



(12) 发明专利申请

(10) 申请公布号 CN 115698307 A

(43) 申请公布日 2023. 02. 03

(21) 申请号 202180038835.4

米克尔·维拉·佩雷洛

(22) 申请日 2021.03.26

(74) 专利代理机构 华进联合专利商标代理有限公司 44224

(30) 优先权数据

20382236.6 2020.03.26 EP

专利代理师 郑元博

(85) PCT国际申请进入国家阶段日

2022.11.28

(51) Int.Cl.

C12N 15/861 (2006.01)

(86) PCT国际申请的申请数据

PCT/EP2021/058016 2021.03.26

(87) PCT国际申请的公布数据

W02021/191447 EN 2021.09.30

(71) 申请人 移接生物有限公司

地址 西班牙巴塞罗那

(72) 发明人 西尔维娅·弗鲁托·多明格斯

杰拉德·凯莱斯·维达尔

安娜贝尔·奥特罗·毕尔巴鄂

权利要求书7页 说明书50页  
序列表251页 附图16页

(54) 发明名称

断裂内含肽及其用途

(57) 摘要

本发明涉及使用工程改造的断裂内含肽以及其与降解信号(去稳定结构域,降解决定子)的组合来重构大基因以用于基因治疗的方法。

1. 一种组合物, 包括:

a. 第一多核苷酸, 所述第一多核苷酸编码包含断裂内含肽N片段的多肽, 其中所述断裂内含肽N片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN、SEQ ID NO 30的CatN和SEQ ID NO 38的Gp41N、或其任何功能等效变体如SEQ ID NO 39的ConN; 和

b. 第二多核苷酸, 所述第二多核苷酸编码包含断裂内含肽C片段的多肽, 其中所述断裂内含肽C片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与所述要重构的蛋白质的C端片段直接连接的SEQ ID NO 28的CfaC、SEQ ID NO 31的CatC和SEQ ID NO 104的Gp41C、或其任何功能等效变体如CfaCmut (SEQ ID NO 29) 或ConC (SEQ ID NO 105);

其中所述组合物的两种多核苷酸可以一起包装在单一制剂中或分别包装在不同制剂中;

其中所述第一多核苷酸和所述第二多核苷酸分别编码所述要重构的蛋白质的所述N端片段和所述C端片段, 使得当两个片段组合时, 所述蛋白质的所述N端片段与所述蛋白质的所述C端片段连接, 从而产生整个蛋白质;

其中所述要重构的蛋白质大于25KDa; 以及

其中所述组合物进一步的特征在于:

- 所述断裂内含肽N片段进一步通过肽键与降解决定子直接连接, 其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接, 并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接; 和/或

- 所述断裂内含肽C片段进一步通过肽键与降解决定子直接连接, 其中所述降解决定子与所述内含肽C片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接, 并且其中所述断裂内含肽C片段的所述C端通过肽键与所述要重构的蛋白质的所述C端片段直接连接。

2. 根据权利要求1所述的组合物, 其中, 所述断裂内含肽N片段是通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN, 以及所述断裂内含肽C片段是通过肽键、可选地通过肽接头与所述要重构的蛋白质的C端片段直接连接的SEQ ID NO 28的CfaC。

3. 根据权利要求1所述的组合物, 其中, 所述断裂内含肽N片段是通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN, 以及所述断裂内含肽C片段是通过肽键、可选地通过肽接头与所述要重构的蛋白质的C端片段直接连接的SEQ ID NO 29的CfaCmut。

4. 根据权利要求1至3中任一项所述的组合物, 其中, 与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自由以下组成的清单: CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。

5. 根据权利要求1至3中任一项所述的组合物, 其中, 与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自由以下组成的清单: DD1、DD3、PEST、SopE、L2、L9、M4或V12。

6. 根据权利要求1至3中任一项所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:SopE、L2、L9、M4或V12。

7. 根据权利要求2所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。

8. 根据权利要求2所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:DD1、DD3、PEST、SopE、L2、L9、M4或V12。

9. 根据权利要求2所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:SopE、L2、L9、M4或V12。

10. 根据权利要求3所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。

11. 根据权利要求3所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:DD1、DD3、PEST、SopE、L2、L9、M4或V12。

12. 根据权利要求3所述的组合物,其中,与所述断裂内含肽N片段和/或断裂内含肽C片段直接连接的所述降解决定子选自自由以下组成的清单:SopE、L2、L9、M4或V12。

13. 根据权利要求1至12中任一项所述的组合物,其中,所述组合物的特征在于:

o所述断裂内含肽N片段进一步通过肽键与降解决定子直接连接,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

o所述断裂内含肽C片段进一步通过肽键与降解决定子直接连接,其中所述降解决定子与所述内含肽C片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽C片段的所述C端通过肽键与所述要重构的蛋白质的所述C端片段直接连接。

14. 根据权利要求13所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,

其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自自由

以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

15. 根据权利要求13所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

16. 根据权利要求13所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或其任何功能等效变体,其中所述降解决定子所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

17. 根据权利要求13所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽, 所述断裂内含肽N片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 38的Gp41N、或其任何功能等效变体, 其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接, 并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接; 以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽, 所述断裂内含肽C片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 104的Gp41C、或其任何功能等效变体, 其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接, 并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

18. 根据权利要求1至17中任一项所述的组合物, 其中, 所述第一多核苷酸和所述第二多核苷酸分别编码ABCA4蛋白的N端片段和C端片段, 使得当这两种多核苷酸被翻译成它们各自的蛋白复合物并根据本发明的方法进行组合时, 所述ABCA4蛋白的所述N端片段与所述ABCA4蛋白的所述C端片段连接, 从而产生完整的ABCA4蛋白。

19. 根据权利要求18所述的组合物, 其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽, 所述断裂内含肽N片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,

其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接, 并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接; 以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽, 所述断裂内含肽C片段选自由以下组成的清单: 通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PESt、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体, 其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接, 并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

其中所述第一多核苷酸编码所述ABCA4蛋白的所述N端片段的第1-1149、1-1139、1-1176或1-1178位; 并且其中所述第二多核苷酸编码所述ABCA4蛋白的所述C端片段的第

1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

20. 根据权利要求18所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

其中所述第一多核苷酸编码所述ABCA4蛋白的所述N端片段的第1-1149、1-1139、1-1176或1-1178位;并且其中所述第二多核苷酸编码所述ABCA4蛋白的所述C端片段的第1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

21. 根据权利要求18所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决

定子在其所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

其中所述第一多核苷酸编码所述ABCA4蛋白的所述N端片段的第1-1149、1-1139、1-1176或1-1178位;并且其中所述第二多核苷酸编码所述ABCA4蛋白的所述C端片段的第1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

22. 根据权利要求18所述的组合物,其中

a. 所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在其所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

b. 所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在其所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

其中所述第一多核苷酸编码所述ABCA4蛋白的所述N端片段的第1-1149位;并且其中第二多核苷酸编码所述ABCA4蛋白的所述C端片段的第1150-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位。

23. 根据权利要求18所述的组合物,其中,所述第一多核苷酸如权利要求17中的a所定义,并且所述第一多核苷酸编码所述ABCA4蛋白的所述N端片段的第1-1095或1-1185位;以及其中所述第二多核苷酸如权利要求17中的b所定义,并且所述第二多核苷酸编码所述ABCA4蛋白的所述C端片段的第1096-2273或1186-2273位,其中当所述第一多核苷酸编码第1-1095位时,所述第二多核苷酸编码第1096-2273位,并且其中当所述第一多核苷酸编码第1-1185位时,所述第二多核苷酸编码第1186-2273位。

24. 根据权利要求1至23中任一项所述的组合物,其中,两种多核苷酸都包含在使得所述多核苷酸在合适的宿主细胞中增殖或插入的载体中。

25. 根据权利要求24所述的组合物,其中,所述载体是腺相关病毒(AAV)。

26. 根据权利要求25所述的组合物,其中,所述载体是血清型1、2、3、4、5、6、7、8或9的AAV。

27. 用于治疗根据权利要求1至26中任一项所定义的组合物的。

28. 一种在细胞中表达目标基因的方法, 包括:

(i) 使细胞与如权利要求1至12中任一项所定义的第一多核苷酸和第二多核苷酸接触, 其中所述多核苷酸中的至少一个编码通过肽键与降解决定子直接连接的断裂内含肽片段,

(ii) 使所述第一多核苷酸和所述第二多核苷酸表达, 以产生第一融合蛋白和第二融合蛋白, 以及

(iii) 使第一蛋白和第二蛋白接触, 使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体, 并且所述内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

29. 一种在细胞中表达目标基因的方法, 包括:

(i) 使细胞与如权利要求13至23中任一项所定义的第一多核苷酸和第二多核苷酸接触, 其中所述多核苷酸中编码通过肽键与降解决定子直接连接的断裂内含肽片段, 以及

(ii) 使所述第一多核苷酸和所述第二多核苷酸表达, 以产生第一融合蛋白和第二融合蛋白, 以及

(iii) 使第一蛋白和第二蛋白接触, 使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体, 并且所述内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

30. 根据权利要求28至29中任一项所述的方法, 其中, 两种多核苷酸都包含在腺相关病毒(AAV)内。



## 断裂内含肽及其用途

### 技术领域

[0001] 本发明属于生物技术领域，具体涉及断裂内含肽及其用途。

### 背景技术

[0002] 众所周知，不能封装在用于基因治疗的AAV(腺相关病毒)中的基因可以断裂成两个片段。因此，每个片段都应该融合到断裂内含肽中，并在它们各自的AAV中传递。感染目标细胞后，内含肽将使得能够产生所需的目标蛋白(参见图1)。

[0003] 然而，该方法的主要限制之一是蛋白质中间体(N-外显肽-ItnN和IntC-C-外显肽)的积累，以及切下的断裂内含肽。为了解决这个问题，在本申请中，我们已经表明某些内含肽可以与某些降解信号结合，从而显著减少此类蛋白质中间体的积累。本发明集中于内含肽和降解信号的这种组合。我们还确定了有助于增加体内剪接产量的某些内含肽-降解决定子组合。

### 发明内容

[0004] 在优选的首要方面，本发明涉及一种组合物，该组合物包括：

[0005] a. 第一多核苷酸，所述第一多核苷酸编码包含断裂内含肽N片段的多肽，其中所述断裂内含肽N片段选自由以下组成的清单：通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN、SEQ ID NO 30的CatN和SEQ ID NO 38的Gp41N、或其任何功能等效变体如SEQ ID NO 39的ConN；和

[0006] b. 第二多核苷酸，所述第二多核苷酸编码包含断裂内含肽C片段的多肽，其中所述断裂内含肽C片段选自由以下组成的清单：通过肽键、可选地通过肽接头与所述要重构的蛋白质的C端片段直接连接的SEQ ID NO 28的CfaC、SEQ ID NO 31的CatC和SEQ ID NO 104的Gp41C、或其任何功能等效变体如CfaCmut (SEQ ID NO 29) 或ConC (SEQ ID NO 105)；

[0007] 其中所述组合物的两种多核苷酸可以一起包装在单一制剂中或分别包装在不同制剂中；

[0008] 其中所述第一多核苷酸和所述第二多核苷酸分别编码所述要重构的蛋白质的所述N端片段和所述C端片段，使得当两个片段组合时，所述蛋白质的所述N端片段与所述蛋白质的所述C端片段连接，从而产生整个蛋白质；

[0009] 其中所述要重构的蛋白质大于25KDa；以及

[0010] 其中所述组合物进一步的特征在于：

[0011] -所述断裂内含肽N片段进一步通过肽键与降解决定子直接连接，其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接，并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接；和/或

[0012] -所述断裂内含肽C片段进一步通过肽键与降解决定子直接连接，其中所述降解决定子在所述内含肽C片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的

所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽C片段的所述C端通过肽键与所述要重构的蛋白质的所述C端片段直接连接。

[0013] 在首选方面的优选实施方式中,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自以下组成的清单:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自以下组成的清单:DD1、DD3、PEST、SopE、L2、L9、M4或V12。更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自以下组成的清单:SopE、L2、L9、M4或V12。

[0014] 在首选方面的另一个优选实施方式中,断裂内含肽N片段是通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN,断裂内含肽C片段是通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接的SEQ ID NO 28的CfaC;其中,优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单;更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单;再更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自SopE、L2、L9、M4或V12组成的清单。

[0015] 在首选方面的另一个优选实施方式中,断裂内含肽N片段是通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 27的CfaN,断裂内含肽C片段是通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接的SEQ ID NO 29的CfaCmut;其中,优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单;更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单;再更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自SopE、L2、L9、M4或V12组成的清单。

[0016] 在首选方面的另一个优选实施方式中,断裂内含肽N片段是通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的SEQ ID NO 32的NpuN,断裂内含肽C片段是通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接的SEQ ID NO 29的CfaCmut或SEQ ID NO 36的NpuCmut;其中,优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单;更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单;再更优选地,与断裂内含肽N片段和/或断裂内含肽C片段直接连接的降解决定子选自SopE、L2、L9、M4或V12组成的清单。

[0017] 在首选方面的另一个优选实施方式中,所述组合物的特征在于包含两个降解决定子,具体地,所述组合物的特征在于:

[0018] o断裂内含肽N片段进一步通过肽键与降解决定子直接连接,其中降解决定子在内含肽N片段和降解决定子之间有或没有接头的情况下通过内含肽的C端与内含肽N片段连接,并且其中断裂内含肽N片段的N端通过肽键与要重构的蛋白质的N端片段直接连接;以及

[0019] o断裂内含肽C片段进一步通过肽键与降解决定子直接连接,其中降解决定子在内含肽C片段和降解决定子之间有或没有接头的情况下通过内含肽的N端与内含肽C片段连接,并且其中断裂内含肽C片段的C端通过肽键与要重构的蛋白质的C端片段直接连接。

[0020] 在首选方面的优选实施方式或其任何优选实施方式中,所述组合物的特征在于其包括:

[0021] a. 第一多核苷酸,所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0022] b. 第二多核苷酸,所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

[0023] 在首选方面的优选实施方式或其任何优选实施方式中,所述组合物包括:

[0024] a. 第一多核苷酸,所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0025] b. 第二多核苷酸,所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含

肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

[0026] 在首选方面的另一个优选实施方式或其任何优选实施方式中,所述组合物包括:

[0027] a. 第一多核苷酸,所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0028] b. 第二多核苷酸,所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、或SEQ ID NO 29的CfaCmut、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

[0029] 在首选方面的另一个优选实施方式或其任何优选实施方式中,所述组合物包括:

[0030] a. 第一多核苷酸,所述第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 38的Gp41N、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0031] b. 第二多核苷酸,所述第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 104的Gp41C、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接。

[0032] 在首选方面的另一个优选实施方式或其任何优选实施方式中,所述第一多核苷酸和所述第二多核苷酸分别编码ABCA4蛋白的N端片段和C端片段,使得当这两种多核苷酸被翻译成它们各自的蛋白复合物并根据本发明的方法进行组合时,所述ABCA4蛋白的所述N端片段与所述ABCA4蛋白的所述C端片段连接,从而产生完整的ABCA4蛋白。

[0033] 关于上述第一和第二多核苷酸分别编码ABCA4蛋白的N端片段和C端片段的实施方

式,本发明提供以下替代方案。

[0034] 第一种替代方案:

[0035] a. 第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0036] b. 第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由CL1、Deg1、PESt、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7组成的清单的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

[0037] 其中所述第一多核苷酸编码ABCA4蛋白的N端片段的第1-1149、1-1139、1-1176或1-1178位;并且其中所述第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

[0038] 第二种替代方案:

[0039] a. 第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0040] b. 第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的

情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

[0041] 其中所述第一多核苷酸编码ABCA4蛋白的N端片段的第1-1149、1-1139、1-1176或1-1178位;并且其中所述第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

[0042] 第三种替代方案:

[0043] a. 第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0044] b. 第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

[0045] 其中所述第一多核苷酸编码ABCA4蛋白的N端片段的第1-1149、1-1139、1-1176或1-1178位;并且其中所述第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273、1140-2273、1177-2273或1179-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位,其中当所述第一多核苷酸编码第1-1139位时,所述第二多核苷酸编码第1140-2273位,其中当所述第一多核苷酸编码第1-1176位时,所述第二多核苷酸编码第1177-2273位,并且其中当所述第一多核苷酸编码第1-1178位时,所述第二多核苷酸编码第1179-2273位。

[0046] 第四种替代方案:

[0047] a. 第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 27的CfaN、或其任何功能等效变体,其中所述降解决定子与所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0048] b. 第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并可选地进一步通过肽键与选自由DD1、DD3、PEST、SopE、L2、L9、M4或V12组成的清单中的降解决定子直接连接的SEQ ID NO 28的CfaC、SEQ ID NO 29的CfaCmut、或SEQ ID NO 36的NpuCmut、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

[0049] 其中所述第一多核苷酸编码ABCA4蛋白的N端片段的第1-1149位;并且其中所述第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273位,其中当所述第一多核苷酸编码第1-1149位时,所述第二多核苷酸编码第1150-2273位。

[0050] 第五种替代方案:

[0051] a. 第一多核苷酸编码包含断裂内含肽N片段的多肽,所述断裂内含肽N片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 38的Gp41N、或其任何功能等效变体,其中所述降解决定子所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述C端与所述内含肽N片段连接,并且其中所述断裂内含肽N片段的所述N端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;以及

[0052] b. 第二多核苷酸编码包含断裂内含肽C片段的多肽,所述断裂内含肽C片段选自由以下组成的清单:通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接、并进一步通过肽键与选自由CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7组成的清单中的降解决定子直接连接的SEQ ID NO 104的Gp41C、或其任何功能等效变体,其中所述降解决定子在所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过所述内含肽的所述N端与所述内含肽C片段连接,并且其中所述断裂内含肽N片段的所述C端通过肽键与所述要重构的蛋白质的所述N端片段直接连接;

[0053] 所述第一多核苷酸编码ABCA4蛋白的N端片段的第1-1095或1-1185位;以及其中所述第二多核苷酸编码ABCA4蛋白的C端片段的第1096-2273或1186-2273位,其中当所述第一多核苷酸编码第1-1095位时,所述第二多核苷酸编码第1096-2273位,并且其中当所述第一多核苷酸编码第1-1185位时,所述第二多核苷酸编码第1186-2273位。

[0054] 在首选方面的进一步优选实施方式或其任何优选实施方式或替代方案中,两种多核苷酸都包含在使得多核苷酸在合适的宿主细胞中增殖或插入的载体中。优选地,所述载体是腺相关病毒(AAV),更优选地,载体是血清型1、2、3、4、5、6、7、8或9的AAV。

[0055] 在首选方面的进一步优选实施方式或其任何优选实施方式或替代方案中,本文所述的组合物用于治疗,特别是用于表1中确定的任何疾病。

[0056] 本发明的另一个方面涉及用于在细胞中表达目标基因的体外或体内方法,该方法包括:

[0057] (i) 使细胞与如前述方面、实施方式或替代方案中任一项所定义的的第一多核苷酸和第二多核苷酸接触,其中优选两种多核苷酸都包含在腺相关病毒(AAV)内,并且其中所述多核苷酸中的至少一个编码通过肽键与降解决定子直接连接的断裂内含肽片段,

[0058] (ii) 使第一多核苷酸和第二多核苷酸表达,以产生第一融合蛋白和第二融合蛋白,以及

[0059] (iii) 使第一蛋白和第二蛋白接触,使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体,并且所述内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

## 附图说明

[0060] 图1. 使用内含肽以及与降解决定子结合的内含肽来重组大蛋白用于基因治疗的策略的整体方案。上图: (1) 目标基因在审慎选择的位置重组断裂,所得的5'端重组融合到IntN,3'端融合到IntC,使得在蛋白质表达时,蛋白质的N端片段将与与其C端融合的IntN一起表达,而蛋白质的C端片段将与与其N端融合的IntC一起表达。(2) 每个构建体都封装在单独的AAV中。将这两种AAV施用于患者,以便将它们共转导至某些细胞(3)。在共转导后,通过AAV递送的DNA将被转录成RNA并翻译成蛋白质,并且在蛋白质水平上,内含肽将进行蛋白质反式剪接反应以重构所期望的剪接产物(4)。下图:内含肽与降解信号相结合,以防止起始材料积累并消除切下的内含肽。降解决定子与N-内含肽的C端和/或C-内含肽的N端融合。

[0061] 图2. 上图:EGFP<sup>N</sup>-IntN-H6和IntC-EGFP<sup>C</sup>-H6构建体之间的反应方案,该反应方案导致形成带有H6标签的全长EGFP,并切除内含肽。下图:使用Cfa或Npu内含肽用N端片段、C端片段转染或用两种片段共转染的细胞的荧光显微镜图像。

[0062] 图3. 用EGFP-内含肽多核苷酸转染的裂解的HEK293细胞的蛋白质印迹分析。左图:用EGFP-内含肽质粒转染的细胞的蛋白质印迹分析。用全长EGFP质粒转染细胞,或用EGFP<sup>N</sup>-IntN、IntC-EGFP<sup>C</sup>质粒或这两者共转染细胞。测试含有Cfa或Npu内含肽的质粒。右图:相对于Npu的剪接产物倍数增加的量化。通过光密度测定法测定产物产量,使用β-微管蛋白作为上样对照。该图表示当用全长EGFP质粒(EGFP)转染细胞,用EGFP<sup>N</sup>-CfaN和CfaC-EGFP<sup>C</sup>(Cfa)或用EGFP<sup>N</sup>-NpuN和NpuC-EGFP<sup>C</sup>(Npu)共转染细胞时,相对于Npu的EGFP产物倍数增加。

[0063] 图4. 通过流式细胞术分析HEK293转染的细胞。左图:用不同构建体或构建体的组合转染的细胞的流式细胞术数据。黑色曲线对应于用EGFP的N端片段或C端片段转染的对照。蓝色是用编码全长EGFP的质粒转染的细胞的4次重复,绿色曲线对应于用EGFP<sup>N</sup>-CfaN和CfaC-EGFP<sup>C</sup>共转染的细胞(EGFP在位置71断裂),黄色曲线对应于用EGFP<sup>N</sup>-NpuN和NpuC-EGFP<sup>C</sup>(EGFP在位置71断裂)共转染的细胞。中图:每组样本获得的平均荧光强度(MFI)图,其表明使用Cfa内含肽使得恢复与全长EGFP相对应的信号的超过90%。右图:代表每个样本中阳性细胞数量的图,显示所有三组样本的转染效率相当。

[0064] 图5:在Cfa和Npu之间对ABCA4位置1150处的剪接产量进行比较。细胞用ABCA4<sup>N</sup>1150-IntN和IntC-ABCA4<sup>C</sup>1150共转染,裂解并通过WB分析。ABCA4<sup>N</sup>1150对应于从第1至1149位残基的ABCA4的N端片段,ABCA4<sup>C</sup>1150对应于从第1150至2273位残基的ABCA4的C端片段。对具有Cfa或Npu的构建体进行了测试。左图示出了使用抗ABCA4 mAb的印迹。右图对应于蛋白质印迹的光密度定量。



[0065] 图6: 在Cfa和Npu之间对ABCA4位置1140处的剪接产量进行比较。细胞用ABCA4<sup>N</sup>1140-IntN和IntC-ABCA4<sup>C</sup>1140共转染,裂解并通过WB分析。ABCA4<sup>N</sup>1140对应于从第1至1139位残基的ABCA4的N端片段,ABCA4<sup>C</sup>1140对应于从第1140至2273位残基的ABCA4的C端片段。对具有Cfa或Npu的构建体进行了测试。左图和中图分别示出了用抗FLAG标签mAb和抗ABCA4 mAb进行印迹的结果。右图对应于蛋白质印迹的光密度定量。

[0066] 图7: 对ABCA4位置1140、1150、1179和1188处的剪接产量进行比较。细胞用相应的ABCA4<sup>N</sup>-CfaN和CfaC (或CfaCmut) -ABCA4<sup>C</sup>构建体共转染,裂解并通过WB分析。图对应于重构ABCA4蛋白的WB光密度定量及其与用编码全长蛋白的质粒转染后获得的ABCA4水平的比较。

[0067] 图8: 包括降解决定子的PTS的反应方案。目标蛋白的N端片段与IntN、接头(在这种情况下为His6标签)和降解决定子融合。蛋白质的C端与IntC融合,IntC的N端与降解决定子连接。剪接反应导致形成所期望的全长蛋白质(没有任何降解决定子与全长蛋白质融合)以及切下的内含肽(切下的内含肽各自带有降解信号)。

[0068] 图9: 将内含肽和降解决定子组合以重构报告蛋白EGFP。HEK293细胞用指定的构建体转染,裂解并使用抗His6标签mAb通过蛋白质印迹进行分析。结果表明,使用将CfaN或C内含肽与降解信号结合的构建体导致由起始材料(EGFP-CfaN-6H)以及内含肽(CfaN-6H)产生的任何信号消失。

[0069] 图10: 将内含肽和降解决定子组合以重构大蛋白ABCA4。在有和没有降解决定子的情况下,HEK293细胞用ABCA4<sup>N</sup>1150-CfaN和CfaC-ABCA4<sup>C</sup>1150转染,裂解并使用抗FLAG标签mAb通过蛋白质印迹进行分析。取两个不同时间点的细胞(24小时和48小时)。上图: 蛋白质印迹分析。下图: 蛋白质印迹的光密度定量。结果表明,使用将CfaN或C内含肽与降解信号结合的构建体导致由起始材料(ABCA4-CfaN和CfaC-ABCA4)产生的信号消失。有趣的是,结果还表明,Cfa内含肽与降解信号的组合导致重构的全长ABCA4的产量增加。

[0070] 图11: 内含肽-降解决定子组合的效果由蛋白酶体介导。在有和没有降解决定子的情况下,细胞用ABCA4<sup>N</sup>1150-CfaN和CfaC-ABCA4<sup>C</sup>1150构建体共转染;24小时后,在存在或不存在蛋白酶体抑制剂MG132的情况下,将细胞孵育指定的时间(30分钟、3小时、6小时和24小时)。在指定的时间后,细胞被裂解并使用抗FLAG mAb通过蛋白质印迹分析。添加蛋白酶体抑制剂MG132导致对应于片段的条带的强度增加,表明它们的降解已被抑制。

[0071] 图12: 使用不同内含肽或内含肽与降解决定子组合的重构产量的比较。左图: 使用Cfa、Cfa-SopE或Npu对在位置1150处断裂的ABCA4通过PTS进行重构的蛋白质印迹。用ABCA4<sup>N</sup>1150-CfaN和CfaC-ABCA4<sup>C</sup>1150 (Cfa)、用ABCA4<sup>N</sup>1150-CfaN-SopE和SopE-CfaC-ABCA4<sup>C</sup>1150 (Cfa-SopE) 或用ABCA4<sup>N</sup>1150-NpuN和NpuC-ABCA4<sup>C</sup>1150 (Npu) 共转染细胞。48小时后收集细胞,裂解并通过WB分析。分析了Cfa构建体的两次重复以及CfaSopE和Npu的三次重复。右图: 用每种内含肽和降解决定子组合获得的产物以及剩余的起始材料的光密度定量。结果显示了当使用Cfa与降解决定子(SopE)的组合时产物的重构程度如何更高。有趣的是,数据显示用Npu进行的重构最低,但它也是未反应的起始材料的剩余水平最高的。

[0072] 图13: 使用CfaCmut在有和没有降解信号的情况下在位置1140重构ABCA4。左图: 用ABCA4<sup>N</sup>1140-CfaN和CfaCmut-ABCA4<sup>C</sup>1140 (Cfa)、用ABCA4<sup>N</sup>1140-CfaN-SopE和SopE-CfaC-ABCA4<sup>C</sup>1140 (Cfa-SopE) 或用全长ABCA4 (ABCA) 共转染细胞。48小时后,收集细胞,裂解并使用抗FLAG标签mAb通过WB分析。右图: 与用全长ABCA4转染相比,ABCA4重构水平的光密度定

量。

[0073] 图14:内含肽和降解决定子组合以重构报告蛋白EGFP,其中使用DD1降解决定子。HEK293细胞用指定的构建体转染,裂解并使用抗His6标签mAb通过蛋白质印迹进行分析。Cfa内含肽与DD1降解决定子的组合导致消除不期望的起始材料和切下的内含肽。

[0074] 图15:质谱分析。用ABCA4<sup>N</sup>1150-CfaN-SopE和SopE-CfaC-ABCA4<sup>C</sup>1150转染细胞,48小时后收集细胞并裂解。将细胞裂解物在SDSPAGE凝胶中电泳,切割约300KDa的条带,蛋白水解(参见材料和方法)并通过LC-MS/MS进行分析。结果总结在图中。绿色显示通过MSMS识别的错误发现率(FDR)低于1%的肽段。黄色是识别的FDR低于5%的肽。红色下划线显示断裂位点的序列。

[0075] 图16:使用正交共有内含肽(orthogonal consensus inteins)的三段式连接。

[0076] 图17:使用正交共有内含肽的三段式连接。图16所示的N、M和C构建体单独转染、成对共转染或三个片段一起共转染到HEK293中。裂解细胞并,使用针对存在于N、M和C端片段的C端的3FT标签的抗体(左图)或针对POIN片段的抗体(右图)通过蛋白质印迹分析细胞。

[0077] 图18:A)分析降解决定子对本发明的断裂内含肽N片段的表达水平的影响。将具有和不具有降解决定子的构建体转染到HEK293细胞中,并通过蛋白质印迹分析表达水平。向N内含肽片段添加降解决定子导致检测到的表达蛋白质水平降低。B)分析降解决定子对本发明的断裂内含肽C片段的表达水平的影响。将具有和不具有降解决定子的构建体转染到HEK293细胞中,并通过蛋白质印迹分析表达水平。向C内含肽片段添加降解决定子导致检测到的表达蛋白质水平降低。C)示出了用N端或C端片段转染或用两种片段共转染的细胞的蛋白质印迹分析。示出了不具有降解决定子(无降解决定子)或具有代表性降解决定子(SopE、L2和L9)的构建体的结果。右图提供了与不具有降解决定子获得的产物相比,使用各指定的降解决定子获得的PTS产物量的量化。可以看出,与不具有降解决定子的构建体相比,一些降解决定子提供更高的产量。有趣的是,所有的降解决定子都有效,并且使用所有的降解决定子都可以重构在不具有降解决定子的情况下获得的产物的至少25%。一些降解决定子允许重构在不具有降解决定子的情况下获得的水平的超过50%,最后,有一些降解决定子产生100%(或更高)的重构。

[0078] 图19.使用不同类型的能够检测内含肽的凝胶通过WB分析用不同降解决定子进行的PTS反应。可以看出,与其他降解决定子(例如SpoE和PEST)相比,几种降解决定子减少了切下的内含肽的量,而其他降解决定子(如L2、L9、M2、M4或DD3)则完全消除了内含肽条带。

[0079] 图20.通过蛋白质印迹分析在具有不同的降解决定子组合和不具有降解决定子的情况下在位置1150的断裂处的PTS反应。在这种情况下,N片段处的降解决定子是固定的(左图L9和右图L2,标有N),C片段处使用不同的降解决定子(L2、L9、M4、M2、V12、DD3和DD1,标有C)。

[0080] 图21:在N端和C端内含肽ABCA4片段中具有或不具有降解决定子L9的情况下位点1140和11179处的PTS反应的WB和量化。

[0081] 图22:使用gp41内含肽通过蛋白质印迹分析PTS反应。左图:使用Cfa内含肽对在位置1150处断裂的ABCA4通过PTS进行重构的蛋白质印迹和使用gp41内含肽对在位置1185处断裂的ABCA4通过PTS进行重构的蛋白质印迹。48小时后收集细胞,裂解并通过WB分析。右图:用各内含肽以及全长蛋白质获得的产物的光密度定量。

[0082] 图23:体内视网膜EGFP:(A)注射了编码全长EGFP的AAV8或编码本发明的N端片段(N,EGFPN-CfaN)和C端片段(C,CfaC-EGFPC)的两种AAV的小鼠的眼底自发荧光(FAF)。(B)盐水或处理过的视网膜的免疫组织化学分析(IHC)。结果示出了光感受器中的天然EGFP荧光,指示了蛋白质剪接介导的EGFP重构。所有构建体都在GRK1启动子的控制下,并且注射了两种不同剂量的N+C构建体。BSS(平衡无菌盐水)。

## 具体实施方式

[0083] 本发明涉及使用工程改造的或天然存在的断裂内含肽以及其与降解信号(去稳定结构域,降解决定子)的组合来重构用于基因治疗的大蛋白的方法。

[0084] 本发明中描述的方法允许在体外、离体和体内重构大蛋白。当在体内使用时,该方法将允许在任何期望的组织中重构所需的大目标蛋白,所述期望的组织包括但不限于:中枢神经系统(CNS)、周围神经系统(PNS)、肌肉、肝脏、眼睛、胰腺、视网膜、肾脏、内耳、心脏、肺、血液、脾脏、皮肤。

[0085] 如本文所用,术语“内含肽”是指天然存在的或人工构建的多肽序列,该多肽序列能够催化从前体蛋白切下内含肽序列并通过肽键加入侧翼序列(N-外显肽和C-外显肽)的蛋白剪接反应。内含肽的大小通常为150-550个氨基酸,也可包含归巢核酸内切酶(homing endonuclease)结构域。已知的内含肽的列表发布在<http://www.inteins.com>和<https://inteins.biocenter.helsinki.fi/index.php>上。

[0086] 如本文所用的术语“断裂内含肽”是指任何这样的内含肽,其中的N端和C端氨基酸序列不通过肽键直接连接,使得N端和C端序列变成单独的片段,所述单独的片段可以非共价重新缔合或重构为对反式剪接反应(trans-splicing reaction)起作用的内含肽。

[0087] 术语“肽键”是指当一个分子的羧基部分(称为羧基组分)与另一个分子的氨基部分(称为氨基组分)反应时,两个分子之间形成的共价化学键-CO-NH-,从而导致分子的释放。例如,蛋白原L-氨基酸在结合时可以形成肽键,同时释放水分子。因此,蛋白质和肽可以看作是由肽键连接在一起的氨基酸残基链。肽键是“酰胺键”或“酰胺连接”。

[0088] 术语“多肽”、“肽”或“蛋白质”在本文中可互换使用以指代氨基酸的聚合物。

[0089] 术语“氨基酸”是指天然存在的氨基酸和合成氨基酸,以及以类似于天然存在的氨基酸的方式起作用的氨基酸类似物和氨基酸模拟物。此外,术语“氨基酸”包括D-氨基酸和L-氨基酸(立体异构体)。

[0090] 术语“天然氨基酸”或“天然存在的氨基酸”包括20种天然存在的氨基酸;这些氨基酸经常在体内进行翻译后修饰,这些氨基酸包括例如羟脯氨酸、磷酸丝氨酸和磷酸苏氨酸;和其他不常见的氨基酸,包括但不限于2-氨基己二酸、羟赖氨酸、异锁链素、正缬氨酸、正亮氨酸和鸟氨酸。

[0091] 如本文所用,术语“非天然氨基酸”或“合成氨基酸”是指在“ $\alpha$ ”位处被胺基取代并且在结构上与天然氨基酸相关的羧酸或其衍生物。修饰的或不常见的氨基酸的说明性非限制性实例包括:2-氨基己二酸、3-氨基己二酸、 $\beta$ -丙氨酸、2-氨基丁酸、4-氨基丁酸、6-氨基己酸、2-氨基庚酸、2-氨基异丁酸、3-氨基异丁酸、2-氨基庚二酸、2,4-二氨基丁酸、锁链素、2,2'-二氨基庚二酸、2,3-二氨基丙酸、N-乙基甘氨酸、N-乙基天冬酰胺、羟基赖氨酸、别羟基赖氨酸(alio hydroxy lysine)、3-羟脯氨酸、4-羟脯氨酸、异锁链素、别异亮氨酸、N-甲

基甘氨酸、N-甲基异亮氨酸、6-N-甲基-赖氨酸、N-甲基缬氨酸、正缬氨酸、正亮氨酸、鸟氨酸、对乙酰苯丙氨酸、对卤代苯丙氨酸、对丙炔氧基苯丙氨酸(p-proparglyoxyphenylalanine)、对叠氮基苯丙氨酸、对苯甲酰基苯丙氨酸等。该组还包括“天然氨基酸”的D-异构体。

[0092] 如本文所用,术语“断裂内含肽N片段”或“N端断裂内含肽”或“N端内含肽片段”或“N端内含肽序列”(缩写为“IntN”)是指任何这样的内含肽,其包含对反式剪接反应起作用、即能够与功能性断裂内含肽C片段缔合以形成完整的内含肽的N端氨基酸序列,该完整的内含肽序列能够将自身从宿主蛋白中切下,催化外显肽或侧翼序列通过肽键连接,或与断裂内含肽C片段缔合时催化“N端切割”,即对外显肽和断裂内含肽N片段的N端之间的肽键的亲核攻击,从而导致所述肽键断裂。因此,IntN还包括在发生反式剪接时被剪掉的序列。IntN可以包含作为天然存在的内含肽序列的N端部分的修饰物的序列。例如,它可以包含额外的氨基酸残基和/或突变的残基,只要包含这些额外的和/或突变的残基不会使IntN在反式剪接中不起作用。优选地,包含额外的和/或突变的残基提高或增强了IntN的反式剪接活性。

[0093] 如本文所用,术语“降解决定子”是指当与另一多肽重组融合时通过蛋白酶体降解途径或任何其他细胞降解机制加速其蛋白质降解的天然存在的或人工构建的多肽序列。

[0094] 如本文可互换使用的,术语“断裂内含肽C片段”或“C端断裂内含肽”或“C端内含肽片段”或“C端内含肽序列”(缩写为“IntC”)是指任何这样的内含肽,其包含对反式剪接反应起作用、即在缔合时能够与功能性断裂内含肽N片段缔合以形成完整的内含肽的C端氨基酸序列,该完整的内含肽序列能够将自身从宿主蛋白中切下,催化外显肽或侧翼序列通过肽键连接,或与分裂的N内含肽缔合时催化“C端切割”,即对外显肽和断裂内含肽C片段的C端之间的肽键的亲核攻击,从而导致所述肽键断裂。因此,IntC还包括在发生反式剪接时被剪掉的序列。IntC可以包含作为天然存在的内含肽序列的C端部分的修饰物的序列。例如,它可以包含额外的氨基酸残基和/或突变的残基,只要包含这些额外的和/或突变的残基不会使IntC在反式剪接中不起作用。优选地,包含额外的和/或突变的残基提高或增强了IntC的反式剪接活性。

[0095] 在此需要说明的是,在本发明的上下文中,“要重构的蛋白质的N端片段”是指蛋白质的N端片段,更具体地,是指超过25KDa、超过50KDa或超过100KDa的蛋白质片段。因此,如本文所用,术语“蛋白质的N端片段”是指包括蛋白质(其成熟或未成熟形式)的N端的长度可变的片段。在一个具体实施方式中,N端片段是包含整个蛋白质长度的小于100%、小于90%、小于80%、小于70%、小于60%、小于50%、小于40%、小于30%、小于20%、小于10%、小于5%的片段。

[0096] 在此需要说明的是,在本发明的上下文中,“要重构的蛋白质的C端片段”是指蛋白质的C端片段,更具体地,是指超过25KDa、超过50KDa或超过100KDa的蛋白质片段。因此,如本文所用,术语“蛋白质的C端片段”是指包括蛋白质的C端的长度可变的片段。在一个具体实施方式中,C端片段是包含整个蛋白质长度的小于100%、小于90%、小于80%、小于70%、小于60%、小于50%、小于40%、小于30%、小于20%、小于10%、小于5%的片段。

[0097] 如本文所用,术语“多核苷酸”是指由通过磷酸二酯键(或其相关结构变体或合成类似物)连接的多个核苷酸单元(脱氧核糖核苷酸或核糖核苷酸,或其相关结构变体或合成类似物)组成的聚合物。术语多核苷酸包括双链或单链基因组和cDNA、RNA、任何合成的和基

因操纵的多核苷酸,以及正义多核苷酸和反义多核苷酸(尽管本发明仅公开了正义链)。这包括单链分子和双链分子,即DNA-DNA、DNA-RNA和RNA-RNA杂合体。

[0098] 断裂内含肽N片段

[0099] 本发明涉及通过肽键与要重构的蛋白质的N端片段直接连接的断裂内含肽N片段。该构建体从N端到C端将具有以下一般架构:

[0100] (要重构的蛋白质的N端片段)-内含肽N。

[0101] 要重构的蛋白质可以是任何其重构可以产生积极的治疗效果的大基因。可以用本发明重构的蛋白质的非限制性例子是ABCA4蛋白质,以及由下表1中列出的基因编码的蛋白质。重构这些蛋白质的目的是通过提供这些基因的正确版本来治疗与其编码基因中的突变相关的疾病。此外,要重构的蛋白质可以是治疗疾病的蛋白质或酶,但是该蛋白质或酶不一定替代突变的蛋白质或酶。例如,要重构的蛋白质可以是用于基因、碱基或先导编辑(prime editing)的CRISPR/Cas9系统。

[0102] 表1.

| 疾病                                | 蛋白质(基因)                                   | Uniprot ID | 编码区域大小 |
|-----------------------------------|-------------------------------------------|------------|--------|
| 乌谢尔综合征(Usher Syndrome) 2C (USH2C) | 粘附 G 蛋白偶联受体 V1 (ADGRV1)                   | Q8WVG9     | 18.9   |
| 年龄相关性黄斑变性 1 (ARMD1)               | Hemicentin-1 (HMCN1)                      | Q96RW7     | 18.9   |
| 家族性高热惊厥 4 (FEB4)                  | 粘附 G 蛋白偶联受体 V1 (ADGRV1)                   | Q8WVG9     | 18.9   |
| 乌谢尔综合征 2A (USH2A)                 | Usherlin (USH2A)                          | O75445     | 15.6   |
| 色素性视网膜炎 39 (RP39)                 | Usherlin (USH2A)                          | O75445     | 15.6   |
| Alstom 综合征 (Alstom Syndrome)      | Alstom 综合征蛋白 1 (ALMS1)                    | Q8TCU4     | 12.5   |
| 杜氏肌营养不良症                          | 抗肌萎缩蛋白 (DMD)                              | P11532     | 11.6   |
| 常染色体隐性遗传耳聋 3 (DFNB3)              | 非常规肌球蛋白-XV (MYO15A)                       | Q9UKN7     | 10.8   |
| 乌谢尔综合征 1D/F (USH1DF)              | 钙粘蛋白-23 (CDH23)                           | Q9H251     | 10.1   |
| 乌谢尔综合征 1D (USH1D)                 | 钙粘蛋白-23 (CDH23)                           | Q9H251     | 10.1   |
| 多种类型垂体腺瘤 5 (PITA5)                | 钙粘蛋白-23 (CDH23)                           | Q9H251     | 10.1   |
| 常染色体隐性遗传耳聋 12 (DFNB12)            | 钙粘蛋白-23 (CDH23)                           | Q9H251     | 10.1   |
| 色素性视网膜炎 25 (RP25)                 | 闭眼蛋白同源物 (Protein eyes shut homolog) (EYS) | Q5T1H1     | 9.4    |
| 肢带型肌营养不良症 ar 23 (LGMDR23)         | 层粘连蛋白亚基 $\alpha$ -2 (LAMA2)               | P24043     | 9.4    |
| 分区蛋白缺陷型先天性肌营养不良症 1A (MDC1A)       | 层粘连蛋白亚基 $\alpha$ -2 (LAMA2)               | P24043     | 9.4    |
| 血管性血友病 1 (VWD1)                   | 血管性血友病因子 (VWF)                            | P04275     | 8.4    |

[0103]

[0104]

|                                    |                                         |        |     |
|------------------------------------|-----------------------------------------|--------|-----|
| 血管性血友病 2 (VWD2)                    | 血管性血友病因子 (VWF)                          | P04275 | 8.4 |
| 血管性血友病 3 (VWD3)                    | 血管性血友病因子 (VWF)                          | P04275 | 8.4 |
| 新生儿暂时性大疱性皮肤松解症 (TBDN)              | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 非综合征型先天性指甲疾病 8 (NDNC8)             | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 伴有角膜下裂的营养不良型大疱性表皮松解症 (EBDSC)       | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 巴特 (Bart) 型营养不良型大疱性表皮松解症 (B-DEB)   | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 痒疹型大疱性表皮松解症 (EBP)                  | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 胚前型营养不良大疱性表皮松解症 (PR-DEB)           | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 营养不良大疱性表皮松解症 ar (RDEB)             | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 营养不良大疱性表皮松解症 ad (DDEB)             | 胶原蛋白 $\alpha$ -1 (VII) 链 (COL7A1)       | Q02388 | 8.1 |
| 脊髓小脑性共济失调 6 (SCA6)                 | 电压依赖性 P/Q 型钙通道亚基 $\alpha$ -1A (CACNA1A) | O00555 | 7.7 |
| 家族性偏瘫型偏头痛 1 (FHM1)                 | 电压依赖性 P/Q 型钙通道亚基 $\alpha$ -1A (CACNA1A) | O00555 | 7.7 |
| 发作性共济失调 2 (EA2)                    | 电压依赖性 P/Q 型钙通道亚基 $\alpha$ -1A (CACNA1A) | O00555 | 7.7 |
| 婴儿早期癫痫性脑病 42 (EIEE42)              | 电压依赖性 P/Q 型钙通道亚基 $\alpha$ -1A (CACNA1A) | O00555 | 7.7 |
| 老年洛肯 (Senior-Loken) 综合征 6 (SLSN6)  | 290kDa 的中心体蛋白 (CEP290)                  | O15078 | 7.5 |
| 麦克尔综合征 4 (MKS4)                    | 290kDa 的中心体蛋白 (CEP290)                  | O15078 | 7.5 |
| 莱伯氏先天性黑朦症 10 (LCA10)               | 290kDa 的中心体蛋白 (CEP290)                  | O15078 | 7.5 |
| 朱伯特综合征 5 (JBTS5)                   | 290kDa 的中心体蛋白 (CEP290)                  | O15078 | 7.5 |
| 巴比二氏 (Bardet-Biedl) 综合征 14 (BBS14) | 290kDa 的中心体蛋白 (CEP290)                  | O15078 | 7.5 |
| 隐匿性黄斑营养不良 (OCMD)                   | 视网膜色素变性 1 样蛋白 (RPIL1)                   | Q8IWN7 | 7.2 |
| 家族性高醛甾酮症 4 (HALD4)                 | 电压依赖性 T 型钙通道亚基 $\alpha$ -1H (CACNA1H)   | O95180 | 7.1 |
| 甲型血友病                              | 凝血因子 FVIII                              | P00451 | 7.1 |
| 特发性全面性癫痫 6 (EIG6)                  | 电压依赖性 T 型钙通道亚基 $\alpha$ -1H (CACNA1H)   | O95180 | 7.1 |
| 儿童失神癫痫 6 (ECA6)                    | 电压依赖性 T 型钙通道亚基 $\alpha$ -1H (CACNA1H)   | O95180 | 7.1 |

[0105]

|                                                              |                                  |        |     |
|--------------------------------------------------------------|----------------------------------|--------|-----|
| 耳聋, ar, 28 (DFNB28)                                          | TRIO 和 F-肌动蛋白结合蛋白 (TRIOBP)       | Q9H2D6 | 7.1 |
| 色素性视网膜炎 13 (RP13)                                            | 前 mRNA 加工剪接因子 8 (PRPF8)          | Q6P2Q9 | 7.0 |
| Stargardt 病 1 (STGD1)                                        | 视网膜特异性磷脂转运 ATP 酶 ABCA4 (ABCA4)   | P78363 | 6.8 |
| 色素性视网膜炎 19 (RP19=)                                           | 视网膜特异性磷脂转运 ATP 酶 ABCA4 (ABCA4)   | P78363 | 6.8 |
| 年龄相关性黄斑变性 2 (ARMD2)                                          | 视网膜特异性磷脂转运 ATP 酶 ABCA4 (ABCA4)   | P78363 | 6.8 |
| 眼底黄斑 (FFM)                                                   | 视网膜特异性磷脂转运 ATP 酶 ABCA4 (ABCA4)   | P78363 | 6.8 |
| 锥体杆体营养不良 3 (CORD3)                                           | 视网膜特异性磷脂转运 ATP 酶 ABCA4 (ABCA4)   | P78363 | 6.8 |
| 乌谢尔综合征 1B (USH1B)                                            | 非常规肌球蛋白-VIIa (MYO7A)             | Q13402 | 6.7 |
| 耳聋 ar 2 (DFNB2)                                              | 非常规肌球蛋白-VIIa (MYO7A)             | Q13402 | 6.7 |
| 耳聋 ad 11 (DFNA11)                                            | 非常规肌球蛋白-VIIa (MYO7A)             | Q13402 | 6.7 |
| 色素性视网膜炎 1 (RP1)                                              | 氧调节蛋白 1 (RP1)                    | P56715 | 6.5 |
| 肢带型肌营养不良症 ar 2 (LGMDR2)                                      | Dysferlin (DYSF)                 | O75923 | 6.5 |
| 三好型肌营养不良症 1 (MMD1)                                           | Dysferlin (DYSF)                 | O75923 | 6.5 |
| 胫骨前群远端肌病 ( Distal myopathy with anterior tibial onset, DMAT) | Dysferlin (DYSF)                 | O75923 | 6.5 |
| 耳聋 ad 12 (DFNA12)                                            | $\alpha$ -tectorin (TECTA)       | O75443 | 6.5 |
| 耳聋 ar 21 (DFNB21)                                            | $\alpha$ -tectorin (TECTA)       | O75443 | 6.5 |
| 色素性视网膜炎 33 (RP33)                                            | U5 小核核糖核蛋白 200kDa 解旋酶 (SNRNP200) | O75643 | 6.4 |
| 进行性家族性心脏传导阻滞 1A (PFHB1A)                                     | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 长 QT 综合征 3 (LQT3)                                            | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 布鲁加达综合征 1 (BRGDA1)                                           | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 病态窦房结综合征 1 (SSS1)                                            | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 家族性阵发性室颤 1 (VF1)                                             | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 婴儿猝死综合征 (SIDS)                                               | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 心房静止 1 (ATRST1)                                              | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 扩张型心肌病 1E (CMD1E)                                            | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 家族性房颤 10 (ATFB10)                                            | 钠通道蛋白 5 型亚基 $\alpha$ (SCN5A)     | Q14524 | 6.2 |
| 良性家族性婴儿癫痫 3 (BFIS3)                                          | 钠通道蛋白 2 型亚基 $\alpha$ (SCN2A)     | Q99250 | 6.2 |
| 家族性偏瘫型偏头痛 3 (FHM3)                                           | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)     | P35498 | 6.2 |
| 顽固性儿童癫痫伴全面性                                                  | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)     | P35498 | 6.2 |

[0106]

|                                         |                                       |        |     |
|-----------------------------------------|---------------------------------------|--------|-----|
| 强直阵挛发作 (ICEGTC)                         |                                       |        |     |
| 婴儿痉挛                                    | 钠通道蛋白 2 型亚基 $\alpha$ (SCN2A)          | Q99250 | 6.2 |
| 全面性癫痫伴高热惊厥附加症 2 (GEFS+2)                | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)          | P35498 | 6.2 |
| 家族性高热惊厥 3A (FEB3A)                      | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)          | P35498 | 6.2 |
| 婴儿早期癫痫性脑病 6 (EIEE6)                     | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)          | P35498 | 6.2 |
| 婴儿早期癫痫性脑病 62 (EIEE62)                   | 钠通道蛋白 3 型亚基 $\alpha$ (SCN3A)          | Q9NY46 | 6.2 |
| 婴儿早期癫痫性脑病 11 (EIEE11)                   | 钠通道蛋白 2 型亚基 $\alpha$ (SCN2A)          | Q99250 | 6.2 |
| 不同病灶的家族性局灶性癫痫 4 (FFEVF4)                | 钠通道蛋白 3 型亚基 $\alpha$ (SCN3A)          | Q9NY46 | 6.2 |
| Dravet 综合征                              | 钠通道蛋白 1 型亚基 $\alpha$ (SCN1A)          | P35498 | 6.2 |
| 耳聋 ar 9 (DFNB9)                         | 耳畸蛋白 (OTOF)                           | Q9HC10 | 6.2 |
| 听神经病变, ar, 1 (AUNB1)                    | 耳畸蛋白 (OTOF)                           | Q9HC10 | 6.2 |
| 耳聋 ad 4A (DFNA4A)                       | 肌球蛋白 14 (MYH14)                       | Q7Z406 | 6.2 |
| 周围神经病变、肌病、声音嘶哑和听力损失 (PNMH)              | 肌球蛋白 14 (MYH14)                       | Q7Z406 | 6.2 |
| 耳聋 ar 77 (DFNB77)                       | 含脂氧合酶同源结构域蛋白 1 (LOXHD1)               | Q8IVV2 | 6.2 |
| 良性家族性婴儿癫痫 5 (BFIS5)                     | 钠通道蛋白 8 型亚基 $\alpha$ (SCN8A)          | Q9UQD0 | 6.1 |
| 家族性肌阵挛 2 (MYOCL2)                       | 钠通道蛋白 8 型亚基 $\alpha$ (SCN8A)          | Q9UQD0 | 6.1 |
| 婴儿早期癫痫性脑病 13 (EIEE13)                   | 钠通道蛋白 8 型亚基 $\alpha$ (SCN8A)          | Q9UQD0 | 6.1 |
| 伴或不伴小脑性共济失调的认知障碍 (CIAT)                 | 钠通道蛋白 8 型亚基 $\alpha$ (SCN8A)          | Q9UQD0 | 6.1 |
| 先天性静止性夜盲症 2A (CSNB2A)                   | 电压依赖性 L 型钙通道亚基 $\alpha$ -1F (CACNA1F) | O60840 | 6.0 |
| X 连锁锥体杆体营养不良 3 (CORDX3)                 | 电压依赖性 L 型钙通道亚基 $\alpha$ -1F (CACNA1F) | O60840 | 6.0 |
| 奥兰岛眼病 (Aaland island eye disease, AIED) | 电压依赖性 L 型钙通道亚基 $\alpha$ -1F (CACNA1F) | O60840 | 6.0 |
| 乌谢尔综合征 1F (USH1F)                       | 光钙粘蛋白 15 (PCDH15)                     | Q96QU1 | 5.9 |
| 乌谢尔综合征 1D/F (USH1DF)                    | 光钙粘蛋白 15 (PCDH15)                     | Q96QU1 | 5.9 |
| 耳聋 ar 23 (DFNB23)                       | 光钙粘蛋白 15 (PCDH15)                     | Q96QU1 | 5.9 |
| 耳聋 ar 16 (DFNB16)                       | Stereocilin (STRC)                    | Q7RTU9 | 5.2 |
| 耳聋-不孕综合征 (DIS)                          | Stereocilin (STRC)                    | Q7RTU9 | 5.2 |
| 耳聋 ar 30 (DFNB30)                       | 肌球蛋白-IIIa (MYO3A)                     | Q8NEV4 | 4.8 |
| 耳脊椎骨骺发育不良 ad (OSMEDA)                   | 胶原蛋白 $\alpha$ -2 (XI) 链 (COL11A2)     | P13942 | 4.7 |
| 耳脊椎骨骺发育不良 ar                            | 胶原蛋白 $\alpha$ -2 (XI) 链 (COL11A2)     | P13942 | 4.7 |



[0107]

| (OSMEDB)                                                    |                                                     |        |     |
|-------------------------------------------------------------|-----------------------------------------------------|--------|-----|
| 耳聋 ad 13 (DFNA13)                                           | 胶原蛋白 $\alpha$ -2 (XI) 链 (COL11A2)                   | P13942 | 4.7 |
| 耳聋 ar 53 (DFNB53)                                           | 胶原蛋白 $\alpha$ -2 (XI) 链 (COL11A2)                   | P13942 | 4.7 |
| 纤维软骨增生症 2(FBCG2)                                            | 胶原蛋白 $\alpha$ -2 (XI) 链 (COL11A2)                   | P13942 | 4.7 |
| 囊性纤维化 (CF)                                                  | 囊性纤维化跨膜电导调节剂 (CFTR)                                 | P13569 | 4.6 |
| 先天性双侧输精管缺失 (CBAVD)                                          | 囊性纤维化跨膜电导调节剂 (CFTR)                                 | P13569 | 4.6 |
| 范可尼贫血互补组 A (Fanconi anemia, complementation group A, FANCA) | 范可尼贫血组 A 蛋白 (Fanconi anemia group A protein, FANCA) | O15360 | 4.4 |
| 色素性视网膜炎 12 (RP12)                                           | 蛋白质 crumbs 同源物 1 (CRB1)                             | P82279 | 4.2 |
| 色素性静脉旁脉络膜视网膜萎缩 (PPCRA)                                      | 蛋白质 crumbs 同源物 1 (CRB1)                             | P82279 | 4.2 |
| 莱伯氏先天性黑朦症 8 (LCA8)                                          | 蛋白质 crumbs 同源物 1 (CRB1)                             | P82279 | 4.2 |
| 耳聋 ad 22 (DFNA22)                                           | 非常规肌球蛋白-VI (MYO6)                                   | Q9UM54 | 4.1 |
| 耳聋 ar 37 (DFNB37)                                           | 非常规肌球蛋白-VI (MYO6)                                   | Q9UM54 | 4.1 |
| 伴有肥厚型心肌病的耳聋 ad 22 (DFNHCM)                                  | 非常规肌球蛋白-VI (MYO6)                                   | Q9UM54 | 4.1 |
| 耳聋 ar 30 (DFNB30)                                           | 肌球蛋白-IIib (MYO3B)                                   | Q8WXR4 | 4.0 |
| 莱伯氏先天性黑朦症 6 (LCA6)                                          | X 连锁色素性视网膜炎 GTP 酶调节因子相互作用蛋白 1 (RPGRIP1)             | Q96KN7 | 4.0 |
| 锥体杆体营养不良 13 (CORD13)                                        | X 连锁色素性视网膜炎 GTP 酶调节因子相互作用蛋白 1 (RPGRIP1)             | Q96KN7 | 4.0 |

[0108] LCA=莱伯氏先天性黑朦症

[0109] RP=色素性视网膜炎

[0110] ad=常染色体显性遗传

[0111] ar=常染色体隐性遗传

[0112] PR=感光器

[0113] RPE=视网膜色素上皮

[0114] ECM=细胞外基质

[0115] 因此,本发明的第一方面涉及通过肽键与要重构的蛋白质的N端片段直接连接的断裂内含肽N片段,其中,如上所反映的,IntN与N端片段的C端直接连接或通过使用接头连接(下文称为“本发明的断裂内含肽N片段”)。

[0116] 本发明的第一方面的优选实施方式是指通过肽键与降解决定子直接连接的断裂内含肽N片段(下文称为“本发明的断裂内含肽N片段降解决定子”),其中降解决定子在内含肽N片段和降解决定子之间有或没有接头的情况下通过内含肽的C端与内含肽N片段连接,并且其中断裂内含肽N片段的N端通过肽键与要重构的蛋白质的N端片段直接连接。

[0117] 因此,本发明的断裂内含肽N片段降解决定子的构建体的架构从N端到C端将是:

[0118] (要重构的蛋白质的N端部分)-(内含肽-N片段)-(降解决定子)。

[0119] 如果在IntN和降解决定子之间引入接头,则本发明的断裂内含肽N片段降解决定子的构建体的架构从N端到C端将是:

[0120] (要重构的蛋白质的N端部分) - (内含肽-N片段) - (接头) - (降解决定子)。

[0121] 优选地,任何的本发明的断裂内含肽N片段或本发明的断裂内含肽N片段降解决定子的内含肽N可以选自下表2中列出的以下中的任意者:

[0122] 表2

| 名称                      | 序列                                                                                                              | SEQ ID NO |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|-----------|
| <b>Cfa<sup>N</sup></b>  | CLSYDTEILTVEYGFLPIGKIVEERIECTVYTVDKNGFV<br>YTQPIAQWHNRGEQEVFEYCLEDGSIIRATKDHKFMFTD<br>GQMLPIDEIFERGLDLKQVDGLP   | 27        |
| <b>Cat<sup>N</sup></b>  | CLSGDTMIEILDGDDGIIQKISMEDLYQRLA                                                                                 | 30        |
| <b>Npu<sup>N</sup></b>  | CLSYETEILTVEYGLLPIGKIVEKRIECTVYSVDNNGNI<br>YTQPVAQWHRGEQEVFEYCLEDGSLIRATKDHKFMFTVD<br>GQMLPIDEIFERELDLMRVDNLPN  | 32        |
| <b>Gp41<sup>N</sup></b> | CLDLKTQVQTPQGMKEISNIQVGDVLSNTGYNEVLNVF<br>PKSKKKSYSKITLEDGKEIICSEEHLPFTQTGEMNISGGL<br>KEGMCLYVKE                | 38        |
| <b>Con<sup>N</sup></b>  | CLSYDTEILTVEYGAVPKIGKIVEENIECTVYSVDENGFLV<br>YTQPIAQWHRGEQEVFEYCLEDGSTIRATKDHKFMFTD<br>GEMLPIDEIFEQGLDLKQVKGLPD | 39        |

[0124] 其中优选地,内含肽N是SEQ ID NO 27的Cfa<sup>N</sup>内含肽或其任何变体,例如SEQ ID NO 39的Con<sup>N</sup>;或SEQ ID NO 30的Cat<sup>N</sup>内含肽或其任何变体;或SEQ ID NO 32的Npu<sup>N</sup>内含肽或其任何变体;或SEQ ID NO 38的Gp41<sup>N</sup>内含肽或其任何变体。

[0125] 如本文所用,术语“变体”是指与特定多肽序列基本相似的多肽分子。在本发明中,我们将Cfa、Npu、Cat或Gp41内含肽的N内含肽或C内含肽的变体称为与任何其多肽序列基本相似的多肽,例如Con内含肽在本文中被理解为Cfa的变体。因此,变体可在结构和生物活性上与衍生出该变体的多肽相似。因此,变体可以指多肽序列的突变体。术语“突变体”是指这样的多肽分子,该多肽分子的序列与衍生出该多肽分子的多肽分子相比具有添加、删除、取代或以其他方式化学修饰的一个或多个氨基酸。突变体可以保留与衍生出该突变体的多肽分子基本相同的特性,或者缺乏所声称的序列的生物学活性。在特定的实施方式中,内含肽变体包括非催化性Cys残基(即N内含肽的第一个残基)已突变为丝氨酸或丙氨酸的突变体。

[0126] 优选地,本发明中通常理解的术语“变体”是指混杂性(promiscuity)增加的变体,其中混杂性理解为内含肽不取决于紧邻断裂位点的残基的身份而进行蛋白质反式剪接(PTS)反应的能力。更具体地说,内含肽混杂性是指它们不取决于紧邻断裂位点(即内含肽插入目标蛋白的位点)的氨基酸的身份进行PTS反应的能力。下面示出了断裂位点的示意图:

[0127] -3 -2 -1 +1+2+3

[0128] X-X-X-内含肽N 内含肽C-X-X-X

[0129] 通常,内含肽对在这些位置上的某些氨基酸具有强烈的偏好。例如,Cat内含肽(SEQ ID NO 30)偏好+1位上的Cys和-1位上的Glu(Stevens, A.J., Sekar, G., Gramespacher, J.A., Cowburn, D., & Muir, T.W. (2018) An Atypical Mechanism of Split Intein Molecular Recognition and Folding. Journal of the American Chemical Society, 140 (37), 11791-11799. <http://doi.org/10.1021/jacs.8b07334>)。更具混杂性的变体将是那些即使在不存在此类优选残基的情况下也能够以良好的产率进行蛋白质反式剪接反应的变体。

[0130] 在具体的实施方式中,内含肽变体包括保留了内含肽的催化残基和第二壳促进剂残基(second shell accelerator residues)的突变体,并且仅非催化残基或第二壳外的残基是突变的。第二壳促进剂残基是与内含肽活性位点相邻的那些残基,它们在调节内含肽的剪接活性中起关键作用。例如,Cfa内含肽和DnaE家族的内含肽的催化残基和促进剂残基是众所周知的,并且已在本领域中描述过(Stevens,A.J.,Brown,Z.Z.,Shah,N.H.,Sekar,G.,Cowburn,D.,&Muir,T.W.(2016).Journal of the American Chemical Society.<http://doi.org/10.1021/jacs.5b13528>)。同样,已经研究和表征了多个其他内含肽家族的催化残基,包括DnaE、GyrA、GyrB、DnaB、TerL、gp41、IMPDH(Shah,N.H.,&Muir,T.W.(2014).Inteins:Nature's Gift to Protein Chemists.Chemical Science(Royal Society of Chemistry:2010),5(1),446-461.<http://doi.org/10.1039/C3SC52951G>)。还描述了识别第二壳促进剂残基的方法(Stevens et al.2016Journal of the American Chemical Society.<http://doi.org/10.1021/jacs.5b13528>),并且所述方法可用于生成具有用于本发明的合适性质的内含肽变体(N内含肽和C内含肽)。

[0131] 在具体的实施方式中,内含肽变体包括保留了内含肽的催化残基的突变体,并且该变体保留了CfaN、NpuN、CatN或gp41N内含肽的关键功能特征,包括在离液剂或高温存在下具有快速剪接速率(半衰期低于5分钟)和高活性。在更具体的实施方式中,CfaN、CatN、NpuN或gp41N内含肽的变体是任何这些序列的功能等效变体。

[0132] 如本文所用,术语“功能等效变体”应理解为指所有通过修饰、插入和/或删除一个或多个氨基酸而从序列衍生出的那些蛋白质,只要功能基本上保持或改善,特别是在断裂内含肽N片段的功能等效变体的情况下,指的是维持其活性。如本文所用,术语“活性”是指断裂内含肽N片段在与断裂内含肽C片段结合后进行蛋白质反式剪接反应的能力。

[0133] CfaN、NpuN、CatN或gp41N内含肽的功能等效变体的例子如下所示:

[0134] -CfaN功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0135] CfaN序列(SEQ ID NO 27),其中Cys28和/或Cys59突变为Ser、Thr或Ala。

[0136] CfaN序列(SEQ ID NO 27),其中在Met1的N端包含额外的氨基酸。例如,接头、降解决定子或用于检测的标签。

[0137] CfaN序列(SEQ ID NO 27),其中其任何残基突变为具有相似物理化学性质的残基,但必须保留的以下残基除外:Cys1、Lys70、His72、Met75、Met81。

[0138] CfaN序列(SEQ ID NO 27),其中其任何残基突变为具有相似物理化学特性的残基,但必须保留的以下残基除外:Cys1、Asp5、Phe15、Glu24、Thr32、Lys35、Phe38、Val39、Ile44、Asn49、Ile65、Thr69、Lys70、His72、Met75、Thr77、Met81、Gly91、Lys95、Gln96、Gly99。

[0139] CfaN序列(SEQ ID NO 27),其中保留了残基Cys1、Lys70、His72、Met75、Met81以及引入了任何以下突变或其任何组合:Asp5Glu、Phe15Leu、Glu24Lys、Thr32Ser、Lys35Asn、Phe38Asn、Val39Ile、Ile44Val、Asn49Asp、Ile65Leu、Thr77Val、Gly91Glu、Lys95Met、Gln96Arg、Gly99Asn。

[0140] CfaN序列(SEQ ID NO 27),其中保留了残基Cys1、Lys70、His72、Met75、Met81以及引入了以下突变中的1至6个(其中1和6包含在范围内)的:Asp5Glu、Phe15Leu、Glu24Lys、Thr32Ser、Lys35Asn、Phe38Asn、Val39Ile、Ile44Val、Asn49Asp、Ile65Leu、Thr77Val、

Gly91Glu、Lys95Met、Gln96Arg、Gly99Asn。

[0141] CfaN序列(SEQ ID NO 27),其中保留残基Cys1、Asp5、Glu24、Phe38、Val39、Ile44、Lys70、His72、Met75、Met81、Gly91、Lys95、Gln96、Gly99并引入了任何以下突变或突变组合:Phe15Ala、Thr32Ser、Lys35Glu、Asn49Asp、Ile65Thr、Thr77Glu。

[0142] -NpuN功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0143] NpuN序列(SEQ ID NO 32),其中Cys28和/或Cys59突变为Ser、Thr或Ala。

[0144] NpuN序列(SEQ ID NO 32),其中NpuN的任何残基可突变为具有相似物理化学性质的残基,但必须保留的以下残基除外:Cys1、Lys70、His72、Met75、Met81。

[0145] NpuN序列(SEQ ID NO 32),其中NpuN的任何残基可突变为CfaN序列中的相应氨基酸。

[0146] -Gp41N功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0147] Gp41N序列(SEQ ID NO 38),其中Cys59和/或Cys83突变为Ser、Thr或Ala。

[0148] Gp41N序列(SEQ ID NO 38),其中Gp41N的任何残基可突变为具有相似物理化学性质的残基,但必须保留的以下残基除外:Cys1、His63,并且残基60是Ser或Thr。

[0149] -CatN功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0150] CatN序列(SEQ ID NO 30),其中CatN的任何残基可突变为具有相似物理化学性质的残基,但必须保留的Cys1残基除外。

[0151] 在具体实施方式中,内含肽N包含以下或由以下组成:分别与SEQ ID NO:27、SEQ ID NO 30、SEQ ID NO 32或SEQ ID NO 38在整个序列上具有至少90%序列同一性的SEQ ID NO:27、SEQ ID NO 30、SEQ ID NO 32或SEQ ID NO 38的氨基酸序列的变体。在具体实施方式中,SEQ ID NO:27、SEQ ID NO 30、SEQ ID NO 32或SEQ ID NO 38的内含肽N的变体分别与SEQ ID NO:27、SEQ ID NO 30、SEQ ID NO 32或SEQ ID NO 38在整个序列上具有至少91%、至少92%、至少93%、在至少94%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性。

[0152] 在两个或更多个氨基酸或核苷酸序列的上下文中,术语“同一性”、“相同”、“百分比同一性”或“序列同一性”是指在不考虑任何保守氨基酸取代作为序列同一性的一部分的情况下,当比较和对齐(如果需要,引入空位)以获得最大对应时,两个或更多个序列或子序列相同或具有特定百分比的相同氨基酸残基。百分比同一性可以使用序列比较软件或算法或通过目测来测量。本领域已知可用于获得氨基酸序列比对的各种算法和软件。序列比对算法的一个这样的非限制性例子是在Karlin et al.,1990,Proc.Natl.Acad.Sci.,87:2264-8中描述、如在Karlin et al.,1993,Proc.Natl.Acad.Sci.,90:5873-7进行修改以及并入N BLAST和XBLAST程序(Altschul et al.,1991,Nucleic Acids Res.,25:3389-402)的算法。在某些实施方式中,可以使用Gapped BLAST,如Altschul et al.,1997,Nucleic Acids Res.25:3389-402中所描述。BLAST-2、WU-BLAST-2(Altschul et al.,1996,Methods in Enzymology,266:460-80)、ALIGN、ALIGN-2(Genentech,加利福尼亚南旧金山)或Megalign(DNASTAR)是其他公开的可用于比对序列的可用软件程序。在某些替代实施方式中,GCG软件包中的GAP程序(其中并入了Needleman和Wunsch的算法(J.Mol.Biol.48:444-53(1970)))可用于确定两个氨基酸序列之间的百分比同一性(例如,使用Blossum 62矩阵或PAM250矩阵,空位权重为16、14、12、10、8、6或4,长度权重为1、2、3、4、5)。可选择地,在某

些实施方式中,氨基酸序列之间的同一性百分比是使用Myers和Miller的算法(CABIOS,4:11-7(1989))确定的。例如,百分比同一性可以使用ALIGN程序(2.0版本)和使用带有残基表、空位长度罚分为12、空位罚分为4的PAM120来确定。本领域技术人员可以通过特定比对软件确定最大比对的适当参数。在某些实施方式中,使用比对软件的默认参数。在某些实施方式中,将第一氨基酸序列与第二氨基酸序列的同一性百分比“X”计算为 $100 \times (Y/Z)$ ,其中Y是在第一序列和第二序列的比对(如通过目视检查或特定的序列比对程序进行比对的)中被评分为相同匹配的氨基酸残基的数目,Z为第二序列中的残基总数。如果第二序列比第一序列长,则使用考虑了两个序列整体的全局比对,因此每个序列中的所有字母和空值都必须进行比对。在这种情况下,可以使用与上述相同的公式,但使用第一和第二序列重叠的区域的长度作为Z值,所述区域的长度与第一序列的长度基本相同。

[0153] 作为非限制性实例,在一些实施方式中,可以使用Bestfit程序(Wisconsin序列分析包,Version 8for Unix,Genetics Computer Group,University Research Park,575Science Drive,Madison,WI 53711)来确定任何特定多肽是否与参考序列具有一定百分比的序列同一性(例如,至少80%同一性、至少85%同一性、至少90%同一性,并且,至少95%、96%、97%、98%或99%同一性)。Bestfit使用Smith和Waterman的局部同源算法(Advances in Applied Mathematics 2:482-9(1981))来寻找两个序列之间的最佳同源片段。当使用Bestfit或任何其他序列比对程序来确定特定序列是否与根据本发明的参考序列具有例如95%的同一性时,设置参数使得在参考氨基酸序列的全长上计算同一性百分比并且允许同源性中的空位最多达参考序列中核苷酸总数的5%。

[0154] 断裂内含肽N片段和降解决定子之间的术语“接头”是指连接内含肽N片段的C端和降解决定子序列的N端的氨基酸序列。接头将优选地是1至100个氨基酸、或1至5、或1至10、或1至50、或1至25个氨基酸的多肽。接头可以是富含Gly的肽或富含Gly-Ser的肽。富含Gly-Ser的肽的例子是序列GGS,或具有通式(GGS) $n$ 的该接头的聚合物,其中 $n$ 可以为1到10。接头的通式为((G) $n$ S) $y$ ,其中 $n$ 为1到5, $y$ 为1到10。此外,表位标签可以用作接头,例如六组氨酸(His6,序列:GHHHHHHG(SEQ ID NO 84)标签,或三重flag标签(3FT,序列:DYKDHDGDYKDHDIDYKDDDDK(SEQ ID NO 103))。

[0155] 在另一个具体实施方式中,通过肽键与断裂内含肽N片段直接连接的降解决定子选自下表3中列出的那些中的任意者:

[0156] 表3

[0157]

| 降解决定子          | 序列                                                                                                          | SEQ ID NO |
|----------------|-------------------------------------------------------------------------------------------------------------|-----------|
| CL1            | ACKNWFSSLSHFVIHL                                                                                            | 40        |
| Deg1           | MNKIPIKDLLNPQITDEFKSSILDINKKLFSICCNLPKL<br>PESVTTEEEVELRDILGFLSRAN                                          | 41        |
| PEST           | RSSSPSDSDTSGFSSGSDHLSDLISSLRIS                                                                              | 42        |
| DD1            | RISFGSPPPMAXG; X=任意氨基酸, 优选 Gly (G)                                                                          | 43        |
| DD2            | GSPPPMAXG; X=任意氨基酸, 优选 Gly (G)                                                                              | 44        |
| DD3 或 VI5      | TNGILKLGCQG                                                                                                 | 45        |
| M1             | CSEIIPMSRSTPISTMG                                                                                           | 46        |
| M2             | VSFAFNLNSLIVGILRFHW                                                                                         | 47        |
| SopE 或 SopE100 | MTKITLSPQNFRIQKQETTLLEKSTEKNSLAKSILAVK<br>NHFIELRSKLSERFISHKNTESSATHFHRGSASEGRAVL<br>TNKVVKDFMLQTLNDIDIRGSA | 48        |
| SopE-1-78      | MTKITLSPQNFRIQKQETTLLEKSTEKNSLAKSILAVK<br>NHFIELRSKLSERFISHKNTESSATHFHRGSASEGRAVL                           | 49        |
| SopE-15-78     | QETTLLEKSTEKNSLAKSILAVKNHFIELRSKLSERFI<br>SHKNTESSATHFHRGSASEGRAVL                                          | 50        |
| SopE-15-50     | QETTLLEKSTEKNSLAKSILAVKNHFIELRSKLS                                                                          | 51        |
| L2 或 CL2       | SLISLPLPTRVKFSSLLIRIMKIITMTFPKKLRS                                                                          | 52        |
| L6             | FYYPIWFARVLLVHYQ                                                                                            | 53        |
| L9 或 CL9       | SNPFSSLFGASLLIDSVSLKSNWDTSSSSCLISFFSSVM<br>FSSTTRS                                                          | 54        |
| L10            | CRQRFSCHLTASYPQSTVTPFLAFLRRDFFFLRHNSAD                                                                      | 55        |
| L11            | GAPHVVLFDLRLITNPLSHIQSVSLQITLIFCSLPSLI<br>LSKFLQV                                                           | 56        |
| L12 或 CL12     | NTPLFSKSFSTTCGVAKKTLLLAQISSLFFLLSSNIAV                                                                      | 57        |
| L15            | PTVKNSPKIFCLSSSPYLAFLNLEYLSLRIFSTLSKCSNT<br>LLTSL                                                           | 58        |
| L16            | SNQLKRLWLWLEVRSDRTLRPWIHLPS                                                                                 | 59        |
| M3             | KSVTLESRSKFLNWFVSLFKVITTG                                                                                   | 34        |
| M4             | YMSILRCASGKISIAAPPYIF                                                                                       | 35        |

