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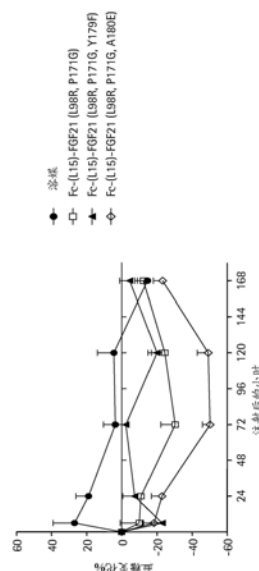
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(54) 发明名称

FGF21突变体及其用途

(57) 摘要

本发明涉及FGF21突变体及其用途,提供编码FGF21突变体多肽的核酸分子、FGF21突变体多肽、包含FGF21突变体多肽的药物组合物、以及使用这类核酸、多肽或药物组合物来治疗代谢紊乱的方法。



1. 一种由SEQ ID NO: 4的氨基酸序列组成的多肽, 其中:
 - (a) 在180位的氨基酸残基选自甘氨酸、脯氨酸、丝氨酸和谷氨酸; 和
 - (b) 在98位的氨基酸残基是精氨酸或在171位的氨基酸残基是甘氨酸。
2. 权利要求1的多肽, 其进一步包含由SEQ ID NO: 31组成的接头序列。
3. 权利要求1或2的多肽, 其进一步包含由SEQ ID NO: 11组成的Fc结构域。
4. 权利要求1-3中任一项的多肽, 其中所述多肽与一种或多种聚合物共价连接。
5. 权利要求4的多肽, 其中所述聚合物是PEG。
6. 一种药物组合物, 包含权利要求1-3中任一项的多肽和药学上可接受的配制剂。
7. 权利要求6的药物组合物, 其中所述药学上可接受的配制剂是水凝胶。
8. 权利要求6或7的药物组合物, 其用于治疗代谢紊乱的方法。
9. 权利要求8的药物组合物, 其中所述代谢紊乱是2型糖尿病或肥胖症。
10. 权利要求8的药物组合物, 其中所述代谢紊乱是非酒精性脂肪性肝炎 (NASH)。
11. 一种编码权利要求1-3中任一项的多肽的核酸。
12. 一种载体, 包含权利要求11的核酸分子。
13. 一种宿主细胞, 包含权利要求11的核酸分子。
14. 一种多聚体, 包含两个或更多个权利要求1-3中任一项的多肽。
15. 权利要求14的多聚体, 其包含第一链和第二链, 所述第一链由以下组成:
 - (a.1) SEQ ID NO: 4的多肽, 其中:
 - (i) 98位的亮氨酸被精氨酸取代;
 - (ii) 171位的脯氨酸被甘氨酸取代; 以及
 - (iii) 180位的丙氨酸被谷氨酸取代;
 - (b.1) 由SEQ ID NO: 31组成的接头序列; 以及
 - (c.1) 由SEQ ID NO: 11组成的Fc结构域; 以及所述第二链由以下组成:
 - (a.2) SEQ ID NO: 4的多肽, 其中:
 - (i) 98位的亮氨酸被精氨酸取代;
 - (ii) 171位的脯氨酸被甘氨酸取代; 以及
 - (iii) 180位的丙氨酸被谷氨酸取代;
 - (b.2) 由SEQ ID NO: 31组成的接头序列; 以及
 - (c.2) 由SEQ ID NO: 11组成的Fc结构域。

FGF21突变体及其用途

[0001] 本申请为分案申请,原申请的申请日为2010年5月4日,申请号为201080031036.6 (PCT/US2010/033478),发明名称为“FGF21突变体及其用途”。

[0002] 本申请要求2009年5月5日提交的美国临时申请号61/175,736和2009年12月9日提交的美国临时申请号61/285,118的权益,全部所述申请通过引用结合到本文中。

发明领域

[0003] 本发明涉及编码FGF21突变体多肽的核酸分子、FGF21突变体多肽、包含FGF21突变体多肽的药物组合物和使用这类核酸、多肽或药物组合物用于治疗代谢紊乱的方法。

[0004] 发明背景

[0005] FGF21是属于包括FGF19、FGF21和FGF23的成纤维细胞生长因子 (FGF) 亚家族的分泌多肽 (Itoh等,2004,Trend Genet.20:563-69)。FGF21是非典型的FGF,因为它不依赖于肝素,并且在葡萄糖、脂质和能量代谢的调节中起激素的作用。

[0006] 从肝cDNA文库中分离出作为肝分泌因子的FGF21。它在肝和胰腺中高表达,并且是主要在肝中表达的FGF家族的唯一成员。过量表达FGF21的转基因小鼠具有生长速率缓慢、血浆葡萄糖和甘油三酯水平低下的代谢表型,并且不存在年龄相关性2型糖尿病、胰岛增大和肥胖症。在啮齿动物和灵长类模型中药理性给予重组FGF21蛋白导致血浆葡萄糖水平正常化、甘油三酯和胆固醇水平降低以及葡萄糖耐量和胰岛素敏感性得到改善。另外,FGF21通过增加能量消耗、体力活动和代谢率而减轻体重和体脂肪。实验研究为药理性给予FGF21以治疗人的2型糖尿病、肥胖症、血脂异常 (dyslipidemia) 和其它代谢病况或代谢紊乱提供了支持。

[0007] 人FGF21具有短的体内半寿期。在小鼠中,人FGF21的半寿期为1-2小时,在食蟹猴 (cynomolgus monkey) 中,半寿期为2.5-3小时。在开发在2型糖尿病的治疗中用作治疗剂的FGF21蛋白时,可能需要延长半寿期。具有半寿期延长的FGF21蛋白可允许较低频率地给予待给予该蛋白质的患者。本文中描述了这类蛋白质。

[0008] 发明概述

[0009] 本发明公开一种分离的多肽,包含SEQ ID NO:4的氨基酸序列,并且还包含:(a)至少一个在180位的氨基酸取代;和(b)选自以下的至少一个氨基酸取代:(i)在171位的取代;和(ii)在98位的取代;以及(c)它们的组合。

[0010] 在一个实施方案中,分离的多肽包含在98位的取代和在180位的取代,并且其中:(a)所述在98位的取代选自精氨酸、半胱氨酸、谷氨酸、谷氨酰胺、赖氨酸和苏氨酸;和(b)所述在180位的取代选自甘氨酸、脯氨酸、丝氨酸或谷氨酸;以及(c)它们的组合。在一个实施方案中,98位的残基是精氨酸并且180位的残基是谷氨酸。还提供了一种融合多肽,包含与异源氨基酸序列融合的分离的多肽。在一个实施方案中,异源氨基酸序列是Fc结构域或其片段,并且可包含SEQ ID NO:11的氨基酸序列。在另一实施方案中,多肽通过接头与Fc结构域融合,以及在又一实施方案中,接头包含GGGSGGGSGGGGS (SEQ ID NO:31)。在一个特定实施方案中,多肽包含SEQ ID NO:47。还公开了一种多聚体,包含两个或更多个融合多肽。

也公开一种药物组合物,包含分离的多肽和诸如水凝胶等药学上可接受的配制剂(formulation agent)。在另一方面,提供了一种治疗代谢紊乱的方法以及在一个实施方案中,该方法包括向有需要的人患者给予本文提供的药物组合物。在一个实施方案中,代谢紊乱是糖尿病和在另一个中,代谢紊乱是肥胖症。也提供了编码分离的多肽的核酸,以及在一个实施方案中核酸包含SEQ ID NO:46。核酸可存在于载体中,所述载体可自身存在于宿主细胞中。在又一实施方案中,多肽包含:(a)不超过8个氨基酸残基的氨基末端截短,其中多肽能够降低哺乳动物的血糖;(b)不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖;或(c)不超过8个氨基酸残基的氨基末端截短和不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖。还在其它的实施方案中,多肽共价连接一种或多种聚合物,例如PEG。

[0011] 在另一实施方案中,分离的多肽包含在171位的取代和在180位的取代,并且其中:(a)所述在180位的取代选自甘氨酸、脯氨酸、丝氨酸和谷氨酸;(b)所述在171位的取代选自丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、组氨酸、赖氨酸、丝氨酸、苏氨酸、色氨酸和酪氨酸;以及(c)它们的组合。在一个实施方案中,在171位的残基是甘氨酸和在180位的残基是谷氨酸。也提供一种融合多肽,包含与异源氨基酸序列融合的分开的多肽。在一个实施方案中,异源氨基酸序列是Fc结构域或其片段,并且可包含SEQ ID NO:11的氨基酸序列。在另一实施方案中,多肽通过接头与所述Fc结构域融合,以及在另一实施方案中,接头包含GGGSGGGSGGGGS (SEQ ID NO:31)。在一个特定实施方案中,多肽包含SEQ ID NO:47。还公开一种多聚体,包含两个或更多个融合多肽。也公开一种药物组合物,包含分离的多肽和诸如水凝胶等药学上可接受的配制剂。在另一方面,提供一种治疗代谢紊乱的方法,以及在一个实施方案中,该方法包括给有需要的人患者给予本文提供的药物组合物。在一个实施方案中,代谢紊乱是糖尿病和在另一个中,代谢紊乱是肥胖症。也提供了编码分离的多肽的核酸,以及在一个实施方案中核酸包含SEQ ID NO:46。核酸可存在于载体中,所述载体可自身存在于宿主细胞中。在又一实施方案中,多肽包含:(a)不超过8个氨基酸残基的氨基末端截短,其中多肽能够降低哺乳动物的血糖;(b)不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖;或(c)不超过8个氨基酸残基的氨基末端截短和不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖。还在其它的实施方案中,多肽共价连接一种或多种聚合物,例如PEG。

[0012] 在又一实施方案中,多肽包含SEQ ID NO:4的在98位的取代、在171位的取代和在180位的取代,并且其中:(a)在171位的取代选自丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、组氨酸、赖氨酸、丝氨酸、苏氨酸、色氨酸或酪氨酸;(b)在98位的取代选自精氨酸、半胱氨酸、谷氨酸、谷氨酰胺、赖氨酸或苏氨酸;以及(c)在180位的取代选自甘氨酸、脯氨酸、丝氨酸或谷氨酸;及其组合。在又一个实施方案中,在98位的残基是精氨酸,在171位的残基是甘氨酸和在180位的残基是谷氨酸。也提供一种融合多肽,包含与异源氨基酸序列融合的分开的多肽。在一个实施方案中,异源氨基酸序列是Fc结构域或其片段,并且可包含SEQ ID NO:11的氨基酸序列。在另一实施方案中,多肽通过接头融合至所述Fc结构域,以及在另一实施方案中,接头包含GGGSGGGSGGGGS (SEQ ID NO:31)。在一个特定实施方案中,多肽包含SEQ ID NO:47。还公开一种多聚体,包含两个或更多个融合多肽。也公开一种药物组合物,包含分离的多肽和诸如水凝胶等药学上可接受的配制剂。在另

一方面,提供一种治疗代谢紊乱的方法,以及在一个实施方案中,该方法包括给有需要的人患者给予本文提供的药物组合物。在一个实施方案中,代谢紊乱是糖尿病和在另一个中,代谢紊乱是肥胖症。也提供了编码分离的多肽的核酸,以及在一个实施方案中核酸包含SEQ ID NO:46。核酸可存在于载体中,所述载体可自身存在于宿主细胞中。在又一实施方案中,多肽包含:(a)不超过8个氨基酸残基的氨基末端截短,其中多肽能够降低哺乳动物的血糖;(b)不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖;或(c)不超过8个氨基酸残基的氨基末端截短和不超过12个氨基酸残基的羧基末端截短,其中多肽能够降低哺乳动物的血糖。还在其它的实施方案中,多肽共价连接一种或多种聚合物,例如PEG。

[0013] 根据下面某些实施方案更详细的说明和权利要求书,本发明的具体实施方案将是显而易见的。

[0014] 附图简述

[0015] 图1A-1B显示对FGF21截短突变体7-181和8-181(图1A)及FGF21截短突变体1-172、1-171、1-169和1-164(图1B)进行的ELK-萤光素酶活性测定结果;各图表示所得到的对于人FGF21对照的结果。

[0016] 图2显示对人FGF21对照及FGF21截短突变体3-181、4-181、5-181、7-181、8-181、1-180、1-178、1-177、1-176、1-175、1-174、1-173、1-172、9-181和1-149进行的ELK-萤光素酶活性测定结果。

[0017] 图3显示在注射PBS(实心条形柱)、人FGF21对照(空心条形柱)或FGF21截短突变体8-181(灰色条形柱)和9-181(点状条形柱)的小鼠中测定的血糖水平。

[0018] 图4显示在注射PBS(实心圆)、Fc-FGF21对照(WT)(空心圆)或者包含氨基酸残基5-181(实心三角)或7-181(空心三角)的截短Fc-FGF21融合蛋白的小鼠中测定的血糖水平变化百分比。

[0019] 图5显示在注射PBS(实心圆)、FGF21-Fc对照(WT)(空心圆)、包含残基1-175的截短FGF21-Fc融合蛋白(实心三角)或包含氨基酸残基1-171的截短Fc-FGF21蛋白(空心三角)的小鼠中测定的血糖水平变化百分比。

[0020] 图6A-6D显示人Fc-(G5)-FGF21(SEQ ID NO:107)对照样品(图6A)和注射后6小时(样品D6;图6B)、24小时(样品D24;图6C)和48小时(样品D48;图6D)从小鼠中抽取的Fc-(G5)-FGF21样品的液相色谱-质谱法(LC-MS)分析结果。

[0021] 图7A-7D显示哺乳动物衍生的人FGF21-(G3)-Fc(SEQ ID NO:105)对照样品(图7A)和注射后6小时(样品E6;图7B)、24小时(样品E24;图7C)和48小时(样品E48;图7D)从小鼠中抽取的FGF21-(G3)-Fc样品的LC-MS分析结果。

[0022] 图8A-8D显示Fc-(L15)-FGF21(SEQ ID NO:49)对照样品(图8A)和注射后6小时(图8B)、24小时(图8C)和48小时(图8D)从小鼠中抽取的Fc-(L15)-FGF21样品的LC-MS分析结果。

[0023] 图9A-9D显示FGF21-(L15)-Fc(SEQ ID NO:41)对照样品(图9A)和注射后6小时(图9B)、24小时(图9C)和48小时(图9D)从小鼠中抽取的FGF21-(L15)-Fc样品的LC-MS分析结果。

[0024] 图10A-10B显示由注射入小鼠的Fc-(L15)-FGF21(图10A,SEQ ID NO:49)和FGF21-

(L15)-Fc(图10B,SEQ ID NO:41)融合蛋白的LC-MS分析而鉴定出的切割位点。

[0025] 图11显示在注射PBS(实心条形柱)、Fc-(L15)-FGF21(SEQ ID NO:49)(空心条形柱)或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E(SEQ ID NO:51)(灰色条形柱)、Fc-(L15)-FGF21P171A(SEQ ID NO:53)(点状条形柱)、Fc-(L15)-FGF21S172L(SEQ ID NO:55)(空心斜线交叉条形柱)、Fc-(L15)-FGF21(G170E,P171A,S172L)(SEQ ID NO:59)(实心水平交叉条形柱)或Fc-(L15)-FGF21G151A(SEQ ID NO:61)(空心斜线交叉条形柱)的小鼠中测定的血糖水平。

[0026] 图12显示在注射PBS(实心圆)、Fc-(L15)-FGF21(SEQ ID NO:49)(空心圆)、或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E(SEQ ID NO:51)(实心三角)、Fc-(L15)-FGF21P171A(SEQ ID NO:53)(空心三角)、Fc-(L15)-FGF21S172L(SEQ ID NO:55)(实心菱形)、Fc-(L15)-FGF21(G170E,P171A,S172L)(SEQ ID NO:59)(空心菱形)或Fc-(L15)-FGF21G151A(SEQ ID NO:61)(实心方形)的小鼠中测定的血糖水平变化百分比。

[0027] 图13显示在注射PBS(实心条形柱)、Fc-(L15)-FGF21(SEQ ID NO:49)(空心条形柱)、或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21(P150A,G151A,I152V)(灰色条形柱)、Fc-(L15)-FGF21G170E(SEQ ID NO:51)(空心斜线交叉条形柱)、Fc-(L15)-FGF21(G170E,P171A)(SEQ ID NO:63)(灰色斜线交叉条形柱)、或Fc-(L15)-FGF21(G170E,S172L)(SEQ ID NO:67)(空心斜线交叉条形柱)的小鼠中测定的血糖水平。

[0028] 图14显示在注射PBS(实心方形)、Fc-(L15)-FGF21(SEQ ID NO:49)(空心方形)、或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21(P150A,G151A,I152V)(SEQ ID NO:65)(实心倒三角)、Fc-(L15)-FGF21G170E(SEQ ID NO:51)(空心倒三角)、Fc-(L15)-FGF21(G170E,P171A)(SEQ ID NO:63)(实心圆)或Fc-(L15)-FGF21(G170E,S172L)(SEQ ID NO:67)(空心圆)的小鼠中测定的血糖水平变化百分比。

[0029] 图15显示在注射PBS(实心条形柱)或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E(SEQ ID NO:51)(空心条形柱)、Fc-(L15)-FGF21G170A(SEQ ID NO:69)(灰色条形柱)、Fc-(L15)-FGF21G170C(SEQ ID NO:71)(空心交叉条形柱)、Fc-(L15)-FGF21G170D(SEQ ID NO:73)(灰色与白色条形柱)、Fc-(L15)-FGF21G170N(SEQ ID NO:75)(实心交叉条形柱)、或者Fc-(L15)-FGF21G170S(SEQ ID NO:77)(空心交叉条形柱)的小鼠中测定的血糖水平。

[0030] 图16显示在注射PBS(实心圆)或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E(SEQ ID NO:51)(空心圆)、Fc-(L15)-FGF21G170A(SEQ ID NO:69)(实心三角)、Fc-(L15)-FGF21G170C(SEQ ID NO:71)(空心三角)、Fc-(L15)-FGF21G170D(SEQ ID NO:73)(实心菱形)、Fc-(L15)-FGF21G170N(SEQ ID NO:75)(空心菱形)、或者Fc-(L15)-FGF21G170S(SEQ ID NO:77)(实心倒三角)的小鼠中测定的血糖水平变化百分比。

