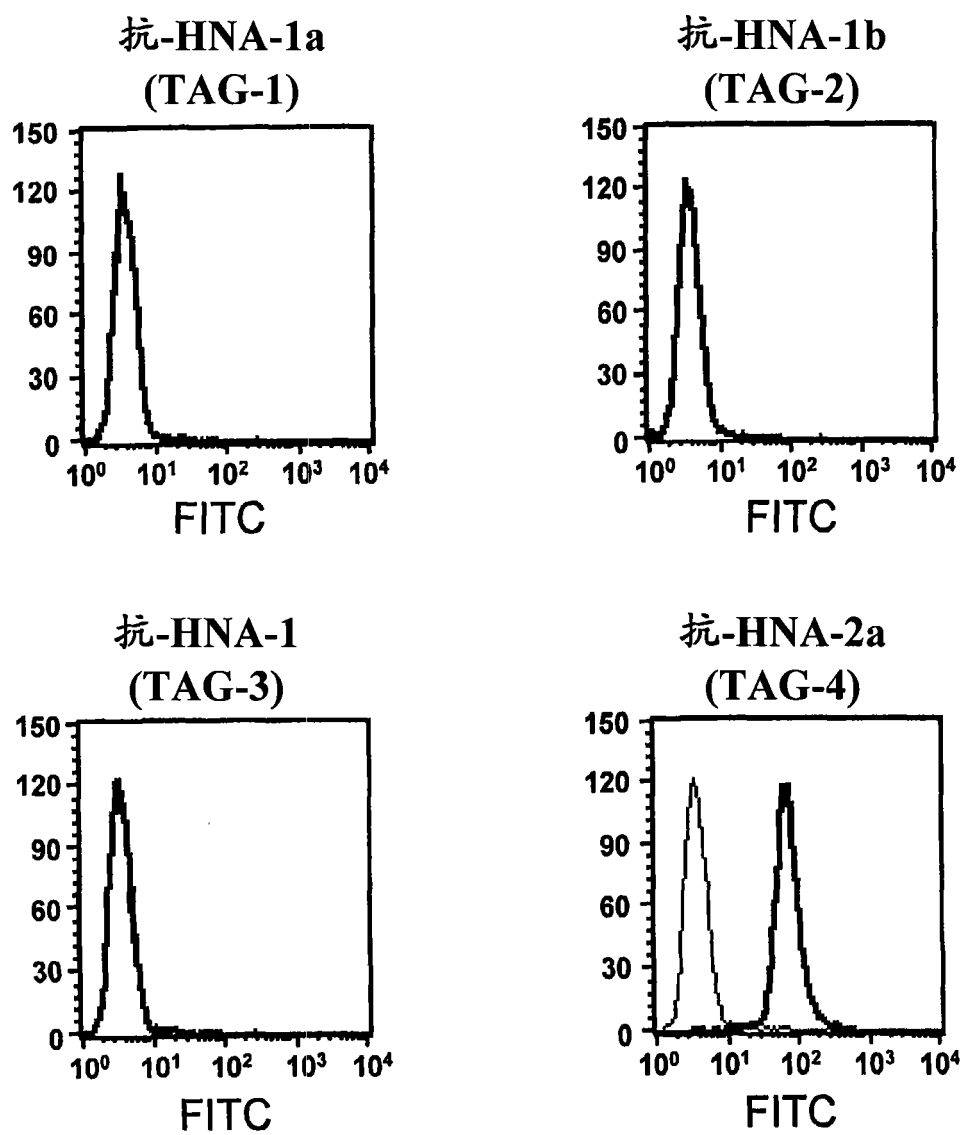


图5