[0158]

|     |                                    |    |
|-----|------------------------------------|----|
| M5  | AGESFNFMVKLLYKHPILPCLKTLLSIRSSCSPR | 37 |
| VI2 | TNGSVLREFTLLEVVTRNTEL              | 85 |
| DD4 | RDSFGSPPPMAXG; X=任意氨基酸, 优选 Gly (G) | 80 |
| DD5 | GFWI                               | 81 |
| DD6 | RFKG                               | 82 |
| DD7 | KFYK                               | 83 |

[0159] 降解决定子的其他非限制性实例包括与DHFR(脱氢叶酸还原酶)、FKBP(FK506结合蛋白)、FRB(FKBP-雷帕霉素结合蛋白)和PDE5(5型磷酸二酯酶)相关的多肽。以及内质网相关降解(ERAD)途径的降解信号。

[0160] 在又一个优选的实施方式中,降解决定子是少于75个氨基酸的多肽,一旦该多肽与本发明的内含肽N片段融合,它就会诱导该内含肽N片段降解。

[0161] 在又一个优选的实施方式中,降解决定子是这样的多肽,当其与本发明的断裂内含肽N端片段或C端片段融合时,则导致所述片段的表达水平降低超过10%,或超过20%,或超过30%,或超过50%,或超过75%,或超过90%。重要的是,在本发明的片段中掺入降解决定子不会显著影响由本发明的断裂内含肽N端片段降解决定子和C端片段降解决定子之间的蛋白质反式剪接产生的重构蛋白质的产量。为了该优选实施方式的目的,表达水平如图18中所述进行测量,即在类似于图18中描述的条件下,将具有降解决定子的片段的表达水平与不具有降解决定子的片段的表达水平进行比较,前者需要比后者低至少10%,或至少20%,或至少30%,或至少50%,或至少75%,或至少90%。

[0162] 在又一个优选实施方式中,本发明的断裂内含肽N片段降解决定子的N内含肽和降解决定子的优选组合选自由以下组成的清单:

[0163] -CfaN或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaN或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4;或者-Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4。

[0164] 在图18A中示出了一些代表性的降解决定子在与分裂的N内含肽片段融合、特别是与CfaN内含肽融合时具有的效果。添加降解决定子(SopE、L2、L9、M4、V12)导致与降解决定子融合的含有N内含肽的融合蛋白的可检测表达水平显著降低。有趣的是,如实施例和图18、20和21中所述,包含一些优选的降解决定子(SopE、L2、L9、M4或V12)不会对剪接产物形成的产量产生负面影响。现有技术并未预料到这一结果,因为当降低蛋白质反式剪接反应的起始材料水平时(如通过添加降解决定子所实现的),人们预计蛋白质剪接产量会降低。

[0165] 在又一个优选实施方式中,断裂内含肽N片段和降解决定子的优选组合选自由以下组成的清单:CfaN内含肽与任何以下降解决定子DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7的组合。

[0166] 因此,我们观察到,当CfaN内含肽与上述任何降解决定子(尤其是以下降解决定子:DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7)组合时,检测到N端内含肽片段表达水平降低(图9、18A)。重要的是,这不会影响蛋白质反式剪接反应的产量(图9、18C、20或21)。这一结果是出乎意料的,根据现有技术,通常情况下,蛋白质反式剪接反应中涉及的两个内含肽片段之一的产量、表达或稳定性的降低会导致形成的剪接产物量的总体减少。

[0167] 我们已经观察到膜蛋白如ABCA4(图18、20和21)以及细胞溶质可溶性蛋白(如EGFP)的这种效果,这说明了效果的普遍性。在图9中,可以观察到向EGFPN-CfaN中添加降解决定子如何导致对应于该蛋白质的条带完全消失。然而,在添加CfaC-EGFPC片段(具有或不具有降解决定子)后,形成的全长EGFP产物的产量与不使用降解决定子的情况相同。该示例说明添加一个或甚至两个降解决定子(每个片段上一个)都不会对目标蛋白的产量产生负面影响。

[0168] 包含断裂内含肽N片段的复合物

[0169] 在另一方面,本发明涉及任何以下复合物:本发明的断裂内含肽N片段或本发明的断裂内含肽N片段降解决定子,下文称为本发明的第一复合物,其中这些复合物中的每个复合物都包括:

[0170] (i) 要重构的目标蛋白的N端片段,和

[0171] (ii) 断裂内含肽N片段或如以上部分中所定义的通过肽键、可选地通过接头与降解决定子直接连接的断裂内含肽N片段(本发明的断裂内含肽N片段降解决定子);

[0172] 其中复合物可选地包含(i)和(ii)之间的接头,并且

[0173] 其中

[0174] -目标蛋白的N端片段通过酰胺键与断裂内含肽N片段的N端连接,或者

[0175] -如果复合物包含接头,则目标蛋白的N端片段通过酰胺键与接头结合和/或接头通过酰胺键与断裂内含肽N片段的N端结合。

[0176] 可用于任何上述复合物的目标蛋白的说明性非限制性实例是上表1中所示的那些。其他目标蛋白可以选自抗体、抗体片段,包括Fc结构域、scFv、纳米抗体、双特异性抗体、蛋白质,并且优选地,大于25KDa、50KDa、100KDa的任何蛋白质。

[0177] 如已经指出的,可选地,目标蛋白和断裂内含肽N片段可以通过接头连接,因此接头位于目标蛋白和N内含肽之间。接头的性质将取决于目标蛋白的性质。在具体实施方式中,接头是肽。在具体实施方式中,接头是长度为1、2、3、4、5、10、20、50、100或更多个氨基酸残基的肽;具体可以是1-3个氨基酸残基。优选地,接头的N端与目标蛋白的C端连接并且接头的C端通过肽键与N-内含肽的N端连接。

[0178] 在另一个具体实施方式中,复合物在目标蛋白的N端片段和断裂内含肽N片段之间不包含接头。在该特定的实施方式中,目标蛋白通过酰胺键与断裂内含肽N片段的N端连接。

[0179] 在另一个具体实施方式中,如果复合物包含接头,则复合物是融合蛋白。术语“融合蛋白”是本领域熟知的,是指人工设计的单个多肽链,其包含来自不同来源的天然和/或人工的两个或更多个序列。根据定义,融合蛋白从未在自然界中被发现。

[0180] 断裂内含肽C片段

[0181] 在另一个方面,本发明涉及通过肽键与要重构的蛋白质的C端片段直接连接的断裂内含肽C片段(下文称为“本发明的断裂内含肽C片段”)。

[0182] 更优选地,本发明涉及通过肽键与降解决定子直接连接的断裂内含肽C片段(下文称为“本发明的断裂内含肽C片段降解决定子”),其中降解决定子在内含肽C片段和降解决定子之间有或没有接头的情况下通过内含肽的N端与内含肽C片段连接,并且其中断裂内含肽C片段的C端通过肽键与要重构的蛋白质的C端片段的N端直接连接。

[0183] 因此,本发明的断裂内含肽C片段降解决定子的构建体的架构从N端到C端将是:

[0184] (降解决定子)-(内含肽-C片段)-(要重构的蛋白质的C端部分)

[0185] 如果在降解决定子和内含肽C之间引入接头,则本发明的断裂内含肽C片段降解决定子的构建体的架构从N端到C端将是:

[0186] (降解决定子)-(接头)-(内含肽-C片段)-(要重构的蛋白质的C端部分)

[0187] 优选地,任何的本发明的断裂内含肽C片段或本发明的断裂内含肽C片段降解决定子的内含肽C选自下表4中列出的以下中的任意者:

[0188] 表4



| 名称                            | 序列                                                                                                                        | SEQ ID NO                             |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| <b>Cfa<sup>C</sup></b>        | MVKIISRKSLGTQNVYDIGVEKDHNFLLKNGLVASN                                                                                      | 28                                    |
| <b>Cfa<sup>Cmut</sup></b>     | MVKIISRKSLGTQNVYDIGVGEPHNFLLKNGLVASN                                                                                      | 29                                    |
| [0189] <b>Cat<sup>C</sup></b> | MFKLNTKNIKVLTSPSGFKSFSGIQKVYKPFYHHIIFDDG<br>SEIKCSDNHSF<br>GKDKIKASTIKVGDYLGQKKVLYNEIVEEGIYLYDLLNV<br>GEDNLYYTNGI<br>VSHN | 31                                    |
|                               | <b>Npu<sup>C</sup></b>                                                                                                    | MIKIATRKYLGKQNVYDIGVERDHNFALKNGFIASN  |
|                               | <b>Npu<sup>Cmut</sup></b>                                                                                                 | MIKIATRKYLGKQNVYDIGVGEPHNFALKNGFIASN  |
|                               | <b>Gp41C</b>                                                                                                              | MMLKKILKIEELDERELIDIEVSGNHLFYANDILTHN |
| <b>ConC</b>                   | MVKIISRQSLGKQNVYDIGVEKDHNFLLANGLIASN                                                                                      | 105                                   |

[0190] 其中优选地,内含肽C是:SEQ ID NO 28的CfaC内含肽或其任何变体,例如CfaCmut (SEQ ID NO 29)或ConC (SEQ ID NO 105);或SEQ ID NO 31的CatC内含肽或其任何变体;或NpuC内含肽 (SEQ ID NO 33)或其任何变体,例如NpuCmut (SEQ ID NO 36);或SEQ ID NO 104的GP41C内含肽或其任何变体;或上述定义的混杂性增加的任何变体。

[0191] 术语变体与针对断裂内含肽N片段的定义相同。内含肽C的变体包括没有N端甲硫氨酸残基的SEQ ID NO 28、29、31、33、36、104和105。

[0192] 在特定的实施方式中,混杂性增加的CfaC、NpuC或ConC变体在第21、22和23位包含氨基酸Gly、Glu和Pro,如Stevens et al. Proc. Natl. Acad. Sci. 2017所述。

[0193] 在特定的实施方式中,CfaC、NpuC、CatC或gp41c内含肽的功能等效变体的实例如下所示:

[0194] -CfaC功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0195] CfaC (SEQ ID NO 28) 序列,其中去除了Met1。

[0196] CfaC (SEQ ID NO 28) 序列,其中在Met1的N端包含额外的氨基酸的。例如,接头、降解决定子或用于检测的标签。

[0197] CfaC (SEQ ID NO 28) 序列,其中CfaC的任何残基突变为具有相似物理化学性质的残基,但应保留的以下残基除外:Asp17、His24、Asn36。

[0198] CfaC (SEQ ID NO 28) 序列,其中CfaC的任何残基突变为具有相似物理化学性质的残基,但应保留的以下残基除外:Asp17、Asp23、His24、Ser35、Asn36。

[0199] CfaC (SEQ ID NO 28) 序列,其中CfaC的任何残基突变为具有相似物理化学性质的残基,但应保留的以下残基除外:Asp17、Asp23、His24、Ser35、Asn36的。

[0200] CfaC (SEQ ID NO 28) 序列,其中保留残基Asp17、Asp23、His24、Ser35、Asn36,并且氨基酸Val12、Ile5、Ser6、Ser9、Lys22、Leu27、Leu32、Val33中的任何氨基酸发生突变。

[0201] CfaC (SEQ ID NO 28) 序列,其中残基Glu21Gly、Lys22Glu和Asp23Pro发生突变。该变体对应于CfaCmut内含肽 (SEQ ID NO 29)。

[0202] CfaC (SEQ ID NO 28) 序列,其中CfaC的任何残基突变为具有相似物理化学性质的残基,但残基Asp17、Gly21、Glu22、Pro23、His24、Asn36应位于在指定位置上的。

[0203] 的CfaC (SEQ ID NO 28) 序列,其中残基Asp17、Gly21、Glu22、Pro23、His24、Ser35、Asn36应位于指定位置并且以下氨基酸中的任何氨基酸发生突变:Val12、Ile5、Ser9、Leu27、Leu32、Val33。

[0204] CfaC (SEQ ID NO 28) 或CfaCmut (SEQ ID NO 29) 序列,其中引入了以下突变中的1

至5个(其中1和5在范围内):Val2Ile、Ile5Ala、Ser6Thr、Ser9Tyr、Thr12Lys、Leu27Ala、Leu32Phe、Val33Ile。

[0205] -NpuC功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0206] NpuC (SEQ ID NO 33) 序列,其中去除了Met1。

[0207] NpuC (SEQ ID NO 33) 序列,其中在Met1的N端包含额外的氨基酸。例如,接头、降解决定子或用于检测的标签。

[0208] NpuC (SEQ ID NO 33) 序列,其中NpuC的任何残基可突变为具有相似物理化学性质的残基,但应保留的残基Asp17、His24、Asn36除外。

[0209] NpuC (SEQ ID NO 33) 序列,其中NpuC的任何残基可突变为具有相似物理化学性质的残基,但需要保留残基Asp17、His24、Ser35、Asn36除外。

[0210] NpuC (SEQ ID NO 33) 序列,其中保留残基Asp17、His24、Ser35、Asn36并且氨基酸Val2、Ile5、Ser9、Leu27、Leu32、Val33中的任何氨基酸发生突变。

[0211] NpuC (SEQ ID NO 33) 序列,其中保留残基Asp17、His24、Ser35、Asn36并且掺入了以下突变Ile2Val,Ala5Ile,Tyr9Ser、Ala27Leu、Phe32Leu、Ile33Val中的任何突变。

[0212] NpuC (SEQ ID NO 33) 序列,其中残基Glu21Gly、Arg22Glu、Asp23Pro发生突变以增加Npu的混杂性。

[0213] -Gp41C功能等效变体可以选自由以下组成的以下列表中的任何变体:

[0214] Gp41C (SEQ ID NO 104) 序列,其中去除了Met1。

[0215] Gp41C (SEQ ID NO 104) 序列,其中在Met1的N端包含额外的氨基酸。例如,接头、降解决定子或用于检测的标签。

[0216] Gp41C (SEQ ID NO 104) 序列,其中Gp41C的任何残基可突变为具有相似物理化学性质的残基,但需要保留的残基His26、His36、Asn37除外。

[0217] 在具体实施方式中,内含肽C包含以下或由以下组成:分别与SEQ ID NO:28、SEQ ID NO:31、SEQ ID NO:33或SEQ ID NO:104在整个序列上具有至少90%序列同一性的SEQ ID NO:28、SEQ ID NO:31、SEQ ID NO:33或SEQ ID NO:104的氨基酸序列的变体。在具体实施方式中,SEQ ID NO:28、SEQ ID NO:31、SEQ ID NO:33或SEQ ID NO:104的内含肽C的变体分别与SEQ ID NO:28、SEQ ID NO:31、SEQ ID NO:33或SEQ ID NO:104在整个序列上具有至少91%、至少92%、至少93%、在至少94%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性。

[0218] 在另一个具体实施方式中,通过肽键与断裂内含肽C片段直接连接的降解决定子选自表3中列出的那些中的任意者:可用于该部分的目标蛋白的说明性非限制性实例是上表1中所示的那些。

[0219] 在又一个优选实施方式中,本发明的断裂内含肽C片段降解决定子的C内含肽和降解决定子的优选组合选自由以下组成的清单:

[0220] -CfaC或其任何功能等效变体(如CfaCmut)与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaC或其任何功能等效变体(如CfaCmut)与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7;或者

[0221] -Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4。

[0222] 在图18B中,可以观察到将降解决定子与C端构建体融合的效果。正如对于N端降解决定子所观察到的,降解决定子与C端构建体的融合降低了构建体的表达水平,但当使用优选的组合时,没有观察到对剪接产量的影响。以下降解决定子与CfaC配合得特别好:DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7。正如对N端片段所观察到的,将降解决定子掺入本发明的C端片段导致其表达降低(如通过WB检测的),但同样有趣的是,对PTS产量没有负面影响,即观察到形成了所需产物。已在若干种蛋白质中观察到该结果,包括这里示出的EGFP和ABCA4的示例。

[0223] 包含断裂内含肽C片段的复合物

[0224] 在另一方面,本发明涉及任何以下复合物:本发明的断裂内含肽C片段或本发明的断裂内含肽C片段降解决定子,下文称为本发明的第二复合物,其中这些复合物中的每个复合物都包括:

[0225] (i) 目标蛋白的C端片段,和

[0226] (ii) 断裂内含肽C片段或如以上部分中所定义的通过肽键、可选地通过接头与降解决定子直接连接的断裂内含肽C片段(本发明的断裂内含肽C片段降解决定子);

[0227] 其中复合物可选地包含(i)和(ii)之间的接头,并且

[0228] 其中

[0229] -目标蛋白的C端片段通过酰胺键与断裂内含肽C片段的C端连接,或者

[0230] -如果复合物包含接头,则目标蛋白的C端片段通过酰胺键与接头结合和/或接头通过酰胺键与断裂内含肽C片段的C端结合。

[0231] 可用于本发明的目标蛋白的说明性非限制性实例是上表1中列出的那些。其他目标蛋白的例子可以选自抗体、抗体片段,包括Fc结构域、scFv、纳米抗体、双特异性抗体、蛋白质,并且优选地,大于25KDa、50KDa、100KDa的任何蛋白质。

[0232] 先前已经结合本发明的第一复合物对术语“目标蛋白”和“接头”进行了定义。本发明的第一复合物的目标蛋白和接头的所有具体实施方式完全适用于本发明的第二复合物。

[0233] 在具体实施方式中,复合物在目标化合物和断裂内含肽C片段之间不包含接头。在该特定的实施方式中,目标化合物通过酰胺键与断裂内含肽C片段的C端连接。

[0234] 在具体实施方式中,复合物在目标化合物和断裂内含肽C片段之间包含接头。在该特定的实施方式中,取决于目标化合物和接头的化学性质,目标化合物可以通过任何合适的方式与接头结合。在该特定的实施方式中,接头通过酰胺键与断裂内含肽C片段的C端结合。在另一个具体实施方式中,目标化合物通过酰胺键与接头结合,在这种情况下接头可以通过任何合适的方式与断裂内含肽C片段的C端结合。在另一个具体实施方式中,目标化合物通过酰胺键与接头结合并且接头通过酰胺键与断裂内含肽C片段的C端结合。

[0235] 在具体实施方式中,如果复合物包含接头,则接头是肽接头。在该特定的实施方式中,复合物是融合蛋白。

[0236] 包含本发明复合物的组合物

[0237] 在另一个方面,本发明涉及一种组合物,以下称为本发明的第一组合物,其包含本发明的第一复合物和/或第二复合物。

[0238] 术语“组合物”旨在涵盖包含特定组分的产物,以及直接或间接由特定量的特定组分组合而成的任何产物。组合物的组分可以一起包装在单一制剂中或分别包装在不同制剂中;因此,在实施方式中,本发明的第一复合物与本发明的第二复合物一起包装在单一制剂中。在另一个实施方式中,本发明的第一复合物和本发明的第二复合物是分开包装的。

[0239] 在特别优选的实施方式中,第一复合物和第二多复合物分别包含相同蛋白质的N端片段和C端片段,使得当根据本发明的方法组合两种复合物时,蛋白质的所述N端片段与所述蛋白质的所述C端片段连接,从而产生整个蛋白质。

[0240] 本发明的多核苷酸、载体和宿主细胞

[0241] 在另一方面,本发明涉及编码本发明的第一复合物或第二复合物的多核苷酸。

[0242] 优选地,在优选的实施方式中,本发明涉及两种多核苷酸,其中这些多核苷酸中的一种编码本发明的第一复合物(下文称为本发明的第一多核苷酸),和另一种编码本发明的第二复合物(在下文中称为本发明的第二多核苷酸),其中本发明的第一和第二多核苷酸分别编码同一蛋白质的N端片段和C端片段,使得当两种多核苷酸都翻译成它们各自的蛋白质复合物时和/或当根据本发明的方法组合时,蛋白质的N端片段与蛋白质的C端片段连接,从而产生要重构的完整蛋白质。值得注意的是,本发明的第一和第二多核苷酸各自优选地编码同一内含肽的断裂内含肽,也就是说,N内含肽和C内含肽是同源对(cognate pairs)(参见Shah et al. Journal of the American Chemical Society 2012<https://doi.org/10.1021/ja303226x>)。内含肽同源对的例子包括CfaN/CfaC(或其任何变体,包括CfaCmut)、NpuN/NpuC(或其任何变体)、CatN/CatC(或其任何变体)、Gp41N/Gp41C(或其任何变体)。然而,无论两种多核苷酸是否编码属于同一内含肽的断裂内含肽这一事实,一旦翻译成蛋白质,每个断裂内含肽的N端序列和C端序列必须变成可非共价重新缔合或重构为对反式剪接反应起作用的内含肽的单独片段。

[0243] 在优选的实施方式中,本发明涉及上述所指的两种多核苷酸,其中这些多核苷酸中的一种编码本发明的断裂内含肽N片段降解决定子(下文称为本发明的编码降解决定子的第一多核苷酸),另一种编码本发明的断裂内含肽C片段降解决定子(下文称为本发明的编码降解决定子的第二多核苷酸),其中本发明的编码降解决定子的第一多核苷酸和本发明的编码降解决定子的第二多核苷酸分别编码同一蛋白质的N端片段和C端片段,使得当两种多核苷酸都翻译成它们各自的蛋白质复合物时复合物并根据本发明的方法组合时,蛋白质的N端片段与蛋白质的C端片段连接,从而产生完整蛋白质。与前述实施方式一样,值得注意的是,本发明的编码降解决定子的第一多核苷酸和本发明的编码降解决定子的第二多核苷酸各自优选编码同一内含肽的断裂内含肽。无论如何,如上所反映的,如本文所用,各多核苷酸必须编码断裂内含肽,使得一旦翻译成蛋白质,N端序列和C端序列会变成可非共价重新缔合或重构为对反式剪接反应起作用的内含肽的单独的片段。

[0244] 在又一个优选实施方式中,本发明涉及使用正交断裂内含肽对的三段式连接策略。在该方法中,存在三种多核苷酸,其中第一多核苷酸编码 $\text{POI}^{\text{N}}$ -CfaN(其中 $\text{POI}^{\text{N}}$ 理解为“目标蛋白”的N片段);其中第二多核苷酸编码CfaC- $\text{POI}^{\text{M}}$ -CatN(其中在这种情况下, $\text{POI}^{\text{M}}$ 是目标蛋白的中间片段);以及其中第三多核苷酸编码CatC- $\text{POI}^{\text{C}}$ (其中 $\text{POI}^{\text{C}}$ 理解为目标蛋白的C片

段)。可选择地,可以交换Cfa和Cat内含肽的位置,以生成具有以下架构的构建体:POI<sup>N</sup>-CatN、CatC-POI<sup>M</sup>-CfaN和CfaC-POI<sup>C</sup>。CfaN是CfaN内含肽片段SEQ ID NO 27及其任何变体。CatN是CatN内含肽片段SEQ ID NO 30及其任何变体。CfaC是CfaC内含肽片段SEQ ID NO 28及其任何变体,包括SEQ ID NO 29。CatC是CatC内含肽片段SEQ ID NO 31及其任何变体。

[0245] 在此要注意的是,对于那些涉及两个多核苷酸的实施方式,第一多核苷酸(或特别是本发明的编码降解决定子的第一多核苷酸)可以是任何本发明的断裂内含肽N片段或任何本发明的断裂内含肽-N降解决定子片段。特别地,本发明的第一多核苷酸(或特别是本发明的编码降解决定子的第一多核苷酸)可以选自由以下组成的清单中的任意者:SEQ ID NO 1、3、5、8、10、12、14、17、19、21、23、24、25、66、68、70、72、74、76和78。更优选地,本发明的编码降解决定子的第一多核苷酸编码内含肽和降解决定子的任何以下特定组合:

[0246] -CfaN或其任何功能等效变体(如ConN)与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaN或其任何功能等效变体(如ConN)与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4;或者

[0247] -Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4。

[0248] 在此还要注意的,对于那些涉及两个多核苷酸的实施方式,第二多核苷酸(或特别是本发明的编码降解决定子的第二多核苷酸)可以是本发明的任何断裂内含肽C片段或本发明的任何断裂内含肽-C降解决定子片段。特别地,本发明的第二多核苷酸(或特别是本发明的编码降解决定子的第二多核苷酸)可以选自由以下组成的清单中的任意者:SEQ ID NO 2、4、6、9、11、13、15、18、20、22、26、67、69、71、73、75、77和79。更优选地,本发明的编码降解决定子的第二多核苷酸编码内含肽和降解决定子的任何以下特定组合:

[0249] -CfaC或其任何功能等效变体(如CfaCmut或ConC)与以下任何降解决定子组合:CL1、Deg1、PESTt、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaC或其任何功能等效变体(如CfaCmut)与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7;或者

[0250] -Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4。

[0251] 在优选的实施方式中,本发明的编码降解决定子的第一多核苷酸和本发明的编码降解决定子的第二多核苷酸分别编码ABCA4蛋白的N端片段和C端片段,使得当这两种多核苷酸被翻译成它们各自的蛋白复合物并根据本发明的方法组合时,ABCA4蛋白的N端片段与ABCA4蛋白的C端片段连接,从而产生完整的ABCA4蛋白。更优选地,本发明的编码降解决定子的第一多核苷酸编码ABCA4蛋白的N端片段的第1-1149、1-1139、1-1178或1-1187位以及

内含肽和降解决定子的任何以下特定组合：

[0252] -CfaN或其任何功能等效变体(如ConN)与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaN或其任何功能等效变体(如ConN)与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4;以及

[0253] 本发明的编码降解决定子的第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273、1140-2273、1179-2273或1188-2273位以及内含肽和降解决定子的任何以下特定组合：

[0254] -CfaC或其任何功能等效变体(如CfaCmut或ConC)与以下任何降解决定子组合:CL1、Deg1、PESt、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6和DD7。优选地,CfaC或其任何功能等效变体(如CfaCmut)与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12、DD4、DD5、DD6或DD7。

[0255] 值得注意的是,由于ABCA4蛋白的N端片段必须与ABCA4蛋白的C端片段连接,从而产生完整的ABCA4蛋白,当本发明的编码降解决定子的第一多核苷酸编码第1-1149位时,则本发明的编码降解决定子的第二多核苷酸编码ABCA4蛋白的C端片段的第1150-2273位。其余位置也一样。

[0256] 使用上述优选的组合,可以观察到,可以获得目标蛋白(在这些实施例中为ABCA4)的有效重构,同时显著降低起始N端片段和C端片段的水平。在构建体之一或这两个构建体中包含至少一个降解决定子,由于降解加速,导致N端片段和/或C端片段的表达减少。根据现有技术水平,预计起始材料水平的这种降低将导致剪接产物的减少。然而,我们观察到相反的表现,全长剪接产物的产量不受影响,并且在某些情况下甚至可以提高。此外,我们观察到,通过使用这里描述的方法重构蛋白质,我们可以生成功能性蛋白质,如使用ATP酶活性测定所测定的。我们还观察到目标蛋白在小鼠视网膜体内的有效重构。

[0257] 在另一个优选的实施方式中,本发明的编码降解决定子的第一多核苷酸编码ABCA4蛋白的N端片段的第1-1095或1-1185位以及内含肽和降解决定子的任何以下特定组合：

[0258] -Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41N或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4;以及

[0259] 本发明的编码降解决定子的第二多核苷酸编码ABCA4蛋白的C端片段的第1096-2273或1186-2273位以及内含肽和降解决定子的任何以下特定组合：

[0260] -Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、PEST、DD1、DD2、DD3、M1、M2、SopE、SopE-1-78、SopE-15-78、SopE-15-50、L2、L6、L9、L10、L11、L12、L15、L16、M3、M4、M5、V12、DD4、DD5、DD6或DD7。优选地,Gp41C或其任何功能等效变体与以下任何降解决定子组合:CL1、Deg1、DD1、DD2、DD3、SopE、L2、L9、M4、V12或DD4。

[0261] 与前面的情况一样,值得注意的是,由于ABCA4蛋白的N端片段必须与ABCA4蛋白的

C端片段连接,从而产生完整的ABCA4蛋白,当本发明的编码降解决定子的第一多核苷酸编码第1-1095位时,则本发明的编码降解决定子的第二多核苷酸编码ABCA4蛋白的C端片段的第1096-2273位。其余位置也一样。

[0262] 编码上述序列的核苷酸序列(分别对于本发明的第一和第二多核苷酸或编码本发明的降解决定子的第一和第二多核苷酸)的其他优选组合选自以下任何对:1和2;3和4;5和6;66和67;68和69;70和71;72和73;74和75;76和77;以及78和79。

[0263] 应注意,术语“本发明的第一和第二多核苷酸”尤其涵盖“编码本发明的降解决定子的第一和第二多核苷酸”,因此在下文中因此,我们只将本发明的第一和第二多核苷酸作为已经涵盖上述所有多核苷酸替代物的术语。

[0264] 优选地,本发明涉及一种组合物,在下文中称为本发明的第二组合物,其包含本发明的第一和/或第二多核苷酸或编码本发明的降解决定子的第一和/或第二多核苷酸,和/或单独或联合地包含使用正交分裂内含肽对的三段连接体系的POI-内含肽片段中的每个。在此特定上下文中,术语“组合物”旨在涵盖含有特定组分的产物。组合物的组分可以一起包在单一制剂中或分别包在不同制剂中。因此,在实施方式中,本发明的第一多核苷酸与本发明的第二多核苷酸一起包装在单一制剂中。在另一个实施方式中,本发明的第一多核苷酸和本发明的第二多核苷酸是分开包装的。更优选地,本发明的第一第二多核苷酸分别编码要重构的蛋白质的N端片段和C端片段,使得当两种复合物根据本发明的方法组合时,蛋白质的N端片段与蛋白质的C端片段连接,从而产生整个要重构的蛋白质。

[0265] 可以发现本发明的所有上述多核苷酸本身是分离的,或形成允许所述多核苷酸在合适的宿主细胞中递送和/或增殖的载体的一部分。因此,在另一个方面,本发明涉及一种载体,该载体包含如上所述的本发明的任何上述多核苷酸。

[0266] 适合插入所述多核苷酸的载体是:衍生自原核生物中的表达载体的载体,例如pUC18、pUC19、Bluescript及其衍生物、mp18、mp19、pBR322、pMB9、ColE1、pCR1、RP4、噬菌体和“穿梭”载体(例如pSA3和pAT28);酵母中的表达载体,例如2微米质粒、整合质粒、YEP载体、着丝粒质粒等类型的载体;昆虫细胞中的表达载体,例如pAC系列和pVL的载体;植物中的表达载体,如pIBI、pEarleyGate、pAVA、pCAMBIA、pGSA、pGWB、pMDC、pMY、pORE系列等;以及真核细胞中的表达载体,包括适用于使用任何市售杆状病毒系统转染昆虫细胞的杆状病毒。用于真核细胞的载体优选包括病毒载体(腺病毒、腺相关病毒(AAV)、与腺病毒相关的病毒(例如逆转录病毒,特别是慢病毒))以及非病毒载体,例如pSilencer4.1-CMV(Ambion), pcDNA3、pcDNA3.1/hyg、pHMCV/Zeo、pCR3.1、pEFI/His、pIND/GS、pRc/HCMV2、pSV40/Zeo2、pTRACER-HCMV、pUB6/V5-His、pVAX1、pZeoSV2、pCI、pSVL和PKSV-10、pBPV-1、pML2d和pTDT1。优选地,载体是腺相关病毒(AAV)。优选地,载体是血清型1、2、3、4、5、6、7、8或9的AAV。二聚型或自身互补AAV载体(scAAV)也可用于插入所述多核苷酸。

[0267] 因此,本发明优选地涉及开发AAV作为基因治疗载体。优选地,这些载体通过从载体的DNA中除去rep和cap而消除了它们的整合能力。所需基因(多核苷酸)与驱动基因转录的启动子一起插入在末端反向重复(ITR)之间,该末端反向重复(ITR)有助于在单链载体DNA被宿主细胞DNA聚合酶复合物转化为双链DNA之后,在细胞核中形成串联体。基于AAV的基因治疗载体在宿主细胞核中形成游离型串联体。在非分裂细胞中,这些串联体在宿主细胞的生命周期内保持完整。在分裂细胞中,AAV DNA通过细胞分裂而丢失,因为游离型DNA不

与宿主细胞DNA一起复制。AAV DNA随机整合到宿主基因组中是可检测的,但发生的频率非常低。

[0268] 所需基因(多核苷酸)可以与在要表达构建体的预期宿主细胞中起作用的调节元件组合。本领域普通技术人员可以选择调节元件用于合适的宿主细胞,例如哺乳动物或人宿主细胞。调节元件包括例如启动子、转录终止序列、翻译终止序列、增强子、信号肽和聚腺苷酸化元件。本发明的多核苷酸可以与启动子序列可操作地连接。考虑用于本发明的启动子包括但不限于:天然基因启动子、巨细胞病毒(CMV)启动子(KF853603.1, bp 149-735)、嵌合CMV/鸡 $\beta$ -肌动蛋白启动子(CBA)和截短形式的CBA(smCBA)启动子(US8298818和AAVGC 1处理的产后鸟苷酸环化酶-1敲除小鼠视网膜的视锥中的光驱动锥阻素易位(Light-Driven Cone Arrestin Translocation in Cones of Postnatal Guanylate Cyclase-1 Knockout Mouse Retina Treated with AAVGC 1))、视紫红质启动子(NG 009115, bp 4205-5010)、感光器间类视黄醇结合蛋白肽(IRBP)启动子(NG\_029718.1, bp 4777-5011)、卵黄样黄斑营养不良2(VMD2)启动子(NG 009033.1, bp 4870-5470)、PR特异性人G蛋白偶联受体激酶1(hGRK1; AY327580.1, bp 1793-2087或bp 1793-1991)(Haire等人, 2006; 美国专利号8,298,818)、近端鼠视紫红质启动子(MOPS)。然而,可以使用本领域已知的任何合适的启动子。在具体的实施方式中,启动子是CMV或hGRK1启动子。在一个实施方式中,启动子是在一种或一组组织中显示选择性活性,但在其他组织中活性较低或无活性的组织特异性启动子。在一个实施方式中,启动子是感光器特异性启动子。在其他实施方式中,启动子是视锥细胞特异性和/或视杆细胞特异性启动子。

[0269] 优选的启动子是CMV、GRK1、CBA和IRBP启动子。还优选的启动子是使来自各种启动子的调节元件组合而成的杂合启动子(例如使来自CMV启动子的增强子、CBA启动子和Sv40嵌合内含子组合而成的嵌合CBA启动子,本文称为CBA杂合启动子)。

[0270] AAV还表现出非常低的免疫原性,似乎仅限于产生中和抗体,而它们不会诱导明确定义的细胞毒性反应。这一特征以及感染静止期细胞的能力表明它们在作为用于人类基因治疗的载体具有优于腺病毒的优势。

[0271] AAV基因组、转录组和蛋白质组: AAV基因组由正义或反义的单链脱氧核糖核酸(ssDNA)构成,其长度约为4.7千碱基。基因组包括位于DNA链两端的末端反向重复(ITR)和两个开放阅读框(ORF): rep和cap。前者由编码AAV生命周期所需的Rep蛋白的四个重叠基因组成,后者包含衣壳蛋白VP1、VP2和VP3的重叠核苷酸序列,衣壳蛋白VP1、VP2和VP3相互作用形成二十面体对称的衣壳。

[0272] 每个末端反向重复(ITR)序列包含145个碱基。它们之所以如此命名是因为它们的对称性,这被证明是有效扩增AAV基因组所必需的。这些序列的另一个特性是它们形成发夹结构的能力,这有助于所谓的自引发,该自引发使得第二条DNA链不依赖于引发酶而进行合成。还表明ITR是将AAV DNA整合到宿主细胞基因组(人类第19条染色体)并从中拯救、以及AAV DNA的有效衣壳化连同产生完全组装的脱氧核糖核酸酶抗性AAV颗粒所必需的。

[0273] 在基因治疗方面, ITR似乎是邻接于治疗基因的以顺式方式需要的唯一序列: 结构(cap)基因和包装(rep)基因可以反式递送。在这种假设下,建立了许多有效产生含有报告基因或治疗基因的重组AAV(rAAV)载体的方法。然而,也有发表称ITR并不是用于有效复制和衣壳化的以顺式方式需要的唯一元件。一些研究小组已经在rep基因的编码序列中确定



了被称为顺式作用Rep依赖元件(CARE)的序列。当以顺式方式存在时,显示出CARE增加了复制和衣壳化。

[0274] 截至2006年,已经描述了11种AAV血清型。所有已知的血清型都可以感染来自多种不同组织类型的细胞。组织特异性由衣壳血清型决定,对AAV载体进行假型化(pseudotyping)以改变其嗜性(tropism)范围可能对其在治疗中的使用很重要。在本发明中,AAV血清型1、2、3、4、5、6、7、8或9的ITR是优选的。

[0275] 血清型2(AAV2)迄今为止受到了最广泛的检验。AAV2呈现出对骨骼肌、神经元、血管平滑肌细胞和肝细胞的天然嗜性。

[0276] 载体还可以包含报告基因或标记基因,所述报告基因或标记基因使得能够识别那些在与载体接触后掺入了载体的细胞。

[0277] 本发明上下文中有用的报告基因包括lacZ、萤光素酶、胸苷激酶、GFP等。本发明上下文中有用的标记基因包括:例如,新霉素抗性基因,赋予对氨基糖苷G418的抗性;潮霉素磷酸转移酶基因,赋予对潮霉素的抗性;ODC基因,赋予对鸟氨酸脱羧酶抑制剂(2-(二氟甲基)-DL-鸟氨酸(DFMO))的抗性;二氢叶酸还原酶基因,赋予对甲氨蝶呤的抗性;嘌呤霉素-N-乙酰转移酶基因,赋予对嘌呤霉素的抗性;ble基因,赋予对博来霉素的抗性;腺苷脱氨酶基因,赋予对9- $\beta$ -D-木呋喃糖腺嘌呤的抗性;胞嘧啶脱氨酶基因,允许细胞在N-(膦乙酰基)-L-天冬氨酸的存在下生长;胸苷激酶,允许细胞在氨基蝶呤存在下生长;黄嘌呤-鸟嘌呤磷酸核糖基转移酶基因,允许细胞在存在黄嘌呤和不存在鸟嘌呤的情况下生长;大肠杆菌的trpB基因,允许细胞在存在吡啶而不是色氨酸的情况下生长;大肠杆菌的hisD基因,允许细胞使用组氨酸代替组氨酸。选择基因被掺入到质粒中,该质粒可以另外包含:适于在真核细胞中表达所述基因的启动子(例如,CMV或SV40启动子)、优化的翻译起始位点(例如,遵循所谓的Kozak规则的位点或IRES)、聚腺苷酸化位点(例如SV40聚腺苷酸化)或磷酸甘油酸激酶位点、内含子(例如 $\beta$ -球蛋白基因内含子)。可选择地,可以在同一载体中同时使用报告基因和标记基因的组合。

[0278] 另一方面,如本领域技术人员所知,载体的选择将取决于随后载体将被导入的宿主细胞。例如,导入所述多核苷酸的载体也可以是酵母人工染色体(YAC)、细菌人工染色体(BAC)或PI衍生的人工染色体(PAC)。YAC、BAC和PAC的特性是本领域技术人员已知的。例如,Giraldo和Montoliu(Giraldo,P.&Montoliu L.,2001Size matters:use of YACs,BACs and PACs in transgenic animals,Transgenic Research 10(2):83-110)已提供了关于所述载体类型的详细信息。本发明的载体可以通过本领域技术人员已知的常规方法获得(Sambrook J.et al.,2000"Molecular cloning,a Laboratory Manual",3rd ed.,Cold Spring Harbor Laboratory Press,N.Y.Vol 1-3)。

[0279] 本发明的多核苷酸可以作为裸DNA质粒体内导入宿主细胞,也可以通过本领域已知的方法使用载体导入宿主细胞,所述方法包括但不限于转染、电穿孔(例如经皮电穿孔)、显微注射、转导、细胞融合、DEAE葡聚糖、磷酸钙沉淀、使用基因枪、或使用DNA载体转运蛋白。配制裸DNA并将其施用于哺乳动物肌肉组织的方法也是已知的。参见Feigner P等人,US5,580,859和US5,589,466。其他分子也可用于促进核酸的体内转染,例如阳离子寡肽、衍生自DNA结合蛋白的肽、或阳离子聚合物。参见Bazile D等人的WO 1995021931和Byk G等人的WO1996025508。

[0280] 可用于将多核苷酸导入宿主细胞的另一种众所周知的方法是粒子轰击(又名生物弹道转化(biolistic transformation))。生物弹道转化通常以几种方式之一完成。一种常见的方法涉及在细胞中推入惰性或生物活性颗粒。参见Sanford J等人,US4,945,050、US5,036,006和US5,100,792。

[0281] 可选择地,可以通过脂质转染将载体进行体内导入。使用阳离子脂质可以促进带负电的核酸的包封,也可以促进与带负电的细胞膜的融合。参见Feigner P, Ringold G, Science 1989;337:387-388。已经描述了用于转移核酸的特别有用的脂质化合物和组合物。参见Feigner P等人的US5,459,127、Behr J等人的W01995018863和Byk G的W01996017823。

[0282] 最后,特别优选的是,可以通过病毒递送系统将载体进行体内导入,所述病毒递送系统包括但不限于腺病毒载体、腺相关病毒(AAV)载体、假型AAV载体、疱疹病毒载体、逆转录病毒载体、慢病毒载体、杆状病毒载体。假型AAV载体是那些在一种AAV血清型的衣壳中包含另一种AAV血清型的基因组的载体;例如,AAV2/8载体包含AAV8衣壳和AAV2基因组(Auricchio et al. (2001) Hum. Mol. Genet. 10 (26) :3075-81)。这样的载体也称为嵌合载体。递送系统的其他实例包括离体递送系统,其包括但不限于DNA转染方法,例如电穿孔、DNA生物弹道技术、脂质介导的转染、压缩DNA介导的转染。

[0283] AAV载体的构建可以按照本领域技术人员已知的程序和技术来进行。一些科学和专利出版物中对腺相关病毒载体构建的理论和实践以及在治疗中的应用进行了说明(以下参考书目通过引用并入本文:Flotte TR. Adeno-associated virus-based gene therapy for inherited disorders. Pediatr Res. 2005 Dec; 58 (6) :1143-7; Goncalves MA. Adeno-associated virus: from defective virus to effective vector, Virol J. 2005 May 6; 2:43; Surace EM, Auricchio A. Adeno-associated viral vectors for retinal gene transfer. Prog Retin Eye Res. 2003 Nov; 22 (6) :705-19; Mandel RJ, Manfredsson FP, Foust KD, Rising A, Reimsnider S, Nash K, Burger C. Recombinant adeno-associated viral vectors as therapeutic agents to treat neurological disorders. Mol Ther. 2006 Mar; 13 (3) :463-83)。

[0284] 含有AAV载体的药物组合物的合适的施用形式包括但不限于可注射溶液或混悬液、眼用洗剂和眼用软膏。因此,另一方面,本发明涉及包含本发明的多核苷酸或载体的宿主细胞。可以通过本领域技术人员已知的常规方法获得细胞(参见例如在上文中引用的Sambrook等人)。

[0285] 如本文所用,术语“宿主细胞”是指已导入本发明的核酸例如根据本发明的多核苷酸或载体并且能够表达本发明的断裂内含肽N片段的细胞或包含所述断裂内含肽N片段的融合蛋白的细胞。术语“宿主细胞”和“重组宿主细胞”在本文中可互换使用。应当理解,这些术语不仅指特定的对象细胞,而且指这种细胞的后代或潜在后代。由于突变或环境影响,在连续的新一代中可能出现一些修饰,因此,这些后代可能实际上与亲代细胞不相同,但也仍然包含在本文中使用的该术语的范围内。该术语包括任何可通过导入异源DNA进行修饰的可培养的细胞。优选地,宿主细胞是本发明的多核苷酸可以在其中稳定表达、翻译后修饰、定位于合适的亚细胞区室并使其接合合适的转录机制的细胞。选择合适的宿主细胞也会受到检测信号选择的影响。例如,如上所述,报告构建体可在响应转录调节蛋白而激活或抑制

基因转录时提供可选择或可筛选的性状;为了实现最佳选择或筛选,将考虑宿主细胞表型。本发明的宿主细胞包括原核细胞和真核细胞。原核生物包括革兰氏阴性或革兰氏阳性生物体,例如大肠杆菌或杆菌(Bacilli)。应当理解,将优选使用原核细胞来增殖本发明的包含转录控制序列的多核苷酸或载体。用于转化的合适的原核宿主细胞包括例如大肠杆菌、枯草芽孢杆菌、鼠伤寒沙门氏菌和假单胞菌属、链霉菌属和葡萄球菌属中的各种其他物种。真核细胞包括但不限于酵母细胞、植物细胞、真菌细胞、昆虫细胞(例如杆状病毒)、哺乳动物细胞和寄生生物(例如锥虫)的细胞。如本文所用,酵母不仅包括严格分类学意义上的酵母,即单细胞生物,还包括丝状真菌的酵母样多细胞真菌。示例性的物种包括乳酸克鲁维酵母(*Kluyverei lactis*)、粟酒裂殖酵母(*Schizosaccharomyces pombe*)和玉米黑穗菌(*Ustilago maydis*),优选的是酿酒酵母。可用于实施本发明的其他酵母是粗糙脉孢菌(*Neurospora crassa*)、黑曲霉(*Aspergillus niger*)、构巢曲霉(*Aspergillus nidulans*)、毕赤酵母(*Pichia pastoris*)、热带念珠菌(*Candida tropicalis*)和多形汉逊酵母(*Hansenula polymorpha*)。哺乳动物宿主细胞培养体系包括已建立的细胞系,例如COS细胞、L细胞、3T3细胞、中国仓鼠卵巢(CHO)细胞、胚胎干细胞,优选BHK、HeK或HeLa细胞。真核细胞优选用于重组基因表达。

[0286] 在优选的实施方式中,本发明的第二组合物用于治疗,更具体地,用于表1中确定的任何疾病,这取决于组合物中编码的基因类型(疾病和基因之间的相关性在表1中清楚地指出,因此对于本领域技术人员来说识别正确的组合是显而易见的)。

[0287] 在细胞中表达编码目标蛋白的基因的方法

[0288] 在另一个方面,本发明涉及一种在细胞中表达目标基因的体外或体内方法,下文称为表达目标基因的第一方法,该第一方法包括:

[0289] (i) 使细胞与以下接触:

[0290] (a) 本发明的第一多核苷酸或本发明的编码降解决定子的第一多核苷酸,和

[0291] (b) 本发明的第二多核苷酸或本发明的编码降解决定子的第二多核苷酸,

[0292] (ii) 使第一多核苷酸和第二多核苷酸表达,以产生第一融合蛋白和第二融合蛋白,以及

[0293] (iii) 使第一蛋白和第二蛋白接触,使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体,并且内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

[0294] 在具体的实施方式中,第一多核苷酸是编码降解决定子的第一多核苷酸,第二多核苷酸是编码降解决定子的第二多核苷酸,其中,优选地,目标蛋白大于25KDa、大于50KDa或大于100KDa,从而在将第一目标多肽的C端与第二目标多肽的N端共价连接后,获得整个蛋白质。

[0295] 细胞与本发明的任何第一多核苷酸和/或第二多核苷酸的接触可以在体外或体内通过使得目标多核苷酸导入细胞中的任何合适的方法进行,例如转染、电穿孔、显微注射、转导、脂质转染、细胞融合、DEAE葡聚糖、磷酸钙沉淀、使用基因枪或使用DNA载体转运蛋白。优选地,载体是腺相关病毒(AAV)。

[0296] 在本发明的优选实施方式中,涉及一种用于在细胞中表达编码目标蛋白的基因的方法,下文称为第一表达目标基因的方法,该方法包括:

[0297] (i) 使细胞与以下接触:

[0298] (a) 第一AAV, 该第一AAV包含本发明的第一多核苷酸或本发明的编码降解决定子的第一多核苷酸, 和

[0299] (b) 第二AAV, 该第二AAV包含本发明的第二个多核苷酸或本发明的编码降解决定子的第二多核苷酸,

[0300] (ii) 使第一多核苷酸和第二多核苷酸表达, 以产生第一融合蛋白和第二融合蛋白, 以及

[0301] (iii) 使第一融合蛋白和第二融合蛋白质接触, 使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体, 并且内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

[0302] 其中优选地, 第一多核苷酸是编码降解决定子的第一多核苷酸, 第二多核苷酸是编码降解决定子的第二多核苷酸, 并且其中, 更优选地, 目标蛋白大于25KDa、大于50KDa或大于100KDa, 从而在将第一目标多肽的C端与第二目标多肽的N端共价连接后, 获得整个蛋白质。

[0303] 从这个意义上说, 如实施例所示, 降解决定子的存在将导致起始材料(即本发明的断裂内含肽N和/或C端片段降解决定子)的快速降解。选择的降解决定子具有与蛋白质剪接相容的降解动力学, 使得在稳定状态下, 相对于没有降解决定子的情况下所观察到的, 起始材料的量有所减少。但是, 相对于没有降解决定子的情况下所观察到的, 剪接产物的水平得以维持或有所增加。

[0304] 在本发明的表达目标基因的方法中, 考虑使细胞与第一多核苷酸和第二多核苷酸同时接触, 或以任何顺序依次与第一多核苷酸和第二多核苷酸接触, 即可以使细胞首先接触第一多核苷酸, 然后再接触第二多核苷酸, 或者首先接触第二多核苷酸, 然后再接触第一多核苷酸。这同样适用于编码所述多核苷酸的载体。

[0305] 任何以前定义为宿主细胞的细胞都可以用于这些方法。

[0306] \*\*\*

[0307] 本发明将通过以下实施例进行描述, 这些实施例被认为仅是说明性的, 而不是对本发明范围的限制。

[0308] 实施例

[0309] 在下表中, 我们建立了命名法来表示通过将本文档中已经列出的序列附加在一起而形成的序列。在下表中, 通过从N端到C端列出构成它们的以SEQ ID NO识别的序列来表示此类序列。例如, 对于SEQ ID NO 106的氨基酸1至1149与SEQ ID NO 27(CfaN) 直接连接, 而SEQ ID NO 27(CfaN) 又与SEQ ID NO103(3FT) 直接连接的序列, 使用的命名法将是: SEQ ID NO 106(1至1149) -SEQ ID NO 27-SEQ ID NO103。这个具体例子应该被解释为这样的序列: 从N端开始, SEQ ID NO 106的氨基酸1至1149, 紧随其后的是通过肽键直接连接的对应于SEQ ID NO 27的多肽, 其后又紧接着的是也通过肽键连接的对应于SEQ ID NO 103的多肽。因此, 序列从N端到C端将具有以下架构:

[0310] [SEQ ID NO 106(残基1至1149)]-[SEQ ID NO 27]-[SEQ ID NO 103]

[0311] 其中括号“[]”中的序列代表该序列中的所有氨基酸, “-”代表连接括号中两个序列的肽键。某个序列的残基x至y, 是指从位置x到位置y的所有氨基酸残基, 包括位置x和位

置y处的氨基酸残基。例如,SEQ ID NO 106 (残基1至1149)是指包含来自SEQ ID NO 106的残基1至残基1149 (包括残基1和残基1149)的序列。

[0312] 表5. 整个实施例中使用的序列的列表:

[0313]

| 构建体   | 序列                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | SEQ NO |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| ABCA4 | M <sup>1</sup> GFVRQIQLLWKNWTLRKRQKIRFVVELVWPLSLFLV<br>LIWLRNANPLYSHHECHFPNKAMPSAGMLPWLQGIFCNV<br>NNPCFQSPTPGESPGIVSNYNNSILARVYRDFQELLMNA<br>PESQHLGRIWTELHILSQFMDTLRTHPERIAGRIRIR<br>ILKDEETLTFLFIKNIGLSDSVVYLLINSQVRPEQFAHG<br>VPDLALKDIACSEALLERFIIFSQRRGAKTVRYALCSLS<br>QGTQWIEDTLYANVDFKLFRLPTLLDSRSQGINLRS<br>WGGILSDMSPRIQEFHRPSMQDLLWVTRPLMQNGGPET<br>FTKLMGILSDLLCGYPEGGGSRVLSFNWYEDNNYKAFLG<br>IDSTRKDPIYSYDRRTTSFCNALIQSLESNPLTKIAWRA<br>AKPLLMGKILYTPDSPAARRILKNANSTFEELEHVRKLV | 106    |

[0314]

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     | KAWEEVGPQIWIYFFDNSTQNMNIRDITLGNPTVKDFLNRQ<br>LGEEGITAEAILNFLYKGPRESQADDMANFDWRDIFNIT<br>DRTLRLVNQYLECLVLDKFESYNDETQLTQRALSLLEEN<br>MFWAGVVFDPMPWTSSLPPHVKYKIRMDIDVVEKTNKI<br>KDRYWDSGPRADPVEDFRYIWGGFAYLQDMVEQGITSQ<br>VQAEAPVGIYLQQMPYPCFVDDSFMIILNRCFPIFMVLA<br>WIYSVSMTVKSIVLEKELRLKETLKNQGVSNVAVIWTWF<br>LDSFSIMSMSIFLLTIFIMHGRILHYSDPFILFLFLAF<br>STATIMLCFLLSTFFSKASLAAACSGVIYFTLYLPHILC<br>FAWQDRMTAELKKAVSLLSPVAFGFGTEYLVRFEEQGLG<br>LQWSNIGNSPTEGDEFSLLSMQMMLLDAAVYGLLAWYL<br>DQVFPGDYGTPLPWYFLLQESYWLGGEGCSTREERALEK<br>TEPLTEETEDPEHPEGIHDSFFEREHPGWVPGVCVKNLV<br>KIFEPCGRPAVDRLNITFYENQITAF LGHNGAGKTTTSL<br>ILTGLLPPTSGTVLVGGRDIETSLDAVRQSLGMCPQHNI<br>LFHHLTVAEHMLFYAQLKGKSQEEAQLMEAMLED TGLH<br>HKRNEEAQDLGGMQRKLSVAIAFVGDAKVVLDEPTSG<br>VDPYS <sup>1096</sup> RRSIWDL L LKYRSGRTIIMSTHMD EADLLG<br>DRIAI IAQGRLYC <sup>1140</sup> SGTPLFLKNC <sup>1150</sup> FGTGLYLT LVR<br>KMKNIQSQRKSGSEGT C <sup>1177</sup> SC <sup>1179</sup> SSKGFS <sup>1185</sup> TTC <sup>1188</sup> P<br>AHVDDLTP EQVLDGDVNELMDVVLHVVPEAKLVEICIGQE<br>LIFLLPNKNFKHAYASLFRELEETLADLGLSSFGISDT<br>PLEEIFLKVTEDSDSGPLFAGGAQQKRENVNPRHPC LGP<br>REKAGQTPQDSNVCS PGAPAAHPEGQPPPEPEC PGQLN<br>TGTQLVLQHVQALLVKRFQHTIRSHKDFLAQIVLPATFV<br>FLALMLSIVIPPFGEYPALTLHPWIYQQYTFFSMDEPG<br>SEQFTVLADVLLNKPFGGNRCLKEGWLPEYPCGNSTPWK<br>TPSVSPNITQLFQKQKWTQVNPS PSCRCSTREKL TMLPE<br>CPEGAGGLPPPQRTQRSTEILQDLTD RNISDFLVKTYPA<br>LIRSSLKSKFWVNEQRYGGISIGGKLPVVPITGEALVGF<br>LSDLGRIMNVSGGPITREASKEIPDFLKHLETEDNIKVW<br>FNNKGWHALVSFLNVAHNAILRASLPKDRSP EEEYGITVI<br>SQPLNLTKEQLSEITVLTTSVDAVVAICVIFSMSFVPAS<br>FVLYLIQERVNKS KHLQFISGVSPTTYWVTNFLWDIMNY<br>SVSAGLVVGIFIGFQKKAYTSPENLPALVALLLLYGWAV<br>IPMMYPASFLFDVPSTAYVALSCANLFIGINSSAITFIL<br>ELFENNRTLLRFNAVLRLKLLIVFPHFCLGRGLIDLALSQ<br>AVTDVYARFGEEHSANPFHWDLIGKNLFAMVVEGVVYFL<br>LTLLVQRHFFLSQWIAEPTKEPIVDEDDDDVAEERQRIIT<br>GGNKTDILRLHELT KIYPGTSSPAVDRLCVGVRPGECFG<br>LLGVNGAGKTTTTFKMLTGDTT VTSGDATVAGKSILTNIS<br>EVHQNMGYCPQFDAIDELLTGREHLYLYARLRGVPAEEI<br>EKVANWSIKSLGLTVYADCLAGTYSGGNKRKLSTAIALI<br>GCPPLVLLDEPTTGMDPQARRMLWNVIVSIIREGRAVVL<br>TSHSMEECEALCTRLAIMVKGAFCMGTIQHLKSKFGDG<br>YIVTMKIKSPKDDLPLDLPVEQFFQGNFPGSVQQRERHY<br>NMLQFQVSSSSSLARIFQLLL SHKDSL LIEEYSVTQT TLD<br>QVFNFAKQQTESHDLP LHPRAAGASRQAQD <sup>2273</sup> |     |
| 3FT | DYKDHDGDYKDHDIDYKDDDDK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 103 |

[0315]

| 构建体                                 | <sup>a</sup> 序列                                        | SEQ NO |
|-------------------------------------|--------------------------------------------------------|--------|
| ABCA4-1150-Cfa <sup>N</sup> -3 FT   | SEQ ID NO 106 (1 至 1149)-SEQ ID NO 27-SEQ ID NO 103    | 1      |
| ABCA4-1150-Cfa <sup>C</sup> -3 FT   | SEQ ID NO 28-SEQ ID NO 106 (1150 至 2273)-SEQ ID NO 103 | 2      |
| ABCA4-1140-Cfa <sup>N</sup> -3 FT   | SEQ ID NO 106 (1 至 1139)-SEQ ID NO 27-SEQ ID NO 103    | 3      |
| ABCA4-1140-Cfa <sup>Cmut</sup> -3FT | SEQ ID 29-SEQ ID NO 106 (1140 至 2273)-SEQ ID 103       | 4      |

[0316]

|                                               |                                                                                                                                                                                                                                                                                 |    |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>ABCA4-1188-Cfa<sup>N</sup>-3 FT</b>        | SEQ ID NO 106 (1至1187)-SEQ ID NO 27-SEQ ID NO 103                                                                                                                                                                                                                               | 5  |
| <b>ABCA4-1188-Cfa<sup>cmut</sup>-3FT</b>      | SEQ ID NO 29-SEQ ID NO 106 (1188 至 2273)-SEQ ID 103                                                                                                                                                                                                                             | 6  |
| <b>ABCA4-3FT</b>                              | SEQ ID NO 106-SEQ ID NO 103                                                                                                                                                                                                                                                     | 7  |
| <b>ABCA4-1150-Npu<sup>N</sup>-3 FT</b>        | SEQ ID NO 106 (1 至 1149)-SEQ ID NO 32-SEQ ID NO 103                                                                                                                                                                                                                             | 8  |
| <b>ABCA4-1150-Npu<sup>C</sup>-3 FT</b>        | SEQ ID NO 33-SEQ ID NO 106 (1150 至 2273)-SEQ ID NO 103                                                                                                                                                                                                                          | 9  |
| <b>ABCA4-1140-Npu<sup>N</sup>-3 FT</b>        | SEQ ID NO 106 (1 至 1139)-SEQ ID NO 32-SEQ ID NO 103                                                                                                                                                                                                                             | 10 |
| <b>ABCA4-1140-Npu<sup>C</sup>-3 FT</b>        | SEQ ID NO 33-SEQ ID NO (1140 至 2273)-SEQ ID NO 103                                                                                                                                                                                                                              | 11 |
| <b>ABCA4-1188-Npu<sup>N</sup>-3 FT</b>        | SEQ ID NO 106 (1至1187)-SEQ ID NO 32- SEQ ID NO 103                                                                                                                                                                                                                              | 12 |
| <b>ABCA4-1188-Npu<sup>C</sup>-3 FT</b>        | SEQ ID NO 33-SEQ ID NO 106 (1188 至 2273)-SEQ Id NO 103                                                                                                                                                                                                                          | 13 |
| <b>EGFP-71- Cfa<sup>N</sup></b>               | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDAT<br>YGKLTLLKFICTTGKLPVPWPTLVTTLTLYGVQCCLSYDTEI<br>LTVEYGFLPIGKIVEERIECTVYTVDKNGFVYTQPIAQW<br>HNRGEQEVFEYCLEDGSIIRATKDHKFMFTTDGQMLPIDE<br>IFERGLDLKQVDGLPGHHHHHHG                                                                         | 14 |
| <b>EGFP-71- Cfa<sup>C</sup></b>               | MVKIISRKSLGTQNVYDIGVEKDNFLLKNGLVASNCFS<br>RYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAE<br>VKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNNSHN<br>YIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIG<br>DGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAG<br>ITLGMDELYKGHHHHHHG                                          | 15 |
| <b>EGFP</b>                                   | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDAT<br>YGKLTLLKFICTTGKLPVPWPTLVTTLTLYGVQCFSRYPDH<br>MKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEG<br>DTLVNRIELKGIDFKEDGNILGHKLEYNNSHN<br>YIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIG<br>DGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAGITLGM<br>DELYKGHHHHHHG | 16 |
| <b>EGFP-71- Npu<sup>N</sup></b>               | MVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDAT<br>YGKLTLLKFICTTGKLPVPWPTLVTTLTLYGVQCCLSYETEI<br>LTVEYGLLPIGKIVEKRIECTVYSVDNNGNIYTQPVAQW<br>HNRGEQEVFEYCLEDGSLIRATKDHKFMFTVDGQMLPIDE<br>IFERELDLMRVDNLPNGHHHHHHG                                                                        | 17 |
| <b>EGFP-71- Npu<sup>C</sup></b>               | MIKIATRKYLGKQNVYDIGVERDHNFALKNGFIASNCFS<br>RYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAE<br>VKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNNSHN<br>YIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIG<br>DGPVLLPDNHYLSTQSALS KDPNEKRDHMLLEFVTAAG<br>ITLGMDELYKGHHHHHHG                                         | 18 |
| <b>ABCA4-1150-Cfa<sup>N</sup>-3 FT-SopE</b>   | SEQ ID NO 106 (1 至 1149)-SEQ ID NO 27-SEQ ID NO 103-SEQ ID NO 48                                                                                                                                                                                                                | 19 |
| <b>ABCA4-1150-Cfa<sup>C</sup>-3 FT-SopE</b>   | SEQ ID NO 28-SEQ ID NO 106 (1150 至 2273)-SEQ ID NO 103-SEQ ID NO 48                                                                                                                                                                                                             | 20 |
| <b>ABCA4-1140-Cfa<sup>N</sup>-3 FT-SopE</b>   | SEQ ID NO 106 (1 至 1139)-SEQ ID NO 27-SEQ Id NO 103-SEQ ID NO 48                                                                                                                                                                                                                | 21 |
| <b>ABCA4-1140-Cfa<sup>cmut</sup>-3FT-SopE</b> | SEQ ID NO 29SEQ ID NO 106 (1140 至 2273)-SEQ ID NO 103-SEQ ID NO 48                                                                                                                                                                                                              | 22 |
| <b>EGFP-71-Cfa<sup>N</sup>-SopE</b>           | SEQ ID NO 14-SEQ ID NO 48                                                                                                                                                                                                                                                       | 23 |
| <b>EGFP-71-Cfa<sup>C</sup>-SopE</b>           | MTKITLSPQNFRIQKQETLLKEKSTEKNSLAKSILAVK<br>NHFIELRSKLSERFISHKNTESSATHFHRGSASEGRAVL<br>TNKVVKDFMLQTLNDIDIRGSAVKIISRKSLGTQNVYDI                                                                                                                                                    | 24 |

[0317]

|                                    |                                                                                                                                                                                                                                                         |    |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                                    | GVEKDHNFLLKNGLVASNCFSRYPDHMKQHDFFKSAMPE<br>GYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGID<br>FKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKVNFKIR<br>HNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSAL<br>SKDPNEKRDHMLLEFVTAAGITLGMDELYKGHHHHHHG                                      |    |
| <b>EGFP-71-Cfa<sup>N</sup>-DD1</b> | SEQ ID NO 14-SEQ ID NO 43                                                                                                                                                                                                                               | 25 |
| <b>EGFP-71-Cfa<sup>C</sup>-DD1</b> | MRISFGSPPPMAGGVKII SRKSLGTQNVYDIGVEKDHNF<br>LLKNGLVASNCFSRYPDHMKQHDFFKSAMPEGYVQERTI<br>FFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNIL<br>GHKLEYNYNSHNVYIMADKQKNGIKVNFKIRHNIEDGSV<br>QLADHYQQNTPIGDGPVLLPDNHYLSTQSALS KDPNEKR<br>DHMLLEFVTAAGITLGMDELYKGHHHHHHG | 26 |

[0318]

| 构建体                                            | <sup>a</sup> 序列                          | SEQ NO |
|------------------------------------------------|------------------------------------------|--------|
| <b>ABCA4<sup>N</sup>-1150</b>                  | SEQ ID NO 106 (1 至 1149)                 | 60     |
| <b>ABCA4<sup>C</sup>-1150</b>                  | SEQ ID NO 106 (1150 至 2273)              | 61     |
| <b>ABCA4<sup>N</sup>-1140</b>                  | SEQ ID NO 106 (1 至 1139)                 | 62     |
| <b>ABCA4<sup>C</sup>-1140</b>                  | SEQ ID NO 106 (1140 至 2273)              | 63     |
| <b>ABCA4<sup>N</sup>-1188</b>                  | SEQ IS NO 106 (1至1187)                   | 64     |
| <b>ABCA4<sup>C</sup>-1188</b>                  | SEQ ID NO 106 (1188 至 2273)              | 65     |
| <b>ABCA4-1150-Cfa<sup>N</sup></b>              | SEQ ID NO 60-SEQ ID NO 27                | 66     |
| <b>ABCA4-1150-Cfa<sup>C</sup></b>              | SEQ ID NO 28-SEQ ID NO 61                | 67     |
| <b>ABCA4-1140-Cfa<sup>N</sup></b>              | SEQ ID NO 62-SEQ ID NO 27                | 68     |
| <b>ABCA4-1140-Cfa<sup>Cmut</sup></b>           | SEQ ID NO 29-SEQ ID NO 63                | 69     |
| <b>ABCA4-1188-Cfa<sup>N</sup></b>              | SEQ ID NO 64-SEQ ID NO 27                | 70     |
| <b>ABCA4-1188-Cfa<sup>Cmut</sup></b>           | SEQ ID NO 29-SEQ ID NO 65                | 71     |
| <b>ABCA4-1150-Cfa<sup>N</sup>-S<br/>opE</b>    | SEQ ID NO 66-SEQ ID NO 103-SEQ ID NO 48  | 72     |
| <b>ABCA4-1150-Cfa<sup>C</sup>-S<br/>opE</b>    | SEQ ID NO 48-SEQ ID NO 67- SEQ ID NO 103 | 73     |
| <b>ABCA4-1140-Cfa<sup>N</sup>-S<br/>opE</b>    | SEQ ID NO 68- SEQ ID NO 103-SEQ ID NO 48 | 74     |
| <b>ABCA4-1140-Cfa<sup>Cmut</sup><br/>-SopE</b> | SEQ ID NO 48-SEQ ID NO 69-SEQ ID NO 103  | 75     |
| <b>ABCA4-1150-Cfa<sup>N</sup>-D<br/>D1</b>     | SEQ ID NO 66-SEQ ID NO 43, 其中 X 是 Gly。   | 76     |
| <b>ABCA4-1150-Cfa<sup>C</sup>-D<br/>D1</b>     | SEQ ID NO 67-SEQ ID NO 43, 其中 X 是 Gly。   | 77     |
| <b>ABCA4-1140-Cfa<sup>N</sup>-D<br/>D1</b>     | SEQ ID NO 68-SEQ ID NO 43, 其中 X 是 Gly。   | 78     |
| <b>ABCA4-1140-Cfa<sup>Cmut</sup><br/>-DD1</b>  | SEQ ID NO 69-SEQ ID NO 43, 其中 X 是 Gly。   | 79     |

[0319] 材料和方法

[0320] 材料:

[0321] 寡核苷酸购自Eurofins genomics。合成基因购自GENEWIZ。用于克隆的Pfu超融合聚合酶和所有限制酶均购自Thermofisher Scientific。用于克隆的高效能细胞由XL10-Gold化学感受态大肠杆菌产生。HEK293T细胞购自ATCC。DNA纯化试剂盒购自Qiagen。所有质粒均由MacroGen测序。Luria Bertani (LB) 培养基和所有缓冲盐均购自Thermofisher Scientific。考马斯亮蓝、MG-132蛋白酶体抑制剂、苯甲磺酰氟、碘乙酰胺、NH<sub>4</sub>HCO<sub>3</sub>、DTT、甲酸、胎牛血清和来自大豆的asolectin购自Sigma-Aldrich。乙腈 (ACN) 购自Carlo-Erba。不含EDTA的完全蛋白酶抑制剂购自Roche。Lipofectamine 2000转染试剂、补充GlutaMAX的高葡萄糖DMEM、补充GlutaMAX的RPMI 1640培养基、RIPA裂解和提取缓冲液、BCA蛋白检测试剂盒、MES-SDS运行缓冲液、预染蛋白梯度物和SDS-PAGE (Bis-tris和Tris-醋酸凝胶) 购自



Thermofisher Scientific。一抗6xHis标签小鼠单克隆抗体、抗flag标签小鼠单克隆抗体、抗ABCA4兔多克隆抗体和抗微管蛋白兔多克隆抗体购自Invitrogen。山羊抗小鼠IgG (H+L) 高度交叉吸附的二抗alexa fluor plus 680和山羊抗兔IgG (H+L) 二抗dylight 800 4X PEG购自Invitrogen。十二烷基麦芽糖苷 (D310) 和胆固醇半琥珀酸酯 (CH210) 溶液购自Anatrace。胰蛋白酶购自Promega。

[0322] 设备:

[0323] 电喷雾电离质谱分析 (ESI-MS) 在与LTQ-Orbitrap Velos (Thermo Scientific) 质谱仪耦合的无Acquity液相色谱仪 (no Acquity liquid chromatographer) (Waters) 上进行。使用LI-COR Odyssey红外成像仪对凝胶和蛋白质印迹进行成像。使用SFX550 Branson超声仪进行细胞裂解。FACS测量在Gallios Beckman Coulter上进行。

[0324] 重组DNA的克隆

[0325] 购买制备构建体ABCA4-1150-CfaN (SEQ ID NO 1) 和ABCA4-1150-CfaC (SEQ ID NO 2) 的合成基因, 并使用KpnI和NotI限制酶将其导入pEGFP-N1表达载体。购买NpuN和NpuC的合成基因, 通过无限制酶克隆将其导入ABCA4-1150-CfaN和ABCA4-1150-CfaC, 以获得构建体ABCA4-1150-NpuN (SEQ ID NO 8) 和ABCA4-1150-NpuC (SEQ ID NO 9)。

[0326] 通过无限制酶克隆来制备构建体ABCA4-3FT (SEQ ID NO 7)、ABCA4-1140-CfaN (SEQ ID NO 3)、ABCA4-1140-CfaCmut (SEQ ID NO 4)、ABCA4-1188-CfaN (SEQ ID NO 5)、ABCA4-1188-CfaCmut (SEQ ID NO 6)、ABCA4-1179-CfaN (SEQ ID NO 93) 和ABCA4-1179-CfaCmut (SEQ ID NO 94)。用Pfu Ultra II HF聚合酶使用反向PCR导入CfaCmut处的突变。通过无限制酶克隆制备ABCA4-1140-NpuN (SEQ ID NO 10)、ABCA4-1140-NpuC (SEQ ID NO 11)、ABCA4-1188-NpuN (SEQ ID NO 12) 和ABCA4-1188-NpuC (SEQ ID NO 13)。

[0327] 通过无限制酶克隆制备构建体EGFP-71-CfaN (SEQ ID NO 14)、EGFP-71-CfaC (SEQ ID NO 15)、EGFP (SEQ ID NO 16)、EGFP-71-NpuN (SEQ ID NO 17) 和EGFP-71-NpuC (SEQ ID NO 18)。

[0328] 购买SopE的合成基因, 并通过无限制酶克隆将其导入ABCA4-1150-CfaN、ABCA4-1150-CfaC、ABCA4-1140-CfaN、ABCA4-1140-CfaC、EGFP-71-CfaN和EGFP-71-CfaC, 以获得构建体ABCA4-1150-CfaN-SopE (SEQ ID NO 19)、ABCA4-1150-CfaC-SopE (SEQ ID NO 20)、ABCA4-1140-CfaN-SopE (SEQ ID NO 21)、ABCA4-1140-CfaC-SopE (SEQ ID NO 22)、EGFP-71-CfaN-SopE (SEQ ID NO 23) 和EGFP-71-CfaC-SopE (SEQ ID NO 24)。通过重叠延伸PCR制备DD1基因, 并通过无限制酶克隆将其导入EGFP-71-CfaN和EGFP-71-CfaC, 以得到构建体EGFP-71-CfaN-DD1 (SEQ ID NO 25) 和EGFP-71-CfaC-DD1 (SEQ ID NO 26)。通过测序确认所有重组质粒的身份, 表1中报告了相应的蛋白质序列。通过将包括断裂蛋白基因、断裂内含肽和降解决定子的不同元件克隆到表达质粒中类似地产生了具有降解决定子的构建体。

[0329] AAV产生

[0330] 使用标准三质粒转染 (triple transfection) 策略产生编码本发明的N片段 (编码具有CfaN内含肽的EGFP或ABCA4片段) 的AAV。具有野生型AAV2 ITR的rAAV8载体是通过聚乙烯亚胺 (PEI) 介导在HEK293细胞中共转染质粒pAAV-Rep2-Cap8、pHelper和AAV-转基因-质粒产生的。

[0331] 转染后48小时收获细胞和培养基。在用0.1% Triton处理后, 病毒从细胞中释放出

来,并且通过PEG沉淀从培养基中获得AAV颗粒。根据Zolotukhin及其同事的方法[Zolotukhin S,Byrne BJ,Mason E,Zolotukhin I,Potter M,Chestnut K,Summerford C,Samulski,RJ,Mucyczka N.(1999) Recombinant adeno-associated virus purification using novel methods improves infectious titer and yield.Gene Ther;6(6):973-85.]通过碘克沙醇梯度纯化粗裂解液并去除空衣壳。

[0332] 使用Vivaspin 20离心浓缩器100.000MWC0(Sartorius,目录号VS0641)将纯化的批次浓缩并配制至 $1 \times 10^{13}$ vg/ml的终浓度,其通过定量聚合酶链反应(qPCR)确定。使用的制剂缓冲液的特征在于BSS(Alcon)+普朗尼克。

[0333] 浓缩后,使用Acrodisc(R)注射器过滤器(Acrodisc PP,PES,0.2 $\mu$ M 1cm<sup>2</sup>)过滤病毒批次,并储存在-80℃。使用ITR特异性PCR引物通过qPCR来确定病毒滴度,病毒滴度以每毫升基因组拷贝数表示。此外,衣壳滴度是使用AAV8 ELISA(Progen)根据制造商的说明获得的。

[0334] 使用Pierce Silver染色试剂盒(Cat#24612)在10% SDS PAGE上分离存在于最终产物中对应于 $1 \times 10^{10}$ vg的蛋白质。可检测到正确化学计量比为1:1:10的VP1、VP2和VP3蛋白,表明AAV制备的纯度>95%。