[0031] 图17显示在注射PBS(实心条形柱)或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E(SEQ ID NO:51)(空心条形柱)、Fc-(L15)-FGF21P171E(SEQ ID NO:79)(灰色条形柱)、Fc-(L15)-FGF21P171H(SEQ ID NO:81)(实心交叉条形柱)Fc-(L15)-FGF21P171Q(SEQ ID NO:83)(空心交叉条形柱)、Fc-(L15)-FGF21P171T(SEQ ID NO:85)(点状条形柱)、或者Fc-(L15)-FGF21P171Y(SEQ ID NO:87)(灰色交叉条形柱)的小鼠中测定的血糖水平。

[0032] 图18显示在注射PBS(实心圆)或者Fc-(L15)-FGF21突变体Fc-(L15)-FGF21G170E

(SEQ ID NO:51) (空心圆)、Fc- (L15) -FGF21P171E (SEQ ID NO:79) (实心三角)、Fc- (L15) -FGF21P171H (SEQ ID NO:81) (空心三角)、Fc- (L15) -FGF21P171Q (SEQ ID NO:83) (实心菱形)、Fc- (L15) -FGF21P171T (SEQ ID NO:85) (空心菱形)、或者Fc- (L15) -FGF21P171Y (SEQ ID NO:87) (实心方形) 的小鼠中测定的血糖水平变化百分比。

[0033] 图19A-19D显示Fc- (L15) -FGF21对照样品 (图19A, SEQ ID NO:49) 和注射后6小时 (图19B)、24小时 (图19C) 和48小时 (图19D) 从小鼠中抽取的样品的LC-MS分析结果。

[0034] 图20A-20D显示Fc- (L15) -FGF21G170E对照样品 (图20A, SEQ ID NO:51) 和注射后6小时 (图20B)、24小时 (图20C) 和48小时 (图20D) 从小鼠中抽取的Fc- (L15) -FGF21G170E样品的LC-MS分析结果。

[0035] 图21A-21D显示Fc- (L15) -FGF21P171A对照样品 (图21A, SEQ ID NO:53) 和注射后6小时 (图21B)、24 (图21C)、48小时 (图21D) 从小鼠中抽取的Fc- (L15) -FGF21P171A样品的LC-MS分析结果。

[0036] 图22A-22D显示Fc- (L15) -FGF21S172L对照样品 (图22A, SEQ ID NO:55) 和注射后6小时 (图22B)、24小时 (图22C) 和48小时 (图22D) 从小鼠中抽取的Fc- (L15) -FGF21S172L样品的LC-MS分析结果。

[0037] 图23A-23D显示由注射入小鼠中的Fc- (L15) -FGF21 (图23A, SEQ ID NO:49)、Fc- (L15) -FGF21G170E (图23B, SEQ ID NO:51)、Fc- (L15) -FGF21P171A (图23C, SEQ ID NO:53) 和Fc- (L15) -FGF21S172L (图23D, SEQ ID NO:55) 融合蛋白的LC-MS分析而鉴定出的切割位点。

[0038] 图24A-24C显示对FGF21突变体FGF21L99R (SEQ ID NO:109)、FGF21L99D (SEQ ID NO:111) 和FGF21A111T (SEQ ID NO:113) (图24A); FGF21突变体FGF21A129D (SEQ ID NO:115)、FGF21A129Q (SEQ ID NO:117) 和FGF21A134K (SEQ ID NO:119) (图24B); 以及FGF21突变体FGF21A134Y (SEQ ID NO:121)、FGF21A134E (SEQ ID NO:123) 和FGF21A129K (SEQ ID NO:125) (图24C) 进行的ELK-萤光素酶活性测定结果; 各图表示所得到的对于人FGF21对照的结果。

[0039] 图25A-25D显示对Fc- (L15) -FGF21突变体Fc- (L15) -FGF21P171G (SEQ ID NO:89)、Fc- (L15) -FGF21P171S (SEQ ID NO:91) 和Fc- (L15) -FGF21P171T (SEQ ID NO:85) (图25A); Fc- (L15) -FGF21突变体Fc- (L15) -FGF21P171Y (SEQ ID NO:87)、Fc- (L15) -FGF21P171W (SEQ ID NO:93) 和Fc- (L15) -FGF21P171C (SEQ ID NO:95) (图25B); Fc- (L15) -FGF21 (SEQ ID NO:49)、Fc- (L15) -FGF21 (A45K、G170E) (SEQ ID NO:97) 和FGF21A45K (SEQ ID NO:99) (图25C); 以及Fc- (L15) -FGF21 (SEQ ID NO:49)、Fc- (L15) -FGF21P171E (SEQ ID NO:79) 和Fc- (L15) -FGF21 (A45K、G170E) (SEQ ID NO:97) (图25D) 进行的ELK-萤光素酶活性测定结果; 各图表示所得到的对于人FGF21对照的结果。

[0040] 图26A-B显示野生型成熟FGF21和各种FGF21突变体随时间而变化的聚集; 图26A显示将65mg/mL蛋白质在4℃下温育1天、2天和4天后FGF21对照 (WT, 实心菱形) 和FGF21A45K (实心圆) 的聚集百分比变化, 而图26B显示将65mg/mL蛋白质在4℃下温育1天、6天和10天后FGF21对照 (WT) (SEQ ID NO:4) 和FGF21P78C (SEQ ID NO:127)、FGF21P78R (SEQ ID NO:129)、FGF21L86T (SEQ ID NO:131)、FGF21L86C (SEQ ID NO:133)、FGF21L98C (SEQ ID NO:135)、FGF21L98R (SEQ ID NO:137)、FGF21A111T (SEQ ID NO:113)、FGF21A129D (SEQ ID NO:

115)、FGF21A129Q (SEQ ID NO:117)、FGF21A129K (SEQ ID NO:125)、FGF21A134K (SEQ ID NO:119)、FGF21A134Y (SEQ ID NO:121) 和 FGF21A134E (SEQ ID NO:123) (在图中均有标记) 的聚集百分比变化。

[0041] 图27显示对人FGF21对照和FGF21突变体FGF21A45K (SEQ ID NO:99)、FGF21L52T (SEQ ID NO:139) 和 FGF21L58E (SEQ ID NO:141) 进行的ELK-萤光素酶活性测定结果。

[0042] 图28A图示在4℃下温育1天、4天和8天后Fc- (L15)-FGF21突变体Fc- (L15)-FGF21 (6-181,G170E) (SEQ ID NO:101) (实心菱形)、Fc- (L15)-FGF21 (A45K,G170E) (SEQ ID NO:97) (空心方形)、Fc- (L15)-FGF21P171E (SEQ ID NO:79) (实心三角)、Fc- (L15)-FGF21P171A (SEQ ID NO:53) (交叉线)、Fc- (L15)-FGF21G170E (SEQ ID NO:51) (空心三角) 和 FGF21对照 (实心圆) 聚集水平的变化,图28B是同样显示温育结果的柱状图。

[0043] 图29显示在注射PBS (溶媒) (实心圆) 或者Fc- (L15)-FGF21突变体Fc- (L15)-FGF21 (A45K,G170E) (SEQ ID NO:97) (空心圆)、Fc- (L15)-FGF21 (A45K,P171G) (SEQ ID NO:103) (实心三角)、或者Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (空心三角) 的小鼠中测定的血糖水平。

[0044] 图30图示对人FGF21 (实心圆,实线)、Fc- (L15)-FGF21 (SEQ ID NO:49) (空心圆,实线) 和 Fc- (L15) FGF21 (L98R,P171G) (SEQ ID NO:43) (实心三角,虚线) 进行的ELK-萤光素酶活性测定结果。

[0045] 图31图示在室温 (图31A) 和4℃ (图31B) 下9天后观察到的FGF21 (SEQ ID NO:4) (实心圆,实线)、Fc- (L15)-FGF21 (SEQ ID NO:49) (空心圆,实线) 和 Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (实心三角,虚线) 的高分子量聚集物百分比。

[0046] 图32是显示在168小时时间内在各个时间点上观察到的Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) 变化的系列MALDI质谱迹线。

[0047] 图33图示ob/ob小鼠中由PBS溶媒对照 (空心圆)、野生型成熟FGF21 (实心方形)、以及 FGF21突变体Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (实心倒三角);Fc- (L15)-FGF21 (L98R,P171G,182P) (SEQ ID NO:143) (空心菱形) 和 Fc- (L15)-FGF21 (L98R,P171G,182G) (SEQ ID NO:145) (实心圆) 中的每一种所引起的血糖水平变化百分比。

[0048] 图34图示ob/ob小鼠中由PBS溶媒对照 (实心圆) 及 FGF21突变体Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (实心三角);Fc- (L15)-FGF21 (L98R,P171G,182G,183G) (SEQ ID NO:147) (空心三角)、Fc- (L15)-FGF21 (L98R,P171G,182G) (SEQ ID NO:145) (实心菱形) 和 Fc- (L15)-FGF21 (L98R,P171G,182P) (SEQ ID NO:143) (空心菱形) 中的每一种所引起的血糖水平变化百分比。

[0049] 图35图示ob/ob小鼠中PBS溶媒对照 (空心圆) 及 FGF21突变体Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (实心方形);Fc- (L15)-FGF21 (L98R,P171G,Y179S) (SEQ ID NO:149) (空心三角)、Fc- (L15)-FGF21 (L98R,P171G,Y179A) (SEQ ID NO:153) (实心倒三角)、Fc- (L15)-FGF21 (L98R,P171G,A180S) (SEQ ID NO:155) (空心菱形) 和 Fc- (L15)-FGF21 (L98R,P171G,A180G) (SEQ ID NO:157) (实心圆) 中的每一种所引起血糖水平变化百分比。

[0050] 图36图示ob/ob小鼠中PBS溶媒对照 (实心圆) 和 FGF21突变体Fc- (L15)-FGF21 (L98R,P171G) (SEQ ID NO:43) (空心方形);Fc- (L15)-FGF21 (L98R,P171G,Y179F) (SEQ ID NO:151) (实心三角) 和 Fc- (L15)-FGF21 (L98R,P171G,A180E) (SEQ ID NO:57) (空心菱形) 中

的每一种所引起的血糖水平变化百分比。

[0051] 图37图示猕猴(Rhesus monkey)中进行6周剂量递增研究的研究设计简图;图中,阴影符号表示在空腹状态下抽血,点状符号表示在进食状态下抽血。

[0052] 图38A-D是描述猕猴在OGTT分布曲线、OGTTAUC和体重方面如何随机化的系列图;图38A表示在化合物或溶媒分配给各组前在OGTT1中的基线葡萄糖水平,实心方形对应于A组,实心圆、实线对应于B组,和空心圆、短划线对应于C组;图38B表示在化合物或溶媒分配给各组前,在OGTT2中的基线葡萄糖水平,实心方形对应于A组,实心圆、实线对应于B组,和空心圆、实线对应于C组;图38C表示以AUC显示的OGTT 1和2的基线葡萄糖水平,点状条形柱对应于A组,阴影条形柱对应于B组,空心条形柱对应于C组;图38D表示基线体重,点状条形柱对应于A组,阴影条形柱对应于B组,空心条形柱对应于C组。

[0053] 图39图示猕猴中溶媒、FGF21 (SEQ ID NO:4) 和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 相对于基线的体重变化百分比;阴影条形柱1和2对应于低剂量下的第1周和第2周,空心条形柱3和4对应于中等剂量下的第3周和第4周,实心条形柱5和6对应于高剂量下的第5周和第6周,点状条形柱7、8和9对应于洗净期(washoutperiod)的第7-9周。

[0054] 图40图示溶媒、FGF21 (SEQ ID NO:4) 和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 对猕猴空腹胰岛素水平的相对于基线的空腹胰岛素变化百分比;阴影条形柱1和2对应于低剂量下的第1周和第2周,空心条形柱3和4对应于中等剂量下的第3周和第4周,实心条形柱5和6对应于高剂量下的第5周和第6周,点状条形柱7和8对应于洗净期的第7和8周。

[0055] 图41图示在研究第5和第6周期间得到的以高剂量给予的溶媒、FGF21 (SEQ ID NO:4) 和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 对猕猴的餐后胰岛素水平的作用;实心条形柱对应于第5周,阴影条形柱对应于第6周。

[0056] 图42图示在两周高剂量Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 治疗结束时进行的OGTT5的葡萄糖分布;实心圆、实线对应于溶媒,空心方形、虚线对应于FGF21,以及实心三角、实线对应于Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43)。

[0057] 图43图示在两周高剂量Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 治疗结束时进行的OGTT5的胰岛素分布;实心圆、实线对应于溶媒,空心方形、虚线对应于FGF21,以及实心三角、实线对应于Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43)。

[0058] 图44图示在猕猴的各剂量期(低、中和高剂量)结束时测定的葡萄糖OGTTAUC3-5自基线的变化百分比;空心条形柱对应于在OGTT3期间由葡萄糖测量值计算的AUC3,实心条形柱对应于在OGTT4期间由葡萄糖测量值计算的AUC4,阴影条形柱对应于在OGTT5期间由葡萄糖测量值计算的AUC5。

[0059] 图45图示溶媒、FGF21和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 对猕猴各组的空腹血浆甘油三酯水平自基线的变化百分比的作用;阴影条形柱1和2对应于低剂量下的第1周和第2周,空心条形柱3和4对应于中等剂量下的第3周和第4周,实心条形柱5和6对应于高剂量下的第5周和第6周和点状条形柱7、8和9对应于洗净期的第7-9周。

[0060] 图46图示在以高剂量用溶媒、FGF21或Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 治疗第5周和第6周期间测量的猕猴各组的餐后血浆甘油三酯水平;阴影条形柱对应于第5周,实心条形柱对应于第6周。

[0061] 图47图示给药前以及5天、12天、19天和26天测定的每只猴的人FGF21水平,其中样

品在每次注射后约21小时获得。

[0062] 图48图示给药前以及5天、12天、19天和26天测定的每只猴的Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 水平,其中样品在每次注射后约5天获得。

[0063] 图49图示根据在各低、中和高剂量后进行的三次OGTT测定的FGF21和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 水平的平均浓度;阴影条形柱对应于低剂量的OGTT3,实心条形柱对应于中等剂量的OGTT4,空心条形柱对应于高剂量的OGTT5。

[0064] 图50是Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 融合蛋白 (SEQ ID NO:47) 的氨基酸序列;IgG1 Fc残基 (SEQ ID NO:11) 呈粗体,(G4S) 3接头 (SEQ ID NO:31) 呈斜体,以及在FGF21序列 (SEQ ID NO:39) 中的点突变呈粗体和加下划线的。

[0065] 图51图示在Erk-萤光素酶测定中试验化合物的剂量反应;测试Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47)、Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57)、野生型FGF21和含野生型FGF21的Fc融合物。

[0066] 图52图示Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 对人(右)和食蟹猴(cyno) β -Klotho(左)的Biacore溶液平衡结合测定法(Biacore solution equilibrium binding assay) 结果。

[0067] 图53图示在单一注射后在db/db小鼠中Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 的剂量反应的两张图;图53A显示在注射溶媒或Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 后db/db小鼠在各个时间点的血糖水平,而图53B显示在单一注射Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 至db/db小鼠后对体重的影响。

[0068] 图54是图示在DIO小鼠中Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 和Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 的给药频率研究的示意图。

[0069] 图55图示在不同的给药频率下用溶媒、Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 或Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 治疗的小鼠的GTT分布图。

[0070] 图56图示在不同的给药频率下用溶媒、Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 或Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 治疗的小鼠中自基线(0天)的体重改变。

[0071] 图57图示包含FGF21 (L98R,P171G) (SEQ ID NO:37) FGF21突变体的水凝胶的体内研究结果。

[0072] 图58图示给予各种水凝胶制剂对8周大db/db小鼠的血糖水平的影响。

[0073] 图59图示给予各种水凝胶制剂对8周大db/db小鼠的血糖水平的影响。

[0074] 图60图示给予各种水凝胶制剂对8周大db/B6小鼠的血糖水平的影响;实心圆表示给予水凝胶对照的小鼠,实心方形表示给予10mg/kg含FGF21 (L98R,P171G) (SEQ ID NO:37) 的水凝胶的小鼠,实心三角表示给予30mg/kg含FGF21 (L98R,P171G) 的水凝胶的小鼠,以及倒三角表示单独给予Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57) 的小鼠。

[0075] 图61图示给予各种水凝胶制剂的8周大db/B6小鼠的血糖水平的变化百分比;实心圆表示给予水凝胶对照的小鼠,实心方形代表给予10mg/kg含FGF21 (L98R,P171G) (SEQ ID NO:37) 的水凝胶的小鼠,实心三角表示给予30mg/kg含FGF21 (L98R,P171G) 的水凝胶的小鼠,以及倒三角表示单独给予Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57) 的小鼠。

鼠。

[0076] 图62图示给予各种水凝胶制剂对8周大db/B6小鼠的体重的影响;实心圆表示给予水凝胶对照的小鼠,实心方形代表给予10mg/kg含FGF21 (L98R,P171G) (SEQ ID NO:37)的水凝胶的小鼠,实心三角表示给予30mg/kg含FGF21 (L98R,P171G)的水凝胶的小鼠,以及倒三角表示单独给予Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57)的小鼠。

[0077] 图63图示给予各种水凝胶制剂的8周大db/B6小鼠重量的变化百分比;实心圆表示给予水凝胶对照的小鼠,实心方形代表给予10mg/kg含FGF21 (L98R,P171G) (SEQ ID NO:37)的水凝胶的小鼠,实心三角表示给予30mg/kg含FGF21 (L98R,P171G)的水凝胶的小鼠,以及倒三角表示单独给予Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57)的小鼠

[0078] 图64是图示在有葡萄糖耐量降低 (IGT) 的食蟹猴中进行的九周剂量递增研究的研究设计的图。

[0079] 图65图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的AM餐食物摄入的影响。

[0080] 图66图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的水果摄入的影响。

[0081] 图67图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的PM餐食物摄入的影响。

[0082] 图68图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的体重的影响。

[0083] 图69图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的体重指数的影响。

[0084] 图70图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的皮褶厚度的影响。

[0085] 图71图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的腹围的影响。

[0086] 图72图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的血浆葡萄糖水平的影响。

[0087] 图73图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的葡萄糖耐量的影响。

[0088] 图74图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的血浆甘油三酯水平的影响。

[0089] 图75图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的血浆总胆固醇水平的影响。

[0090] 图76图示溶媒、Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (SEQ ID NO:47) 对研究的IGT食蟹猴的血浆HDL-胆固醇水平的影响。