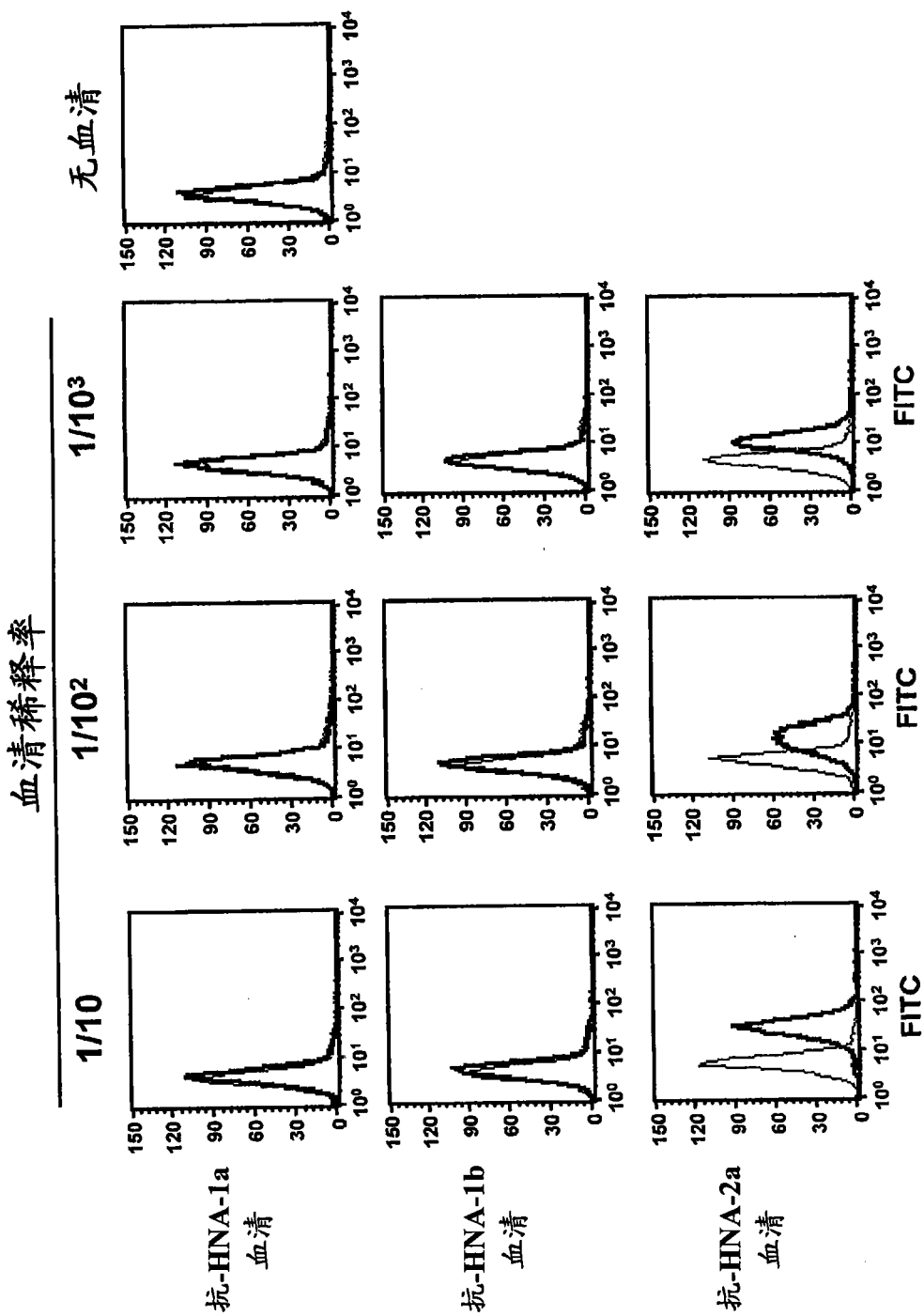


图6