[0335] 在HEK293细胞中转染内含肽质粒:

[0336] HEK293T细胞在37℃和6%CO<sub>2</sub>气氛下在含有10%FBS和抗生素的DMEM中维持。以6孔板的形式,使用Lipofectamine 2000和1.25 $\mu$ g各质粒在汇合度约80%时共转染细胞。对于使用编码全长基因的质粒的实验,当使用两个内含肽质粒时,将乱序质粒(scramble plasmid)与全长质粒共转染以实现相同量的转染的DNA。转染后48小时收获细胞,并通过蛋白质印迹分析EGFP。

[0337] 在HEK293细胞中转染降解决定子-内含肽质粒:

[0338] 以6孔板的形式,使用Lipofectamine 2000和1.25 $\mu$ g各质粒在汇合度约80%时共转染细胞。转染后48小时收获用内含肽-降解决定子质粒转染的细胞并通过蛋白质印迹分析。对于时程实验,在转染后24小时和48小时后收获细胞并通过蛋白质印迹分析。

[0339] 使用MG-132抑制剂进行蛋白酶体抑制剂实验。共转染细胞并在转染后24小时加入DMSO或MG-132(溶解在DMSO中)至终浓度为50 $\mu$ M。在30分钟、3小时、6小时和24小时后收获细胞并通过蛋白质印迹分析。

[0340] 蛋白质印迹分析:

[0341] 将EGFP转染细胞(HEK293和WERI-RB1细胞)在补充有蛋白酶抑制剂和1mM苯甲基磺酰的RIPA缓冲液中裂解。裂解后,通过BCA蛋白质测定试剂盒对样本进行定量。将含有10 $\mu$ g总蛋白的样本在1XLaemmli样本缓冲液中于95℃变性10分钟。将裂解物通过12% Bis-tris SDS-PAGE凝胶在165V下分离40分钟。用于免疫印迹的抗体是抗6xHis标签抗体,以检测EGFP和作为上样对照的 $\beta$ -微管蛋白。使用LI-COR Odyssey红外成像仪对通过蛋白质印迹检测到的EGFP条带进行定量。

[0342] 将ABCA4转染细胞(HEK293)在十二烷基麦芽糖苷(D310)和胆固醇半琥珀酸酯(CH210)的PBS溶液(1:1)(补充有蛋白酶抑制剂和1mM苯甲基磺酰基)中裂解。裂解后,ABCA4样本通过BCA蛋白检测试剂盒进行定量。含有25 $\mu$ g总蛋白的样本在含有2.5mg/ml asolectin的1X Laemmli样本缓冲液中于37℃变性15分钟。将裂解物通过3%-8%Tris-乙

酸盐SDS-PAGE凝胶在150V下分离1.5小时。用于免疫印迹的抗体是抗flag标签或抗ABCA4抗体,以检测ABCA4蛋白和作为上样对照的抗 $\beta$ -微管蛋白。使用LI-COR Odyssey红外成像仪对通过蛋白质印迹检测到的ABCA4带进行定量。

[0343] 荧光激活细胞分选测量:

[0344] HEK293T细胞用2 $\mu$ g各EGFP-内含肽质粒共转染,作为阴性对照的HEK293T细胞生长但不进行转染。对于使用编码全长基因的质粒的实验,当使用两个内含肽质粒时,将乱序质粒与全长质粒共转染以实现相同量的转染的DNA。转染后48小时后通过流式细胞术分析细胞。转染和未转染的细胞分别重悬于FACS分析缓冲液(PBS,2%FSA,2mM EDTA)中。通过使用Kaluza流式细胞术分析软件在Beckman Coulter Gallios流式细胞仪中对不同的转染细胞和未转染细胞进行比较来评估EGFP+细胞的百分比。使用Dapi染色来检测死细胞的数量。

[0345] 质谱分析:

[0346] 用碳酸氢铵(50mM  $\text{NH}_4\text{HCO}_3$ )和乙腈(ACN)洗涤凝胶条带。样本在60 $^\circ\text{C}$ 下用20mM DTT还原60分钟,然后在25 $^\circ\text{C}$ 下用55mM碘乙酰胺避光进行烷基化30分钟。之后,将样本在37 $^\circ\text{C}$ 下用胰蛋白酶(序列级改良胰蛋白酶)双重消化2小时并过夜。最后,用5%甲酸(FA)的50%ACN溶液、和100%ACN从凝胶基质中提取得到的肽混合物,并在SpeedVac真空系统中干燥。根据制造商的方案,使用C18吸头(PolyLC Inc.)对所得的肽混合物进行清洗。最后,将清洗后的肽溶液干燥。将胰蛋白酶消化混合物重悬于1%FA溶液中,对于每个样本,注入等分试样进行色谱分离。将肽捕获在Symmetry C18捕集柱(5 $\mu\text{m}$ 180 $\mu\text{m}$  $\times$ 20mm;Waters)上,并使用C18反相毛细管柱(ACQUITY UPLC M-Class Peptide BEH柱;130 $\text{\AA}$ ,1.7 $\mu\text{m}$ ,75 $\mu\text{m}$  $\times$ 250mm,Waters)进行分离。用于洗脱肽的梯度为25分钟内1%至40%B,然后是5分钟内从40%至60%的梯度(A:0.1%FA;B:100%ACN,0.1%FA),流速为250nL/min。洗脱的肽在施加电压为2000V的发射针(PicoTip<sup>TM</sup>,New Objective)中进行电喷雾电离。在数据依赖模式下分析肽质量( $m/z$  300-1700),其中在Orbitrap中在400 $m/z$ 下以60,000FWHM的分辨率获得全扫描MS。从各MS扫描中选择前15种最丰富的肽(最小强度为500个计数),然后使用CID(38%归一化碰撞能量)以氦作为碰撞气体在线性离子阱中进行片段化。使用Thermo Proteome Discover用Sequest HT搜索引擎进行数据库搜索。

[0347] 体内实验

[0348] 用4周龄的129Sv品系野生型动物进行实验。用测试样本对小鼠进行视网膜下注射。

[0349] 在瞳孔扩张后使用5ml Hamilton注射器上的33G针头进行视网膜下注射。使用与数字成像系统连接的佳能UVI视网膜相机实现了注射后4周的EGFP表达眼底评估。使用Spectralis成像系统(Heidelberg Engineering Inc.)通过SD-OCT(光学相干断层扫描)来评估视网膜结构和外核层(ONL)的定量。

[0350] 成像后,对动物实施安乐死,摘除眼睛以通过免疫组织化学和蛋白质印迹进行进一步分析。进行了另外的实验,其中将载体注射到6周C57BL/6小鼠的内耳中。

[0351] 结果和讨论

[0352] 最近,基于共有设计(consensus design)而工程改造了若干新的内含肽((Stevens et al.,2016;Stevens,Sekar,Gramespacher,Cowburn,&Muir,2018))并证明其具有优于天然存在的内含肽的特性。这些内含肽中一种被称为Cfa的内含肽是由DnaE内含

肽的比对通过共有设计产生的,并显示出比DnaE家族中一些性能最好的内含肽(如Npu)更优越的特性。据报道,Cfa具有更快的动力学、更高的表达水平和对极端条件(例如高温和变性剂浓度)的高耐受性。有趣的是,具有90%或更高程度的同源性的Cfa变体显示出相似的特性。将相同的共有设计策略应用于TerL-AceL内含肽家族,产生了称为Cat的共有序列,相对于TerL-AceL家族的其他成员,Cat也显示出改进的特性。

[0353] 为了证明共有内含肽通过蛋白质反式剪接为蛋白质重构提供了用于基因治疗应用的益处,进行了直接比较。通过用纯化的质粒转染细胞进行比较。

[0354] 最初的实验是使用EGFP作为报告基因进行的。简而言之,EGFP在位置71处断裂,N端片段(残基1-70,EGFPN)与N内含肽重组融合,而C端片段(残基71-239,EGFPC)与C内含肽重组融合。生成了以下四种构建体:EGFPN-CfaN、EGFPN-NpuN、CfaC-EGFPC和NpuC-EGFPC,从而比较Cfa共有序列与Npu的重构效率。用等摩尔量的编码N端片段和C端片段的质粒共转染培养的HEK293细胞,并通过荧光显微镜、流式细胞术分析和蛋白质印迹监测剪接效率。

[0355] 我们的结果(参见图2、图3和图4)表明,与Npu内含肽相比,共有Cfa内含肽使EGFP重构增加至2.5倍,这表明通过共有设计获得的内含肽在共转染时提供了更高产量的目标蛋白。需要指出的是,尽管已知Cfa在体外以比Npu更快的速度断裂,它的N端片段在单独转化或转染到细胞中时表达更好,但是当两个片段共转染到同一个细胞中时,这是否会带来益处尚未被证明。通过这些实验,我们证明,当IntN和IntC片段在同一细胞中表达时,与先前已知的超快速断裂内含肽(例如Npu)相比,使用Cfa在目标蛋白的重构产量方面提供了明显的益处。编码EGFP的N片段和C片段以及N内含肽和C内含肽的基因也被掺入到重组AAV中用于其体内递送。结果表明,Cfa内含肽介导的蛋白质剪接导致EGFP在包括视网膜和内耳在内的几个器官中重构(图23)。

[0356] 为了证实在其他蛋白质中观察到Cfa共有序列的这种积极特征,我们使用ABCA4蛋白质重复了实验。ABCA4是一种大蛋白,其在Stargardt病中发生突变,并且ABCA4重构已被提议作为治疗该疾病的可行策略。目前正在探索几种基于AAV基因治疗的方法对ABCA4进行重构。由于其大小较大,ABCA4不能封装到单个AAV中,因此已经提出了不同的策略以便能够将ABCA4以两个片段进行递送,从而在靶细胞内重构。为了确认工程改造的共有序列(如Cfa)提供了优于天然存在的内含肽(如Npu)的益处,我们在位置1150处使ABCA4断裂,并将N内含肽和C内含肽分别克隆到蛋白的N端片段和C端片段。

[0357] 具有Cfa内含肽或Npu内含肽的ABCA4N(1至1149)-IntN和IntC-ABCA4<sup>C</sup>(1150至2273)被克隆到表达质粒中并共转染到HEK293细胞中。裂解细胞并通过蛋白质印迹测定蛋白质重构产量。全长ABCA4也被共转染作为对照。

[0358] 正如对EGFP观察到的那样,我们观察到Cfa的重构产量高于Npu(见图5)。

[0359] 最近还报道了一种Cfa变体,它在CfaC片段中包含特定突变,称为CfaCmut((Stevens et al.,2017)),它可以增加Cfa的益处。特别是CfaCmut变体已被证明能够有效地剪接蛋白质片段,即便C外显肽的+2位置不包含天然Phe残基。如上定义的+2位置是指位置+2(相对于IntC的最后一个氨基酸)。当ABCA4在位置1150处断裂时,在C外显肽+2位置为Phe,其对于Npu和Cfa是最佳残基。

[0360] 尽管可以通过在位置1150位处使ABCA4断裂来重构ABCA4,但这可能不是用于治疗目的的最佳位置。为了测试我们通过在1150以外的不同位点使ABCA4断裂来重构ABCA4的能

力,我们使用了CfaCmut,以便不限制于在+2位置(相对于内含肽)处呈现Phe的位置。

[0361] 克隆了若干ABCA4构建体,其中ABCA4蛋白在断裂位点的位置+2处不包含Phe的位点断裂。测试的另外两个位点是位置1140,其对应于+2位点处为Ser,以及位置1188,其对应于+2位点处为Pro。如上所示进行克隆并测试构建体。具体而言,使用ABCA4(1至1139)-IntN、IntC-ABCA4(1140至2273)构建体来评估ABCA4在位置1140处的剪接。使用ABCA4(1至1187)-IntN和IntC-ABCA4(1188至2273)来评估在位置1188处使ABCA4断裂。根据ABCA4的拓扑结构并考虑折叠结构域的存在来选择位点。在ABCA4细胞内侧明确定义的折叠结构域之外选择位点。对不同的位点进行了测试,对所有这些位点都观察到Cfa和Cfa变体提供比Npu更高的重构产量,并且效率也因断裂位点而异(图5、6和7)。我们还证明了该方法允许ABCA4在位置1179和1177处断裂重构。克隆了与上面1140和1188所定义的类似的构建体,并用于测试位置1179和1177处的剪接效率,位置1179的结果显示在图21中。

[0362] 我们还证明了其他有效的内含肽(如gp41)可用于由断裂片段重构ABCA4。设计了在位置1185和1095处断裂的ABCA4构建体,克隆了与N端内含肽和C端内含肽的相应融合物,并如上所述分析了它们的剪接活性。通过蛋白质印迹对断裂位置1096处的PTS反应和gp41内含肽的分析如图22所示。

[0363] 下表7示出了当蛋白质在不同位点(1177、1179、1096和1185)断裂时获得的ABCA4片段的序列以及相应的ABCA4-内含肽N或内含肽C-ABCA4融合体。

[0364] 除了重构产量之外,在基因治疗中使用断裂内含肽的另一个主要限制是存在未反应的起始材料和/或内含肽。为了防止不需要的起始材料的积累并消除切下的内含肽片段,我们向构建体添加了降解决定子,一般架构如图8所示。

[0365] 我们已经确定了几种可以与内含肽结合使用的降解决定子,以开发可以转化出由其他大基因突变引起的疾病的ABCA4的基因治疗方法以及重构蛋白质来治疗这些疾病,例如重构CRISPR/Cas9系统。

[0366] 为了识别合适的降解决定子-内含肽组合,克隆了将选定的降解决定子包括在内的EGFP-Int构建体。在N内含肽的C端和C内含肽的N端克隆了降解决定子。为了检测目的,将His6标签包含在两个元件之间作为接头。为了证明原理,使用了SopE去稳定结构域(1-100),以及由肽序列DD1组成的降解决定子(参见表3)

[0367] 结果表明,包含降解决定子确实去除了任何可检测量的起始材料和内含肽(参见图9、图14)。重要且出乎意料的是,事实证明,同时包含两种降解决定子可以去除任何未反应的起始材料,而不会损失蛋白质剪接反应的产率。

[0368] 有趣的是,当降解决定子策略应用于大基因ABCA4时,我们观察到类似的结果,而且剪接ABCA4产物的水平也有所增加,这表明共有内含肽和降解决定子之间存在出乎意料的协同效应(见图10)。

[0369] 还研究了蛋白体抑制剂对这些结果的影响(图11)。我们发现蛋白体抑制剂降低了降解决定子的作用,从而证实了SopE降解是蛋白酶体介导的。有趣的是,我们观察到将内含肽与降解决定子相结合,我们不仅能够消除起始材料的存在,而且能够维持甚至提高ABCA4的重构水平(图10)。

[0370] 我们还进行了实验来研究将共有内含肽Cfa与降解决定子相结合的效果,并将其与不存在降解决定子或使用其他内含肽进行比较。有趣的是,我们观察到(图12)将Cfa与降

解决定子一起使用非常显著地降低了起始材料的水平,并且还增加了产物的量。我们还确认了在ABCA4的位置1140(图13和图21)和1179(图21)也观察到了这种效果。重要的是,我们表明,将Cfa(和Cfamut)内含肽与几种不同的降解决定子(这些降解决定子具有某些共同的特征)结合所观察到的效果得以维持(参见实施例3)。

[0371] 基于ABCA4获得的结果,可以应用该方法的其他疾病、基因和蛋白质包括表1中所示的那些。

[0372] 实施例2.使用正交断裂内含肽对的三段式连接策略

[0373] 材料与方法:

[0374] 在HEK293细胞中转染三段式质粒:

[0375] 以6孔板的形式,使用Lipofectamine 2000和1.25 $\mu$ g各质粒在汇合度约80%时共转染细胞。转染后48小时收获用三段式质粒转染的细胞并通过蛋白质印迹分析。作为对照,用两种质粒(P0IN-CfaN+CfaC-P0IM-CatN、CfaC-P0IM-CatN+CatC-P0IC和P0IN-CfaN+CatC-P0IC)共转染细胞。

[0376] 蛋白质印迹分析:

[0377] 将三段式转染细胞(HEK293)在补充有蛋白酶抑制剂和1mM苯甲基磺酰的RIPA缓冲液中裂解。裂解后,通过BCA蛋白质测定试剂盒对样本进行定量。将含有10 $\mu$ g总蛋白的样本在1X Laemmli样本缓冲液中于95 $^{\circ}$ C变性10分钟。将裂解物通过12%Bis-tris SDS-PAGE凝胶在165V下分离40分钟。用于免疫印迹的抗体是抗flag标签抗体,以检测POI和作为上样对照的抗 $\beta$ -微管蛋白。

[0378] 结果

[0379] 我们表明,将超快共有内含肽与降解决定子组合是重构大蛋白的可行策略,同时降低了起始材料和切下的内含肽的水平。该策略可用于基因治疗,以在基因替换策略中重构大蛋白,以及在与合适的递送载体(例如本文公开的递送载体)组合时在体内产生治疗剂。然而,对于更大的蛋白质,这种策略可能还不够。例如,对于编码区大于7kb-8kb的蛋白质,将其编码基因断裂成两个片段不足以产生可封装在AAV载体中的片段。对于这样的蛋白质,编码基因可能需要断裂成三段。为了使用内含肽从三个单独的片段组装蛋白质,需要正交内含肽对。为实现最大重构产量,需要高效的正交内含肽。我们决定将Cfa与Cat内含肽结合使用。这两个内含肽是通过共有设计获得的,并具有一些共同特征,包括高表达产量、热稳定性、对离液剂的耐受性和快速的剪接动力学。我们按照图16中描述的结构设计了一系列构建体:P0IN-CfaN、CfaC-P0IM-CatN和CatC-P0IC。可选择地,可以交换Cfa和Cat内含子的位置,以生成具有以下架构的构建体:P0IN-CatN、CatC-P0IM-CfaN和CfaC-P0IC。

[0380] 我们测试了它们的正交性,证明了两个内含肽确实是正交的,它们不相互反应,即Cfa或Cat内含肽的N片段仅与其各自的同源对反应。当三个片段以等摩尔量共转染时,检测到的主要产物是由三个片段组装成全长期产物而产生的产物。重要的是,我们只检测到低水平的未反应材料,我们没有检测到任何中间产物,即仅由两个片段反应产生的产物。该结果表明使用高活性正交共有内含肽对是由三个单独的片段组装大蛋白的合适策略。

[0381] 实施例3.

[0382] 为了实践本发明,测试了若干个降解决定子。根据它们的大小从文献中选择降解决定子,对于AAV基因治疗应用,小于75个氨基酸的降解决定子将是优选的,以使所得转基

因的大小最小化。在某些情况下,降解决定子是通过组合已知的N端降解决定子或C端降解决定子来设计的。

[0383] 在N片段的C端和C片段的N端克隆了降解决定子,这两个片段都旨在重构全长EGFP蛋白,作为可溶性细胞溶质蛋白的代表性例子。在图9中可以观察到结果的总结,其中可以看出包含一个或两个降解决定子(每个EGFP片段上一个)消除了不需要的起始材料片段,而不会对剪接产量产生负面影响。使用不同的降解决定子观察到类似的结果(图14),说明了该方法的通用性。

[0384] 在N片段的C端和C片段的N端克隆了降解决定子,这两个片段旨在在不同的断裂位置(作为代表性示例,包括1140、1150和1179)重构全长ABCA4蛋白。下面的表6示出了所有测试的降解决定子,包括大小、序列、它们的来源以及负责它们泛素化和最终降解的连接酶。

[0385] 表6.

| 名称     |     |                                                             | DD来源                                 | 人直系同源物 |
|--------|-----|-------------------------------------------------------------|--------------------------------------|--------|
| DD1    | 39  | RISFGSPPPMAGG                                               | 智人<br>( <i>H. sapiens</i> )          | KLHDC2 |
| L2     | 105 | SLISLPLPTRVKFSSLLIRIMKIITMTFPKKLRS                          | 酿酒酵母<br>( <i>S. cerevisiae</i> )     | UBE2G2 |
| L9     | 139 | SNPFSSLFGASLLIDSVLSKSNWDTSSSCLISFFSSVMFSSTTRS               | 酿酒酵母                                 | UBE2G2 |
| SopE50 | 105 | QETTLLEKSTEKNSLAKSILAVKNHFIELRSKLS                          | 鼠伤寒沙门氏菌<br>( <i>S. typhimurium</i> ) | UBE2D3 |
| SopE70 | 189 | QETTLLEKSTEKNSLAKSILAVKNHFIELRSKLSERFISHKNTSEATHFHRGSAEGRVL | 鼠伤寒沙门氏菌                              | UBE2D3 |
| PEST   | 90  | RSSSPSDSDTSGFSSGSDHLSLISLRIS                                | 爪蟾属 ( <i>xenopus</i> )               | KLHDC2 |
| [0386] | M2  | VSFAFNLSLIVGILRFHW                                          | 酿酒酵母                                 | TEB4   |
|        | M4  | YMSILRCASGKISIAAPPYIF                                       | 酿酒酵母                                 | LTN1   |
|        | V12 | TNGSVLREFTLLELEVTRNTEL                                      | 酿酒酵母                                 | TEB4   |
|        | DD3 | TNGILKLGCCQ                                                 | 酿酒酵母                                 | TEB4   |
|        | DD4 | RDSFGSPPPMAGG                                               | 智人                                   | KLHDC2 |
|        | DD5 | GFWI                                                        | 酿酒酵母                                 | KLHDC2 |
|        | DD6 | RFKG                                                        | 酿酒酵母                                 | TEB4   |
|        | DD7 | KFYK                                                        | 酿酒酵母                                 | TEB4   |
|        | T1  | SVLEENRPFAQQLSNVYFTIL                                       | 酿酒酵母                                 | TEB4   |
|        | T2  | KLKGLGKRCKRREDLEIRFIL                                       | 酿酒酵母                                 | TEB4   |
|        | T3  | WKLLLVWGLVLVKHHDGAH                                         | 酿酒酵母                                 | TEB4   |

[0387] 对降解决定子进行测试以确认它们是否能够诱导起始材料和切离的内含肽的降解,并确认它们对蛋白质反式剪接反应产量的影响,即它们重构全长ABCA4蛋白的能力。用含有上述不同降解决定子的N端构建体和C端构建体共转染细胞。裂解细胞并通过蛋白质印迹分析以检测具有和不具有降解决定子的PTS产物的存在。在图18中,示出了在N片段和C片段上使用相同降解决定子的结果。左图(图18C)上的凝胶显示了每个反应的PTS产物(ABCA4)以及起始材料(ABCAN-IntN-DD和DD-IntC-ABCAC)。PTS对应于没有使用降解决定子时的结果,其他泳道中的标签指示在每种情况下使用了哪种降解决定子。右图(图18C)提供了每种情况下PTS产物量的量化。可以看出,令人惊讶的是,与不具有降解决定子的构建体相比,一些降解决定子提供更高的产量。有趣的是,所有的降解决定子都有效,并且使用所有的降解决定子都可以重构在不具有降解决定子的情况下获得的产物的至少25%。一些降解决定子允许重构在不具有降解决定子的情况下获得的水平的超过50%,最后,有一些降解决定子产生100%(或更高)的重构。具体而言,产生100%(或更高)重构的降解决定子如下:DD1、V12、M4、L2、L9、DD3和SopE100。

[0388] 还研究了降解决定子对切下的内含肽的影响(图19)。使用高百分比丙烯酰胺凝胶检测内含肽,通过WB(蛋白质印迹)分析具有不同降解决定子的PTS反应。可以看出,与其他降解决定子(例如SpoE和PEST)相比,几种降解决定子减少了切下的内含肽的量,而其他降解决定子(如L2(SEQ ID NO 52)、L9(SEQ ID NO 54)、M2(SEQ ID NO 47)、M4(SEQ ID NO 35)或DD3(SEQ ID NO 45))则完全消除了内含肽条带。

[0389] 此外,我们还进行了实验以研究在N端位置或C端位置使用不同的降解决定子的影响。例如,在图20中,我们示出了蛋白质印迹分析,其中N片段处的降解决定子是固定的,而C片段处的降解决定子是变化的。图20中所示的结果表明,将一些优选的降解决定子组合可以获得进一步改进的结果,从而在不降低所需剪接产物的产量的情况下实现了起始材料的进一步减少。这些组合可能对某些应用,特别是当完全消除任何起始材料至关重要时是有用的。

[0390] 根据获得的结果,我们可以将降解决定子分为三类:

[0391] • 使得能够以没有降解决定子时获得的产量的至少25%重构目标蛋白的降解决定子。

[0392] • 使得能够以没有降解决定子时获得的产量的约50%以上的产量重构目标蛋白的降解决定子。

[0393] • 使得能够以等于或优于没有降解决定子时获得的产量的产量重构目标蛋白的降解决定子。

[0394] 当使用CfaN和CfaC内含肽或CfaCmut内含肽的组合时,表明ABCA4中的几个位点适合于在此描述的本发明的使用。具体来说,是核苷酸结合结构域1(NBD1)的C端与第七跨膜结构域(TMD)之间的位点,包括位置1140、1150、1177、1179和1188。ABCA4重构产量在位置1140、1150和1179处是最佳的,虽然位置1188的工作效率非常低,但仍然导致ABCA4重构水平高于使用非共有Npu内含肽获得的重构水平。

[0395] CfaN和CfaCmut内含肽的组合提供了增加的混杂性。事实上,我们在这里首次展示了这种增加的混杂性是在跨膜蛋白(如ABCA4)中观察到的,其中在不同剪接位点使用CfaN-CfaCmutant对获得了高重构率。此外,当使用这些内含肽(CfaN和CfaCmut内含肽)时,这种剪接反应显示出非常有效,因为观察到的每种起始材料不到10%(如图12中所述估计)。这是根据先前报道的使用Npu内含肽与ABCA4的结果(Auricchio et al.2019)所无法预期的,因为其中很大一部分起始材料仍然没有反应,这表明蛋白质反式剪接对于这种膜蛋白来说本来就更具挑战性。

[0396] 根据此处报告的结果,我们得出结论,当使用共有内含肽对CfaN和CfaCmutant时,具有以下特征的任何位点都将有效工作:(1)酶促结构域或跨膜结构域之外的位点;(2)诸如断裂位点的+1位置(如上所述)的位点应该对应于亲核残基(如Cys或Ser),并且+2位置可以是除Pro外的任何位点。

[0397] 表7

| [0398] | 构建体                      | * 序列                        | SEQ NO |
|--------|--------------------------|-----------------------------|--------|
|        | ABCA4 <sup>N</sup> -1177 | SEQ ID NO 106 (1 至 1176)    | 87     |
|        | ABCA4 <sup>C</sup> -1177 | SEQ ID NO 106 (1177 至 2273) | 88     |
|        | ABCA4 <sup>N</sup> -1179 | SEQ ID NO 106 (1 至 1178)    | 89     |



[0399]

|                                      |                             |     |
|--------------------------------------|-----------------------------|-----|
| <b>ABCA4<sup>C</sup>-1179</b>        | SEQ ID NO 106 (1179 至 2273) | 90  |
| <b>ABCA4-1177-Cfa<sup>N</sup></b>    | SEQ ID NO 87-SEQ ID NO 27   | 91  |
| <b>ABCA4-1177-Cfa<sup>Cmut</sup></b> | SEQ ID NO 29-SEQ ID NO 88   | 92  |
| <b>ABCA4-1179-Cfa<sup>N</sup></b>    | SEQ ID NO 89-SEQ ID NO 27   | 93  |
| <b>ABCA4-1179-Cfa<sup>Cmut</sup></b> | SEQ ID NO 29-SEQ ID NO 90   | 94  |
| <b>ABCA4<sup>N</sup>-1096</b>        | SEQ ID NO 106 (1 至 1095)    | 95  |
| <b>ABCA4<sup>C</sup>-1096</b>        | SEQ ID NO 106 (1096 至 2273) | 96  |
| <b>ABCA4<sup>N</sup>-1185</b>        | SEQ ID NO 106 (1 至 1184)    | 97  |
| <b>ABCA4<sup>C</sup>-1185</b>        | SEQ ID NO 106 (1185 至 2273) | 98  |
| <b>ABCA4-1096-gp41<sup>N</sup></b>   | SEQ ID NO 95-SEQ ID NO 38   | 99  |
| <b>ABCA4-1096-gp41<sup>C</sup></b>   | SEQ ID NO 104-SEQ ID NO 96  | 100 |
| <b>ABCA4-1185-gp41<sup>N</sup></b>   | SEQ ID NO 97-SEQ ID NO 38   | 101 |
| <b>ABCA4-1185-gp41<sup>C</sup></b>   | SEQ ID NO 104-SEQ ID NO 98  | 102 |

[0400] 条款

[0401] 1、一种组合物，该组合物包括第一多核苷酸和第二多核苷酸，所述第一多核苷酸编码包含通过肽键、可选地通过肽接头与要重构的蛋白质的N端片段直接连接的断裂内含肽N片段的多核苷酸，所述第二多核苷酸编码包含通过肽键、可选地通过肽接头与要重构的蛋白质的C端片段直接连接的断裂内含肽C片段的多核苷酸；

[0402] 其中所述组合物的两种组分可以一起包装在单一制剂中或分别包装在不同制剂中；

[0403] 其中所述第一多核苷酸和所述第二多核苷酸分别编码所述要重构的蛋白质的所述N端片段和所述C端片段，使得当两个片段组合时，所述蛋白质的所述N端片段与所述蛋白质的所述C端片段连接，从而产生整个蛋白质；

[0404] 其中各多核苷酸必须编码断裂内含肽，使得一旦翻译成蛋白质，所述N端序列和所述C端序列会变成可非共价重新缔合或重构为对反式剪接反应起作用的内含肽的单独的片段；以及其中

[0405] 所述要重构的蛋白质大于25KDa。

[0406] 2、根据条款2所述的组合物，其中，所述第一多核苷酸编码通过肽键与降解决定子直接连接的断裂内含肽N片段，其中所述降解决定子在该所述内含肽N片段和所述降解决定子之间有或没有接头的情况下通过内含肽的C端与所述内含肽N片段连接，并且其中所述断裂内含肽N片段的N端通过肽键与所述要重构的蛋白质的N端片段直接连接；以及其中，所述第二多核苷酸编码通过肽键与降解决定子直接连接的断裂内含肽C片段，其中所述降解决定子在内含肽C片段和降解决定子之间有或没有接头的情况下通过内含肽的N端与所述内含肽C片段连接，并且其中所述断裂内含肽C片段的C端通过肽键与所述要重构的蛋白质的C端片段直接连接。

[0407] 3、根据条款1或2中任一项所述的组合物，其中，所述第一多核苷酸编码SEQ ID NO 27的CfaN内含肽或其任何变体，并且所述第二多核苷酸编码SEQ ID NO 28的CfaC内含肽或其任何变体，其中变体被理解为与这些序列中的任何序列具有至少90%序列同一性的SEQ ID NO:27或SEQ ID NO 28的断裂内含肽N片段或C片段，如CfaCmut (SEQ ID NO 29)。

[0408] 4、根据条款2或3中任一项所述的组合物，其中，降解决定子选自SEQ ID NO 40-59、34、35和37组成的清单。

[0409] 5、根据条款2所述的组合物，其中，所述断裂内含肽如权利要求3所定义，并且其中

所述降解决定子选自SEQ ID NO 42、43、49、50、51、54和34组成的清单。

[0410] 6、根据条款1至5中任一项所述的组合物,其中,两种多核苷酸都包含在使得所述多核苷酸在合适的宿主细胞中增殖的载体中。

[0411] 7、根据条款6所述的组合物,其中,所述载体是腺相关病毒(AAV)。

[0412] 8、根据条款7所述的组合物,其中,所述载体是血清型1、2、3、4、5、6、7、8或9的AAV。

[0413] 9、根据条款1至8中任一项所述的组合物,其中,编码整个蛋白质的基因选自表1中列出的任何蛋白质组成的清单。

[0414] 10、用于治疗根据条款1至9中任一项所定义的组合物。

[0415] 11、一种在细胞中表达目标基因的方法,包括:

[0416] (i) 使细胞与以下接触:

[0417] (a) 条款1中定义的第一多核苷酸,和

[0418] (b) 条款1中定义的第二多核苷酸,

[0419] (ii) 使第一多核苷酸和第二多核苷酸表达,以产生第一融合蛋白和第二融合蛋白,以及

[0420] (iii) 使第一蛋白和第二蛋白接触,使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体,并且内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

[0421] 12、一种在细胞中表达目标基因的方法,包括:

[0422] (i) 使细胞与以下接触:

[0423] (a) 条款2中定义的第一多核苷酸,和

[0424] (b) 条款2中定义的第二多核苷酸,

[0425] (ii) 使第一多核苷酸和第二多核苷酸表达,以产生第一融合蛋白和第二融合蛋白,以及

[0426] (iii) 使第一蛋白和第二蛋白接触,使得断裂内含肽N片段与断裂内含肽C片段结合以形成内含肽中间体,并且内含肽中间体反应以将第一目标多肽的C端与第二目标多肽的N端共价连接。

[0427] 13、根据条款11或12中任一项所述的方法,其中,所述第一多核苷酸编码SEQ ID NO 27的CfaN内含肽或其任何变体,并且所述第二多核苷酸编码SEQ ID NO 28的CfaC内含肽或其任何变体,其中变体被理解为与这些序列中的任何序列具有至少90%序列同一性的SEQ ID NO:27或SEQ ID NO 28的断裂内含肽N片段或C片段,如CfaCmut (SEQ ID NO 29)。

[0428] 14、根据条款11或12中任一项所述的方法,其中,所述断裂内含肽如权利要求3所定义,并且其中所述降解决定子选自SEQ ID NO 42、43、49、50、51、54和34组成的清单。

[0429] 15、根据条款11至14中任一项所述的方法,其中,两种多核苷酸都包含在腺相关病毒(AAV)中。

## 序列表

&lt;110&gt; 移接生物有限公司

&lt;120&gt; 断裂内含子及其用途

&lt;130&gt; 905 992

&lt;140&gt; EPPCT/2021/058016

&lt;141&gt; 2020-03-26

&lt;160&gt; 108

&lt;170&gt; BiSSAP 1.3.6

&lt;210&gt; 1

&lt;211&gt; 1272

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4-1150-CfaN-3FT

&lt;400&gt; 1

```

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr
1           5           10           15
Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro
          20           25           30
Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu
          35           40           45
Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala
          50           55           60
Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro
65           70           75           80
Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn
          85           90           95
Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
          100          105          110
Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
          115          120          125
Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
          130          135          140
Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu
145          150          155          160
Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
          165          170          175
Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala

```

|                             |                         |             |
|-----------------------------|-------------------------|-------------|
| 180                         | 185                     | 190         |
| His Gly Val Pro Asp Leu Ala | Leu Lys Asp Ile Ala Cys | Ser Glu Ala |
| 195                         | 200                     | 205         |
| Leu Leu Glu Arg Phe Ile Ile | Phe Ser Gln Arg Arg Gly | Ala Lys Thr |
| 210                         | 215                     | 220         |
| Val Arg Tyr Ala Leu Cys Ser | Leu Ser Gln Gly Thr Leu | Gln Trp Ile |
| 225                         | 230                     | 235         |
| Glu Asp Thr Leu Tyr Ala Asn | Val Asp Phe Phe Lys Leu | Phe Arg Val |
| 245                         | 250                     | 255         |
| Leu Pro Thr Leu Leu Asp Ser | Arg Ser Gln Gly Ile Asn | Leu Arg Ser |
| 260                         | 265                     | 270         |
| Trp Gly Gly Ile Leu Ser Asp | Met Ser Pro Arg Ile Gln | Glu Phe Ile |
| 275                         | 280                     | 285         |
| His Arg Pro Ser Met Gln Asp | Leu Leu Trp Val Thr Arg | Pro Leu Met |
| 290                         | 295                     | 300         |
| Gln Asn Gly Gly Pro Glu Thr | Phe Thr Lys Leu Met Gly | Ile Leu Ser |
| 305                         | 310                     | 315         |
| Asp Leu Leu Cys Gly Tyr Pro | Glu Gly Gly Gly Ser Arg | Val Leu Ser |
| 325                         | 330                     | 335         |
| Phe Asn Trp Tyr Glu Asp Asn | Asn Tyr Lys Ala Phe Leu | Gly Ile Asp |
| 340                         | 345                     | 350         |
| Ser Thr Arg Lys Asp Pro Ile | Tyr Ser Tyr Asp Arg Arg | Thr Thr Ser |
| 355                         | 360                     | 365         |
| Phe Cys Asn Ala Leu Ile Gln | Ser Leu Glu Ser Asn Pro | Leu Thr Lys |
| 370                         | 375                     | 380         |
| Ile Ala Trp Arg Ala Ala Lys | Pro Leu Leu Met Gly Lys | Ile Leu Tyr |
| 385                         | 390                     | 395         |
| Thr Pro Asp Ser Pro Ala Ala | Arg Arg Ile Leu Lys Asn | Ala Asn Ser |
| 405                         | 410                     | 415         |
| Thr Phe Glu Glu Leu Glu His | Val Arg Lys Leu Val Lys | Ala Trp Glu |
| 420                         | 425                     | 430         |
| Glu Val Gly Pro Gln Ile Trp | Tyr Phe Phe Asp Asn Ser | Thr Gln Met |
| 435                         | 440                     | 445         |
| Asn Met Ile Arg Asp Thr Leu | Gly Asn Pro Thr Val Lys | Asp Phe Leu |
| 450                         | 455                     | 460         |
| Asn Arg Gln Leu Gly Glu Glu | Gly Ile Thr Ala Glu Ala | Ile Leu Asn |
| 465                         | 470                     | 475         |
| Phe Leu Tyr Lys Gly Pro Arg | Glu Ser Gln Ala Asp Asp | Met Ala Asn |
| 485                         | 490                     | 495         |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |

|                                                                 |      |      |      |      |      |
|-----------------------------------------------------------------|------|------|------|------|------|
|                                                                 | 805  |      | 810  |      | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |      |      |      |
|                                                                 | 820  |      | 825  |      | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |      |      |      |
|                                                                 | 835  |      | 840  |      | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |      |      |      |
|                                                                 | 850  |      | 855  |      | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |      |      |      |
| 865                                                             |      | 870  |      | 875  | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |      |      |      |
|                                                                 | 885  |      | 890  |      | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |      |      |      |
|                                                                 | 900  |      | 905  |      | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |      |      |      |
|                                                                 | 915  |      | 920  |      | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |      |      |      |
|                                                                 | 930  |      | 935  |      | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |      |      |      |
| 945                                                             |      | 950  |      | 955  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |      |      |      |
|                                                                 | 965  |      | 970  |      | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |      |      |
|                                                                 | 980  |      | 985  |      | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |      |      |
|                                                                 | 995  |      | 1000 |      | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |      |      |
|                                                                 | 1010 |      | 1015 |      | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |      |      |
| 1025                                                            |      | 1030 |      | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |      |      |
|                                                                 | 1045 |      | 1050 |      | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |      |      |
|                                                                 | 1060 |      | 1065 |      | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |      |      |
|                                                                 | 1075 |      | 1080 |      | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |      |      |
|                                                                 | 1090 |      | 1095 |      | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |      |      |
| 1105                                                            |      | 1110 |      | 1115 | 1120 |

Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly  
 1125 1130 1135  
 Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Leu Ser  
 1140 1145 1150  
 Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly  
 1155 1160 1165  
 Lys Ile Val Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys  
 1170 1175 1180  
 Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly  
 1185 1190 1195 1200  
 Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg  
 1205 1210 1215  
 Ala Thr Lys Asp His Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro  
 1220 1225 1230  
 Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly  
 1235 1240 1245  
 Leu Pro Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile  
 1250 1255 1260  
 Asp Tyr Lys Asp Asp Asp Asp Lys  
 1265 1270  
 <210> 2  
 <211> 1182  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1150-CfaC-3FT  
 <400> 2  
 Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr  
 1 5 10 15  
 Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys Asn Gly Leu  
 20 25 30  
 Val Ala Ser Asn Cys Phe Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg  
 35 40 45  
 Lys Met Lys Asn Ile Gln Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys  
 50 55 60  
 Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val Asp  
 65 70 75 80  
 Asp Leu Thr Pro Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu Met  
 85 90 95

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Asp Val Val Leu His His Val Pro Glu Ala Lys Leu Val Glu Cys Ile |     |     |
| 100                                                             | 105 | 110 |
| Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His Arg |     |     |
| 115                                                             | 120 | 125 |
| Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu |     |     |
| 130                                                             | 135 | 140 |
| Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe |     |     |
| 145                                                             | 150 | 155 |
| Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly |     |     |
| 165                                                             | 170 | 175 |
| Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly |     |     |
| 180                                                             | 185 | 190 |
| Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser |     |     |
| 195                                                             | 200 | 205 |
| Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro |     |     |
| 210                                                             | 215 | 220 |
| Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln |     |     |
| 225                                                             | 230 | 235 |
| His Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser |     |     |
| 245                                                             | 250 | 255 |
| His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe |     |     |
| 260                                                             | 265 | 270 |
| Leu Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro |     |     |
| 275                                                             | 280 | 285 |
| Ala Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe |     |     |
| 290                                                             | 295 | 300 |
| Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val |     |     |
| 305                                                             | 310 | 315 |
| Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp |     |     |
| 325                                                             | 330 | 335 |
| Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser |     |     |
| 340                                                             | 345 | 350 |
| Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln |     |     |
| 355                                                             | 360 | 365 |
| Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr |     |     |
| 370                                                             | 375 | 380 |
| Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln |     |     |
| 385                                                             | 390 | 395 |
| Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn |     |     |



|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
|                                                                 | 405 | 410 | 415 |
| Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu     |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu |     |     |     |
| 705                                                             | 710 | 715 | 720 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala |      |      |
| 725                                                             | 730  | 735  |
| Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His |      |      |
| 740                                                             | 745  | 750  |
| Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala |      |      |
| 755                                                             | 760  | 765  |
| Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln |      |      |
| 770                                                             | 775  | 780  |
| Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro |      |      |
| 785                                                             | 790  | 800  |
| Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile |      |      |
| 805                                                             | 810  | 815  |
| Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys |      |      |
| 820                                                             | 825  | 830  |
| Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly |      |      |
| 835                                                             | 840  | 845  |
| Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly |      |      |
| 850                                                             | 855  | 860  |
| Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser |      |      |
| 865                                                             | 870  | 880  |
| Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu |      |      |
| 885                                                             | 890  | 895  |
| Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu |      |      |
| 900                                                             | 905  | 910  |
| Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser |      |      |
| 930                                                             | 935  | 940  |
| Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly |      |      |
| 945                                                             | 950  | 960  |
| Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro |      |      |
| 965                                                             | 970  | 975  |
| Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala |      |      |
| 980                                                             | 985  | 990  |
| Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg |      |      |
| 995                                                             | 1000 | 1005 |
| Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys |      |      |
| 1010                                                            | 1015 | 1020 |
| Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1025                                                            | 1030 | 1035 | 1040 |
| Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Gly Ala Ser Arg Gln Ala Gln Asp Asp Tyr Lys Asp His Asp Gly Asp |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys         |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| <210> 3                                                         |      |      |      |
| <211> 1262                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1140-CfaN-3FT                                       |      |      |      |
| <400> 3                                                         |      |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |      |
|                                                                 | 35   | 40   | 45   |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |      |
|                                                                 | 50   | 55   | 60   |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |      |
| 65                                                              | 70   | 75   | 80   |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |      |      |      |
|                                                                 | 85   | 90   | 95   |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |      |      |      |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 100                                                             | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |

|      |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
|------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|
|      |     |     |     | 725  |     |     |     | 730  |     |     |     | 735  |     |     |     |
| Leu  | Leu | Ala | Phe | Ser  | Thr | Ala | Thr | Ile  | Met | Leu | Cys | Phe  | Leu | Leu | Ser |
|      |     |     |     | 740  |     |     |     | 745  |     |     |     | 750  |     |     |     |
| Thr  | Phe | Phe | Ser | Lys  | Ala | Ser | Leu | Ala  | Ala | Ala | Cys | Ser  | Gly | Val | Ile |
|      |     |     |     | 755  |     |     |     | 760  |     |     |     | 765  |     |     |     |
| Tyr  | Phe | Thr | Leu | Tyr  | Leu | Pro | His | Ile  | Leu | Cys | Phe | Ala  | Trp | Gln | Asp |
|      |     |     |     | 770  |     |     |     | 775  |     |     |     | 780  |     |     |     |
| Arg  | Met | Thr | Ala | Glu  | Leu | Lys | Lys | Ala  | Val | Ser | Leu | Leu  | Ser | Pro | Val |
| 785  |     |     |     | 790  |     |     |     | 795  |     |     |     | 800  |     |     |     |
| Ala  | Phe | Gly | Phe | Gly  | Thr | Glu | Tyr | Leu  | Val | Arg | Phe | Glu  | Glu | Gln | Gly |
|      |     |     |     | 805  |     |     |     | 810  |     |     |     | 815  |     |     |     |
| Leu  | Gly | Leu | Gln | Trp  | Ser | Asn | Ile | Gly  | Asn | Ser | Pro | Thr  | Glu | Gly | Asp |
|      |     |     |     | 820  |     |     |     | 825  |     |     |     | 830  |     |     |     |
| Glu  | Phe | Ser | Phe | Leu  | Leu | Ser | Met | Gln  | Met | Met | Leu | Leu  | Asp | Ala | Ala |
|      |     |     |     | 835  |     |     |     | 840  |     |     |     | 845  |     |     |     |
| Val  | Tyr | Gly | Leu | Leu  | Ala | Trp | Tyr | Leu  | Asp | Gln | Val | Phe  | Pro | Gly | Asp |
| 850  |     |     |     | 855  |     |     |     | 860  |     |     |     |      |     |     |     |
| Tyr  | Gly | Thr | Pro | Leu  | Pro | Trp | Tyr | Phe  | Leu | Leu | Gln | Glu  | Ser | Tyr | Trp |
| 865  |     |     |     | 870  |     |     |     | 875  |     |     |     | 880  |     |     |     |
| Leu  | Gly | Gly | Glu | Gly  | Cys | Ser | Thr | Arg  | Glu | Glu | Arg | Ala  | Leu | Glu | Lys |
|      |     |     |     | 885  |     |     |     | 890  |     |     |     | 895  |     |     |     |
| Thr  | Glu | Pro | Leu | Thr  | Glu | Glu | Thr | Glu  | Asp | Pro | Glu | His  | Pro | Glu | Gly |
|      |     |     |     | 900  |     |     |     | 905  |     |     |     | 910  |     |     |     |
| Ile  | His | Asp | Ser | Phe  | Phe | Glu | Arg | Glu  | His | Pro | Gly | Trp  | Val | Pro | Gly |
|      |     |     |     | 915  |     |     |     | 920  |     |     |     | 925  |     |     |     |
| Val  | Cys | Val | Lys | Asn  | Leu | Val | Lys | Ile  | Phe | Glu | Pro | Cys  | Gly | Arg | Pro |
| 930  |     |     |     | 935  |     |     |     | 940  |     |     |     |      |     |     |     |
| Ala  | Val | Asp | Arg | Leu  | Asn | Ile | Thr | Phe  | Tyr | Glu | Asn | Gln  | Ile | Thr | Ala |
| 945  |     |     |     | 950  |     |     |     | 955  |     |     |     | 960  |     |     |     |
| Phe  | Leu | Gly | His | Asn  | Gly | Ala | Gly | Lys  | Thr | Thr | Thr | Leu  | Ser | Ile | Leu |
|      |     |     |     | 965  |     |     |     | 970  |     |     |     | 975  |     |     |     |
| Thr  | Gly | Leu | Leu | Pro  | Pro | Thr | Ser | Gly  | Thr | Val | Leu | Val  | Gly | Gly | Arg |
|      |     |     |     | 980  |     |     |     | 985  |     |     |     | 990  |     |     |     |
| Asp  | Ile | Glu | Thr | Ser  | Leu | Asp | Ala | Val  | Arg | Gln | Ser | Leu  | Gly | Met | Cys |
|      |     |     |     | 995  |     |     |     | 1000 |     |     |     | 1005 |     |     |     |
| Pro  | Gln | His | Asn | Ile  | Leu | Phe | His | His  | Leu | Thr | Val | Ala  | Glu | His | Met |
| 1010 |     |     |     | 1015 |     |     |     | 1020 |     |     |     |      |     |     |     |
| Leu  | Phe | Tyr | Ala | Gln  | Leu | Lys | Gly | Lys  | Ser | Gln | Glu | Glu  | Ala | Gln | Leu |
| 1025 |     |     |     | 1030 |     |     |     | 1035 |     |     |     | 1040 |     |     |     |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
| 1045                                                            | 1050 | 1055 |      |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
| 1060                                                            | 1065 | 1070 |      |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
| 1075                                                            | 1080 | 1085 |      |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
| 1090                                                            | 1095 | 1100 |      |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
| 1125                                                            | 1130 | 1135 |      |
| Arg Leu Tyr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |      |
| 1140                                                            | 1145 | 1150 |      |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |      |
| 1155                                                            | 1160 | 1165 |      |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |      |
| 1170                                                            | 1175 | 1180 |      |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |      |
| 1205                                                            | 1210 | 1215 |      |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |      |
| 1220                                                            | 1225 | 1230 |      |
| Leu Lys Gln Val Asp Gly Leu Pro Asp Tyr Lys Asp His Asp Gly Asp |      |      |      |
| 1235                                                            | 1240 | 1245 |      |
| Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys         |      |      |      |
| 1250                                                            | 1255 | 1260 |      |
| <210> 4                                                         |      |      |      |
| <211> 1192                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1140-CfaCmut-3FT                                    |      |      |      |
| <400> 4                                                         |      |      |      |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |      |      |      |
| 20                                                              | 25   | 30   |      |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ala | Ser | Asn | Cys | Ser | Gly | Thr | Pro | Leu | Phe | Leu | Lys | Asn | Cys | Phe |
| 35  |     |     |     | 40  |     |     |     | 45  |     |     |     |     |     |     |     |
| Gly | Thr | Gly | Leu | Tyr | Leu | Thr | Leu | Val | Arg | Lys | Met | Lys | Asn | Ile | Gln |
| 50  |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |     |     |
| Ser | Gln | Arg | Lys | Gly | Ser | Glu | Gly | Thr | Cys | Ser | Cys | Ser | Ser | Lys | Gly |
| 65  |     |     |     | 70  |     |     |     | 75  |     |     |     | 80  |     |     |     |
| Phe | Ser | Thr | Thr | Cys | Pro | Ala | His | Val | Asp | Asp | Leu | Thr | Pro | Glu | Gln |
| 85  |     |     |     | 90  |     |     |     | 95  |     |     |     |     |     |     |     |
| Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met | Asp | Val | Val | Leu | His | His |
| 100 |     |     |     | 105 |     |     |     | 110 |     |     |     |     |     |     |     |
| Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile | Gly | Gln | Glu | Leu | Ile | Phe |
| 115 |     |     |     | 120 |     |     |     | 125 |     |     |     |     |     |     |     |
| Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr | Ala | Ser | Leu | Phe |
| 130 |     |     |     | 135 |     |     |     | 140 |     |     |     |     |     |     |     |
| Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu | Ser | Ser | Phe | Gly |
| 145 |     |     |     | 150 |     |     |     | 155 |     |     |     | 160 |     |     |     |
| Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys | Val | Thr | Glu | Asp |
| 165 |     |     |     | 170 |     |     |     | 175 |     |     |     |     |     |     |     |
| Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu |
| 180 |     |     |     | 185 |     |     |     | 190 |     |     |     |     |     |     |     |
| Asn | Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly |
| 195 |     |     |     | 200 |     |     |     | 205 |     |     |     |     |     |     |     |
| Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala |
| 210 |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |     |     |
| His | Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln |
| 225 |     |     |     | 230 |     |     |     | 235 |     |     |     | 240 |     |     |     |
| Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln | His | Val | Gln | Ala | Leu | Leu |
| 245 |     |     |     | 250 |     |     |     | 255 |     |     |     |     |     |     |     |
| Val | Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser | His | Lys | Asp | Phe | Leu | Ala |
| 260 |     |     |     | 265 |     |     |     | 270 |     |     |     |     |     |     |     |
| Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala | Leu | Met | Leu | Ser |
| 275 |     |     |     | 280 |     |     |     | 285 |     |     |     |     |     |     |     |
| Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro |
| 290 |     |     |     | 295 |     |     |     | 300 |     |     |     |     |     |     |     |
| Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly |
| 305 |     |     |     | 310 |     |     |     | 315 |     |     |     | 320 |     |     |     |
| Ser | Glu | Gln | Phe | Thr | Val | Leu | Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly |
| 325 |     |     |     | 330 |     |     |     | 335 |     |     |     |     |     |     |     |
| Phe | Gly | Asn | Arg | Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro | Cys |



|                                         |                                 |     |
|-----------------------------------------|---------------------------------|-----|
| 340                                     | 345                             | 350 |
| Gly Asn Ser Thr Pro Trp Lys Thr         | Pro Ser Val Ser Pro Asn Ile Thr |     |
| 355                                     | 360                             | 365 |
| Gln Leu Phe Gln Lys Gln Lys Trp Thr     | Gln Val Asn Pro Ser Pro Ser     |     |
| 370                                     | 375                             | 380 |
| Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr | Met Leu Pro Glu Cys Pro         |     |
| 385                                     | 390                             | 395 |
| Glu Gly Ala Gly Gly Leu Pro Pro Pro     | Gln Arg Thr Gln Arg Ser Thr     |     |
| 405                                     | 410                             | 415 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg     | Asn Ile Ser Asp Phe Leu Val     |     |
| 420                                     | 425                             | 430 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser     | Ser Leu Lys Ser Lys Phe Trp     |     |
| 435                                     | 440                             | 445 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile     | Ser Ile Gly Gly Lys Leu Pro     |     |
| 450                                     | 455                             | 460 |
| Val Val Pro Ile Thr Gly Glu Ala Leu     | Val Gly Phe Leu Ser Asp Leu     |     |
| 465                                     | 470                             | 475 |
| Gly Arg Ile Met Asn Val Ser Gly Gly     | Pro Ile Thr Arg Glu Ala Ser     |     |
| 485                                     | 490                             | 495 |
| Lys Glu Ile Pro Asp Phe Leu Lys His     | Leu Glu Thr Glu Asp Asn Ile     |     |
| 500                                     | 505                             | 510 |
| Lys Val Trp Phe Asn Asn Lys Gly Trp     | His Ala Leu Val Ser Phe Leu     |     |
| 515                                     | 520                             | 525 |
| Asn Val Ala His Asn Ala Ile Leu Arg     | Ala Ser Leu Pro Lys Asp Arg     |     |
| 530                                     | 535                             | 540 |
| Ser Pro Glu Glu Tyr Gly Ile Thr Val     | Ile Ser Gln Pro Leu Asn Leu     |     |
| 545                                     | 550                             | 555 |
| Thr Lys Glu Gln Leu Ser Glu Ile Thr     | Val Leu Thr Thr Ser Val Asp     |     |
| 565                                     | 570                             | 575 |
| Ala Val Val Ala Ile Cys Val Ile Phe     | Ser Met Ser Phe Val Pro Ala     |     |
| 580                                     | 585                             | 590 |
| Ser Phe Val Leu Tyr Leu Ile Gln Glu     | Arg Val Asn Lys Ser Lys His     |     |
| 595                                     | 600                             | 605 |
| Leu Gln Phe Ile Ser Gly Val Ser Pro     | Thr Thr Tyr Trp Val Thr Asn     |     |
| 610                                     | 615                             | 620 |
| Phe Leu Trp Asp Ile Met Asn Tyr Ser     | Val Ser Ala Gly Leu Val Val     |     |
| 625                                     | 630                             | 635 |
| Gly Ile Phe Ile Gly Phe Gln Lys Lys     | Ala Tyr Thr Ser Pro Glu Asn     |     |
| 645                                     | 650                             | 655 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Pro Ala Leu Val Ala Leu Leu Leu Tyr Gly Trp Ala Val Ile     |     |     |
| 660                                                             | 665 | 670 |
| Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala |     |     |
| 675                                                             | 680 | 685 |
| Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser |     |     |
| 690                                                             | 695 | 700 |
| Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu |     |     |
| 705                                                             | 710 | 715 |
| Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe |     |     |
| 725                                                             | 730 | 735 |
| Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr |     |     |
| 740                                                             | 745 | 750 |
| Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His |     |     |
| 755                                                             | 760 | 765 |
| Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val |     |     |
| 770                                                             | 775 | 780 |
| Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser |     |     |
| 785                                                             | 790 | 795 |
| Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp |     |     |
| 805                                                             | 810 | 815 |
| Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr |     |     |
| 820                                                             | 825 | 830 |
| Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser |     |     |
| 835                                                             | 840 | 845 |
| Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys |     |     |
| 850                                                             | 855 | 860 |
| Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys |     |     |
| 865                                                             | 870 | 875 |
| Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala |     |     |
| 885                                                             | 890 | 895 |
| Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly |     |     |
| 900                                                             | 905 | 910 |
| Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu |     |     |
| 915                                                             | 920 | 925 |
| His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile |     |     |
| 930                                                             | 935 | 940 |
| Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr |     |     |
| 945                                                             | 950 | 955 |
| Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu |     |     |

|                                                                 |      |      |      |      |      |
|-----------------------------------------------------------------|------|------|------|------|------|
|                                                                 | 965  |      | 970  |      | 975  |
| Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp |      |      |      |      |      |
|                                                                 | 980  |      | 985  |      | 990  |
| Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn |      |      |      |      |      |
|                                                                 | 995  |      | 1000 |      | 1005 |
| Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser |      |      |      |      |      |
|                                                                 | 1010 |      | 1015 |      | 1020 |
| His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met |      |      |      |      |      |
| 1025                                                            |      | 1030 |      | 1035 | 1040 |
| Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser |      |      |      |      |      |
|                                                                 | 1045 |      | 1050 |      | 1055 |
| Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys |      |      |      |      |      |
|                                                                 | 1060 |      | 1065 |      | 1070 |
| Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly |      |      |      |      |      |
|                                                                 | 1075 |      | 1080 |      | 1085 |
| Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln |      |      |      |      |      |
|                                                                 | 1090 |      | 1095 |      | 1100 |
| Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu |      |      |      |      |      |
| 1105                                                            |      | 1110 |      | 1115 | 1120 |
| Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr |      |      |      |      |      |
|                                                                 | 1125 |      | 1130 |      | 1135 |
| Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser |      |      |      |      |      |
|                                                                 | 1140 |      | 1145 |      | 1150 |
| His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala |      |      |      |      |      |
|                                                                 | 1155 |      | 1160 |      | 1165 |
| Gln Asp Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile |      |      |      |      |      |
|                                                                 | 1170 |      | 1175 |      | 1180 |
| Asp Tyr Lys Asp Asp Asp Asp Lys                                 |      |      |      |      |      |
| 1185                                                            |      | 1190 |      |      |      |
| <210> 5                                                         |      |      |      |      |      |
| <211> 1310                                                      |      |      |      |      |      |
| <212> PRT                                                       |      |      |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |      |      |
| <220>                                                           |      |      |      |      |      |
| <223> ABCA4-1188-CfaN-3FT                                       |      |      |      |      |      |
| <400> 5                                                         |      |      |      |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |      |      |      |
| 1                                                               |      | 5    |      | 10   | 15   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |      |      |      |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|     |     |     | 20  |     |     |     | 25  |     |     |     | 30  |     |     |     |     |     |  |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |     |  |
|     |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |     |  |
|     |     |     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |  |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |     |  |
| 65  |     |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |     |  |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |     |  |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |     |  |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |  |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |     |  |
|     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |     |  |
| 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |     |  |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |     |  |
| 145 |     |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |     |  |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |  |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |     |  |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |  |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |     |  |
| 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |     |  |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |     |  |
| 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |     |  |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |     |  |
| 225 |     |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |     |  |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |     |  |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |     |  |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |  |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |     |  |
| 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     |     |  |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |     |  |
| 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |     |  |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |     |  |
| 305 |     |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |     |  |
|     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |  |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |     |     |     |     |  |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys |  |
| 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |     |     |     |  |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |  |
| 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |     |     |  |
| Gln | Gly | Val | Ser | Asn | Ala | Val | Ile | Trp | Cys | Thr | Trp | Phe | Leu | Asp | Ser |  |
| 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |     |  |
| Phe | Ser | Ile | Met | Ser | Met | Ser | Ile | Phe | Leu | Leu | Thr | Ile | Phe | Ile | Met |  |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |  |
| His | Gly | Arg | Ile | Leu | His | Tyr | Ser | Asp | Pro | Phe | Ile | Leu | Phe | Leu | Phe |  |
| 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |     |     |     |     |  |
| Leu | Leu | Ala | Phe | Ser | Thr | Ala | Thr | Ile | Met | Leu | Cys | Phe | Leu | Leu | Ser |  |
| 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |     |     |     |     |  |
| Thr | Phe | Phe | Ser | Lys | Ala | Ser | Leu | Ala | Ala | Ala | Cys | Ser | Gly | Val | Ile |  |
| 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |     |     |     |     |  |
| Tyr | Phe | Thr | Leu | Tyr | Leu | Pro | His | Ile | Leu | Cys | Phe | Ala | Trp | Gln | Asp |  |
| 770 |     |     |     |     | 775 |     |     |     |     | 780 |     |     |     |     |     |  |
| Arg | Met | Thr | Ala | Glu | Leu | Lys | Lys | Ala | Val | Ser | Leu | Leu | Ser | Pro | Val |  |
| 785 |     |     |     |     | 790 |     |     |     |     | 795 |     |     |     |     | 800 |  |
| Ala | Phe | Gly | Phe | Gly | Thr | Glu | Tyr | Leu | Val | Arg | Phe | Glu | Glu | Gln | Gly |  |
| 805 |     |     |     |     | 810 |     |     |     |     | 815 |     |     |     |     |     |  |
| Leu | Gly | Leu | Gln | Trp | Ser | Asn | Ile | Gly | Asn | Ser | Pro | Thr | Glu | Gly | Asp |  |
| 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |     |     |     |     |  |
| Glu | Phe | Ser | Phe | Leu | Leu | Ser | Met | Gln | Met | Met | Leu | Leu | Asp | Ala | Ala |  |
| 835 |     |     |     |     | 840 |     |     |     |     | 845 |     |     |     |     |     |  |
| Val | Tyr | Gly | Leu | Leu | Ala | Trp | Tyr | Leu | Asp | Gln | Val | Phe | Pro | Gly | Asp |  |
| 850 |     |     |     |     | 855 |     |     |     |     | 860 |     |     |     |     |     |  |
| Tyr | Gly | Thr | Pro | Leu | Pro | Trp | Tyr | Phe | Leu | Leu | Gln | Glu | Ser | Tyr | Trp |  |
| 865 |     |     |     |     | 870 |     |     |     |     | 875 |     |     |     |     | 880 |  |
| Leu | Gly | Gly | Glu | Gly | Cys | Ser | Thr | Arg | Glu | Glu | Arg | Ala | Leu | Glu | Lys |  |
| 885 |     |     |     |     | 890 |     |     |     |     | 895 |     |     |     |     |     |  |
| Thr | Glu | Pro | Leu | Thr | Glu | Glu | Thr | Glu | Asp | Pro | Glu | His | Pro | Glu | Gly |  |
| 900 |     |     |     |     | 905 |     |     |     |     | 910 |     |     |     |     |     |  |
| Ile | His | Asp | Ser | Phe | Phe | Glu | Arg | Glu | His | Pro | Gly | Trp | Val | Pro | Gly |  |
| 915 |     |     |     |     | 920 |     |     |     |     | 925 |     |     |     |     |     |  |
| Val | Cys | Val | Lys | Asn | Leu | Val | Lys | Ile | Phe | Glu | Pro | Cys | Gly | Arg | Pro |  |
| 930 |     |     |     |     | 935 |     |     |     |     | 940 |     |     |     |     |     |  |
| Ala | Val | Asp | Arg | Leu | Asn | Ile | Thr | Phe | Tyr | Glu | Asn | Gln | Ile | Thr | Ala |  |
| 945 |     |     |     |     | 950 |     |     |     |     | 955 |     |     |     |     | 960 |  |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |
| 1140                                                            | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |
| 1155                                                            | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |
| 1170                                                            | 1175 | 1180 |
| Ser Thr Thr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |
| 1185                                                            | 1190 | 1195 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |
| 1205                                                            | 1210 | 1215 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |
| 1220                                                            | 1225 | 1230 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |
| 1235                                                            | 1240 | 1245 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |
| 1250                                                            | 1255 | 1260 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1265                                                            | 1270 | 1275 | 1280 |
| Leu Lys Gln Val Asp Gly Leu Pro Asp Tyr Lys Asp His Asp Gly Asp |      |      |      |
|                                                                 | 1285 | 1290 | 1295 |
| Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys         |      |      |      |
|                                                                 | 1300 | 1305 | 1310 |
| <210> 6                                                         |      |      |      |
| <211> 1144                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1188-Cfacmut-3FT                                    |      |      |      |
| <400> 6                                                         |      |      |      |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Val Ala Ser Asn Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln |      |      |      |
|                                                                 | 35   | 40   | 45   |
| Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His |      |      |      |
|                                                                 | 50   | 55   | 60   |
| Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe |      |      |      |
| 65                                                              | 70   | 75   | 80   |
| Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe |      |      |      |
|                                                                 | 85   | 90   | 95   |
| Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly |      |      |      |
|                                                                 | 100  | 105  | 110  |
| Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp |      |      |      |
|                                                                 | 115  | 120  | 125  |
| Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu |      |      |      |
|                                                                 | 130  | 135  | 140  |
| Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly |      |      |      |
| 145                                                             | 150  | 155  | 160  |
| Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala |      |      |      |
|                                                                 | 165  | 170  | 175  |
| His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln |      |      |      |
|                                                                 | 180  | 185  | 190  |
| Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu |      |      |      |
|                                                                 | 195  | 200  | 205  |
| Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala |      |      |      |



|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 210                                                             | 215 | 220 |
| Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser |     |     |
| 225                                                             | 230 | 235 |
| Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro |     | 240 |
|                                                                 | 245 | 250 |
| Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly |     | 255 |
|                                                                 | 260 | 265 |
| Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly |     | 270 |
|                                                                 | 275 | 280 |
| Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys |     | 285 |
| 290                                                             | 295 | 300 |
| Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr |     |     |
| 305                                                             | 310 | 315 |
| Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser |     | 320 |
|                                                                 | 325 | 330 |
| Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro |     | 335 |
|                                                                 | 340 | 345 |
| Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr |     | 350 |
|                                                                 | 355 | 360 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val |     | 365 |
| 370                                                             | 375 | 380 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp |     |     |
| 385                                                             | 390 | 395 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro |     | 400 |
|                                                                 | 405 | 410 |
| Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu |     | 415 |
|                                                                 | 420 | 425 |
| Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser |     | 430 |
|                                                                 | 435 | 440 |
| Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile |     | 445 |
|                                                                 | 450 | 455 |
| Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu |     | 460 |
| 465                                                             | 470 | 475 |
| Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg |     | 480 |
|                                                                 | 485 | 490 |
| Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu |     | 495 |
|                                                                 | 500 | 505 |
| Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp |     | 510 |
| 515                                                             | 520 | 525 |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala |     |         |
| 530                                                             | 535 | 540     |
| Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His |     |         |
| 545                                                             | 550 | 555 560 |
| Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn |     |         |
|                                                                 | 565 | 570 575 |
| Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val |     |         |
|                                                                 | 580 | 585 590 |
| Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn |     |         |
|                                                                 | 595 | 600 605 |
| Leu Pro Ala Leu Val Ala Leu Leu Leu Tyr Gly Trp Ala Val Ile     |     |         |
|                                                                 | 610 | 615 620 |
| Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala |     |         |
| 625                                                             | 630 | 635 640 |
| Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser |     |         |
|                                                                 | 645 | 650 655 |
| Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu |     |         |
|                                                                 | 660 | 665 670 |
| Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe |     |         |
|                                                                 | 675 | 680 685 |
| Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr |     |         |
|                                                                 | 690 | 695 700 |
| Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His |     |         |
| 705                                                             | 710 | 715 720 |
| Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val |     |         |
|                                                                 | 725 | 730 735 |
| Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser |     |         |
|                                                                 | 740 | 745 750 |
| Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp |     |         |
|                                                                 | 755 | 760 765 |
| Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr |     |         |
|                                                                 | 770 | 775 780 |
| Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser |     |         |
| 785                                                             | 790 | 795 800 |
| Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys |     |         |
|                                                                 | 805 | 810 815 |
| Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys |     |         |
|                                                                 | 820 | 825 830 |
| Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala |     |         |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 835                                                             | 840  | 845  |
| Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly |      |      |
| 850                                                             | 855  | 860  |
| Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu |      |      |
| 865                                                             | 870  | 875  |
| His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile |      | 880  |
| 885                                                             | 890  | 895  |
| Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr |      |      |
| 900                                                             | 905  | 910  |
| Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu |      |      |
| 915                                                             | 920  | 925  |
| Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp |      |      |
| 930                                                             | 935  | 940  |
| Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn |      |      |
| 945                                                             | 950  | 955  |
| Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser |      |      |
| 965                                                             | 970  | 975  |
| His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met |      |      |
| 980                                                             | 985  | 990  |
| Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser |      |      |
| 995                                                             | 1000 | 1005 |
| Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys |      |      |
| 1010                                                            | 1015 | 1020 |
| Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly |      |      |
| 1025                                                            | 1030 | 1035 |
| Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln |      |      |
| 1045                                                            | 1050 | 1055 |
| Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu |      |      |
| 1060                                                            | 1065 | 1070 |
| Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser |      |      |
| 1090                                                            | 1095 | 1100 |
| His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala |      |      |
| 1105                                                            | 1110 | 1115 |
| Gln Asp Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile |      |      |
| 1125                                                            | 1130 | 1135 |
| Asp Tyr Lys Asp Asp Asp Asp Lys                                 |      |      |
| 1140                                                            |      |      |

&lt;210&gt; 7

&lt;211&gt; 2295

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4-3FT

&lt;400&gt; 7

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Leu | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |
|     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |
|     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |
| 65  |     |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |
|     |     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     | 95  |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |
|     |     |     |     |     |     | 100 |     |     |     |     | 105 |     |     |     | 110 |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |
|     |     |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     | 125 |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
|     |     |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     | 140 |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     |     |     |     |     |     |     | 150 |     |     |     | 155 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     |     |     | 165 |     |     |     |     |     |     |     |     | 170 |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     |     |     |     | 180 |     |     |     |     |     |     |     |     | 185 |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     |     |     |     |     | 195 |     |     |     |     |     |     |     |     | 200 |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     |     |     |     |     |     | 210 |     |     |     |     |     |     |     |     | 215 |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
| 225 |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 230 |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     |     |     |     | 245 |     |     |     |     |     |     |     |     | 250 |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 255 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |  |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly |  |  |
|     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |  |  |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe |  |  |
|     |     |     |     | 595 |     |     |     | 600 |     |     |     |     |     | 605 |     |  |  |
| Ala | Tyr | Leu | Gln | Asp | Met | Val | Glu | Gln | Gly | Ile | Thr | Arg | Ser | Gln | Val |  |  |
|     |     |     |     | 610 |     |     |     | 615 |     |     |     |     |     | 620 |     |  |  |
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro |  |  |
| 625 |     |     |     |     |     | 630 |     |     |     | 635 |     |     |     | 640 |     |  |  |
| Cys | Phe | Val | Asp | Asp | Ser | Phe | Met | Ile | Ile | Leu | Asn | Arg | Cys | Phe | Pro |  |  |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |  |  |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys |  |  |
|     |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |  |  |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |  |  |
|     |     |     |     | 675 |     |     |     | 680 |     |     |     |     |     | 685 |     |  |  |
| Gln | Gly | Val | Ser | Asn | Ala | Val | Ile | Trp | Cys | Thr | Trp | Phe | Leu | Asp | Ser |  |  |
|     |     |     |     | 690 |     |     |     | 695 |     |     |     |     |     | 700 |     |  |  |
| Phe | Ser | Ile | Met | Ser | Met | Ser | Ile | Phe | Leu | Leu | Thr | Ile | Phe | Ile | Met |  |  |
| 705 |     |     |     |     |     | 710 |     |     |     | 715 |     |     |     | 720 |     |  |  |
| His | Gly | Arg | Ile | Leu | His | Tyr | Ser | Asp | Pro | Phe | Ile | Leu | Phe | Leu | Phe |  |  |
|     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |  |  |
| Leu | Leu | Ala | Phe | Ser | Thr | Ala | Thr | Ile | Met | Leu | Cys | Phe | Leu | Leu | Ser |  |  |
|     |     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |  |  |
| Thr | Phe | Phe | Ser | Lys | Ala | Ser | Leu | Ala | Ala | Ala | Cys | Ser | Gly | Val | Ile |  |  |
|     |     |     |     | 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |  |  |
| Tyr | Phe | Thr | Leu | Tyr | Leu | Pro | His | Ile | Leu | Cys | Phe | Ala | Trp | Gln | Asp |  |  |
|     |     |     |     | 770 |     |     |     | 775 |     |     |     |     |     | 780 |     |  |  |
| Arg | Met | Thr | Ala | Glu | Leu | Lys | Lys | Ala | Val | Ser | Leu | Leu | Ser | Pro | Val |  |  |
| 785 |     |     |     |     |     | 790 |     |     |     | 795 |     |     |     | 800 |     |  |  |
| Ala | Phe | Gly | Phe | Gly | Thr | Glu | Tyr | Leu | Val | Arg | Phe | Glu | Glu | Gln | Gly |  |  |
|     |     |     |     | 805 |     |     |     |     | 810 |     |     |     |     | 815 |     |  |  |
| Leu | Gly | Leu | Gln | Trp | Ser | Asn | Ile | Gly | Asn | Ser | Pro | Thr | Glu | Gly | Asp |  |  |
|     |     |     |     | 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |  |  |
| Glu | Phe | Ser | Phe | Leu | Leu | Ser | Met | Gln | Met | Met | Leu | Leu | Asp | Ala | Ala |  |  |
|     |     |     |     | 835 |     |     |     | 840 |     |     |     |     |     | 845 |     |  |  |
| Val | Tyr | Gly | Leu | Leu | Ala | Trp | Tyr | Leu | Asp | Gln | Val | Phe | Pro | Gly | Asp |  |  |
|     |     |     |     | 850 |     |     |     | 855 |     |     |     |     |     | 860 |     |  |  |
| Tyr | Gly | Thr | Pro | Leu | Pro | Trp | Tyr | Phe | Leu | Leu | Gln | Glu | Ser | Tyr | Trp |  |  |
| 865 |     |     |     |     |     | 870 |     |     |     | 875 |     |     |     | 880 |     |  |  |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |
| 1140                                                            | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |
| 1155                                                            | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |
| 1170                                                            | 1175 | 1180 |
| Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1185                                                            | 1190 | 1195 | 1200 |
| Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser |      |      |      |
| 1265                                                            | 1270 | 1275 | 1280 |
| Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn |      |      |      |
|                                                                 | 1285 | 1290 | 1295 |
| Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln |      |      |      |
|                                                                 | 1300 | 1305 | 1310 |
| Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His |      |      |      |
|                                                                 | 1315 | 1320 | 1325 |
| Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu |      |      |      |
|                                                                 | 1330 | 1335 | 1340 |
| Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val |      |      |      |
| 1345                                                            | 1350 | 1355 | 1360 |
| Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln |      |      |      |
|                                                                 | 1365 | 1370 | 1375 |
| Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile |      |      |      |
|                                                                 | 1380 | 1385 | 1390 |
| Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp |      |      |      |
|                                                                 | 1395 | 1400 | 1405 |
| Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser |      |      |      |
|                                                                 | 1410 | 1415 | 1420 |
| Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe |      |      |      |
| 1425                                                            | 1430 | 1435 | 1440 |
| Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly |      |      |      |
|                                                                 | 1445 | 1450 | 1455 |
| Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln |      |      |      |
|                                                                 | 1460 | 1465 | 1470 |
| Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys |      |      |      |
|                                                                 | 1475 | 1480 | 1485 |
| Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu |      |      |      |
| 1490                                                            | 1495 | 1500 |      |



|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu |      |      |      |
| 1505                                                            | 1510 | 1515 | 1520 |
| Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys |      |      |      |
|                                                                 | 1525 | 1530 | 1535 |
| Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val |      |      |      |
|                                                                 | 1540 | 1545 | 1550 |
| Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val |      |      |      |
|                                                                 | 1555 | 1560 | 1565 |
| Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly |      |      |      |
|                                                                 | 1570 | 1575 | 1580 |
| Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys |      |      |      |
| 1585                                                            | 1590 | 1595 | 1600 |
| Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys |      |      |      |
|                                                                 | 1605 | 1610 | 1615 |
| Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn |      |      |      |
|                                                                 | 1620 | 1625 | 1630 |
| Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser |      |      |      |
|                                                                 | 1635 | 1640 | 1645 |
| Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr |      |      |      |
|                                                                 | 1650 | 1655 | 1660 |
| Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala |      |      |      |
| 1665                                                            | 1670 | 1675 | 1680 |
| Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser |      |      |      |
|                                                                 | 1685 | 1690 | 1695 |
| Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu |      |      |      |
|                                                                 | 1700 | 1705 | 1710 |
| Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe |      |      |      |
|                                                                 | 1715 | 1720 | 1725 |
| Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly |      |      |      |
|                                                                 | 1730 | 1735 | 1740 |
| Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu |      |      |      |
| 1745                                                            | 1750 | 1755 | 1760 |
| Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro |      |      |      |
|                                                                 | 1765 | 1770 | 1775 |
| Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr |      |      |      |
|                                                                 | 1780 | 1785 | 1790 |
| Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala |      |      |      |
|                                                                 | 1795 | 1800 | 1805 |
| Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg |      |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1810                                                            | 1815 | 1820 |
| Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys |      |      |
| 1825                                                            | 1830 | 1835 |
| Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp |      |      |
|                                                                 | 1845 | 1850 |
| Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp |      |      |
|                                                                 | 1860 | 1865 |
| Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val |      |      |
|                                                                 | 1875 | 1880 |
| Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln |      |      |
| 1890                                                            | 1895 | 1900 |
| Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp |      |      |
| 1905                                                            | 1910 | 1915 |
| Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp |      |      |
|                                                                 | 1925 | 1930 |
| Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser |      |      |
|                                                                 | 1940 | 1945 |
| Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe |      |      |
| 1955                                                            | 1960 | 1965 |
| Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met |      |      |
| 1970                                                            | 1975 | 1980 |
| Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly |      |      |
| 1985                                                            | 1990 | 1995 |
| Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr |      |      |
|                                                                 | 2005 | 2010 |
| Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His |      |      |
|                                                                 | 2020 | 2025 |
| Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu |      |      |
| 2035                                                            | 2040 | 2045 |
| Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala |      |      |
| 2050                                                            | 2055 | 2060 |
| Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser |      |      |
| 2065                                                            | 2070 | 2075 |
| Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu |      |      |
|                                                                 | 2085 | 2090 |
| Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val |      |      |
|                                                                 | 2100 | 2105 |
| Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His |      |      |
| 2115                                                            | 2120 | 2125 |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val |      |           |
| 2130                                                            | 2135 | 2140      |
| Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys |      |           |
| 2145                                                            | 2150 | 2155 2160 |
| Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp |      |           |
| 2165                                                            | 2170 | 2175      |
| Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn |      |           |
| 2180                                                            | 2185 | 2190      |
| Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe |      |           |
| 2195                                                            | 2200 | 2205      |
| Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser |      |           |
| 2210                                                            | 2215 | 2220      |
| His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr |      |           |
| 2225                                                            | 2230 | 2235 2240 |
| Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His |      |           |
| 2245                                                            | 2250 | 2255      |
| Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln |      |           |
| 2260                                                            | 2265 | 2270      |
| Asp Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile Asp |      |           |
| 2275                                                            | 2280 | 2285      |
| Tyr Lys Asp Asp Asp Asp Lys                                     |      |           |
| 2290                                                            | 2295 |           |
| <210> 8                                                         |      |           |
| <211> 1273                                                      |      |           |
| <212> PRT                                                       |      |           |
| <213> 人工序列(Artificial Sequence)                                 |      |           |
| <220>                                                           |      |           |
| <223> ABCA4-1150-NpuN-3FT                                       |      |           |
| <400> 8                                                         |      |           |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |           |
| 1                                                               | 5    | 10 15     |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |           |
| 20                                                              | 25   | 30        |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |           |
| 35                                                              | 40   | 45        |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |           |
| 50                                                              | 55   | 60        |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |           |
| 65                                                              | 70   | 75 80     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |  |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |  |
|     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |  |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |  |
|     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |  |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |  |
|     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |  |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |  |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |  |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |  |
|     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |  |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |  |
|     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |  |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |  |
|     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |  |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |  |
|     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |  |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |  |
|     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |  |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |  |
|     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |  |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |  |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |  |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |  |
|     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |  |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |  |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |  |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |  |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |     |
|                                                                 | 690 | 695 | 700 |

|                                                                 |     |      |      |
|-----------------------------------------------------------------|-----|------|------|
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |      |      |
| 705                                                             | 710 | 715  | 720  |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |      |      |
|                                                                 | 725 | 730  | 735  |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |      |      |
|                                                                 | 740 | 745  | 750  |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |      |      |
|                                                                 | 755 | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |      |      |
|                                                                 | 770 | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |      |      |
|                                                                 | 785 | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |      |      |
|                                                                 | 805 | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |      |      |
|                                                                 | 820 | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |      |      |
|                                                                 | 835 | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |     |      |      |
|                                                                 | 850 | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |     |      |      |
|                                                                 | 865 | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |     |      |      |
|                                                                 | 885 | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |     |      |      |
|                                                                 | 900 | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |     |      |      |
|                                                                 | 915 | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |     |      |      |
|                                                                 | 930 | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |     |      |      |
|                                                                 | 945 | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |     |      |      |
|                                                                 | 965 | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |     |      |      |
|                                                                 | 980 | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |     |      |      |
|                                                                 | 995 | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |     |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1010                                                            | 1015 | 1020 |      |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Leu Ser |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Tyr Glu Thr Glu Ile Leu Thr Val Glu Tyr Gly Leu Leu Pro Ile Gly |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Lys Ile Val Glu Lys Arg Ile Glu Cys Thr Val Tyr Ser Val Asp Asn |      |      |      |
| 1170                                                            | 1175 | 1180 |      |
| Asn Gly Asn Ile Tyr Thr Gln Pro Val Ala Gln Trp His Asp Arg Gly |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Leu Ile Arg |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Ala Thr Lys Asp His Lys Phe Met Thr Val Asp Gly Gln Met Leu Pro |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Ile Asp Glu Ile Phe Glu Arg Glu Leu Asp Leu Met Arg Val Asp Asn |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Leu Pro Asn Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Ile Asp Tyr Lys Asp Asp Asp Asp Lys                             |      |      |      |
| 1265                                                            | 1270 |      |      |
| <210> 9                                                         |      |      |      |
| <211> 1182                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1150-NpuC-3FT                                       |      |      |      |