[0091] 图77是显示在168小时时间段内的各个时间点下,观察的Fc- (L15) -FGF21 (L98R,

P171G) (左图,SEQ ID NO:43) 和Fc- (L15) -FGF21 (L98R,P171G,A180E) (右图,SEQ ID NO:57) 变化的一系列的MALDI质谱迹线。

[0092] 图78图示在Asp-N消化后,如通过MRM LC/MS/MS分析的全长C-末端肽占由Fc- (L15) -FGF21 (L98R,P171G) 和Fc- (L15) -FGF21 (L98R,P171G,A180E) 衍生的总C-末端肽片段的相对丰度(%)。

[0093] 图79图示在给小鼠静脉内注射后240小时内,完整全长的Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 和Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57) 的血浆浓度的ELISA测定结果,

[0094] 图80图示对阴性对照;人FGF21 (SEQ ID NO:4);和FGF21糖基化突变体FGF21 (Y179N,S181T) (SEQ ID NO:161)、FGF21Y179N (SEQ ID NO:163) 和FGF21P124S (SEQ ID NO:165) 进行的ELK-荧光素酶活性测定结果。

[0095] 发明详述

[0096] 可以采用本文公开的方法和标准分子生物学方法制备具有改进性质(例如半寿期延长和/或聚集减少)的人FGF21蛋白。任选可通过抗体或其部分与野生型FGF21序列的N末端或C末端融合而使半寿期进一步延长。还可通过将氨基酸取代引入蛋白质中而进一步延长野生型FGF21蛋白的半寿期或减少聚集。这类经过修饰的蛋白质在本文被称为突变体或FGF21突变体,并构成本发明的实施方案。

[0097] 本文(包括在实施例)使用的重组核酸方法一般是Sambrook等,Molecular Cloning:A Laboratory Manual (Cold Spring Harbor Laboratory Press,1989)或Current Protocols in Molecular Biology (Ausubel等,主编,Green Publishers Inc.和Wiley和Sons 1994)中给出的方法,两个参考文献均通过引用并入到本文中用于任何目的。

[0098] 1.一般定义

[0099] 术语“分离的核酸分子”是指本文提供的核酸分子,其:1)从当总核酸从来源细胞分离时与之天然共存的至少约50%的蛋白质、脂质、碳水化合物或其它材料中分离出来,(2)不与“分离核酸分子”天然连接的多核苷酸的全部或部分连接,(3)与天然不与之连接的多核苷酸有效连接,或(4)天然不作为较大多核苷酸序列的部分存在。优选地,分离的核酸分子基本上无任何其它的污染核酸分子或在其自然环境存在的可能干扰其在多肽产生中的用途或其治疗、诊断、预防或研究用途的其它污染物。

[0100] 术语“载体”用来指用于向宿主细胞传递编码信息的任何分子(例如核酸、质粒或病毒)。

[0101] 术语“表达载体”是指适于宿主细胞转化并含有指导和/或控制插入异源核酸序列表达的核酸序列的载体。表达包括但不限于诸如转录、翻译和RNA剪接(如果内含子存在的话)等过程。

[0102] 术语“有效连接”本文用来指侧翼序列的排列方式,其中配置或装配如此所述的侧翼序列从而发挥其常规功能。因此,与编码序列有效连接的侧翼序列可能能够实现编码序列的复制、转录和/或翻译。例如,当启动子能够指导编码序列转录时,该编码序列与该启动子有效连接。侧翼序列不必与编码序列邻接,只要其正确起作用即可。因此,例如,间插的非翻译但却转录的序列可存在于启动子序列和编码序列之间,启动子序列仍可被视为与编码序列“有效连接”。

[0103] 术语“宿主细胞”用来指被核酸序列(例如本文提供的核酸)转化或能够被所述核酸序列转化然后能够表达选定的目标基因的细胞。该术语包括亲代细胞的子代,无论子代在形态或遗传组成上是否与最初亲代相同,只要存在选定的基因。

[0104] 术语“分离的多肽”是指本发文明提供的多肽,其:(1)从当从来源细胞分离时与之天然共存的至少约50%的多核苷酸、脂质、碳水化合物或其它物质中分离出来,(2)不与“分离多肽”天然连接的多肽的全部或部分连接(通过共价或非共价相互作用),(3)与天然不与之连接的多肽有效连接(通过共价或非共价相互作用),或(4)天然不存在。优选分离多肽基本上无任何其它污染多肽或在其自然环境中存在的可能干扰其治疗、诊断、预防或研究用途的其它污染物。

[0105] 术语“天然存在的”当与生物材料例如核酸分子、多肽、宿主细胞等联用时,是指自然界中存在的且未受人为操作的材料。同样,本文使用的“非天然存在的”是指自然界不存在的或经过人为在结构上修饰或合成的材料。当与核苷酸联用时,术语“天然存在的”是指碱基腺嘌呤(A)、胞嘧啶(C)、鸟嘌呤(G)、胸腺嘧啶(T)和尿嘧啶(U)。当与氨基酸联用时,术语“天然存在的”是指20种氨基酸,即丙氨酸(A)、半胱氨酸(C)、天冬氨酸(D)、谷氨酸(E)、苯丙氨酸(F)、甘氨酸(G)、组氨酸(H)、异亮氨酸(I)、赖氨酸(K)、亮氨酸(L)、甲硫氨酸(M)、天冬酰胺(N)、脯氨酸(P)、谷氨酰胺(Q)、精氨酸(R)、丝氨酸(S)、苏氨酸(T)、缬氨酸(V)、色氨酸(W)和酪氨酸(Y)。

[0106] 术语“FGF21多肽”是指在人体内表达的天然存在的野生型多肽。对于本公开内容的目的,术语“FGF21多肽”可互换使用,是指任何全长FGF21多肽,例如由209个氨基酸残基组成并分别由SEQ ID NO:1和5的核苷酸序列编码的SEQ ID NO:2和6;多肽的任何成熟形式,例如由181个氨基酸残基组成并分别由SEQ ID NO:3和7的核苷酸序列编码的SEQ ID NO:4和8,其中剔除了在全长FGF21多肽的氨基末端的28个氨基酸残基(即,其构成信号肽)。全长和成熟FGF21多肽可但不要求包含氨基末端甲硫氨酸,其可由工程改造引入或作为细菌表达过程的结果。

[0107] 术语“FGF21多肽突变体”和“FGF21突变体”可互换使用,并且是指其中天然存在的FGF21氨基酸序列(例如,SEQ ID NO:2、4、6或8)已被修饰的FGF21多肽。这类修饰包括但不限于一个或多个氨基酸取代,包括被非天然存在的氨基酸和非天然存在的氨基酸类似物的取代;和截短。因此,FGF21多肽突变体包括但不限于本文所述的位点定向FGF21突变体、截短FGF21多肽、蛋白酶抗性FGF21突变体、聚集减少的FGF21突变体、FGF21组合突变体和FGF21融合蛋白。为了鉴定本发明的FGF21突变体的具体截短和氨基酸取代,截短或突变的氨基酸残基编号与成熟181-残基FGF21多肽的编号相对应。FGF21突变体可以但不要求包含氨基末端甲硫氨酸,其可由工程改造引入或作为细菌表达过程的结果。在本发明的其它实施方案中,FGF21多肽突变体包含与突变体FGF21的氨基酸序列有至少约85%同一性的氨基酸序列,但是其中为FGF21多肽突变体提供所需性质(例如蛋白酶抗性、半寿期延长或聚集减少性质及其组合)的特定残基不被进一步修饰。换句话讲,除已被修饰以提供蛋白酶抗性、减少聚集或其它性质的FGF21突变体序列中的残基之外,在FGF21突变体序列中约15%的所有其它氨基酸残基都可被修饰。例如在FGF21突变体Q173E中,至多15%的所有氨基酸残基都可被修饰,除取代173位上的谷氨酰胺的谷氨酸残基以外。还在其它的实施方案中,FGF21多肽突变体包含与突变体FGF21的氨基酸序列有至少约90%,或约95%、96%、

97%、98%或99%同一性的氨基酸序列,但是其中赋予FGF21多肽突变体蛋白酶解抗性或聚集减少性质的特定残基不被进一步修饰。这类FGF21多肽突变体具有至少一种野生型FGF21多肽的活性。

[0108] 本发明还涵盖编码FGF21多肽突变体的核酸分子,所述FGF21多肽突变体包含与突变体FGF21的氨基酸序列有至少约85%同一性的氨基酸序列,但是其中赋予FGF21多肽突变体所需性质(例如蛋白酶解抗性、半寿期延长或聚集减少性质及其组合)的特定残基不被进一步修饰。

[0109] 换句话讲,除已被修饰以提供蛋白酶解抗性、减少聚集或其它性质的FGF21突变体序列的残基之外,FGF21突变体序列中约15%的所有其它氨基酸残基都可被修饰。例如在FGF21突变体Q173E中,至多15%的所有氨基酸残基都可被修饰,除取代173位上的谷氨酰胺的谷氨酸残基的氨基酸残基以外。本发明还涵盖包含与编码FGF21突变体的核苷酸序列有至少约90%、或约95%、96%、97%、98%或99%同一性的核苷酸序列的核酸分子,但是其中编码赋予编码的FGF21多肽突变体蛋白酶解抗性或聚集减少性质的氨基酸残基的核苷酸不被进一步修饰。这类核酸分子编码具有至少一种野生型FGF21多肽的活性的FGF21突变体多肽。

[0110] 术语“有生物活性的FGF21多肽突变体”是指不论已引入FGF21多肽突变体的修饰的类型或数目,具有野生型FGF21多肽活性的本文所述的任何FGF21多肽突变体,所述活性为例如降低血糖、胰岛素、甘油三酯或胆固醇的能力;减轻体重的能力;和改善葡萄糖耐量、能量消耗或胰岛素敏感性的能力。虽然如此,与野生型FGF21多肽相比,FGF21活性的水平略微降低的FGF21多肽突变体仍可视为是有生物活性的FGF21多肽突变体。

[0111] 术语“有效量”和“治疗有效量”各自是指用来支持野生型FGF21多肽的一种或多种生物活性的可观察水平的FGF21多肽突变体的量,例如降低血糖、胰岛素、甘油三酯或胆固醇水平的能力;减轻体重的能力;或改善葡萄糖耐量、能量消耗或胰岛素敏感性的能力。

[0112] 本文使用的术语“药学上可接受的载体”或“生理学上可接受的载体”是指适用于完成或促进FGF21多肽突变体递送至人体或非人受试者的一种或多种配制剂。该术语包括生理上相容的任何和所有溶剂、分散介质、包衣材料、抗菌剂和抗真菌剂、等渗剂和吸收延迟剂等。药学上可接受的载体的实例包括水、盐水、磷酸缓冲盐水、右旋糖、甘油、乙醇等及其组合的一种或多种。在一些情况下,优选在药物组合物中包含等渗剂,例如,糖;诸如甘露醇、山梨醇等多元醇;或氯化钠。增加FGF21多肽突变体的保存期或效力的药学上可接受的物质(例如润湿物质或少量的辅助物质,例如润湿剂或乳化剂、防腐剂或缓冲剂)也可作为或形成载体的组分。

[0113] 术语“抗原”是指能够被抗体结合,并且还能够用于动物中以产生能结合该抗原表位的抗体的分子或分子部分。抗原可具有一个或多个表位。

[0114] 术语“天然Fc”是指不论是以单体形式还是以多聚体形式包含非抗原结合片段的序列的分子或序列,并且可含有铰链区,所述非抗原结合片段由整个抗体消化得到或通过其它方法产生。天然Fc最初的免疫球蛋白源优选、但并不一定为人源的,并可以是任一种免疫球蛋白,尽管优选为IgG1和IgG2。也可使用IgG4。天然Fc分子由可通过共价(即二硫键)和非共价缔合连接成二聚体或多聚体形式的单体多肽构成。天然Fc分子的单体亚基之间的分子间二硫键的数目为1至4的范围,这取决于类别(例如IgG、IgA和IgE)或亚类(例如IgG1、

IgG2、IgG3、IgG4、IgA1和IgGA2)。天然Fc的一个实例是由木瓜蛋白酶消化IgG得到的二硫键键合的二聚体(参见Ellison等,1982,Nucleic Acids Res.10:4071-9)。本文使用的术语“天然Fc”通用于单体、二聚体和多聚体形式。Fc多肽序列的实例见SEQ ID NO:11,其由人IgG1分子衍生。天然Fc可以但不要求包含氨基末端甲硫氨酸,其可通过工程改造或作为细菌表达过程的结果引入;这类Fc分子依然被认为是“天然Fc”分子。

[0115] 术语“Fc变体”是指是自天然Fc修饰但仍包含补救受体(salvage receptor)FcRn(新生Fc受体)的结合位点的分子或序列。国际申请号W0 97/34631和W0 96/32478描述示例性Fc变体以及与补救受体的相互作用,并通过引用并入本文。因此,术语“Fc变体”可包含从非人类天然Fc人源化的分子或序列。此外,天然Fc包含可被剔除的区域,因为它们提供本发明FGF21突变体的融合分子不需要的结构特征或生物活性。因此,术语“Fc变体”包含缺失一个或多个天然Fc位点或残基,或者其中一个或多个Fc位点或残基被修饰的分子或序列,所述Fc位点或残基影响或参与:(1)二硫键形成,(2)与所选的宿主细胞不相容,(3)在选定宿主细胞中表达时的N末端异质性,(4)糖基化,(5)与补体相互作用,(6)与补救受体以外的Fc受体结合,或(7)抗体依赖性细胞毒性(ADCC)。下文中将进一步详述Fc变体。Fc变体可以但不要求包含氨基末端甲硫氨酸,其可通过工程改造或作为细菌表达过程的结果引入;这类Fc分子依然被认为是“Fc变体”。

[0116] 术语“Fc结构域”涵盖天然Fc和Fc变体及如上定义的序列。至于Fc变体和天然Fc分子,术语“Fc结构域”包括单体或多聚体形式的分子,不论是由整个抗体消化还是通过其它方法产生。在本发明的一些实施方案中,Fc结构域可通过例如Fc结构域和FGF21序列之间的共价键与FGF21或FGF21突变体(包括FGF21或FGF21突变体的截短形式)融合。这类融合蛋白可通过Fc结构域的缔合形成多聚体,这些融合蛋白及其多聚体两者均属于本发明的方面。Fc结构域可以但不要求包含氨基末端甲硫氨酸,其可通过工程改造或作为细菌表达过程的结果引入。

[0117] 2.FGF21突变体

[0118] 术语“FGF21突变体”是指具有以下氨基酸序列的FGF21突变体多肽,所述氨基酸序列因一个或多个氨基酸而不同于天然存在的FGF21多肽序列(例如SEQ ID NO:2、4、6或8)的氨基酸序列。FGF21突变体可通过利用天然或非天然存在的氨基酸在FGF21多肽的特定位置引入保守或非保守的一个或多个氨基酸取代,来产生。

[0119] “保守氨基酸取代”可包括天然氨基酸残基(即存在于野生型FGF21多肽序列给定位置上的残基)被非天然残基(即不存在于野生型FGF21多肽序列给定位置上的残基)取代,使得对该位置上的氨基酸残基的极性或电荷几乎没有或没有影响。保守氨基酸取代还包括通常通过化学上的肽合成而不是通过在生物系统中的合成而掺入的非天然存在的氨基酸残基。这些包括肽模拟物(peptidomimetics)和氨基酸部分的其它反转形式或反向形式。

[0120] 可根据共同的侧链性质将天然存在的残基分为以下几类:

[0121] (1)疏水性:正亮氨酸、Met、Ala、Val、Leu、Ile;

[0122] (2)中性亲水性:Cys、Ser、Thr;

[0123] (3)酸性:Asp、Glu;

[0124] (4)碱性:Asn、Gln、His、Lys、Arg;

[0125] (5)影响链方向的残基:Gly、Pro;和

[0126] (6) 芳族的: Trp、Tyr、Phe。

[0127] 保守取代可包括这些类别之一的成员被同一类别的另一个成员交换。非保守取代可包括这些类别之一的成员被另一类别的成员交换。

[0128] 本领域的技术人员在需要这类取代时, 可确定所需要的氨基酸取代(不管是保守还是非保守)。示例性(但不是限制性的)氨基酸取代表见表1。

[0129] 表1

[0130] 氨基酸取代

初始残基	示例性取代
Ala	Val, Leu, Ile
Arg	Lys, Gln, Asn
Asn	Gln
Asp	Glu
Cys	Ser, Ala
Gln	Asn
Glu	Asp
Gly	Pro, Ala
His	Asn, Gln, Lys, Arg
Ile	Leu, Val, Met, Ala, Phe
Leu	Ile, Val, Met, Ala, Phe
Lys	Arg, Gln, Asn
Met	Leu, Phe, Ile
Phe	Leu, Val, Ile, Ala, Tyr
Pro	Ala
Ser	Thr, Ala, Cys
Thr	Ser
Trp	Tyr, Phe
Tyr	Trp, Phe, Thr, Ser
Val	Ile, Met, Leu, Phe, Ala

[0132] 3. 截短的FGF21多肽

[0133] 本发明的一个实施方案涉及成熟FGF21多肽或FGF21突变体的截短形式。本发明的这个实施方案起因于鉴定截短FGF21多肽的努力, 所述截短FGF21多肽能够提供类似于及在某些情况下优于成熟FGF21多肽的截短形式的活性。

[0134] 本文使用的术语“截短FGF21多肽”是指其中已从FGF21多肽的氨基末端(或N末端)剔除氨基酸残基、已从FGF21多肽的羧基末端(或C末端)剔除氨基酸残基或者已从FGF21多肽的氨基末端和羧基末端两者中剔除氨基酸残基的FGF21多肽。本文公开的各种截短物按照本文实施例3和实施例6中所述方法制备。

[0135] 可采用如实施例4所描述的体外ELK- 萤光素酶测定法来测定N末端截短的FGF21多肽和C末端截短的FGF21多肽的活性。可用于测定截短FGF21多肽的活性的体外测定法的具体详情可参见实施例4。

[0136] 本发明的截短FGF21多肽的活性也可用体内测定法来评价,例如实施例5和实施例7所示db/db小鼠或ob/ob小鼠。一般来讲,为了评价截短FGF21多肽的体内活性,可将截短FGF21多肽腹腔内给予试验动物。在所需要的孵育时间(例如1小时或更久)后,可抽取血样,并可测定血糖水平。可用于测定截短FGF21多肽的活性的体内测定法的具体详情可参见实施例5和实施例7。