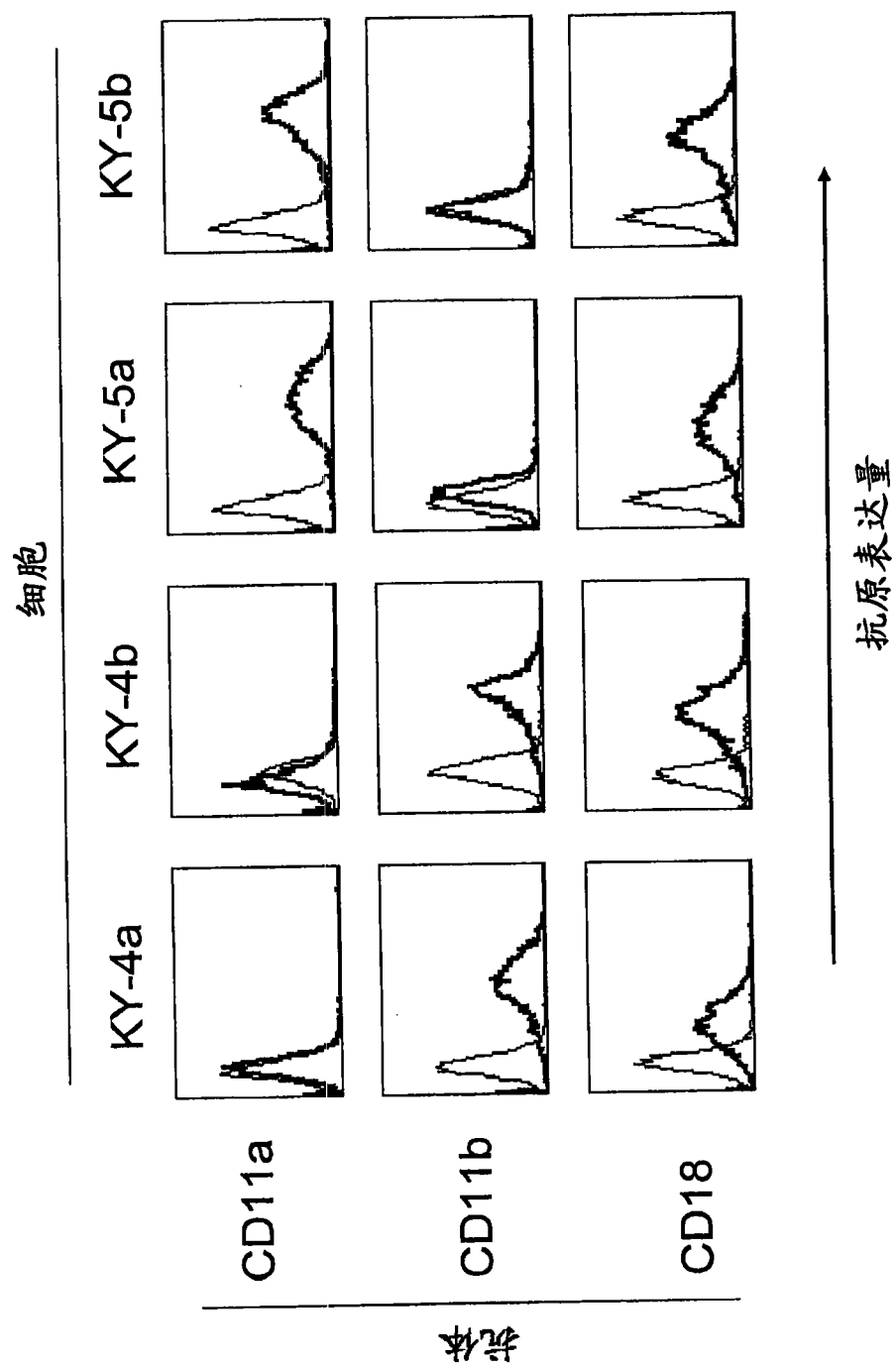


图7

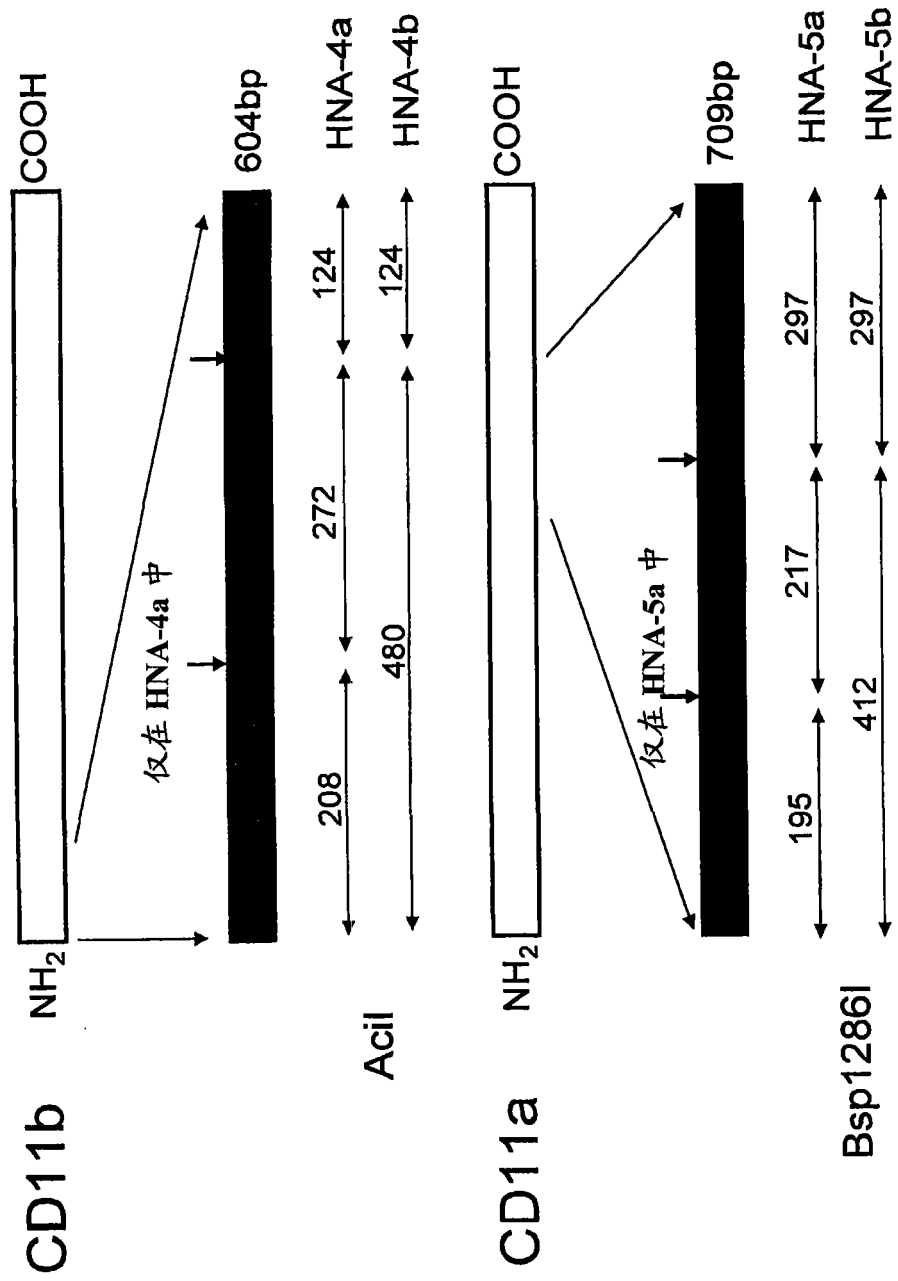