&lt;400&gt; 9

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Lys | Ile | Ala | Thr | Arg | Lys | Tyr | Leu | Gly | Lys | Gln | Asn | Val | Tyr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Asp | Ile | Gly | Val | Glu | Arg | Asp | His | Asn | Phe | Ala | Leu | Lys | Asn | Gly | Phe |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Ile | Ala | Ser | Asn | Cys | Phe | Gly | Thr | Gly | Leu | Tyr | Leu | Thr | Leu | Val | Arg |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Lys | Met | Lys | Asn | Ile | Gln | Ser | Gln | Arg | Lys | Gly | Ser | Glu | Gly | Thr | Cys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Ser | Cys | Ser | Ser | Lys | Gly | Phe | Ser | Thr | Thr | Cys | Pro | Ala | His | Val | Asp |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Asp | Leu | Thr | Pro | Glu | Gln | Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     | 95  |     |     |
| Asp | Val | Val | Leu | His | His | Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Gly | Gln | Glu | Leu | Ile | Phe | Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Ala | Tyr | Ala | Ser | Leu | Phe | Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Gly | Leu | Ser | Ser | Phe | Gly | Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe |
| 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |     |
| Leu | Lys | Val | Thr | Glu | Asp | Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly |
|     |     |     | 165 |     |     |     |     |     | 170 |     |     |     | 175 |     |     |
| Ala | Gln | Gln | Lys | Arg | Glu | Asn | Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Pro | Arg | Glu | Lys | Ala | Gly | Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser |
|     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |
| Pro | Gly | Ala | Pro | Ala | Ala | His | Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro |
|     | 210 |     |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |
| Glu | Cys | Pro | Gly | Pro | Gln | Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     | 240 |     |
| His | Val | Gln | Ala | Leu | Leu | Val | Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     | 255 |     |     |
| His | Lys | Asp | Phe | Leu | Ala | Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Leu | Ala | Leu | Met | Leu | Ser | Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Ala | Leu | Thr | Leu | His | Pro | Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |



|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val |     |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 610                                                             | 615 | 620 |
| Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala |     |     |
| 625                                                             | 630 | 635 |
| Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu Leu |     | 640 |
| 645                                                             | 650 | 655 |
| Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe |     |     |
| 660                                                             | 665 | 670 |
| Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe |     |     |
| 675                                                             | 680 | 685 |
| Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu |     |     |
| 690                                                             | 695 | 700 |
| Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu |     |     |
| 705                                                             | 710 | 715 |
| Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala |     |     |
| 725                                                             | 730 | 735 |
| Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His |     |     |
| 740                                                             | 745 | 750 |
| Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala |     |     |
| 755                                                             | 760 | 765 |
| Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln |     |     |
| 770                                                             | 775 | 780 |
| Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro |     |     |
| 785                                                             | 790 | 795 |
| Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile |     |     |
| 805                                                             | 810 | 815 |
| Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys |     |     |
| 820                                                             | 825 | 830 |
| Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly |     |     |
| 835                                                             | 840 | 845 |
| Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly |     |     |
| 850                                                             | 855 | 860 |
| Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser |     |     |
| 865                                                             | 870 | 875 |
| Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu |     |     |
| 885                                                             | 890 | 895 |
| Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu |     |     |
| 900                                                             | 905 | 910 |
| Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly |     |     |
| 915                                                             | 920 | 925 |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser |      |           |
| 930                                                             | 935  | 940       |
| Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly |      |           |
| 945                                                             | 950  | 955 960   |
| Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro |      |           |
| 965                                                             | 970  | 975       |
| Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala |      |           |
| 980                                                             | 985  | 990       |
| Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg |      |           |
| 995                                                             | 1000 | 1005      |
| Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys |      |           |
| 1010                                                            | 1015 | 1020      |
| Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr |      |           |
| 1025                                                            | 1030 | 1035 1040 |
| Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met |      |           |
| 1045                                                            | 1050 | 1055      |
| Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val |      |           |
| 1060                                                            | 1065 | 1070      |
| Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg |      |           |
| 1075                                                            | 1080 | 1085      |
| His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg |      |           |
| 1090                                                            | 1095 | 1100      |
| Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu |      |           |
| 1105                                                            | 1110 | 1115 1120 |
| Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala |      |           |
| 1125                                                            | 1130 | 1135      |
| Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala |      |           |
| 1140                                                            | 1145 | 1150      |
| Gly Ala Ser Arg Gln Ala Gln Asp Asp Tyr Lys Asp His Asp Gly Asp |      |           |
| 1155                                                            | 1160 | 1165      |
| Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys         |      |           |
| 1170                                                            | 1175 | 1180      |
| <210> 10                                                        |      |           |
| <211> 1263                                                      |      |           |
| <212> PRT                                                       |      |           |
| <213> 人工序列(Artificial Sequence)                                 |      |           |
| <220>                                                           |      |           |
| <223> ABCA4-1140-NpuN-3FT                                       |      |           |
| <400> 10                                                        |      |           |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Leu | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |
|     |     |     |     | 85  |     |     |     | 90  |     |     |     |     |     | 95  |     |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     | 255 |     |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     |     | 270 |     |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     |     | 285 |     |     |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
|     | 290 |     |     |     |     | 295 |     |     |     |     |     | 300 |     |     |     |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 305                                                             | 310 | 315 | 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |
| 610                                                             | 615 | 620 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro |
| 625 |     |     |     |     |     |     | 630 |     |     | 635 |     |     |     |     | 640 |
| Cys | Phe | Val | Asp | Asp | Ser | Phe | Met | Ile | Ile | Leu | Asn | Arg | Cys | Phe | Pro |
|     |     |     |     |     |     |     | 645 |     |     | 650 |     |     |     |     | 655 |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys |
|     |     |     |     |     |     |     | 660 |     |     | 665 |     |     |     |     | 670 |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |
|     |     |     |     |     |     |     | 675 |     |     | 680 |     |     |     |     | 685 |
| Gln | Gly | Val | Ser | Asn | Ala | Val | Ile | Trp | Cys | Thr | Trp | Phe | Leu | Asp | Ser |
|     |     |     |     |     |     |     | 690 |     |     | 695 |     |     |     |     | 700 |
| Phe | Ser | Ile | Met | Ser | Met | Ser | Ile | Phe | Leu | Leu | Thr | Ile | Phe | Ile | Met |
| 705 |     |     |     |     |     |     | 710 |     |     | 715 |     |     |     |     | 720 |
| His | Gly | Arg | Ile | Leu | His | Tyr | Ser | Asp | Pro | Phe | Ile | Leu | Phe | Leu | Phe |
|     |     |     |     |     |     |     | 725 |     |     | 730 |     |     |     |     | 735 |
| Leu | Leu | Ala | Phe | Ser | Thr | Ala | Thr | Ile | Met | Leu | Cys | Phe | Leu | Leu | Ser |
|     |     |     |     |     |     |     | 740 |     |     | 745 |     |     |     |     | 750 |
| Thr | Phe | Phe | Ser | Lys | Ala | Ser | Leu | Ala | Ala | Ala | Cys | Ser | Gly | Val | Ile |
|     |     |     |     |     |     |     | 755 |     |     | 760 |     |     |     |     | 765 |
| Tyr | Phe | Thr | Leu | Tyr | Leu | Pro | His | Ile | Leu | Cys | Phe | Ala | Trp | Gln | Asp |
|     |     |     |     |     |     |     | 770 |     |     | 775 |     |     |     |     | 780 |
| Arg | Met | Thr | Ala | Glu | Leu | Lys | Lys | Ala | Val | Ser | Leu | Leu | Ser | Pro | Val |
| 785 |     |     |     |     |     |     | 790 |     |     | 795 |     |     |     |     | 800 |
| Ala | Phe | Gly | Phe | Gly | Thr | Glu | Tyr | Leu | Val | Arg | Phe | Glu | Glu | Gln | Gly |
|     |     |     |     |     |     |     | 805 |     |     | 810 |     |     |     |     | 815 |
| Leu | Gly | Leu | Gln | Trp | Ser | Asn | Ile | Gly | Asn | Ser | Pro | Thr | Glu | Gly | Asp |
|     |     |     |     |     |     |     | 820 |     |     | 825 |     |     |     |     | 830 |
| Glu | Phe | Ser | Phe | Leu | Leu | Ser | Met | Gln | Met | Met | Leu | Leu | Asp | Ala | Ala |
|     |     |     |     |     |     |     | 835 |     |     | 840 |     |     |     |     | 845 |
| Val | Tyr | Gly | Leu | Leu | Ala | Trp | Tyr | Leu | Asp | Gln | Val | Phe | Pro | Gly | Asp |
|     |     |     |     |     |     |     | 850 |     |     | 855 |     |     |     |     | 860 |
| Tyr | Gly | Thr | Pro | Leu | Pro | Trp | Tyr | Phe | Leu | Leu | Gln | Glu | Ser | Tyr | Trp |
| 865 |     |     |     |     |     |     | 870 |     |     | 875 |     |     |     |     | 880 |
| Leu | Gly | Gly | Glu | Gly | Cys | Ser | Thr | Arg | Glu | Glu | Arg | Ala | Leu | Glu | Lys |
|     |     |     |     |     |     |     | 885 |     |     | 890 |     |     |     |     | 895 |
| Thr | Glu | Pro | Leu | Thr | Glu | Glu | Thr | Glu | Asp | Pro | Glu | His | Pro | Glu | Gly |
|     |     |     |     |     |     |     | 900 |     |     | 905 |     |     |     |     | 910 |
| Ile | His | Asp | Ser | Phe | Phe | Glu | Arg | Glu | His | Pro | Gly | Trp | Val | Pro | Gly |
|     |     |     |     |     |     |     | 915 |     |     | 920 |     |     |     |     | 925 |
| Val | Cys | Val | Lys | Asn | Leu | Val | Lys | Ile | Phe | Glu | Pro | Cys | Gly | Arg | Pro |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Leu Ser Tyr Glu Thr Glu Ile Leu Thr Val Glu Tyr |      |      |
| 1140                                                            | 1145 | 1150 |
| Gly Leu Leu Pro Ile Gly Lys Ile Val Glu Lys Arg Ile Glu Cys Thr |      |      |
| 1155                                                            | 1160 | 1165 |
| Val Tyr Ser Val Asp Asn Asn Gly Asn Ile Tyr Thr Gln Pro Val Ala |      |      |
| 1170                                                            | 1175 | 1180 |
| Gln Trp His Asp Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |
| 1185                                                            | 1190 | 1195 |
| Asp Gly Ser Leu Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Val |      |      |
| 1205                                                            | 1210 | 1215 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Glu Leu Asp |      |      |
| 1220                                                            | 1225 | 1230 |
| Leu Met Arg Val Asp Asn Leu Pro Asn Asp Tyr Lys Asp His Asp Gly |      |      |
| 1235                                                            | 1240 | 1245 |

Asp Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys  
 1250 1255 1260  
 <210> 11  
 <211> 1192  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1140-NpuC-3FT  
 <400> 11  
 Met Ile Lys Ile Ala Thr Arg Lys Tyr Leu Gly Lys Gln Asn Val Tyr  
 1 5 10 15  
 Asp Ile Gly Val Glu Arg Asp His Asn Phe Ala Leu Lys Asn Gly Phe  
 20 25 30  
 Ile Ala Ser Asn Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe  
 35 40 45  
 Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln  
 50 55 60  
 Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly  
 65 70 75 80  
 Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln  
 85 90 95  
 Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His  
 100 105 110  
 Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe  
 115 120 125  
 Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe  
 130 135 140  
 Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly  
 145 150 155 160  
 Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp  
 165 170 175  
 Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu  
 180 185 190  
 Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly  
 195 200 205  
 Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala  
 210 215 220  
 His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln  
 225 230 235 240



|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu |     |     |
| 245                                                             | 250 | 255 |
| Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala |     |     |
| 260                                                             | 265 | 270 |
| Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser |     |     |
| 275                                                             | 280 | 285 |
| Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro |     |     |
| 290                                                             | 295 | 300 |
| Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly |     |     |
| 305                                                             | 310 | 315 |
| Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly |     |     |
| 325                                                             | 330 | 335 |
| Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys |     |     |
| 340                                                             | 345 | 350 |
| Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr |     |     |
| 355                                                             | 360 | 365 |
| Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser |     |     |
| 370                                                             | 375 | 380 |
| Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro |     |     |
| 385                                                             | 390 | 395 |
| Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr |     |     |
| 405                                                             | 410 | 415 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val |     |     |
| 420                                                             | 425 | 430 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp |     |     |
| 435                                                             | 440 | 445 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro |     |     |
| 450                                                             | 455 | 460 |
| Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu |     |     |
| 465                                                             | 470 | 475 |
| Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser |     |     |
| 485                                                             | 490 | 495 |
| Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile |     |     |
| 500                                                             | 505 | 510 |
| Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu |     |     |
| 515                                                             | 520 | 525 |
| Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg |     |     |
| 530                                                             | 535 | 540 |
| Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 545                                                             | 550 | 555 | 560 |
| Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Leu Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val |     |     |     |
|                                                                 | 770 | 775 | 780 |
| Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser |     |     |     |
| 785                                                             | 790 | 795 | 800 |
| Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp |     |     |     |
|                                                                 | 805 | 810 | 815 |
| Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr |     |     |     |
|                                                                 | 820 | 825 | 830 |
| Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser |     |     |     |
|                                                                 | 835 | 840 | 845 |
| Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys |     |     |     |
| 850                                                             | 855 | 860 |     |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys |      |      |      |
| 865                                                             | 870  | 875  | 880  |
| Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala |      |      |      |
|                                                                 | 885  | 890  | 895  |
| Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly |      |      |      |
|                                                                 | 900  | 905  | 910  |
| Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu |      |      |      |
|                                                                 | 915  | 920  | 925  |
| His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile |      |      |      |
|                                                                 | 930  | 935  | 940  |
| Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Gln Asp Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile |      |      |      |

| 1170                                                            | 1175 | 1180 |
|-----------------------------------------------------------------|------|------|
| Asp Tyr Lys Asp Asp Asp Asp Lys                                 |      |      |
| 1185                                                            | 1190 |      |
| <210> 12                                                        |      |      |
| <211> 1311                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1188-NpuN-3FT                                       |      |      |
| <400> 12                                                        |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |
| 1 5 10 15                                                       |      |      |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |
| 20 25 30                                                        |      |      |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |
| 35 40 45                                                        |      |      |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |
| 50 55 60                                                        |      |      |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |
| 65 70 75 80                                                     |      |      |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |      |      |
| 85 90 95                                                        |      |      |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |      |      |
| 100 105 110                                                     |      |      |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |      |      |
| 115 120 125                                                     |      |      |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |      |      |
| 130 135 140                                                     |      |      |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |      |      |
| 145 150 155 160                                                 |      |      |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |      |      |
| 165 170 175                                                     |      |      |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |      |      |
| 180 185 190                                                     |      |      |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |      |      |
| 195 200 205                                                     |      |      |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |      |      |
| 210 215 220                                                     |      |      |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |      |      |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 225                                                             | 230 | 235 | 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |     |
|                                                                 | 275 | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |
|                                                                 | 530 | 535 | 540 |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |
| 610                                                             | 615 | 620 |     |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |     |
| 690                                                             | 695 | 700 |     |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |     |
| 770                                                             | 775 | 780 |     |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |     |
| 785                                                             | 790 | 795 | 800 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |     |
|                                                                 | 805 | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |     |
|                                                                 | 820 | 825 | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |     |     |
|                                                                 | 835 | 840 | 845 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |     |     |     |

|                     |                     |                         |
|---------------------|---------------------|-------------------------|
| 850                 | 855                 | 860                     |
| Tyr Gly Thr Pro Leu | Pro Trp Tyr Phe Leu | Leu Gln Glu Ser Tyr Trp |
| 865                 | 870                 | 875                     |
| Leu Gly Gly Glu Gly | Cys Ser Thr Arg Glu | Glu Arg Ala Leu Glu Lys |
| 885                 | 890                 | 895                     |
| Thr Glu Pro Leu Thr | Glu Glu Thr Glu Asp | Pro Glu His Pro Glu Gly |
| 900                 | 905                 | 910                     |
| Ile His Asp Ser Phe | Phe Glu Arg Glu His | Pro Gly Trp Val Pro Gly |
| 915                 | 920                 | 925                     |
| Val Cys Val Lys Asn | Leu Val Lys Ile Phe | Glu Pro Cys Gly Arg Pro |
| 930                 | 935                 | 940                     |
| Ala Val Asp Arg Leu | Asn Ile Thr Phe Tyr | Glu Asn Gln Ile Thr Ala |
| 945                 | 950                 | 955                     |
| Phe Leu Gly His Asn | Gly Ala Gly Lys Thr | Thr Thr Leu Ser Ile Leu |
| 965                 | 970                 | 975                     |
| Thr Gly Leu Leu Pro | Pro Thr Ser Gly Thr | Val Leu Val Gly Gly Arg |
| 980                 | 985                 | 990                     |
| Asp Ile Glu Thr Ser | Leu Asp Ala Val Arg | Gln Ser Leu Gly Met Cys |
| 995                 | 1000                | 1005                    |
| Pro Gln His Asn Ile | Leu Phe His His Leu | Thr Val Ala Glu His Met |
| 1010                | 1015                | 1020                    |
| Leu Phe Tyr Ala Gln | Leu Lys Gly Lys Ser | Gln Glu Glu Ala Gln Leu |
| 1025                | 1030                | 1035                    |
| Glu Met Glu Ala Met | Leu Glu Asp Thr Gly | Leu His His Lys Arg Asn |
| 1045                | 1050                | 1055                    |
| Glu Glu Ala Gln Asp | Leu Ser Gly Gly Met | Gln Arg Lys Leu Ser Val |
| 1060                | 1065                | 1070                    |
| Ala Ile Ala Phe Val | Gly Asp Ala Lys Val | Val Ile Leu Asp Glu Pro |
| 1075                | 1080                | 1085                    |
| Thr Ser Gly Val Asp | Pro Tyr Ser Arg Arg | Ser Ile Trp Asp Leu Leu |
| 1090                | 1095                | 1100                    |
| Leu Lys Tyr Arg Ser | Gly Arg Thr Ile Ile | Met Ser Thr His His Met |
| 1105                | 1110                | 1115                    |
| Asp Glu Ala Asp Leu | Leu Gly Asp Arg Ile | Ala Ile Ile Ala Gln Gly |
| 1125                | 1130                | 1135                    |
| Arg Leu Tyr Cys Ser | Gly Thr Pro Leu Phe | Leu Lys Asn Cys Phe Gly |
| 1140                | 1145                | 1150                    |
| Thr Gly Leu Tyr Leu | Thr Leu Val Arg Lys | Met Lys Asn Ile Gln Ser |
| 1155                | 1160                | 1165                    |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |           |
| 1170                                                            | 1175 | 1180      |
| Ser Thr Thr Cys Leu Ser Tyr Glu Thr Glu Ile Leu Thr Val Glu Tyr |      |           |
| 1185                                                            | 1190 | 1195 1200 |
| Gly Leu Leu Pro Ile Gly Lys Ile Val Glu Lys Arg Ile Glu Cys Thr |      |           |
|                                                                 | 1205 | 1210 1215 |
| Val Tyr Ser Val Asp Asn Asn Gly Asn Ile Tyr Thr Gln Pro Val Ala |      |           |
|                                                                 | 1220 | 1225 1230 |
| Gln Trp His Asp Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |           |
|                                                                 | 1235 | 1240 1245 |
| Asp Gly Ser Leu Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Val |      |           |
|                                                                 | 1250 | 1255 1260 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Glu Leu Asp |      |           |
| 1265                                                            | 1270 | 1275 1280 |
| Leu Met Arg Val Asp Asn Leu Pro Asn Asp Tyr Lys Asp His Asp Gly |      |           |
|                                                                 | 1285 | 1290 1295 |
| Asp Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys     |      |           |
|                                                                 | 1300 | 1305 1310 |
| <210> 13                                                        |      |           |
| <211> 1144                                                      |      |           |
| <212> PRT                                                       |      |           |
| <213> 人工序列(Artificial Sequence)                                 |      |           |
| <220>                                                           |      |           |
| <223> ABCA4-1188-NpuC-3FT                                       |      |           |
| <400> 13                                                        |      |           |
| Met Ile Lys Ile Ala Thr Arg Lys Tyr Leu Gly Lys Gln Asn Val Tyr |      |           |
| 1                                                               | 5    | 10 15     |
| Asp Ile Gly Val Glu Arg Asp His Asn Phe Ala Leu Lys Asn Gly Phe |      |           |
|                                                                 | 20   | 25 30     |
| Ile Ala Ser Asn Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln |      |           |
|                                                                 | 35   | 40 45     |
| Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His |      |           |
|                                                                 | 50   | 55 60     |
| Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe |      |           |
| 65                                                              | 70   | 75 80     |
| Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe |      |           |
|                                                                 | 85   | 90 95     |
| Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly |      |           |
|                                                                 | 100  | 105 110   |



|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp |     |     |
| 115                                                             | 120 | 125 |
| Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu |     |     |
| 130                                                             | 135 | 140 |
| Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly |     |     |
| 145                                                             | 150 | 155 |
| Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala |     |     |
|                                                                 | 165 | 170 |
| His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln |     |     |
|                                                                 | 180 | 185 |
| Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu |     |     |
|                                                                 | 195 | 200 |
| Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala |     |     |
|                                                                 | 210 | 215 |
| Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser |     |     |
| 225                                                             | 230 | 235 |
| Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro |     |     |
|                                                                 | 245 | 250 |
| Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly |     |     |
|                                                                 | 260 | 265 |
| Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly |     |     |
|                                                                 | 275 | 280 |
| Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys |     |     |
|                                                                 | 290 | 295 |
| Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr |     |     |
| 305                                                             | 310 | 315 |
| Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser |     |     |
|                                                                 | 325 | 330 |
| Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro |     |     |
|                                                                 | 340 | 345 |
| Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr |     |     |
|                                                                 | 355 | 360 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val |     |     |
|                                                                 | 370 | 375 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp |     |     |
| 385                                                             | 390 | 395 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro |     |     |
|                                                                 | 405 | 410 |
| Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu |     |     |

|                             |                         |                 |
|-----------------------------|-------------------------|-----------------|
| 420                         | 425                     | 430             |
| Gly Arg Ile Met Asn Val Ser | Gly Gly Pro Ile Thr     | Arg Glu Ala Ser |
| 435                         | 440                     | 445             |
| Lys Glu Ile Pro Asp Phe Leu | Lys His Leu Glu Thr     | Glu Asp Asn Ile |
| 450                         | 455                     | 460             |
| Lys Val Trp Phe Asn Asn Lys | Gly Trp His Ala Leu Val | Ser Phe Leu     |
| 465                         | 470                     | 475             |
| Asn Val Ala His Asn Ala Ile | Leu Arg Ala Ser Leu Pro | Lys Asp Arg     |
| 485                         | 490                     | 495             |
| Ser Pro Glu Glu Tyr Gly Ile | Thr Val Ile Ser Gln Pro | Leu Asn Leu     |
| 500                         | 505                     | 510             |
| Thr Lys Glu Gln Leu Ser Glu | Ile Thr Val Leu Thr Thr | Ser Val Asp     |
| 515                         | 520                     | 525             |
| Ala Val Val Ala Ile Cys Val | Ile Phe Ser Met Ser Phe | Val Pro Ala     |
| 530                         | 535                     | 540             |
| Ser Phe Val Leu Tyr Leu Ile | Gln Glu Arg Val Asn Lys | Ser Lys His     |
| 545                         | 550                     | 555             |
| Leu Gln Phe Ile Ser Gly Val | Ser Pro Thr Thr Tyr Trp | Val Thr Asn     |
| 565                         | 570                     | 575             |
| Phe Leu Trp Asp Ile Met Asn | Tyr Ser Val Ser Ala Gly | Leu Val Val     |
| 580                         | 585                     | 590             |
| Gly Ile Phe Ile Gly Phe Gln | Lys Lys Ala Tyr Thr Ser | Pro Glu Asn     |
| 595                         | 600                     | 605             |
| Leu Pro Ala Leu Val Ala Leu | Leu Leu Leu Tyr Gly Trp | Ala Val Ile     |
| 610                         | 615                     | 620             |
| Pro Met Met Tyr Pro Ala Ser | Phe Leu Phe Asp Val Pro | Ser Thr Ala     |
| 625                         | 630                     | 635             |
| Tyr Val Ala Leu Ser Cys Ala | Asn Leu Phe Ile Gly Ile | Asn Ser Ser     |
| 645                         | 650                     | 655             |
| Ala Ile Thr Phe Ile Leu Glu | Leu Phe Glu Asn Asn Arg | Thr Leu Leu     |
| 660                         | 665                     | 670             |
| Arg Phe Asn Ala Val Leu Arg | Lys Leu Leu Ile Val Phe | Pro His Phe     |
| 675                         | 680                     | 685             |
| Cys Leu Gly Arg Gly Leu Ile | Asp Leu Ala Leu Ser Gln | Ala Val Thr     |
| 690                         | 695                     | 700             |
| Asp Val Tyr Ala Arg Phe Gly | Glu Glu His Ser Ala Asn | Pro Phe His     |
| 705                         | 710                     | 715             |
| Trp Asp Leu Ile Gly Lys Asn | Leu Phe Ala Met Val Val | Glu Gly Val     |
| 725                         | 730                     | 735             |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser |      |      |
| 740                                                             | 745  | 750  |
| Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp |      |      |
| 755                                                             | 760  | 765  |
| Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr |      |      |
| 770                                                             | 775  | 780  |
| Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser |      |      |
| 785                                                             | 790  | 795  |
| Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys |      |      |
| 805                                                             | 810  | 815  |
| Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys |      |      |
| 820                                                             | 825  | 830  |
| Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala |      |      |
| 835                                                             | 840  | 845  |
| Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly |      |      |
| 850                                                             | 855  | 860  |
| Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu |      |      |
| 865                                                             | 870  | 875  |
| His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile |      |      |
| 885                                                             | 890  | 895  |
| Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr |      |      |
| 900                                                             | 905  | 910  |
| Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu |      |      |
| 915                                                             | 920  | 925  |
| Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp |      |      |
| 930                                                             | 935  | 940  |
| Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn |      |      |
| 945                                                             | 950  | 955  |
| Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser |      |      |
| 965                                                             | 970  | 975  |
| His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met |      |      |
| 980                                                             | 985  | 990  |
| Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser |      |      |
| 995                                                             | 1000 | 1005 |
| Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys |      |      |
| 1010                                                            | 1015 | 1020 |
| Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly |      |      |
| 1025                                                            | 1030 | 1035 |
| Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln |      |      |

|       |                           |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
|-------|---------------------------|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|
|       |                           |     |     |     | 1045 |     |     |     |     | 1050 |     |     |     |     | 1055 |
| Phe   | Gln                       | Val | Ser | Ser | Ser  | Ser | Leu | Ala | Arg | Ile  | Phe | Gln | Leu | Leu | Leu  |
|       |                           |     |     |     | 1060 |     |     |     |     | 1065 |     |     |     |     | 1070 |
| Ser   | His                       | Lys | Asp | Ser | Leu  | Leu | Ile | Glu | Glu | Tyr  | Ser | Val | Thr | Gln | Thr  |
|       |                           |     |     |     | 1075 |     |     |     |     | 1080 |     |     |     |     | 1085 |
| Thr   | Leu                       | Asp | Gln | Val | Phe  | Val | Asn | Phe | Ala | Lys  | Gln | Gln | Thr | Glu | Ser  |
|       |                           |     |     |     | 1090 |     |     |     |     | 1095 |     |     |     |     | 1100 |
| His   | Asp                       | Leu | Pro | Leu | His  | Pro | Arg | Ala | Ala | Gly  | Ala | Ser | Arg | Gln | Ala  |
| 1105  |                           |     |     |     |      |     |     |     |     |      |     |     |     |     | 1120 |
| Gln   | Asp                       | Asp | Tyr | Lys | Asp  | His | Asp | Gly | Asp | Tyr  | Lys | Asp | His | Asp | Ile  |
|       |                           |     |     |     | 1125 |     |     |     |     | 1130 |     |     |     |     | 1135 |
| Asp   | Tyr                       | Lys | Asp | Asp | Asp  | Asp | Lys |     |     |      |     |     |     |     |      |
|       |                           |     |     |     | 1140 |     |     |     |     |      |     |     |     |     |      |
| <210> | 14                        |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <211> | 179                       |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <212> | PRT                       |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <213> | 人工序列(Artificial Sequence) |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <220> |                           |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <223> | EGFP-71- CfaN             |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| <400> | 14                        |     |     |     |      |     |     |     |     |      |     |     |     |     |      |
| Met   | Val                       | Ser | Lys | Gly | Glu  | Glu | Leu | Phe | Thr | Gly  | Val | Val | Pro | Ile | Leu  |
| 1     |                           |     |     | 5   |      |     |     |     | 10  |      |     |     |     | 15  |      |
| Val   | Glu                       | Leu | Asp | Gly | Asp  | Val | Asn | Gly | His | Lys  | Phe | Ser | Val | Ser | Gly  |
|       |                           |     |     | 20  |      |     |     |     | 25  |      |     |     |     | 30  |      |
| Glu   | Gly                       | Glu | Gly | Asp | Ala  | Thr | Tyr | Gly | Lys | Leu  | Thr | Leu | Lys | Phe | Ile  |
|       |                           |     |     | 35  |      |     |     |     | 40  |      |     |     |     | 45  |      |
| Cys   | Thr                       | Thr | Gly | Lys | Leu  | Pro | Val | Pro | Trp | Pro  | Thr | Leu | Val | Thr | Thr  |
|       |                           |     |     | 50  |      |     |     |     | 55  |      |     |     |     | 60  |      |
| Leu   | Thr                       | Tyr | Gly | Val | Gln  | Cys | Leu | Ser | Tyr | Asp  | Thr | Glu | Ile | Leu | Thr  |
| 65    |                           |     |     |     | 70   |     |     |     |     | 75   |     |     |     |     | 80   |
| Val   | Glu                       | Tyr | Gly | Phe | Leu  | Pro | Ile | Gly | Lys | Ile  | Val | Glu | Glu | Arg | Ile  |
|       |                           |     |     | 85  |      |     |     |     |     | 90   |     |     |     |     | 95   |
| Glu   | Cys                       | Thr | Val | Tyr | Thr  | Val | Asp | Lys | Asn | Gly  | Phe | Val | Tyr | Thr | Gln  |
|       |                           |     |     | 100 |      |     |     |     | 105 |      |     |     |     | 110 |      |
| Pro   | Ile                       | Ala | Gln | Trp | His  | Asn | Arg | Gly | Glu | Gln  | Glu | Val | Phe | Glu | Tyr  |
|       |                           |     |     | 115 |      |     |     |     | 120 |      |     |     |     | 125 |      |
| Cys   | Leu                       | Glu | Asp | Gly | Ser  | Ile | Ile | Arg | Ala | Thr  | Lys | Asp | His | Lys | Phe  |
|       |                           |     |     | 130 |      |     |     |     | 135 |      |     |     |     | 140 |      |
| Met   | Thr                       | Thr | Asp | Gly | Gln  | Met | Leu | Pro | Ile | Asp  | Glu | Ile | Phe | Glu | Arg  |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 145                                                             | 150 | 155 | 160 |
| Gly Leu Asp Leu Lys Gln Val Asp Gly Leu Pro Gly His His His His |     |     |     |
|                                                                 | 165 | 170 | 175 |
| His His Gly                                                     |     |     |     |
| <210> 15                                                        |     |     |     |
| <211> 213                                                       |     |     |     |
| <212> PRT                                                       |     |     |     |
| <213> 人工序列(Artificial Sequence)                                 |     |     |     |
| <220>                                                           |     |     |     |
| <223> EGFP-71- CfaC                                             |     |     |     |
| <400> 15                                                        |     |     |     |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |     |     |     |
| 1 5 10 15                                                       |     |     |     |
| Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys Asn Gly Leu |     |     |     |
| 20 25 30                                                        |     |     |     |
| Val Ala Ser Asn Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His |     |     |     |
| 35 40 45                                                        |     |     |     |
| Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr |     |     |     |
| 50 55 60                                                        |     |     |     |
| Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys |     |     |     |
| 65 70 75 80                                                     |     |     |     |
| Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp |     |     |     |
| 85 90 95                                                        |     |     |     |
| Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr |     |     |     |
| 100 105 110                                                     |     |     |     |
| Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile |     |     |     |
| 115 120 125                                                     |     |     |     |
| Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln |     |     |     |
| 130 135 140                                                     |     |     |     |
| Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val |     |     |     |
| 145 150 155 160                                                 |     |     |     |
| Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys |     |     |     |
| 165 170 175                                                     |     |     |     |
| Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr |     |     |     |
| 180 185 190                                                     |     |     |     |
| Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Gly His His |     |     |     |
| 195 200 205                                                     |     |     |     |
| His His His His Gly                                             |     |     |     |
| 210                                                             |     |     |     |

&lt;210&gt; 16

&lt;211&gt; 247

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; EGFP

&lt;400&gt; 16

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

1 5 10 15

Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly

20 25 30

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile

35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr

50 55 60

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys

65 70 75 80

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu

85 90 95

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu

100 105 110

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly

115 120 125

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

130 135 140

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn

145 150 155 160

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser

165 170 175

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly

180 185 190

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu

195 200 205

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe

210 215 220

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Gly

225 230 235 240

His His His His His His Gly

245

&lt;210&gt; 17

&lt;211&gt; 180

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; EGFP-71- NpuN

&lt;400&gt; 17

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

1 5 10 15

Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly

20 25 30

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile

35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr

50 55 60

Leu Thr Tyr Gly Val Gln Cys Leu Ser Tyr Glu Thr Glu Ile Leu Thr

65 70 75 80

Val Glu Tyr Gly Leu Leu Pro Ile Gly Lys Ile Val Glu Lys Arg Ile

85 90 95

Glu Cys Thr Val Tyr Ser Val Asp Asn Asn Gly Asn Ile Tyr Thr Gln

100 105 110

Pro Val Ala Gln Trp His Asp Arg Gly Glu Gln Glu Val Phe Glu Tyr

115 120 125

Cys Leu Glu Asp Gly Ser Leu Ile Arg Ala Thr Lys Asp His Lys Phe

130 135 140

Met Thr Val Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg

145 150 155 160

Glu Leu Asp Leu Met Arg Val Asp Asn Leu Pro Asn Gly His His His

165 170 175

His His His Gly

180

&lt;210&gt; 18

&lt;211&gt; 213

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; EGFP-71- NpuC

&lt;400&gt; 18

Met Ile Lys Ile Ala Thr Arg Lys Tyr Leu Gly Lys Gln Asn Val Tyr

|                                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
|---------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|
| 1                               |     |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |  |  |  |  |  |
| Asp                             | Ile | Gly | Val | Glu | Arg | Asp | His | Asn | Phe | Ala | Leu | Lys | Asn | Gly | Phe |  |  |  |  |  |
|                                 |     |     |     | 20  |     |     |     | 25  |     |     |     | 30  |     |     |     |  |  |  |  |  |
| Ile                             | Ala | Ser | Asn | Cys | Phe | Ser | Arg | Tyr | Pro | Asp | His | Met | Lys | Gln | His |  |  |  |  |  |
|                                 |     |     |     | 35  |     |     |     | 40  |     |     |     | 45  |     |     |     |  |  |  |  |  |
| Asp                             | Phe | Phe | Lys | Ser | Ala | Met | Pro | Glu | Gly | Tyr | Val | Gln | Glu | Arg | Thr |  |  |  |  |  |
|                                 |     |     |     | 50  |     |     |     | 55  |     |     |     | 60  |     |     |     |  |  |  |  |  |
| Ile                             | Phe | Phe | Lys | Asp | Asp | Gly | Asn | Tyr | Lys | Thr | Arg | Ala | Glu | Val | Lys |  |  |  |  |  |
| 65                              |     |     |     |     | 70  |     |     |     | 75  |     |     |     | 80  |     |     |  |  |  |  |  |
| Phe                             | Glu | Gly | Asp | Thr | Leu | Val | Asn | Arg | Ile | Glu | Leu | Lys | Gly | Ile | Asp |  |  |  |  |  |
|                                 |     |     |     | 85  |     |     |     | 90  |     |     |     | 95  |     |     |     |  |  |  |  |  |
| Phe                             | Lys | Glu | Asp | Gly | Asn | Ile | Leu | Gly | His | Lys | Leu | Glu | Tyr | Asn | Tyr |  |  |  |  |  |
|                                 |     |     |     | 100 |     |     |     | 105 |     |     |     | 110 |     |     |     |  |  |  |  |  |
| Asn                             | Ser | His | Asn | Val | Tyr | Ile | Met | Ala | Asp | Lys | Gln | Lys | Asn | Gly | Ile |  |  |  |  |  |
|                                 |     |     |     | 115 |     |     |     | 120 |     |     |     | 125 |     |     |     |  |  |  |  |  |
| Lys                             | Val | Asn | Phe | Lys | Ile | Arg | His | Asn | Ile | Glu | Asp | Gly | Ser | Val | Gln |  |  |  |  |  |
|                                 |     |     |     | 130 |     |     |     | 135 |     |     |     | 140 |     |     |     |  |  |  |  |  |
| Leu                             | Ala | Asp | His | Tyr | Gln | Gln | Asn | Thr | Pro | Ile | Gly | Asp | Gly | Pro | Val |  |  |  |  |  |
| 145                             |     |     |     |     | 150 |     |     |     | 155 |     |     |     | 160 |     |     |  |  |  |  |  |
| Leu                             | Leu | Pro | Asp | Asn | His | Tyr | Leu | Ser | Thr | Gln | Ser | Ala | Leu | Ser | Lys |  |  |  |  |  |
|                                 |     |     |     | 165 |     |     |     | 170 |     |     |     | 175 |     |     |     |  |  |  |  |  |
| Asp                             | Pro | Asn | Glu | Lys | Arg | Asp | His | Met | Val | Leu | Leu | Glu | Phe | Val | Thr |  |  |  |  |  |
|                                 |     |     |     | 180 |     |     |     | 185 |     |     |     | 190 |     |     |     |  |  |  |  |  |
| Ala                             | Ala | Gly | Ile | Thr | Leu | Gly | Met | Asp | Glu | Leu | Tyr | Lys | Gly | His | His |  |  |  |  |  |
|                                 |     |     |     | 195 |     |     |     | 200 |     |     |     | 205 |     |     |     |  |  |  |  |  |
| His                             | His | His | His | Gly |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| 210                             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <210> 19                        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <211> 1371                      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <212> PRT                       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <213> 人工序列(Artificial Sequence) |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <220>                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <223> ABCA4-1150-CfaN-3FT-SopE  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| <400> 19                        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |  |
| Met                             | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |  |  |  |  |  |
| 1                               |     |     |     |     | 5   |     |     |     | 10  |     |     |     | 15  |     |     |  |  |  |  |  |
| Leu                             | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |  |  |  |  |  |
|                                 |     |     |     | 20  |     |     |     | 25  |     |     |     | 30  |     |     |     |  |  |  |  |  |
| Leu                             | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |  |  |  |  |  |



|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 35                                                              | 40  | 45  |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |     |     |
| 50                                                              | 55  | 60  |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |     |     |
| 65                                                              | 70  | 75  |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |     |     |
| 85                                                              | 90  | 95  |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |
| 100                                                             | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
|                                                                 | 405 | 410 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
|                                                                 | 420 | 425 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
|                                                                 | 435 | 440 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
|                                                                 | 450 | 455 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
|                                                                 | 485 | 490 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
|                                                                 | 500 | 505 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
|                                                                 | 515 | 520 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
|                                                                 | 530 | 535 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
|                                                                 | 565 | 570 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
|                                                                 | 580 | 585 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
|                                                                 | 595 | 600 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
|                                                                 | 610 | 615 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
|                                                                 | 645 | 650 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |
| 805                                                             | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |
| 820                                                             | 825 | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |     |
| 835                                                             | 840 | 845 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |     |     |
| 850                                                             | 855 | 860 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |     |     |
| 865                                                             | 870 | 875 |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |     |     |
| 885                                                             | 890 | 895 |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |     |     |
| 900                                                             | 905 | 910 |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |     |     |
| 915                                                             | 920 | 925 |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |     |     |
| 930                                                             | 935 | 940 |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |     |     |
| 945                                                             | 950 | 955 |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |     |     |
| 965                                                             | 970 | 975 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Leu Ser |      |      |
| 1140                                                            | 1145 | 1150 |
| Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly |      |      |
| 1155                                                            | 1160 | 1165 |
| Lys Ile Val Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys |      |      |
| 1170                                                            | 1175 | 1180 |
| Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly |      |      |
| 1185                                                            | 1190 | 1195 |
| Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg |      |      |
| 1205                                                            | 1210 | 1215 |
| Ala Thr Lys Asp His Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro |      |      |
| 1220                                                            | 1225 | 1230 |
| Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly |      |      |
| 1235                                                            | 1240 | 1245 |
| Leu Pro Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile |      |      |
| 1250                                                            | 1255 | 1260 |
| Asp Tyr Lys Asp Asp Asp Asp Lys Thr Lys Ile Thr Leu Ser Pro Gln |      |      |
| 1265                                                            | 1270 | 1275 |
| Asn Phe Arg Ile Gln Lys Gln Glu Thr Thr Leu Leu Lys Glu Lys Ser |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
|                                                                 | 1285 | 1290 | 1295 |
| Thr Glu Lys Asn Ser Leu Ala Lys Ser Ile Leu Ala Val Lys Asn His |      |      |      |
| 1300                                                            | 1305 | 1310 |      |
| Phe Ile Glu Leu Arg Ser Lys Leu Ser Glu Arg Phe Ile Ser His Lys |      |      |      |
| 1315                                                            | 1320 | 1325 |      |
| Asn Thr Glu Ser Ser Ala Thr His Phe His Arg Gly Ser Ala Ser Glu |      |      |      |
| 1330                                                            | 1335 | 1340 |      |
| Gly Arg Ala Val Leu Thr Asn Lys Val Val Lys Asp Phe Met Leu Gln |      |      |      |
| 1345                                                            | 1350 | 1355 | 1360 |
| Thr Leu Asn Asp Ile Asp Ile Arg Gly Ser Ala                     |      |      |      |
| 1365                                                            | 1370 |      |      |
| <210> 20                                                        |      |      |      |
| <211> 1281                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1150-CfaC-3FT-SopE                                  |      |      |      |
| <400> 20                                                        |      |      |      |
| Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala |      |      |      |
| 20                                                              | 25   | 30   |      |
| Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys |      |      |      |
| 35                                                              | 40   | 45   |      |
| Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr |      |      |      |
| 50                                                              | 55   | 60   |      |
| His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn |      |      |      |
| 65                                                              | 70   | 75   | 80   |
| Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile |      |      |      |
| 85                                                              | 90   | 95   |      |
| Arg Gly Ser Ala Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln |      |      |      |
| 100                                                             | 105  | 110  |      |
| Asn Val Tyr Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys |      |      |      |
| 115                                                             | 120  | 125  |      |
| Asn Gly Leu Val Ala Ser Asn Cys Phe Gly Thr Gly Leu Tyr Leu Thr |      |      |      |
| 130                                                             | 135  | 140  |      |
| Leu Val Arg Lys Met Lys Asn Ile Gln Ser Gln Arg Lys Gly Ser Glu |      |      |      |
| 145                                                             | 150  | 155  | 160  |
| Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala |      |      |      |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
|     |     |     |     | 165 |     |     |     |     |     | 170 |     |     |     |     | 175 |  |  |  |  |
| His | Val | Asp | Asp | Leu | Thr | Pro | Glu | Gln | Val | Leu | Asp | Gly | Asp | Val | Asn |  |  |  |  |
|     |     |     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |  |  |  |  |
| Glu | Leu | Met | Asp | Val | Val | Leu | His | His | Val | Pro | Glu | Ala | Lys | Leu | Val |  |  |  |  |
|     |     |     |     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |  |  |  |  |
| Glu | Cys | Ile | Gly | Gln | Glu | Leu | Ile | Phe | Leu | Leu | Pro | Asn | Lys | Asn | Phe |  |  |  |  |
|     |     |     |     | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |  |  |  |  |
| Lys | His | Arg | Ala | Tyr | Ala | Ser | Leu | Phe | Arg | Glu | Leu | Glu | Glu | Thr | Leu |  |  |  |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |  |  |  |
| Ala | Asp | Leu | Gly | Leu | Ser | Ser | Phe | Gly | Ile | Ser | Asp | Thr | Pro | Leu | Glu |  |  |  |  |
|     |     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |  |  |  |  |
| Glu | Ile | Phe | Leu | Lys | Val | Thr | Glu | Asp | Ser | Asp | Ser | Gly | Pro | Leu | Phe |  |  |  |  |
|     |     |     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |  |  |  |  |
| Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu | Asn | Val | Asn | Pro | Arg | His | Pro |  |  |  |  |
|     |     |     |     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |  |  |  |  |
| Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly | Gln | Thr | Pro | Gln | Asp | Ser | Asn |  |  |  |  |
|     |     |     |     | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |  |  |  |  |
| Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala | His | Pro | Glu | Gly | Gln | Pro | Pro |  |  |  |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |  |  |  |
| Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln | Leu | Asn | Thr | Gly | Thr | Gln | Leu |  |  |  |  |
|     |     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |  |  |  |  |
| Val | Leu | Gln | His | Val | Gln | Ala | Leu | Leu | Val | Lys | Arg | Phe | Gln | His | Thr |  |  |  |  |
|     |     |     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |  |  |  |  |
| Ile | Arg | Ser | His | Lys | Asp | Phe | Leu | Ala | Gln | Ile | Val | Leu | Pro | Ala | Thr |  |  |  |  |
|     |     |     |     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |  |  |  |  |
| Phe | Val | Phe | Leu | Ala | Leu | Met | Leu | Ser | Ile | Val | Ile | Pro | Pro | Phe | Gly |  |  |  |  |
|     |     |     |     | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |  |  |  |  |
| Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro | Trp | Ile | Tyr | Gly | Gln | Gln | Tyr |  |  |  |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |  |  |  |
| Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly | Ser | Glu | Gln | Phe | Thr | Val | Leu |  |  |  |  |
|     |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |  |  |  |  |
| Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly | Phe | Gly | Asn | Arg | Cys | Leu | Lys |  |  |  |  |
|     |     |     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |  |  |  |  |
| Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro | Cys | Gly | Asn | Ser | Thr | Pro | Trp | Lys |  |  |  |  |
|     |     |     |     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |  |  |  |  |
| Thr | Pro | Ser | Val | Ser | Pro | Asn | Ile | Thr | Gln | Leu | Phe | Gln | Lys | Gln | Lys |  |  |  |  |
|     |     |     |     | 450 |     |     |     |     |     | 455 |     |     |     |     | 460 |  |  |  |  |
| Trp | Thr | Gln | Val | Asn | Pro | Ser | Pro | Ser | Cys | Arg | Cys | Ser | Thr | Arg | Glu |  |  |  |  |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |  |  |  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Leu | Thr | Met | Leu | Pro | Glu | Cys | Pro | Glu | Gly | Ala | Gly | Gly | Leu | Pro |
|     |     |     |     | 485 |     |     |     | 490 |     |     |     | 495 |     |     |     |
| Pro | Pro | Gln | Arg | Thr | Gln | Arg | Ser | Thr | Glu | Ile | Leu | Gln | Asp | Leu | Thr |
|     |     |     |     | 500 |     |     |     | 505 |     |     |     | 510 |     |     |     |
| Asp | Arg | Asn | Ile | Ser | Asp | Phe | Leu | Val | Lys | Thr | Tyr | Pro | Ala | Leu | Ile |
|     |     |     |     | 515 |     |     |     | 520 |     |     |     | 525 |     |     |     |
| Arg | Ser | Ser | Leu | Lys | Ser | Lys | Phe | Trp | Val | Asn | Glu | Gln | Arg | Tyr | Gly |
|     |     |     |     | 530 |     |     |     | 535 |     |     |     | 540 |     |     |     |
| Gly | Ile | Ser | Ile | Gly | Gly | Lys | Leu | Pro | Val | Val | Pro | Ile | Thr | Gly | Glu |
| 545 |     |     |     | 550 |     |     |     | 555 |     |     |     | 560 |     |     |     |
| Ala | Leu | Val | Gly | Phe | Leu | Ser | Asp | Leu | Gly | Arg | Ile | Met | Asn | Val | Ser |
|     |     |     |     | 565 |     |     |     | 570 |     |     |     | 575 |     |     |     |
| Gly | Gly | Pro | Ile | Thr | Arg | Glu | Ala | Ser | Lys | Glu | Ile | Pro | Asp | Phe | Leu |
|     |     |     |     | 580 |     |     |     | 585 |     |     |     | 590 |     |     |     |
| Lys | His | Leu | Glu | Thr | Glu | Asp | Asn | Ile | Lys | Val | Trp | Phe | Asn | Asn | Lys |
|     |     |     |     | 595 |     |     |     | 600 |     |     |     | 605 |     |     |     |
| Gly | Trp | His | Ala | Leu | Val | Ser | Phe | Leu | Asn | Val | Ala | His | Asn | Ala | Ile |
| 610 |     |     |     | 615 |     |     |     | 620 |     |     |     |     |     |     |     |
| Leu | Arg | Ala | Ser | Leu | Pro | Lys | Asp | Arg | Ser | Pro | Glu | Glu | Tyr | Gly | Ile |
| 625 |     |     |     | 630 |     |     |     | 635 |     |     |     | 640 |     |     |     |
| Thr | Val | Ile | Ser | Gln | Pro | Leu | Asn | Leu | Thr | Lys | Glu | Gln | Leu | Ser | Glu |
|     |     |     |     | 645 |     |     |     | 650 |     |     |     | 655 |     |     |     |
| Ile | Thr | Val | Leu | Thr | Thr | Ser | Val | Asp | Ala | Val | Val | Ala | Ile | Cys | Val |
|     |     |     |     | 660 |     |     |     | 665 |     |     |     | 670 |     |     |     |
| Ile | Phe | Ser | Met | Ser | Phe | Val | Pro | Ala | Ser | Phe | Val | Leu | Tyr | Leu | Ile |
|     |     |     |     | 675 |     |     |     | 680 |     |     |     | 685 |     |     |     |
| Gln | Glu | Arg | Val | Asn | Lys | Ser | Lys | His | Leu | Gln | Phe | Ile | Ser | Gly | Val |
| 690 |     |     |     | 695 |     |     |     | 700 |     |     |     |     |     |     |     |
| Ser | Pro | Thr | Thr | Tyr | Trp | Val | Thr | Asn | Phe | Leu | Trp | Asp | Ile | Met | Asn |
| 705 |     |     |     | 710 |     |     |     | 715 |     |     |     | 720 |     |     |     |
| Tyr | Ser | Val | Ser | Ala | Gly | Leu | Val | Val | Gly | Ile | Phe | Ile | Gly | Phe | Gln |
|     |     |     |     | 725 |     |     |     | 730 |     |     |     | 735 |     |     |     |
| Lys | Lys | Ala | Tyr | Thr | Ser | Pro | Glu | Asn | Leu | Pro | Ala | Leu | Val | Ala | Leu |
|     |     |     |     | 740 |     |     |     | 745 |     |     |     | 750 |     |     |     |
| Leu | Leu | Leu | Tyr | Gly | Trp | Ala | Val | Ile | Pro | Met | Met | Tyr | Pro | Ala | Ser |
| 755 |     |     |     | 760 |     |     |     | 765 |     |     |     |     |     |     |     |
| Phe | Leu | Phe | Asp | Val | Pro | Ser | Thr | Ala | Tyr | Val | Ala | Leu | Ser | Cys | Ala |
| 770 |     |     |     | 775 |     |     |     | 780 |     |     |     |     |     |     |     |
| Asn | Leu | Phe | Ile | Gly | Ile | Asn | Ser | Ser | Ala | Ile | Thr | Phe | Ile | Leu | Glu |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 785                                                             | 790  | 795  | 800  |
| Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg |      |      |      |
|                                                                 | 805  | 810  | 815  |
| Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile |      |      |      |
|                                                                 | 820  | 825  | 830  |
| Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly |      |      |      |
|                                                                 | 835  | 840  | 845  |
| Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn |      |      |      |
|                                                                 | 850  | 855  | 860  |
| Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu |      |      |      |
| 865                                                             | 870  | 875  | 880  |
| Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr |      |      |      |
|                                                                 | 885  | 890  | 895  |
| Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln |      |      |      |
|                                                                 | 900  | 905  | 910  |
| Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu |      |      |      |
|                                                                 | 915  | 920  | 925  |
| Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu |      |      |      |
|                                                                 | 930  | 935  | 940  |
| Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Val Thr Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Ile Ser Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Ile Asp Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Leu Arg Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Gly Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |



|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Glu Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp Asp Tyr Lys Asp His |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Asp Gly Asp Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp |      |      |      |
| 1265                                                            | 1270 | 1275 | 1280 |
| Lys                                                             |      |      |      |
| <210> 21                                                        |      |      |      |
| <211> 1361                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1140-CfaN-3FT-SopE                                  |      |      |      |
| <400> 21                                                        |      |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |      |
|                                                                 | 35   | 40   | 45   |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |      |
|                                                                 | 50   | 55   | 60   |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |      |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 65                                                              | 70  | 75  | 80  |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |     |     |     |
|                                                                 | 85  | 90  | 95  |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |     |
|                                                                 | 100 | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |     |
|                                                                 | 115 | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |     |
|                                                                 | 130 | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |     |
|                                                                 | 165 | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |     |
|                                                                 | 180 | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |     |
|                                                                 | 195 | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |     |
|                                                                 | 210 | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |     |
|                                                                 | 275 | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |     |
|                                                                 | 370 | 375 | 380 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
| 385 |     |     |     |     |     | 390 |     |     |     | 395 |     |     |     |     | 400 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     |     |     | 405 |     |     |     | 410 |     |     |     |     | 415 |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     |     |     |     | 420 |     |     |     | 425 |     |     |     |     | 430 |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |
|     |     |     |     |     |     | 435 |     |     |     | 440 |     |     |     |     | 445 |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu |
|     |     |     |     |     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |
| Asn | Arg | Gln | Leu | Gly | Glu | Glu | Gly | Ile | Thr | Ala | Glu | Ala | Ile | Leu | Asn |
| 465 |     |     |     |     |     | 470 |     |     |     | 475 |     |     |     |     | 480 |
| Phe | Leu | Tyr | Lys | Gly | Pro | Arg | Glu | Ser | Gln | Ala | Asp | Asp | Met | Ala | Asn |
|     |     |     |     |     |     | 485 |     |     |     | 490 |     |     |     |     | 495 |
| Phe | Asp | Trp | Arg | Asp | Ile | Phe | Asn | Ile | Thr | Asp | Arg | Thr | Leu | Arg | Leu |
|     |     |     |     |     |     | 500 |     |     |     | 505 |     |     |     |     | 510 |
| Val | Asn | Gln | Tyr | Leu | Glu | Cys | Leu | Val | Leu | Asp | Lys | Phe | Glu | Ser | Tyr |
|     |     |     |     |     |     | 515 |     |     |     | 520 |     |     |     |     | 525 |
| Asn | Asp | Glu | Thr | Gln | Leu | Thr | Gln | Arg | Ala | Leu | Ser | Leu | Leu | Glu | Glu |
|     |     |     |     |     |     | 530 |     |     |     | 535 |     |     |     |     | 540 |
| Asn | Met | Phe | Trp | Ala | Gly | Val | Val | Phe | Pro | Asp | Met | Tyr | Pro | Trp | Thr |
| 545 |     |     |     |     |     | 550 |     |     |     | 555 |     |     |     |     | 560 |
| Ser | Ser | Leu | Pro | Pro | His | Val | Lys | Tyr | Lys | Ile | Arg | Met | Asp | Ile | Asp |
|     |     |     |     |     |     | 565 |     |     |     | 570 |     |     |     |     | 575 |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly |
|     |     |     |     |     |     | 580 |     |     |     | 585 |     |     |     |     | 590 |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe |
|     |     |     |     |     |     | 595 |     |     |     | 600 |     |     |     |     | 605 |
| Ala | Tyr | Leu | Gln | Asp | Met | Val | Glu | Gln | Gly | Ile | Thr | Arg | Ser | Gln | Val |
|     |     |     |     |     |     | 610 |     |     |     | 615 |     |     |     |     | 620 |
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro |
| 625 |     |     |     |     |     | 630 |     |     |     | 635 |     |     |     |     | 640 |
| Cys | Phe | Val | Asp | Asp | Ser | Phe | Met | Ile | Ile | Leu | Asn | Arg | Cys | Phe | Pro |
|     |     |     |     |     |     | 645 |     |     |     | 650 |     |     |     |     | 655 |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys |
|     |     |     |     |     |     | 660 |     |     |     | 665 |     |     |     |     | 670 |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |
|     |     |     |     |     |     | 675 |     |     |     | 680 |     |     |     |     | 685 |
| Gln | Gly | Val | Ser | Asn | Ala | Val | Ile | Trp | Cys | Thr | Trp | Phe | Leu | Asp | Ser |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 690                                                             | 695  | 700  |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |      |      |
| 705                                                             | 710  | 715  |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |      |      |
|                                                                 | 725  | 730  |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |      |      |
|                                                                 | 740  | 745  |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
|                                                                 | 755  | 760  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
|                                                                 | 805  | 810  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
|                                                                 | 820  | 825  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
|                                                                 | 835  | 840  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
|                                                                 | 885  | 890  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
|                                                                 | 900  | 905  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
|                                                                 | 915  | 920  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
|                                                                 | 965  | 970  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
|                                                                 | 980  | 985  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
| 1010                                                            | 1015 | 1020 |      |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Leu Lys Gln Val Asp Gly Leu Pro Asp Tyr Lys Asp His Asp Gly Asp |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Tyr Lys Asp His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys Thr Lys |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln Glu Thr Thr |      |      |      |
| 1265                                                            | 1270 | 1275 | 1280 |
| Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala Lys Ser Ile |      |      |      |
|                                                                 | 1285 | 1290 | 1295 |
| Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys Leu Ser Glu |      |      |      |
|                                                                 | 1300 | 1305 | 1310 |
| Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr His Phe His |      |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1315                                                            | 1320 | 1325 |
| Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn Lys Val Val |      |      |
| 1330                                                            | 1335 | 1340 |
| Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile Arg Gly Ser |      |      |
| 1345                                                            | 1350 | 1355 |
| Ala                                                             |      | 1360 |
| <210> 22                                                        |      |      |
| <211> 1291                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1140-CfaC-3FT-SopE                                  |      |      |
| <400> 22                                                        |      |      |
| Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln |      |      |
| 1                                                               | 5    | 10   |
| Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala |      |      |
| 20                                                              | 25   | 30   |
| Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys |      |      |
| 35                                                              | 40   | 45   |
| Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr |      |      |
| 50                                                              | 55   | 60   |
| His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn |      |      |
| 65                                                              | 70   | 75   |
| Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile |      |      |
| 85                                                              | 90   | 95   |
| Arg Gly Ser Ala Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln |      |      |
| 100                                                             | 105  | 110  |
| Asn Val Tyr Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys |      |      |
| 115                                                             | 120  | 125  |
| Asn Gly Leu Val Ala Ser Asn Cys Ser Gly Thr Pro Leu Phe Leu Lys |      |      |
| 130                                                             | 135  | 140  |
| Asn Cys Phe Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys |      |      |
| 145                                                             | 150  | 155  |
| Asn Ile Gln Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser |      |      |
| 165                                                             | 170  | 175  |
| Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr |      |      |
| 180                                                             | 185  | 190  |
| Pro Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val |      |      |
| 195                                                             | 200  | 205  |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Leu His His Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu |     |     |     |
| 210                                                             | 215 | 220 |     |
| Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln |     |     |     |
|                                                                 | 275 | 280 | 285 |
| Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp |     |     |     |

|                                                                 |                     |                     |
|-----------------------------------------------------------------|---------------------|---------------------|
| 515                                                             | 520                 | 525                 |
| Phe Leu Val Lys Thr Tyr Pro                                     | Ala Leu Ile Arg Ser | Ser Ser Leu Lys Ser |
| 530                                                             | 535                 | 540                 |
| Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly                     | Ile Ser Ile Gly Gly |                     |
| 545                                                             | 550                 | 555                 |
| Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu |                     |                     |
| 565                                                             | 570                 | 575                 |
| Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg |                     |                     |
| 580                                                             | 585                 | 590                 |
| Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu |                     |                     |
| 595                                                             | 600                 | 605                 |
| Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val |                     |                     |
| 610                                                             | 615                 | 620                 |
| Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro |                     |                     |
| 625                                                             | 630                 | 635                 |
| Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro |                     |                     |
| 645                                                             | 650                 | 655                 |
| Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr |                     |                     |
| 660                                                             | 665                 | 670                 |
| Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe |                     |                     |
| 675                                                             | 680                 | 685                 |
| Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys |                     |                     |
| 690                                                             | 695                 | 700                 |
| Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp |                     |                     |
| 705                                                             | 710                 | 715                 |
| Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly |                     |                     |
| 725                                                             | 730                 | 735                 |
| Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser |                     |                     |
| 740                                                             | 745                 | 750                 |
| Pro Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp |                     |                     |
| 755                                                             | 760                 | 765                 |
| Ala Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro |                     |                     |
| 770                                                             | 775                 | 780                 |
| Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile |                     |                     |
| 785                                                             | 790                 | 795                 |
| Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg |                     |                     |
| 805                                                             | 810                 | 815                 |
| Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe |                     |                     |
| 820                                                             | 825                 | 830                 |



|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln |      |      |
| 835                                                             | 840  | 845  |
| Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn |      |      |
| 850                                                             | 855  | 860  |
| Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val |      |      |
| 865                                                             | 870  | 875  |
| Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe |      |      |
| 885                                                             | 890  | 895  |
| Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp |      |      |
| 900                                                             | 905  | 910  |
| Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly |      |      |
| 915                                                             | 920  | 925  |
| Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro |      |      |
| 930                                                             | 935  | 940  |
| Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro |      |      |
| 945                                                             | 950  | 955  |
| Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr |      |      |
| 965                                                             | 970  | 975  |
| Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala |      |      |
| 980                                                             | 985  | 990  |
| Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln |      |      |
| 995                                                             | 1000 | 1005 |
| Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr |      |      |
| 1010                                                            | 1015 | 1020 |
| Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu |      |      |
| 1045                                                            | 1050 | 1055 |
| Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys |      |      |
| 1060                                                            | 1065 | 1070 |
| Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val |      |      |
| 1075                                                            | 1080 | 1085 |
| Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val |      |      |
| 1105                                                            | 1110 | 1115 |
| Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu |      |      |
| 1125                                                            | 1130 | 1135 |
| Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1140                                                            | 1145 | 1150 |
| Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys |      |      |
| 1155                                                            | 1160 | 1165 |
| Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe |      |      |
| 1170                                                            | 1175 | 1180 |
| Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn |      |      |
| 1185                                                            | 1190 | 1195 |
| Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln |      |      |
| 1205                                                            | 1210 | 1215 |
| Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val |      |      |
| 1220                                                            | 1225 | 1230 |
| Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln |      |      |
| 1235                                                            | 1240 | 1245 |
| Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser |      |      |
| 1250                                                            | 1255 | 1260 |
| Arg Gln Ala Gln Asp Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp |      |      |
| 1265                                                            | 1270 | 1275 |
| His Asp Ile Asp Tyr Lys Asp Asp Asp Asp Lys                     |      |      |
| 1285                                                            | 1290 |      |

&lt;210&gt; 23

&lt;211&gt; 278

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; EGFP-71-CfaN-SopE

&lt;400&gt; 23

|                                                                 |    |    |
|-----------------------------------------------------------------|----|----|
| Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu |    |    |
| 1                                                               | 5  | 10 |
| Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly |    |    |
| 20                                                              | 25 | 30 |
| Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile |    |    |
| 35                                                              | 40 | 45 |
| Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr |    |    |
| 50                                                              | 55 | 60 |
| Leu Thr Tyr Gly Val Gln Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr |    |    |
| 65                                                              | 70 | 75 |
| Val Glu Tyr Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile |    |    |
| 85                                                              | 90 | 95 |
| Glu Cys Thr Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln |    |    |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 100                                                             | 105 | 110 |
| Pro Ile Ala Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr |     |     |
| 115                                                             | 120 | 125 |
| Cys Leu Glu Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe |     |     |
| 130                                                             | 135 | 140 |
| Met Thr Thr Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg |     |     |
| 145                                                             | 150 | 155 |
| Gly Leu Asp Leu Lys Gln Val Asp Gly Leu Pro Gly His His His His |     |     |
| 165                                                             | 170 | 175 |
| His His Gly Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln |     |     |
| 180                                                             | 185 | 190 |
| Lys Gln Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser |     |     |
| 195                                                             | 200 | 205 |
| Leu Ala Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg |     |     |
| 210                                                             | 215 | 220 |
| Ser Lys Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser |     |     |
| 225                                                             | 230 | 235 |
| Ala Thr His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu |     |     |
| 245                                                             | 250 | 255 |
| Thr Asn Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile |     |     |
| 260                                                             | 265 | 270 |
| Asp Ile Arg Gly Ser Ala                                         |     |     |
| 275                                                             |     |     |
| <210> 24                                                        |     |     |
| <211> 312                                                       |     |     |
| <212> PRT                                                       |     |     |
| <213> 人工序列(Artificial Sequence)                                 |     |     |
| <220>                                                           |     |     |
| <223> EGFP-71-CfaC-SopE                                         |     |     |
| <400> 24                                                        |     |     |
| Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln |     |     |
| 1                                                               | 5   | 10  |
| Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala |     |     |
| 20                                                              | 25  | 30  |
| Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys |     |     |
| 35                                                              | 40  | 45  |
| Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr |     |     |
| 50                                                              | 55  | 60  |
| His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 65                                                              | 70  | 75  | 80  |
| Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile |     |     |     |
|                                                                 | 85  | 90  | 95  |
| Arg Gly Ser Ala Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln |     |     |     |
|                                                                 | 100 | 105 | 110 |
| Asn Val Tyr Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys |     |     |     |
|                                                                 | 115 | 120 | 125 |
| Asn Gly Leu Val Ala Ser Asn Cys Phe Ser Arg Tyr Pro Asp His Met |     |     |     |
|                                                                 | 130 | 135 | 140 |
| Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala |     |     |     |
|                                                                 | 165 | 170 | 175 |
| Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys |     |     |     |
|                                                                 | 180 | 185 | 190 |
| Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu |     |     |     |
|                                                                 | 195 | 200 | 205 |
| Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys |     |     |     |
|                                                                 | 210 | 215 | 220 |
| Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu |     |     |     |
|                                                                 | 275 | 280 | 285 |
| Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Gly His His His His His His Gly                                 |     |     |     |
| 305                                                             | 310 |     |     |
| <210> 25                                                        |     |     |     |
| <211> 192                                                       |     |     |     |
| <212> PRT                                                       |     |     |     |
| <213> 人工序列(Artificial Sequence)                                 |     |     |     |
| <220>                                                           |     |     |     |
| <223> EGFP-71-CfaN-DD1                                          |     |     |     |
| <400> 25                                                        |     |     |     |
| Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu |     |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 1                                                               | 5   | 10  | 15  |
| Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly |     |     |     |
| 20                                                              | 25  | 30  |     |
| Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile |     |     |     |
| 35                                                              | 40  | 45  |     |
| Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr |     |     |     |
| 50                                                              | 55  | 60  |     |
| Leu Thr Tyr Gly Val Gln Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr |     |     |     |
| 65                                                              | 70  | 75  | 80  |
| Val Glu Tyr Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile |     |     |     |
| 85                                                              | 90  | 95  |     |
| Glu Cys Thr Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln |     |     |     |
| 100                                                             | 105 | 110 |     |
| Pro Ile Ala Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr |     |     |     |
| 115                                                             | 120 | 125 |     |
| Cys Leu Glu Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe |     |     |     |
| 130                                                             | 135 | 140 |     |
| Met Thr Thr Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| Gly Leu Asp Leu Lys Gln Val Asp Gly Leu Pro Gly His His His His |     |     |     |
| 165                                                             | 170 | 175 |     |
| His His Gly Arg Ile Ser Phe Gly Ser Pro Pro Pro Met Ala Gly Gly |     |     |     |
| 180                                                             | 185 | 190 |     |