[0137] a.N-末端截短

[0138] 在本发明的一些实施方案中,N末端截短包括自成熟FGF21多肽或FGF21突变体的N末端起去除1、2、3、4、5、6、7或8个氨基酸残基。正如在例如实施例5和图3中显示的一样,具有少于9个氨基酸残基的N末端截短的截短FGF21多肽保持成熟FGF21多肽在个体中降低血糖的能力。因此,在具体的实施方案中,本发明包括具有1、2、3、4、5、6、7或8个氨基酸残基的N末端截短的成熟FGF21多肽或FGF21多肽突变体的截短形式。

[0139] b.C-末端截短

[0140] 在本发明的一些实施方案中,C末端截短包括自成熟FGF21多肽的C末端起去除1、2、3、4、5、6、7、8、9、10、11或12个氨基酸残基。正如在例如实施例4和图1B中所显示的一样,在体外ELK-萤光素酶测定法中,具有少于13个氨基酸残基的C末端截短的截短FGF21多肽的功效是野生型FGF21功效的至少50%,这就表明这些FGF21突变体保持成熟FGF21多肽在个体中降低血糖的能力。因此,在具体的实施方案中,本发明包括具有1、2、3、4、5、6、7、8、9、10、11或12个氨基酸残基的C末端截短的成熟FGF21多肽或FGF21多肽突变体的截短形式。

[0141] c.N-末端和C-末端截短

[0142] 在本发明的一些实施方案中,截短FGF21多肽可具有N末端和C末端截短的组合。具有N末端和C末端截短组合的截短FGF21多肽共有相应的只具有N末端或C末端截短的截短FGF21多肽的活性。换句话讲,具有少于9个氨基酸残基的N末端截短和少于13个氨基酸残基的C末端截短两者的截短FGF21多肽,具有与具有少于9个氨基酸残基的N末端截短的截短FGF21多肽或具有少于13个氨基酸残基的C末端截短的截短FGF21多肽类似或较高的生物活性,例如血糖降低活性。因此,在具体的实施方案中,本发明包括具有1、2、3、4、5、6、7或8个氨基酸残基的N末端截短和1、2、3、4、5、6、7、8、9、10、11或12个氨基酸残基的C末端截短两者的成熟FGF21多肽或FGF21多肽突变体的截短形式。

[0143] 至于本发明的所有FGF21突变体,截短FGF21多肽和FGF21突变体可任选包含氨基末端甲硫氨酸残基,其可通过定向突变或作为细菌表达过程的结果而引入。

[0144] 本发明的截短FGF21多肽可按照实施例3和实施例6中描述的方法制备。本领域熟悉标准分子生物学技术的普通技术人员可应用该知识结合本公开内容来制备和使用本发明的截短FGF21多肽。标准技术可用于重组DNA、寡核苷酸合成、组织培养和转化(例如电穿孔、脂转染)。参见例如Sambrook等,Molecular Cloning:A Laboratory Manual,同上,其通过引用结合到本文中用于任何目的。酶促反应和纯化技术可以按照生产商的说明书、按本领域通常进行的一样或按本文所述方法进行。除非另有明确定义,否则结合本文所述的分析化学、合成有机化学及医药化学使用的术语以及这些化学的实验室程序和是本领域众所周知并普遍用于本领域的。标准技术可用于化学合成;化学分析;药物制备、制剂和递送;以及患者的治疗。

[0145] 本发明的截短FGF21多肽还可与另一实体融合,这可赋予截短FGF21多肽额外的性

质。在本发明的一个实施方案中,截短FGF21多肽可与Fc序列融合。这类融合可采用已知分子生物学方法和/或本文提供的指导完成。本文将更详尽地论述这类融合多肽的益处以及制备这类融合多肽的方法。

[0146] 4. 蛋白酶解抗性FGF21突变体

[0147] 正如实施例8中所描述的一样,发现成熟FGF21在体内经历降解,最终确定这起因于蛋白水解攻击。发现成熟FGF21的体内降解导致较短的有效半寿期,这可负面影响分子的治疗潜力。因此,进行了定向研究以鉴定具有蛋白酶解抗性的FGF21突变体。由于这项研究的结果,被确定为特别容易遭受蛋白酶解的成熟FGF21多肽的位点包括在4-5、20-21、151-152、171-172和178-181位上的氨基酸残基之间的肽键。

[0148] 进行了大量而集中的定向研究以鉴定清除所观察到的蛋白水解作用同时又不影响蛋白质活性到不可接受的程度的特定取代。表8和表11突出显示了一些已制备和测试过的突变体。正如例如实施例13和实施例14中所述的一样,并非所有FGF21突变体都具有理想的特征;一些突变体赋予蛋白酶解抗性但却以损害FGF21活性为代价。其它突变保持FGF21活性但却不赋予蛋白酶解抗性。若干突变体,包括例如FGF21P171G,保持与野生型FGF21类似的活性水平同时又具有蛋白酶降解抗性。

[0149] 鉴定所需要的蛋白酶解抗性FGF21突变体的一个选择标准是FGF21突变体的活性与野生型FGF21的活性基本相同或大于野生型FGF21的活性。因此,本发明的另一个实施方案涉及对蛋白酶解有抗性并仍保持与野生型FGF21基本一样的活性或大于野生型FGF21的活性的FGF21突变体。虽然在某些情况下较不理想,但是对蛋白酶解有抗性而活性稍有降低的FGF21突变体构成本发明的另一个实施方案。在某些情况下,可能需要保持一定程度的蛋白酶解,因此,允许出现某种程度的蛋白酶解的FGF21突变体也构成本发明的另一个实施方案。

[0150] 至于本文提供的所有FGF21突变体,本发明的蛋白酶解抗性FGF21突变体可按照本文所述方法制备。本领域的普通技术人员,例如熟悉标准分子生物学技术的技术人员,可应用该知识结合本公开内容来制备和使用本文公开的蛋白酶解抗性FGF21突变体。标准技术可用于重组DNA、寡核苷酸合成、组织培养和转化(例如电穿孔、脂转染)。参见例如Sambrook等,Molecular Cloning: A Laboratory Manual,同上,其通过引用结合到本文中用于任何目的。酶促反应和纯化技术可以按照生产商的说明书、按本领域通常进行的一样或按本文所述方法进行。除非另有明确定义,否则结合本文所述的分析化学、合成有机化学及医药化学使用的术语以及这些化学的实验室程序和技术是本领域众所周知并普遍用于本领域的。标准技术可用于化学合成;化学分析;药物制备、制剂和递送;以及患者的治疗。

[0151] 本发明的蛋白酶解抗性FGF21突变体可与另一实体融合,这可赋予蛋白酶解抗性FGF21突变体额外的性质。在本发明的一个实施方案中,蛋白酶解抗性FGF21突变体可与IgGFc序列(例如SEQ ID NO:11)融合。这类融合可采用已知的分子生物学方法和/或本文提供的指导完成。这类融合多肽的益处以及制备这类融合多肽的方法是已知的,本文将更详尽地论述。

[0152] 5. 聚集减少的FGF21突变体

[0153] 正如实施例15中描述的一样,野生型FGF21多肽的一种性质是其聚集倾向。在室温下,在约5mg/mL以上的浓度下,聚体速率高。正如本文所显示和描述的一样,野生型FGF21多

肽的聚体速率既依赖于浓度又依赖于温度。

[0154] 当在这些浓度下例如在治疗制剂的情况下用野生型FGF21操作时,聚集可被证明是一种挑战。因此,进行了定向研究以鉴定FGF21聚集减少的FGF21突变体。然后检测各种浓度下所得到的FGF21突变体的聚集倾向。

[0155] 进行了大量而集中的定向研究以鉴定消除或减少所观察到的野生型FGF21的聚集作用同时不影响蛋白质的活性到不可接受的程度的特定取代。实施例15中描述了用于鉴定合适的聚集减少突变体的方法。表16突出显示了已制备并经检验的一些突变体。正如例如实施例17中所述,并非所有的FGF21突变体都具有理想的特征。一些突变体(例如FGF21L58E)损害了FGF21活性,不再进一步研究。其它突变(例如FGF21A134E)则保持FGF21活性但未赋予聚集减少的性质。若干突变体(例如FGF21L98R)保持FGF21活性并且也显示聚集减少。一种突变体(FGF21A45K)出乎意料地显示FGF21活性提高同时又具有聚集减少的性质。

[0156] 用于鉴定所需要的聚集减少FGF21突变体的一个选择标准是FGF21突变体的活性与野生型FGF21的活性基本相似或大于野生型FGF21的活性。因此,本发明的另一个实施方案涉及聚集性质减弱但仍保持与野生型FGF21相似的活性或大于FGF21活性的FGF21突变体。虽然在某些情况下较不理想,但是聚集性质减弱但FGF21活性稍有降低的FGF21突变体构成本发明的另一个实施方案。在某些情况下,可能需要保持一定程度的聚集,因此,允许出现某种程度的聚集的FGF21突变体也构成本发明的另一个实施方案。

[0157] 至于本文中提供的所有FGF21突变体,本文中提供的聚集减少的FGF21突变体可按照本文所述方法制备。熟悉标准分子生物学技术的本领域的普通技术人员,可应用该知识结合本公开内容来制备和使用本发明的聚集减少的FGF21突变体。标准技术可用于重组DNA、寡核苷酸合成、组织培养和转化(例如电穿孔、脂转染)。参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 同上,其通过引用结合到本文中用于任何目的。酶促反应和纯化技术可以按照生产商的说明书、按本领域通常进行的一样或按本文所述方法进行。除非另有明确定义,否则结合本文所述的分析化学、合成有机化学及医药化学使用的术语以及这些化学的实验室程序和技术是本领域众所周知并普遍用于本领域的。标准技术可用于化学合成;化学分析;药物制备、制剂和递送;以及患者的治疗。

[0158] 本发明的聚集减少FGF21突变体可与另一实体融合,这可赋予聚集减少的FGF21突变体额外的性质。在本发明的一个实施方案中,聚集减少的FGF21突变体可与IgG Fc序列(例如SEQ ID NO:11)融合。这类融合可采用已知分子生物学方法和/或本文提供的指导完成。本文将更详尽地论述这类融合多肽的益处,以及制备这类融合多肽的方法。

[0159] 6.FGF21组合突变体

[0160] 如本文所述,当FGF21用作治疗分子时,野生型FGF21序列具有可能出现严重挑战的若干性质。在这些挑战中有蛋白质易受降解及其在高浓度下聚集的倾向。在鉴定克服每一种这些挑战的FGF21多肽的大量努力之后,进行了定向研究以确定提供蛋白酶解抗性的氨基酸取代以及提供聚集减少性质的氨基酸取代是否可在单一多肽序列中以加合或协同方式联合在一起同时维持等于或大于野生型FGF21活性的活性水平。这代表着一个重要挑战,因为本领域已知在给定多肽中导入多个突变有时可能会对表达、活性及随后的蛋白质生产产生不利影响。

[0161] 出人意料的是,正如例如实施例19和实施例20中所表明的一样,发现若干FGF21突变体的所需性质确实可以加合或协同方式联合以产生药学性质得到提高的FGF21突变体。本文公开了对蛋白酶解有抗性、聚集速率降低以及仍保持与野生型FGF21相同或大于野生型FGF21的活性的FGF21突变体。

[0162] 用于鉴定所需要的FGF21组合突变体的一个选择标准是FGF21突变体的活性与野生型FGF21的活性相似或大于野生型FGF21的活性。因此,本发明的另一个实施方案涉及对蛋白酶解有抗性且聚集性质减弱同时仍保持与野生型FGF21相似或大于野生型FGF21的FGF21活性的FGF21突变体。虽然在某些情况下较不理想,但对蛋白酶解有抗性且聚集性质减弱而FGF21活性稍有降低的FGF21突变体构成本发明的另一个实施方案。在某些情况下,可能需要保持一定程度的蛋白酶解和/或聚集,因此,允许某种程度的蛋白酶解和/或聚集的FGF21突变体也构成本发明的另一个实施方案。

[0163] 至于本发明的所有FGF21突变体,本发明的FGF21组合突变体可按照本文所述方法制备。熟悉标准分子生物学技术的本领域的普通技术人员,可应用该知识结合本公开内容来制备和使用本发明的FGF21组合突变体。标准技术可用于重组DNA、寡核苷酸合成、组织培养和转化(例如电穿孔、脂转染)。参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 同上,其通过引用结合到本文中用于任何目的。酶促反应和纯化技术可以按照生产商的说明书、按本领域通常进行的一样或按本文所述方法进行。除非另有明确定义,否则结合本文所述的分析化学、合成有机化学及医药化学使用的术语以及这些化学的实验室程序和技术是本领域众所周知并普遍用于本领域的。标准技术可用于化学合成;化学分析;药物制备、制剂和递送;以及患者的治疗。

[0164] 本发明的FGF21组合突变体可与另一实体融合,这可赋予FGF21组合突变体额外的性质。在本发明的一个实施方案中,FGF21组合突变体可与IgG Fc序列(例如SEQ ID NO:11)融合。这类融合可采用已知分子生物学方法和/或本文提供的指导完成。本文将更详尽地论述这类融合多肽的益处以及制备这类融合多肽的方法。

[0165] 7.FGF21融合蛋白

[0166] 本文使用的术语“FGF21融合多肽”或“FGF21融合蛋白”是指一个或多个氨基酸残基(例如异源蛋白或肽)在本文所述的任何FGF21多肽突变体的N末端或C末端的融合。

[0167] 异源肽和多肽包括但不限于可供检测和/或分离FGF21多肽突变体的表位;跨膜受体蛋白或其部分,例如胞外结构域或跨膜和胞内结构域;与跨膜受体蛋白结合的配体或其部分;酶或其有催化活性的部分;促进寡聚化的多肽或肽,例如亮氨酸拉链域;提高稳定性的多肽或肽,例如免疫球蛋白恒定区(例如,Fc结构域);半寿期延长序列,其包含两个或更多个(例如,2、5、10、15、20、25个等)天然存在或非天然存在的、带电荷和/或不带电荷的氨基酸(例如,丝氨酸、甘氨酸、谷氨酸或天冬氨酸)的组合,将其设计形成主要亲水的或主要疏水的FGF21突变体的融合配偶体;功能性或非功能性抗体,或者其重链或轻链;以及具有不同于本发明FGF21多肽突变体的诸如治疗活性等活性的多肽。本发明还包括与人血清白蛋白(HSA)融合的FGF21突变体。

[0168] FGF21融合蛋白可通过使异源序列与FGF21多肽突变体的N末端或C末端融合来制备。本文所述的异源序列可以是氨基酸序列或含有非氨基酸的聚合物。异源序列可与FGF21多肽突变体直接融合或者通过接头或衔接分子融合。接头或衔接分子可为一个或多个氨基

酸残基(或氨基酸聚体),例如1、2、3、4、5、6、7、8或9个残基(或氨基酸聚体),优选10-50个氨基酸残基(或氨基酸聚体),例如10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45或50个残基(或氨基酸聚体),更优选15-35个氨基酸残基(或氨基酸聚体)。接头或衔接分子还可设计成具有DNA限制性内切核酸酶或蛋白酶的切割位点以供分离融合部分。

[0169] a.Fc融合物

[0170] 在本发明的一个实施方案中,FGF21多肽突变体与Fc结构域例如人IgG的Fc区的一个或多个结构域融合。抗体包含两个在功能上独立的部分,称为“Fab”的与抗原结合的可变结构域和称为“Fc”的参与效应物功能(例如补体活化和被吞噬细胞攻击)的恒定结构域。Fc具有长的血清半寿期,而Fab是短寿的(Capon等,1989,Nature 337:525-31)。当与治疗蛋白质连接在一起时,Fc结构域可提供较长的半寿期,或者掺入如Fc受体结合、蛋白A结合、补体结合或许甚至胎盘转移的这类功能(Capon等,1989)。

[0171] 体内药代动力学分析表明人FGF21在小鼠中由于快速清除和体内降解而具有约1小时的短半寿期。因此,为了延长FGF21的半寿期,将天然的Fc序列与FGF21多肽的N末端或C末端融合。Fc序列与野生型FGF21的融合,特别是Fc与野生型FGF21N末端的融合,并不如预期那样延长半寿期,然而,该观察导致了对体内FGF21的蛋白酶降解和对抵抗这类降解的FGF21突变体的鉴定的研究。在例如实施例9和实施例11描述了这类突变体,这类突变体具有比野生型FGF21长的半寿期。这些FGF21融合蛋白和其它FGF21融合蛋白构成本发明的实施方案。

[0172] 在整个本公开内容中,Fc-FGF21是指其中Fc序列与FGF21的N末端融合的融合蛋白。同样,在整个本公开内容中,FGF21-Fc是指其中Fc序列与FGF21的C末端融合的融合蛋白。

[0173] 所得到的FGF21融合蛋白可以通过例如使用蛋白A亲和柱来纯化。研究发现与Fc区融合的肽和蛋白质具有比未融合的对对应物明显较大的体内半寿期。同样,与Fc区的融合可供融合多肽的二聚化/多聚化。Fc区可以是天然存在的Fc区,或可被改变以改进某些性质,例如治疗特性、循环时间或聚集减少。

[0174] 国际公布号W0 00/024782详细论述了通过与抗体的“Fc”结构域融合的蛋白质治疗剂的有益修饰,其通过引用以其整体并入本文中。

[0175] b.融合蛋白接头

[0176] 当形成本发明的融合蛋白时,可以使用但不一定使用接头。当接头存在时,接头的化学结构可能不是决定性的,因为它主要起间隔基的作用。接头可由通过肽键连接在一起的氨基酸构成。在本发明的一些实施方案中,接头由通过肽键连接的1-20个氨基酸构成,其中氨基酸选自20种天然存在的氨基酸。在多个实施方案中,1-20个氨基酸选自氨基酸甘氨酸、丝氨酸、丙氨酸、脯氨酸、天冬酰胺、谷氨酰胺和赖氨酸。在一些实施方案中,接头由空间上不受阻碍的多个氨基酸例如甘氨酸和丙氨酸构成。在一些实施方案中,接头是聚甘氨酸(例如(Gly)₄(SEQ ID NO:29)和(Gly)₅(SEQ ID NO:30))、聚丙氨酸、甘氨酸和丙氨酸的组合(例如聚(Gly-Ala))或甘氨酸和丝氨酸的组合(例如聚(Gly-Ser))。其它合适的接头包括:(Gly)₅-Ser-(Gly)₃-Ser-(Gly)₄-Ser(SEQ ID NO:28)、(Gly)₄-Ser-(Gly)₄-Ser-(Gly)₄-Ser(SEQ ID NO:31)、(Gly)₃-Lys-(Gly)₄(SEQ ID NO:32)、(Gly)₃-Asn-Gly-Ser-(Gly)₂(SEQ ID NO:33)、(Gly)₃-Cys-(Gly)₄(SEQ ID NO:34)和Gly-Pro-Asn-Gly-Gly(SEQ ID NO:35)。