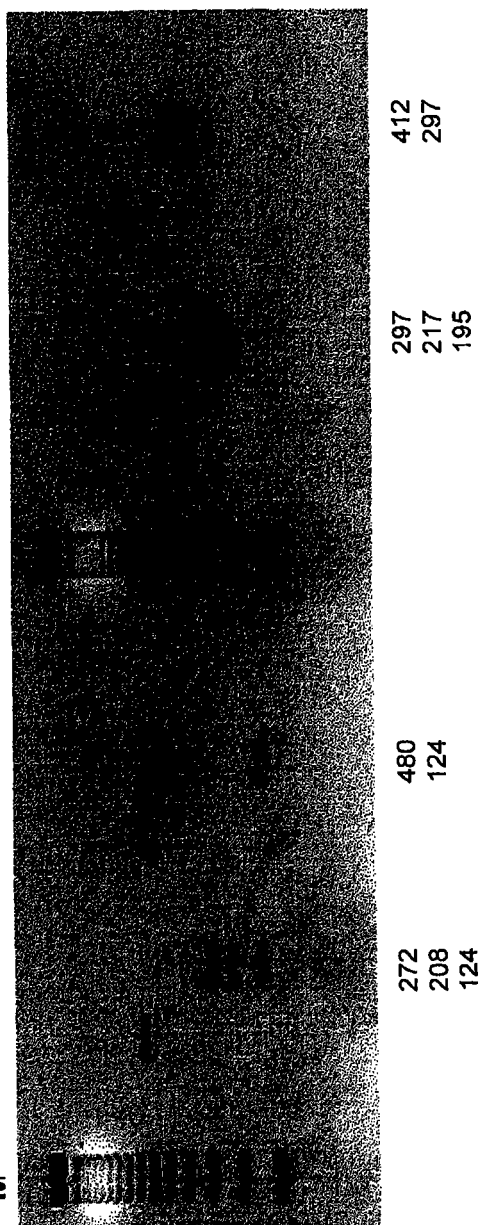