&lt;210&gt; 26

&lt;211&gt; 226

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; EGFP-71-CfaC-DD1

&lt;400&gt; 26

|                                                                 |    |    |    |
|-----------------------------------------------------------------|----|----|----|
| Met Arg Ile Ser Phe Gly Ser Pro Pro Pro Met Ala Gly Gly Val Lys |    |    |    |
| 1                                                               | 5  | 10 | 15 |
| Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr Asp Ile Gly |    |    |    |
| 20                                                              | 25 | 30 |    |
| Val Glu Lys Asp His Asn Phe Leu Leu Lys Asn Gly Leu Val Ala Ser |    |    |    |
| 35                                                              | 40 | 45 |    |
| Asn Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe |    |    |    |
| 50                                                              | 55 | 60 |    |
| Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe |    |    |    |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 65                                                              | 70  | 75  | 80  |
| Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly |     |     |     |
|                                                                 | 85  | 90  | 95  |
| Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu |     |     |     |
|                                                                 | 100 | 105 | 110 |
| Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His |     |     |     |
|                                                                 | 115 | 120 | 125 |
| Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn |     |     |     |
|                                                                 | 130 | 135 | 140 |
| Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro |     |     |     |
|                                                                 | 165 | 170 | 175 |
| Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn |     |     |     |
|                                                                 | 180 | 185 | 190 |
| Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly |     |     |     |
|                                                                 | 195 | 200 | 205 |
| Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Gly His His His His His |     |     |     |
|                                                                 | 210 | 215 | 220 |
| His Gly                                                         |     |     |     |
| 225                                                             |     |     |     |
| <210> 27                                                        |     |     |     |
| <211> 101                                                       |     |     |     |
| <212> PRT                                                       |     |     |     |
| <213> 人工序列(Artificial Sequence)                                 |     |     |     |
| <220>                                                           |     |     |     |
| <223> CfaN                                                      |     |     |     |
| <400> 27                                                        |     |     |     |
| Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu |     |     |     |
| 1                                                               | 5   | 10  | 15  |
| Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr |     |     |     |
|                                                                 | 20  | 25  | 30  |
| Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala Gln Trp His |     |     |     |
|                                                                 | 35  | 40  | 45  |
| Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser |     |     |     |
|                                                                 | 50  | 55  | 60  |
| Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr Asp Gly Gln |     |     |     |
| 65                                                              | 70  | 75  | 80  |
| Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln |     |     |     |

|                                                                 | 85 | 90 | 95 |
|-----------------------------------------------------------------|----|----|----|
| Val Asp Gly Leu Pro                                             |    |    |    |
| 100                                                             |    |    |    |
| <210> 28                                                        |    |    |    |
| <211> 36                                                        |    |    |    |
| <212> PRT                                                       |    |    |    |
| <213> 人工序列(Artificial Sequence)                                 |    |    |    |
| <220>                                                           |    |    |    |
| <223> CfaC                                                      |    |    |    |
| <400> 28                                                        |    |    |    |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |    |    |    |
| 1 5 10 15                                                       |    |    |    |
| Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys Asn Gly Leu |    |    |    |
| 20 25 30                                                        |    |    |    |
| Val Ala Ser Asn                                                 |    |    |    |
| 35                                                              |    |    |    |
| <210> 29                                                        |    |    |    |
| <211> 36                                                        |    |    |    |
| <212> PRT                                                       |    |    |    |
| <213> 人工序列(Artificial Sequence)                                 |    |    |    |
| <220>                                                           |    |    |    |
| <223> CfaCmut                                                   |    |    |    |
| <400> 29                                                        |    |    |    |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |    |    |    |
| 1 5 10 15                                                       |    |    |    |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |    |    |    |
| 20 25 30                                                        |    |    |    |
| Val Ala Ser Asn                                                 |    |    |    |
| 35                                                              |    |    |    |
| <210> 30                                                        |    |    |    |
| <211> 30                                                        |    |    |    |
| <212> PRT                                                       |    |    |    |
| <213> 人工序列(Artificial Sequence)                                 |    |    |    |
| <220>                                                           |    |    |    |
| <223> CatN                                                      |    |    |    |
| <400> 30                                                        |    |    |    |
| Cys Leu Ser Gly Asp Thr Met Ile Glu Ile Leu Asp Asp Asp Gly Ile |    |    |    |
| 1 5 10 15                                                       |    |    |    |
| Ile Gln Lys Ile Ser Met Glu Asp Leu Tyr Gln Arg Leu Ala         |    |    |    |

<210> 32  
<211> 102  
<212> PRT  
<213> 人工序列(Artificial Sequence)  
<220>  
<223> NpuN  
<400> 32  
Cys Leu Ser Tyr Glu Thr Glu Ile Leu Thr Val Glu Tyr Gly Leu Leu  
1 5 10 15  
Pro Ile Gly Lys Ile Val Glu Lys Arg Ile Glu Cys Thr Val Tyr Ser  
20 25 30  
Val Asp Asn Asn Gly Asn Ile Tyr Thr Gln Pro Val Ala Gln Trp His  
35 40 45  
Asp Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser  
50 55 60  
Leu Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Val Asp Gly Gln  
65 70 75 80



Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Glu Leu Asp Leu Met Arg  
85 90 95

Val Asp Asn Leu Pro Asn  
100

<210> 33

<211> 36

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> NpuC

<400> 33

Met Ile Lys Ile Ala Thr Arg Lys Tyr Leu Gly Lys Gln Asn Val Tyr  
1 5 10 15

Asp Ile Gly Val Glu Arg Asp His Asn Phe Ala Leu Lys Asn Gly Phe  
20 25 30

Ile Ala Ser Asn  
35

<210> 34

<211> 28

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> M3

<400> 34

Lys Ser Val Thr Leu Glu Ser Arg Ser Pro Lys Phe Leu Asn Trp Phe  
1 5 10 15

Ser Val Phe Ser Leu Phe Lys Val Ile Thr Thr Gly  
20 25

<210> 35

<211> 21

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> M4

<400> 35

Tyr Met Ser Ile Leu Arg Cys Ala Ser Gly Lys Ile Ser Ile Ala Ala  
1 5 10 15

Pro Pro Tyr Ile Phe  
20

&lt;210&gt; 36

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; NpuCmut

&lt;400&gt; 36

Met Ile Lys Ile Ala Thr Arg Lys Tyr Leu Gly Lys Gln Asn Val Tyr

1 5 10 15

Asp Ile Gly Val Gly Glu Pro His Asn Phe Ala Leu Lys Asn Gly Phe

20 25 30

Ile Ala Ser Asn

35

&lt;210&gt; 37

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; M5

&lt;400&gt; 37

Ala Gly Glu Ser Phe Asn Phe Met Val Lys Leu Leu Tyr Lys His Pro

1 5 10 15

Ile Leu Pro Cys Leu Lys Thr Leu Leu Ser Ile Arg Ser Ser Cys Ser

20 25 30

Pro Arg

&lt;210&gt; 38

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; GP41N

&lt;400&gt; 38

Cys Leu Asp Leu Lys Thr Gln Val Gln Thr Pro Gln Gly Met Lys Glu

1 5 10 15

Ile Ser Asn Ile Gln Val Gly Asp Leu Val Leu Ser Asn Thr Gly Tyr

20 25 30

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

35 40 45

Ile Thr Leu Glu Asp Gly Lys Glu Ile Ile Cys Ser Glu Glu His Leu

### 〈213〉 人工序列(Artificial Sequence)

<220>

<223> Deg1

<400> 41

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asn | Lys | Ile | Pro | Ile | Lys | Asp | Leu | Leu | Asn | Pro | Gln | Ile | Thr | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Glu | Phe | Lys | Ser | Ser | Ile | Leu | Asp | Ile | Asn | Lys | Lys | Leu | Phe | Ser | Ile |
|     |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |
| Cys | Cys | Asn | Leu | Pro | Lys | Leu | Pro | Glu | Ser | Val | Thr | Thr | Glu | Glu | Glu |
|     |     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |
| Val | Glu | Leu | Arg | Asp | Ile | Leu | Gly | Phe | Leu | Ser | Arg | Ala | Asn |     |     |
|     |     |     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |

<210> 42

<211> 30

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> PEST

<400> 42

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ser | Ser | Ser | Pro | Ser | Asp | Ser | Asp | Thr | Ser | Gly | Phe | Ser | Ser | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ser | Asp | His | Leu | Ser | Asp | Leu | Ile | Ser | Ser | Leu | Arg | Ile | Ser |     |     |
|     |     |     |     | 20  |     |     |     |     | 25  |     |     |     | 30  |     |     |

<210> 43

<211> 13

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> DD1

<220>

<221> 变体

<222> 12

<223> X= 任意氨基酸,优选Gly

<400> 43

|     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Ser | Phe | Gly | Ser | Pro | Pro | Pro | Met | Ala | Xaa | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |

<210> 44

<211> 9

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> DD2

<220>

<221> 变体

<222> 8

<223> X= 任意氨基酸,优选Gly

<400> 44

Gly Ser Pro Pro Pro Met Ala Xaa Gly

1 5

<210> 45

<211> 11

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> DD3

<400> 45

Thr Asn Gly Ile Leu Lys Leu Gly Cys Gln Gly

1 5 10

<210> 46

<211> 17

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> M1

<400> 46

Cys Ser Glu Ile Ile Pro Met Ser Arg Ser Thr Pro Ile Ser Thr Met

1 5 10 15

Gly

<210> 47

<211> 19

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> M2

<400> 47

Val Ser Phe Ala Phe Asn Leu Asn Ser Leu Ile Val Gly Ile Leu Arg

1 5 10 15

Phe His Trp

<210> 48

&lt;211&gt; 100

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; SopE

&lt;400&gt; 48

```

Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln
1           5           10           15
Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala
           20           25           30
Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys
           35           40           45
Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr
           50           55           60
His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn
65           70           75           80
Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile
           85           90           95
Arg Gly Ser Ala
           100

```

&lt;210&gt; 49

&lt;211&gt; 78

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; SopE-1-78

&lt;400&gt; 49

```

Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln
1           5           10           15
Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala
           20           25           30
Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys
           35           40           45
Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr
           50           55           60
His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu
65           70           75

```

&lt;210&gt; 50

&lt;211&gt; 63

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> SopE-15-78

<400> 50

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Thr | Thr | Leu | Leu | Lys | Glu | Lys | Ser | Thr | Glu | Lys | Asn | Ser | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ala | Lys | Ser | Ile | Leu | Ala | Val | Lys | Asn | His | Phe | Ile | Glu | Leu | Arg | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Lys | Leu | Ser | Glu | Arg | Phe | Ile | Ser | His | Lys | Asn | Thr | Glu | Ser | Ser | Ala |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Thr | His | Phe | His | Arg | Gly | Ser | Ala | Ser | Glu | Gly | Arg | Ala | Val | Leu |     |
|     |     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |

<210> 51

<211> 35

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> SopE-15-50

<400> 51

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Thr | Thr | Leu | Leu | Lys | Glu | Lys | Ser | Thr | Glu | Lys | Asn | Ser | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ala | Lys | Ser | Ile | Leu | Ala | Val | Lys | Asn | His | Phe | Ile | Glu | Leu | Arg | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Lys | Leu | Ser |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     | 35  |     |     |     |     |     |     |     |     |     |     |     |     |

<210> 52

<211> 35

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L2

<400> 52

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Ile | Ser | Leu | Pro | Leu | Pro | Thr | Arg | Val | Lys | Phe | Ser | Ser | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Leu | Leu | Ile | Arg | Ile | Met | Lys | Ile | Ile | Thr | Met | Thr | Phe | Pro | Lys | Lys |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Leu | Arg | Ser |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     | 35  |     |     |     |     |     |     |     |     |     |     |     |     |

<210> 53

<211> 16

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L6

<400> 53

Phe Tyr Tyr Pro Ile Trp Phe Ala Arg Val Leu Leu Val His Tyr Gln  
1 5 10 15

<210> 54

<211> 46

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L9

<400> 54

Ser Asn Pro Phe Ser Ser Leu Phe Gly Ala Ser Leu Leu Ile Asp Ser  
1 5 10 15  
Val Ser Leu Lys Ser Asn Trp Asp Thr Ser Ser Ser Ser Cys Leu Ile  
20 25 30  
Ser Phe Phe Ser Ser Val Met Phe Ser Ser Thr Thr Arg Ser  
35 40 45

<210> 55

<211> 39

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L10

<400> 55

Cys Arg Gln Arg Phe Ser Cys His Leu Thr Ala Ser Tyr Pro Gln Ser  
1 5 10 15  
Thr Val Thr Pro Phe Leu Ala Phe Leu Arg Arg Asp Phe Phe Phe Leu  
20 25 30  
Arg His Asn Ser Ser Ala Asp  
35

<210> 56

<211> 46

<212> PRT

<213> 人工序列(Artificial Sequence)



<220>

<223> L11

<400> 56

Gly Ala Pro His Val Val Leu Phe Asp Phe Glu Leu Arg Ile Thr Asn  
1                    5                    10                    15  
Pro Leu Ser His Ile Gln Ser Val Ser Leu Gln Ile Thr Leu Ile Phe  
                  20                    25                    30  
Cys Ser Leu Pro Ser Leu Ile Leu Ser Lys Phe Leu Gln Val  
                  35                    40                    45

<210> 57

<211> 39

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L12

<400> 57

Asn Thr Pro Leu Phe Ser Lys Ser Phe Ser Thr Thr Cys Gly Val Ala  
1                    5                    10                    15  
Lys Lys Thr Leu Leu Leu Ala Gln Ile Ser Ser Leu Phe Phe Leu Leu  
                  20                    25                    30  
Leu Ser Ser Asn Ile Ala Val  
                  35

<210> 58

<211> 45

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> L15

<400> 58

Pro Thr Val Lys Asn Ser Pro Lys Ile Phe Cys Leu Ser Ser Ser Pro  
1                    5                    10                    15  
Tyr Leu Ala Phe Asn Leu Glu Tyr Leu Ser Leu Arg Ile Phe Ser Thr  
                  20                    25                    30  
Leu Ser Lys Cys Ser Asn Thr Leu Leu Thr Ser Leu Ser  
                  35                    40                    45

<210> 59

<211> 30

<212> PRT

<213> 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; L16

&lt;400&gt; 59

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asn | Gln | Leu | Lys | Arg | Leu | Trp | Leu | Trp | Leu | Leu | Glu | Val | Arg | Ser |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Phe | Asp | Arg | Thr | Leu | Arg | Arg | Pro | Trp | Ile | His | Leu | Pro | Ser |     |     |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

&lt;210&gt; 60

&lt;211&gt; 1149

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4N-1150

&lt;400&gt; 60

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Leu | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |
|     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |
|     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |
| 65  |     |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |
|     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |
|     |     |     | 115 |     |     |     |     | 120 |     |     |     |     |     | 125 |     |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
|     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     | 175 |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     |     |     |     | 180 |     |     |     | 185 |     |     |     |     | 190 |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |
| 805                                                             | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |

Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn  
 1140 1145  
 <210> 61  
 <211> 1124  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4C-1150  
 <400> 61  
 Cys Phe Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn  
 1 5 10 15  
 Ile Gln Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser  
 20 25 30  
 Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro  
 35 40 45  
 Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu  
 50 55 60  
 His His Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu  
 65 70 75 80  
 Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser  
 85 90 95  
 Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser  
 100 105 110  
 Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr  
 115 120 125  
 Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys  
 130 135 140  
 Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys  
 145 150 155 160  
 Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro  
 165 170 175  
 Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly  
 180 185 190  
 Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala  
 195 200 205  
 Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe  
 210 215 220  
 Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met  
 225 230 235 240

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu |     |     |
| 245                                                             | 250 | 255 |
| His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu |     |     |
| 260                                                             | 265 | 270 |
| Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys |     |     |
| 275                                                             | 280 | 285 |
| Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr |     |     |
| 290                                                             | 295 | 300 |
| Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn |     |     |
| 305                                                             | 310 | 315 |
| Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser |     |     |
| 325                                                             | 330 | 335 |
| Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu |     |     |
| 340                                                             | 345 | 350 |
| Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg |     |     |
| 355                                                             | 360 | 365 |
| Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe |     |     |
| 370                                                             | 375 | 380 |
| Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys |     |     |
| 385                                                             | 390 | 395 |
| Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys |     |     |
| 405                                                             | 410 | 415 |
| Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser |     |     |
| 420                                                             | 425 | 430 |
| Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu |     |     |
| 435                                                             | 440 | 445 |
| Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp |     |     |
| 450                                                             | 455 | 460 |
| Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys |     |     |
| 485                                                             | 490 | 495 |
| Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu |     |     |
| 500                                                             | 505 | 510 |
| Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser |     |     |
| 515                                                             | 520 | 525 |
| Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val |     |     |
| 530                                                             | 535 | 540 |
| Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 545                                                             | 550 | 555 | 560 |
| Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro |     |     |     |
|                                                                 | 675 | 680 | 685 |
| His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn |     |     |     |
|                                                                 | 770 | 775 | 780 |
| Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly |     |     |     |
| 785                                                             | 790 | 795 | 800 |
| Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly |     |     |     |
|                                                                 | 805 | 810 | 815 |
| Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr |     |     |     |
|                                                                 | 820 | 825 | 830 |
| Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr |     |     |     |
|                                                                 | 835 | 840 | 845 |
| Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn |     |     |     |
|                                                                 | 850 | 855 | 860 |



|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly |      |      |      |
| 865                                                             | 870  | 875  | 880  |
| Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu |      |      |      |
|                                                                 | 885  | 890  | 895  |
| Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr |      |      |      |
|                                                                 | 900  | 905  | 910  |
| Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg |      |      |      |
|                                                                 | 915  | 920  | 925  |
| Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu |      |      |      |
|                                                                 | 930  | 935  | 940  |
| Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Gln Ala Gln Asp                                                 |      |      |      |
| <210> 62                                                        |      |      |      |
| <211> 1139                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4N-1140                                               |      |      |      |

&lt;400&gt; 62

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |     |
| Leu | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
|     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     | 180 |     |     |     | 185 |     |     |     |     |     | 190 |     |     |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     |     | 210 |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     | 240 |     |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     | 260 |     |     |     |     | 265 |     |     |     |     |     | 270 |     |     |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
|     |     | 290 |     |     |     | 295 |     |     |     |     |     | 300 |     |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Ser Arg Val Leu Ser     |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |

|                                                 |                         |     |
|-------------------------------------------------|-------------------------|-----|
| 610                                             | 615                     | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu         | Gln Gln Met Pro Tyr Pro |     |
| 625                                             | 630                     | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu     | Asn Arg Cys Phe Pro     |     |
| 645                                             | 650                     | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val     | Ser Met Thr Val Lys     |     |
| 660                                             | 665                     | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu | Thr Leu Lys Asn         |     |
| 675                                             | 680                     | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr     | Trp Phe Leu Asp Ser     |     |
| 690                                             | 695                     | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr | Ile Phe Ile Met         |     |
| 705                                             | 710                     | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile | Leu Phe Leu Phe         |     |
| 725                                             | 730                     | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys | Phe Leu Leu Ser         |     |
| 740                                             | 745                     | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys | Ser Gly Val Ile         |     |
| 755                                             | 760                     | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe | Ala Trp Gln Asp         |     |
| 770                                             | 775                     | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu | Leu Ser Pro Val         |     |
| 785                                             | 790                     | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe | Glu Glu Gln Gly         |     |
| 805                                             | 810                     | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro | Thr Glu Gly Asp         |     |
| 820                                             | 825                     | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu | Leu Asp Ala Ala         |     |
| 835                                             | 840                     | 845 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val | Phe Pro Gly Asp         |     |
| 850                                             | 855                     | 860 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln | Glu Ser Tyr Trp         |     |
| 865                                             | 870                     | 875 |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg | Ala Leu Glu Lys         |     |
| 885                                             | 890                     | 895 |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu | His Pro Glu Gly         |     |
| 900                                             | 905                     | 910 |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly | Trp Val Pro Gly         |     |
| 915                                             | 920                     | 925 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |      |
| 930                                                             | 935  | 940  |      |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr                                                     |      |      |      |
| <210> 63                                                        |      |      |      |
| <211> 1134                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4C-1140                                               |      |      |      |
| <400> 63                                                        |      |      |      |
| Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly Thr Gly Leu |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser Gln Arg Lys |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr |      |      |      |

|                                 |                                     |     |
|---------------------------------|-------------------------------------|-----|
| 35                              | 40                                  | 45  |
| Cys Pro Ala His Val Asp Asp     | Leu Thr Pro Glu Gln Val Leu Asp Gly |     |
| 50                              | 55                                  | 60  |
| Asp Val Asn Glu Leu Met Asp     | Val Val Leu His His Val Pro Glu Ala |     |
| 65                              | 70                                  | 75  |
| Lys Leu Val Glu Cys Ile Gly     | Gln Glu Leu Ile Phe Leu Leu Pro Asn |     |
| 85                              | 90                                  | 95  |
| Lys Asn Phe Lys His Arg Ala Tyr | Ala Ser Leu Phe Arg Glu Leu Glu     |     |
| 100                             | 105                                 | 110 |
| Glu Thr Leu Ala Asp Leu Gly     | Leu Ser Ser Phe Gly Ile Ser Asp Thr |     |
| 115                             | 120                                 | 125 |
| Pro Leu Glu Glu Ile Phe Leu Lys | Val Thr Glu Asp Ser Asp Ser Gly     |     |
| 130                             | 135                                 | 140 |
| Pro Leu Phe Ala Gly Gly Ala Gln | Gln Lys Arg Glu Asn Val Asn Pro     |     |
| 145                             | 150                                 | 155 |
| Arg His Pro Cys Leu Gly Pro Arg | Glu Lys Ala Gly Gln Thr Pro Gln     |     |
| 165                             | 170                                 | 175 |
| Asp Ser Asn Val Cys Ser Pro Gly | Ala Pro Ala Ala His Pro Glu Gly     |     |
| 180                             | 185                                 | 190 |
| Gln Pro Pro Pro Glu Pro Glu Cys | Pro Gly Pro Gln Leu Asn Thr Gly     |     |
| 195                             | 200                                 | 205 |
| Thr Gln Leu Val Leu Gln His Val | Gln Ala Leu Leu Val Lys Arg Phe     |     |
| 210                             | 215                                 | 220 |
| Gln His Thr Ile Arg Ser His Lys | Asp Phe Leu Ala Gln Ile Val Leu     |     |
| 225                             | 230                                 | 235 |
| Pro Ala Thr Phe Val Phe Leu Ala | Leu Met Leu Ser Ile Val Ile Pro     |     |
| 245                             | 250                                 | 255 |
| Pro Phe Gly Glu Tyr Pro Ala Leu | Thr Leu His Pro Trp Ile Tyr Gly     |     |
| 260                             | 265                                 | 270 |
| Gln Gln Tyr Thr Phe Phe Ser Met | Asp Glu Pro Gly Ser Glu Gln Phe     |     |
| 275                             | 280                                 | 285 |
| Thr Val Leu Ala Asp Val Leu Leu | Asn Lys Pro Gly Phe Gly Asn Arg     |     |
| 290                             | 295                                 | 300 |
| Cys Leu Lys Glu Gly Trp Leu Pro | Glu Tyr Pro Cys Gly Asn Ser Thr     |     |
| 305                             | 310                                 | 315 |
| Pro Trp Lys Thr Pro Ser Val Ser | Pro Asn Ile Thr Gln Leu Phe Gln     |     |
| 325                             | 330                                 | 335 |
| Lys Gln Lys Trp Thr Gln Val Asn | Pro Ser Pro Ser Cys Arg Cys Ser     |     |
| 340                             | 345                                 | 350 |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly |     |         |
| 355                                                             | 360 | 365     |
| Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln |     |         |
| 370                                                             | 375 | 380     |
| Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro |     |         |
| 385                                                             | 390 | 395 400 |
| Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln |     |         |
| 405                                                             | 410 | 415     |
| Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile |     |         |
| 420                                                             | 425 | 430     |
| Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met |     |         |
| 435                                                             | 440 | 445     |
| Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro |     |         |
| 450                                                             | 455 | 460     |
| Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe |     |         |
| 465                                                             | 470 | 475 480 |
| Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His |     |         |
| 485                                                             | 490 | 495     |
| Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu |     |         |
| 500                                                             | 505 | 510     |
| Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln |     |         |
| 515                                                             | 520 | 525     |
| Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala |     |         |
| 530                                                             | 535 | 540     |
| Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu |     |         |
| 545                                                             | 550 | 555 560 |
| Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile |     |         |
| 565                                                             | 570 | 575     |
| Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp |     |         |
| 580                                                             | 585 | 590     |
| Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile |     |         |
| 595                                                             | 600 | 605     |
| Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu |     |         |
| 610                                                             | 615 | 620     |
| Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr |     |         |
| 625                                                             | 630 | 635 640 |
| Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu |     |         |
| 645                                                             | 650 | 655     |
| Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe |     |         |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 660                                                             | 665 | 670 |
| Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala |     |     |
| 675                                                             | 680 | 685 |
| Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg |     |     |
| 690                                                             | 695 | 700 |
| Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala |     |     |
| 705                                                             | 710 | 715 |
| Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile |     |     |
| 725                                                             | 730 | 735 |
| Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu |     |     |
| 740                                                             | 745 | 750 |
| Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala |     |     |
| 755                                                             | 760 | 765 |
| Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu |     |     |
| 770                                                             | 775 | 780 |
| Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg |     |     |
| 785                                                             | 790 | 795 |
| Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val |     |     |
| 805                                                             | 810 | 815 |
| Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu |     |     |
| 820                                                             | 825 | 830 |
| Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly |     |     |
| 835                                                             | 840 | 845 |
| Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile |     |     |
| 850                                                             | 855 | 860 |
| Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln |     |     |
| 865                                                             | 870 | 875 |
| Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu |     |     |
| 885                                                             | 890 | 895 |
| Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala |     |     |
| 900                                                             | 905 | 910 |
| Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu |     |     |
| 915                                                             | 920 | 925 |
| Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile |     |     |
| 930                                                             | 935 | 940 |
| Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr |     |     |
| 945                                                             | 950 | 955 |
| Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser |     |     |
| 965                                                             | 970 | 975 |



Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu  
 980 985 990  
 Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala  
 995 1000 1005  
 Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp  
 1010 1015 1020  
 Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu  
 1025 1030 1035 1040  
 Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly  
 1045 1050 1055  
 Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser  
 1060 1065 1070  
 Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp  
 1075 1080 1085  
 Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln  
 1090 1095 1100  
 Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro  
 1105 1110 1115 1120  
 Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp  
 1125 1130

<210> 64

<211> 1187

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> ABCA4N-1188

<400> 64

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15  
 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30  
 Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45  
 Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
 50 55 60  
 Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro  
 65 70 75 80  
 Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn  
 85 90 95

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |
| 100                                                             | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |

|                                                                 |     |     |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|-----|-----|
|                                                                 | 405 |     | 410 |     | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |     |     |
|                                                                 | 420 |     | 425 |     | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |     |     |
|                                                                 | 435 |     | 440 |     | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |     |     |
|                                                                 | 450 |     | 455 |     | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |     |     |
| 465                                                             |     | 470 |     | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |     |     |
|                                                                 | 485 |     | 490 |     | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |     |     |
|                                                                 | 500 |     | 505 |     | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |     |     |
|                                                                 | 515 |     | 520 |     | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |     |     |
|                                                                 | 530 |     | 535 |     | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |     |     |
| 545                                                             |     | 550 |     | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |     |     |
|                                                                 | 565 |     | 570 |     | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |     |     |
|                                                                 | 580 |     | 585 |     | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |     |     |
|                                                                 | 595 |     | 600 |     | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |     |     |
|                                                                 | 610 |     | 615 |     | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |     |     |     |
| 625                                                             |     | 630 |     | 635 | 640 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |     |     |     |
|                                                                 | 645 |     | 650 |     | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |     |     |     |
|                                                                 | 660 |     | 665 |     | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |     |     |     |
|                                                                 | 675 |     | 680 |     | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |     |     |     |
|                                                                 | 690 |     | 695 |     | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |     |     |     |
| 705                                                             |     | 710 |     | 715 | 720 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |      |      |
| 725                                                             | 730  | 735  |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |      |      |
| 740                                                             | 745  | 750  |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 800  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
| 805                                                             | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Ser Thr Thr                                                     |      |      |      |
| 1185                                                            |      |      |      |
| <210> 65                                                        |      |      |      |
| <211> 1086                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4C-1188                                               |      |      |      |
| <400> 65                                                        |      |      |      |
| Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp Gly |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val Pro Glu Ala |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn |      |      |      |
|                                                                 | 35   | 40   | 45   |
| Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu |      |      |      |
|                                                                 | 50   | 55   | 60   |
| Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr |      |      |      |
| 65                                                              | 70   | 75   | 80   |
| Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser Gly |      |      |      |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |  |
| Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu | Asn | Val | Asn | Pro |  |  |
|     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |  |  |
| Arg | His | Pro | Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly | Gln | Thr | Pro | Gln |  |  |
|     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |  |  |
| Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala | His | Pro | Glu | Gly |  |  |
|     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |  |  |
| Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln | Leu | Asn | Thr | Gly |  |  |
| 145 |     |     |     |     |     |     | 150 |     |     |     | 155 |     |     |     | 160 |  |  |
| Thr | Gln | Leu | Val | Leu | Gln | His | Val | Gln | Ala | Leu | Leu | Val | Lys | Arg | Phe |  |  |
|     |     |     |     |     |     |     | 165 |     |     |     | 170 |     |     |     | 175 |  |  |
| Gln | His | Thr | Ile | Arg | Ser | His | Lys | Asp | Phe | Leu | Ala | Gln | Ile | Val | Leu |  |  |
|     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |  |  |
| Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala | Leu | Met | Leu | Ser | Ile | Val | Ile | Pro |  |  |
|     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |  |  |
| Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro | Trp | Ile | Tyr | Gly |  |  |
|     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |  |  |
| Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly | Ser | Glu | Gln | Phe |  |  |
| 225 |     |     |     |     |     |     | 230 |     |     |     | 235 |     |     |     | 240 |  |  |
| Thr | Val | Leu | Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly | Phe | Gly | Asn | Arg |  |  |
|     |     |     |     |     |     |     | 245 |     |     |     | 250 |     |     |     | 255 |  |  |
| Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro | Cys | Gly | Asn | Ser | Thr |  |  |
|     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |  |  |
| Pro | Trp | Lys | Thr | Pro | Ser | Val | Ser | Pro | Asn | Ile | Thr | Gln | Leu | Phe | Gln |  |  |
|     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |  |  |
| Lys | Gln | Lys | Trp | Thr | Gln | Val | Asn | Pro | Ser | Pro | Ser | Cys | Arg | Cys | Ser |  |  |
|     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |  |  |
| Thr | Arg | Glu | Lys | Leu | Thr | Met | Leu | Pro | Glu | Cys | Pro | Glu | Gly | Ala | Gly |  |  |
| 305 |     |     |     |     |     |     | 310 |     |     |     | 315 |     |     |     | 320 |  |  |
| Gly | Leu | Pro | Pro | Pro | Gln | Arg | Thr | Gln | Arg | Ser | Thr | Glu | Ile | Leu | Gln |  |  |
|     |     |     |     |     |     |     | 325 |     |     |     | 330 |     |     |     | 335 |  |  |
| Asp | Leu | Thr | Asp | Arg | Asn | Ile | Ser | Asp | Phe | Leu | Val | Lys | Thr | Tyr | Pro |  |  |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |  |  |
| Ala | Leu | Ile | Arg | Ser | Ser | Leu | Lys | Ser | Lys | Phe | Trp | Val | Asn | Glu | Gln |  |  |
|     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |  |  |
| Arg | Tyr | Gly | Gly | Ile | Ser | Ile | Gly | Gly | Lys | Leu | Pro | Val | Val | Pro | Ile |  |  |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |  |  |
| Thr | Gly | Glu | Ala | Leu | Val | Gly | Phe | Leu | Ser | Asp | Leu | Gly | Arg | Ile | Met |  |  |
| 385 |     |     |     |     |     |     | 390 |     |     |     | 395 |     |     |     | 400 |  |  |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro |     |     |
| 405                                                             | 410 | 415 |
| Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe |     |     |
| 420                                                             | 425 | 430 |
| Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His |     |     |
| 435                                                             | 440 | 445 |
| Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu |     |     |
| 450                                                             | 455 | 460 |
| Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln |     |     |
| 465                                                             | 470 | 475 |
| Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala |     |     |
| 485                                                             | 490 | 495 |
| Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu |     |     |
| 500                                                             | 505 | 510 |
| Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile |     |     |
| 515                                                             | 520 | 525 |
| Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp |     |     |
| 530                                                             | 535 | 540 |
| Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile |     |     |
| 545                                                             | 550 | 555 |
| Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu |     |     |
| 565                                                             | 570 | 575 |
| Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr |     |     |
| 580                                                             | 585 | 590 |
| Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu |     |     |
| 595                                                             | 600 | 605 |
| Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe |     |     |
| 610                                                             | 615 | 620 |
| Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala |     |     |
| 625                                                             | 630 | 635 |
| Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg |     |     |
| 645                                                             | 650 | 655 |
| Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala |     |     |
| 660                                                             | 665 | 670 |
| Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile |     |     |
| 675                                                             | 680 | 685 |
| Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu |     |     |
| 690                                                             | 695 | 700 |
| Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala |     |     |

|                     |                                             |                     |         |
|---------------------|---------------------------------------------|---------------------|---------|
| 705                 | 710                                         | 715                 | 720     |
| Glu Pro Thr Lys     | Glu Pro Ile Val Asp                         | Glu Asp Asp Asp Val | Ala Glu |
| 725                 | 730                                         | 735                 |         |
| Glu Arg Gln Arg     | Ile Ile Thr Gly Gly Asn Lys Thr Asp         | Ile Leu Arg         |         |
| 740                 | 745                                         | 750                 |         |
| Leu His Glu Leu Thr | Lys Ile Tyr Pro Gly Thr Ser Ser             | Pro Ala Val         |         |
| 755                 | 760                                         | 765                 |         |
| Asp Arg Leu Cys Val | Gly Val Arg Pro Gly Glu Cys Phe Gly         | Leu Leu             |         |
| 770                 | 775                                         | 780                 |         |
| Gly Val Asn Gly Ala | Gly Lys Thr Thr Thr Phe Lys Met             | Leu Thr Gly         |         |
| 785                 | 790                                         | 795                 | 800     |
| Asp Thr Thr Val Thr | Ser Gly Asp Ala Thr Val Ala Gly Lys Ser     | Ile                 |         |
| 805                 | 810                                         | 815                 |         |
| Leu Thr Asn Ile Ser | Glu Val His Gln Asn Met Gly Tyr Cys         | Pro Gln             |         |
| 820                 | 825                                         | 830                 |         |
| Phe Asp Ala Ile Asp | Glu Leu Leu Thr Gly Arg Glu His Leu Tyr     | Leu                 |         |
| 835                 | 840                                         | 845                 |         |
| Tyr Ala Arg Leu Arg | Gly Val Pro Ala Glu Glu Ile Glu Lys Val     | Ala                 |         |
| 850                 | 855                                         | 860                 |         |
| Asn Trp Ser Ile Lys | Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys     | Leu                 |         |
| 865                 | 870                                         | 875                 | 880     |
| Ala Gly Thr Tyr Ser | Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala     | Ile                 |         |
| 885                 | 890                                         | 895                 |         |
| Ala Leu Ile Gly Cys | Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr |                     |         |
| 900                 | 905                                         | 910                 |         |
| Gly Met Asp Pro Gln | Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser |                     |         |
| 915                 | 920                                         | 925                 |         |
| Ile Ile Arg Glu Gly | Arg Ala Val Val Leu Thr Ser His Ser Met     | Glu                 |         |
| 930                 | 935                                         | 940                 |         |
| Glu Cys Glu Ala Leu | Cys Thr Arg Leu Ala Ile Met Val Lys Gly     | Ala                 |         |
| 945                 | 950                                         | 955                 | 960     |
| Phe Arg Cys Met Gly | Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp |                     |         |
| 965                 | 970                                         | 975                 |         |
| Gly Tyr Ile Val Thr | Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu |                     |         |
| 980                 | 985                                         | 990                 |         |
| Pro Asp Leu Asn Pro | Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly |                     |         |
| 995                 | 1000                                        | 1005                |         |
| Ser Val Gln Arg Glu | Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser |                     |         |
| 1010                | 1015                                        | 1020                |         |



Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp  
 1025 1030 1035 1040  
 Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln  
 1045 1050 1055  
 Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro  
 1060 1065 1070  
 Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp  
 1075 1080 1085  
 <210> 66  
 <211> 1250  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1150-CfaN  
 <400> 66  
 Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15  
 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30  
 Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45  
 Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
 50 55 60  
 Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro  
 65 70 75 80  
 Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn  
 85 90 95  
 Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu  
 100 105 110  
 Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu  
 115 120 125  
 Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu  
 130 135 140  
 Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu  
 145 150 155 160  
 Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser  
 165 170 175  
 Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala  
 180 185 190

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |         |
| 195                                                             | 200 | 205     |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |         |
| 210                                                             | 215 | 220     |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |         |
| 225                                                             | 230 | 235 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |         |
| 245                                                             | 250 | 255     |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |         |
| 260                                                             | 265 | 270     |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |         |
| 275                                                             | 280 | 285     |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |         |
| 290                                                             | 295 | 300     |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |         |
| 305                                                             | 310 | 315 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |         |
| 325                                                             | 330 | 335     |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |         |
| 340                                                             | 345 | 350     |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |         |
| 355                                                             | 360 | 365     |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |         |
| 370                                                             | 375 | 380     |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |         |
| 385                                                             | 390 | 395 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |         |
| 405                                                             | 410 | 415     |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |         |
| 420                                                             | 425 | 430     |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |         |
| 435                                                             | 440 | 445     |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |         |
| 450                                                             | 455 | 460     |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |         |
| 465                                                             | 470 | 475 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |         |
| 485                                                             | 490 | 495     |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |         |

|                             |                         |             |
|-----------------------------|-------------------------|-------------|
| 500                         | 505                     | 510         |
| Val Asn Gln Tyr Leu Glu Cys | Leu Val Leu Asp Lys Phe | Glu Ser Tyr |
| 515                         | 520                     | 525         |
| Asn Asp Glu Thr Gln Leu Thr | Gln Arg Ala Leu Ser Leu | Leu Glu Glu |
| 530                         | 535                     | 540         |
| Asn Met Phe Trp Ala Gly Val | Val Phe Pro Asp Met Tyr | Pro Trp Thr |
| 545                         | 550                     | 555         |
| Ser Ser Leu Pro Pro His Val | Lys Tyr Lys Ile Arg Met | Asp Ile Asp |
| 565                         | 570                     | 575         |
| Val Val Glu Lys Thr Asn Lys | Ile Lys Asp Arg Tyr Trp | Asp Ser Gly |
| 580                         | 585                     | 590         |
| Pro Arg Ala Asp Pro Val Glu | Asp Phe Arg Tyr Ile Trp | Gly Gly Phe |
| 595                         | 600                     | 605         |
| Ala Tyr Leu Gln Asp Met Val | Glu Gln Gly Ile Thr Arg | Ser Gln Val |
| 610                         | 615                     | 620         |
| Gln Ala Glu Ala Pro Val Gly | Ile Tyr Leu Gln Gln Met | Pro Tyr Pro |
| 625                         | 630                     | 635         |
| Cys Phe Val Asp Asp Ser Phe | Met Ile Ile Leu Asn Arg | Cys Phe Pro |
| 645                         | 650                     | 655         |
| Ile Phe Met Val Leu Ala Trp | Ile Tyr Ser Val Ser Met | Thr Val Lys |
| 660                         | 665                     | 670         |
| Ser Ile Val Leu Glu Lys Glu | Leu Arg Leu Lys Glu Thr | Leu Lys Asn |
| 675                         | 680                     | 685         |
| Gln Gly Val Ser Asn Ala Val | Ile Trp Cys Thr Trp Phe | Leu Asp Ser |
| 690                         | 695                     | 700         |
| Phe Ser Ile Met Ser Met Ser | Ile Phe Leu Leu Thr Ile | Phe Ile Met |
| 705                         | 710                     | 715         |
| His Gly Arg Ile Leu His Tyr | Ser Asp Pro Phe Ile Leu | Phe Leu Phe |
| 725                         | 730                     | 735         |
| Leu Leu Ala Phe Ser Thr Ala | Thr Ile Met Leu Cys Phe | Leu Leu Ser |
| 740                         | 745                     | 750         |
| Thr Phe Phe Ser Lys Ala Ser | Leu Ala Ala Ala Cys Ser | Gly Val Ile |
| 755                         | 760                     | 765         |
| Tyr Phe Thr Leu Tyr Leu Pro | His Ile Leu Cys Phe Ala | Trp Gln Asp |
| 770                         | 775                     | 780         |
| Arg Met Thr Ala Glu Leu Lys | Lys Ala Val Ser Leu Leu | Ser Pro Val |
| 785                         | 790                     | 795         |
| Ala Phe Gly Phe Gly Thr Glu | Tyr Leu Val Arg Phe Glu | Glu Gln Gly |
| 805                         | 810                     | 815         |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
|                                                                 | 885  | 890  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
|                                                                 | 900  | 905  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
|                                                                 | 915  | 920  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
|                                                                 | 930  | 935  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
|                                                                 | 965  | 970  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
|                                                                 | 980  | 985  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
|                                                                 | 995  | 1000 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
|                                                                 | 1010 | 1015 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
|                                                                 | 1045 | 1050 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
|                                                                 | 1060 | 1065 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
|                                                                 | 1075 | 1080 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
|                                                                 | 1090 | 1095 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |

|                                 |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
|---------------------------------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|
|                                 |     |     |     | 1125 |     |     |     | 1130 |     |     |     | 1135 |     |     |     |
| Arg                             | Leu | Tyr | Cys | Ser  | Gly | Thr | Pro | Leu  | Phe | Leu | Lys | Asn  | Cys | Leu | Ser |
|                                 |     |     |     | 1140 |     |     |     | 1145 |     |     |     | 1150 |     |     |     |
| Tyr                             | Asp | Thr | Glu | Ile  | Leu | Thr | Val | Glu  | Tyr | Gly | Phe | Leu  | Pro | Ile | Gly |
|                                 |     |     |     | 1155 |     |     |     | 1160 |     |     |     | 1165 |     |     |     |
| Lys                             | Ile | Val | Glu | Glu  | Arg | Ile | Glu | Cys  | Thr | Val | Tyr | Thr  | Val | Asp | Lys |
|                                 |     |     |     | 1170 |     |     |     | 1175 |     |     |     | 1180 |     |     |     |
| Asn                             | Gly | Phe | Val | Tyr  | Thr | Gln | Pro | Ile  | Ala | Gln | Trp | His  | Asn | Arg | Gly |
| 1185                            |     |     |     | 1190 |     |     |     | 1195 |     |     |     | 1200 |     |     |     |
| Glu                             | Gln | Glu | Val | Phe  | Glu | Tyr | Cys | Leu  | Glu | Asp | Gly | Ser  | Ile | Ile | Arg |
|                                 |     |     |     | 1205 |     |     |     | 1210 |     |     |     | 1215 |     |     |     |
| Ala                             | Thr | Lys | Asp | His  | Lys | Phe | Met | Thr  | Thr | Asp | Gly | Gln  | Met | Leu | Pro |
|                                 |     |     |     | 1220 |     |     |     | 1225 |     |     |     | 1230 |     |     |     |
| Ile                             | Asp | Glu | Ile | Phe  | Glu | Arg | Gly | Leu  | Asp | Leu | Lys | Gln  | Val | Asp | Gly |
|                                 |     |     |     | 1235 |     |     |     | 1240 |     |     |     | 1245 |     |     |     |
| Leu Pro                         |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| 1250                            |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <210> 67                        |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <211> 1160                      |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <212> PRT                       |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <213> 人工序列(Artificial Sequence) |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <220>                           |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <223> ABCA4-1150-CfaC           |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <400> 67                        |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| Met                             | Val | Lys | Ile | Ile  | Ser | Arg | Lys | Ser  | Leu | Gly | Thr | Gln  | Asn | Val | Tyr |
| 1                               |     |     |     | 5    |     |     |     | 10   |     |     |     | 15   |     |     |     |
| Asp                             | Ile | Gly | Val | Glu  | Lys | Asp | His | Asn  | Phe | Leu | Leu | Lys  | Asn | Gly | Leu |
|                                 |     |     |     | 20   |     |     |     | 25   |     |     |     | 30   |     |     |     |
| Val                             | Ala | Ser | Asn | Cys  | Phe | Gly | Thr | Gly  | Leu | Tyr | Leu | Thr  | Leu | Val | Arg |
|                                 |     |     |     | 35   |     |     |     | 40   |     |     |     | 45   |     |     |     |
| Lys                             | Met | Lys | Asn | Ile  | Gln | Ser | Gln | Arg  | Lys | Gly | Ser | Glu  | Gly | Thr | Cys |
| 50                              |     |     |     | 55   |     |     |     | 60   |     |     |     |      |     |     |     |
| Ser                             | Cys | Ser | Ser | Lys  | Gly | Phe | Ser | Thr  | Thr | Cys | Pro | Ala  | His | Val | Asp |
| 65                              |     |     |     | 70   |     |     |     | 75   |     |     |     | 80   |     |     |     |
| Asp                             | Leu | Thr | Pro | Glu  | Gln | Val | Leu | Asp  | Gly | Asp | Val | Asn  | Glu | Leu | Met |
|                                 |     |     |     | 85   |     |     |     | 90   |     |     |     | 95   |     |     |     |
| Asp                             | Val | Val | Leu | His  | His | Val | Pro | Glu  | Ala | Lys | Leu | Val  | Glu | Cys | Ile |
|                                 |     |     |     | 100  |     |     |     | 105  |     |     |     | 110  |     |     |     |
| Gly                             | Gln | Glu | Leu | Ile  | Phe | Leu | Leu | Pro  | Asn | Lys | Asn | Phe  | Lys | His | Arg |

|                                                                 |                                     |     |
|-----------------------------------------------------------------|-------------------------------------|-----|
| 115                                                             | 120                                 | 125 |
| Ala Tyr Ala Ser Leu Phe Arg                                     | Glu Leu Glu Glu Thr Leu Ala Asp Leu |     |
| 130                                                             | 135                                 | 140 |
| Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe |                                     |     |
| 145                                                             | 150                                 | 155 |
| Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly |                                     |     |
| 165                                                             | 170                                 | 175 |
| Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly |                                     |     |
| 180                                                             | 185                                 | 190 |
| Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser |                                     |     |
| 195                                                             | 200                                 | 205 |
| Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro |                                     |     |
| 210                                                             | 215                                 | 220 |
| Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln |                                     |     |
| 225                                                             | 230                                 | 235 |
| His Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser |                                     |     |
| 245                                                             | 250                                 | 255 |
| His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe |                                     |     |
| 260                                                             | 265                                 | 270 |
| Leu Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro |                                     |     |
| 275                                                             | 280                                 | 285 |
| Ala Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe |                                     |     |
| 290                                                             | 295                                 | 300 |
| Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val |                                     |     |
| 305                                                             | 310                                 | 315 |
| Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp |                                     |     |
| 325                                                             | 330                                 | 335 |
| Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser |                                     |     |
| 340                                                             | 345                                 | 350 |
| Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln |                                     |     |
| 355                                                             | 360                                 | 365 |
| Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr |                                     |     |
| 370                                                             | 375                                 | 380 |
| Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln |                                     |     |
| 385                                                             | 390                                 | 395 |
| Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn |                                     |     |
| 405                                                             | 410                                 | 415 |
| Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser |                                     |     |
| 420                                                             | 425                                 | 430 |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser |     |         |
| 435                                                             | 440 | 445     |
| Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val |     |         |
| 450                                                             | 455 | 460     |
| Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro |     |         |
| 465                                                             | 470 | 475 480 |
| Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu |     |         |
|                                                                 | 485 | 490 495 |
| Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His |     |         |
|                                                                 | 500 | 505 510 |
| Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala |     |         |
|                                                                 | 515 | 520 525 |
| Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile |     |         |
|                                                                 | 530 | 535 540 |
| Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val |     |         |
| 545                                                             | 550 | 555 560 |
| Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser |     |         |
|                                                                 | 565 | 570 575 |
| Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg |     |         |
|                                                                 | 580 | 585 590 |
| Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr |     |         |
|                                                                 | 595 | 600 605 |
| Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val |     |         |
| 610                                                             | 615 | 620     |
| Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala |     |         |
| 625                                                             | 630 | 635 640 |
| Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu Leu |     |         |
|                                                                 | 645 | 650 655 |
| Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe |     |         |
|                                                                 | 660 | 665 670 |
| Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe |     |         |
|                                                                 | 675 | 680 685 |
| Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu |     |         |
| 690                                                             | 695 | 700     |
| Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu |     |         |
| 705                                                             | 710 | 715 720 |
| Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala |     |         |
|                                                                 | 725 | 730 735 |
| Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His |     |         |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 740                                                             | 745  | 750  |
| Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala |      |      |
| 755                                                             | 760  | 765  |
| Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln |      |      |
| 770                                                             | 775  | 780  |
| Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro |      |      |
| 785                                                             | 790  | 795  |
| Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile |      | 800  |
| 805                                                             | 810  | 815  |
| Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys |      |      |
| 820                                                             | 825  | 830  |
| Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly |      |      |
| 835                                                             | 840  | 845  |
| Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly |      |      |
| 850                                                             | 855  | 860  |
| Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser |      |      |
| 865                                                             | 870  | 875  |
| Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu |      |      |
| 885                                                             | 890  | 895  |
| Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu |      |      |
| 900                                                             | 905  | 910  |
| Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser |      |      |
| 930                                                             | 935  | 940  |
| Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly |      |      |
| 945                                                             | 950  | 955  |
| Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro |      |      |
| 965                                                             | 970  | 975  |
| Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala |      |      |
| 980                                                             | 985  | 990  |
| Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg |      |      |
| 995                                                             | 1000 | 1005 |
| Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys |      |      |
| 1010                                                            | 1015 | 1020 |
| Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr |      |      |
| 1025                                                            | 1030 | 1035 |
| Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met |      | 1040 |
| 1045                                                            | 1050 | 1055 |



Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val  
 1060 1065 1070  
 Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg  
 1075 1080 1085  
 His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg  
 1090 1095 1100  
 Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu  
 1105 1110 1115 1120  
 Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala  
 1125 1130 1135  
 Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala  
 1140 1145 1150  
 Gly Ala Ser Arg Gln Ala Gln Asp  
 1155 1160  
 <210> 68  
 <211> 1240  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1140-CfaN  
 <400> 68  
 Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15  
 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30  
 Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45  
 Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
 50 55 60  
 Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro  
 65 70 75 80  
 Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn  
 85 90 95  
 Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu  
 100 105 110  
 Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu  
 115 120 125  
 Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu  
 130 135 140

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     | 175 |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     |     |     |     | 180 |     |     |     | 185 |     |     |     |     | 190 |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     |     |     |     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     |     |     |     |     |     | 210 |     |     |     | 215 |     |     |     |     | 220 |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
|     |     |     |     |     |     | 225 |     |     |     | 230 |     |     |     |     | 235 |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     |     |     |     | 240 |     |     |     | 245 |     |     |     |     | 250 |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     |     |     |     |     | 255 |     |     |     | 260 |     |     |     |     | 265 |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     |     |     |     |     |     | 270 |     |     |     | 275 |     |     |     |     | 280 |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
|     |     |     |     |     |     | 285 |     |     |     | 290 |     |     |     |     | 295 |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |
|     |     |     |     |     |     | 300 |     |     |     | 305 |     |     |     |     | 310 |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |
|     |     |     |     |     |     | 315 |     |     |     | 320 |     |     |     |     | 325 |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |
|     |     |     |     |     |     | 325 |     |     |     | 330 |     |     |     |     | 335 |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |
|     |     |     |     |     |     | 340 |     |     |     | 345 |     |     |     |     | 350 |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |
|     |     |     |     |     |     | 355 |     |     |     | 360 |     |     |     |     | 365 |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
|     |     |     |     |     |     | 370 |     |     |     | 375 |     |     |     |     | 380 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     |     |     | 385 |     |     |     | 390 |     |     |     |     | 395 |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     |     |     |     | 400 |     |     |     | 405 |     |     |     |     | 410 |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |
|     |     |     |     |     |     | 415 |     |     |     | 420 |     |     |     |     | 425 |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu |
|     |     |     |     |     |     | 430 |     |     |     | 435 |     |     |     |     | 440 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |      |
| 770                                                             | 775  | 780  |      |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |      |
| 785                                                             | 790  | 795  | 800  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |      |
|                                                                 | 805  | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |      |
|                                                                 | 820  | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |      |
|                                                                 | 835  | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |      |
|                                                                 | 850  | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |      |
| 865                                                             | 870  | 875  | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |      |
|                                                                 | 885  | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |      |
|                                                                 | 900  | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |      |
|                                                                 | 915  | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |      |
|                                                                 | 930  | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |
| 1140                                                            | 1145 | 1150 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |
| 1155                                                            | 1160 | 1165 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |
| 1170                                                            | 1175 | 1180 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |
| 1185                                                            | 1190 | 1195 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |
| 1205                                                            | 1210 | 1215 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |
| 1220                                                            | 1225 | 1230 |
| Leu Lys Gln Val Asp Gly Leu Pro                                 |      |      |
| 1235                                                            | 1240 |      |
| <210> 69                                                        |      |      |
| <211> 1170                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1140-CfaCmut                                        |      |      |
| <400> 69                                                        |      |      |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |      |      |
| 1                                                               | 5    | 10   |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |      |      |
| 20                                                              | 25   | 30   |
| Val Ala Ser Asn Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe |      |      |
| 35                                                              | 40   | 45   |
| Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln |      |      |
| 50                                                              | 55   | 60   |
| Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly |      |      |
| 65                                                              | 70   | 75   |
| Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln |      |      |

| 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met | Asp | Val | Val | Leu | His |
| 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |     |
| Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile | Gly | Gln | Glu | Leu | Ile |
| 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |
| Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr | Ala | Ser | Leu |
| 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu | Ser | Ser | Phe |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     |
| Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys | Val | Thr | Glu |
| 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     |
| Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg |
| 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |     |
| Asn | Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala |
| 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |
| Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala |
| 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| His | Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     |
| Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln | His | Val | Gln | Ala | Leu |
| 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |     |     |
| Val | Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser | His | Lys | Asp | Phe | Leu |
| 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |     |
| Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala | Leu | Met | Leu |
| 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     |
| Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His |
| 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     |
| Ser | Glu | Gln | Phe | Thr | Val | Leu | Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro |
| 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |     |
| Phe | Gly | Asn | Arg | Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro |
| 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |     |     |
| Gly | Asn | Ser | Thr | Pro | Trp | Lys | Thr | Pro | Ser | Val | Ser | Pro | Asn | Ile |
| 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     |
| Gln | Leu | Phe | Gln | Lys | Gln | Lys | Trp | Thr | Gln | Val | Asn | Pro | Ser | Pro |
| 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Cys | Arg | Cys | Ser | Thr | Arg | Glu | Lys | Leu | Thr | Met | Leu | Pro | Glu | Cys |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     | 400 |     |     |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr |     |     |
| 405                                                             | 410 | 415 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val |     |     |
| 420                                                             | 425 | 430 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp |     |     |
| 435                                                             | 440 | 445 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro |     |     |
| 450                                                             | 455 | 460 |
| Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu |     |     |
| 465                                                             | 470 | 475 |
| Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser |     |     |
| 485                                                             | 490 | 495 |
| Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile |     |     |
| 500                                                             | 505 | 510 |
| Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu |     |     |
| 515                                                             | 520 | 525 |
| Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg |     |     |
| 530                                                             | 535 | 540 |
| Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu |     |     |
| 545                                                             | 550 | 555 |
| Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp |     |     |
| 565                                                             | 570 | 575 |
| Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala |     |     |
| 580                                                             | 585 | 590 |
| Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His |     |     |
| 595                                                             | 600 | 605 |
| Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn |     |     |
| 610                                                             | 615 | 620 |
| Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val |     |     |
| 625                                                             | 630 | 635 |
| Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn |     |     |
| 645                                                             | 650 | 655 |
| Leu Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile |     |     |
| 660                                                             | 665 | 670 |
| Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala |     |     |
| 675                                                             | 680 | 685 |
| Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser |     |     |
| 690                                                             | 695 | 700 |
| Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu |     |     |

|                     |                         |                         |     |
|---------------------|-------------------------|-------------------------|-----|
| 705                 | 710                     | 715                     | 720 |
| Arg Phe Asn Ala Val | Leu Arg Lys Leu Leu     | Ile Val Phe Pro His     | Phe |
| 725                 | 730                     | 735                     |     |
| Cys Leu Gly Arg Gly | Leu Ile Asp Leu Ala Leu | Ser Gln Ala Val Thr     |     |
| 740                 | 745                     | 750                     |     |
| Asp Val Tyr Ala Arg | Phe Gly Glu Glu His     | Ser Ala Asn Pro Phe     | His |
| 755                 | 760                     | 765                     |     |
| Trp Asp Leu Ile Gly | Lys Asn Leu Phe Ala Met | Val Val Glu Gly Val     |     |
| 770                 | 775                     | 780                     |     |
| Val Tyr Phe Leu Leu | Thr Leu Leu Val Gln Arg | His Phe Phe Leu Ser     |     |
| 785                 | 790                     | 795                     | 800 |
| Gln Trp Ile Ala Glu | Pro Thr Lys Glu Pro     | Ile Val Asp Glu Asp Asp |     |
| 805                 | 810                     | 815                     |     |
| Asp Val Ala Glu Glu | Arg Gln Arg Ile Ile     | Thr Gly Gly Asn Lys Thr |     |
| 820                 | 825                     | 830                     |     |
| Asp Ile Leu Arg Leu | His Glu Leu Thr Lys     | Ile Tyr Pro Gly Thr Ser |     |
| 835                 | 840                     | 845                     |     |
| Ser Pro Ala Val Asp | Arg Leu Cys Val Gly     | Val Arg Pro Gly Glu Cys |     |
| 850                 | 855                     | 860                     |     |
| Phe Gly Leu Leu Gly | Val Asn Gly Ala Gly     | Lys Thr Thr Thr Phe Lys |     |
| 865                 | 870                     | 875                     | 880 |
| Met Leu Thr Gly Asp | Thr Thr Val Thr Ser     | Gly Asp Ala Thr Val Ala |     |
| 885                 | 890                     | 895                     |     |
| Gly Lys Ser Ile Leu | Thr Asn Ile Ser Glu     | Val His Gln Asn Met Gly |     |
| 900                 | 905                     | 910                     |     |
| Tyr Cys Pro Gln Phe | Asp Ala Ile Asp Glu     | Leu Leu Thr Gly Arg Glu |     |
| 915                 | 920                     | 925                     |     |
| His Leu Tyr Leu Tyr | Ala Arg Leu Arg Gly     | Val Pro Ala Glu Glu Ile |     |
| 930                 | 935                     | 940                     |     |
| Glu Lys Val Ala Asn | Trp Ser Ile Lys Ser     | Leu Gly Leu Thr Val Tyr |     |
| 945                 | 950                     | 955                     | 960 |
| Ala Asp Cys Leu Ala | Gly Thr Tyr Ser Gly     | Gly Asn Lys Arg Lys Leu |     |
| 965                 | 970                     | 975                     |     |
| Ser Thr Ala Ile Ala | Leu Ile Gly Cys Pro     | Pro Leu Val Leu Leu Asp |     |
| 980                 | 985                     | 990                     |     |
| Glu Pro Thr Thr Gly | Met Asp Pro Gln Ala     | Arg Arg Met Leu Trp Asn |     |
| 995                 | 1000                    | 1005                    |     |
| Val Ile Val Ser Ile | Ile Arg Glu Gly Arg     | Ala Val Val Leu Thr Ser |     |
| 1010                | 1015                    | 1020                    |     |



His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met  
 1025 1030 1035 1040  
 Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser  
 1045 1050 1055  
 Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys  
 1060 1065 1070  
 Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly  
 1075 1080 1085  
 Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln  
 1090 1095 1100  
 Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu  
 1105 1110 1115 1120  
 Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr  
 1125 1130 1135  
 Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser  
 1140 1145 1150  
 His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala  
 1155 1160 1165  
 Gln Asp  
 1170  
 <210> 70  
 <211> 1288  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1188-CfaN  
 <400> 70  
 Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15  
 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30  
 Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45  
 Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
 50 55 60  
 Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro  
 65 70 75 80  
 Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn  
 85 90 95

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |
| 100                                                             | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |

|                                                                 |     |     |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|-----|-----|
|                                                                 | 405 |     | 410 |     | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |     |     |
|                                                                 | 420 |     | 425 |     | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |     |     |
|                                                                 | 435 |     | 440 |     | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |     |     |
|                                                                 | 450 |     | 455 |     | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |     |     |
| 465                                                             |     | 470 |     | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |     |     |
|                                                                 | 485 |     | 490 |     | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |     |     |
|                                                                 | 500 |     | 505 |     | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |     |     |
|                                                                 | 515 |     | 520 |     | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |     |     |
|                                                                 | 530 |     | 535 |     | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |     |     |     |
| 545                                                             |     | 550 |     | 555 | 560 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |     |     |     |
|                                                                 | 565 |     | 570 |     | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |     |     |     |
|                                                                 | 580 |     | 585 |     | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |     |     |     |
|                                                                 | 595 |     | 600 |     | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |     |     |     |
|                                                                 | 610 |     | 615 |     | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |     |     |     |
| 625                                                             |     | 630 |     | 635 | 640 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |     |     |     |
|                                                                 | 645 |     | 650 |     | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |     |     |     |
|                                                                 | 660 |     | 665 |     | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |     |     |     |
|                                                                 | 675 |     | 680 |     | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |     |     |     |
|                                                                 | 690 |     | 695 |     | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |     |     |     |
| 705                                                             |     | 710 |     | 715 | 720 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |      |      |
| 725                                                             | 730  | 735  |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |      |      |
| 740                                                             | 745  | 750  |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 800  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
| 805                                                             | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
|                                                                 | 1105 | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Ser Thr Thr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |      |
|                                                                 | 1185 | 1190 | 1195 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |      |
|                                                                 | 1265 | 1270 | 1275 |
| Leu Lys Gln Val Asp Gly Leu Pro                                 |      |      | 1280 |
|                                                                 | 1285 |      |      |

&lt;210&gt; 71

&lt;211&gt; 1122

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4-1188-Cfacmut

&lt;400&gt; 71

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Lys | Ile | Ile | Ser | Arg | Lys | Ser | Leu | Gly | Thr | Gln | Asn | Val | Tyr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Asp | Ile | Gly | Val | Gly | Glu | Pro | His | Asn | Phe | Leu | Leu | Lys | Asn | Gly | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Val | Ala | Ser | Asn | Cys | Pro | Ala | His | Val | Asp | Asp | Leu | Thr | Pro | Glu | Gln |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met | Asp | Val | Val | Leu | His | His |
|     | 50  |     |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |
| Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile | Gly | Gln | Glu | Leu | Ile | Phe |
| 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |
| Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr | Ala | Ser | Leu | Phe |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu | Ser | Ser | Phe | Gly |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |
| Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys | Val | Thr | Glu | Asp |
|     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |
| Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu |
|     | 130 |     |     |     |     | 135 |     |     |     | 140 |     |     |     |     |     |
| Asn | Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly |
| 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |     |
| Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |
| His | Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln |
|     | 180 |     |     |     |     |     |     | 185 |     |     |     | 190 |     |     |     |
| Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln | His | Val | Gln | Ala | Leu | Leu |
|     | 195 |     |     |     |     | 200 |     |     |     |     |     | 205 |     |     |     |
| Val | Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser | His | Lys | Asp | Phe | Leu | Ala |
|     | 210 |     |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |
| Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala | Leu | Met | Leu | Ser |
| 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |
| Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |
| Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly |
|     | 260 |     |     |     |     |     |     | 265 |     |     |     | 270 |     |     |     |
| Ser | Glu | Gln | Phe | Thr | Val | Leu | Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Phe | Gly | Asn | Arg | Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro | Cys |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Leu Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile |     |     |     |

|                     |                     |                         |
|---------------------|---------------------|-------------------------|
| 610                 | 615                 | 620                     |
| Pro Met Met Tyr Pro | Ala Ser Phe Leu Phe | Asp Val Pro Ser Thr Ala |
| 625                 | 630                 | 635                     |
| Tyr Val Ala Leu Ser | Cys Ala Asn Leu Phe | Ile Gly Ile Asn Ser Ser |
| 645                 | 650                 | 655                     |
| Ala Ile Thr Phe Ile | Leu Glu Leu Phe Glu | Asn Asn Arg Thr Leu Leu |
| 660                 | 665                 | 670                     |
| Arg Phe Asn Ala Val | Leu Arg Lys Leu Leu | Ile Val Phe Pro His Phe |
| 675                 | 680                 | 685                     |
| Cys Leu Gly Arg Gly | Leu Ile Asp Leu Ala | Leu Ser Gln Ala Val Thr |
| 690                 | 695                 | 700                     |
| Asp Val Tyr Ala Arg | Phe Gly Glu Glu His | Ser Ala Asn Pro Phe His |
| 705                 | 710                 | 715                     |
| Trp Asp Leu Ile Gly | Lys Asn Leu Phe Ala | Met Val Val Glu Gly Val |
| 725                 | 730                 | 735                     |
| Val Tyr Phe Leu Leu | Thr Leu Leu Val Gln | Arg His Phe Phe Leu Ser |
| 740                 | 745                 | 750                     |
| Gln Trp Ile Ala Glu | Pro Thr Lys Glu Pro | Ile Val Asp Glu Asp Asp |
| 755                 | 760                 | 765                     |
| Asp Val Ala Glu Glu | Arg Gln Arg Ile Ile | Thr Gly Gly Asn Lys Thr |
| 770                 | 775                 | 780                     |
| Asp Ile Leu Arg Leu | His Glu Leu Thr Lys | Ile Tyr Pro Gly Thr Ser |
| 785                 | 790                 | 795                     |
| Ser Pro Ala Val Asp | Arg Leu Cys Val Gly | Val Arg Pro Gly Glu Cys |
| 805                 | 810                 | 815                     |
| Phe Gly Leu Leu Gly | Val Asn Gly Ala Gly | Lys Thr Thr Thr Phe Lys |
| 820                 | 825                 | 830                     |
| Met Leu Thr Gly Asp | Thr Thr Val Thr Ser | Gly Asp Ala Thr Val Ala |
| 835                 | 840                 | 845                     |
| Gly Lys Ser Ile Leu | Thr Asn Ile Ser Glu | Val His Gln Asn Met Gly |
| 850                 | 855                 | 860                     |
| Tyr Cys Pro Gln Phe | Asp Ala Ile Asp Glu | Leu Leu Thr Gly Arg Glu |
| 865                 | 870                 | 875                     |
| His Leu Tyr Leu Tyr | Ala Arg Leu Arg Gly | Val Pro Ala Glu Glu Ile |
| 885                 | 890                 | 895                     |
| Glu Lys Val Ala Asn | Trp Ser Ile Lys Ser | Leu Gly Leu Thr Val Tyr |
| 900                 | 905                 | 910                     |
| Ala Asp Cys Leu Ala | Gly Thr Tyr Ser Gly | Gly Asn Lys Arg Lys Leu |
| 915                 | 920                 | 925                     |



Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp  
 930 935 940  
 Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn  
 945 950 955 960  
 Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser  
 965 970 975  
 His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met  
 980 985 990  
 Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser  
 995 1000 1005  
 Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys  
 1010 1015 1020  
 Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly  
 1025 1030 1035 1040  
 Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln  
 1045 1050 1055  
 Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu  
 1060 1065 1070  
 Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr  
 1075 1080 1085  
 Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser  
 1090 1095 1100  
 His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala  
 1105 1110 1115 1120  
 Gln Asp  
 <210> 72  
 <211> 1349  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4-1150-CfaN-SopE  
 <400> 72  
 Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15  
 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30  
 Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45  
 Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala

|                                                                 |                                             |     |
|-----------------------------------------------------------------|---------------------------------------------|-----|
| 50                                                              | 55                                          | 60  |
| Gly Met Leu Pro Trp                                             | Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |     |
| 65                                                              | 70                                          | 75  |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |                                             | 80  |
|                                                                 | 85                                          | 90  |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |                                             | 95  |
|                                                                 | 100                                         | 105 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |                                             | 110 |
|                                                                 | 115                                         | 120 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |                                             | 125 |
|                                                                 | 130                                         | 135 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |                                             | 140 |
| 145                                                             | 150                                         | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |                                             | 160 |
|                                                                 | 165                                         | 170 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |                                             | 175 |
|                                                                 | 180                                         | 185 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |                                             | 190 |
|                                                                 | 195                                         | 200 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |                                             | 205 |
|                                                                 | 210                                         | 215 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |                                             | 220 |
| 225                                                             | 230                                         | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |                                             | 240 |
|                                                                 | 245                                         | 250 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |                                             | 255 |
|                                                                 | 260                                         | 265 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |                                             | 270 |
|                                                                 | 275                                         | 280 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |                                             | 285 |
|                                                                 | 290                                         | 295 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |                                             | 300 |
| 305                                                             | 310                                         | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |                                             | 320 |
|                                                                 | 325                                         | 330 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |                                             | 335 |
|                                                                 | 340                                         | 345 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |                                             | 350 |
|                                                                 | 355                                         | 360 |
|                                                                 |                                             | 365 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys | 370 | 375 | 380 |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr | 385 | 390 | 395 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser | 405 | 410 | 415 |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu | 420 | 425 | 430 |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met | 435 | 440 | 445 |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu | 450 | 455 | 460 |
| Asn | Arg | Gln | Leu | Gly | Glu | Glu | Gly | Ile | Thr | Ala | Glu | Ala | Ile | Leu | Asn | 465 | 470 | 475 |
| Phe | Leu | Tyr | Lys | Gly | Pro | Arg | Glu | Ser | Gln | Ala | Asp | Asp | Met | Ala | Asn | 485 | 490 | 495 |
| Phe | Asp | Trp | Arg | Asp | Ile | Phe | Asn | Ile | Thr | Asp | Arg | Thr | Leu | Arg | Leu | 500 | 505 | 510 |
| Val | Asn | Gln | Tyr | Leu | Glu | Cys | Leu | Val | Leu | Asp | Lys | Phe | Glu | Ser | Tyr | 515 | 520 | 525 |
| Asn | Asp | Glu | Thr | Gln | Leu | Thr | Gln | Arg | Ala | Leu | Ser | Leu | Leu | Glu | Glu | 530 | 535 | 540 |
| Asn | Met | Phe | Trp | Ala | Gly | Val | Val | Phe | Pro | Asp | Met | Tyr | Pro | Trp | Thr | 545 | 550 | 555 |
| Ser | Ser | Leu | Pro | Pro | His | Val | Lys | Tyr | Lys | Ile | Arg | Met | Asp | Ile | Asp | 565 | 570 | 575 |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly | 580 | 585 | 590 |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe | 595 | 600 | 605 |
| Ala | Tyr | Leu | Gln | Asp | Met | Val | Glu | Gln | Gly | Ile | Thr | Arg | Ser | Gln | Val | 610 | 615 | 620 |
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro | 625 | 630 | 635 |
| Cys | Phe | Val | Asp | Asp | Ser | Phe | Met | Ile | Ile | Leu | Asn | Arg | Cys | Phe | Pro | 645 | 650 | 655 |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys | 660 | 665 | 670 |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |     |     |     |

|                                 |                                     |     |
|---------------------------------|-------------------------------------|-----|
| 675                             | 680                                 | 685 |
| Gln Gly Val Ser Asn Ala Val     | Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |
| 690                             | 695                                 | 700 |
| Phe Ser Ile Met Ser Met Ser     | Ile Phe Leu Leu Thr Ile Phe Ile Met |     |
| 705                             | 710                                 | 715 |
| 720                             | 725                                 | 730 |
| His Gly Arg Ile Leu His Tyr Ser | Asp Pro Phe Ile Leu Phe Leu Phe     |     |
| 735                             | 740                                 | 745 |
| Leu Leu Ala Phe Ser Thr Ala Thr | Ile Met Leu Cys Phe Leu Leu Ser     |     |
| 750                             | 755                                 | 760 |
| Thr Phe Phe Ser Lys Ala Ser Leu | Ala Ala Ala Cys Ser Gly Val Ile     |     |
| 765                             | 770                                 | 775 |
| Tyr Phe Thr Leu Tyr Leu Pro His | Ile Leu Cys Phe Ala Trp Gln Asp     |     |
| 780                             | 785                                 | 790 |
| Arg Met Thr Ala Glu Leu Lys Lys | Ala Val Ser Leu Leu Ser Pro Val     |     |
| 795                             | 800                                 | 805 |
| Ala Phe Gly Phe Gly Thr Glu Tyr | Leu Val Arg Phe Glu Glu Gln Gly     |     |
| 810                             | 815                                 | 820 |
| Leu Gly Leu Gln Trp Ser Asn Ile | Gly Asn Ser Pro Thr Glu Gly Asp     |     |
| 825                             | 830                                 | 835 |
| Glu Phe Ser Phe Leu Leu Ser Met | Gln Met Met Leu Leu Asp Ala Ala     |     |
| 840                             | 845                                 | 850 |
| Val Tyr Gly Leu Leu Ala Trp Tyr | Leu Asp Gln Val Phe Pro Gly Asp     |     |
| 855                             | 860                                 | 865 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr | Phe Leu Leu Gln Glu Ser Tyr Trp     |     |
| 870                             | 875                                 | 880 |
| Leu Gly Gly Glu Gly Cys Ser Thr | Arg Glu Glu Arg Ala Leu Glu Lys     |     |
| 885                             | 890                                 | 895 |
| Thr Glu Pro Leu Thr Glu Glu Thr | Glu Asp Pro Glu His Pro Glu Gly     |     |
| 900                             | 905                                 | 910 |
| Ile His Asp Ser Phe Phe Glu Arg | Glu His Pro Gly Trp Val Pro Gly     |     |
| 915                             | 920                                 | 925 |
| Val Cys Val Lys Asn Leu Val Lys | Ile Phe Glu Pro Cys Gly Arg Pro     |     |
| 930                             | 935                                 | 940 |
| Ala Val Asp Arg Leu Asn Ile Thr | Phe Tyr Glu Asn Gln Ile Thr Ala     |     |
| 945                             | 950                                 | 955 |
| 960                             | 965                                 | 970 |
| Phe Leu Gly His Asn Gly Ala Gly | Lys Thr Thr Thr Leu Ser Ile Leu     |     |
| 975                             | 980                                 | 985 |
| Thr Gly Leu Leu Pro Pro Thr Ser | Gly Thr Val Leu Val Gly Gly Arg     |     |
| 990                             |                                     |     |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |           |
| 995                                                             | 1000 | 1005      |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |           |
| 1010                                                            | 1015 | 1020      |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |           |
| 1025                                                            | 1030 | 1035 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |           |
|                                                                 | 1045 | 1050 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |           |
|                                                                 | 1060 | 1065 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |           |
|                                                                 | 1075 | 1080 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |           |
|                                                                 | 1090 | 1095 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |           |
| 1105                                                            | 1110 | 1115 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |           |
|                                                                 | 1125 | 1130 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Leu Ser |      |           |
|                                                                 | 1140 | 1145 1150 |
| Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly |      |           |
|                                                                 | 1155 | 1160 1165 |
| Lys Ile Val Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys |      |           |
|                                                                 | 1170 | 1175 1180 |
| Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly |      |           |
| 1185                                                            | 1190 | 1195 1200 |
| Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg |      |           |
|                                                                 | 1205 | 1210 1215 |
| Ala Thr Lys Asp His Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro |      |           |
|                                                                 | 1220 | 1225 1230 |
| Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly |      |           |
|                                                                 | 1235 | 1240 1245 |
| Leu Pro Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys |      |           |
|                                                                 | 1250 | 1255 1260 |
| Gln Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu |      |           |
| 1265                                                            | 1270 | 1275 1280 |
| Ala Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser |      |           |
|                                                                 | 1285 | 1290 1295 |
| Lys Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala |      |           |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1300                                                            | 1305 | 1310 |
| Thr His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr |      |      |
| 1315                                                            | 1320 | 1325 |
| Asn Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp |      |      |
| 1330                                                            | 1335 | 1340 |
| Ile Arg Gly Ser Ala                                             |      |      |
| 1345                                                            |      |      |
| <210> 73                                                        |      |      |
| <211> 1259                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1150-CfaC-SopE                                      |      |      |
| <400> 73                                                        |      |      |
| Met Thr Lys Ile Thr Leu Ser Pro Gln Asn Phe Arg Ile Gln Lys Gln |      |      |
| 1 5 10 15                                                       |      |      |
| Glu Thr Thr Leu Leu Lys Glu Lys Ser Thr Glu Lys Asn Ser Leu Ala |      |      |
| 20 25 30                                                        |      |      |
| Lys Ser Ile Leu Ala Val Lys Asn His Phe Ile Glu Leu Arg Ser Lys |      |      |
| 35 40 45                                                        |      |      |
| Leu Ser Glu Arg Phe Ile Ser His Lys Asn Thr Glu Ser Ser Ala Thr |      |      |
| 50 55 60                                                        |      |      |
| His Phe His Arg Gly Ser Ala Ser Glu Gly Arg Ala Val Leu Thr Asn |      |      |
| 65 70 75 80                                                     |      |      |
| Lys Val Val Lys Asp Phe Met Leu Gln Thr Leu Asn Asp Ile Asp Ile |      |      |
| 85 90 95                                                        |      |      |
| Arg Gly Ser Ala Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln |      |      |
| 100 105 110                                                     |      |      |
| Asn Val Tyr Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Lys |      |      |
| 115 120 125                                                     |      |      |
| Asn Gly Leu Val Ala Ser Asn Cys Phe Gly Thr Gly Leu Tyr Leu Thr |      |      |
| 130 135 140                                                     |      |      |
| Leu Val Arg Lys Met Lys Asn Ile Gln Ser Gln Arg Lys Gly Ser Glu |      |      |
| 145 150 155 160                                                 |      |      |
| Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala |      |      |
| 165 170 175                                                     |      |      |
| His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp Gly Asp Val Asn |      |      |
| 180 185 190                                                     |      |      |
| Glu Leu Met Asp Val Val Leu His His Val Pro Glu Ala Lys Leu Val |      |      |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 195                                                             | 200 | 205 |
| Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe |     |     |
| 210                                                             | 215 | 220 |
| Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu |     |     |
| 225                                                             | 230 | 235 |
| Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu |     |     |
| 245                                                             | 250 | 255 |
| Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe |     |     |
| 260                                                             | 265 | 270 |
| Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro |     |     |
| 275                                                             | 280 | 285 |
| Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn |     |     |
| 290                                                             | 295 | 300 |
| Val Cys Ser Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro |     |     |
| 305                                                             | 310 | 315 |
| Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu |     |     |
| 325                                                             | 330 | 335 |
| Val Leu Gln His Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr |     |     |
| 340                                                             | 345 | 350 |
| Ile Arg Ser His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr |     |     |
| 355                                                             | 360 | 365 |
| Phe Val Phe Leu Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly |     |     |
| 370                                                             | 375 | 380 |
| Glu Tyr Pro Ala Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Phe Phe Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu |     |     |
| 405                                                             | 410 | 415 |
| Ala Asp Val Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys |     |     |
| 420                                                             | 425 | 430 |
| Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys |     |     |
| 435                                                             | 440 | 445 |
| Thr Pro Ser Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys |     |     |
| 450                                                             | 455 | 460 |
| Trp Thr Gln Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu |     |     |
| 465                                                             | 470 | 475 |
| Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro |     |     |
| 485                                                             | 490 | 495 |
| Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr |     |     |
| 500                                                             | 505 | 510 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile |     |     |
| 515                                                             | 520 | 525 |
| Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly |     |     |
| 530                                                             | 535 | 540 |
| Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu |     |     |
| 545                                                             | 550 | 555 |
| Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser |     |     |
| 565                                                             | 570 | 575 |
| Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu |     |     |
| 580                                                             | 585 | 590 |
| Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys |     |     |
| 595                                                             | 600 | 605 |
| Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile |     |     |
| 610                                                             | 615 | 620 |
| Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile |     |     |
| 625                                                             | 630 | 635 |
| Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu |     |     |
| 645                                                             | 650 | 655 |
| Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val |     |     |
| 660                                                             | 665 | 670 |
| Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile |     |     |
| 675                                                             | 680 | 685 |
| Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val |     |     |
| 690                                                             | 695 | 700 |
| Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn |     |     |
| 705                                                             | 710 | 715 |
| Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln |     |     |
| 725                                                             | 730 | 735 |
| Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu |     |     |
| 740                                                             | 745 | 750 |
| Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser |     |     |
| 755                                                             | 760 | 765 |
| Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala |     |     |
| 770                                                             | 775 | 780 |
| Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu |     |     |
| 785                                                             | 790 | 795 |
| Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg |     |     |
| 805                                                             | 810 | 815 |
| Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile |     |     |



|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 820                                                             | 825  | 830  |
| Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly |      |      |
| 835                                                             | 840  | 845  |
| Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn |      |      |
| 850                                                             | 855  | 860  |
| Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu |      |      |
| 865                                                             | 870  | 875  |
| Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr |      |      |
| 885                                                             | 890  | 895  |
| Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln |      |      |
| 900                                                             | 905  | 910  |
| Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu |      |      |
| 915                                                             | 920  | 925  |
| Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu |      |      |
| 930                                                             | 935  | 940  |
| Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn |      |      |
| 945                                                             | 950  | 955  |
| Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr |      |      |
| 965                                                             | 970  | 975  |
| Val Thr Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn |      |      |
| 980                                                             | 985  | 990  |
| Ile Ser Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala |      |      |
| 995                                                             | 1000 | 1005 |
| Ile Asp Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Arg Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser |      |      |
| 1025                                                            | 1030 | 1035 |
| Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr |      |      |
| 1045                                                            | 1050 | 1055 |
| Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile |      |      |
| 1060                                                            | 1065 | 1070 |
| Gly Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp |      |      |
| 1075                                                            | 1080 | 1085 |
| Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg |      |      |
| 1090                                                            | 1095 | 1100 |
| Glu Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu |      |      |
| 1105                                                            | 1110 | 1115 |
| Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys |      |      |
| 1125                                                            | 1130 | 1135 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile |      |      |
| 1140                                                            | 1145 | 1150 |
| Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu |      |      |
| 1155                                                            | 1160 | 1165 |
| Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln |      |      |
| 1170                                                            | 1175 | 1180 |
| Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser |      |      |
| 1185                                                            | 1190 | 1195 |
| Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu |      |      |
| 1205                                                            | 1210 | 1215 |
| Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val |      |      |
| 1220                                                            | 1225 | 1230 |
| Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro |      |      |
| 1235                                                            | 1240 | 1245 |
| Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp                     |      |      |
| 1250                                                            | 1255 |      |
| <210> 74                                                        |      |      |
| <211> 1339                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1140-CfaN-SopE                                      |      |      |
| <400> 74                                                        |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |
| 1                                                               | 5    | 10   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |
| 20                                                              | 25   | 30   |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |
| 35                                                              | 40   | 45   |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |
| 50                                                              | 55   | 60   |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |
| 65                                                              | 70   | 75   |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |      |      |
| 85                                                              | 90   | 95   |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |      |      |
| 100                                                             | 105  | 110  |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |      |      |
| 115                                                             | 120  | 125  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
| 130 |     |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     | 320 |     |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     |     | 350 |     |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |
|     |     | 355 |     |     |     |     | 360 |     |     |     | 365 |     |     |     |     |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     | 400 |     |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
|                                                                 | 805  | 810  |
|                                                                 |      | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
|                                                                 | 820  | 825  |
|                                                                 |      | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
|                                                                 | 835  | 840  |
|                                                                 |      | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
|                                                                 | 850  | 855  |
|                                                                 |      | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
|                                                                 |      | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
|                                                                 | 885  | 890  |
|                                                                 |      | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
|                                                                 | 900  | 905  |
|                                                                 |      | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
|                                                                 | 915  | 920  |
|                                                                 |      | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
|                                                                 | 930  | 935  |
|                                                                 |      | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
|                                                                 |      | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
|                                                                 | 965  | 970  |
|                                                                 |      | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
|                                                                 | 980  | 985  |
|                                                                 |      | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
|                                                                 | 995  | 1000 |
|                                                                 |      | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
|                                                                 | 1010 | 1015 |
|                                                                 |      | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
|                                                                 |      | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
|                                                                 | 1045 | 1050 |
|                                                                 |      | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |

|                                                                 |                                     |      |
|-----------------------------------------------------------------|-------------------------------------|------|
| 1060                                                            | 1065                                | 1070 |
| Ala Ile Ala Phe Val Gly Asp                                     | Ala Lys Val Val Ile Leu Asp Glu Pro |      |
| 1075                                                            | 1080                                | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |                                     |      |
| 1090                                                            | 1095                                | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |                                     |      |
| 1105                                                            | 1110                                | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |                                     |      |
| 1125                                                            | 1130                                | 1135 |
| Arg Leu Tyr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |                                     |      |
| 1140                                                            | 1145                                | 1150 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |                                     |      |
| 1155                                                            | 1160                                | 1165 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |                                     |      |
| 1170                                                            | 1175                                | 1180 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |                                     |      |
| 1185                                                            | 1190                                | 1195 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |                                     |      |
| 1205                                                            | 1210                                | 1215 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |                                     |      |
| 1220                                                            | 1225                                | 1230 |
| Leu Lys Gln Val Asp Gly Leu Pro Thr Lys Ile Thr Leu Ser Pro Gln |                                     |      |
| 1235                                                            | 1240                                | 1245 |
| Asn Phe Arg Ile Gln Lys Gln Glu Thr Thr Leu Leu Lys Glu Lys Ser |                                     |      |
| 1250                                                            | 1255                                | 1260 |
| Thr Glu Lys Asn Ser Leu Ala Lys Ser Ile Leu Ala Val Lys Asn His |                                     |      |
| 1265                                                            | 1270                                | 1275 |
| Phe Ile Glu Leu Arg Ser Lys Leu Ser Glu Arg Phe Ile Ser His Lys |                                     |      |
| 1285                                                            | 1290                                | 1295 |
| Asn Thr Glu Ser Ser Ala Thr His Phe His Arg Gly Ser Ala Ser Glu |                                     |      |
| 1300                                                            | 1305                                | 1310 |
| Gly Arg Ala Val Leu Thr Asn Lys Val Val Lys Asp Phe Met Leu Gln |                                     |      |
| 1315                                                            | 1320                                | 1325 |
| Thr Leu Asn Asp Ile Asp Ile Arg Gly Ser Ala                     |                                     |      |
| 1330                                                            | 1335                                |      |
| <210> 75                                                        |                                     |      |
| <211> 1269                                                      |                                     |      |
| <212> PRT                                                       |                                     |      |
| <213> 人工序列(Artificial Sequence)                                 |                                     |      |