虽然发现对于FGF21融合蛋白,15个氨基酸残基的接头发挥特别好的作用,但是本发明考虑任何长度或组成的接头。当使用接头连接异源性序列例如Fc结构域和FGF21多肽或FGF21突变体时,该接头表示在圆括号内。

[0177] 本文所述接头是示例性的,本发明考虑长得多的接头以及包含其它残基的接头。本发明还考虑非肽接头。例如可以使用烷基接头,例如 $\text{-NH-(CH}_2\text{)}_s\text{-C(=O)-}$,其中 $s=2-20$ 。这些烷基接头可被任何无空间位阻的基团进一步取代,所述基团包括但不限于低级烷基(例如C1-C6)、低级酰基、卤素(例如Cl、Br)、CN、NH₂或苯基。示例性的非肽接头为聚乙二醇接头,其中接头的分子量为100-5000kD,例如100-500kD。

[0178] 8. 化学修饰的FGF21突变体

[0179] 鉴于本文描述的公开内容,本领域的技术人员可以制备本文描述的FGF21多肽突变体的化学修饰形式,包括本文所述的FGF21的截短形式。改变这类化学修饰的FGF21突变体,使得化学修饰的FGF21突变体在天然与FGF21突变体连接的分子的类型或位置方面不同于未修饰的FGF21突变体。化学修饰的FGF21突变体可包括通过脱去一个或多个天然连接的化学基团而形成的分子。

[0180] 在一个实施方案中,本发明的FGF21多肽突变体可通过一种或多种聚合物的共价连接而被修饰。例如,所选择的聚合物通常是水溶性的,使得与之连接的蛋白质不会在水性环境例如生理环境中沉淀。包括在合适聚合物范围内的有聚合物的混合物。优选对于制成品制剂的治疗用途,聚合物应是药学上可接受的。与本发明的FGF21多肽突变体缀合的非水溶性聚合物也构成本发明的方面。

[0181] 示例性聚合物各自可具有任何的分子量,并可以是支链或无支链的。各聚合物通常具有约2kDa-约100kDa的平均分子量(术语“约”表示在水溶性聚合物制剂中,一些分子将比指定的分子量重,一些则比指定的分子重量轻)。各聚合物的平均分子量优选介于约5kDa和约50kDa之间,更优选介于约12kDa和约40kDa,最优选介于约20kDa和约35kDa之间。

[0182] 合适的水溶性聚合物或其混合物包括但不限于N联糖或O联糖、糖、磷酸酯、聚乙二醇(PEG)(包括用于使蛋白质衍生化的PEG形式,包括单-(C₁-C₁₀)聚乙二醇、烷氧基-聚乙二醇或芳氧基-聚乙二醇)、单甲氧基-聚乙二醇、葡聚糖(例如约6kD的低分子量葡聚糖)、纤维素或其它糖基聚合物、聚-(N-乙烯基吡咯烷酮)聚乙二醇、丙二醇均聚物、聚环氧丙烷/环氧乙烷共聚物、聚氧乙基化多元醇(例如甘油)和聚乙烯醇。本发明还考虑可以用来制备共价连接的FGF21多肽突变体多聚体的双官能交联分子。本发明还考虑与多聚唾液酸共价连接的FGF21突变体。

[0183] 在本发明的一些实施方案中,FGF21突变体经过共价或化学修饰以包括一种或多种水溶性聚合物,其包括但不限于聚乙二醇(PEG)、聚氧乙二醇或聚丙二醇。参见例如美国专利号4,640,835、4,496,689、4,301,144、4,670,417、4,791,192和4,179,337。在本发明的一些实施方案中,FGF21突变体包含一种或多种聚合物,包括但不限于单甲氧基-聚乙二醇、葡聚糖、纤维素、其它糖基聚合物、聚-(N-乙烯基吡咯烷酮)-聚乙二醇、丙二醇均聚物、聚环氧丙烷/环氧乙烷共聚物、聚氧乙基化多元醇(例如甘油)、聚乙烯醇或这类聚合物的混合物。

[0184] 在本发明的一些实施方案中,FGF21突变体是用PEG亚基共价修饰的。在一些实施方案中,一种或多种水溶性聚合物在FGF21突变体的一个或多个特定位置(例如在N末端)上

键合。在一些实施方案中,一种或多种水溶性聚合物与FGF21突变体的一个或多个侧链随机连接。在一些实施方案中,使用PEG来改进FGF21突变体的治疗能力。例如,在美国专利号6,133,426中论述了某些这类方法,所述专利通过引用并入本文用于任何目的。

[0185] 在其中聚合物是PEG的本发明的实施方案中,PEG基团可具有任何合适的分子量,并且可以是直链或支链。PEG基团的平均分子量的范围优选为约2kD-约100kDa,更优选约5kDa-约50kDa,例如10kDa、20kDa、30kDa、40kDa或50kDa。PEG基团一般通过PEG部分上的反应基团(例如醛、氨基、巯基或酯基)与FGF21突变体上的反应基团(例如醛、氨基或酯基)进行酰化或还原性烷基化而与FGF21突变体连接。

[0186] 多肽(包括本发明的FGF21突变体)的聚乙二醇化可采用本领域已知的任何聚乙二醇化反应来具体进行。这类反应参见例如下列参考文献:Francis等,1992,Focus on Growth Factors 3:4-10;欧洲专利号0154316和0401384;以及美国专利号4,179,337。例如,可通过与本文所述的反应性聚乙二醇分子(或类似反应性水溶性聚合物)的酰化反应或烷基化反应来进行聚乙二醇化。对于酰化反应,选定的聚合物应具有单个反应性酯基。对于还原性烷基化,选定的聚合物应具有单个反应性醛基。反应性醛例如水稳定性的聚乙二醇丙醛或其单C₁-C₁₀烷氧基或芳氧基衍生物(参见例如美国专利号5,252,714)。

[0187] 在本发明的一些实施方案中,用于使PEG基团与多肽连接的有用策略包括使肽和PEG部分(各自带有彼此相互反应的特定官能团)在溶液中形成缀合连接而结合。可容易地用常规固相合成法制备肽。在特定位点上,肽被合适的官能团“预活化”。在与PEG部分反应前,前体已经过纯化并充分表征。肽与PEG的连接一般发生在水相中,并且可易于通过反相分析型HPLC监测。聚乙二醇化肽可容易地通过制备型HPLC纯化,并通过分析型HPLC、氨基酸分析和激光解吸质谱法进行表征。

[0188] 多糖聚合物是可用于蛋白质修饰的水溶性聚合物的另一种类型。因此,与多糖聚合物融合的本发明的FGF21突变体构成本发明的实施方案。葡聚糖是由主要通过 α 1-6键连接的葡萄糖的各个亚基组成的多糖聚合物。葡聚糖本身可以多种分子量范围获得,并容易以约1 kD-约70kD的分子量获得。葡聚糖是本身用作载体或与另一种载体(例如Fc)联用的合适水溶性聚合物。参见例如国际公布号W0 96/11953。研究报告了与治疗或诊断免疫球蛋白缀合的葡聚糖的用途。参见例如欧洲专利公布号0315456,所述专利通过引用并入本文。本发明还包括约1kD-约20kD的葡聚糖的用途。

[0189] 一般可在用来使蛋白质与活化聚合物分子反应的任何合适的条件下进行化学修饰。制备化学修饰的多肽的方法一般可包括以下步骤:(a)使多肽与活化聚合物分子(例如聚合物分子的反应性酯或醛衍生物)在FGF21多肽突变体由此成为与一个或多个聚合物分子连接的条件反应,和(b)得到反应产物。可根据已知参数和所需结果确定最适反应条件。这方面的实例是,聚合物分子与蛋白质之比越大,所连接的聚合物分子的百分比越大。在本发明的一个实施方案中,化学修饰的FGF21突变体在氨基末端可具有单个聚合物分子部分(参见例如美国专利号5,234,784)。

[0190] 在本发明的另一个实施方案中,FGF21多肽突变体可与生物素化学偶联。然后生物素/FGF21多肽突变体可与抗生物素蛋白结合,产生四价的抗生物素蛋白/生物素/FGF21多肽突变体。FGF21多肽突变体还可与二硝基苯酚(DNP)或三硝基苯酚(TNP)共价偶联,所得缀合物与抗DNP或抗TNP-IgM一起沉淀形成化合价为10的十聚体缀合物。

[0191] 一般而言,可通过给予公开的化学修饰的FGF21突变体减轻或调节的病况包括本文对FGF21多肽突变体描述的那些病况。然而,本文公开的化学修饰的FGF21突变体可具有另外的活性、升高或降低的生物活性或者其它特征,例如与未修饰的FGF21突变体相比时半寿期延长或缩短。

[0192] 9.FGF21突变体的药物组合物及其给予

[0193] 包含FGF21突变体的药物组合物属于本发明的范围,并根据对具有改进性质的若干突变体FGF21序列的鉴定,特别考虑所述药物组合物。这类FGF21突变体药物组合物可包含治疗有效量的FGF21多肽突变体和选择适于给药方式的药理学上或生理学上可接受的配制剂。

[0194] 可接受的配制剂优选在所采用的剂量和浓度下对接受者无毒性。

[0195] 药物组合物可含有用于改变、保持或保存例如组合物的pH、同渗溶摩、粘度、透明度、颜色、等渗性、气味、无菌性、稳定性、溶出或释放速率、吸收或渗透的配制剂。合适的配制剂包括但不限于氨基酸(例如甘氨酸、谷氨酰胺、天冬酰胺、精氨酸或赖氨酸)、抗微生物剂、抗氧化剂(例如抗坏血酸、亚硫酸钠或亚硫酸氢钠)、缓冲剂(例如硼酸盐、碳酸氢盐、Tris-HCl、柠檬酸盐、磷酸盐或其它有机酸)、膨胀剂(例如甘露醇或甘氨酸)、螯合剂(例如乙二胺四乙酸(EDTA))、络合剂(例如咖啡因、聚乙烯吡咯烷酮、 β -环糊精或羟丙基- β -环糊精)、填充剂、单糖、双糖和其它糖(例如葡萄糖、甘露糖或糊精)、蛋白质(例如血清白蛋白、明胶或免疫球蛋白)、着色剂、矫味剂和稀释剂、乳化剂、亲水聚合物(例如聚乙烯吡咯烷酮)、低分子量多肽、成盐抗衡离子(例如钠)、防腐剂(例如苯扎氯铵、苯甲酸、水杨酸、硫柳汞、苯乙醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、氯己定、山梨酸或过氧化氢)、溶剂(例如甘油、丙二醇或聚乙二醇)、糖醇(例如甘露醇或山梨醇)、助悬剂、表面活性剂或湿润剂(例如普流罗尼克;PEG;脱水山梨糖醇酯;聚山梨酯,例如聚山梨酯20或聚山梨酯80;曲通(triton);氨丁三醇;卵磷脂;胆固醇或四丁酚酯)、稳定性增强剂(例如蔗糖或山梨醇)、张力增强剂(例如碱金属卤化物—优选氧化钠或氯化钾—或甘露醇山梨醇)、递药载体、稀释剂、赋形剂和/或药物辅助剂(参见例如Remington's Pharmaceutical Sciences(第18版, A.R.Gennaro, 编辑, Mack Publishing Company 1990)及其之后的版本,通过引用结合到本文中用于任何目的)。

[0196] 可由技术人员根据例如预期给药途径、递送方式和所需剂量来确定最优药物组合物(参见例如Remington's Pharmaceutical Sciences,同上)。这类组合物可影响FGF21多肽突变体的物理状态、稳定性、体内释放速率和体内清除率。

[0197] 药物组合物中的主要溶媒或载体的性质可以是含水或无水的。例如,用于注射的合适溶媒或载体可以是水、生理盐溶液或人工脑脊液,可能补充了组合物中常用于胃肠外给药的其它物质。中性缓冲盐水或与血清白蛋白混合的盐水是另外的示例性溶媒。其它示例性的药物组合物包含约pH 7.0-8.5的Tris缓冲液或约pH 4.0-5.5的乙酸盐缓冲液,其还可包括山梨醇或合适的替代物。在本发明的一个实施方案中,可以通过将选定的具有所需纯度的组合物与任选的配制剂(Remington's Pharmaceutical Sciences,同上)混合来制备以冻干饼或水溶液形式用于贮存的FGF21多肽突变体组合物。此外,使用合适的赋形剂(例如蔗糖)将FGF21多肽突变体产品配制成冻干产物。

[0198] 可以选择FGF21多肽突变体药物组合物用于胃肠外递送。或者,可以选择组合物用

于吸入或用于通过消化道递送,例如口服。这类药学上可接受的组合物的制备尽在本领域技术人员掌握之中。

[0199] 制剂组分以对于给药部位是可接受的浓度存在。例如,使用缓冲剂以维持组合物在生理pH下或在略低的pH下,通常在约5-约8的pH范围内。

[0200] 当预期胃肠外给药时,用于本发明的治疗组合物可以是无热原、胃肠外可接受的包含所需FGF21多肽突变体与药学上可接受的溶媒的水溶液形式。对于胃肠外注射的特别合适的溶媒是无菌蒸馏水,其中将FGF21多肽突变体配制成适当防腐的无菌等渗溶液。又一种制备物可包括所需分子与某种物质(例如可注射微球、可生物蚀解的颗粒、聚合物(例如聚乳酸或聚乙醇酸)、珠粒或脂质体)的制剂,所述物质提供用于控释或缓释产品,所述产品然后可通过积存注射递送。还可使用透明质酸,这可具有促进循环中持续时间延长的作用。用于引入所需分子的其它合适方法包括可植入递药装置。

[0201] 在一个实施方案中,可以配制药剂组合物用于吸入。例如,可将FGF21多肽突变体制成吸入用干粉剂。还可使用气溶胶递送用的抛射剂配制FGF21多肽突变体吸入溶液剂。在又一个实施方案中,可使溶液剂雾化。国际公布号W0 94/20069中更多地描述了经肺给药,其描述了化学修饰蛋白质的经肺递送。

[0202] 还考虑可口服给予某些制剂。在本发明的一个实施方案中,以这种方式给予的FGF21多肽突变体可以用或不用常用于配制固体剂型(例如片剂和胶囊剂)中的载体来配制。例如,可以设计胶囊剂以使制剂的活性部分在胃肠道的生物利用度最大化且系统前降解最小化时的点上释放。可包括促进FGF21多肽突变体吸收的其它物质。还可以使用稀释剂、调味剂、低熔点蜡、植物油、润滑剂、助悬剂、片剂崩解剂和粘合剂。

[0203] 另一种的药物组合物可包含有效量的FGF21多肽突变体与适用于片剂制备的无毒赋形剂的混合物。通过将片剂溶于无菌水或另一种合适的溶媒中,以单位剂型制备溶液剂。合适的赋形剂包括但不限于惰性稀释剂,例如碳酸钙、碳酸钠或碳酸氢钠、乳糖或磷酸钙;或粘合剂,例如淀粉、明胶或阿拉伯树胶;或润滑剂,例如硬脂酸镁、硬脂酸或滑石粉。

[0204] 另外的FGF21多肽突变体药物组合物对本领域技术人员而言是显而易见的,包括在持续递送或受控递送制剂中包含FGF21多肽突变体的制剂。配制多种其它持续递送或受控递送工具的技术,例如脂质体载体、可生物蚀解微粒或多孔珠粒和积存注射剂也为本领域技术人员所知(参见例如国际公布号W0 93/15722,该专利披露了用于药物组合物递送的多孔聚合微粒的控释,以及Wischke&Schwendeman,2008,Int.J.Pharm.364:298-327,和Freiberg&Zhu,2004,Int.J.Pharm.282:1-18,其论述了微球/微粒制剂和用途)。如本文所述的,水凝胶是持续递送或受控递送制剂的实例。

[0205] 缓释制剂的其它实例包括成形制品形式的半透性聚合物基质,例如膜剂或微胶囊剂。缓释基质可包括聚酯、水凝胶、聚丙交酯(美国专利号3,773,919和欧洲专利号0058481)、L-谷氨酸和L-谷氨酸- γ 乙酯的共聚物(Sidman等,1983,Biopolymers 22:547-56)、聚(甲基丙烯酸2-羟乙酯)(Langer等,1981,J.Biomed.Mater.Res.15:167-277和Langer,1982,Chem.Tech.12:98-105)、乙烯乙酸乙烯酯(Langer等,同上)或聚-D(-)-3-羟基丁酸(欧洲专利号0133988)。缓释组合物还可包括脂质体,其可通过本领域已知的若干方法中的任一种制备。参见例如Epstein等,1985,Proc.Natl.Acad.Sci.U.S.A.82:3688-92;以及欧洲专利号0036676、0088046和0143949。

[0206] 用于体内给药的FGF21多肽突变体药物组合物通常应该是无菌的。这可通过除菌滤膜过滤实现。如果将组合物冻干,则采用该方法的除菌可在冻干和复溶之前或之后进行。用于胃肠外给药的组合物可以冻干形式保存,或者保存在溶液中。另外,一般将胃肠外组合物装入具有无菌入口的容器中,例如具有皮下注射针可刺穿的塞子的静脉内注射用溶液袋或小瓶。

[0207] 一旦制成药物组合物,便可将之作为溶液剂、混悬剂、凝胶剂、乳剂、固体剂或作为脱水粉剂或冻干粉剂保存在无菌小瓶中。这类制剂可以随时可用的形式或需要在给药前复溶的形式(例如冻干形式)保存。

[0208] 在一个具体的实施方案中,本发明涉及用于产生单剂量给药单位的药盒。药盒可各自含有具有干燥蛋白质的第一容器和具有含水制剂的第二容器两者。本发明的范围还包括包含单室预灌装注射器和多室预灌装注射器(例如液体剂注射器和冻干剂注射器(lyosyringe))的药盒。