图8

CD11b				CD11a				引物
KY-4a	KY-4b	KY-模拟 (pn)		KY-5a	KY-5b	KY-模拟 (pn)		模板
-	+	-	+	+	+	+	+	RT
-	-	+	+	-	-	-	+	酶
Acil				Bsp1286I				

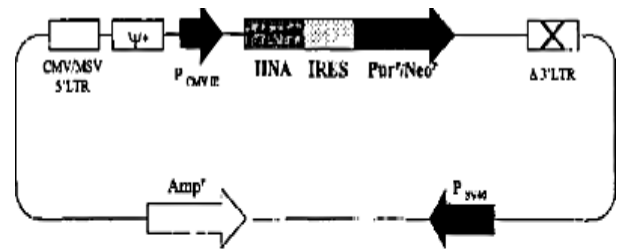


9

专利名称(译)	用于粒细胞抗体检测的谱细胞		
公开(公告)号	CN101448934A	公开(公告)日	2009-06-03
申请号	CN200780018380.X	申请日	2007-03-13
[标]申请(专利权)人(译)	日本红十字会		
申请(专利权)人(译)	日本红十字会		
当前申请(专利权)人(译)	日本红十字会		
[标]发明人	保井一太 平山文也 古田星佳 松山宣树 小岛芳隆 宫崎孔 池田久实 渡边嘉久		
发明人	保井一太 平山文也 古田星佳 松山宣树 小岛芳隆 宫崎孔 池田久实 渡边嘉久		
IPC分类号	C12N5/10 C07K16/18 C12N15/09 G01N33/53 G01N33/543		
CPC分类号	G01N2800/22 G01N2333/70539 C12N2510/00 G01N33/564 G01N33/6854		
代理人(译)	刘冬 付磊		
优先权	2006081236 2006-03-23 JP		
其他公开文献	CN101448934B		
外部链接	Espacenet SIPO		

摘要(译)

公开了用于检测抗 - HNA抗体的谱细胞。所述谱细胞通过在用于检测操作的条件下，以可表达的形式，将编码与抗 - HNA抗体对应的HNA抗原的DNA导入细胞来获得，而此细胞在导入DNA之前不表现与以下抗体的通过检测操作可检测的应答：抗 - HLA - ABC抗体、抗 - HLA - DR抗体、抗 - HLA - DQ抗体、抗 - HLA - DP抗体、抗 - HNA - 1抗体、抗 - HNA - 2a抗体、抗 - HNA - 3a抗体、抗 - HNA - 4抗体、抗 - HNA - 5抗体和来自健康受试者的血清。通过使用上述谱细胞，对粒细胞抗体的准确和快速检测成为可能。



CMV/MSV 5'LTR: 巨细胞病毒(CMV)I型增强子和小鼠肉瘤病毒(MSV)启动子,
R区
U5区

Ψ^+ : 延长的包装信号

$P_{CMV IE}$: CMV IE启动子

HNA : HNA-1a, HNA-1b, HNA-2a, CD11b Mar(+)、CD11b Mar(-),
CD11a Oxd(+), CD11a Oxd(-), 或CD18

IRES : 内部核糖体进入位点

Pur^r/Neo^r : 嘌呤霉素抗性基因或新霉素抗性基因

$\Delta 3' LTR$: 3' MolMuLV LTR(U3缺失)

P_{SV40} : SV40启动子

Amp^r : 氨苄青霉素抗性基因