&lt;220&gt;

&lt;223&gt; ABCA4-1140-CfaCmut-SopE

&lt;400&gt; 75

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Thr | Lys | Ile | Thr | Leu | Ser | Pro | Gln | Asn | Phe | Arg | Ile | Gln | Lys | Gln |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Glu | Thr | Thr | Leu | Leu | Lys | Glu | Lys | Ser | Thr | Glu | Lys | Asn | Ser | Leu | Ala |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |
| Lys | Ser | Ile | Leu | Ala | Val | Lys | Asn | His | Phe | Ile | Glu | Leu | Arg | Ser | Lys |
|     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |
| Leu | Ser | Glu | Arg | Phe | Ile | Ser | His | Lys | Asn | Thr | Glu | Ser | Ser | Ala | Thr |
|     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |
| His | Phe | His | Arg | Gly | Ser | Ala | Ser | Glu | Gly | Arg | Ala | Val | Leu | Thr | Asn |
| 65  |     |     |     |     |     |     |     | 70  |     |     |     |     |     | 75  | 80  |
| Lys | Val | Val | Lys | Asp | Phe | Met | Leu | Gln | Thr | Leu | Asn | Asp | Ile | Asp | Ile |
|     |     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |
| Arg | Gly | Ser | Ala | Val | Lys | Ile | Ile | Ser | Arg | Lys | Ser | Leu | Gly | Thr | Gln |
|     |     |     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |
| Asn | Val | Tyr | Asp | Ile | Gly | Val | Gly | Glu | Pro | His | Asn | Phe | Leu | Leu | Lys |
|     |     |     |     | 115 |     |     |     |     |     | 120 |     |     |     |     | 125 |
| Asn | Gly | Leu | Val | Ala | Ser | Asn | Cys | Ser | Gly | Thr | Pro | Leu | Phe | Leu | Lys |
|     |     |     |     | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |
| Asn | Cys | Phe | Gly | Thr | Gly | Leu | Tyr | Leu | Thr | Leu | Val | Arg | Lys | Met | Lys |
| 145 |     |     |     |     |     |     |     | 150 |     |     |     |     |     | 155 | 160 |
| Asn | Ile | Gln | Ser | Gln | Arg | Lys | Gly | Ser | Glu | Gly | Thr | Cys | Ser | Cys | Ser |
|     |     |     |     |     |     |     |     | 165 |     |     |     |     |     |     | 175 |
| Ser | Lys | Gly | Phe | Ser | Thr | Thr | Cys | Pro | Ala | His | Val | Asp | Asp | Leu | Thr |
|     |     |     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |
| Pro | Glu | Gln | Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met | Asp | Val | Val |
|     |     |     |     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |
| Leu | His | His | Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile | Gly | Gln | Glu |
|     |     |     |     |     |     |     |     | 210 |     |     |     |     |     | 215 | 220 |
| Leu | Ile | Phe | Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr | Ala |
| 225 |     |     |     |     |     |     |     | 230 |     |     |     |     |     | 235 | 240 |
| Ser | Leu | Phe | Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu | Ser |
|     |     |     |     |     |     |     |     | 245 |     |     |     |     |     |     | 255 |
| Ser | Phe | Gly | Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys | Val |
|     |     |     |     |     |     |     |     | 260 |     |     |     |     |     |     | 270 |
| Thr | Glu | Asp | Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln |
|     |     |     |     |     |     |     |     | 275 |     |     |     |     |     |     | 285 |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu |     |         |
| 290                                                             | 295 | 300     |
| Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala |     |         |
| 305                                                             | 310 | 315 320 |
| Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro |     |         |
|                                                                 | 325 | 330 335 |
| Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln |     |         |
|                                                                 | 340 | 345 350 |
| Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp |     |         |
|                                                                 | 355 | 360 365 |
| Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu |     |         |
|                                                                 | 370 | 375 380 |
| Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr |     |         |
| 385                                                             | 390 | 395 400 |
| Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp |     |         |
|                                                                 | 405 | 410 415 |
| Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn |     |         |
|                                                                 | 420 | 425 430 |
| Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu |     |         |
|                                                                 | 435 | 440 445 |
| Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro |     |         |
|                                                                 | 450 | 455 460 |
| Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro |     |         |
| 465                                                             | 470 | 475 480 |
| Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro |     |         |
|                                                                 | 485 | 490 495 |
| Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln |     |         |
|                                                                 | 500 | 505 510 |
| Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp |     |         |
|                                                                 | 515 | 520 525 |
| Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser |     |         |
|                                                                 | 530 | 535 540 |
| Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly |     |         |
| 545                                                             | 550 | 555 560 |
| Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu |     |         |
|                                                                 | 565 | 570 575 |
| Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg |     |         |
|                                                                 | 580 | 585 590 |
| Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu |     |         |



|                             |                         |                 |
|-----------------------------|-------------------------|-----------------|
| 595                         | 600                     | 605             |
| Asp Asn Ile Lys Val Trp Phe | Asn Asn Lys Gly Trp His | Ala Leu Val     |
| 610                         | 615                     | 620             |
| Ser Phe Leu Asn Val Ala His | Asn Ala Ile Leu Arg     | Ala Ser Leu Pro |
| 625                         | 630                     | 635             |
| Lys Asp Arg Ser Pro Glu Glu | Tyr Gly Ile Thr Val     | Ile Ser Gln Pro |
| 645                         | 650                     | 655             |
| Leu Asn Leu Thr Lys Glu Gln | Leu Ser Glu Ile Thr Val | Leu Thr Thr     |
| 660                         | 665                     | 670             |
| Ser Val Asp Ala Val Val Ala | Ile Cys Val Ile Phe Ser | Met Ser Phe     |
| 675                         | 680                     | 685             |
| Val Pro Ala Ser Phe Val Leu | Tyr Leu Ile Gln Glu Arg | Val Asn Lys     |
| 690                         | 695                     | 700             |
| Ser Lys His Leu Gln Phe Ile | Ser Gly Val Ser Pro Thr | Thr Tyr Trp     |
| 705                         | 710                     | 715             |
| Val Thr Asn Phe Leu Trp Asp | Ile Met Asn Tyr Ser Val | Ser Ala Gly     |
| 725                         | 730                     | 735             |
| Leu Val Val Gly Ile Phe Ile | Gly Phe Gln Lys Lys Ala | Tyr Thr Ser     |
| 740                         | 745                     | 750             |
| Pro Glu Asn Leu Pro Ala Leu | Val Ala Leu Leu Leu Tyr | Gly Trp         |
| 755                         | 760                     | 765             |
| Ala Val Ile Pro Met Met Tyr | Pro Ala Ser Phe Leu Phe | Asp Val Pro     |
| 770                         | 775                     | 780             |
| Ser Thr Ala Tyr Val Ala Leu | Ser Cys Ala Asn Leu Phe | Ile Gly Ile     |
| 785                         | 790                     | 795             |
| Asn Ser Ser Ala Ile Thr Phe | Ile Leu Glu Leu Phe Glu | Asn Asn Arg     |
| 805                         | 810                     | 815             |
| Thr Leu Leu Arg Phe Asn Ala | Val Leu Arg Lys Leu Leu | Ile Val Phe     |
| 820                         | 825                     | 830             |
| Pro His Phe Cys Leu Gly Arg | Gly Leu Ile Asp Leu Ala | Leu Ser Gln     |
| 835                         | 840                     | 845             |
| Ala Val Thr Asp Val Tyr Ala | Arg Phe Gly Glu Glu His | Ser Ala Asn     |
| 850                         | 855                     | 860             |
| Pro Phe His Trp Asp Leu Ile | Gly Lys Asn Leu Phe Ala | Met Val Val     |
| 865                         | 870                     | 875             |
| Glu Gly Val Val Tyr Phe Leu | Leu Thr Leu Leu Val Gln | Arg His Phe     |
| 885                         | 890                     | 895             |
| Phe Leu Ser Gln Trp Ile Ala | Glu Pro Thr Lys Glu Pro | Ile Val Asp     |
| 900                         | 905                     | 910             |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly |      |      |
| 915                                                             | 920  | 925  |
| Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro |      |      |
| 930                                                             | 935  | 940  |
| Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro |      |      |
| 945                                                             | 950  | 955  |
| Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr |      |      |
| 965                                                             | 970  | 975  |
| Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala |      |      |
| 980                                                             | 985  | 990  |
| Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln |      |      |
| 995                                                             | 1000 | 1005 |
| Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr |      |      |
| 1010                                                            | 1015 | 1020 |
| Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu |      |      |
| 1045                                                            | 1050 | 1055 |
| Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys |      |      |
| 1060                                                            | 1065 | 1070 |
| Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val |      |      |
| 1075                                                            | 1080 | 1085 |
| Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val |      |      |
| 1105                                                            | 1110 | 1115 |
| Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu |      |      |
| 1125                                                            | 1130 | 1135 |
| Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His |      |      |
| 1140                                                            | 1145 | 1150 |
| Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys |      |      |
| 1155                                                            | 1160 | 1165 |
| Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe |      |      |
| 1170                                                            | 1175 | 1180 |
| Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn |      |      |
| 1185                                                            | 1190 | 1195 |
| Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln |      |      |
| 1205                                                            | 1210 | 1215 |
| Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val |      |      |

|       |                           |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
|-------|---------------------------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|
|       | 1220                      |     |     |     |     | 1225 |     |     |     |     | 1230 |     |     |     |     |
| Thr   | Gln                       | Thr | Thr | Leu | Asp | Gln  | Val | Phe | Val | Asn | Phe  | Ala | Lys | Gln | Gln |
|       | 1235                      |     |     |     |     | 1240 |     |     |     |     | 1245 |     |     |     |     |
| Thr   | Glu                       | Ser | His | Asp | Leu | Pro  | Leu | His | Pro | Arg | Ala  | Ala | Gly | Ala | Ser |
|       | 1250                      |     |     |     |     | 1255 |     |     |     |     | 1260 |     |     |     |     |
| Arg   | Gln                       | Ala | Gln | Asp |     |      |     |     |     |     |      |     |     |     |     |
| 1265  |                           |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <210> | 76                        |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <211> | 1263                      |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <212> | PRT                       |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <213> | 人工序列(Artificial Sequence) |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <220> |                           |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <223> | ABCA4-1150-CfaN-DD1       |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| <400> | 76                        |     |     |     |     |      |     |     |     |     |      |     |     |     |     |
| Met   | Gly                       | Phe | Val | Arg | Gln | Ile  | Gln | Leu | Leu | Leu | Trp  | Lys | Asn | Trp | Thr |
| 1     |                           |     | 5   |     |     |      |     | 10  |     |     |      |     | 15  |     |     |
| Leu   | Arg                       | Lys | Arg | Gln | Lys | Ile  | Arg | Phe | Val | Val | Glu  | Leu | Val | Trp | Pro |
|       |                           |     | 20  |     |     |      |     | 25  |     |     |      |     | 30  |     |     |
| Leu   | Ser                       | Leu | Phe | Leu | Val | Leu  | Ile | Trp | Leu | Arg | Asn  | Ala | Asn | Pro | Leu |
|       |                           |     | 35  |     |     |      |     | 40  |     |     |      |     | 45  |     |     |
| Tyr   | Ser                       | His | His | Glu | Cys | His  | Phe | Pro | Asn | Lys | Ala  | Met | Pro | Ser | Ala |
|       |                           |     | 50  |     |     |      |     | 55  |     |     |      |     | 60  |     |     |
| Gly   | Met                       | Leu | Pro | Trp | Leu | Gln  | Gly | Ile | Phe | Cys | Asn  | Val | Asn | Asn | Pro |
| 65    |                           |     |     |     |     | 70   |     |     |     |     | 75   |     |     |     | 80  |
| Cys   | Phe                       | Gln | Ser | Pro | Thr | Pro  | Gly | Glu | Ser | Pro | Gly  | Ile | Val | Ser | Asn |
|       |                           |     |     |     |     | 85   |     |     |     |     | 90   |     |     |     | 95  |
| Tyr   | Asn                       | Asn | Ser | Ile | Leu | Ala  | Arg | Val | Tyr | Arg | Asp  | Phe | Gln | Glu | Leu |
|       |                           |     | 100 |     |     |      |     |     | 105 |     |      |     |     | 110 |     |
| Leu   | Met                       | Asn | Ala | Pro | Glu | Ser  | Gln | His | Leu | Gly | Arg  | Ile | Trp | Thr | Glu |
|       |                           |     | 115 |     |     |      |     |     | 120 |     |      |     |     | 125 |     |
| Leu   | His                       | Ile | Leu | Ser | Gln | Phe  | Met | Asp | Thr | Leu | Arg  | Thr | His | Pro | Glu |
|       |                           |     | 130 |     |     |      |     |     | 135 |     |      |     |     | 140 |     |
| Arg   | Ile                       | Ala | Gly | Arg | Gly | Ile  | Arg | Ile | Arg | Asp | Ile  | Leu | Lys | Asp | Glu |
| 145   |                           |     |     |     |     | 150  |     |     |     |     | 155  |     |     |     | 160 |
| Glu   | Thr                       | Leu | Thr | Leu | Phe | Leu  | Ile | Lys | Asn | Ile | Gly  | Leu | Ser | Asp | Ser |
|       |                           |     |     |     |     | 165  |     |     |     |     | 170  |     |     |     | 175 |
| Val   | Val                       | Tyr | Leu | Leu | Ile | Asn  | Ser | Gln | Val | Arg | Pro  | Glu | Gln | Phe | Ala |
|       |                           |     | 180 |     |     |      |     |     | 185 |     |      |     |     | 190 |     |
| His   | Gly                       | Val | Pro | Asp | Leu | Ala  | Leu | Lys | Asp | Ile | Ala  | Cys | Ser | Glu | Ala |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |
| 805                                                             | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |

|                                 |                                 |      |
|---------------------------------|---------------------------------|------|
| 820                             | 825                             | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met | Gln Met Met Leu Leu Asp Ala Ala |      |
| 835                             | 840                             | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr | Leu Asp Gln Val Phe Pro Gly Asp |      |
| 850                             | 855                             | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr | Phe Leu Leu Gln Glu Ser Tyr Trp |      |
| 865                             | 870                             | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr | Arg Glu Glu Arg Ala Leu Glu Lys |      |
| 885                             | 890                             | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr | Glu Asp Pro Glu His Pro Glu Gly |      |
| 900                             | 905                             | 910  |
| Ile His Asp Ser Phe Phe Glu Arg | Glu His Pro Gly Trp Val Pro Gly |      |
| 915                             | 920                             | 925  |
| Val Cys Val Lys Asn Leu Val Lys | Ile Phe Glu Pro Cys Gly Arg Pro |      |
| 930                             | 935                             | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr | Phe Tyr Glu Asn Gln Ile Thr Ala |      |
| 945                             | 950                             | 955  |
| Phe Leu Gly His Asn Gly Ala Gly | Lys Thr Thr Thr Leu Ser Ile Leu |      |
| 965                             | 970                             | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser | Gly Thr Val Leu Val Gly Gly Arg |      |
| 980                             | 985                             | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala | Val Arg Gln Ser Leu Gly Met Cys |      |
| 995                             | 1000                            | 1005 |
| Pro Gln His Asn Ile Leu Phe His | His Leu Thr Val Ala Glu His Met |      |
| 1010                            | 1015                            | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly | Lys Ser Gln Glu Glu Ala Gln Leu |      |
| 1025                            | 1030                            | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp | Thr Gly Leu His His Lys Arg Asn |      |
| 1045                            | 1050                            | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly | Gly Met Gln Arg Lys Leu Ser Val |      |
| 1060                            | 1065                            | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala | Lys Val Val Ile Leu Asp Glu Pro |      |
| 1075                            | 1080                            | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser | Arg Arg Ser Ile Trp Asp Leu Leu |      |
| 1090                            | 1095                            | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr | Ile Ile Met Ser Thr His His Met |      |
| 1105                            | 1110                            | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp | Arg Ile Ala Ile Ile Ala Gln Gly |      |
| 1125                            | 1130                            | 1135 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Leu Ser |      |      |
| 1140                                                            | 1145 | 1150 |
| Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly |      |      |
| 1155                                                            | 1160 | 1165 |
| Lys Ile Val Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys |      |      |
| 1170                                                            | 1175 | 1180 |
| Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly |      |      |
| 1185                                                            | 1190 | 1195 |
| Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg |      |      |
| 1205                                                            | 1210 | 1215 |
| Ala Thr Lys Asp His Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro |      |      |
| 1220                                                            | 1225 | 1230 |
| Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly |      |      |
| 1235                                                            | 1240 | 1245 |
| Leu Pro Arg Ile Ser Phe Gly Ser Pro Pro Pro Met Ala Gly Gly     |      |      |
| 1250                                                            | 1255 | 1260 |
| <210> 77                                                        |      |      |
| <211> 1173                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1150-CfaC-DD1                                       |      |      |
| <400> 77                                                        |      |      |
| Met Arg Ile Ser Phe Gly Ser Pro Pro Pro Met Ala Gly Gly Val Lys |      |      |
| 1                                                               | 5    | 10   |
| Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr Asp Ile Gly |      |      |
| 20                                                              | 25   | 30   |
| Val Glu Lys Asp His Asn Phe Leu Leu Lys Asn Gly Leu Val Ala Ser |      |      |
| 35                                                              | 40   | 45   |
| Asn Cys Phe Gly Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys |      |      |
| 50                                                              | 55   | 60   |
| Asn Ile Gln Ser Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser |      |      |
| 65                                                              | 70   | 75   |
| Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr |      |      |
| 85                                                              | 90   | 95   |
| Pro Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val |      |      |
| 100                                                             | 105  | 110  |
| Leu His His Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu |      |      |
| 115                                                             | 120  | 125  |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala |     |         |
| 130                                                             | 135 | 140     |
| Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser |     |         |
| 145                                                             | 150 | 155 160 |
| Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val |     |         |
|                                                                 | 165 | 170 175 |
| Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln |     |         |
|                                                                 | 180 | 185 190 |
| Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu |     |         |
|                                                                 | 195 | 200 205 |
| Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala |     |         |
|                                                                 | 210 | 215 220 |
| Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro |     |         |
| 225                                                             | 230 | 235 240 |
| Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln |     |         |
|                                                                 | 245 | 250 255 |
| Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp |     |         |
|                                                                 | 260 | 265 270 |
| Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu |     |         |
|                                                                 | 275 | 280 285 |
| Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr |     |         |
|                                                                 | 290 | 295 300 |
| Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp |     |         |
| 305                                                             | 310 | 315 320 |
| Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn |     |         |
|                                                                 | 325 | 330 335 |
| Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu |     |         |
|                                                                 | 340 | 345 350 |
| Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro |     |         |
|                                                                 | 355 | 360 365 |
| Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro |     |         |
|                                                                 | 370 | 375 380 |
| Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro |     |         |
| 385                                                             | 390 | 395 400 |
| Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln |     |         |
|                                                                 | 405 | 410 415 |
| Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp |     |         |
|                                                                 | 420 | 425 430 |
| Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser |     |         |



|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 435                                                             | 440 | 445 |
| Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly |     |     |
| 450                                                             | 455 | 460 |
| Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu |     |     |
| 465                                                             | 470 | 475 |
| Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg |     |     |
| 485                                                             | 490 | 495 |
| Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu |     |     |
| 500                                                             | 505 | 510 |
| Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val |     |     |
| 515                                                             | 520 | 525 |
| Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro |     |     |
| 530                                                             | 535 | 540 |
| Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro |     |     |
| 545                                                             | 550 | 555 |
| Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr |     |     |
| 565                                                             | 570 | 575 |
| Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe |     |     |
| 580                                                             | 585 | 590 |
| Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys |     |     |
| 595                                                             | 600 | 605 |
| Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp |     |     |
| 610                                                             | 615 | 620 |
| Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly |     |     |
| 625                                                             | 630 | 635 |
| Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser |     |     |
| 645                                                             | 650 | 655 |
| Pro Glu Asn Leu Pro Ala Leu Val Ala Leu Leu Leu Tyr Gly Trp     |     |     |
| 660                                                             | 665 | 670 |
| Ala Val Ile Pro Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro |     |     |
| 675                                                             | 680 | 685 |
| Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile |     |     |
| 690                                                             | 695 | 700 |
| Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg |     |     |
| 705                                                             | 710 | 715 |
| Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe |     |     |
| 725                                                             | 730 | 735 |
| Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln |     |     |
| 740                                                             | 745 | 750 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn |      |      |
| 755                                                             | 760  | 765  |
| Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val |      |      |
| 770                                                             | 775  | 780  |
| Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe |      |      |
| 785                                                             | 790  | 795  |
| 800                                                             |      |      |
| Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp |      |      |
| 805                                                             | 810  | 815  |
| Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly |      |      |
| 820                                                             | 825  | 830  |
| Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro |      |      |
| 835                                                             | 840  | 845  |
| Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro |      |      |
| 850                                                             | 855  | 860  |
| Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr |      |      |
| 865                                                             | 870  | 875  |
| 880                                                             |      |      |
| Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala |      |      |
| 885                                                             | 890  | 895  |
| Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln |      |      |
| 900                                                             | 905  | 910  |
| Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr |      |      |
| 915                                                             | 920  | 925  |
| Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala |      |      |
| 930                                                             | 935  | 940  |
| Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu |      |      |
| 945                                                             | 950  | 955  |
| 960                                                             |      |      |
| Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys |      |      |
| 965                                                             | 970  | 975  |
| Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val |      |      |
| 980                                                             | 985  | 990  |
| Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met |      |      |
| 995                                                             | 1000 | 1005 |
| Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| 1040                                                            |      |      |
| Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His |      |      |
| 1045                                                            | 1050 | 1055 |
| Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1060                                                            | 1065 | 1070 |
| Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe |      |      |
| 1075                                                            | 1080 | 1085 |
| Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn |      |      |
| 1090                                                            | 1095 | 1100 |
| Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln |      |      |
| 1105                                                            | 1110 | 1115 |
| Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val |      |      |
| 1125                                                            | 1130 | 1135 |
| Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln |      |      |
| 1140                                                            | 1145 | 1150 |
| Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser |      |      |
| 1155                                                            | 1160 | 1165 |
| Arg Gln Ala Gln Asp                                             |      |      |
| 1170                                                            |      |      |
| <210> 78                                                        |      |      |
| <211> 1253                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1140-CfaN-DD1                                       |      |      |
| <400> 78                                                        |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |
| 1 5 10 15                                                       |      |      |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |
| 20 25 30                                                        |      |      |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |
| 35 40 45                                                        |      |      |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |
| 50 55 60                                                        |      |      |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |
| 65 70 75 80                                                     |      |      |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |      |      |
| 85 90 95                                                        |      |      |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |      |      |
| 100 105 110                                                     |      |      |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |      |      |
| 115 120 125                                                     |      |      |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |      |      |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |

|                                                                 |         |         |
|-----------------------------------------------------------------|---------|---------|
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |         |         |
| 450                                                             | 455     | 460     |
| Asn Arg Gln Leu Gly Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn     |         |         |
| 465                                                             | 470     | 475 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |         |         |
|                                                                 | 485 490 | 495     |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |         |         |
|                                                                 | 500 505 | 510     |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |         |         |
|                                                                 | 515 520 | 525     |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |         |         |
|                                                                 | 530 535 | 540     |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |         |         |
| 545                                                             | 550 555 | 560     |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |         |         |
|                                                                 | 565 570 | 575     |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |         |         |
|                                                                 | 580 585 | 590     |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |         |         |
|                                                                 | 595 600 | 605     |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |         |         |
| 610                                                             | 615     | 620     |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |         |         |
| 625                                                             | 630 635 | 640     |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |         |         |
|                                                                 | 645 650 | 655     |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |         |         |
|                                                                 | 660 665 | 670     |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |         |         |
|                                                                 | 675 680 | 685     |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |         |         |
|                                                                 | 690 695 | 700     |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |         |         |
| 705                                                             | 710 715 | 720     |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |         |         |
|                                                                 | 725 730 | 735     |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |         |         |
|                                                                 | 740 745 | 750     |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |         |         |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
| 805                                                             | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |
| 1090                                                            | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |
| 1105                                                            | 1110 | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |
| 1125                                                            | 1130 | 1135 |
| Arg Leu Tyr Cys Leu Ser Tyr Asp Thr Glu Ile Leu Thr Val Glu Tyr |      |      |
| 1140                                                            | 1145 | 1150 |
| Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu Arg Ile Glu Cys Thr |      |      |
| 1155                                                            | 1160 | 1165 |
| Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr Thr Gln Pro Ile Ala |      |      |
| 1170                                                            | 1175 | 1180 |
| Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe Glu Tyr Cys Leu Glu |      |      |
| 1185                                                            | 1190 | 1195 |
| Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His Lys Phe Met Thr Thr |      |      |
| 1205                                                            | 1210 | 1215 |
| Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe Glu Arg Gly Leu Asp |      |      |
| 1220                                                            | 1225 | 1230 |
| Leu Lys Gln Val Asp Gly Leu Pro Arg Ile Ser Phe Gly Ser Pro Pro |      |      |
| 1235                                                            | 1240 | 1245 |
| Pro Met Ala Gly Gly                                             |      |      |
| 1250                                                            |      |      |
| <210> 79                                                        |      |      |
| <211> 1183                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1140-CfaCmut-DD1                                    |      |      |
| <400> 79                                                        |      |      |
| Met Arg Ile Ser Phe Gly Ser Pro Pro Pro Met Ala Gly Gly Val Lys |      |      |
| 1                                                               | 5    | 10   |
| Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr Asp Ile Gly |      |      |
| 20                                                              | 25   | 30   |
| Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu Val Ala Ser |      |      |
| 35                                                              | 40   | 45   |
| Asn Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly Thr Gly |      |      |
| 50                                                              | 55   | 60   |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser Gln Arg |     |     |     |
| 65                                                              | 70  | 75  | 80  |
| Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr |     |     |     |
|                                                                 | 85  | 90  | 95  |
| Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp |     |     |     |
|                                                                 | 100 | 105 | 110 |
| Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val Pro Glu |     |     |     |
|                                                                 | 115 | 120 | 125 |
| Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro |     |     |     |
|                                                                 | 130 | 135 | 140 |
| Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp |     |     |     |
|                                                                 | 165 | 170 | 175 |
| Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser |     |     |     |
|                                                                 | 180 | 185 | 190 |
| Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn Val Asn |     |     |     |
|                                                                 | 195 | 200 | 205 |
| Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro |     |     |     |
|                                                                 | 210 | 215 | 220 |
| Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His Pro Glu |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val Lys Arg |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln Ile Val |     |     |     |
|                                                                 | 275 | 280 | 285 |
| Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile Val Ile |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp Ile Tyr |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser Glu Gln |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe Gly Asn |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln Leu Phe |     |     |     |



|                                                                 |                     |                     |
|-----------------------------------------------------------------|---------------------|---------------------|
| 370                                                             | 375                 | 380                 |
| Gln Lys Gln Lys Trp Thr                                         | Gln Val Asn Pro Ser | Pro Ser Cys Arg Cys |
| 385                                                             | 390                 | 395                 |
| Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala |                     | 400                 |
| 405                                                             | 410                 | 415                 |
| Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu |                     |                     |
| 420                                                             | 425                 | 430                 |
| Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr |                     |                     |
| 435                                                             | 440                 | 445                 |
| Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu |                     |                     |
| 450                                                             | 455                 | 460                 |
| Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro |                     |                     |
| 465                                                             | 470                 | 475                 |
| Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile |                     |                     |
| 485                                                             | 490                 | 495                 |
| Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile |                     |                     |
| 500                                                             | 505                 | 510                 |
| Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp |                     |                     |
| 515                                                             | 520                 | 525                 |
| Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala |                     |                     |
| 530                                                             | 535                 | 540                 |
| His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu |                     |                     |
| 545                                                             | 550                 | 555                 |
| Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu |                     |                     |
| 565                                                             | 570                 | 575                 |
| Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val |                     |                     |
| 580                                                             | 585                 | 590                 |
| Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val |                     |                     |
| 595                                                             | 600                 | 605                 |
| Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe |                     |                     |
| 610                                                             | 615                 | 620                 |
| Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp |                     |                     |
| 625                                                             | 630                 | 635                 |
| Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe |                     |                     |
| 645                                                             | 650                 | 655                 |
| Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala |                     |                     |
| 660                                                             | 665                 | 670                 |
| Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met |                     |                     |
| 675                                                             | 680                 | 685                 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Pro | Ala | Ser | Phe | Leu | Phe | Asp | Val | Pro | Ser | Thr | Ala | Tyr | Val | Ala |
| 690 |     |     |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |
| Leu | Ser | Cys | Ala | Asn | Leu | Phe | Ile | Gly | Ile | Asn | Ser | Ser | Ala | Ile | Thr |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     | 720 |     |
| Phe | Ile | Leu | Glu | Leu | Phe | Glu | Asn | Asn | Arg | Thr | Leu | Leu | Arg | Phe | Asn |
|     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |
| Ala | Val | Leu | Arg | Lys | Leu | Leu | Ile | Val | Phe | Pro | His | Phe | Cys | Leu | Gly |
|     |     |     |     | 740 |     |     |     |     | 745 |     |     |     | 750 |     |     |
| Arg | Gly | Leu | Ile | Asp | Leu | Ala | Leu | Ser | Gln | Ala | Val | Thr | Asp | Val | Tyr |
|     |     | 755 |     |     |     |     | 760 |     |     |     |     |     | 765 |     |     |
| Ala | Arg | Phe | Gly | Glu | Glu | His | Ser | Ala | Asn | Pro | Phe | His | Trp | Asp | Leu |
|     |     | 770 |     |     |     |     | 775 |     |     |     |     |     | 780 |     |     |
| Ile | Gly | Lys | Asn | Leu | Phe | Ala | Met | Val | Val | Glu | Gly | Val | Val | Tyr | Phe |
| 785 |     |     |     | 790 |     |     |     |     |     | 795 |     |     |     |     | 800 |
| Leu | Leu | Thr | Leu | Leu | Val | Gln | Arg | His | Phe | Phe | Leu | Ser | Gln | Trp | Ile |
|     |     |     |     | 805 |     |     |     |     | 810 |     |     |     |     |     | 815 |
| Ala | Glu | Pro | Thr | Lys | Glu | Pro | Ile | Val | Asp | Glu | Asp | Asp | Asp | Val | Ala |
|     |     |     |     | 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |
| Glu | Glu | Arg | Gln | Arg | Ile | Ile | Thr | Gly | Gly | Asn | Lys | Thr | Asp | Ile | Leu |
|     |     | 835 |     |     |     |     | 840 |     |     |     |     |     | 845 |     |     |
| Arg | Leu | His | Glu | Leu | Thr | Lys | Ile | Tyr | Pro | Gly | Thr | Ser | Ser | Pro | Ala |
|     |     | 850 |     |     |     |     | 855 |     |     |     |     |     | 860 |     |     |
| Val | Asp | Arg | Leu | Cys | Val | Gly | Val | Arg | Pro | Gly | Glu | Cys | Phe | Gly | Leu |
| 865 |     |     |     | 870 |     |     |     |     |     | 875 |     |     |     |     | 880 |
| Leu | Gly | Val | Asn | Gly | Ala | Gly | Lys | Thr | Thr | Thr | Phe | Lys | Met | Leu | Thr |
|     |     |     |     | 885 |     |     |     |     | 890 |     |     |     |     | 895 |     |
| Gly | Asp | Thr | Thr | Val | Thr | Ser | Gly | Asp | Ala | Thr | Val | Ala | Gly | Lys | Ser |
|     |     | 900 |     |     |     |     |     |     | 905 |     |     |     | 910 |     |     |
| Ile | Leu | Thr | Asn | Ile | Ser | Glu | Val | His | Gln | Asn | Met | Gly | Tyr | Cys | Pro |
|     |     | 915 |     |     |     |     | 920 |     |     |     |     |     | 925 |     |     |
| Gln | Phe | Asp | Ala | Ile | Asp | Glu | Leu | Leu | Thr | Gly | Arg | Glu | His | Leu | Tyr |
|     |     | 930 |     |     |     |     | 935 |     |     |     |     |     | 940 |     |     |
| Leu | Tyr | Ala | Arg | Leu | Arg | Gly | Val | Pro | Ala | Glu | Glu | Ile | Glu | Lys | Val |
| 945 |     |     |     | 950 |     |     |     |     |     | 955 |     |     |     |     | 960 |
| Ala | Asn | Trp | Ser | Ile | Lys | Ser | Leu | Gly | Leu | Thr | Val | Tyr | Ala | Asp | Cys |
|     |     |     |     | 965 |     |     |     |     | 970 |     |     |     |     | 975 |     |
| Leu | Ala | Gly | Thr | Tyr | Ser | Gly | Gly | Asn | Lys | Arg | Lys | Leu | Ser | Thr | Ala |
|     |     | 980 |     |     |     |     |     |     | 985 |     |     |     | 990 |     |     |
| Ile | Ala | Leu | Ile | Gly | Cys | Pro | Pro | Leu | Val | Leu | Leu | Asp | Glu | Pro | Thr |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 995                                                             | 1000 | 1005 |
| Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val |      |      |
| 1010                                                            | 1015 | 1020 |
| Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His Ser Met |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly |      | 1040 |
| 1045                                                            | 1050 | 1055 |
| Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly |      |      |
| 1060                                                            | 1065 | 1070 |
| Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu |      |      |
| 1075                                                            | 1080 | 1085 |
| Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro |      |      |
| 1090                                                            | 1095 | 1100 |
| Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val |      |      |
| 1105                                                            | 1110 | 1115 |
| Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys |      | 1120 |
| 1125                                                            | 1130 | 1135 |
| Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp |      |      |
| 1140                                                            | 1145 | 1150 |
| Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu |      |      |
| 1155                                                            | 1160 | 1165 |
| Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp     |      |      |
| 1170                                                            | 1175 | 1180 |
| <210> 80                                                        |      |      |
| <211> 13                                                        |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> DD4                                                       |      |      |
| <220>                                                           |      |      |
| <221> 变体                                                        |      |      |
| <222> 12                                                        |      |      |
| <223> X= 任意氨基酸,优选Gly                                            |      |      |
| <400> 80                                                        |      |      |
| Arg Asp Ser Phe Gly Ser Pro Pro Pro Met Ala Xaa Gly             |      |      |
| 1                                                               | 5    | 10   |
| <210> 81                                                        |      |      |
| <211> 4                                                         |      |      |
| <212> PRT                                                       |      |      |

<213> 人工序列(Artificial Sequence)  
<220>  
<223> DD5  
<400> 81  
Gly Phe Trp Ile  
1  
<210> 82  
<211> 4  
<212> PRT  
<213> 人工序列(Artificial Sequence)  
<220>  
<223> DD6  
<400> 82  
Arg Phe Lys Gly  
1  
<210> 83  
<211> 4  
<212> PRT  
<213> 人工序列(Artificial Sequence)  
<220>  
<223> DD7  
<400> 83  
Lys Phe Tyr Lys  
1  
<210> 84  
<211> 8  
<212> PRT  
<213> 人工序列(Artificial Sequence)  
<220>  
<223> 六聚组氨酸  
<400> 84  
Gly His His His His His His Gly  
1 5  
<210> 85  
<211> 23  
<212> PRT  
<213> 人工序列(Artificial Sequence)  
<220>  
<223> V12

&lt;400&gt; 85

Thr Asn Gly Ser Val Leu Arg Glu Phe Thr Leu Leu Glu Leu Glu Val

1 5 10 15

Val Thr Arg Asn Thr Glu Leu

20

&lt;210&gt; 86

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; T1

&lt;400&gt; 86

Ser Val Leu Glu Glu Asn Arg Pro Phe Ala Gln Gln Leu Ser Asn Val

1 5 10 15

Tyr Phe Thr Ile Leu

20

&lt;210&gt; 87

&lt;211&gt; 1176

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4N-1177

&lt;400&gt; 87

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr

1 5 10 15

Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro

20 25 30

Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu

35 40 45

Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala

50 55 60

Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro

65 70 75 80

Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn

85 90 95

Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu

100 105 110

Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu

115 120 125

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
|                                                                 | 165 | 170 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
|                                                                 | 180 | 185 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
|                                                                 | 195 | 200 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
|                                                                 | 210 | 215 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
|                                                                 | 245 | 250 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
|                                                                 | 260 | 265 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
|                                                                 | 275 | 280 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
|                                                                 | 290 | 295 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
|                                                                 | 325 | 330 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
|                                                                 | 340 | 345 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
|                                                                 | 355 | 360 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
|                                                                 | 370 | 375 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
|                                                                 | 405 | 410 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
|                                                                 | 420 | 425 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |           |
| 755                                                             | 760  | 765       |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |           |
| 770                                                             | 775  | 780       |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |           |
| 785                                                             | 790  | 795 800   |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |           |
|                                                                 | 805  | 810 815   |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |           |
|                                                                 | 820  | 825 830   |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |           |
|                                                                 | 835  | 840 845   |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |           |
|                                                                 | 850  | 855 860   |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |           |
| 865                                                             | 870  | 875 880   |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |           |
|                                                                 | 885  | 890 895   |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |           |
|                                                                 | 900  | 905 910   |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |           |
|                                                                 | 915  | 920 925   |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |           |
|                                                                 | 930  | 935 940   |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |           |
| 945                                                             | 950  | 955 960   |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |           |
|                                                                 | 965  | 970 975   |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |           |
|                                                                 | 980  | 985 990   |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |           |
|                                                                 | 995  | 1000 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |           |
|                                                                 | 1010 | 1015 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |           |
| 1025                                                            | 1030 | 1035 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |           |
|                                                                 | 1045 | 1050 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |           |



|                                                                 |                                     |      |
|-----------------------------------------------------------------|-------------------------------------|------|
| 1060                                                            | 1065                                | 1070 |
| Ala Ile Ala Phe Val Gly Asp                                     | Ala Lys Val Val Ile Leu Asp Glu Pro |      |
| 1075                                                            | 1080                                | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |                                     |      |
| 1090                                                            | 1095                                | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |                                     |      |
| 1105                                                            | 1110                                | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |                                     | 1120 |
| 1125                                                            | 1130                                | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |                                     |      |
| 1140                                                            | 1145                                | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |                                     |      |
| 1155                                                            | 1160                                | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr                                 |                                     |      |
| 1170                                                            | 1175                                |      |
| <210> 88                                                        |                                     |      |
| <211> 1097                                                      |                                     |      |
| <212> PRT                                                       |                                     |      |
| <213> 人工序列(Artificial Sequence)                                 |                                     |      |
| <220>                                                           |                                     |      |
| <223> ABCA4C-1177                                               |                                     |      |
| <400> 88                                                        |                                     |      |
| Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val |                                     |      |
| 1                                                               | 5                                   | 10   |
| Asp Asp Leu Thr Pro Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu |                                     |      |
| 20                                                              | 25                                  | 30   |
| Met Asp Val Val Leu His His Val Pro Glu Ala Lys Leu Val Glu Cys |                                     |      |
| 35                                                              | 40                                  | 45   |
| Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His |                                     |      |
| 50                                                              | 55                                  | 60   |
| Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp |                                     |      |
| 65                                                              | 70                                  | 75   |
| Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile |                                     |      |
| 85                                                              | 90                                  | 95   |
| Phe Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly |                                     |      |
| 100                                                             | 105                                 | 110  |
| Gly Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu |                                     |      |
| 115                                                             | 120                                 | 125  |
| Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys |                                     |      |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 130                                                             | 135 | 140 |
| Ser Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu |     |     |
| 145                                                             | 150 | 155 |
| Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu |     |     |
| 165                                                             | 170 | 175 |
| Gln His Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg |     |     |
| 180                                                             | 185 | 190 |
| Ser His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val |     |     |
| 195                                                             | 200 | 205 |
| Phe Leu Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr |     |     |
| 210                                                             | 215 | 220 |
| Pro Ala Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe |     |     |
| 225                                                             | 230 | 235 |
| Phe Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp |     |     |
| 245                                                             | 250 | 255 |
| Val Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly |     |     |
| 260                                                             | 265 | 270 |
| Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro |     |     |
| 275                                                             | 280 | 285 |
| Ser Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr |     |     |
| 290                                                             | 295 | 300 |
| Gln Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu |     |     |
| 305                                                             | 310 | 315 |
| Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro |     |     |
| 325                                                             | 330 | 335 |
| Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg |     |     |
| 340                                                             | 345 | 350 |
| Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser |     |     |
| 355                                                             | 360 | 365 |
| Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile |     |     |
| 370                                                             | 375 | 380 |
| Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu |     |     |
| 385                                                             | 390 | 395 |
| Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly |     |     |
| 405                                                             | 410 | 415 |
| Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His |     |     |
| 420                                                             | 425 | 430 |
| Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp |     |     |
| 435                                                             | 440 | 445 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ala | Leu | Val | Ser | Phe | Leu | Asn | Val | Ala | His | Asn | Ala | Ile | Leu | Arg |
| 450 |     |     |     |     |     |     | 455 |     |     |     | 460 |     |     |     |     |
| Ala | Ser | Leu | Pro | Lys | Asp | Arg | Ser | Pro | Glu | Glu | Tyr | Gly | Ile | Thr | Val |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Ile | Ser | Gln | Pro | Leu | Asn | Leu | Thr | Lys | Glu | Gln | Leu | Ser | Glu | Ile | Thr |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Val | Leu | Thr | Thr | Ser | Val | Asp | Ala | Val | Val | Ala | Ile | Cys | Val | Ile | Phe |
|     |     |     |     | 500 |     |     |     | 505 |     |     |     |     |     | 510 |     |
| Ser | Met | Ser | Phe | Val | Pro | Ala | Ser | Phe | Val | Leu | Tyr | Leu | Ile | Gln | Glu |
|     |     |     |     | 515 |     |     |     | 520 |     |     |     |     |     | 525 |     |
| Arg | Val | Asn | Lys | Ser | Lys | His | Leu | Gln | Phe | Ile | Ser | Gly | Val | Ser | Pro |
|     |     |     |     |     |     | 535 |     |     |     |     |     |     |     | 540 |     |
| Thr | Thr | Tyr | Trp | Val | Thr | Asn | Phe | Leu | Trp | Asp | Ile | Met | Asn | Tyr | Ser |
| 545 |     |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     | 560 |
| Val | Ser | Ala | Gly | Leu | Val | Val | Gly | Ile | Phe | Ile | Gly | Phe | Gln | Lys | Lys |
|     |     |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     | 575 |
| Ala | Tyr | Thr | Ser | Pro | Glu | Asn | Leu | Pro | Ala | Leu | Val | Ala | Leu | Leu | Leu |
|     |     |     |     |     |     | 580 |     |     |     |     |     |     |     | 585 | 590 |
| Leu | Tyr | Gly | Trp | Ala | Val | Ile | Pro | Met | Met | Tyr | Pro | Ala | Ser | Phe | Leu |
|     |     |     |     |     |     | 595 |     |     |     |     |     |     |     | 600 | 605 |
| Phe | Asp | Val | Pro | Ser | Thr | Ala | Tyr | Val | Ala | Leu | Ser | Cys | Ala | Asn | Leu |
|     |     |     |     |     |     | 610 |     |     |     |     |     |     |     | 615 | 620 |
| Phe | Ile | Gly | Ile | Asn | Ser | Ser | Ala | Ile | Thr | Phe | Ile | Leu | Glu | Leu | Phe |
| 625 |     |     |     |     |     |     | 630 |     |     |     |     |     |     | 635 | 640 |
| Glu | Asn | Asn | Arg | Thr | Leu | Leu | Arg | Phe | Asn | Ala | Val | Leu | Arg | Lys | Leu |
|     |     |     |     |     |     |     | 645 |     |     |     |     |     |     | 650 | 655 |
| Leu | Ile | Val | Phe | Pro | His | Phe | Cys | Leu | Gly | Arg | Gly | Leu | Ile | Asp | Leu |
|     |     |     |     |     |     |     | 660 |     |     |     |     |     |     | 665 | 670 |
| Ala | Leu | Ser | Gln | Ala | Val | Thr | Asp | Val | Tyr | Ala | Arg | Phe | Gly | Glu | Glu |
|     |     |     |     |     |     |     | 675 |     |     |     |     |     |     | 680 | 685 |
| His | Ser | Ala | Asn | Pro | Phe | His | Trp | Asp | Leu | Ile | Gly | Lys | Asn | Leu | Phe |
|     |     |     |     |     |     |     | 690 |     |     |     |     |     |     | 695 | 700 |
| Ala | Met | Val | Val | Glu | Gly | Val | Val | Tyr | Phe | Leu | Leu | Thr | Leu | Leu | Val |
| 705 |     |     |     |     |     |     |     |     |     |     |     |     |     | 710 | 715 |
| Gln | Arg | His | Phe | Phe | Leu | Ser | Gln | Trp | Ile | Ala | Glu | Pro | Thr | Lys | Glu |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     | 725 | 730 |
| Pro | Ile | Val | Asp | Glu | Asp | Asp | Asp | Val | Ala | Glu | Glu | Arg | Gln | Arg | Ile |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     | 740 | 745 |
| Ile | Thr | Gly | Gly | Asn | Lys | Thr | Asp | Ile | Leu | Arg | Leu | His | Glu | Leu | Thr |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|                                                                 |                                     |      |
|-----------------------------------------------------------------|-------------------------------------|------|
| 755                                                             | 760                                 | 765  |
| Lys Ile Tyr Pro Gly Thr Ser                                     | Ser Pro Ala Val Asp Arg Leu Cys Val |      |
| 770                                                             | 775                                 | 780  |
| Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala |                                     |      |
| 785                                                             | 790                                 | 795  |
| Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr |                                     |      |
| 805                                                             | 810                                 | 815  |
| Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser |                                     |      |
| 820                                                             | 825                                 | 830  |
| Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp |                                     |      |
| 835                                                             | 840                                 | 845  |
| Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg |                                     |      |
| 850                                                             | 855                                 | 860  |
| Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys |                                     |      |
| 865                                                             | 870                                 | 875  |
| Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser |                                     |      |
| 885                                                             | 890                                 | 895  |
| Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys |                                     |      |
| 900                                                             | 905                                 | 910  |
| Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln |                                     |      |
| 915                                                             | 920                                 | 925  |
| Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly |                                     |      |
| 930                                                             | 935                                 | 940  |
| Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu |                                     |      |
| 945                                                             | 950                                 | 955  |
| Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly |                                     |      |
| 965                                                             | 970                                 | 975  |
| Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr |                                     |      |
| 980                                                             | 985                                 | 990  |
| Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro |                                     |      |
| 995                                                             | 1000                                | 1005 |
| Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu |                                     |      |
| 1010                                                            | 1015                                | 1020 |
| Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala |                                     |      |
| 1025                                                            | 1030                                | 1035 |
| Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu |                                     |      |
| 1045                                                            | 1050                                | 1055 |
| Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe |                                     |      |
| 1060                                                            | 1065                                | 1070 |

Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala  
 1075 1080 1085

Ala Gly Ala Ser Arg Gln Ala Gln Asp  
 1090 1095

<210> 89  
 <211> 1178  
 <212> PRT  
 <213> 人工序列(Artificial Sequence)  
 <220>  
 <223> ABCA4N-1179  
 <400> 89

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr  
 1 5 10 15

Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro  
 20 25 30

Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu  
 35 40 45

Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
 50 55 60

Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro  
 65 70 75 80

Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn  
 85 90 95

Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu  
 100 105 110

Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu  
 115 120 125

Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu  
 130 135 140

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

Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser  
 165 170 175

Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala  
 180 185 190

His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala  
 195 200 205

Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr  
 210 215 220

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |     |
|                                                                 | 275 | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |
| 805                                                             | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |
| 820                                                             | 825 | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |     |
| 835                                                             | 840 | 845 |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |           |
| 850                                                             | 855  | 860       |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |           |
| 865                                                             | 870  | 875 880   |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |           |
|                                                                 | 885  | 890 895   |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |           |
|                                                                 | 900  | 905 910   |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |           |
|                                                                 | 915  | 920 925   |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |           |
|                                                                 | 930  | 935 940   |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |           |
| 945                                                             | 950  | 955 960   |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |           |
|                                                                 | 965  | 970 975   |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |           |
|                                                                 | 980  | 985 990   |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |           |
|                                                                 | 995  | 1000 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |           |
|                                                                 | 1010 | 1015 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |           |
| 1025                                                            | 1030 | 1035 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |           |
|                                                                 | 1045 | 1050 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |           |
|                                                                 | 1060 | 1065 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |           |
|                                                                 | 1075 | 1080 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |           |
|                                                                 | 1090 | 1095 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |           |
| 1105                                                            | 1110 | 1115 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |           |
|                                                                 | 1125 | 1130 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |           |
|                                                                 | 1140 | 1145 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |           |



|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1155                                                            | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser                         |      |      |
| 1170                                                            | 1175 |      |
| <210> 90                                                        |      |      |
| <211> 1095                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4C-1179                                               |      |      |
| <400> 90                                                        |      |      |
| Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala His Val Asp Asp |      |      |
| 1 5 10 15                                                       |      |      |
| Leu Thr Pro Glu Gln Val Leu Asp Gly Asp Val Asn Glu Leu Met Asp |      |      |
| 20 25 30                                                        |      |      |
| Val Val Leu His His Val Pro Glu Ala Lys Leu Val Glu Cys Ile Gly |      |      |
| 35 40 45                                                        |      |      |
| Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe Lys His Arg Ala |      |      |
| 50 55 60                                                        |      |      |
| Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly |      |      |
| 65 70 75 80                                                     |      |      |
| Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu |      |      |
| 85 90 95                                                        |      |      |
| Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala |      |      |
| 100 105 110                                                     |      |      |
| Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro Cys Leu Gly Pro |      |      |
| 115 120 125                                                     |      |      |
| Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn Val Cys Ser Pro |      |      |
| 130 135 140                                                     |      |      |
| Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu |      |      |
| 145 150 155 160                                                 |      |      |
| Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu Val Leu Gln His |      |      |
| 165 170 175                                                     |      |      |
| Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr Ile Arg Ser His |      |      |
| 180 185 190                                                     |      |      |
| Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr Phe Val Phe Leu |      |      |
| 195 200 205                                                     |      |      |
| Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala |      |      |
| 210 215 220                                                     |      |      |
| Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser |      |      |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 225                                                             | 230 | 235 | 240 |
| Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu Ala Asp Val Leu |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val |     |     |     |
|                                                                 | 275 | 280 | 285 |
| Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys Leu Thr Met |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala Leu Val Gly |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly Gly Pro Ile |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys His Leu Glu |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu Arg Ala Ser |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile Thr Val Leu |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val Ile Phe Ser Met |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln Glu Arg Val |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser Pro Thr Thr |     |     |     |
|                                                                 | 530 | 535 | 540 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Trp | Val | Thr | Asn | Phe | Leu | Trp | Asp | Ile | Met | Asn | Tyr | Ser | Val | Ser |
| 545 |     |     |     |     |     | 550 |     |     |     | 555 |     |     |     |     | 560 |
| Ala | Gly | Leu | Val | Val | Gly | Ile | Phe | Ile | Gly | Phe | Gln | Lys | Lys | Ala | Tyr |
|     |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |
| Thr | Ser | Pro | Glu | Asn | Leu | Pro | Ala | Leu | Val | Ala | Leu | Leu | Leu | Leu | Tyr |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     |     | 590 |     |
| Gly | Trp | Ala | Val | Ile | Pro | Met | Met | Tyr | Pro | Ala | Ser | Phe | Leu | Phe | Asp |
|     | 595 |     |     |     |     |     | 600 |     |     |     |     |     | 605 |     |     |
| Val | Pro | Ser | Thr | Ala | Tyr | Val | Ala | Leu | Ser | Cys | Ala | Asn | Leu | Phe | Ile |
|     | 610 |     |     |     |     |     | 615 |     |     |     |     |     | 620 |     |     |
| Gly | Ile | Asn | Ser | Ser | Ala | Ile | Thr | Phe | Ile | Leu | Glu | Leu | Phe | Glu | Asn |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Asn | Arg | Thr | Leu | Leu | Arg | Phe | Asn | Ala | Val | Leu | Arg | Lys | Leu | Leu | Ile |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     |     | 655 |
| Val | Phe | Pro | His | Phe | Cys | Leu | Gly | Arg | Gly | Leu | Ile | Asp | Leu | Ala | Leu |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     |     |     | 670 |
| Ser | Gln | Ala | Val | Thr | Asp | Val | Tyr | Ala | Arg | Phe | Gly | Glu | Glu | His | Ser |
|     | 675 |     |     |     |     |     |     | 680 |     |     |     |     |     |     | 685 |
| Ala | Asn | Pro | Phe | His | Trp | Asp | Leu | Ile | Gly | Lys | Asn | Leu | Phe | Ala | Met |
|     | 690 |     |     |     |     |     | 695 |     |     |     |     |     |     |     | 700 |
| Val | Val | Glu | Gly | Val | Val | Tyr | Phe | Leu | Leu | Thr | Leu | Leu | Val | Gln | Arg |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |
| His | Phe | Phe | Leu | Ser | Gln | Trp | Ile | Ala | Glu | Pro | Thr | Lys | Glu | Pro | Ile |
|     |     |     | 725 |     |     |     |     |     | 730 |     |     |     |     |     | 735 |
| Val | Asp | Glu | Asp | Asp | Asp | Val | Ala | Glu | Glu | Arg | Gln | Arg | Ile | Ile | Thr |
|     |     | 740 |     |     |     |     |     | 745 |     |     |     |     |     |     | 750 |
| Gly | Gly | Asn | Lys | Thr | Asp | Ile | Leu | Arg | Leu | His | Glu | Leu | Thr | Lys | Ile |
|     |     | 755 |     |     |     |     | 760 |     |     |     |     |     |     |     | 765 |
| Tyr | Pro | Gly | Thr | Ser | Ser | Pro | Ala | Val | Asp | Arg | Leu | Cys | Val | Gly | Val |
|     | 770 |     |     |     |     |     | 775 |     |     |     |     |     |     |     | 780 |
| Arg | Pro | Gly | Glu | Cys | Phe | Gly | Leu | Leu | Gly | Val | Asn | Gly | Ala | Gly | Lys |
| 785 |     |     |     |     | 790 |     |     |     |     | 795 |     |     |     |     | 800 |
| Thr | Thr | Thr | Phe | Lys | Met | Leu | Thr | Gly | Asp | Thr | Thr | Val | Thr | Ser | Gly |
|     |     |     | 805 |     |     |     |     |     | 810 |     |     |     |     |     | 815 |
| Asp | Ala | Thr | Val | Ala | Gly | Lys | Ser | Ile | Leu | Thr | Asn | Ile | Ser | Glu | Val |
|     |     | 820 |     |     |     |     |     | 825 |     |     |     |     |     |     | 830 |
| His | Gln | Asn | Met | Gly | Tyr | Cys | Pro | Gln | Phe | Asp | Ala | Ile | Asp | Glu | Leu |
|     | 835 |     |     |     |     |     |     | 840 |     |     |     |     |     |     | 845 |
| Leu | Thr | Gly | Arg | Glu | His | Leu | Tyr | Leu | Tyr | Ala | Arg | Leu | Arg | Gly | Val |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 850                                                             | 855  | 860  |
| Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu |      |      |
| 865                                                             | 870  | 875  |
| Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly |      | 880  |
| 885                                                             | 890  | 895  |
| Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro |      |      |
| 900                                                             | 905  | 910  |
| Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg |      |      |
| 915                                                             | 920  | 925  |
| Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala |      |      |
| 930                                                             | 935  | 940  |
| Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr |      |      |
| 945                                                             | 950  | 955  |
| Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile |      |      |
| 965                                                             | 970  | 975  |
| Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys |      |      |
| 980                                                             | 985  | 990  |
| Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu |      |      |
| 995                                                             | 1000 | 1005 |
| Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His |      |      |
| 1010                                                            | 1015 | 1020 |
| Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile |      |      |
| 1025                                                            | 1030 | 1035 |
| Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr |      |      |
| 1045                                                            | 1050 | 1055 |
| Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys |      |      |
| 1060                                                            | 1065 | 1070 |
| Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala Gly |      |      |
| 1075                                                            | 1080 | 1085 |
| Ala Ser Arg Gln Ala Gln Asp                                     |      |      |
| 1090                                                            | 1095 |      |
| <210> 91                                                        |      |      |
| <211> 1277                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1177-CfaN                                           |      |      |
| <400> 91                                                        |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 1                                                               | 5   | 10  | 15  |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |     |     |     |
| 20                                                              | 25  | 30  |     |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |     |     |     |
| 35                                                              | 40  | 45  |     |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |     |     |     |
| 50                                                              | 55  | 60  |     |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |     |     |     |
| 65                                                              | 70  | 75  | 80  |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |     |     |     |
| 85                                                              | 90  | 95  |     |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |     |
| 100                                                             | 105 | 110 |     |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |     |
| 115                                                             | 120 | 125 |     |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |     |
| 130                                                             | 135 | 140 |     |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |     |
| 145                                                             | 150 | 155 | 160 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |     |
| 165                                                             | 170 | 175 |     |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |     |
| 180                                                             | 185 | 190 |     |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |     |
| 195                                                             | 200 | 205 |     |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |     |
| 210                                                             | 215 | 220 |     |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |     |
| 245                                                             | 250 | 255 |     |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |     |
| 260                                                             | 265 | 270 |     |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |     |
| 275                                                             | 280 | 285 |     |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |     |
| 290                                                             | 295 | 300 |     |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |     |
| 305                                                             | 310 | 315 | 320 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |
|     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
| 385 |     |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     | 400 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     |     |     | 405 |     |     |     | 410 |     |     |     |     | 415 |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     |     |     |     | 420 |     |     |     | 425 |     |     |     |     | 430 |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |
|     |     |     |     |     |     | 435 |     |     |     | 440 |     |     |     |     | 445 |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu |
|     |     |     |     |     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |
| Asn | Arg | Gln | Leu | Gly | Glu | Glu | Gly | Ile | Thr | Ala | Glu | Ala | Ile | Leu | Asn |
| 465 |     |     |     |     |     | 470 |     |     |     | 475 |     |     |     |     | 480 |
| Phe | Leu | Tyr | Lys | Gly | Pro | Arg | Glu | Ser | Gln | Ala | Asp | Asp | Met | Ala | Asn |
|     |     |     |     |     |     | 485 |     |     |     | 490 |     |     |     |     | 495 |
| Phe | Asp | Trp | Arg | Asp | Ile | Phe | Asn | Ile | Thr | Asp | Arg | Thr | Leu | Arg | Leu |
|     |     |     |     |     |     | 500 |     |     |     | 505 |     |     |     |     | 510 |
| Val | Asn | Gln | Tyr | Leu | Glu | Cys | Leu | Val | Leu | Asp | Lys | Phe | Glu | Ser | Tyr |
|     |     |     |     |     |     | 515 |     |     |     | 520 |     |     |     |     | 525 |
| Asn | Asp | Glu | Thr | Gln | Leu | Thr | Gln | Arg | Ala | Leu | Ser | Leu | Leu | Glu | Glu |
|     |     |     |     |     |     | 530 |     |     |     | 535 |     |     |     |     | 540 |
| Asn | Met | Phe | Trp | Ala | Gly | Val | Val | Phe | Pro | Asp | Met | Tyr | Pro | Trp | Thr |
| 545 |     |     |     |     |     | 550 |     |     |     | 555 |     |     |     |     | 560 |
| Ser | Ser | Leu | Pro | Pro | His | Val | Lys | Tyr | Lys | Ile | Arg | Met | Asp | Ile | Asp |
|     |     |     |     |     |     | 565 |     |     |     | 570 |     |     |     |     | 575 |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly |
|     |     |     |     |     |     | 580 |     |     |     | 585 |     |     |     |     | 590 |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe |
|     |     |     |     |     |     | 595 |     |     |     | 600 |     |     |     |     | 605 |
| Ala | Tyr | Leu | Gln | Asp | Met | Val | Glu | Gln | Gly | Ile | Thr | Arg | Ser | Gln | Val |
|     |     |     |     |     |     | 610 |     |     |     | 615 |     |     |     |     | 620 |
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 625                                                             | 630 | 635 | 640 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |     |
|                                                                 | 770 | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |     |
| 785                                                             | 790 | 795 | 800 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |     |
|                                                                 | 805 | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |     |
|                                                                 | 820 | 825 | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |     |     |
|                                                                 | 835 | 840 | 845 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |     |     |     |
|                                                                 | 850 | 855 | 860 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |     |     |     |
| 865                                                             | 870 | 875 | 880 |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |     |     |     |
|                                                                 | 885 | 890 | 895 |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |     |     |     |
|                                                                 | 900 | 905 | 910 |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |     |     |     |
|                                                                 | 915 | 920 | 925 |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |     |     |     |
|                                                                 | 930 | 935 | 940 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Leu Ser Tyr Asp Thr Glu Ile |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly Lys Ile Val Glu Glu |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys Asn Gly Phe Val Tyr |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly Glu Gln Glu Val Phe |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg Ala Thr Lys Asp His |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro Ile Asp Glu Ile Phe |      |      |      |



|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1250                                                            | 1255 | 1260 |
| Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly Leu Pro             |      |      |
| 1265                                                            | 1270 | 1275 |
| <210> 92                                                        |      |      |
| <211> 1133                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1177-CfaCmut                                        |      |      |
| <400> 92                                                        |      |      |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |      |      |
| 1                                                               | 5    | 10   |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |      |      |
| 20                                                              | 25   | 30   |
| Val Ala Ser Asn Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys |      |      |
| 35                                                              | 40   | 45   |
| Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp Gly Asp |      |      |
| 50                                                              | 55   | 60   |
| Val Asn Glu Leu Met Asp Val Val Leu His His Val Pro Glu Ala Lys |      |      |
| 65                                                              | 70   | 75   |
| Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys |      |      |
| 85                                                              | 90   | 95   |
| Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu |      |      |
| 100                                                             | 105  | 110  |
| Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro |      |      |
| 115                                                             | 120  | 125  |
| Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro |      |      |
| 130                                                             | 135  | 140  |
| Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg |      |      |
| 145                                                             | 150  | 155  |
| His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp |      |      |
| 165                                                             | 170  | 175  |
| Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln |      |      |
| 180                                                             | 185  | 190  |
| Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr |      |      |
| 195                                                             | 200  | 205  |
| Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val Lys Arg Phe Gln |      |      |
| 210                                                             | 215  | 220  |
| His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro |      |      |

|                     |                     |                     |     |
|---------------------|---------------------|---------------------|-----|
| 225                 | 230                 | 235                 | 240 |
| Ala Thr Phe Val Phe | Leu Ala Leu Met Leu | Ser Ile Val Ile Pro | Pro |
| 245                 | 250                 | 255                 |     |
| Phe Gly Glu Tyr Pro | Ala Leu Thr Leu His | Pro Trp Ile Tyr Gly | Gln |
| 260                 | 265                 | 270                 |     |
| Gln Tyr Thr Phe Phe | Ser Met Asp Glu Pro | Gly Ser Glu Gln Phe | Thr |
| 275                 | 280                 | 285                 |     |
| Val Leu Ala Asp Val | Leu Leu Asn Lys Pro | Gly Phe Gly Asn Arg | Cys |
| 290                 | 295                 | 300                 |     |
| Leu Lys Glu Gly Trp | Leu Pro Glu Tyr Pro | Cys Gly Asn Ser Thr | Pro |
| 305                 | 310                 | 315                 | 320 |
| Trp Lys Thr Pro Ser | Val Ser Pro Asn Ile | Thr Gln Leu Phe Gln | Lys |
| 325                 | 330                 | 335                 |     |
| Gln Lys Trp Thr Gln | Val Asn Pro Ser Pro | Ser Cys Arg Cys Ser | Thr |
| 340                 | 345                 | 350                 |     |
| Arg Glu Lys Leu Thr | Met Leu Pro Glu Cys | Pro Glu Gly Ala Gly | Gly |
| 355                 | 360                 | 365                 |     |
| Leu Pro Pro Pro Gln | Arg Thr Gln Arg Ser | Thr Glu Ile Leu Gln | Asp |
| 370                 | 375                 | 380                 |     |
| Leu Thr Asp Arg Asn | Ile Ser Asp Phe Leu | Val Lys Thr Tyr Pro | Ala |
| 385                 | 390                 | 395                 | 400 |
| Leu Ile Arg Ser Ser | Leu Lys Ser Lys Phe | Trp Val Asn Glu Gln | Arg |
| 405                 | 410                 | 415                 |     |
| Tyr Gly Gly Ile Ser | Ile Gly Gly Lys Leu | Pro Val Val Pro Ile | Thr |
| 420                 | 425                 | 430                 |     |
| Gly Glu Ala Leu Val | Gly Phe Leu Ser Asp | Leu Gly Arg Ile Met | Asn |
| 435                 | 440                 | 445                 |     |
| Val Ser Gly Gly Pro | Ile Thr Arg Glu Ala | Ser Lys Glu Ile Pro | Asp |
| 450                 | 455                 | 460                 |     |
| Phe Leu Lys His Leu | Glu Thr Glu Asp Asn | Ile Lys Val Trp Phe | Asn |
| 465                 | 470                 | 475                 | 480 |
| Asn Lys Gly Trp His | Ala Leu Val Ser Phe | Leu Asn Val Ala His | Asn |
| 485                 | 490                 | 495                 |     |
| Ala Ile Leu Arg Ala | Ser Leu Pro Lys Asp | Arg Ser Pro Glu Glu | Tyr |
| 500                 | 505                 | 510                 |     |
| Gly Ile Thr Val Ile | Ser Gln Pro Leu Asn | Leu Thr Lys Glu Gln | Leu |
| 515                 | 520                 | 525                 |     |
| Ser Glu Ile Thr Val | Leu Thr Thr Ser Val | Asp Ala Val Val Ala | Ile |
| 530                 | 535                 | 540                 |     |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val |     |     |     |
| 610                                                             | 615 | 620 |     |
| Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly |     |     |     |
| 690                                                             | 695 | 700 |     |
| Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu |     |     |     |
|                                                                 | 770 | 775 | 780 |
| Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu |     |     |     |
| 785                                                             | 790 | 795 | 800 |
| His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp |     |     |     |
|                                                                 | 805 | 810 | 815 |
| Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly |     |     |     |
|                                                                 | 820 | 825 | 830 |
| Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp |     |     |     |
|                                                                 | 835 | 840 | 845 |
| Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu |     |     |     |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 850                                                             | 855  | 860  |
| Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe |      |      |
| 865                                                             | 870  | 875  |
| Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr |      | 880  |
|                                                                 | 885  | 890  |
| Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn |      | 895  |
|                                                                 | 900  | 905  |
| Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala |      | 910  |
|                                                                 | 915  | 920  |
| Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala |      | 925  |
|                                                                 | 930  | 935  |
| Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly |      | 940  |
| 945                                                             | 950  | 955  |
| Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile |      | 960  |
|                                                                 | 965  | 970  |
| Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu |      | 975  |
|                                                                 | 980  | 985  |
| Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe |      | 990  |
|                                                                 | 995  | 1000 |
| Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly |      | 1005 |
|                                                                 | 1010 | 1015 |
| Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro |      | 1020 |
| 1025                                                            | 1030 | 1035 |
| Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser |      | 1040 |
|                                                                 | 1045 | 1050 |
| Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser |      | 1055 |
|                                                                 | 1060 | 1065 |
| Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser |      | 1070 |
|                                                                 | 1075 | 1080 |
| Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val |      | 1085 |
|                                                                 | 1090 | 1095 |
| Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu |      | 1100 |
| 1105                                                            | 1110 | 1115 |
| His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp             |      | 1120 |
|                                                                 | 1125 | 1130 |