[0209] 治疗上采用的FGF21多肽突变体药物组合物的有效量将取决于例如治疗背景和目的。本领域技术人员应了解的是,用于治疗的合适剂量水平因此将部分随所递送的分子、FGF21多肽突变体所应用的适应症、给药途径和患者的大小(体重、体表或器官大小)和状况(年龄和一般健康状况)而变化。因此,临床工作人员可以确定剂量并改变给药途径以获得最佳治疗效果。典型的剂量可从约0.1 μ g/kg到高达约100mg/kg或更大,这取决于上述因素。在其它实施方案中,剂量可从0.1 μ g/kg到高达约100mg/kg;或1 μ g/kg到高达约100mg/kg;或5 μ g/kg、10 μ g/kg、15 μ g/kg、20 μ g/kg、25 μ g/kg、30 μ g/kg、35 μ g/kg、40 μ g/kg、45 μ g/kg、50 μ g/kg、55 μ g/kg、60 μ g/kg、65 μ g/kg、70 μ g/kg、75 μ g/kg到高达约100mg/kg。在另外其它的实施方案中,剂量可为50 μ g/kg、100 μ g/kg、150 μ g/kg、200 μ g/kg、250 μ g/kg、300 μ g/kg、350 μ g/kg、400 μ g/kg、450 μ g/kg、500 μ g/kg、550 μ g/kg、600 μ g/kg、650 μ g/kg、700 μ g/kg、750 μ g/kg、800 μ g/kg、850 μ g/kg、900 μ g/kg、950 μ g/kg、100 μ g/kg、200 μ g/kg、300 μ g/kg、400 μ g/kg、500 μ g/kg、600 μ g/kg、700 μ g/kg、800 μ g/kg、900 μ g/kg、1000 μ g/kg、2000 μ g/kg、3000 μ g/kg、4000 μ g/kg、5000 μ g/kg、6000 μ g/kg、7000 μ g/kg、8000 μ g/kg、9000 μ g/kg或10mg/kg。

[0210] 给药频率将取决于所用制剂中FGF21多肽突变体的药代动力学参数。临床工作人员通常可以给予组合物直到达到获得所需效果的剂量为止。因此,可随时间以单剂量、以两次或更多次剂量(其可含有或不含等量的所需分子)或者通过植入装置或导管以连续输注给予组合物。合适剂量的进一步精化通常由本领域的普通技术人员进行,并且属于他们日常进行的工作范围。通过应用适当的剂量反应数据可以确定合适的剂量。

[0211] 所述药物组合物的给药途径与已知方法一致,例如口服;通过静脉内、腹膜内、脑内(脑实质内)、脑室内、肌内、眼内、动脉内、门静脉内或病灶内途径注射;通过缓释系统(其也可被注射);或通过植入装置。需要时,可通过推注或连续通过输注,或者通过植入装置给予组合物。

[0212] 备选地或另外地,通过植入在其上已吸收或包封了所需分子的膜、海棉或其它合适的材料局部给予组合物。在使用植入装置时,可将该装置植入任何合适的组织或器官,并且可通过扩散、定时释药推注(timed-release bolus)或连续给药递送所需分子。

[0213] 为了以预设的速率递送药物(例如本文中公开的FGF21突变体),使得药物浓度可在延长的期间内维持期望的治疗效果水平,可使用多种不同的方法。在一个实例中,可使用

包含诸如明胶(例如,牛明胶、人明胶或来自另一种来源的明胶)等聚合物或天然存在的或合成产生的聚合物的水凝胶。可将任何百分比的聚合物(例如,明胶)用于水凝胶,例如5%、10%、15%或20%。恰当的浓度的选择可取决于多种因素,例如期望的治疗分布和治疗分子的药代动力学分布。

[0214] 可掺入水凝胶的聚合物的实例包括聚乙二醇(“PEG”)、聚环氧乙烷、聚环氧乙烷-聚环氧丙烷共聚物、聚环氧乙烷嵌段或无规共聚物、聚乙烯醇、聚(乙烯基吡咯烷酮)、聚(氨基酸)、葡聚糖、肝素、多糖、聚醚等。

[0215] 产生水凝胶制剂时可考虑的另一因素是水凝胶和交联剂的交联程度。在一个实施方案中,经由涉及甲基丙烯酸酐的甲基丙烯酸化反应可获得交联。在一些情况中,高度交联可以是期望的,然而在其它的情况中,较低程度的交联是优选的。在一些情况下,较高程度的交联提供更久的持续释放。较高程度的交联可提供更坚固的水凝胶和更长的药物递送时期。

[0216] 可使用聚合物与交联剂(例如,甲基丙烯酸酐)的任何比率来产生有期望性质的水凝胶。例如,聚合物与交联剂的比率可为,例如8:1、16:1、24:1或32:1。例如,当水凝胶聚合物是明胶以及交联剂是甲基丙烯酸酯时,可使用8:1、16:1、24:1或32:1比率的甲基丙烯酸酐:明胶。

[0217] 10.FGF21多肽突变体的治疗用途

[0218] FGF21多肽突变体可用来治疗、诊断、改善或预防多种疾病、病症或病况,包括但不限于代谢紊乱。在一个实施方案中,待治疗的代谢紊乱是糖尿病,例如2型糖尿病。在另一个实施方案中,代谢紊乱是肥胖症。其它实施方案包括代谢病况或代谢紊乱例如血脂异常;高血压;肝脂肪变性,例如非酒精性脂肪性肝炎(NASH);心血管疾病,例如动脉粥样硬化;以及老化。

[0219] 在应用中,可通过以治疗有效剂量的量给予有需要的患者本文所述的FGF21多肽突变体来治疗诸如糖尿病或肥胖症等病症或病况。可按本文所述方法给药,例如通过静脉内注射、腹膜内注射、肌内注射,或者以片剂或液体制剂的形式口服。在大多数情况下,所需剂量可按本文所述由临床工作人员确定,并且可代表FGF21突变体多肽的治疗有效剂量。对本领域技术人员显而易见的是,治疗有效剂量的FGF21突变体多肽尤其将取决于给药方案、所给予的物质的单位剂量(不论核酸分子或多肽是否与其它治疗剂组合给予)、免疫状态和接受者的健康状况。本文使用的术语“治疗有效剂量”意指由研究人员、医学博士或其它临床医师所寻求的在组织系统、动物或人中引发生物反应或药物反应的FGF21突变体多肽的量,它包括减轻待治疗的疾病或病症的症状。

[0220] 11. 抗体

[0221] 与本发明的FGF21突变体多肽特异性结合但不与野生型FGF21多肽特异性结合的抗体和抗体片段包括在并属于本发明的范围内。抗体可以是多克隆抗体(包括单特异性多克隆抗体)、单克隆抗体(MAb)、重组抗体、嵌合抗体、人源化抗体(例如互补决定区(CDR)移植抗体)、人抗体、单链抗体和/或双特异性抗体及其片段、变体或化学修饰分子。抗体片段包括与FGF21突变体多肽的表位特异性结合的抗体的部分。这类片段的实例包括通过酶促切割全长抗体而产生的Fab和F(ab')片段。其它结合片段包括由重组DNA技术产生的片段,例如含有编码抗体可变区的核酸序列的重组质粒的表达。

[0222] 当用于抗体的上下文中时,术语“特异性结合”意指:在蛋白质的异质群体和/或其它的生物材料存在下,抗体与它的靶标结合。更具体地,当抗体与它的靶标特异性结合时,这意指在预定的免疫测定条件下,抗体与它的靶结合,并且不会以显著量与存在于样品中的其它蛋白结合。可使用任何适宜的免疫测定方式以鉴定特异性结合其靶标的抗体,例如,固相ELISA免疫测定法。例如,参见Harlow和Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York。针对FGF21突变体多肽的多克隆抗体通常通过多次FGF21突变体多肽和辅助剂的皮下或腹膜内注射在动物(例如兔或小鼠)中制备。将FGF21突变体多肽与在待免疫物种中有免疫原性的载体蛋白缀合可能是有益的,所述载体蛋白例如匙孔血蓝蛋白、血清、白蛋白、牛甲状腺球蛋白或大豆胰蛋白酶抑制剂。同样,使用聚集剂(例如明矾)来增强免疫应答。在免疫后,采集动物血,测定血清的抗FGF21突变体抗体效价。

[0223] 可采用通过培养中的传代细胞系以供产生抗体分子的任何方法来产生针对FGF21突变体多肽的单克隆抗体。用于产生单克隆抗体的合适方法的实例包括杂交瘤方法(Kohler等,1975, *Nature* 256:495-97) 和人B细胞杂交瘤方法(Kozbor,1984, *J. Immunol.* 133:3001; Brodeur等, *Monoclonal Antibody Production Techniques and Applications* 51-63 (Marcel Dekker, Inc., 1987))。本发明还提供产生与FGF21突变体多肽反应的单克隆抗体的杂交瘤细胞系。

[0224] 可对本发明的单克隆抗体进行修饰以用作治疗剂。在一个实施方案中,单克隆抗体为“嵌合”抗体,其中重(H)链和/或轻(L)链的一部分与从特定物种得到的抗体或者属于特定抗体类别或亚类的抗体中的相应序列相同或同源,而链的其余部分则与从另一物种得到的抗体或者属于另一种抗体类别或亚类的抗体中的相应序列相同或同源。还包括这类抗体的片段,只要它们具有所需要的生物活性。参见例如美国专利号4,816,567; Morrison等,1985, *Proc. Natl. Acad. Sci. U.S.A.* 81:6851-55。

[0225] 在另一个实施方案中,本发明的单克隆抗体是“人源化”抗体。用于使非人类抗体人源化的方法是本领域众所周知的。参见例如美国专利号5,585,089和5,693,762。人源化抗体一般具有一个或多个从非人类来源引入其中的氨基酸残基。例如,可以采用本领域记载的方法,通过用啮齿动物互补决定区的至少一部分取代人抗体的相应区域来进行人源化(参见例如Jones等,1986, *Nature* 321:522-25; Riechmann等,1998, *Nature* 332:323-27; Verhoeyen等,1988, *Science* 239:1534-36)。

[0226] 本发明还包括结合本发明的FGF21突变体多肽的人抗体。使用能够在不存在内源免疫球蛋白产生的情况下产生人抗体库的转基因动物(例如小鼠),通过用任选与载体缀合的由FGF21突变体衍生的抗原(即具有至少6个连续氨基酸)免疫接种来产生这类抗体。参见例如Jakobovits等,1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:2551-55; Jakobovits等,1993, *Nature* 362:255-58; Bruggermann等,1993, *Year in Immuno.* 7:33。在一种方法中,通过使在其中编码免疫球蛋白重链和轻链的内源基因座失去作用,将编码人重链和轻链蛋白的基因座插入其基因组中,来产生这类转基因动物。然后使部分修饰的动物(即,具有少于全互补修饰的动物)杂交以获得具有全部所需要的免疫系统修饰的动物。当给予免疫原时,这些转基因动物产生具有人(而不是例如鼠)氨基酸序列(包括对于这些抗原有免疫特异性的可变区)的抗体。参见例如国际公布号W0 96/33735和W0 94/02602。其它的方法参见美国专利号

5,545,807、国际公布号W0 91/10741和W090/04036以及欧洲专利号0546073。按本文所述,可通过在宿主细胞中表达重组DNA或通过杂交瘤细胞表达来产生人抗体。

[0227] 在一个备选的实施方案中,还可从噬菌体展示文库制备人抗体(参见例如Hoogenboom等,1991,J.Mol.Biol.227:381;Marks等,1991,J.Mol.Biol.222:581)。这些方法模拟通过在丝状噬菌体的表面展示抗体库,随后通过其与所选抗原的结合选出噬菌体这一免疫选择。

[0228] 嵌合抗体、CDR移植抗体和人源化抗体通常通过重组方法产生。应用本文所述材料与方法,将编码抗体的核酸导入宿主细胞并使之表达。在一个实施方案中,抗体在哺乳动物宿主细胞(例如CHO细胞)中产生。单克隆(例如人)抗体可按本文所述方法通过重组DNA在宿主细胞中表达或通过在杂交瘤细胞中表达而产生。

[0229] 本发明的抗FGF21突变体抗体可用于任何已知的测定方法,例如用于FGF21突变体多肽的检测和定量的竞争性结合测定法、直接和间接夹心测定法及免疫沉淀测定法(参见例如Sola,Monoclonal Antibodies:A Manual of Techniques 147-158(CRC Press,Inc.,1987),通过引用以其整体并入本文中)。抗体以适于所采用的测定方法的亲和力与FGF21突变体多肽结合。

[0230] 在某些实施方案中,对于诊断应用,抗FGF21突变体抗体可用可检测部分标记。可检测部分可以是任何能够直接或间接产生可检测信号的部分。例如,可检测部分可以是放射性同位素,例如³H、¹⁴C、³²P、³⁵S、¹²⁵I、⁹⁹Tc、¹¹¹In或⁶⁷Ga;荧光或化学发光化合物,例如异硫氰酸荧光素、罗丹明或萤光素;或酶,例如碱性磷酸酶、β-半乳糖苷酶或辣根过氧化物酶(Bayer等,1990,Meth.Enz.184:138-63)。

[0231] 竞争性结合测定法取决于标记的标准品(例如FGF21突变体多肽或其免疫反应性部分)与试验样品分析物(例如FGF21突变体多肽)竞争结合有限量的抗FGF21突变体抗体的能力。试验样品中FGF21突变体多肽的量与结合抗体的标准品的量成反比。为了有利于测定已结合的标准品的量,抗体在竞争之前或之后通常是不溶解的,使得与抗体结合的标准品和分析物可方便地与保持未结合的标准品和分析物分离。

[0232] 夹心测定法通常包括使用两种抗体,每种抗体能够与待检测和/或定量的蛋白质的不同免疫原性部分或表位结合。在夹心测定法中,试验样品分析物通常被在固相支持体上固定化的第一抗体结合,之后,第二抗体与分析物结合,由此形成不溶性三组成部分复合物。参见例如美国专利号4,376,110。第二抗体本身可用可检测部分标记(直接夹心测定法)或可以使用用可检测部分标记的抗免疫球蛋白抗体测定(间接夹心测定法)。例如,夹心测定法的一种类型是酶联免疫吸附测定(ELISA),在该情况下可检测部分为酶。

[0233] 本发明的抗FGF21突变体抗体还可用于体内成像。可将用可检测部分标记的抗体给予动物,优选进入血流中,然后测定标记抗体在宿主中的存在情况和位置。抗体可用在动物内不论是通过核磁共振、放射学还是本领域已知的其它检测方法可检出的任何部分标记。

[0234] 本发明的FGF21突变体抗体可用作治疗剂。这些治疗剂一般是激动剂或拮抗剂,因为它们分别提高或降低至少一种FGF21突变体多肽的生物活性。在一个实施方案中,本发明的拮抗剂抗体是能够与FGF21突变体多肽特异性结合并且能够抑制或消除FGF21突变体多肽体内或体外的功能活性的抗体或其结合片段。在一些实施方案中,拮抗剂抗体可抑制

FGF21突变体多肽的功能活性达至少约50%，优选达至少约80%。在另一个实施方案中，抗FGF21突变体抗体能够干扰FGF21突变体多肽和FGF受体之间的相互作用，从而在体外或体内抑制或消除FGF21突变体多肽活性。激动剂和拮抗剂抗FGF21突变体抗体通过本领域众所周知的筛选测定法来鉴定。

[0235] 本发明还涉及包含FGF21突变体抗体和可用于检测生物样品中的FGF21突变体多肽水平的其它试剂的药盒。这类试剂可包括可检测标记、封闭血清、阳性和阴性对照样品及检测试剂。

实施例

[0236] 下面的实施例说明本发明的具体实施方案及其各种用途。这些实施例仅以说明目的来提供，不应解释为以任何方式限制本发明的范围。

[0237] 实施例1

[0238] FGF21表达构建体的制备

[0239] 使用具有对应于成熟FGF21序列的5'末端和3'末端的核苷酸序列的引物，通过聚合酶链式反应(PCR)扩增，得到编码成熟FGF21多肽的核酸序列。表2列举了用来扩增成熟FGF21序列的引物。

[0240] 表2

[0241] 用于制备FGF21构建体的PCR引物

[0242]	引物	序列	SEQ ID NO:
	正义	5'-AGGAGGAATAACATATGCATCCAATTCCAGATTCTTCTCC-3'	12
	反义	5'-TAGTGAGCTCGAATTCTTAGGAAGCGTAGCTGG-3'	13

[0243] 将用于制备成熟FGF21表达构建体的引物掺入用于将序列定向克隆至合适的表达载体(例如pET30(Novagen/EMD Biosciences;San Diego,CA)或pAMG33(Amgen;Thousand Oaks,CA))中的限制性内切核酸酶位点(NdeI位点还包含用于细菌表达的N-末端甲硫氨酸)上。表达载体pAMG33含有低拷贝数R-100复制起点、改进的lac启动子和卡那霉素抗性基因。表达载体pET30含有pBR322衍生的复制起点、诱导型T7启动子和卡那霉素抗性基因。虽然发现pAMG33的表达较高，但却发现pET30是更可靠的克隆载体。因此，本公开内容中所描述的大多数构建体首先在pET30中产生，然后筛选功效。然后将选出的序列转移至pAMG33用于进一步的扩增。

[0244] 使FGF21序列在含有40.65μLdH2O、5μLPfuUltra II反应缓冲液(10x)、1.25μLdNTPMix(40mM-4x 10mM)、0.1μL模板(100ng/mL)、1μL引物1(10μM)、1μL引物2(10μM)和1μLPfuUltra II融合HS DNA聚合酶(Stratagene;La Jolla,CA)的反应混合物中扩增。扩增反应如下进行：在95℃下加热2分钟；接着每千碱基所需产物在95℃下20秒钟、60℃20秒钟(每次循环减去额外1℃)和72℃15秒钟10次循环；接着每千碱基所需产物在94℃下20秒钟、55℃20秒钟和72℃15秒钟20次循环；接着72℃3分钟。扩增产物用限制性内切核酸酶NdeI、DpnI和EcoRI消化，与合适的载体连接，然后转化至感受态细胞中。

[0245] 实施例2

[0246] 从细菌中纯化FGF21蛋白

[0247] 在下列实施例中,在细菌表达系统中表达各种FGF21蛋白,包括野生型FGF21多肽、截短FGF21多肽、FGF21突变体和FGF21融合蛋白。在下面将描述的表达之后,FGF21蛋白按本实施例中所述方法纯化,除非另有说明。