&lt;210&gt; 93

&lt;211&gt; 1279

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4-1179-CfaN

&lt;400&gt; 93

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Phe | Val | Arg | Gln | Ile | Gln | Leu | Leu | Leu | Trp | Lys | Asn | Trp | Thr |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Leu | Arg | Lys | Arg | Gln | Lys | Ile | Arg | Phe | Val | Val | Glu | Leu | Val | Trp | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |
| Leu | Ser | Leu | Phe | Leu | Val | Leu | Ile | Trp | Leu | Arg | Asn | Ala | Asn | Pro | Leu |
|     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |
| Tyr | Ser | His | His | Glu | Cys | His | Phe | Pro | Asn | Lys | Ala | Met | Pro | Ser | Ala |
|     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |
| Gly | Met | Leu | Pro | Trp | Leu | Gln | Gly | Ile | Phe | Cys | Asn | Val | Asn | Asn | Pro |
| 65  |     |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |
| Cys | Phe | Gln | Ser | Pro | Thr | Pro | Gly | Glu | Ser | Pro | Gly | Ile | Val | Ser | Asn |
|     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |
| Tyr | Asn | Asn | Ser | Ile | Leu | Ala | Arg | Val | Tyr | Arg | Asp | Phe | Gln | Glu | Leu |
|     |     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |
| Leu | Met | Asn | Ala | Pro | Glu | Ser | Gln | His | Leu | Gly | Arg | Ile | Trp | Thr | Glu |
|     |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |
| Leu | His | Ile | Leu | Ser | Gln | Phe | Met | Asp | Thr | Leu | Arg | Thr | His | Pro | Glu |
|     |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     | 175 |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     |     |     |     |     | 210 |     |     |     |     |     |     |     |     |     | 220 |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
|     |     |     |     |     | 225 |     |     |     |     |     |     |     |     |     | 240 |
|     |     |     |     |     | 230 |     |     |     |     |     |     |     |     |     |     |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     |     |     | 245 |     |     |     |     |     |     |     |     |     | 255 |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     |     |     |     | 260 |     |     |     |     |     |     |     |     |     | 270 |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     |     |     |     |     | 275 |     |     |     |     |     |     |     |     |     | 285 |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
| 290 |     |     |     |     |     | 295 |     |     |     |     |     | 300 |     |     |     |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |
|     |     |     |     | 325 |     |     |     |     |     | 330 |     |     |     | 335 |     |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |
|     |     |     | 355 |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |
|     |     |     |     | 370 |     |     | 375 |     |     |     |     | 380 |     |     |     |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
| 385 |     |     |     |     |     | 390 |     |     |     | 395 |     |     |     |     | 400 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     | 415 |     |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |
|     |     |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu |
|     |     |     |     | 450 |     |     | 455 |     |     |     |     | 460 |     |     |     |
| Asn | Arg | Gln | Leu | Gly | Glu | Glu | Gly | Ile | Thr | Ala | Glu | Ala | Ile | Leu | Asn |
| 465 |     |     |     |     |     | 470 |     |     |     | 475 |     |     |     |     | 480 |
| Phe | Leu | Tyr | Lys | Gly | Pro | Arg | Glu | Ser | Gln | Ala | Asp | Asp | Met | Ala | Asn |
|     |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     | 495 |     |
| Phe | Asp | Trp | Arg | Asp | Ile | Phe | Asn | Ile | Thr | Asp | Arg | Thr | Leu | Arg | Leu |
|     |     |     |     | 500 |     |     |     |     | 505 |     |     |     | 510 |     |     |
| Val | Asn | Gln | Tyr | Leu | Glu | Cys | Leu | Val | Leu | Asp | Lys | Phe | Glu | Ser | Tyr |
|     |     |     |     | 515 |     |     |     | 520 |     |     |     |     | 525 |     |     |
| Asn | Asp | Glu | Thr | Gln | Leu | Thr | Gln | Arg | Ala | Leu | Ser | Leu | Leu | Glu | Glu |
|     |     |     |     | 530 |     |     | 535 |     |     |     | 540 |     |     |     |     |
| Asn | Met | Phe | Trp | Ala | Gly | Val | Val | Phe | Pro | Asp | Met | Tyr | Pro | Trp | Thr |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Ser | Ser | Leu | Pro | Pro | His | Val | Lys | Tyr | Lys | Ile | Arg | Met | Asp | Ile | Asp |
|     |     |     |     | 565 |     |     |     |     |     | 570 |     |     |     | 575 |     |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly |
|     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe |

|                                                                 |                                     |     |
|-----------------------------------------------------------------|-------------------------------------|-----|
| 595                                                             | 600                                 | 605 |
| Ala Tyr Leu Gln Asp Met Val                                     | Glu Gln Gly Ile Thr Arg Ser Gln Val |     |
| 610                                                             | 615                                 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |                                     |     |
| 625                                                             | 630                                 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |                                     | 640 |
|                                                                 | 645                                 | 650 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |                                     | 655 |
|                                                                 | 660                                 | 665 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |                                     | 670 |
| 675                                                             | 680                                 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |                                     |     |
| 690                                                             | 695                                 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |                                     |     |
| 705                                                             | 710                                 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |                                     |     |
|                                                                 | 725                                 | 730 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |                                     | 735 |
|                                                                 | 740                                 | 745 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |                                     | 750 |
| 755                                                             | 760                                 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |                                     |     |
| 770                                                             | 775                                 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |                                     |     |
| 785                                                             | 790                                 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |                                     |     |
|                                                                 | 805                                 | 810 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |                                     | 815 |
|                                                                 | 820                                 | 825 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |                                     | 830 |
|                                                                 | 835                                 | 840 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |                                     | 845 |
|                                                                 | 850                                 | 855 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |                                     |     |
| 865                                                             | 870                                 | 875 |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |                                     | 880 |
|                                                                 | 885                                 | 890 |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |                                     | 895 |
|                                                                 | 900                                 | 905 |
|                                                                 |                                     | 910 |

|                                                                 |      |           |
|-----------------------------------------------------------------|------|-----------|
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |           |
| 915                                                             | 920  | 925       |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |           |
| 930                                                             | 935  | 940       |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |           |
| 945                                                             | 950  | 955 960   |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |           |
|                                                                 | 965  | 970 975   |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |           |
|                                                                 | 980  | 985 990   |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |           |
|                                                                 | 995  | 1000 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |           |
| 1010                                                            | 1015 | 1020      |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |           |
| 1025                                                            | 1030 | 1035 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |           |
|                                                                 | 1045 | 1050 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |           |
|                                                                 | 1060 | 1065 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |           |
|                                                                 | 1075 | 1080 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |           |
|                                                                 | 1090 | 1095 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |           |
| 1105                                                            | 1110 | 1115 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |           |
|                                                                 | 1125 | 1130 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |           |
|                                                                 | 1140 | 1145 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |           |
|                                                                 | 1155 | 1160 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Leu Ser Tyr Asp Thr |      |           |
|                                                                 | 1170 | 1175 1180 |
| Glu Ile Leu Thr Val Glu Tyr Gly Phe Leu Pro Ile Gly Lys Ile Val |      |           |
| 1185                                                            | 1190 | 1195 1200 |
| Glu Glu Arg Ile Glu Cys Thr Val Tyr Thr Val Asp Lys Asn Gly Phe |      |           |
|                                                                 | 1205 | 1210 1215 |
| Val Tyr Thr Gln Pro Ile Ala Gln Trp His Asn Arg Gly Glu Gln Glu |      |           |



|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1220                                                            | 1225 | 1230 |
| Val Phe Glu Tyr Cys Leu Glu Asp Gly Ser Ile Ile Arg Ala Thr Lys |      |      |
| 1235                                                            | 1240 | 1245 |
| Asp His Lys Phe Met Thr Thr Asp Gly Gln Met Leu Pro Ile Asp Glu |      |      |
| 1250                                                            | 1255 | 1260 |
| Ile Phe Glu Arg Gly Leu Asp Leu Lys Gln Val Asp Gly Leu Pro     |      |      |
| 1265                                                            | 1270 | 1275 |
| <210> 94                                                        |      |      |
| <211> 1131                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1179-CfaCmut                                        |      |      |
| <400> 94                                                        |      |      |
| Met Val Lys Ile Ile Ser Arg Lys Ser Leu Gly Thr Gln Asn Val Tyr |      |      |
| 1 5 10 15                                                       |      |      |
| Asp Ile Gly Val Gly Glu Pro His Asn Phe Leu Leu Lys Asn Gly Leu |      |      |
| 20 25 30                                                        |      |      |
| Val Ala Ser Asn Cys Ser Ser Lys Gly Phe Ser Thr Thr Cys Pro Ala |      |      |
| 35 40 45                                                        |      |      |
| His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp Gly Asp Val Asn |      |      |
| 50 55 60                                                        |      |      |
| Glu Leu Met Asp Val Val Leu His His Val Pro Glu Ala Lys Leu Val |      |      |
| 65 70 75 80                                                     |      |      |
| Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro Asn Lys Asn Phe |      |      |
| 85 90 95                                                        |      |      |
| Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu Glu Glu Thr Leu |      |      |
| 100 105 110                                                     |      |      |
| Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp Thr Pro Leu Glu |      |      |
| 115 120 125                                                     |      |      |
| Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser Gly Pro Leu Phe |      |      |
| 130 135 140                                                     |      |      |
| Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn Val Asn Pro Arg His Pro |      |      |
| 145 150 155 160                                                 |      |      |
| Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro Gln Asp Ser Asn |      |      |
| 165 170 175                                                     |      |      |
| Val Cys Ser Pro Gly Ala Pro Ala Ala His Pro Glu Gly Gln Pro Pro |      |      |
| 180 185 190                                                     |      |      |
| Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr Gly Thr Gln Leu |      |      |

|                                                                 |                                                 |     |
|-----------------------------------------------------------------|-------------------------------------------------|-----|
| 195                                                             | 200                                             | 205 |
| Val Leu Gln His                                                 | Val Gln Ala Leu Leu Val Lys Arg Phe Gln His Thr |     |
| 210                                                             | 215                                             | 220 |
| Ile Arg Ser His Lys Asp Phe Leu Ala Gln Ile Val Leu Pro Ala Thr |                                                 |     |
| 225                                                             | 230                                             | 235 |
| Phe Val Phe Leu Ala Leu Met Leu Ser Ile Val Ile Pro Pro Phe Gly |                                                 |     |
| 245                                                             | 250                                             | 255 |
| Glu Tyr Pro Ala Leu Thr Leu His Pro Trp Ile Tyr Gly Gln Gln Tyr |                                                 |     |
| 260                                                             | 265                                             | 270 |
| Thr Phe Phe Ser Met Asp Glu Pro Gly Ser Glu Gln Phe Thr Val Leu |                                                 |     |
| 275                                                             | 280                                             | 285 |
| Ala Asp Val Leu Leu Asn Lys Pro Gly Phe Gly Asn Arg Cys Leu Lys |                                                 |     |
| 290                                                             | 295                                             | 300 |
| Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys |                                                 |     |
| 305                                                             | 310                                             | 315 |
| Thr Pro Ser Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys |                                                 |     |
| 325                                                             | 330                                             | 335 |
| Trp Thr Gln Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu |                                                 |     |
| 340                                                             | 345                                             | 350 |
| Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro |                                                 |     |
| 355                                                             | 360                                             | 365 |
| Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr |                                                 |     |
| 370                                                             | 375                                             | 380 |
| Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile |                                                 |     |
| 385                                                             | 390                                             | 395 |
| Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly |                                                 |     |
| 405                                                             | 410                                             | 415 |
| Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu |                                                 |     |
| 420                                                             | 425                                             | 430 |
| Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser |                                                 |     |
| 435                                                             | 440                                             | 445 |
| Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu |                                                 |     |
| 450                                                             | 455                                             | 460 |
| Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys |                                                 |     |
| 465                                                             | 470                                             | 475 |
| Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile |                                                 |     |
| 485                                                             | 490                                             | 495 |
| Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile |                                                 |     |
| 500                                                             | 505                                             | 510 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu |     |     |
| 515                                                             | 520 | 525 |
| Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val |     |     |
| 530                                                             | 535 | 540 |
| Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile |     |     |
| 545                                                             | 550 | 555 |
| Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val |     |     |
|                                                                 | 565 | 570 |
| Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn |     |     |
|                                                                 | 580 | 585 |
| Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln |     |     |
|                                                                 | 595 | 600 |
| Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu |     |     |
| 610                                                             | 615 | 620 |
| Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser |     |     |
| 625                                                             | 630 | 635 |
| Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala |     |     |
|                                                                 | 645 | 650 |
| Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu |     |     |
|                                                                 | 660 | 665 |
| Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg |     |     |
|                                                                 | 675 | 680 |
| Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile |     |     |
| 690                                                             | 695 | 700 |
| Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly |     |     |
| 705                                                             | 710 | 715 |
| Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn |     |     |
|                                                                 | 725 | 730 |
| Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu |     |     |
|                                                                 | 740 | 745 |
| Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr |     |     |
|                                                                 | 755 | 760 |
| Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln |     |     |
|                                                                 | 770 | 775 |
| Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu |     |     |
| 785                                                             | 790 | 795 |
| Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu |     |     |
|                                                                 | 805 | 810 |
| Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn |     |     |

|      |     |     |     |     |     |      |     |     |     |     |     |      |     |     |     |  |  |      |  |
|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|-----|--|--|------|--|
| 820  |     |     |     |     |     | 825  |     |     |     |     |     | 830  |     |     |     |  |  |      |  |
| Gly  | Ala | Gly | Lys | Thr | Thr | Thr  | Phe | Lys | Met | Leu | Thr | Gly  | Asp | Thr | Thr |  |  |      |  |
| 835  |     |     |     |     |     | 840  |     |     |     |     |     | 845  |     |     |     |  |  |      |  |
| Val  | Thr | Ser | Gly | Asp | Ala | Thr  | Val | Ala | Gly | Lys | Ser | Ile  | Leu | Thr | Asn |  |  |      |  |
| 850  |     |     |     |     |     | 855  |     |     |     |     |     | 860  |     |     |     |  |  |      |  |
| Ile  | Ser | Glu | Val | His | Gln | Asn  | Met | Gly | Tyr | Cys | Pro | Gln  | Phe | Asp | Ala |  |  |      |  |
| 865  |     |     |     |     |     | 870  |     |     |     |     |     | 875  |     |     |     |  |  | 880  |  |
| Ile  | Asp | Glu | Leu | Leu | Thr | Gly  | Arg | Glu | His | Leu | Tyr | Leu  | Tyr | Ala | Arg |  |  |      |  |
| 885  |     |     |     |     |     | 890  |     |     |     |     |     | 895  |     |     |     |  |  |      |  |
| Leu  | Arg | Gly | Val | Pro | Ala | Glu  | Glu | Ile | Glu | Lys | Val | Ala  | Asn | Trp | Ser |  |  |      |  |
| 900  |     |     |     |     |     | 905  |     |     |     |     |     | 910  |     |     |     |  |  |      |  |
| Ile  | Lys | Ser | Leu | Gly | Leu | Thr  | Val | Tyr | Ala | Asp | Cys | Leu  | Ala | Gly | Thr |  |  |      |  |
| 915  |     |     |     |     |     | 920  |     |     |     |     |     | 925  |     |     |     |  |  |      |  |
| Tyr  | Ser | Gly | Gly | Asn | Lys | Arg  | Lys | Leu | Ser | Thr | Ala | Ile  | Ala | Leu | Ile |  |  |      |  |
| 930  |     |     |     |     |     | 935  |     |     |     |     |     | 940  |     |     |     |  |  |      |  |
| Gly  | Cys | Pro | Pro | Leu | Val | Leu  | Leu | Asp | Glu | Pro | Thr | Thr  | Gly | Met | Asp |  |  |      |  |
| 945  |     |     |     |     |     | 950  |     |     |     |     |     | 955  |     |     |     |  |  | 960  |  |
| Pro  | Gln | Ala | Arg | Arg | Met | Leu  | Trp | Asn | Val | Ile | Val | Ser  | Ile | Ile | Arg |  |  |      |  |
| 965  |     |     |     |     |     | 970  |     |     |     |     |     | 975  |     |     |     |  |  |      |  |
| Glu  | Gly | Arg | Ala | Val | Val | Leu  | Thr | Ser | His | Ser | Met | Glu  | Glu | Cys | Glu |  |  |      |  |
| 980  |     |     |     |     |     | 985  |     |     |     |     |     | 990  |     |     |     |  |  |      |  |
| Ala  | Leu | Cys | Thr | Arg | Leu | Ala  | Ile | Met | Val | Lys | Gly | Ala  | Phe | Arg | Cys |  |  |      |  |
| 995  |     |     |     |     |     | 1000 |     |     |     |     |     | 1005 |     |     |     |  |  |      |  |
| Met  | Gly | Thr | Ile | Gln | His | Leu  | Lys | Ser | Lys | Phe | Gly | Asp  | Gly | Tyr | Ile |  |  |      |  |
| 1010 |     |     |     |     |     | 1015 |     |     |     |     |     | 1020 |     |     |     |  |  |      |  |
| Val  | Thr | Met | Lys | Ile | Lys | Ser  | Pro | Lys | Asp | Asp | Leu | Leu  | Pro | Asp | Leu |  |  |      |  |
| 1025 |     |     |     |     |     | 1030 |     |     |     |     |     | 1035 |     |     |     |  |  | 1040 |  |
| Asn  | Pro | Val | Glu | Gln | Phe | Phe  | Gln | Gly | Asn | Phe | Pro | Gly  | Ser | Val | Gln |  |  |      |  |
| 1045 |     |     |     |     |     | 1050 |     |     |     |     |     | 1055 |     |     |     |  |  |      |  |
| Arg  | Glu | Arg | His | Tyr | Asn | Met  | Leu | Gln | Phe | Gln | Val | Ser  | Ser | Ser | Ser |  |  |      |  |
| 1060 |     |     |     |     |     | 1065 |     |     |     |     |     | 1070 |     |     |     |  |  |      |  |
| Leu  | Ala | Arg | Ile | Phe | Gln | Leu  | Leu | Leu | Ser | His | Lys | Asp  | Ser | Leu | Leu |  |  |      |  |
| 1075 |     |     |     |     |     | 1080 |     |     |     |     |     | 1085 |     |     |     |  |  |      |  |
| Ile  | Glu | Glu | Tyr | Ser | Val | Thr  | Gln | Thr | Thr | Leu | Asp | Gln  | Val | Phe | Val |  |  |      |  |
| 1090 |     |     |     |     |     | 1095 |     |     |     |     |     | 1100 |     |     |     |  |  |      |  |
| Asn  | Phe | Ala | Lys | Gln | Gln | Thr  | Glu | Ser | His | Asp | Leu | Pro  | Leu | His | Pro |  |  |      |  |
| 1105 |     |     |     |     |     | 1110 |     |     |     |     |     | 1115 |     |     |     |  |  | 1120 |  |
| Arg  | Ala | Ala | Gly | Ala | Ser | Arg  | Gln | Ala | Gln | Asp |     |      |     |     |     |  |  |      |  |
| 1125 |     |     |     |     |     | 1130 |     |     |     |     |     |      |     |     |     |  |  |      |  |

&lt;210&gt; 95

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; ABCA4N-1096

&lt;400&gt; 95

```

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr
1           5           10           15
Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro
20           25           30
Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu
35           40           45
Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala
50           55           60
Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro
65           70           75           80
Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn
85           90           95
Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
100          105          110
Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
115          120          125
Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
130          135          140
Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu
145          150          155          160
Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
165          170          175
Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala
180          185          190
His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala
195          200          205
Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr
210          215          220
Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile
225          230          235          240
Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val
245          250          255

```

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |  |
| Val | Val | Glu | Lys | Thr | Asn | Lys | Ile | Lys | Asp | Arg | Tyr | Trp | Asp | Ser | Gly |  |  |
|     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |  |  |
| Pro | Arg | Ala | Asp | Pro | Val | Glu | Asp | Phe | Arg | Tyr | Ile | Trp | Gly | Gly | Phe |  |  |
|     |     |     |     | 595 |     |     |     | 600 |     |     |     |     |     | 605 |     |  |  |
| Ala | Tyr | Leu | Gln | Asp | Met | Val | Glu | Gln | Gly | Ile | Thr | Arg | Ser | Gln | Val |  |  |
|     |     |     |     | 610 |     |     |     | 615 |     |     |     |     |     | 620 |     |  |  |
| Gln | Ala | Glu | Ala | Pro | Val | Gly | Ile | Tyr | Leu | Gln | Gln | Met | Pro | Tyr | Pro |  |  |
| 625 |     |     |     |     |     | 630 |     |     |     | 635 |     |     |     | 640 |     |  |  |
| Cys | Phe | Val | Asp | Asp | Ser | Phe | Met | Ile | Ile | Leu | Asn | Arg | Cys | Phe | Pro |  |  |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |  |  |
| Ile | Phe | Met | Val | Leu | Ala | Trp | Ile | Tyr | Ser | Val | Ser | Met | Thr | Val | Lys |  |  |
|     |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |  |  |
| Ser | Ile | Val | Leu | Glu | Lys | Glu | Leu | Arg | Leu | Lys | Glu | Thr | Leu | Lys | Asn |  |  |
|     |     |     |     | 675 |     |     |     | 680 |     |     |     |     |     | 685 |     |  |  |
| Gln | Gly | Val | Ser | Asn | Ala | Val | Ile | Trp | Cys | Thr | Trp | Phe | Leu | Asp | Ser |  |  |
|     |     |     |     | 690 |     |     |     | 695 |     |     |     |     |     | 700 |     |  |  |
| Phe | Ser | Ile | Met | Ser | Met | Ser | Ile | Phe | Leu | Leu | Thr | Ile | Phe | Ile | Met |  |  |
| 705 |     |     |     |     |     | 710 |     |     |     | 715 |     |     |     | 720 |     |  |  |
| His | Gly | Arg | Ile | Leu | His | Tyr | Ser | Asp | Pro | Phe | Ile | Leu | Phe | Leu | Phe |  |  |
|     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |  |  |
| Leu | Leu | Ala | Phe | Ser | Thr | Ala | Thr | Ile | Met | Leu | Cys | Phe | Leu | Leu | Ser |  |  |
|     |     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |  |  |
| Thr | Phe | Phe | Ser | Lys | Ala | Ser | Leu | Ala | Ala | Ala | Cys | Ser | Gly | Val | Ile |  |  |
|     |     |     |     | 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |  |  |
| Tyr | Phe | Thr | Leu | Tyr | Leu | Pro | His | Ile | Leu | Cys | Phe | Ala | Trp | Gln | Asp |  |  |
|     |     |     |     | 770 |     |     |     | 775 |     |     |     |     |     | 780 |     |  |  |
| Arg | Met | Thr | Ala | Glu | Leu | Lys | Lys | Ala | Val | Ser | Leu | Leu | Ser | Pro | Val |  |  |
| 785 |     |     |     |     |     | 790 |     |     |     | 795 |     |     |     | 800 |     |  |  |
| Ala | Phe | Gly | Phe | Gly | Thr | Glu | Tyr | Leu | Val | Arg | Phe | Glu | Glu | Gln | Gly |  |  |
|     |     |     |     | 805 |     |     |     |     | 810 |     |     |     |     | 815 |     |  |  |
| Leu | Gly | Leu | Gln | Trp | Ser | Asn | Ile | Gly | Asn | Ser | Pro | Thr | Glu | Gly | Asp |  |  |
|     |     |     |     | 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |  |  |
| Glu | Phe | Ser | Phe | Leu | Leu | Ser | Met | Gln | Met | Met | Leu | Leu | Asp | Ala | Ala |  |  |
|     |     |     |     | 835 |     |     |     | 840 |     |     |     |     |     | 845 |     |  |  |
| Val | Tyr | Gly | Leu | Leu | Ala | Trp | Tyr | Leu | Asp | Gln | Val | Phe | Pro | Gly | Asp |  |  |
|     |     |     |     | 850 |     |     |     | 855 |     |     |     |     |     | 860 |     |  |  |
| Tyr | Gly | Thr | Pro | Leu | Pro | Trp | Tyr | Phe | Leu | Leu | Gln | Glu | Ser | Tyr | Trp |  |  |
| 865 |     |     |     |     |     | 870 |     |     |     | 875 |     |     |     | 880 |     |  |  |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
| 1045                                                            | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |
| 1060                                                            | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr                                     |      |      |
| 1090                                                            | 1095 |      |
| <210> 96                                                        |      |      |
| <211> 1178                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4C-1096                                               |      |      |
| <400> 96                                                        |      |      |
| Ser Arg Arg Ser Ile Trp Asp Leu Leu Leu Lys Tyr Arg Ser Gly Arg |      |      |
| 1                                                               | 5    | 10   |
| Thr Ile Ile Met Ser Thr His His Met Asp Glu Ala Asp Leu Leu Gly |      |      |
| 20                                                              | 25   | 30   |



|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Arg | Ile | Ala | Ile | Ile | Ala | Gln | Gly | Arg | Leu | Tyr | Cys | Ser | Gly | Thr |
| 35  |     |     |     | 40  |     |     |     | 45  |     |     |     |     |     |     |     |
| Pro | Leu | Phe | Leu | Lys | Asn | Cys | Phe | Gly | Thr | Gly | Leu | Tyr | Leu | Thr | Leu |
| 50  |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |     |     |
| Val | Arg | Lys | Met | Lys | Asn | Ile | Gln | Ser | Gln | Arg | Lys | Gly | Ser | Glu | Gly |
| 65  |     |     |     | 70  |     |     |     | 75  |     |     |     | 80  |     |     |     |
| Thr | Cys | Ser | Cys | Ser | Ser | Lys | Gly | Phe | Ser | Thr | Thr | Cys | Pro | Ala | His |
| 85  |     |     |     | 90  |     |     |     | 95  |     |     |     |     |     |     |     |
| Val | Asp | Asp | Leu | Thr | Pro | Glu | Gln | Val | Leu | Asp | Gly | Asp | Val | Asn | Glu |
| 100 |     |     |     | 105 |     |     |     | 110 |     |     |     |     |     |     |     |
| Leu | Met | Asp | Val | Val | Leu | His | His | Val | Pro | Glu | Ala | Lys | Leu | Val | Glu |
| 115 |     |     |     | 120 |     |     |     | 125 |     |     |     |     |     |     |     |
| Cys | Ile | Gly | Gln | Glu | Leu | Ile | Phe | Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys |
| 130 |     |     |     | 135 |     |     |     | 140 |     |     |     |     |     |     |     |
| His | Arg | Ala | Tyr | Ala | Ser | Leu | Phe | Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala |
| 145 |     |     |     | 150 |     |     |     | 155 |     |     |     | 160 |     |     |     |
| Asp | Leu | Gly | Leu | Ser | Ser | Phe | Gly | Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu |
| 165 |     |     |     | 170 |     |     |     | 175 |     |     |     |     |     |     |     |
| Ile | Phe | Leu | Lys | Val | Thr | Glu | Asp | Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala |
| 180 |     |     |     | 185 |     |     |     | 190 |     |     |     |     |     |     |     |
| Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu | Asn | Val | Asn | Pro | Arg | His | Pro | Cys |
| 195 |     |     |     | 200 |     |     |     | 205 |     |     |     |     |     |     |     |
| Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly | Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val |
| 210 |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |     |     |
| Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala | His | Pro | Glu | Gly | Gln | Pro | Pro | Pro |
| 225 |     |     |     | 230 |     |     |     | 235 |     |     |     | 240 |     |     |     |
| Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln | Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val |
| 245 |     |     |     | 250 |     |     |     | 255 |     |     |     |     |     |     |     |
| Leu | Gln | His | Val | Gln | Ala | Leu | Leu | Val | Lys | Arg | Phe | Gln | His | Thr | Ile |
| 260 |     |     |     | 265 |     |     |     | 270 |     |     |     |     |     |     |     |
| Arg | Ser | His | Lys | Asp | Phe | Leu | Ala | Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe |
| 275 |     |     |     | 280 |     |     |     | 285 |     |     |     |     |     |     |     |
| Val | Phe | Leu | Ala | Leu | Met | Leu | Ser | Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu |
| 290 |     |     |     | 295 |     |     |     | 300 |     |     |     |     |     |     |     |
| Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro | Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr |
| 305 |     |     |     | 310 |     |     |     | 315 |     |     |     | 320 |     |     |     |
| Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly | Ser | Glu | Gln | Phe | Thr | Val | Leu | Ala |
| 325 |     |     |     | 330 |     |     |     | 335 |     |     |     |     |     |     |     |
| Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly | Phe | Gly | Asn | Arg | Cys | Leu | Lys | Glu |

|                                                                 |     |     |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|-----|-----|
|                                                                 | 340 |     | 345 |     | 350 |
| Gly Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr |     |     |     |     |     |
|                                                                 | 355 |     | 360 |     | 365 |
| Pro Ser Val Ser Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp |     |     |     |     |     |
|                                                                 | 370 |     | 375 |     | 380 |
| Thr Gln Val Asn Pro Ser Pro Ser Cys Arg Cys Ser Thr Arg Glu Lys |     |     |     |     |     |
| 385                                                             |     | 390 |     | 395 | 400 |
| Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro Pro |     |     |     |     |     |
|                                                                 | 405 |     | 410 |     | 415 |
| Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr Asp |     |     |     |     |     |
|                                                                 | 420 |     | 425 |     | 430 |
| Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile Arg |     |     |     |     |     |
|                                                                 | 435 |     | 440 |     | 445 |
| Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly Gly |     |     |     |     |     |
|                                                                 | 450 |     | 455 |     | 460 |
| Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu Ala |     |     |     |     |     |
| 465                                                             |     | 470 |     | 475 | 480 |
| Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser Gly |     |     |     |     |     |
|                                                                 | 485 |     | 490 |     | 495 |
| Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu Lys |     |     |     |     |     |
|                                                                 | 500 |     | 505 |     | 510 |
| His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys Gly |     |     |     |     |     |
|                                                                 | 515 |     | 520 |     | 525 |
| Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile Leu |     |     |     |     |     |
|                                                                 | 530 |     | 535 |     | 540 |
| Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile Thr |     |     |     |     |     |
| 545                                                             |     | 550 |     | 555 | 560 |
| Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu Ile |     |     |     |     |     |
|                                                                 | 565 |     | 570 |     | 575 |
| Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val Ile |     |     |     |     |     |
|                                                                 | 580 |     | 585 |     | 590 |
| Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile Gln |     |     |     |     |     |
|                                                                 | 595 |     | 600 |     | 605 |
| Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val Ser |     |     |     |     |     |
|                                                                 | 610 |     | 615 |     | 620 |
| Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn Tyr |     |     |     |     |     |
| 625                                                             |     | 630 |     | 635 | 640 |
| Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln Lys |     |     |     |     |     |
|                                                                 | 645 |     | 650 |     | 655 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ala | Tyr | Thr | Ser | Pro | Glu | Asn | Leu | Pro | Ala | Leu | Val | Ala | Leu | Leu |
| 660 |     |     |     | 665 |     |     |     | 670 |     |     |     |     |     |     |     |
| Leu | Leu | Tyr | Gly | Trp | Ala | Val | Ile | Pro | Met | Met | Tyr | Pro | Ala | Ser | Phe |
| 675 |     |     |     | 680 |     |     |     | 685 |     |     |     |     |     |     |     |
| Leu | Phe | Asp | Val | Pro | Ser | Thr | Ala | Tyr | Val | Ala | Leu | Ser | Cys | Ala | Asn |
| 690 |     |     |     | 695 |     |     |     | 700 |     |     |     |     |     |     |     |
| Leu | Phe | Ile | Gly | Ile | Asn | Ser | Ser | Ala | Ile | Thr | Phe | Ile | Leu | Glu | Leu |
| 705 |     |     |     | 710 |     |     |     | 715 |     |     |     | 720 |     |     |     |
| Phe | Glu | Asn | Asn | Arg | Thr | Leu | Leu | Arg | Phe | Asn | Ala | Val | Leu | Arg | Lys |
| 725 |     |     |     | 730 |     |     |     | 735 |     |     |     |     |     |     |     |
| Leu | Leu | Ile | Val | Phe | Pro | His | Phe | Cys | Leu | Gly | Arg | Gly | Leu | Ile | Asp |
| 740 |     |     |     | 745 |     |     |     | 750 |     |     |     |     |     |     |     |
| Leu | Ala | Leu | Ser | Gln | Ala | Val | Thr | Asp | Val | Tyr | Ala | Arg | Phe | Gly | Glu |
| 755 |     |     |     | 760 |     |     |     | 765 |     |     |     |     |     |     |     |
| Glu | His | Ser | Ala | Asn | Pro | Phe | His | Trp | Asp | Leu | Ile | Gly | Lys | Asn | Leu |
| 770 |     |     |     | 775 |     |     |     | 780 |     |     |     |     |     |     |     |
| Phe | Ala | Met | Val | Val | Glu | Gly | Val | Val | Tyr | Phe | Leu | Leu | Thr | Leu | Leu |
| 785 |     |     |     | 790 |     |     |     | 795 |     |     |     | 800 |     |     |     |
| Val | Gln | Arg | His | Phe | Phe | Leu | Ser | Gln | Trp | Ile | Ala | Glu | Pro | Thr | Lys |
| 805 |     |     |     | 810 |     |     |     | 815 |     |     |     |     |     |     |     |
| Glu | Pro | Ile | Val | Asp | Glu | Asp | Asp | Asp | Val | Ala | Glu | Glu | Arg | Gln | Arg |
| 820 |     |     |     | 825 |     |     |     | 830 |     |     |     |     |     |     |     |
| Ile | Ile | Thr | Gly | Gly | Asn | Lys | Thr | Asp | Ile | Leu | Arg | Leu | His | Glu | Leu |
| 835 |     |     |     | 840 |     |     |     | 845 |     |     |     |     |     |     |     |
| Thr | Lys | Ile | Tyr | Pro | Gly | Thr | Ser | Ser | Pro | Ala | Val | Asp | Arg | Leu | Cys |
| 850 |     |     |     | 855 |     |     |     | 860 |     |     |     |     |     |     |     |
| Val | Gly | Val | Arg | Pro | Gly | Glu | Cys | Phe | Gly | Leu | Leu | Gly | Val | Asn | Gly |
| 865 |     |     |     | 870 |     |     |     | 875 |     |     |     | 880 |     |     |     |
| Ala | Gly | Lys | Thr | Thr | Thr | Phe | Lys | Met | Leu | Thr | Gly | Asp | Thr | Thr | Val |
| 885 |     |     |     | 890 |     |     |     | 895 |     |     |     |     |     |     |     |
| Thr | Ser | Gly | Asp | Ala | Thr | Val | Ala | Gly | Lys | Ser | Ile | Leu | Thr | Asn | Ile |
| 900 |     |     |     | 905 |     |     |     | 910 |     |     |     |     |     |     |     |
| Ser | Glu | Val | His | Gln | Asn | Met | Gly | Tyr | Cys | Pro | Gln | Phe | Asp | Ala | Ile |
| 915 |     |     |     | 920 |     |     |     | 925 |     |     |     |     |     |     |     |
| Asp | Glu | Leu | Leu | Thr | Gly | Arg | Glu | His | Leu | Tyr | Leu | Tyr | Ala | Arg | Leu |
| 930 |     |     |     | 935 |     |     |     | 940 |     |     |     |     |     |     |     |
| Arg | Gly | Val | Pro | Ala | Glu | Glu | Ile | Glu | Lys | Val | Ala | Asn | Trp | Ser | Ile |
| 945 |     |     |     | 950 |     |     |     | 955 |     |     |     | 960 |     |     |     |
| Lys | Ser | Leu | Gly | Leu | Thr | Val | Tyr | Ala | Asp | Cys | Leu | Ala | Gly | Thr | Tyr |

|                                                                 |      |  |      |  |      |
|-----------------------------------------------------------------|------|--|------|--|------|
|                                                                 | 965  |  | 970  |  | 975  |
| Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly |      |  |      |  |      |
|                                                                 | 980  |  | 985  |  | 990  |
| Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro |      |  |      |  |      |
|                                                                 | 995  |  | 1000 |  | 1005 |
| Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu |      |  |      |  |      |
|                                                                 | 1010 |  | 1015 |  | 1020 |
| Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala |      |  |      |  |      |
|                                                                 | 1025 |  | 1030 |  | 1035 |
| Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met |      |  |      |  |      |
|                                                                 | 1045 |  | 1050 |  | 1055 |
| Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val |      |  |      |  |      |
|                                                                 | 1060 |  | 1065 |  | 1070 |
| Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn |      |  |      |  |      |
|                                                                 | 1075 |  | 1080 |  | 1085 |
| Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg |      |  |      |  |      |
|                                                                 | 1090 |  | 1095 |  | 1100 |
| Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu |      |  |      |  |      |
|                                                                 | 1105 |  | 1110 |  | 1115 |
| Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile |      |  |      |  |      |
|                                                                 | 1125 |  | 1130 |  | 1135 |
| Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn |      |  |      |  |      |
|                                                                 | 1140 |  | 1145 |  | 1150 |
| Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg |      |  |      |  |      |
|                                                                 | 1155 |  | 1160 |  | 1165 |
| Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp                         |      |  |      |  |      |
|                                                                 | 1170 |  | 1175 |  |      |
| <210> 97                                                        |      |  |      |  |      |
| <211> 1184                                                      |      |  |      |  |      |
| <212> PRT                                                       |      |  |      |  |      |
| <213> 人工序列(Artificial Sequence)                                 |      |  |      |  |      |
| <220>                                                           |      |  |      |  |      |
| <223> ABCA4N-1185                                               |      |  |      |  |      |
| <400> 97                                                        |      |  |      |  |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |  |      |  |      |
| 1                                                               | 5    |  | 10   |  | 15   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |  |      |  |      |
|                                                                 | 20   |  | 25   |  | 30   |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |  |      |  |      |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 35                                                              | 40  | 45  |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |     |     |
| 50                                                              | 55  | 60  |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |     |     |
| 65                                                              | 70  | 75  |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |     |     |
| 85                                                              | 90  | 95  |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |
| 100                                                             | 105 | 110 |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
|                                                                 | 405 | 410 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |
|                                                                 | 420 | 425 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
|                                                                 | 435 | 440 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
|                                                                 | 450 | 455 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
|                                                                 | 485 | 490 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
|                                                                 | 500 | 505 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
|                                                                 | 515 | 520 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
|                                                                 | 530 | 535 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
|                                                                 | 565 | 570 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
|                                                                 | 580 | 585 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
|                                                                 | 595 | 600 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
|                                                                 | 610 | 615 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
|                                                                 | 645 | 650 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |     |     |
| 770                                                             | 775 | 780 |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |     |     |
| 785                                                             | 790 | 795 |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |     |     |
| 805                                                             | 810 | 815 |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |     |     |
| 820                                                             | 825 | 830 |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |     |     |
| 835                                                             | 840 | 845 |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |     |     |
| 850                                                             | 855 | 860 |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |     |     |
| 865                                                             | 870 | 875 |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |     |     |
| 885                                                             | 890 | 895 |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |     |     |
| 900                                                             | 905 | 910 |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |     |     |
| 915                                                             | 920 | 925 |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |     |     |
| 930                                                             | 935 | 940 |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |     |     |
| 945                                                             | 950 | 955 |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |     |     |
| 965                                                             | 970 | 975 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |
| 980                                                             | 985  | 990  |      |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |
| 995                                                             | 1000 | 1005 |      |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
| 1010                                                            | 1015 | 1020 |      |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
| 1045                                                            | 1050 | 1055 |      |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
| 1060                                                            | 1065 | 1070 |      |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
| 1075                                                            | 1080 | 1085 |      |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
| 1090                                                            | 1095 | 1100 |      |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
| 1125                                                            | 1130 | 1135 |      |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |      |
| 1140                                                            | 1145 | 1150 |      |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |      |
| 1155                                                            | 1160 | 1165 |      |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |      |
| 1170                                                            | 1175 | 1180 |      |
| <210> 98                                                        |      |      |      |
| <211> 1089                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4C-1185                                               |      |      |      |
| <400> 98                                                        |      |      |      |
| Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val |      |      |      |
| 20                                                              | 25   | 30   |      |
| Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu |      |      |      |
| 35                                                              | 40   | 45   |      |



|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr | Ala | Ser | Leu | Phe | Arg |
| 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu | Ser | Ser | Phe | Gly | Ile |
| 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |     |
| Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys | Val | Thr | Glu | Asp | Ser |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln | Gln | Lys | Arg | Glu | Asn |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |
| Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly | Pro | Arg | Glu | Lys | Ala | Gly | Gln |
|     |     | 115 |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |
| Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly | Ala | Pro | Ala | Ala | His |
|     |     | 130 |     |     |     | 135 |     |     |     | 140 |     |     |     |     |     |
| Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys | Pro | Gly | Pro | Gln | Leu |
| 145 |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |     |
| Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln | His | Val | Gln | Ala | Leu | Leu | Val |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     | 175 |     |     |
| Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser | His | Lys | Asp | Phe | Leu | Ala | Gln |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |
| Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala | Leu | Met | Leu | Ser | Ile |
|     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |
| Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu | Thr | Leu | His | Pro | Trp |
|     |     | 210 |     |     |     | 215 |     |     |     | 220 |     |     |     |     |     |
| Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met | Asp | Glu | Pro | Gly | Ser |
| 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |
| Glu | Gln | Phe | Thr | Val | Leu | Ala | Asp | Val | Leu | Leu | Asn | Lys | Pro | Gly | Phe |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Gly | Asn | Arg | Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro | Glu | Tyr | Pro | Cys | Gly |
|     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |
| Asn | Ser | Thr | Pro | Trp | Lys | Thr | Pro | Ser | Val | Ser | Pro | Asn | Ile | Thr | Gln |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Leu | Phe | Gln | Lys | Gln | Lys | Trp | Thr | Gln | Val | Asn | Pro | Ser | Pro | Ser | Cys |
|     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Arg | Cys | Ser | Thr | Arg | Glu | Lys | Leu | Thr | Met | Leu | Pro | Glu | Cys | Pro | Glu |
| 305 |     |     |     |     | 310 |     |     |     | 315 |     |     |     |     | 320 |     |
| Gly | Ala | Gly | Gly | Leu | Pro | Pro | Pro | Gln | Arg | Thr | Gln | Arg | Ser | Thr | Glu |
|     |     |     |     | 325 |     |     |     | 330 |     |     |     |     |     | 335 |     |
| Ile | Leu | Gln | Asp | Leu | Thr | Asp | Arg | Asn | Ile | Ser | Asp | Phe | Leu | Val | Lys |
|     |     |     | 340 |     |     |     | 345 |     |     |     |     | 350 |     |     |     |
| Thr | Tyr | Pro | Ala | Leu | Ile | Arg | Ser | Ser | Leu | Lys | Ser | Lys | Phe | Trp | Val |

|                                 |                                 |                 |
|---------------------------------|---------------------------------|-----------------|
| 355                             | 360                             | 365             |
| Asn Glu Gln Arg Tyr Gly Gly     | Ile Ser Ile Gly Gly             | Lys Leu Pro Val |
| 370                             | 375                             | 380             |
| Val Pro Ile Thr Gly Glu Ala Leu | Val Gly Phe Leu Ser Asp Leu Gly |                 |
| 385                             | 390                             | 395             |
| Arg Ile Met Asn Val Ser Gly Gly | Pro Ile Thr Arg Glu Ala Ser Lys |                 |
| 405                             | 410                             | 415             |
| Glu Ile Pro Asp Phe Leu Lys His | Leu Glu Thr Glu Asp Asn Ile Lys |                 |
| 420                             | 425                             | 430             |
| Val Trp Phe Asn Asn Lys Gly Trp | His Ala Leu Val Ser Phe Leu Asn |                 |
| 435                             | 440                             | 445             |
| Val Ala His Asn Ala Ile Leu Arg | Ala Ser Leu Pro Lys Asp Arg Ser |                 |
| 450                             | 455                             | 460             |
| Pro Glu Glu Tyr Gly Ile Thr Val | Ile Ser Gln Pro Leu Asn Leu Thr |                 |
| 465                             | 470                             | 475             |
| Lys Glu Gln Leu Ser Glu Ile Thr | Val Leu Thr Thr Ser Val Asp Ala |                 |
| 485                             | 490                             | 495             |
| Val Val Ala Ile Cys Val Ile Phe | Ser Met Ser Phe Val Pro Ala Ser |                 |
| 500                             | 505                             | 510             |
| Phe Val Leu Tyr Leu Ile Gln Glu | Arg Val Asn Lys Ser Lys His Leu |                 |
| 515                             | 520                             | 525             |
| Gln Phe Ile Ser Gly Val Ser Pro | Thr Thr Tyr Trp Val Thr Asn Phe |                 |
| 530                             | 535                             | 540             |
| Leu Trp Asp Ile Met Asn Tyr Ser | Val Ser Ala Gly Leu Val Val Gly |                 |
| 545                             | 550                             | 555             |
| Ile Phe Ile Gly Phe Gln Lys Lys | Ala Tyr Thr Ser Pro Glu Asn Leu |                 |
| 565                             | 570                             | 575             |
| Pro Ala Leu Val Ala Leu Leu Leu | Tyr Gly Trp Ala Val Ile Pro     |                 |
| 580                             | 585                             | 590             |
| Met Met Tyr Pro Ala Ser Phe Leu | Phe Asp Val Pro Ser Thr Ala Tyr |                 |
| 595                             | 600                             | 605             |
| Val Ala Leu Ser Cys Ala Asn Leu | Phe Ile Gly Ile Asn Ser Ser Ala |                 |
| 610                             | 615                             | 620             |
| Ile Thr Phe Ile Leu Glu Leu Phe | Glu Asn Asn Arg Thr Leu Leu Arg |                 |
| 625                             | 630                             | 635             |
| Phe Asn Ala Val Leu Arg Lys Leu | Leu Ile Val Phe Pro His Phe Cys |                 |
| 645                             | 650                             | 655             |
| Leu Gly Arg Gly Leu Ile Asp Leu | Ala Leu Ser Gln Ala Val Thr Asp |                 |
| 660                             | 665                             | 670             |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp |     |     |
| 675                                                             | 680 | 685 |
| Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val |     |     |
| 690                                                             | 695 | 700 |
| Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln |     |     |
| 705                                                             | 710 | 715 |
| Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp |     |     |
|                                                                 | 725 | 730 |
| Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp |     |     |
|                                                                 | 740 | 745 |
| Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser |     |     |
|                                                                 | 755 | 760 |
| Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe |     |     |
|                                                                 | 770 | 775 |
| Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met |     |     |
| 785                                                             | 790 | 795 |
| Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly |     |     |
|                                                                 | 805 | 810 |
| Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr |     |     |
|                                                                 | 820 | 825 |
| Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His |     |     |
|                                                                 | 835 | 840 |
| Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu |     |     |
|                                                                 | 850 | 855 |
| Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala |     |     |
| 865                                                             | 870 | 875 |
| Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser |     |     |
|                                                                 | 885 | 890 |
| Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu |     |     |
|                                                                 | 900 | 905 |
| Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val |     |     |
|                                                                 | 915 | 920 |
| Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His |     |     |
|                                                                 | 930 | 935 |
| Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val |     |     |
| 945                                                             | 950 | 955 |
| Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys |     |     |
|                                                                 | 965 | 970 |
| Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp |     |     |

|                                 |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
|---------------------------------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|
| 980                             |     |     |     | 985  |     |     |     | 990  |     |     |     |      |     |     |     |
| Asp                             | Leu | Leu | Pro | Asp  | Leu | Asn | Pro | Val  | Glu | Gln | Phe | Phe  | Gln | Gly | Asn |
| 995                             |     |     |     | 1000 |     |     |     | 1005 |     |     |     |      |     |     |     |
| Phe                             | Pro | Gly | Ser | Val  | Gln | Arg | Glu | Arg  | His | Tyr | Asn | Met  | Leu | Gln | Phe |
| 1010                            |     |     |     | 1015 |     |     |     | 1020 |     |     |     |      |     |     |     |
| Gln                             | Val | Ser | Ser | Ser  | Ser | Leu | Ala | Arg  | Ile | Phe | Gln | Leu  | Leu | Leu | Ser |
| 1025                            |     |     |     | 1030 |     |     |     | 1035 |     |     |     | 1040 |     |     |     |
| His                             | Lys | Asp | Ser | Leu  | Leu | Ile | Glu | Glu  | Tyr | Ser | Val | Thr  | Gln | Thr | Thr |
| 1045                            |     |     |     | 1050 |     |     |     | 1055 |     |     |     |      |     |     |     |
| Leu                             | Asp | Gln | Val | Phe  | Val | Asn | Phe | Ala  | Lys | Gln | Gln | Thr  | Glu | Ser | His |
| 1060                            |     |     |     | 1065 |     |     |     | 1070 |     |     |     |      |     |     |     |
| Asp                             | Leu | Pro | Leu | His  | Pro | Arg | Ala | Ala  | Gly | Ala | Ser | Arg  | Gln | Ala | Gln |
| 1075                            |     |     |     | 1080 |     |     |     | 1085 |     |     |     |      |     |     |     |
| Asp                             |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <210> 99                        |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <211> 1183                      |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <212> PRT                       |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <213> 人工序列(Artificial Sequence) |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <220>                           |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <223> ABCA4-1096-gp41N          |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| <400> 99                        |     |     |     |      |     |     |     |      |     |     |     |      |     |     |     |
| Met                             | Gly | Phe | Val | Arg  | Gln | Ile | Gln | Leu  | Leu | Leu | Trp | Lys  | Asn | Trp | Thr |
| 1                               |     |     |     | 5    |     |     |     | 10   |     |     |     | 15   |     |     |     |
| Leu                             | Arg | Lys | Arg | Gln  | Lys | Ile | Arg | Phe  | Val | Val | Glu | Leu  | Val | Trp | Pro |
| 20                              |     |     |     | 25   |     |     |     | 30   |     |     |     |      |     |     |     |
| Leu                             | Ser | Leu | Phe | Leu  | Val | Leu | Ile | Trp  | Leu | Arg | Asn | Ala  | Asn | Pro | Leu |
| 35                              |     |     |     | 40   |     |     |     | 45   |     |     |     |      |     |     |     |
| Tyr                             | Ser | His | His | Glu  | Cys | His | Phe | Pro  | Asn | Lys | Ala | Met  | Pro | Ser | Ala |
| 50                              |     |     |     | 55   |     |     |     | 60   |     |     |     |      |     |     |     |
| Gly                             | Met | Leu | Pro | Trp  | Leu | Gln | Gly | Ile  | Phe | Cys | Asn | Val  | Asn | Asn | Pro |
| 65                              |     |     |     | 70   |     |     |     | 75   |     |     |     | 80   |     |     |     |
| Cys                             | Phe | Gln | Ser | Pro  | Thr | Pro | Gly | Glu  | Ser | Pro | Gly | Ile  | Val | Ser | Asn |
| 85                              |     |     |     | 90   |     |     |     | 95   |     |     |     |      |     |     |     |
| Tyr                             | Asn | Asn | Ser | Ile  | Leu | Ala | Arg | Val  | Tyr | Arg | Asp | Phe  | Gln | Glu | Leu |
| 100                             |     |     |     | 105  |     |     |     | 110  |     |     |     |      |     |     |     |
| Leu                             | Met | Asn | Ala | Pro  | Glu | Ser | Gln | His  | Leu | Gly | Arg | Ile  | Trp | Thr | Glu |
| 115                             |     |     |     | 120  |     |     |     | 125  |     |     |     |      |     |     |     |
| Leu                             | His | Ile | Leu | Ser  | Gln | Phe | Met | Asp  | Thr | Leu | Arg | Thr  | His | Pro | Glu |
| 130                             |     |     |     | 135  |     |     |     | 140  |     |     |     |      |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Ala | Gly | Arg | Gly | Ile | Arg | Ile | Arg | Asp | Ile | Leu | Lys | Asp | Glu |
| 145 |     |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |
| Glu | Thr | Leu | Thr | Leu | Phe | Leu | Ile | Lys | Asn | Ile | Gly | Leu | Ser | Asp | Ser |
|     |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |
| Val | Val | Tyr | Leu | Leu | Ile | Asn | Ser | Gln | Val | Arg | Pro | Glu | Gln | Phe | Ala |
|     |     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |
| His | Gly | Val | Pro | Asp | Leu | Ala | Leu | Lys | Asp | Ile | Ala | Cys | Ser | Glu | Ala |
|     |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |
| Leu | Leu | Glu | Arg | Phe | Ile | Ile | Phe | Ser | Gln | Arg | Arg | Gly | Ala | Lys | Thr |
|     |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |
| Val | Arg | Tyr | Ala | Leu | Cys | Ser | Leu | Ser | Gln | Gly | Thr | Leu | Gln | Trp | Ile |
|     |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |
| Glu | Asp | Thr | Leu | Tyr | Ala | Asn | Val | Asp | Phe | Phe | Lys | Leu | Phe | Arg | Val |
|     |     |     |     |     | 240 |     |     |     |     | 245 |     |     |     |     | 250 |
| Leu | Pro | Thr | Leu | Leu | Asp | Ser | Arg | Ser | Gln | Gly | Ile | Asn | Leu | Arg | Ser |
|     |     |     |     |     | 255 |     |     |     |     | 260 |     |     |     |     | 265 |
| Trp | Gly | Gly | Ile | Leu | Ser | Asp | Met | Ser | Pro | Arg | Ile | Gln | Glu | Phe | Ile |
|     |     |     |     |     | 270 |     |     |     |     | 275 |     |     |     |     | 280 |
| His | Arg | Pro | Ser | Met | Gln | Asp | Leu | Leu | Trp | Val | Thr | Arg | Pro | Leu | Met |
|     |     |     |     |     | 285 |     |     |     |     | 290 |     |     |     |     | 295 |
| Gln | Asn | Gly | Gly | Pro | Glu | Thr | Phe | Thr | Lys | Leu | Met | Gly | Ile | Leu | Ser |
|     |     |     |     |     | 300 |     |     |     |     | 305 |     |     |     |     | 310 |
| Asp | Leu | Leu | Cys | Gly | Tyr | Pro | Glu | Gly | Gly | Gly | Ser | Arg | Val | Leu | Ser |
|     |     |     |     |     | 315 |     |     |     |     | 320 |     |     |     |     | 325 |
| Phe | Asn | Trp | Tyr | Glu | Asp | Asn | Asn | Tyr | Lys | Ala | Phe | Leu | Gly | Ile | Asp |
|     |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |     | 340 |
| Ser | Thr | Arg | Lys | Asp | Pro | Ile | Tyr | Ser | Tyr | Asp | Arg | Arg | Thr | Thr | Ser |
|     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |     |     | 355 |
| Phe | Cys | Asn | Ala | Leu | Ile | Gln | Ser | Leu | Glu | Ser | Asn | Pro | Leu | Thr | Lys |
|     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     | 370 |
| Ile | Ala | Trp | Arg | Ala | Ala | Lys | Pro | Leu | Leu | Met | Gly | Lys | Ile | Leu | Tyr |
|     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     | 385 |
| Thr | Pro | Asp | Ser | Pro | Ala | Ala | Arg | Arg | Ile | Leu | Lys | Asn | Ala | Asn | Ser |
|     |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Thr | Phe | Glu | Glu | Leu | Glu | His | Val | Arg | Lys | Leu | Val | Lys | Ala | Trp | Glu |
|     |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |
| Glu | Val | Gly | Pro | Gln | Ile | Trp | Tyr | Phe | Phe | Asp | Asn | Ser | Thr | Gln | Met |
|     |     |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |
| Asn | Met | Ile | Arg | Asp | Thr | Leu | Gly | Asn | Pro | Thr | Val | Lys | Asp | Phe | Leu |
|     |     |     |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |     |     |
| 755                                                             | 760 | 765 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |      |
| 770                                                             | 775  | 780  |      |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |      |
| 785                                                             | 790  | 795  | 800  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |      |
|                                                                 | 805  | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |      |
|                                                                 | 820  | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |      |
|                                                                 | 835  | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |      |
|                                                                 | 850  | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |      |
| 865                                                             | 870  | 875  | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |      |
|                                                                 | 885  | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |      |
|                                                                 | 900  | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |      |
|                                                                 | 915  | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |      |
|                                                                 | 930  | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |      |
| 945                                                             | 950  | 955  | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |      |
|                                                                 | 965  | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |      |
|                                                                 | 980  | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |      |
|                                                                 | 995  | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |      |
|                                                                 | 1010 | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |      |
| 1025                                                            | 1030 | 1035 | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |      |
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| 1075                                                            | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Cys Leu Asp Leu Lys Thr Gln Val Gln |      |      |
| 1090                                                            | 1095 | 1100 |
| Thr Pro Gln Gly Met Lys Glu Ile Ser Asn Ile Gln Val Gly Asp Leu |      |      |
| 1105                                                            | 1110 | 1115 |
| Val Leu Ser Asn Thr Gly Tyr Asn Glu Val Leu Asn Val Phe Pro Lys |      | 1120 |
|                                                                 | 1125 | 1130 |
| Ser Lys Lys Lys Ser Tyr Lys Ile Thr Leu Glu Asp Gly Lys Glu Ile |      | 1135 |
|                                                                 | 1140 | 1145 |
| Ile Cys Ser Glu Glu His Leu Phe Pro Thr Gln Thr Gly Glu Met Asn |      | 1150 |
|                                                                 | 1155 | 1160 |
| Ile Ser Gly Gly Leu Lys Glu Gly Met Cys Leu Tyr Val Lys Glu     |      | 1165 |
|                                                                 | 1170 | 1175 |
|                                                                 |      | 1180 |
| <210> 100                                                       |      |      |
| <211> 1215                                                      |      |      |
| <212> PRT                                                       |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |
| <220>                                                           |      |      |
| <223> ABCA4-1096-gp41C                                          |      |      |
| <400> 100                                                       |      |      |
| Met Met Leu Lys Lys Ile Leu Lys Ile Glu Glu Leu Asp Glu Arg Glu |      |      |
| 1                                                               | 5    | 10   |
| Leu Ile Asp Ile Glu Val Ser Gly Asn His Leu Phe Tyr Ala Asn Asp |      | 15   |
|                                                                 | 20   | 25   |
| Ile Leu Thr His Asn Ser Arg Arg Ser Ile Trp Asp Leu Leu Leu Lys |      | 30   |
|                                                                 | 35   | 40   |
| Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met Asp Glu |      | 45   |
|                                                                 | 50   | 55   |
| Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly Arg Leu |      | 60   |
| 65                                                              | 70   | 75   |
| Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly Thr Gly |      | 80   |
|                                                                 | 85   | 90   |
| Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser Gln Arg |      | 95   |
|                                                                 | 100  | 105  |
| Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe Ser Thr |      | 110  |
|                                                                 | 115  | 120  |
| Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val Leu Asp |      | 125  |
|                                                                 | 130  | 135  |
| Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val Pro Glu |      | 140  |



|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 145                                                             | 150 | 155 | 160 |
| Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu Leu Pro |     |     |     |
|                                                                 | 165 | 170 | 175 |
| Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg Glu Leu |     |     |     |
|                                                                 | 180 | 185 | 190 |
| Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile Ser Asp |     |     |     |
|                                                                 | 195 | 200 | 205 |
| Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser Asp Ser |     |     |     |
|                                                                 | 210 | 215 | 220 |
| Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn Val Asn |     |     |     |
| 225                                                             | 230 | 235 | 240 |
| Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln Thr Pro |     |     |     |
|                                                                 | 245 | 250 | 255 |
| Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His Pro Glu |     |     |     |
|                                                                 | 260 | 265 | 270 |
| Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu Asn Thr |     |     |     |
|                                                                 | 275 | 280 | 285 |
| Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val Lys Arg |     |     |     |
|                                                                 | 290 | 295 | 300 |
| Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln Ile Val |     |     |     |
| 305                                                             | 310 | 315 | 320 |
| Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile Val Ile |     |     |     |
|                                                                 | 325 | 330 | 335 |
| Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp Ile Tyr |     |     |     |
|                                                                 | 340 | 345 | 350 |
| Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser Glu Gln |     |     |     |
|                                                                 | 355 | 360 | 365 |
| Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe Gly Asn |     |     |     |
|                                                                 | 370 | 375 | 380 |
| Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly Asn Ser |     |     |     |
| 385                                                             | 390 | 395 | 400 |
| Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln Leu Phe |     |     |     |
|                                                                 | 405 | 410 | 415 |
| Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys Arg Cys |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu |     |     |     |
|                                                                 | 450 | 455 | 460 |

|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr |     |     |     |
| 465                                                             | 470 | 475 | 480 |
| Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala |     |     |     |
|                                                                 | 565 | 570 | 575 |
| His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val |     |     |     |
| 625                                                             | 630 | 635 | 640 |
| Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met |     |     |     |
| 705                                                             | 710 | 715 | 720 |
| Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg Phe Asn |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly |     |     |     |

|                     |                     |                         |
|---------------------|---------------------|-------------------------|
| 770                 | 775                 | 780                     |
| Arg Gly Leu Ile Asp | Leu Ala Leu Ser Gln | Ala Val Thr Asp Val Tyr |
| 785                 | 790                 | 795                     |
| Ala Arg Phe Gly Glu | Glu His Ser Ala Asn | Pro Phe His Trp Asp Leu |
| 805                 | 810                 | 815                     |
| Ile Gly Lys Asn Leu | Phe Ala Met Val Val | Glu Gly Val Val Tyr Phe |
| 820                 | 825                 | 830                     |
| Leu Leu Thr Leu Leu | Val Gln Arg His Phe | Phe Leu Ser Gln Trp Ile |
| 835                 | 840                 | 845                     |
| Ala Glu Pro Thr Lys | Glu Pro Ile Val Asp | Glu Asp Asp Asp Val Ala |
| 850                 | 855                 | 860                     |
| Glu Glu Arg Gln Arg | Ile Ile Thr Gly Gly | Asn Lys Thr Asp Ile Leu |
| 865                 | 870                 | 875                     |
| Arg Leu His Glu Leu | Thr Lys Ile Tyr Pro | Gly Thr Ser Ser Pro Ala |
| 885                 | 890                 | 895                     |
| Val Asp Arg Leu Cys | Val Gly Val Arg Pro | Gly Glu Cys Phe Gly Leu |
| 900                 | 905                 | 910                     |
| Leu Gly Val Asn Gly | Ala Gly Lys Thr Thr | Thr Phe Lys Met Leu Thr |
| 915                 | 920                 | 925                     |
| Gly Asp Thr Thr Val | Thr Ser Gly Asp Ala | Thr Val Ala Gly Lys Ser |
| 930                 | 935                 | 940                     |
| Ile Leu Thr Asn Ile | Ser Glu Val His Gln | Asn Met Gly Tyr Cys Pro |
| 945                 | 950                 | 955                     |
| Gln Phe Asp Ala Ile | Asp Glu Leu Leu Thr | Gly Arg Glu His Leu Tyr |
| 965                 | 970                 | 975                     |
| Leu Tyr Ala Arg Leu | Arg Gly Val Pro Ala | Glu Glu Ile Glu Lys Val |
| 980                 | 985                 | 990                     |
| Ala Asn Trp Ser Ile | Lys Ser Leu Gly Leu | Thr Val Tyr Ala Asp Cys |
| 995                 | 1000                | 1005                    |
| Leu Ala Gly Thr Tyr | Ser Gly Gly Asn Lys | Arg Lys Leu Ser Thr Ala |
| 1010                | 1015                | 1020                    |
| Ile Ala Leu Ile Gly | Cys Pro Pro Leu Val | Leu Leu Asp Glu Pro Thr |
| 1025                | 1030                | 1035                    |
| Thr Gly Met Asp Pro | Gln Ala Arg Arg Met | Leu Trp Asn Val Ile Val |
| 1045                | 1050                | 1055                    |
| Ser Ile Ile Arg Glu | Gly Arg Ala Val Val | Leu Thr Ser His Ser Met |
| 1060                | 1065                | 1070                    |
| Glu Glu Cys Glu Ala | Leu Cys Thr Arg Leu | Ala Ile Met Val Lys Gly |
| 1075                | 1080                | 1085                    |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly |      |      |      |
| 1090                                                            | 1095 | 1100 |      |
| Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp |      |      |      |
|                                                                 | 1170 | 1175 | 1180 |
| Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp     |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| <210> 101                                                       |      |      |      |
| <211> 1272                                                      |      |      |      |
| <212> PRT                                                       |      |      |      |
| <213> 人工序列(Artificial Sequence)                                 |      |      |      |
| <220>                                                           |      |      |      |
| <223> ABCA4-1185-gp41N                                          |      |      |      |
| <400> 101                                                       |      |      |      |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |      |      |      |
| 1                                                               | 5    | 10   | 15   |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |      |      |      |
|                                                                 | 20   | 25   | 30   |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |      |      |      |
|                                                                 | 35   | 40   | 45   |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |      |      |      |
|                                                                 | 50   | 55   | 60   |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |      |      |      |
| 65                                                              | 70   | 75   | 80   |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |      |      |      |
|                                                                 | 85   | 90   | 95   |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |      |      |      |
|                                                                 | 100  | 105  | 110  |
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |      |      |      |
|                                                                 | 115  | 120  | 125  |

|                                                                 |     |         |
|-----------------------------------------------------------------|-----|---------|
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |         |
| 130                                                             | 135 | 140     |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |         |
| 145                                                             | 150 | 155 160 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |         |
|                                                                 | 165 | 170 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |         |
|                                                                 | 180 | 185 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |         |
|                                                                 | 195 | 200 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |         |
|                                                                 | 210 | 215 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |         |
| 225                                                             | 230 | 235 240 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |         |
|                                                                 | 245 | 250 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |         |
|                                                                 | 260 | 265 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |         |
|                                                                 | 275 | 280 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |         |
|                                                                 | 290 | 295 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |         |
| 305                                                             | 310 | 315 320 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |         |
|                                                                 | 325 | 330 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |         |
|                                                                 | 340 | 345 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |         |
|                                                                 | 355 | 360 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |         |
|                                                                 | 370 | 375 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |         |
| 385                                                             | 390 | 395 400 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |         |
|                                                                 | 405 | 410 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |         |
|                                                                 | 420 | 425 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |         |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |     |     |
| 740                                                             | 745 | 750 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
|                                                                 | 805  | 810  |
|                                                                 |      | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
|                                                                 | 820  | 825  |
|                                                                 |      | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
|                                                                 | 835  | 840  |
|                                                                 |      | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
|                                                                 | 850  | 855  |
|                                                                 |      | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
|                                                                 |      | 880  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
|                                                                 | 885  | 890  |
|                                                                 |      | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
|                                                                 | 900  | 905  |
|                                                                 |      | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
|                                                                 | 915  | 920  |
|                                                                 |      | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
|                                                                 | 930  | 935  |
|                                                                 |      | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
|                                                                 |      | 960  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
|                                                                 | 965  | 970  |
|                                                                 |      | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
|                                                                 | 980  | 985  |
|                                                                 |      | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
|                                                                 | 995  | 1000 |
|                                                                 |      | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
|                                                                 | 1010 | 1015 |
|                                                                 |      | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
|                                                                 |      | 1040 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |
|                                                                 | 1045 | 1050 |
|                                                                 |      | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |

|                                                                 |                                     |      |
|-----------------------------------------------------------------|-------------------------------------|------|
| 1060                                                            | 1065                                | 1070 |
| Ala Ile Ala Phe Val Gly Asp                                     | Ala Lys Val Val Ile Leu Asp Glu Pro |      |
| 1075                                                            | 1080                                | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |                                     |      |
| 1090                                                            | 1095                                | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |                                     |      |
| 1105                                                            | 1110                                | 1115 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |                                     |      |
| 1125                                                            | 1130                                | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |                                     |      |
| 1140                                                            | 1145                                | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |                                     |      |
| 1155                                                            | 1160                                | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |                                     |      |
| 1170                                                            | 1175                                | 1180 |
| Cys Leu Asp Leu Lys Thr Gln Val Gln Thr Pro Gln Gly Met Lys Glu |                                     |      |
| 1185                                                            | 1190                                | 1195 |
| Ile Ser Asn Ile Gln Val Gly Asp Leu Val Leu Ser Asn Thr Gly Tyr |                                     |      |
| 1205                                                            | 1210                                | 1215 |
| Asn Glu Val Leu Asn Val Phe Pro Lys Ser Lys Lys Lys Ser Tyr Lys |                                     |      |
| 1220                                                            | 1225                                | 1230 |
| Ile Thr Leu Glu Asp Gly Lys Glu Ile Ile Cys Ser Glu Glu His Leu |                                     |      |
| 1235                                                            | 1240                                | 1245 |
| Phe Pro Thr Gln Thr Gly Glu Met Asn Ile Ser Gly Gly Leu Lys Glu |                                     |      |
| 1250                                                            | 1255                                | 1260 |
| Gly Met Cys Leu Tyr Val Lys Glu                                 |                                     |      |
| 1265                                                            | 1270                                |      |
| <210> 102                                                       |                                     |      |
| <211> 1126                                                      |                                     |      |
| <212> PRT                                                       |                                     |      |
| <213> 人工序列(Artificial Sequence)                                 |                                     |      |
| <220>                                                           |                                     |      |
| <223> ABCA4-1185-gp41C                                          |                                     |      |
| <400> 102                                                       |                                     |      |
| Met Met Leu Lys Lys Ile Leu Lys Ile Glu Glu Leu Asp Glu Arg Glu |                                     |      |
| 1                                                               | 5                                   | 10   |
| Leu Ile Asp Ile Glu Val Ser Gly Asn His Leu Phe Tyr Ala Asn Asp |                                     |      |
| 20                                                              | 25                                  | 30   |
| Ile Leu Thr His Asn Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu |                                     |      |



|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |  |
| Thr | Pro | Glu | Gln | Val | Leu | Asp | Gly | Asp | Val | Asn | Glu | Leu | Met | Asp | Val |  |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| Val | Leu | His | His | Val | Pro | Glu | Ala | Lys | Leu | Val | Glu | Cys | Ile | Gly | Gln |  |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| Glu | Leu | Ile | Phe | Leu | Leu | Pro | Asn | Lys | Asn | Phe | Lys | His | Arg | Ala | Tyr |  |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Ala | Ser | Leu | Phe | Arg | Glu | Leu | Glu | Glu | Thr | Leu | Ala | Asp | Leu | Gly | Leu |  |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| Ser | Ser | Phe | Gly | Ile | Ser | Asp | Thr | Pro | Leu | Glu | Glu | Ile | Phe | Leu | Lys |  |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| Val | Thr | Glu | Asp | Ser | Asp | Ser | Gly | Pro | Leu | Phe | Ala | Gly | Gly | Ala | Gln |  |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| Gln | Lys | Arg | Glu | Asn | Val | Asn | Pro | Arg | His | Pro | Cys | Leu | Gly | Pro | Arg |  |
| 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |     |  |
| Glu | Lys | Ala | Gly | Gln | Thr | Pro | Gln | Asp | Ser | Asn | Val | Cys | Ser | Pro | Gly |  |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |  |
| Ala | Pro | Ala | Ala | His | Pro | Glu | Gly | Gln | Pro | Pro | Pro | Glu | Pro | Glu | Cys |  |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |  |
| Pro | Gly | Pro | Gln | Leu | Asn | Thr | Gly | Thr | Gln | Leu | Val | Leu | Gln | His | Val |  |
|     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |  |
| Gln | Ala | Leu | Leu | Val | Lys | Arg | Phe | Gln | His | Thr | Ile | Arg | Ser | His | Lys |  |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| Asp | Phe | Leu | Ala | Gln | Ile | Val | Leu | Pro | Ala | Thr | Phe | Val | Phe | Leu | Ala |  |
| 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |  |
| Leu | Met | Leu | Ser | Ile | Val | Ile | Pro | Pro | Phe | Gly | Glu | Tyr | Pro | Ala | Leu |  |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |  |
| Thr | Leu | His | Pro | Trp | Ile | Tyr | Gly | Gln | Gln | Tyr | Thr | Phe | Phe | Ser | Met |  |
|     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |  |
| Asp | Glu | Pro | Gly | Ser | Glu | Gln | Phe | Thr | Val | Leu | Ala | Asp | Val | Leu | Leu |  |
|     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     |  |
| Asn | Lys | Pro | Gly | Phe | Gly | Asn | Arg | Cys | Leu | Lys | Glu | Gly | Trp | Leu | Pro |  |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| Glu | Tyr | Pro | Cys | Gly | Asn | Ser | Thr | Pro | Trp | Lys | Thr | Pro | Ser | Val | Ser |  |
| 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |     |  |
| Pro | Asn | Ile | Thr | Gln | Leu | Phe | Gln | Lys | Gln | Lys | Trp | Thr | Gln | Val | Asn |  |
|     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |  |
| Pro | Ser | Pro | Ser | Cys | Arg | Cys | Ser | Thr | Arg | Glu | Lys | Leu | Thr | Met | Leu |  |
|     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |     |  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Pro | Glu | Cys | Pro | Glu | Gly | Ala | Gly | Gly | Leu | Pro | Pro | Pro | Gln | Arg | Thr |  |
| 355 |     |     |     |     |     | 360 |     |     |     |     |     | 365 |     |     |     |  |
| Gln | Arg | Ser | Thr | Glu | Ile | Leu | Gln | Asp | Leu | Thr | Asp | Arg | Asn | Ile | Ser |  |
| 370 |     |     |     |     |     | 375 |     |     |     |     |     | 380 |     |     |     |  |
| Asp | Phe | Leu | Val | Lys | Thr | Tyr | Pro | Ala | Leu | Ile | Arg | Ser | Ser | Leu | Lys |  |
| 385 |     |     |     |     |     | 390 |     |     |     |     |     | 395 |     |     | 400 |  |
| Ser | Lys | Phe | Trp | Val | Asn | Glu | Gln | Arg | Tyr | Gly | Gly | Ile | Ser | Ile | Gly |  |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     |     | 415 |  |
| Gly | Lys | Leu | Pro | Val | Val | Pro | Ile | Thr | Gly | Glu | Ala | Leu | Val | Gly | Phe |  |
|     |     |     | 420 |     |     |     |     |     | 425 |     |     |     |     |     | 430 |  |
| Leu | Ser | Asp | Leu | Gly | Arg | Ile | Met | Asn | Val | Ser | Gly | Gly | Pro | Ile | Thr |  |
| 435 |     |     |     |     |     | 440 |     |     |     |     |     | 445 |     |     |     |  |
| Arg | Glu | Ala | Ser | Lys | Glu | Ile | Pro | Asp | Phe | Leu | Lys | His | Leu | Glu | Thr |  |
| 450 |     |     |     |     |     | 455 |     |     |     |     |     | 460 |     |     |     |  |
| Glu | Asp | Asn | Ile | Lys | Val | Trp | Phe | Asn | Asn | Lys | Gly | Trp | His | Ala | Leu |  |
| 465 |     |     |     |     |     | 470 |     |     |     |     |     | 475 |     |     | 480 |  |
| Val | Ser | Phe | Leu | Asn | Val | Ala | His | Asn | Ala | Ile | Leu | Arg | Ala | Ser | Leu |  |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     |     | 495 |  |
| Pro | Lys | Asp | Arg | Ser | Pro | Glu | Glu | Tyr | Gly | Ile | Thr | Val | Ile | Ser | Gln |  |
| 500 |     |     |     |     |     | 505 |     |     |     |     |     | 510 |     |     |     |  |
| Pro | Leu | Asn | Leu | Thr | Lys | Glu | Gln | Leu | Ser | Glu | Ile | Thr | Val | Leu | Thr |  |
| 515 |     |     |     |     |     | 520 |     |     |     |     |     | 525 |     |     |     |  |
| Thr | Ser | Val | Asp | Ala | Val | Val | Ala | Ile | Cys | Val | Ile | Phe | Ser | Met | Ser |  |
| 530 |     |     |     |     |     | 535 |     |     |     |     |     | 540 |     |     |     |  |
| Phe | Val | Pro | Ala | Ser | Phe | Val | Leu | Tyr | Leu | Ile | Gln | Glu | Arg | Val | Asn |  |
| 545 |     |     |     |     |     | 550 |     |     |     |     |     | 555 |     |     | 560 |  |
| Lys | Ser | Lys | His | Leu | Gln | Phe | Ile | Ser | Gly | Val | Ser | Pro | Thr | Thr | Tyr |  |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     |     | 575 |  |
| Trp | Val | Thr | Asn | Phe | Leu | Trp | Asp | Ile | Met | Asn | Tyr | Ser | Val | Ser | Ala |  |
|     |     |     | 580 |     |     |     |     |     | 585 |     |     |     |     |     | 590 |  |
| Gly | Leu | Val | Val | Gly | Ile | Phe | Ile | Gly | Phe | Gln | Lys | Lys | Ala | Tyr | Thr |  |
| 595 |     |     |     |     |     | 600 |     |     |     |     |     | 605 |     |     |     |  |
| Ser | Pro | Glu | Asn | Leu | Pro | Ala | Leu | Val | Ala | Leu | Leu | Leu | Leu | Tyr | Gly |  |
| 610 |     |     |     |     |     | 615 |     |     |     |     |     | 620 |     |     |     |  |
| Trp | Ala | Val | Ile | Pro | Met | Met | Tyr | Pro | Ala | Ser | Phe | Leu | Phe | Asp | Val |  |
| 625 |     |     |     |     |     | 630 |     |     |     |     |     | 635 |     |     | 640 |  |
| Pro | Ser | Thr | Ala | Tyr | Val | Ala | Leu | Ser | Cys | Ala | Asn | Leu | Phe | Ile | Gly |  |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     |     | 655 |  |
| Ile | Asn | Ser | Ser | Ala | Ile | Thr | Phe | Ile | Leu | Glu | Leu | Phe | Glu | Asn | Asn |  |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 660                                                             | 665 | 670 |
| Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val |     |     |
| 675                                                             | 680 | 685 |
| Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser |     |     |
| 690                                                             | 695 | 700 |
| Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala |     |     |
| 705                                                             | 710 | 715 |
| Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val |     |     |
| 725                                                             | 730 | 735 |
| Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His |     |     |
| 740                                                             | 745 | 750 |
| Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val |     |     |
| 755                                                             | 760 | 765 |
| Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly |     |     |
| 770                                                             | 775 | 780 |
| Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr |     |     |
| 785                                                             | 790 | 795 |
| Pro Gly Thr Ser Ser Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg |     |     |
| 805                                                             | 810 | 815 |
| Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr |     |     |
| 820                                                             | 825 | 830 |
| Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp |     |     |
| 835                                                             | 840 | 845 |
| Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His |     |     |
| 850                                                             | 855 | 860 |
| Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu |     |     |
| 865                                                             | 870 | 875 |
| Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro |     |     |
| 885                                                             | 890 | 895 |
| Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly |     |     |
| 900                                                             | 905 | 910 |
| Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn |     |     |
| 915                                                             | 920 | 925 |
| Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu |     |     |
| 930                                                             | 935 | 940 |
| Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg |     |     |
| 945                                                             | 950 | 955 |
| Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val |     |     |
| 965                                                             | 970 | 975 |

Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg  
 980 985 990  
 Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln  
 995 1000 1005  
 His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile  
 1010 1015 1020  
 Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln  
 1025 1030 1035 1040  
 Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr  
 1045 1050 1055  
 Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe  
 1060 1065 1070  
 Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser  
 1075 1080 1085  
 Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln  
 1090 1095 1100  
 Gln Thr Glu Ser His Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala  
 1105 1110 1115 1120  
 Ser Arg Gln Ala Gln Asp  
 1125

&lt;210&gt; 103

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; 3FT

&lt;400&gt; 103

Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile Asp Tyr  
 1 5 10 15

Lys Asp Asp Asp Asp Lys  
 20

&lt;210&gt; 104

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; 人工序列(Artificial Sequence)

&lt;220&gt;

&lt;223&gt; GP41C

&lt;400&gt; 104

Met Met Leu Lys Lys Ile Leu Lys Ile Glu Glu Leu Asp Glu Arg Glu

|                                                                 |     |     |    |
|-----------------------------------------------------------------|-----|-----|----|
| 1                                                               | 5   | 10  | 15 |
| Leu Ile Asp Ile Glu Val Ser Gly Asn His Leu Phe Tyr Ala Asn Asp |     |     |    |
| 20                                                              | 25  | 30  |    |
| Ile Leu Thr His Asn                                             |     |     |    |
| 35                                                              |     |     |    |
| <210> 105                                                       |     |     |    |
| <211> 36                                                        |     |     |    |
| <212> PRT                                                       |     |     |    |
| <213> 人工序列(Artificial Sequence)                                 |     |     |    |
| <220>                                                           |     |     |    |
| <223> ConC                                                      |     |     |    |
| <400> 105                                                       |     |     |    |
| Met Val Lys Ile Ile Ser Arg Gln Ser Leu Gly Lys Gln Asn Val Tyr |     |     |    |
| 1                                                               | 5   | 10  | 15 |
| Asp Ile Gly Val Glu Lys Asp His Asn Phe Leu Leu Ala Asn Gly Leu |     |     |    |
| 20                                                              | 25  | 30  |    |
| Ile Ala Ser Asn                                                 |     |     |    |
| 35                                                              |     |     |    |
| <210> 106                                                       |     |     |    |
| <211> 2273                                                      |     |     |    |
| <212> PRT                                                       |     |     |    |
| <213> 人工序列(Artificial Sequence)                                 |     |     |    |
| <220>                                                           |     |     |    |
| <223> ABCA4                                                     |     |     |    |
| <400> 106                                                       |     |     |    |
| Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr |     |     |    |
| 1                                                               | 5   | 10  | 15 |
| Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro |     |     |    |
| 20                                                              | 25  | 30  |    |
| Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu |     |     |    |
| 35                                                              | 40  | 45  |    |
| Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala |     |     |    |
| 50                                                              | 55  | 60  |    |
| Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro |     |     |    |
| 65                                                              | 70  | 75  | 80 |
| Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn |     |     |    |
| 85                                                              | 90  | 95  |    |
| Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu |     |     |    |
| 100                                                             | 105 | 110 |    |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu |     |     |
| 115                                                             | 120 | 125 |
| Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu |     |     |
| 130                                                             | 135 | 140 |
| Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu |     |     |
| 145                                                             | 150 | 155 |
| Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser |     |     |
| 165                                                             | 170 | 175 |
| Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala |     |     |
| 180                                                             | 185 | 190 |
| His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala |     |     |
| 195                                                             | 200 | 205 |
| Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr |     |     |
| 210                                                             | 215 | 220 |
| Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile |     |     |
| 225                                                             | 230 | 235 |
| Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val |     |     |
| 245                                                             | 250 | 255 |
| Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser |     |     |
| 260                                                             | 265 | 270 |
| Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile |     |     |
| 275                                                             | 280 | 285 |
| His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met |     |     |
| 290                                                             | 295 | 300 |
| Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser |     |     |
| 305                                                             | 310 | 315 |
| Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser |     |     |
| 325                                                             | 330 | 335 |
| Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp |     |     |
| 340                                                             | 345 | 350 |
| Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser |     |     |
| 355                                                             | 360 | 365 |
| Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys |     |     |
| 370                                                             | 375 | 380 |
| Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr |     |     |
| 385                                                             | 390 | 395 |
| Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser |     |     |
| 405                                                             | 410 | 415 |
| Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu |     |     |

|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 420                                                             | 425 | 430 |
| Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met |     |     |
| 435                                                             | 440 | 445 |
| Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu |     |     |
| 450                                                             | 455 | 460 |
| Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn |     |     |
| 465                                                             | 470 | 475 |
| Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn |     |     |
| 485                                                             | 490 | 495 |
| Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu |     |     |
| 500                                                             | 505 | 510 |
| Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr |     |     |
| 515                                                             | 520 | 525 |
| Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu |     |     |
| 530                                                             | 535 | 540 |
| Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr |     |     |
| 545                                                             | 550 | 555 |
| Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp |     |     |
| 565                                                             | 570 | 575 |
| Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly |     |     |
| 580                                                             | 585 | 590 |
| Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe |     |     |
| 595                                                             | 600 | 605 |
| Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val |     |     |
| 610                                                             | 615 | 620 |
| Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro |     |     |
| 625                                                             | 630 | 635 |
| Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro |     |     |
| 645                                                             | 650 | 655 |
| Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys |     |     |
| 660                                                             | 665 | 670 |
| Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn |     |     |
| 675                                                             | 680 | 685 |
| Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser |     |     |
| 690                                                             | 695 | 700 |
| Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met |     |     |
| 705                                                             | 710 | 715 |
| His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe |     |     |
| 725                                                             | 730 | 735 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser |      |      |
| 740                                                             | 745  | 750  |
| Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile |      |      |
| 755                                                             | 760  | 765  |
| Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp |      |      |
| 770                                                             | 775  | 780  |
| Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val |      |      |
| 785                                                             | 790  | 795  |
| Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly |      |      |
| 805                                                             | 810  | 815  |
| Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp |      |      |
| 820                                                             | 825  | 830  |
| Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala |      |      |
| 835                                                             | 840  | 845  |
| Val Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp |      |      |
| 850                                                             | 855  | 860  |
| Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp |      |      |
| 865                                                             | 870  | 875  |
| Leu Gly Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys |      |      |
| 885                                                             | 890  | 895  |
| Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly |      |      |
| 900                                                             | 905  | 910  |
| Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly |      |      |
| 915                                                             | 920  | 925  |
| Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro |      |      |
| 930                                                             | 935  | 940  |
| Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala |      |      |
| 945                                                             | 950  | 955  |
| Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu |      |      |
| 965                                                             | 970  | 975  |
| Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg |      |      |
| 980                                                             | 985  | 990  |
| Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys |      |      |
| 995                                                             | 1000 | 1005 |
| Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met |      |      |
| 1010                                                            | 1015 | 1020 |
| Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu |      |      |
| 1025                                                            | 1030 | 1035 |
| Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn |      |      |



|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
|                                                                 | 1045 | 1050 | 1055 |
| Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val |      |      |      |
|                                                                 | 1060 | 1065 | 1070 |
| Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro |      |      |      |
|                                                                 | 1075 | 1080 | 1085 |
| Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu |      |      |      |
|                                                                 | 1090 | 1095 | 1100 |
| Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Ser Thr His His Met |      |      |      |
| 1105                                                            | 1110 | 1115 | 1120 |
| Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly |      |      |      |
|                                                                 | 1125 | 1130 | 1135 |
| Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly |      |      |      |
|                                                                 | 1140 | 1145 | 1150 |
| Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser |      |      |      |
|                                                                 | 1155 | 1160 | 1165 |
| Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe |      |      |      |
| 1170                                                            | 1175 | 1180 |      |
| Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val |      |      |      |
| 1185                                                            | 1190 | 1195 | 1200 |
| Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val |      |      |      |
|                                                                 | 1205 | 1210 | 1215 |
| Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu |      |      |      |
|                                                                 | 1220 | 1225 | 1230 |
| Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg |      |      |      |
|                                                                 | 1235 | 1240 | 1245 |
| Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile |      |      |      |
|                                                                 | 1250 | 1255 | 1260 |
| Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser |      |      |      |
| 1265                                                            | 1270 | 1275 | 1280 |
| Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn |      |      |      |
|                                                                 | 1285 | 1290 | 1295 |
| Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln |      |      |      |
|                                                                 | 1300 | 1305 | 1310 |
| Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His |      |      |      |
|                                                                 | 1315 | 1320 | 1325 |
| Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu |      |      |      |
|                                                                 | 1330 | 1335 | 1340 |
| Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val |      |      |      |
| 1345                                                            | 1350 | 1355 | 1360 |

|                                                                 |      |      |
|-----------------------------------------------------------------|------|------|
| Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln |      |      |
| 1365                                                            | 1370 | 1375 |
| Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile |      |      |
| 1380                                                            | 1385 | 1390 |
| Val Ile Pro Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp |      |      |
| 1395                                                            | 1400 | 1405 |
| Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser |      |      |
| 1410                                                            | 1415 | 1420 |
| Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe |      |      |
| 1425                                                            | 1430 | 1435 |
| Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly |      |      |
| 1445                                                            | 1450 | 1455 |
| Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln |      |      |
| 1460                                                            | 1465 | 1470 |
| Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys |      |      |
| 1475                                                            | 1480 | 1485 |
| Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu |      |      |
| 1490                                                            | 1495 | 1500 |
| Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu |      |      |
| 1505                                                            | 1510 | 1515 |
| Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys |      |      |
| 1525                                                            | 1530 | 1535 |
| Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val |      |      |
| 1540                                                            | 1545 | 1550 |
| Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val |      |      |
| 1555                                                            | 1560 | 1565 |
| Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly |      |      |
| 1570                                                            | 1575 | 1580 |
| Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys |      |      |
| 1585                                                            | 1590 | 1595 |
| Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys |      |      |
| 1605                                                            | 1610 | 1615 |
| Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn |      |      |
| 1620                                                            | 1625 | 1630 |
| Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser |      |      |
| 1635                                                            | 1640 | 1645 |
| Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr |      |      |
| 1650                                                            | 1655 | 1660 |
| Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala |      |      |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 1665                                                            | 1670 | 1675 | 1680 |
| Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser |      |      |      |
|                                                                 | 1685 | 1690 | 1695 |
| Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu |      |      |      |
|                                                                 | 1700 | 1705 | 1710 |
| Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe |      |      |      |
|                                                                 | 1715 | 1720 | 1725 |
| Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly |      |      |      |
|                                                                 | 1730 | 1735 | 1740 |
| Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu |      |      |      |
| 1745                                                            | 1750 | 1755 | 1760 |
| Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro |      |      |      |
|                                                                 | 1765 | 1770 | 1775 |
| Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr |      |      |      |
|                                                                 | 1780 | 1785 | 1790 |
| Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala |      |      |      |
|                                                                 | 1795 | 1800 | 1805 |
| Ile Thr Phe Ile Leu Glu Leu Phe Glu Asn Asn Arg Thr Leu Leu Arg |      |      |      |
|                                                                 | 1810 | 1815 | 1820 |
| Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys |      |      |      |
| 1825                                                            | 1830 | 1835 | 1840 |
| Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp |      |      |      |
|                                                                 | 1845 | 1850 | 1855 |
| Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp |      |      |      |
|                                                                 | 1860 | 1865 | 1870 |
| Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val |      |      |      |
|                                                                 | 1875 | 1880 | 1885 |
| Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln |      |      |      |
|                                                                 | 1890 | 1895 | 1900 |
| Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp |      |      |      |
| 1905                                                            | 1910 | 1915 | 1920 |
| Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp |      |      |      |
|                                                                 | 1925 | 1930 | 1935 |
| Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Pro Gly Thr Ser Ser |      |      |      |
|                                                                 | 1940 | 1945 | 1950 |
| Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe |      |      |      |
|                                                                 | 1955 | 1960 | 1965 |
| Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met |      |      |      |
|                                                                 | 1970 | 1975 | 1980 |

|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly |      |      |      |
| 1985                                                            | 1990 | 1995 | 2000 |
| Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr |      |      |      |
|                                                                 | 2005 | 2010 | 2015 |
| Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His |      |      |      |
|                                                                 | 2020 | 2025 | 2030 |
| Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu |      |      |      |
|                                                                 | 2035 | 2040 | 2045 |
| Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala |      |      |      |
|                                                                 | 2050 | 2055 | 2060 |
| Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser |      |      |      |
| 2065                                                            | 2070 | 2075 | 2080 |
| Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu |      |      |      |
|                                                                 | 2085 | 2090 | 2095 |
| Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val |      |      |      |
|                                                                 | 2100 | 2105 | 2110 |
| Ile Val Ser Ile Ile Arg Glu Gly Arg Ala Val Val Leu Thr Ser His |      |      |      |
|                                                                 | 2115 | 2120 | 2125 |
| Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val |      |      |      |
|                                                                 | 2130 | 2135 | 2140 |
| Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys |      |      |      |
| 2145                                                            | 2150 | 2155 | 2160 |
| Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp |      |      |      |
|                                                                 | 2165 | 2170 | 2175 |
| Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn |      |      |      |
|                                                                 | 2180 | 2185 | 2190 |
| Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe |      |      |      |
|                                                                 | 2195 | 2200 | 2205 |
| Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser |      |      |      |
|                                                                 | 2210 | 2215 | 2220 |
| His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr |      |      |      |
| 2225                                                            | 2230 | 2235 | 2240 |
| Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His |      |      |      |
|                                                                 | 2245 | 2250 | 2255 |
| Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln |      |      |      |
|                                                                 | 2260 | 2265 | 2270 |
| Asp                                                             |      |      |      |
| <210> 107                                                       |      |      |      |
| <211> 21                                                        |      |      |      |

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> T2

<400> 107

Lys Leu Lys Gly Leu Gly Lys Arg Cys Lys Arg Arg Glu Asp Leu Glu

1 5 10 15

Ile Arg Phe Ile Leu

20

<210> 108

<211> 21

<212> PRT

<213> 人工序列(Artificial Sequence)

<220>

<223> T3

<400> 108

Trp Lys Leu Leu Leu Trp Val Gly Leu Val Leu Val Leu Lys His His

1 5 10 15

Asp Gly Ala Ala His

20

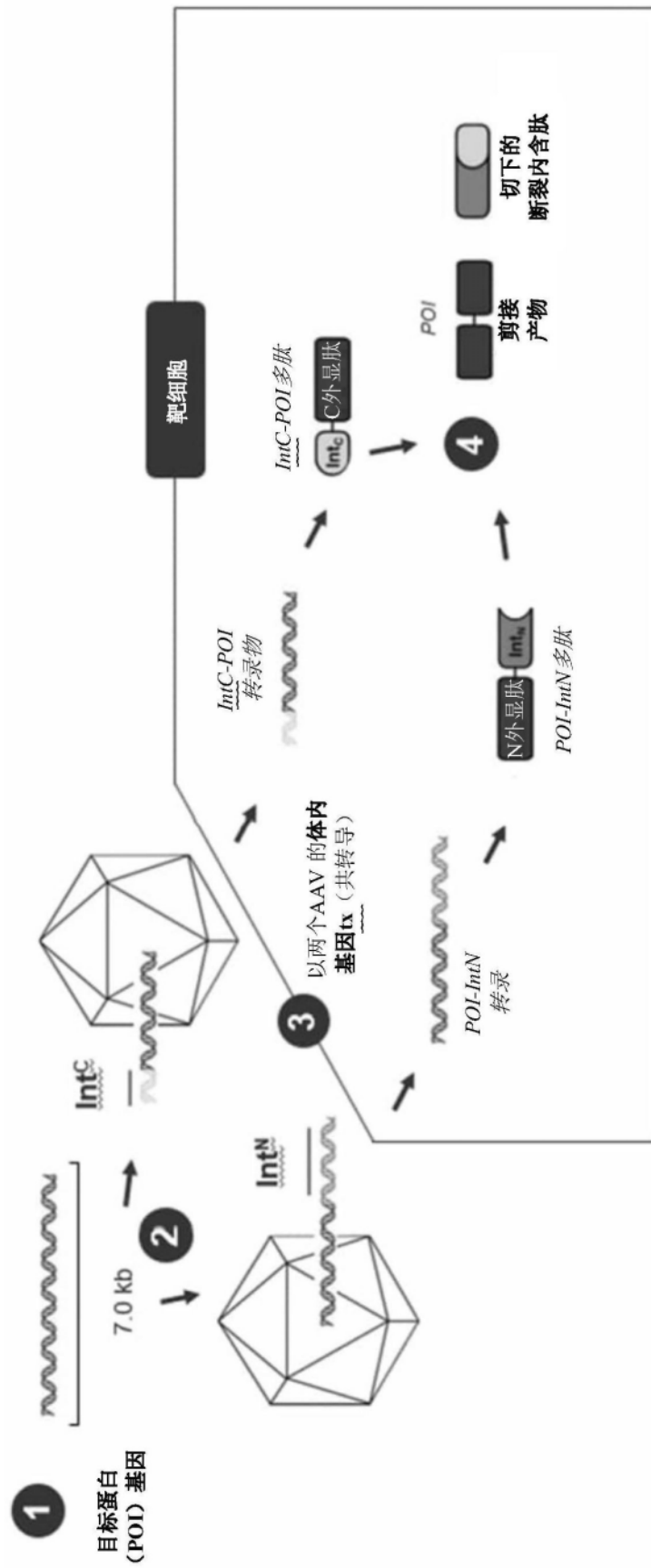


图1

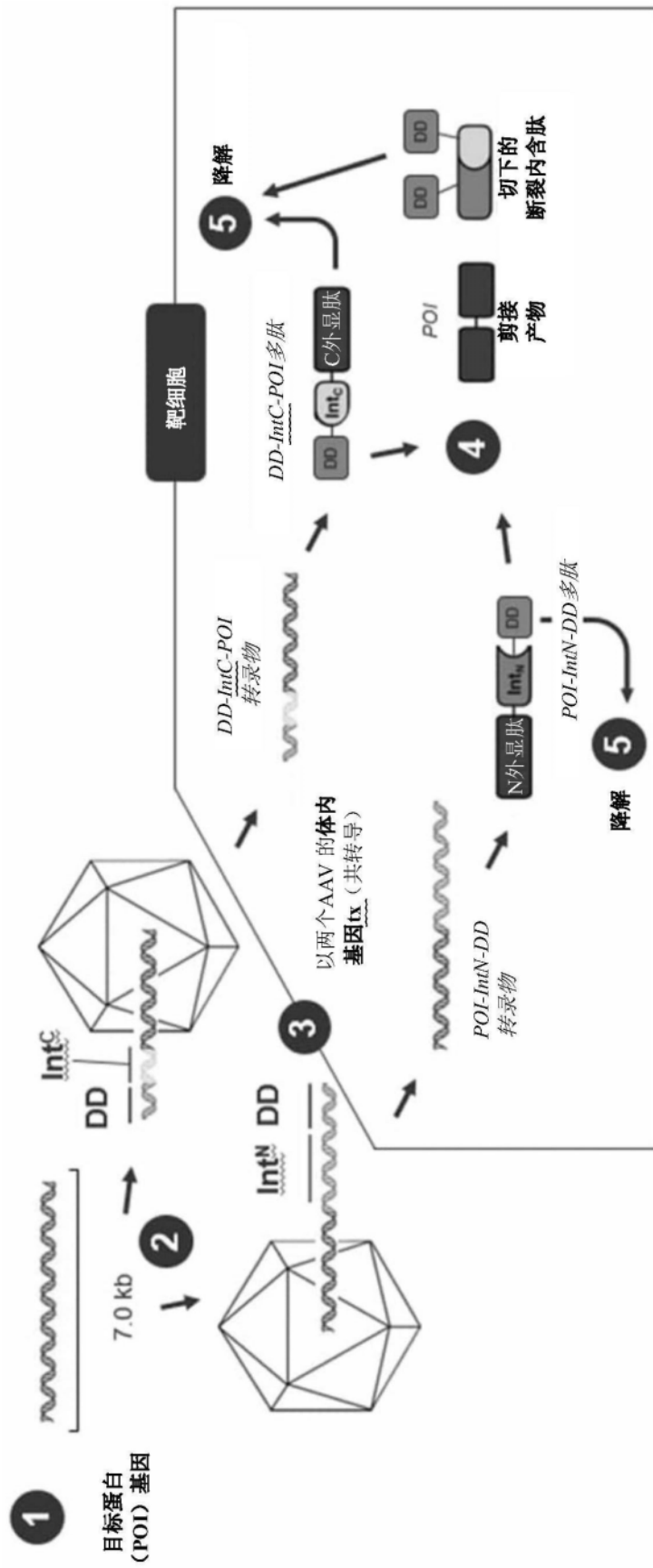


图1 (续)

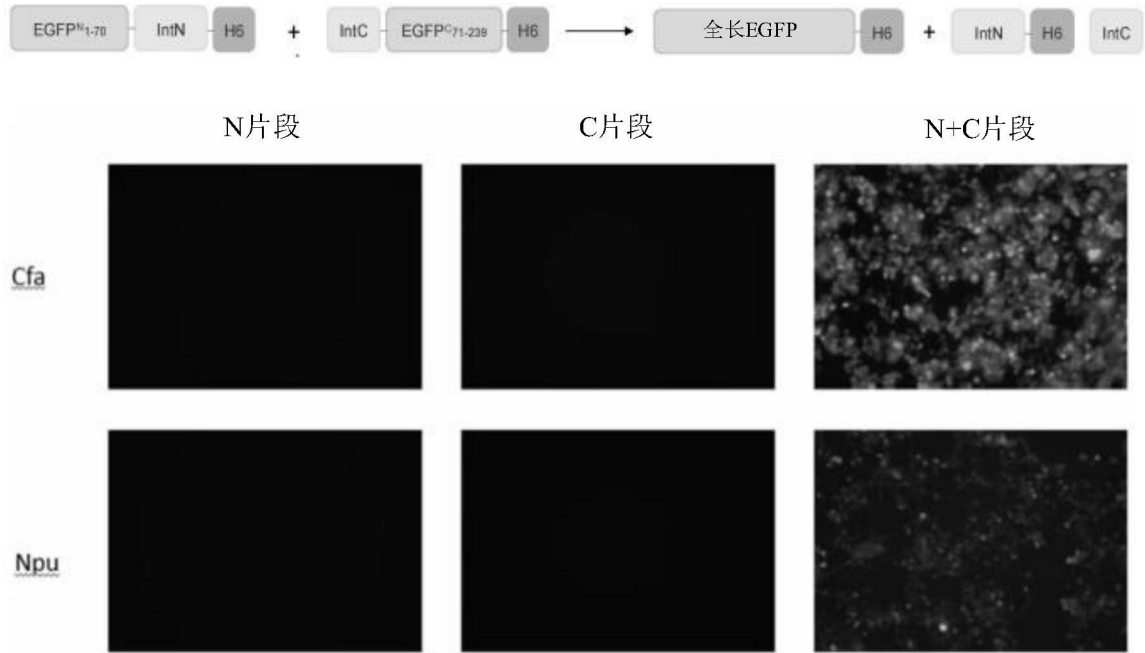


图2

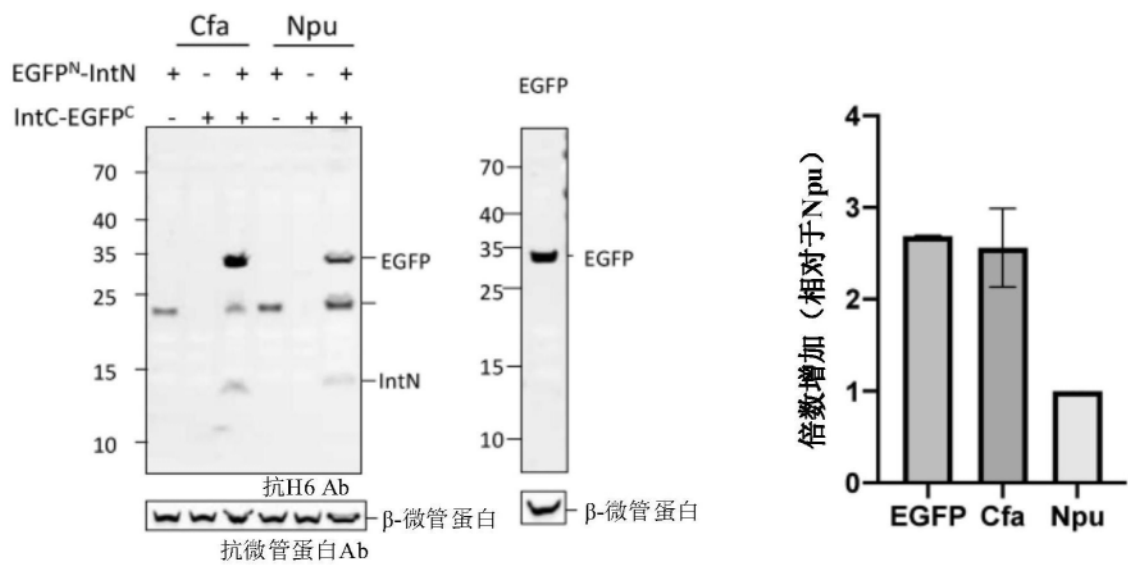


图3



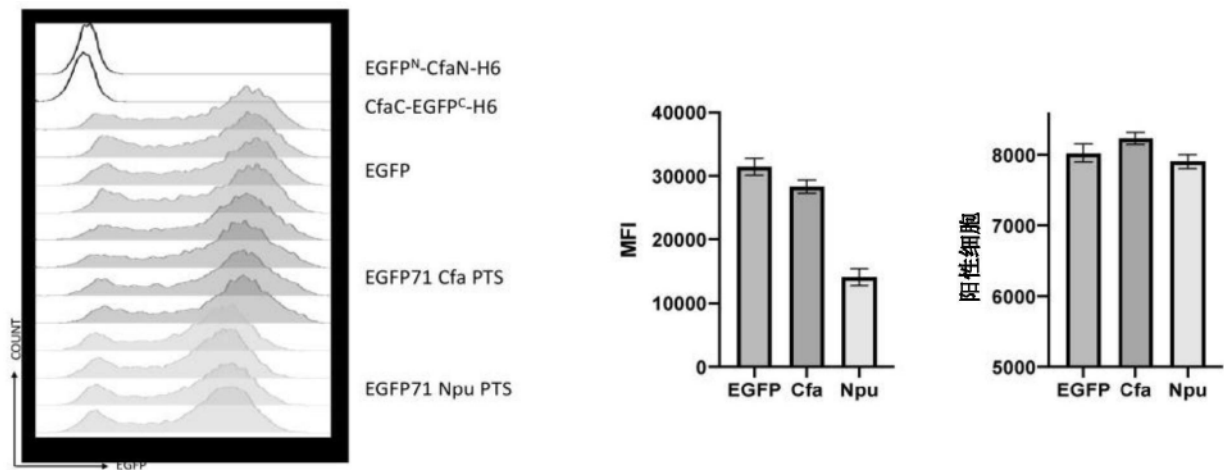


图4

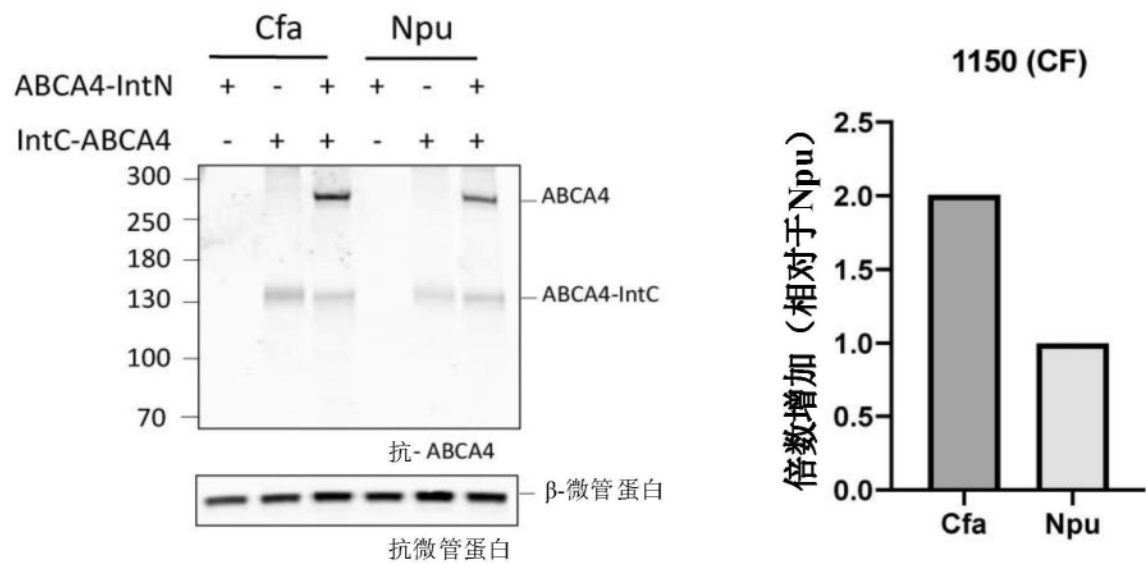


图5

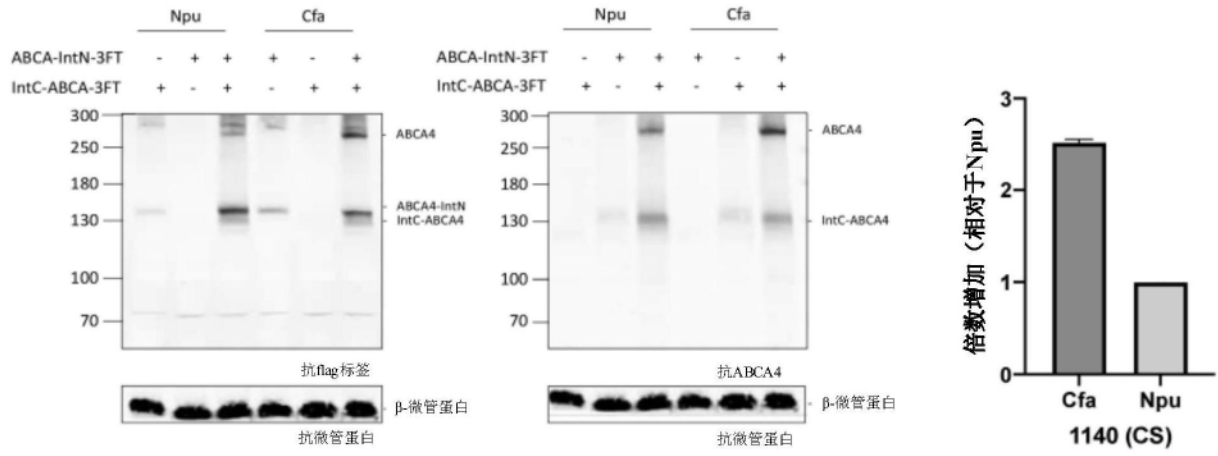


图6

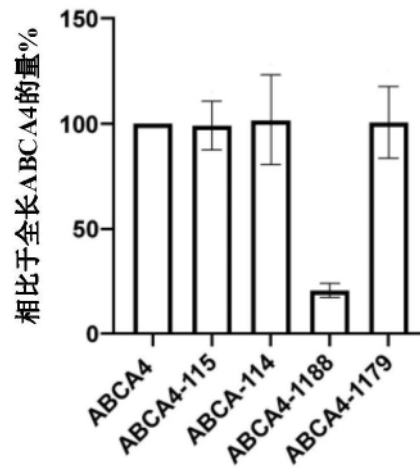


图7

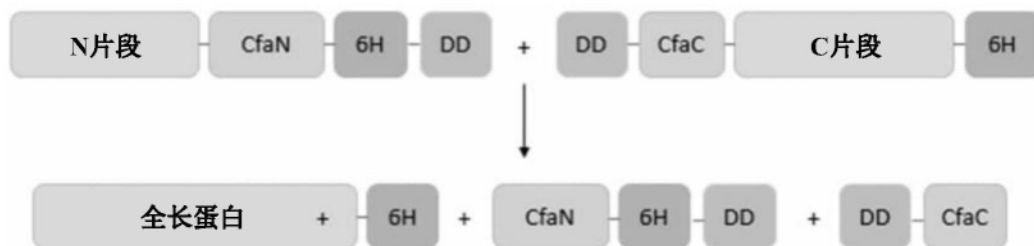


图8

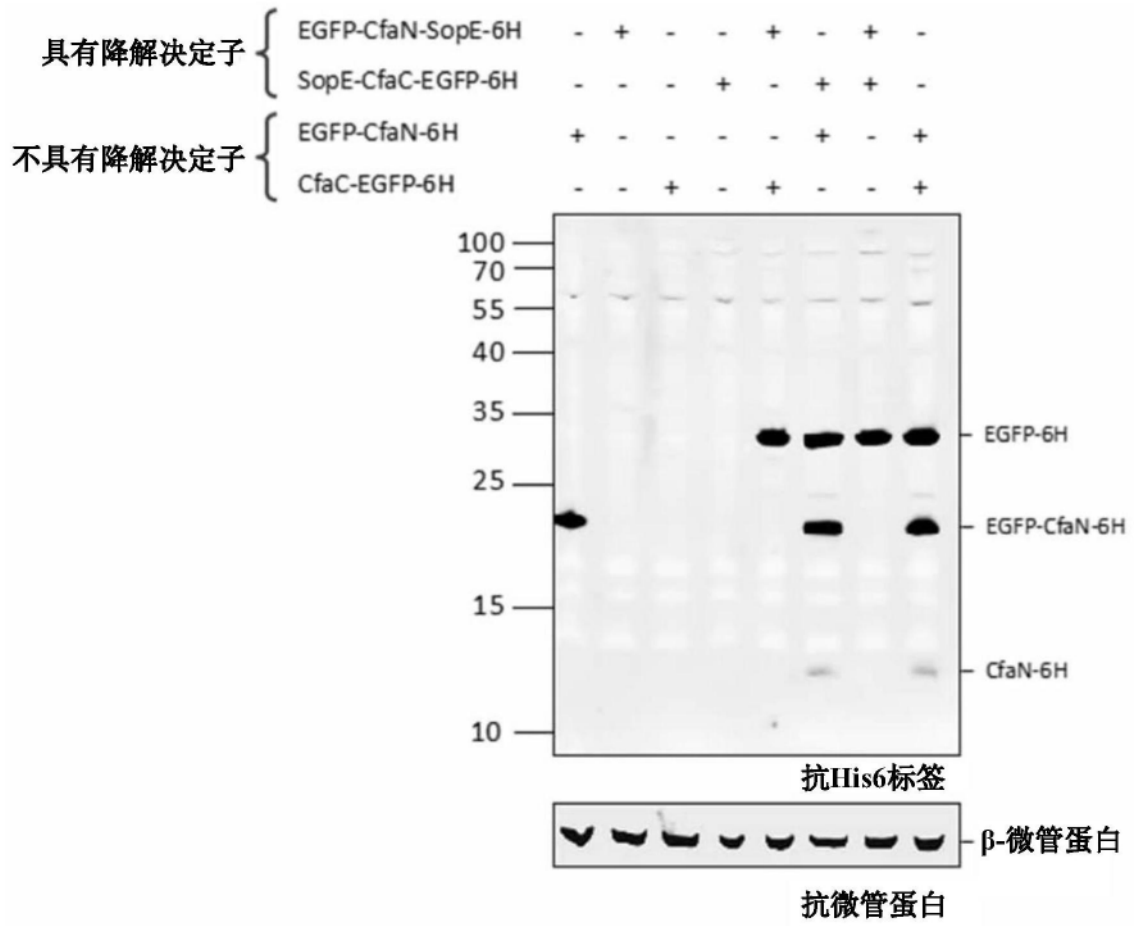


图9

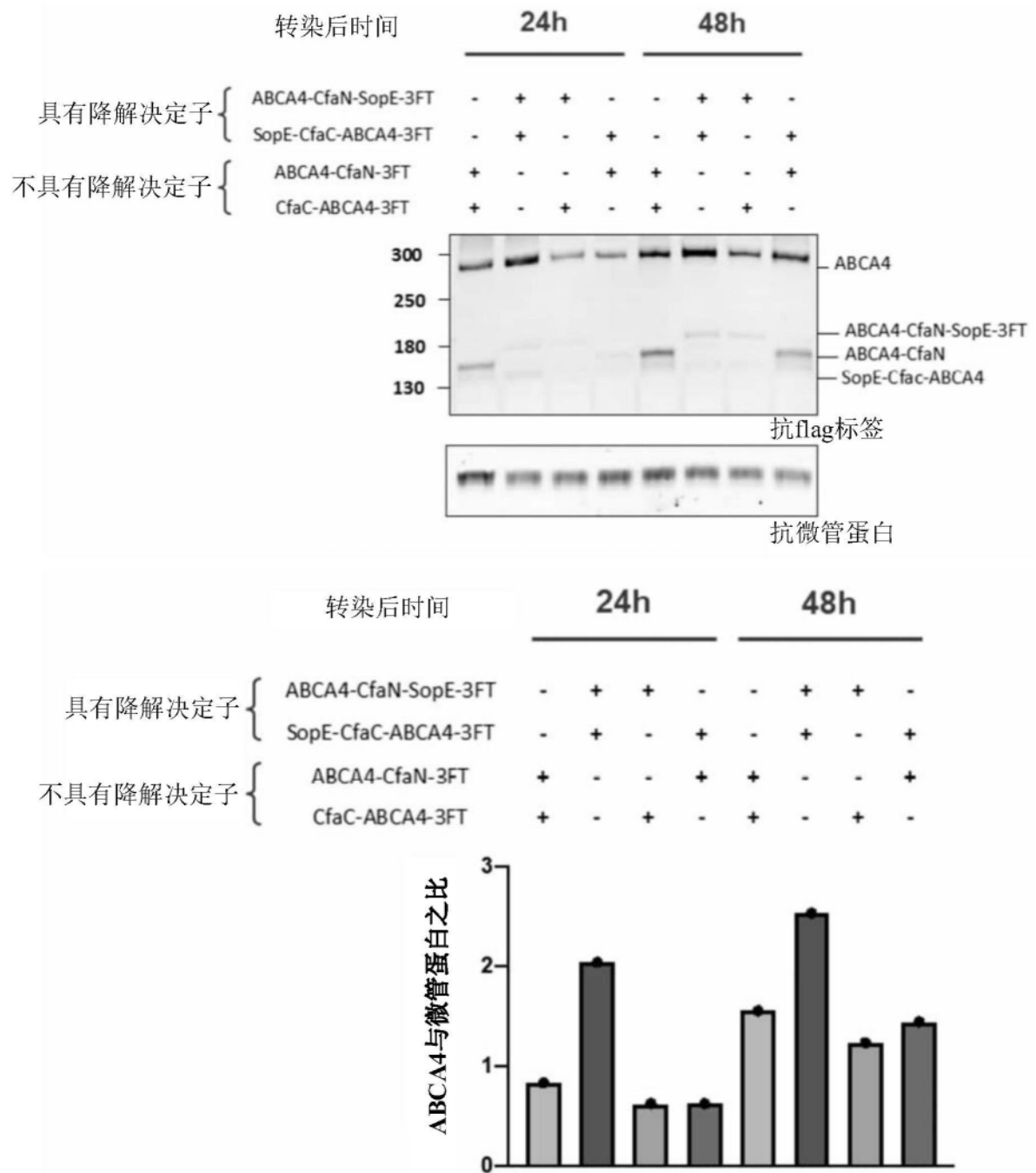


图10

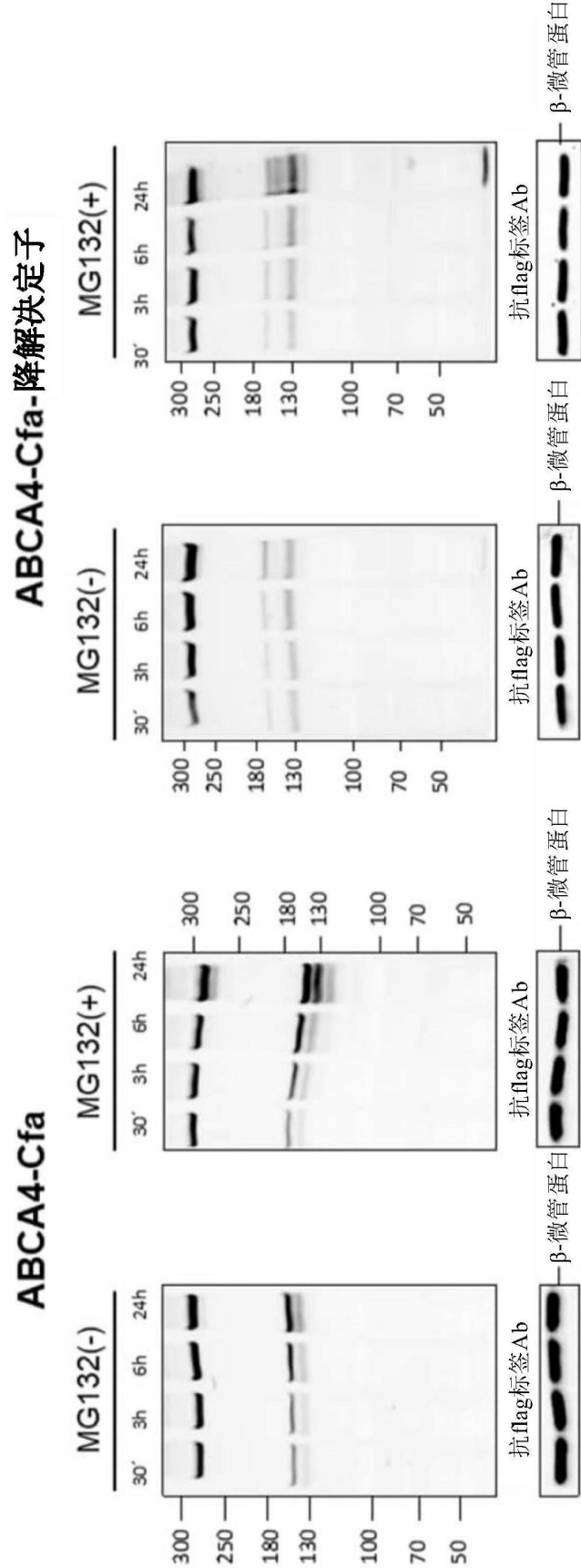


图11

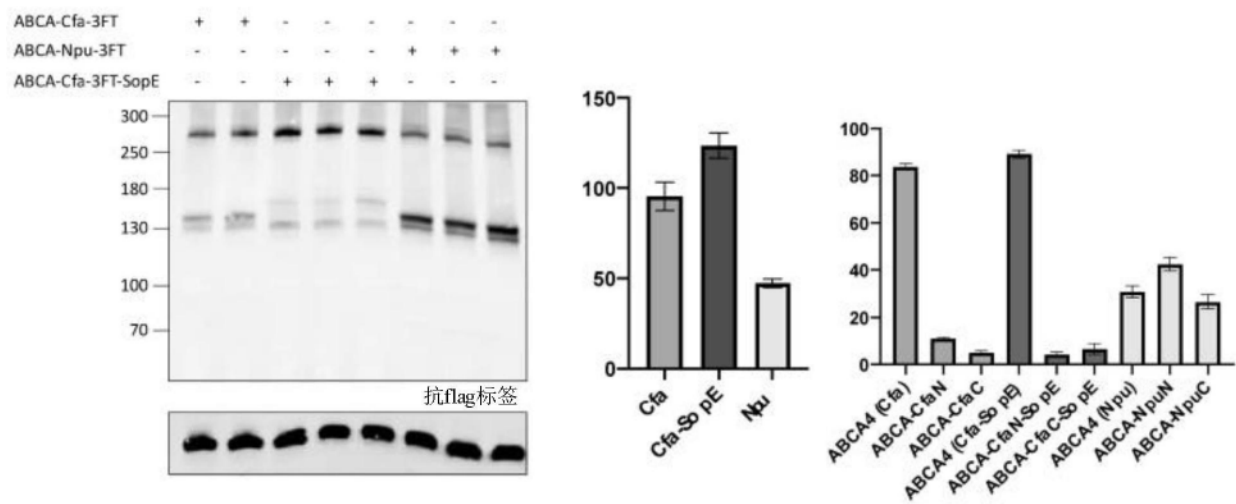


图12

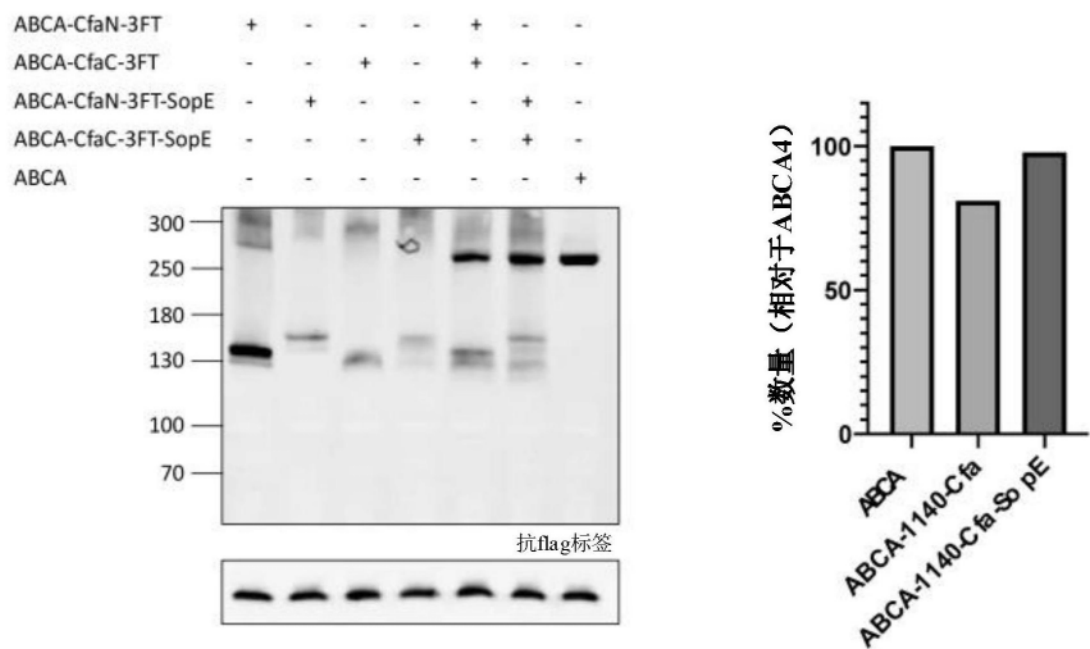


图13

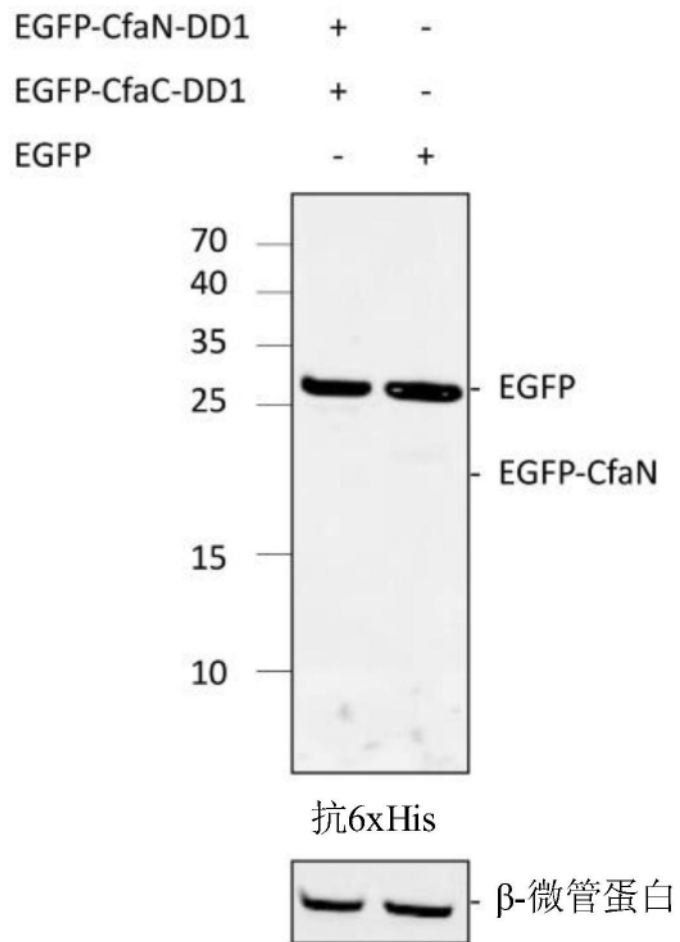


图14

| 序列比较 |            |             |             |             |             |             |             |             |            |            |
|------|------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|------------|
| 1    | 11         | 21          | 31          | 41          | 51          | 61          | 71          | 81          | 91         |            |
| 1    | MGFVRDQJLL | LM/NWTLKR   | QKIRFVELV   | WPLSLFLVI   | WLRNANPLYS  | HHECFPNKA   | MPSAGMLPWL  | QGIFCNVNNP  | CFQSPITGES | PGIVSNYNN  |
| 101  | ILARVDRDFO | ELIANAPESQ  | HLCRWTELH   | ILSQHNDTLR  | THPERIAGRG  | IRIRDILKDE  | ETLTLFLIKN  | IGLSDSVVYL  | LINSQVRPEQ | FAHGVDDIAL |
| 201  | KDIACSEALL | ERFIIFSQR   | CAKTURYALC  | SLSQOTLQWI  | EDTLVANYDE  | FKLFRVLPVL  | LDSRSQCINL  | RSWCGILSDM  | SPRIQEFIHR | PSMQDILLMT |
| 301  | RPLAQNGOPE | TFTKLNGOPE  | DLLCGYEGG   | GSRVLSFNNY  | EDNNYKAFUG  | IDSTRKDPIY  | SYDRRTTSEC  | NALIQSLESN  | PUTKIARAA  | KPLIAGKILY |
| 401  | TPDSPAARRI | LKNANSTFEE  | LEHVRKLVA   | WEEVGFQIY   | FFDNSTQMM   | IDDTLGNPTV  | KDFLNRQJCE  | EGITAEAILN  | FLYKGFRESQ | ADDMANFDMR |
| 501  | DIFNITDRIL | RLVNQYLECL  | VLDKFESYND  | ETQLTORALS  | LLEENMFAG   | VVFPDMYPMI  | SSLPPHVVKYK | IRMDIDVVEK  | INKIKDRYMD | SGPRADFEVD |
| 601  | FRYIWCGFAY | LODAVEQCIT  | RSQVQAEAPV  | CIVLOQMPYP  | CFVDDSEMI   | LNRCEPIFMV  | LAWIYVSMT   | VKSIVLEKEL  | RLKETILNQC | VSNNAVICTW |
| 701  | FLDSFSIMSM | SIFLLTIIFM  | HGRILHYSDP  | FILFELLLAF  | STATIMLCFL  | LSTFFSKASL  | AAACSGVIYF  | TIYLPHELFC  | AWQDRITAEI | KIYAVSLSPV |
| 801  | AFGFGTEYLV | RFEQGLGLQ   | WSNIGNSPTE  | GDEFSILLSM  | QMILLDAAVY  | GILLAWYLDQV | FFGDYGTPLP  | WYFLQESYN   | LGEGCGSTRE | ERALEKTEPL |
| 901  | TEETEDPEHP | EGIHDSFFER  | EHQGWPGVC   | VKNLVKIFEP  | CGRPADVRLN  | ITFYENQITA  | FLCHNCAGKT  | TTLTILTCGL  | PPTSGTVLVG | GRDIETSLDA |
| 1001 | VRQSLGMCPO | BNILFHHLTV  | AEHULFYAQL  | KGSQEEAQL   | EHEAMLEDTG  | LHHKNEEAQ   | DLSCGQRKL   | SVAIAFVGDA  | KVILDEPTS  | GVDPYSRRSI |
| 1101 | WDLILKYRSG | RTIIMSTHIM  | DEADLLGDRI  | ALIAQCRLYC  | SGTPIFLKNC  | ECTGLYLTIV  | RKMKLIQSOR  | KGSECTCSGS  | SKCFSTTCDA | HVDDLTPQV  |
| 1201 | LDGQVNEIMD | VVLHNVPEAK  | LVEICIGQELI | FLLPHNNTKH  | RAYASLFRRL  | EETLADLGLS  | SEGISDTPLE  | EIFLKVTEDS  | DSGPIFAGGA | QOKRENVNPR |
| 1301 | HPCLGPRJKA | QOTPODSHVC  | SPGAPAAHPE  | QOPPEPECP   | GPQINTGTOL  | VLOHVOALLV  | IRFQHTIRSH  | KDFLAQIVLP  | ATFVFLALML | SIVIPFFGEY |
| 1401 | PALTLPWYIY | GQYITFFSMD  | EPGSEQFTVL  | ADVLINKPGF  | GNRCILKEGML | PEYPCGNSTP  | WMTPSVSPNI  | TOLFQKQMT   | QVNPSPSCRC | STREKLTMLP |
| 1501 | ECPEGACGLP | PPORTQORSTE | ILQDLTRNI   | SDFLVKTYPDA | LIRSLKSKF   | WYNEQRYGCI  | SIGCKLPVVP  | ITGEALVGFEL | SDLGRIMNVS | CGPITREASK |
| 1601 | EIPDFLHLE  | TEDNIKVWFN  | NKGCHALYSE  | LNVAHNAILR  | ASLPKDRSPE  | EYGITVVISQP | LNLTKEQLSE  | ITVLTISVDA  | VVAICVIFSM | STVPASFVLY |
| 1701 | LIQERVNKS  | HLQFISGVSP  | ITYWVTFILW  | DIMNYSVSAG  | LVVGIFIGFQ  | KKAYTSPENL  | PALVALLILY  | GWAVIPMMYP  | ASFELFVPSI | AYVALSCANL |
| 1801 | FIGINSSAIT | FILELFENNR  | TLLR/NAVLR  | KLLIVFPBFC  | LGRGLIDIAL  | SOAVTDVYAR  | FGEHSANPF   | HMDLCKNLF   | AMVVEGVVYF | LLTILVQRHF |
| 1901 | FLSQMIAEPT | KEPIVDEDD   | VAEERQRIIT  | CGNKTIDILL  | HELTKLYPOT  | SSPAVDRLCV  | GVRPCECFGL  | LOVNGCAGKIT | TFKMLTGDIT | VTSQDATVAG |
| 2001 | KSILTNISEV | HQNMICYCPOF | DAIDELLTCR  | EHLVLYABLR  | GVPAEEIEIV  | ANWSIKSLGL  | TYVADCLACT  | YSCGHRKULS  | TAIALICCPP | LVLLEPTTG  |
| 2101 | MDPOARRILW | NVIVSIIREG  | RAVVLTSISM  | EECEALCTEL  | ALIMVGAFTC  | MCTIQHLKSK  | FGDGIVIVTEK | IKSPKDDLLP  | DINPVEOFFQ | GNFPGSVQRE |
| 2201 | RHYNMLOFOV | SSSSLIARIFQ | LLLSHKDSLL  | IEEYSVTQTT  | LDQVFVNEAF  | QOTESHDLP   | HPRAAGASRQ  | AQDDYKHG    | DYKDHIDYK  | DDDDK      |

图15



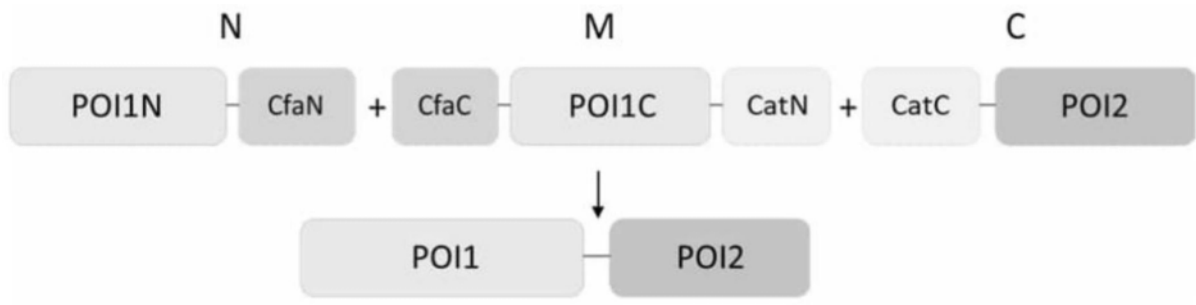


图16

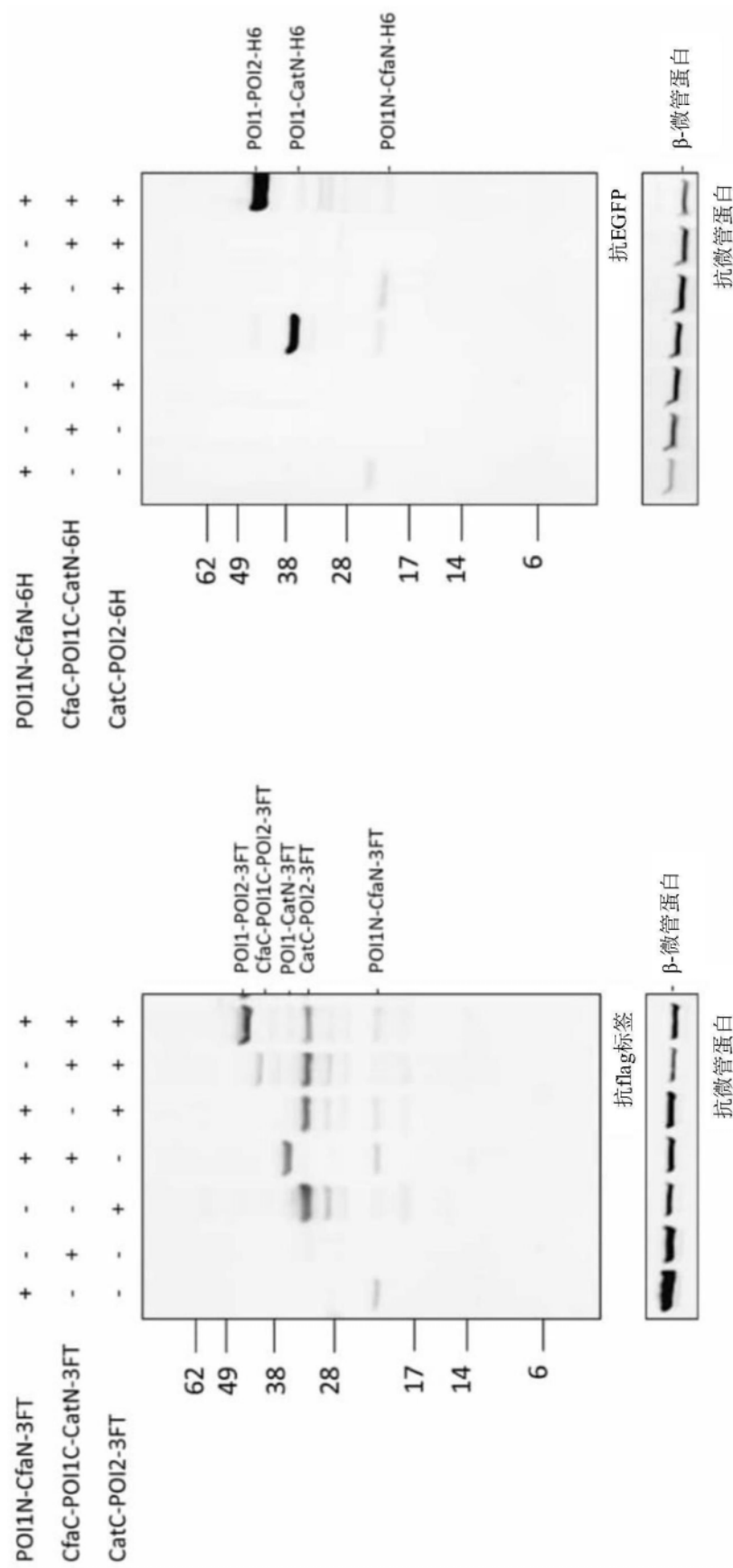


图17

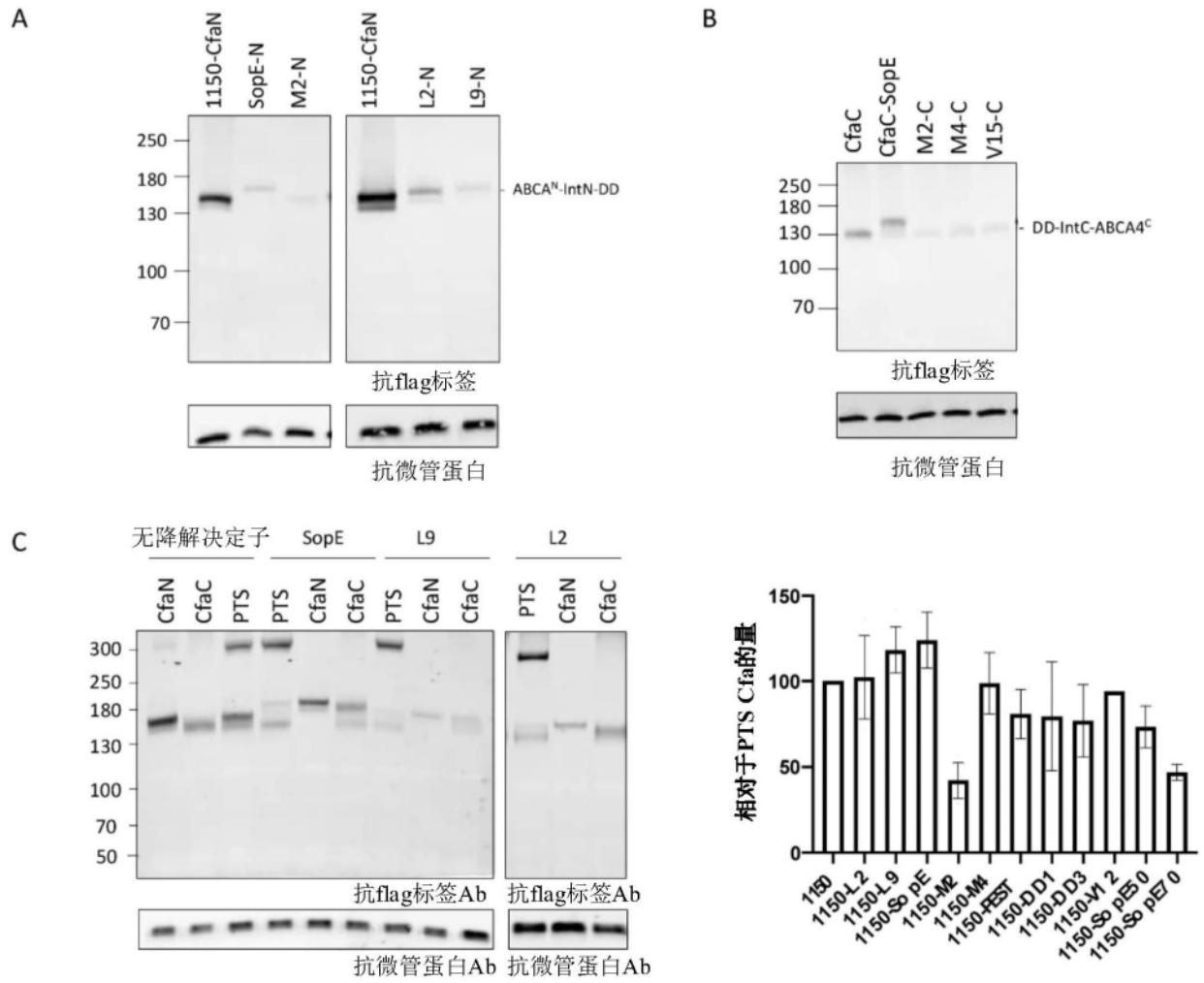


图18

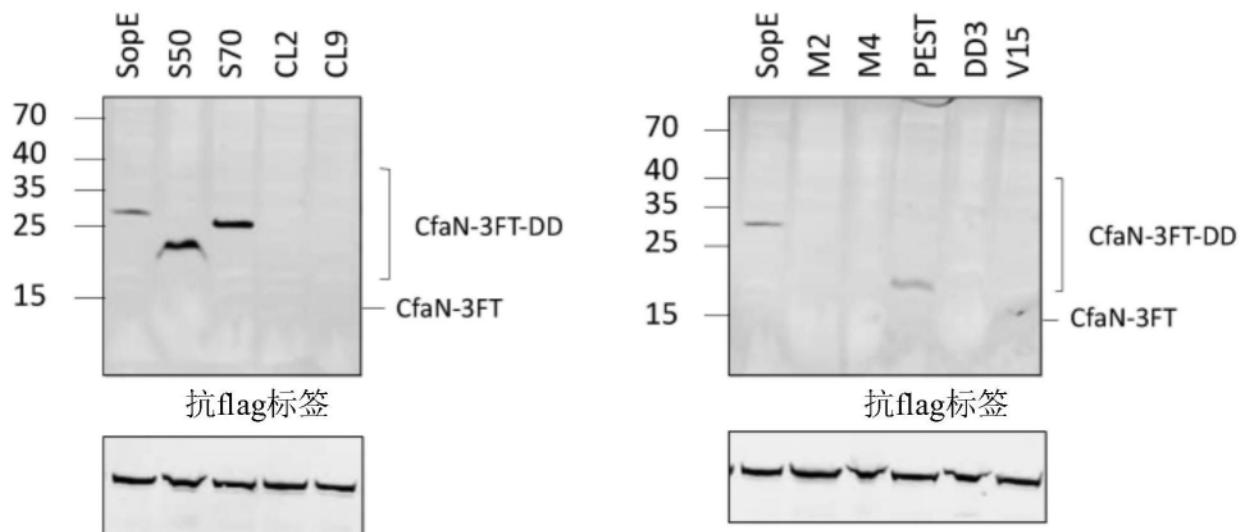


图19

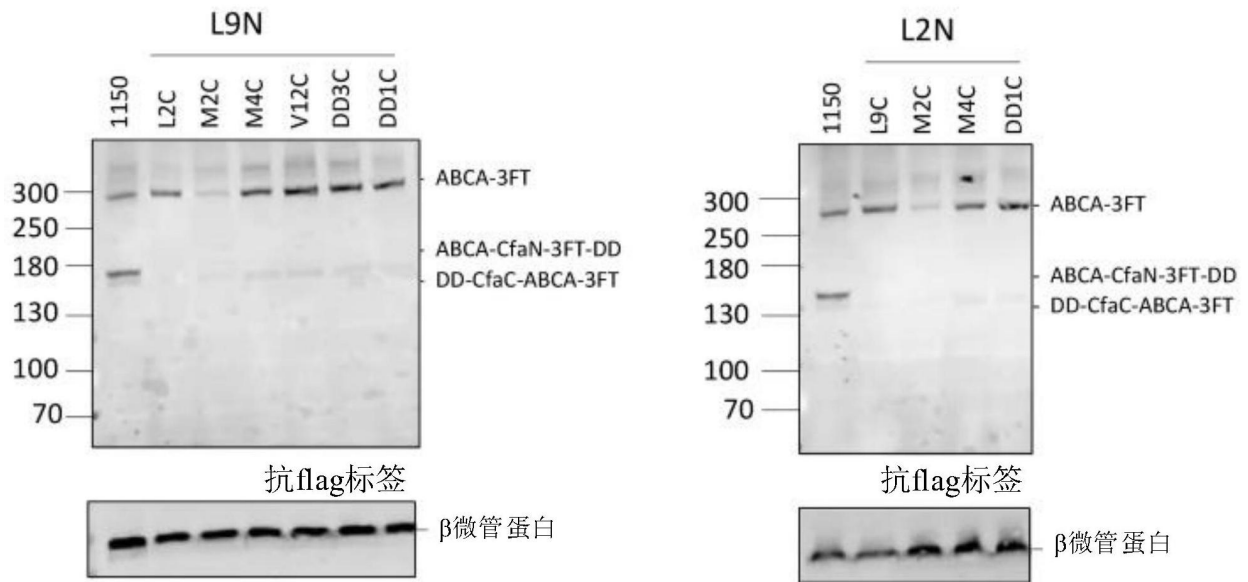


图20

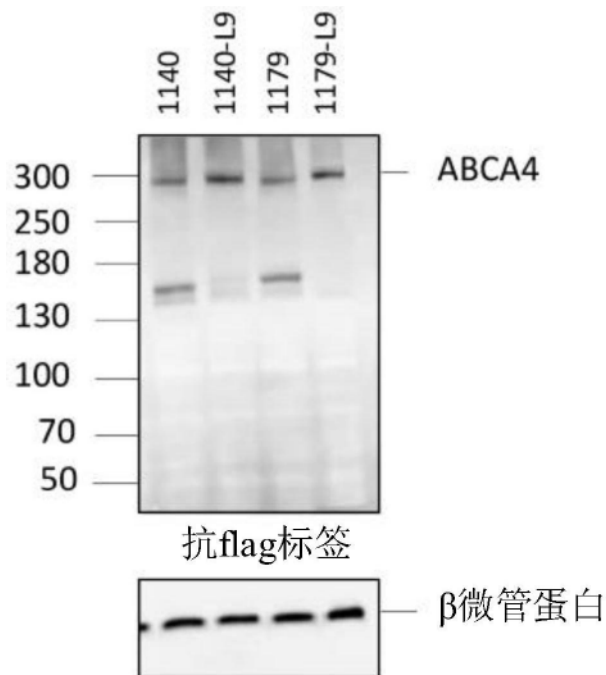


图21

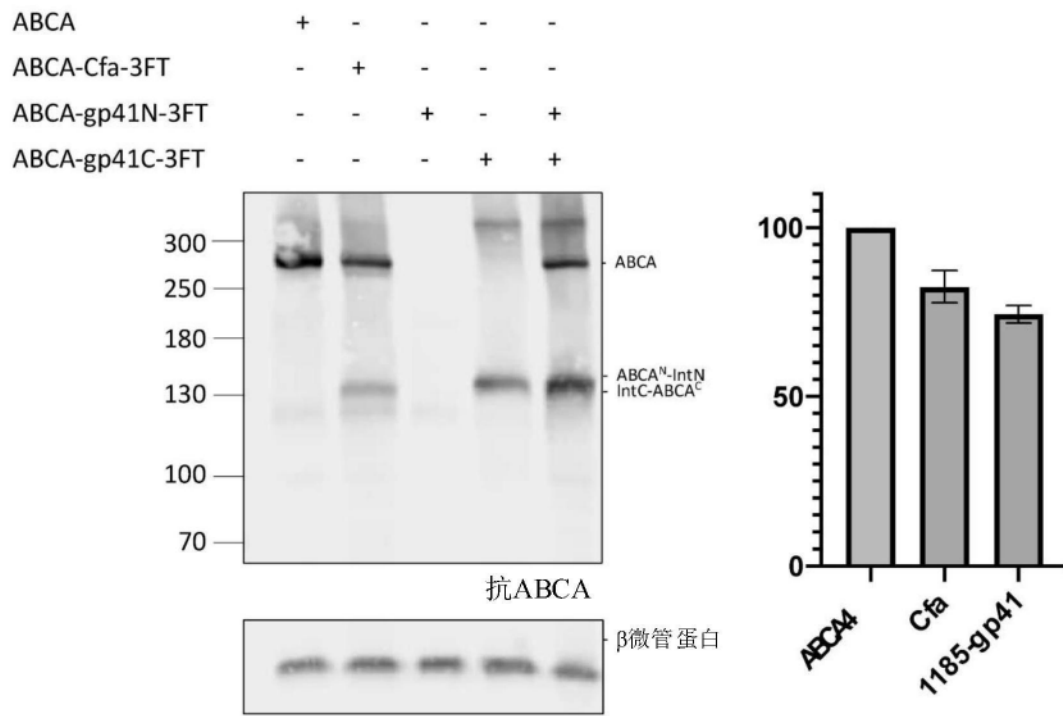


图22

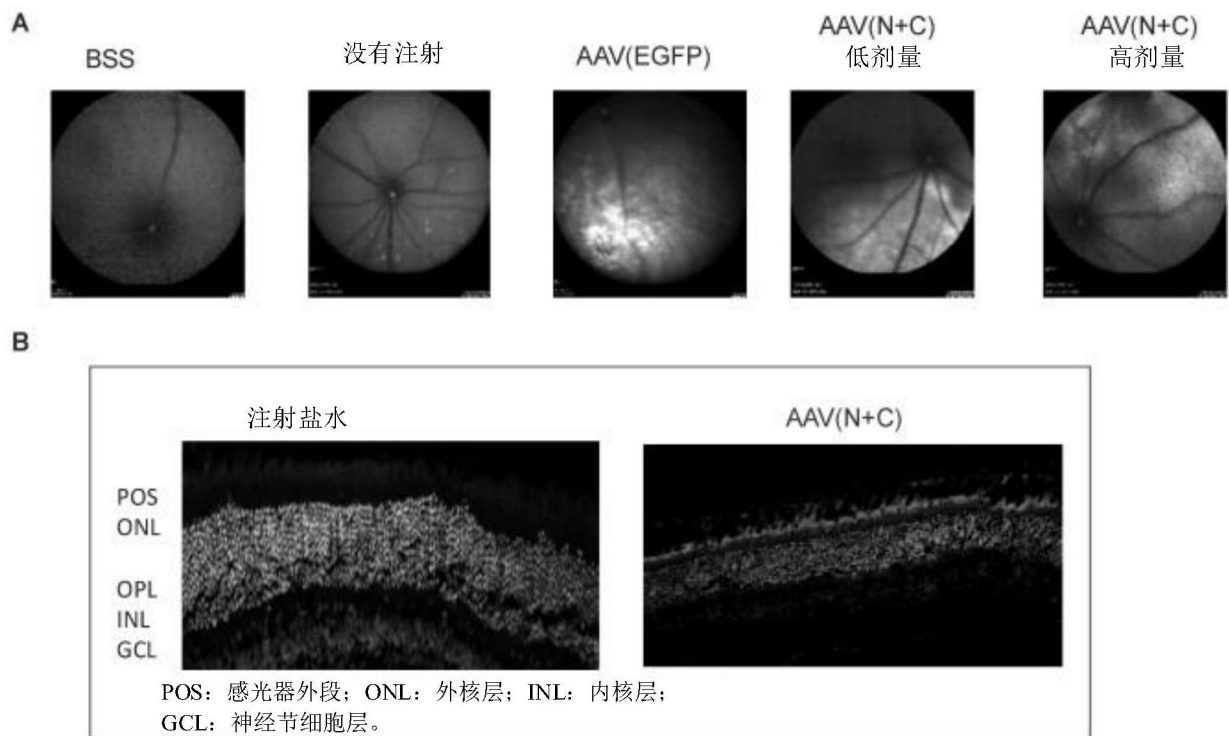


图23