[0248] 为了从细菌包含体中纯化出野生型FGF21多肽、截短FGF21多肽和FGF21突变体,使双洗涤(double-washed)包含体(DWIB)在含有盐酸胍和DTT/Tris缓冲液的增溶缓冲液(pH 8.5)中增溶,然后将它们在室温下混合1小时,将增溶混合物加入含有脲、精氨酸、半胱氨酸和盐酸胱胺的再折叠缓冲液(pH 9.5)中,然后在5℃下混合24小时(参见例如Clarke,1998,Curr.Opin.Biotechnol.9:157-63;Mannall等,2007,Biotechnol.Bioeng.97:1523-34;Rudolph等,1997,"Folding proteins,"Protein Function:A Practical Approach (Creighton,ed.,New York,IRL Press) 57-99;and Ishibashi等,2005,Protein Expr.Purif.42:1-6)。

[0249] 在增溶和再折叠后,将混合物通过0.45微米过滤器过滤。然后将再折叠合并物用10kD截留分子量Pall Omega盒在20psi的跨膜压(TMP)下浓缩至约10倍,并用3柱体积的20mM Tris (pH 8.0)在20psi的TMP下渗滤。

[0250] 然后使用Q琼脂糖凝胶(Sepharose)HP树脂对澄清样品进行阴离子交换(AEX)层析法。以0-250mMNaCl/20mM Tris的线性盐梯度在pH 8.0、5℃下过柱。峰值流分通过SDS-PAGE分析后合并。

[0251] 然后使用苯基琼脂糖凝胶HP树脂对AEX洗脱合并物进行疏水相互作用层析法(HIC)。在pH 8.0和环境温度下,蛋白质用递减线性梯度的0.7M-0M硫酸铵洗脱。峰值流分通过SDS-PAGE (Laemmli,1970,Nature 227:680-85)分析后合并。

[0252] 将HIC合并物用10kD截留分子量Pall Omega 0.2m²盒在20psi的TMP下浓缩至7mg/mL。在20psi的TMP下,浓缩物用5柱体积的制备缓冲剂渗滤,将回收的浓缩物稀释成5mg/mL。最后,使溶液通过Pall mini-Kleenpac 0.2μm Posidyne膜过滤。

[0253] 为了从细菌包含体中纯化出FGF21融合蛋白和FGF21融合突变体蛋白,将双洗涤包含体(DWIB)在含有盐酸胍和DTT/Tris缓冲液的增溶缓冲液(pH 8.5)中增溶,然后在室温下混合1小时。然后将增溶混合物加入含有脲、精氨酸、半胱氨酸和盐酸胱胺的再折叠缓冲液(pH 9.5)中,然后在5℃下混合24小时(参见例如Clarke,1998,Curr.Opin.Biotechnol.9:157-63;Mannall等,2007,Biotechnol.Bioeng.97:1523-34;Rudolph等,1997,"Folding proteins,"Protein Function:A Practical Approach (Creighton,ed.,New York,IRL Press) 57-99;以及Ishibashi等,2005,Protein Expr.Purif.42:1-6)。

[0254] 在增溶和再折叠后,使用10kD透析管,使混合物用5体积的20mM Tris (pH 8.0)透析。用50%乙酸调节透析再折叠的pH至5.0,然后在4K下离心30分钟澄清。

[0255] 然后使用Q琼脂糖凝胶HP树脂,对澄清样品进行阴离子交换(AEX)层析法。在pH 8.0、5℃下,使0-250mMNaCl/20mM Tris的线性盐梯度过柱。峰值流分通过SDS-PAGE (Laemmli,1970,Nature 227:680-85)分析后合并。

[0256] 然后使用苯基琼脂糖凝胶HP树脂,对AEX洗脱合并物进行疏水相互作用层析法(HIC)。在pH 8.0、环境温度下,蛋白质使用递减线性梯度的0.6M-0M硫酸铵洗脱。峰值流分通过SDS-PAGE分析后合并。

[0257] 在HIC步骤后,然后将合并物用60体积的制备缓冲剂透析,用Pall Jumbosep将透

析合并物浓缩至5mg/mL。最后,将溶液通过Pall mini-Kleenpac 0.2 μ M Posidyne膜过滤。

[0258] 实施例3

[0259] 截短FGF21蛋白的制备和表达

[0260] 按照下述方法通过野生型FGF21表达载体的PCR扩增来制备表3中所列的编码截短FGF21蛋白的构建体(野生型FGF21表达载体的构建见实施例1)。

[0261] 表3

[0262] FGF21截短

[0263]

氨基酸残基	截短的*残基数量
C-末端截短	
1 – 180	1
1 – 179	2
1 – 178	3
1 – 177	4
1 – 176	5
1 – 175	6
1 – 174	7
1 – 173	8
1 – 172	9
1 – 171	10
1 – 169	12
1 – 168	13
1 – 167	14
1 – 166	15
1 – 165	16
1 – 164	17
1 – 160	21
1 – 156	25
1 – 152	29
1 – 149	32
1 – 113	68
N-末端截短	
2 – 181	1
3 – 181	2
4 – 181	3
5 – 181	4
6 – 181	5
7 – 181	6
8 – 181	7
9 – 181	8
C-和 N-末端截短	
5 – 174	11
7 – 172	17

[0264]

氨基酸残基	截短的*残基数量
9 – 169	20
9 – 149	40
15 – 169	26
15 – 149	46
15 – 113	82

[0265] *相对于成熟FGF21多肽

[0266] 使用具有与待缺失(导致截短)密码子(或多个密码子)的上游区和下游区同源的序列的引物来制备截短FGF21蛋白构建体。用于这类扩增反应的引物还提供约15个核苷酸的重叠序列以供扩增产物再循环,即整个载体此时具有所需要的突变体或截短物。

[0267] 使用表4所示引物,来制备编码示例性截短FGF21构建体,其在成熟FGF21序列1位缺失组氨酸残基的FGF21蛋白(即2-181截短突变体)。

[0268] 表4

[0269] 制备示例性截短FGF21突变体的PCR引物

[0270]	引物	序列	SEQ ID NO:
	正义	5'-GGAGATATACATATGCCAATTCCAGATTCTTCTCCATTATT-3'	14
	反义	5'-CATATGTATATCTCCTTCTTAAAGTTAAACAAAA-3'	15

[0271] 表4所示引物可供如下所示的组氨酸残基的缺失,其中在上序列(SEQ ID NO:9)是包含N末端甲硫氨酸的成熟FGF21多肽的一部分,第二序列为正义引物(SEQ ID NO:14),第三和第四序列(SEQ ID NO:17和18)是FGF21表达构建体的部分,第五序列是反义引物(SEQ ID NO:16):

MetHisProIleProAspSerSerProLeu

5' -GGAGATATACATATG---

CCAATTCCAGATTCTTCTCCATTATT

[0272] TTTTGTTTAACTTTAAGAAGGAGATATACATATGCATCCAATTCCAGATTCTTCTCCATTAT

T

AAAACAAATTGAAATTCTTCCTCTATATGTATACGTAGGTTAAGGTCTAAGAAGAGGTAATA

A

AAAACAAATTGAAATTCTTCCTCTATATGTATAC-5'

[0273] 基本上采用实施例1中描述的PCR条件制备截短FGF21蛋白构建体。扩增产物用限制性内切核酸酶DpnI消化,然后转化进入感受态细胞中。对所得克隆进行了测序以证实不存在聚合酶生成错误。

[0274] 通过用编码特定截短FGF21蛋白的构建体转化感受态BL21(DE3)或BL21Star(Invitrogen;Carlsbad,CA)细胞,来表达截短FGF21蛋白。在补充了40μg/mL卡那霉素的TB培养基中使转化体在有限通气下生长过夜,次日早晨通气,在短暂恢复期后,用0.4mM IPTG诱导。在诱导后,通过离心18-20小时收获FGF21突变体。

[0275] 实施例4

[0276] 截短FGF21蛋白的体外活性

[0277] 在ELK-萤光素酶体外测定法中进行了实验,以鉴定保持野生型FGF21活性的截短FGF21蛋白。表5概括了所获得的在N末端、C末端或在N末端和C末端两末端具有截短的FGF21蛋白的结果。使用重组人293T肾细胞系统进行了ELK-萤光素酶测定法,其中293T细胞过量表达β-Klotho和萤光素酶报导分子构建体。这些构建体还含有编码GAL4-ELK1和5xUAS-Luc的序列,是一种由含有5个Gal4结合位点串联拷贝的启动子驱动的萤光素酶报导分子。β-

Klotho是FGF21用于激活其FGF受体和诱导胞内信号转导所必须的共同受体,其进而导致Erk和ELK磷酸化。萤光素酶活性受磷酸化Erk/ELK1的水平调节,可用于间接监测和测定量测定FGF21活性。

[0278] 通过将293T细胞在不同浓度的野生型FGF21或FGF21突变体多肽存在时培养6小时,来进行ELK-萤光素酶测定法,然后测定细胞裂解物的萤光素酶活性。图1A-1B表示FGF21截短突变体7-181和8-181(图1A)和FGF21截短突变体1-172、1-171、1-169和1-164(图1B)的ELK-萤光素酶活性测定结果。在ELK-萤光素酶测定法得到的每种FGF21截短突变体3-181、4-181、5-181、7-181、8-181、1-180、1-178、1-177、1-176、1-175、1-174、1-173、1-172、9-181和1-149的发光见图2。

[0279] 将FGF21突变体多肽与野生型FGF21标准品进行了比较,具有野生型FGF21功效的至少50%功效的突变体被视为未丧失FGF21活性,在表5中标为“+”。

[0280] 表5

[0281] 截短的FGF21蛋白:体外测定法

C-末端截短		
氨基酸残基	功效	活性(+/-)
1 - 180	93.2%	+
1 - 178	95.0%	+
1 - 177	112.0%	+
1 - 176	104.8%	+
1 - 174	104.6%	+
1 - 173	96.1%	+
1 - 172	97.5%	+
1 - 171	113.0%	+
1 - 169	84.9%	+
1 - 167	20%	-
1 - 166	20%	-
1 - 165	10%	-
N-末端截短		
氨基酸残基	功效	活性(+/-)
2 - 181	112.5%	+
3 - 181	130.3%	+
4 - 181	117.0%	+
5 - 181	119.6%	+
7 - 181	74.2%	+
8 - 181	24.9%	-
9 - 181	12.5%	-

[0283] 总的来说,表5中所提供的结果表明,14个或更多个氨基酸残基的C末端缺失(即由氨基酸残基1-167和更短的蛋白质组成的C末端截短FGF21蛋白)消除了FGF21的活性。另外,表5表明7个或更多个氨基酸残基的N末端缺失(即由氨基酸残基8-181和更短的蛋白质组成的N末端截短FGF21蛋白)消除了FGF21的活性。并不出人意料的是,在ELK-萤光素酶测定法中,发现具有8-14个残基的N末端截短和12个或32个残基的C末端截短的截短FGF21蛋白缺

乏活性。

[0284] 与表5所示数据一致,具有7个以下氨基酸残基的N末端截短的截短FGF21多肽构成本发明的实施方案。同样,13个以下氨基酸残基的C末端截短的截短FGF21多肽构成本发明的实施方案。

[0285] 实施例5

[0286] 截短的FGF21蛋白质的体内活性

[0287] FGF21具有多种生物活性,包括降低血糖、胰岛素、甘油三酯或胆固醇水平的能力;减轻体重;或改善葡萄糖耐量、能量消耗或胰岛素敏感性。通过将截短FGF21多肽引入胰岛素抵抗ob/ob小鼠,进一步分析了截短FGF21多肽的体内FGF21活性,并测定特定截短FGF21多肽降低血糖的能力。将待测定的截短FGF21多肽注射到8周龄ob/ob小鼠(Jackson Laboratory)腹膜内,在一次注射后的不同时间点,例如注射后0小时、6小时、24小时、72小时、120小时和168小时获取血样。用OneTouch血糖计(LifeScan, Inc. Milpitas, CA)测定了血糖水平,结果用相对于基线血糖水平(即0时)的血糖变化百分比表示。

[0288] 一项实验的结果见图3,其表示在注射FGF21截短突变体8-181和9-181的小鼠中检测的血糖量。该项实验表明包含氨基酸残基8-181的截短FGF21融合蛋白具有体内血糖降低活性,然而在注射后3小时候和6小时,活性略低于野生型FGF21的活性,但是包含氨基酸残基9-181的截短FGF21融合蛋白无这类活性。因此,截短FGF21多肽的体内分析表明,从成熟FGF21N末端缺失至多7个氨基酸不会破坏该分子的生物活性(与体外分析相反,体外分析表明从成熟FGF21的N末端缺失7个氨基酸可破坏活性)。

[0289] 在体外和体内测定法中,用特定的N末端截短的FGF21多肽(例如FGF218-181)得到的不同结果可用在引起信号转导时FGF21与 β -Klotho和FGF受体的相互作用来解释。具体地讲,FGF21激活包含共同受体 β -Klotho和FGF受体(FGFR)的二受体复合物,这引发了包括酪氨酸激酶的信号转导级联。研究表明,FGF21的N末端参与FGFR的结合和活化,而FGF21的C末端是 β -Klotho相互作用所必须的(Yie等,2009FEBS Lett. 583:19-24)。在其中共同受体 β -Klotho过量表达,FGFR以正常水平表达的293肾细胞中进行了ELK-萤光素酶体外测定法。FGFR的量相对于 β -Klotho的量较低,因此,293细胞中 β -Klotho与FGFR之比不是生理性的,其可能影响受体复合物形成及最终的配体结合和FGFR的活化。293体外系统似乎对N末端截短的FGF21多肽更敏感,因此得到几个受测N末端截短突变体(例如FGF218-181)失去活性的结果。因此,在测定具体的N末端截短FGF21突变体是否保持野生型FGF21活性时,在体内测定法中该FGF21突变体的活性被视作决定性的。因此,本发明包括具有8个氨基酸残基以下N末端截短的截短FGF21多肽。

[0290] 实施例6

[0291] 截短的FGF21融合蛋白的制备和表达

[0292] 因为可通过将蛋白质与Fc序列融合来延长蛋白质的半寿期,所以制备了包含截短FGF21多肽的融合蛋白并进行了分析。通过SOEing(经重叠延伸的基因剪接)PCR由扩增的FGF21序列制备了表6中所列的截短FGF21融合蛋白。制备了FGF21融合蛋白使得人免疫球蛋白IgG1基因的Fc部分(SEQ ID NO:11)与FGF21蛋白的N末端或C末端融合。

[0293] 表6

[0294] 截短的FGF21融合蛋白

[0295]

氨基酸残基	Fc 位	接头
C-末端截短		
1 – 178	-NH ₂	15
1 – 175	-NH ₂	14
1 – 175	-COOH	15
1 – 171	-NH ₂	15
1 – 171	-COOH	15
1 – 170	-COOH	15
N-末端截短		
5 – 181	-NH ₂	15
5 – 181	-COOH	15
7 – 181	-NH ₂	15
7 – 181	-COOH	15
C- 和 N-末端截短		
5 – 175	-NH ₂	15
5 – 175	-COOH	15
5 – 171	-NH ₂	15
5 – 171	-COOH	15
6 – 170	-COOH	15
7 – 178	-COOH	35
7 – 175	-NH ₂	15
7 – 175	-COOH	15
7 – 174	-COOH	35
7 – 172	-COOH	35
7 – 171	-NH ₂	15
7 – 171	-COOH	35
7 – 171	-COOH	15

[0296] 具体地讲,基本上采用实施例1中所描述的反应条件,在一系列的三扩增反应中制备了FGF21融合蛋白构建体(包括编码截短FGF21融合蛋白的构建体)。在第一反应中,设计引物对以产生含有NdeI克隆位点(包括用于细菌表达的N-末端甲硫氨酸)、Fc区和接头序列的序列。在第二反应中,设计引物对以产生含有接头的重叠部分、FGF21编码序列的部分和EcoRI克隆位点的序列。最后,在第三反应中,设计了引物对用于连接头两个反应的产物的目的。用于构建Fc-FGF211-181的示例性的引物组见表7。

[0297] 表7

[0298] 用于制备示例性FGF21融合蛋白构建体的PCR引物

引物	序列	SEQ ID NO:
反应 1		
正义	5'-AGGAGGAATAACATATGGACAAAACCTCACACATG-3'	19
反义	5'-GGATCCACCACCACCGCTACCAC-3'	20
反应 2		
正义	5'-GGTGGTGGTGGATCCCATCCAATTCCAGATTCTTCTCCA-3'	21
反义	5'-TAGTGAGCTCGAATTCTTAGGAAGCGTAGCTGG-3'	22
反应 3		
正义	5'-AGGAGGAATAACATATGGACAAAACCTCACACATG-3'	19
反义	5'-TAGTGAGCTCGAATTCTTAGGAAGCGTAGCTGG-3'	22

[0300] 最终反应的产物用限制性内切核酸酶NdeI和EcoRI消化,与pET30载体连接,然后转化至感受态细胞中。对所得克隆进行了测序以证实不存在聚合酶生成错误。

[0301] 实施例7

[0302] 截短FGF21融合蛋白的体内活性

[0303] 制备了包含与Fc序列融合的截短FGF21序列的融合蛋白,并测定了体内活性。通过将IgG1 Fc分子与截短FGF21蛋白的N末端或C末端融合形成单一连续序列来制备截短FGF21融合蛋白。为了区分N末端和C末端融合物,把其中Fc分子与FGF21蛋白的N末端融合的FGF21融合蛋白称为Fc-FGF21,其中Fc分子与FGF21蛋白的C末端融合的融合蛋白称为FGF21-Fc。

[0304] FGF21具有多种生物活性,包括降低血糖、胰岛素、甘油三酯或胆固醇水平的能力;减轻体重;或改善葡萄糖耐量、能量消耗或胰岛素敏感性。为了评价体内FGF21活性,将FGF21多肽、FGF21突变体多肽和FGF21融合多肽引入胰岛素抵抗ob/ob小鼠中,并测定具体FGF21蛋白降低血糖水平的能力。将待测定的FGF21多肽、FGF21突变体多肽或FGF21融合多肽注射到8周龄ob/ob小鼠(Jackson Laboratory)腹膜内,并在一次注射后的不同时间点,例如在注射后0小时、6小时、24小时、72小时、120小时和168小时,获取血样。用OneTouch血糖计(LifeScan, Inc. Milpitas, CA)测定血糖水平,结果用相对于基线血糖水平(即0时)的血糖变化百分比表示。

[0305] 一项实验的结果见图4,该图表示在注射PBS对照、包含氨基酸残基1-181的野生型Fc-FGF21对照或包含氨基酸残基5-181或7-181的截短Fc-FGF21融合蛋白的小鼠中观察到的血糖水平变化百分比。该项实验表明,包含氨基酸残基5-181或7-181的截短Fc-FGF21融合蛋白的血糖降低活性类似于在注射后6小时野生型Fc-FGF21的活性。因此,截短FGF21多肽的体内分析表明,从成熟FGF21的N末端缺失至多6个氨基酸不会影响该分子的生物活性。然而,体内分析还表明,截短FGF21多肽降低血糖的能力降低,血糖水平在注射后24小时回到基线(用野生型FGF21得到类似结果)。发现短暂的体内活性是FGF21的蛋白酶降解的结果,正如实施例8中所描述的一样。

[0306] 另一项实验的结果见图5,该图表示在注射PBS对照、包含氨基酸残基1-181的野生型FGF21-Fc对照、包含残基1-175的截短FGF21-Fc融合蛋白或包含氨基酸残基1-171的截短Fc-FGF21蛋白的小鼠中观察到的血糖水平变化百分比。该项实验表明,包含氨基酸残基1-181的野生型FGF21-Fc具有持续的葡萄糖降低活性,导致在注射后24小时-120小时时间内

血糖水平下降约30%。包含氨基酸残基1-171的截短Fc-FGF21蛋白具有延时的血糖降低活性,只是在注射后72小时变得明显。然而,所观察到活性与野生型FGF21-Fc的活性相同。包含残基1-175的截短FGF21-Fc融合蛋白在体内降低血糖方面没有活性。

[0307] 总的来说,本文所述的截短实验表明,具有N末端截短的截短FGF21融合蛋白的血糖降低活性类似于野生型FGF21融合蛋白的血糖降低活性,此外,其中Fc分子与截短FGF21蛋白的N末端融合的截短FGF21融合蛋白的活性比其中Fc分子与截短FGF21蛋白的C末端融合的融合蛋白的大。

[0308] 实施例8

[0309] 观察到的FGF21的体内降解

[0310] 用FGF21Fc融合蛋白构建体首次对FGF21降解进行了观察,正如实施例7中所描述的一样。体内药代动力学分析表明,人FGF21由于快速清除和体内降解而在小鼠中具有约1小时的短暂半寿期。因此,为了延长FGF21的半寿期,将Fc序列与FGF21多肽的N末端或C末端融合。然而,Fc区的融合无法完全解决半寿期问题,因为其中Fc序列与FGF21多肽的N末端或C末端融合的融合蛋白(特别是Fc-FGF21融合物,即其中Fc序列与成熟FGF21的N末端融合)不具有预期的体内功效,反而发现在ob/ob小鼠中保持血糖降低活性超过24小时。如图4所示,在注射后6小时,Fc-FGF21融合蛋白降低血糖水平达约30-40%,而在24小时内,血糖水平回到基线水平。

[0311] 随后对野生型FGF21的蛋白酶降解进行了研究,发现Fc-FGF21融合蛋白体内活性的快速丧失是FGF21体内降解的结果。蛋白酶降解导致低的分子体内生物活性和由此引起的较短的有效半寿期,这类降解不利地影响该分子的治疗用途。因此,所观察到的FGF21Fc融合蛋白的降解导致对体内FGF21蛋白酶降解的研究和对抵抗这类降解的FGF21突变体的鉴定。

[0312] 为了确定降解位点,对在给雄性C57B6小鼠注射的不同时间点上得到的野生型人FGF21和FGF21Fc融合蛋白进行了LC-MS分析和Edman测序。Edman测序有助于确定是蛋白质的N末端还是蛋白质的C末端进行了降解。当Fc序列与人FGF21的N末端融合时,发现降解发生在融合分子的人FGF21部分的氨基酸残基151和152之间以及氨基酸残基171和172之间的肽键上(上述残基编号以成熟FGF21序列为基础,不包括融合蛋白的Fc部分)。发现首先发生在171-172上的降解,接着在151-152上发生降解。在171-172上的降解似乎是限速步骤,在分子的半寿期中起作用。当Fc序列与FGF21的C末端融合时,发现降解发生在氨基酸残基4和5之间及氨基酸残基20和21之间的肽键上。由于这些实验的结果,因此断定Fc序列似乎保护与Fc序列邻近的FGF21序列的部分免遭降解。在食蟹猴中,对野生型FGF21和Fc-FGF21融合蛋白的体内降解进行了进一步的分析。这些研究证实,在氨基酸残基171-172上的FGF21切割位点在猴中是主要的降解位点,且该降解位点在鼠和灵长类之间是保守的。

[0313] 实施例9

[0314] FGF21蛋白酶解抗性突变体的鉴定

[0315] 通过实验测定了是主要的蛋白水解活性的位点的野生型FGF21序列的位置,来鉴定合适的FGF21突变体,并将特定的氨基酸取代引入这些位点。氨基酸取代以具有其它物种的FGF21序列保守性(正如实施例8中所描述的一样)和具有氨基酸残基的生化保守性为基础。已引入或可引入野生型FGF21蛋白的氨基酸取代表见表8,然而表8只是示例性的,并

且可进行其它取代。表8中给定的位置数对应于由181个氨基酸残基组成的成熟FGF21蛋白的残基位点。

[0316] 表8

[0317] FGF21残基突变

[0318]

氨基酸位点	天然残基	突变
19	Arg	Gln, Ile, Lys
20	Tyr	His, Leu, Phe
21	Leu	Ile, Phe, Tyr, Val
22	Tyr	Ile, Phe, Val
150	Pro	Ala, Arg
151	Gly	Ala, Val
152	Ile	His, Leu, Phe, Val
170	Gly	Ala, Asn, Asp, Cys, Gln, Glu, Pro, Ser
171	Pro	Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Lys, Ser, Thr, Trp, Tyr
172	Ser	Leu, Thr
173	Gln	Arg, Glu

[0319] 实施例10

[0320] Fc-FGF21和FGF21-Fc降解的体内分析

[0321] 通过给小鼠注射融合蛋白,在不同时间点抽取小鼠血液,并用液相层析法-质谱法(LC-MS)分析血清,来测定FGF21Fc融合蛋白的体内稳定性。具体地讲,将10mg/kg Fc-(G5)-FGF21 (SEQ ID NO:107) (在大肠杆菌(E.coli)中表达,按实施例2所述方法纯化)或FGF21-(G3)-Fc (SEQ ID NO:105) (在哺乳动物细胞中表达,按照标准方法纯化)注射到小鼠腹腔内。小鼠在注射后6小时、24小时和48小时抽取小鼠血液(表9),收集到用蛋白酶抑制剂混合物(Roche Diagnostics)预治疗的EDTA管中。将样品在12,000×g下离心10分钟分离出血浆。用抗人-Fc琼脂糖树脂从血液中亲和纯化出FGF21蛋白。

[0322] 表9

[0323] FGF21样品

[0324]

样品	给予的蛋白	抽血
D6	Fc-(G5)-FGF21	6小时
D24	Fc-(G5)-FGF21	24小时
D48	Fc-(G5)-FGF21	48小时
E6	FGF21-(G3)-Fc	6小时
E24	FGF21-(G3)-Fc	24小时
E48	FGF21-(G3)-Fc	48小时

[0325] 在通过LC-MS分析亲和纯化样品前,对Fc-(G5)-FGF21和FGF21-(G3)-Fc蛋白标准品进行了分析作为参比。蛋白质标准品用三[2-羧乙基]膦(TCEP)还原或不还原。通过LC-MS使用ACE cyano 0.3mmx 30cm柱将柱流出液喷雾至LCQ Classic离子阱质谱仪来分析还原和未还原标准品。由于还原样品的去卷积谱更清晰,因此在LC-MS分析前将亲和纯化样品还原。

[0326] 观察到的还原Fc-(G5)-FGF21标准和样品D6、D24和D48的质量见图6A-6D。观察到的还原FGF21-(G3)-Fc标准和样品E6、E24和E48的质量见图7A-7D。将一些标准品和样品洗出液进行Edman测序以证实通过LC-MS测定的蛋白质和片段的N末端。标准品和样品的LC-MS分析结果见表10。

[0327] 表10

[0328] LC-MS分析结果和预测片段

[0329]	FGF21 样品	主要观察质量	片段	完整 N-末端
	Fc-(G5)-FGF21 标准品	45,339 Da	1-414	是
	D6	45,338 Da 44,317 Da	1-414 1-404	是
	D24	44,321 Da	1-404	是
	D48	44,327 Da 42,356 Da	1-404 ?	是
	FGF21-(G3)-Fc 标准品	46,408 Da (糖基化, G0F) 44,964 Da (非糖基化)	1-410 1-410	是
	E6	45,963 Da (糖基化, G0F) 44,516 Da (非糖基化)	5-410 5-410	否
	E24	45,963 Da (糖基化, G0F) 44,526 Da (非糖基化) 44,130 Da (糖基化, G0F)	5-410 5-410 21-410	否
	E48	45,984 Da 44,130 Da 44,022 Da	5-410? 21-410 ?	否

[0330] 表10中表明,所有的亲和纯化样品在循环仅6小时后都显示某种程度的降解。在循环24小时后,Fc-(G5)-FGF21的主要产物是由氨基酸残基1-404组成的片段,这也存在于D和E样品中。然而,在E样品中,FGF21-(G3)-Fc的主要产物是由氨基酸残基5-410组成的片段。至于所测试的两种融合蛋白,融合蛋白的FGF21部分比蛋白质的Fc部分更易被降解。

[0331] 实施例11

[0332] 蛋白酶解抗性FGF21突变体和融合蛋白的制备和表达

[0333] 按下文所述方法,通过PCR扩增野生型FGF21表达载体,来制备列于表11的编码FGF21突变体的构建体(野生型FGF21表达载体的构建见实施例1)。当将接头包含在构建体中时,所用接头是GGGGSGGGSGGGGS(“L15,” SEQ ID NO:28)。这些实验的目的是产生对蛋白酶解有抗性和具有较长半寿期的FGF21突变体。

[0334] 表11

[0335] 蛋白酶解抗性FGF21突变体

[0336]

突变	Fc	接头
R19I		
R19I	-COOH	L15
R19K		
R19K	-COOH	L15
R19Q		
R19Q	-COOH	L15
R19K, Y20H		
R19K, Y20H	-COOH	L15
R19K, L21I		
R19K, L21I	-COOH	L15
R19K, Y20H, L21I		
R19K, Y20H, L21I	-COOH	L15
Y20F		
Y20F	-COOH	L15
Y20H		
Y20H	-COOH	L15
Y20L		
Y20L	-COOH	L15
Y20H, L21I		
Y20H, L21I	-COOH	L15
L21I		
L21I	-COOH	L15
L21F		
L21F	-COOH	L15
L21V		
L21V	-COOH	L15
L21Y		
L21Y	-COOH	L15
Y22F		
Y22F	-COOH	L15
Y22I		
Y22I	-COOH	L15
Y22V		
Y22V	-COOH	L15
P150A		
P150A	-NH ₂	L15

[0337]

突变	Fc	接头
P150R	-NH ₂	L15
P150A, G151A		
P150A, G151A	-NH ₂	L15
P150A, I152V		
P150A, I152V	-NH ₂	L15
P150A, G151A, I152V		
P150A, G151A, I152V	-NH ₂	L15
G151A		
G151A	-NH ₂	L15
G151V		
G151V	-NH ₂	L15
G151A, I152V		
G151A, I152V	-NH ₂	L15
I152F		
I152F	-NH ₂	L15
I152H		
I152H	-NH ₂	L15
I152L		
I152L	-NH ₂	L15
I152V		
G170A		
G170A	-NH ₂	L15
G170C		
G170C	-NH ₂	L15
G170D		
G170D	-NH ₂	L15
G170E		
G170E	-NH ₂	L15
G170N		
G170N	-NH ₂	L15
G170P		
G170P	-NH ₂	L15
G170Q		
G170Q	-NH ₂	L15
G170S		
G170S	-NH ₂	L15
G170E, P171A		
G170E, P171A	-NH ₂	L15
G170E, S172L		
G170E, S172L	-NH ₂	L15
G170E, P171A, S172L		

[0338]

突变	Fc	接头
G170E, P171A, S172L	-NH ₂	L15
P171A		
P171A	-NH ₂	L15
P171C	-NH ₂	L15
P171D	-NH ₂	L15
P171E	-NH ₂	L15
P171G	-NH ₂	L15
P171H	-NH ₂	L15
P171K	-NH ₂	L15
P171N	-NH ₂	L15
P171Q	-NH ₂	L15
P171S	-NH ₂	L15
P171T	-NH ₂	L15
P171W	-NH ₂	L15
P171Y	-NH ₂	L15
P171A, S172L		
P171A, S172L	-NH ₂	L15
S172L	-NH ₂	L15
S172T		
S172T	-NH ₂	L15
Q173E		
Q173E	-NH ₂	L15
Q173R		
Q173R	-NH ₂	L15

[0339] 使用具有与待突变的密码子(或多个密码子)的上游和下游区同源的序列的引物,来制备FGF21突变体构建体。用于这类扩增反应的引物也提供约15个核苷酸的重叠序列以供扩增产物再循环,即整个载体此时具有所需要的突变体。

[0340] 使用表12中所示引物,制备编码170位上具有谷氨酸残基而不是天然甘氨酸残基的FGF21突变体(即G170E突变体)的示例性的FGF21突变体构建体。

[0341] 表12

[0342] 制备示例性FGF21突变体的PCR引物

[0343]

引物	序列	SEQ ID NO:
----	----	------------

[0344]

正义	5'-ATGGTGGAACCTTCCCAGGGCCGAAGC-3'	23
反义	5'-GGAAGGTTCCACCATGCTCAGAGGGTCCGA-3'	24

[0345] 表12中所示引物可供按下面所示方法用谷氨酸残基取代甘氨酸残基,其中上面的序列为正义引物(SEQ ID NO:23),第二和第三序列(SEQ ID NO:25和27)是FGF21表达构建体的部分,第四序列是反义引物(SEQ ID NO:26):

5' - ATGGTGGAACCTTCCCAGGGCCGAAGC

[0346] CTCTCGGACCCTCTGAGCATGGTGGGACCTTCCCAGGGCCGAAGCCCCA
GAGGAGCCTGGGAGACTCGTACCACCCTGGAAGGGTCCCGGCTTCGGGGT
AGCCTGGGAGACTCGTACCACCTGGAAGG-5'

[0347] 基本上采用实施例1中描述的PCR条件制备FGF21突变体构建体。扩增产物用限制性内切核酸酶DpnI消化,然后转化至感受态细胞。对所得到的克隆进行测序以证实不存在聚合酶生成错误。Fc- (L15) -FGF21和FGF21- (L15) -Fc融合蛋白按本文所述方法(例如实施例6)制备。

[0348] 通过用编码特定突变体的构建体转化感受态BL21 (DE3) 或BL21Star (Invitrogen; Carlsbad, CA) 细胞,使FGF21突变体表达。在补充了40μg/mL卡那霉素的TB培养基中使转化体在有限通气下生长过夜,次日早晨通气,在短暂恢复期后,用0.4mM IPTG诱导。在诱导后,通过离心18-20小时收获FGF21突变体多肽。

[0349] 还分析了FGF21突变体以预测免疫原性。在主要组织相容性复合物(MHC) II类结合位点上通过抗原加工和呈递提高对蛋白质的免疫应答。这种相互作用对有利于识别蛋白质的抗体成熟的T细胞是必须的。由于已表征了MHC II类分子的结合位点,因此预测蛋白质是否具有与一系列普通人等位基因结合的特定序列是可能的。根据文献参考资料创建了计算机算法,而且决定是否是线性氨基酸肽序列的MHC II类晶体结构具有破坏免疫耐受的潜力。应用TEPITOPE计算机程序测定特定FGF21突变体的点突变是否可在多数人中增加抗原特异性T细胞。根据对各FGF21突变体的线性蛋白质序列的分析,预测突变体无一提高免疫原性。

[0350] 实施例12

[0351] 接头序列对FGF21降解的作用

[0352] 为了确定在Fc序列和FGF21序列之间存在较长的氨基酸接头是否影响FGF21降解,给小鼠注射其中Fc区与FGF21序列被15个氨基酸接头(序列GGGGSGGGSGGGGS(命名为“L15,”SEQ ID NO:28)分隔的FGF21融合蛋白,在不同时间点抽取小鼠血液,通过LC-MS分析血清。具体地讲,以23mg/kg给小鼠注射Fc- (L15) -FGF21或FGF21- (L15) -Fc(得自大肠杆菌),在6小时、24小时和48小时抽血,抽取的血液使用抗人-Fc琼脂糖树脂进行亲和纯化。

[0353] 在通过LC-MS分析纯样品前,将Fc- (L15) -FGF21和FGF21- (L15) -Fc蛋白标准品作为参比进行了分析。蛋白质标准品用TCEP还原或未还原。通过LC-MS使用ACE cyano 0.3mm x 30cm柱将柱流出液喷雾到LCQ Classic离子阱质谱仪中来分析还原和未还原标准品两者。由于还原样品的去卷积谱更清晰,因此在LC-MS分析前将亲和纯化样品还原。

[0354] 观察到的在不同时间点抽取的还原Fc- (L15) -FGF21标准品和相应的亲和纯化样品的质量见图8A-8D。观察到的在不同时间点抽取的还原FGF21- (L15) -Fc标准品和相应的亲和纯化样品的质量见图9A-9D。将一些标准品和样品洗出液进行Edman测序以证实蛋白质的N末端,并有利于预测通过LC-MS观察到的片段的特征。标准品和样品的LC-MS分析结果和预测片段的指标见表13。

[0355] 表13

[0356] LC-MS分析结果和预测片段

[0357]	FGF21 样品	观察的主要质量	总百分比	片段	完整 N-末端?
	Fc-(L15)-FGF21 标准品	46,002 Da	100%	1-424	是
	Fc-(L15)-FGF21 6 小时	46,000 Da 44,978 Da	65% 35%	1-424 1-414	是
	Fc-(L15)-FGF21 24 小时	44,978 Da 43,022 Da	85% 15%	1-414 1-394	是
	Fc-(L15)-FGF21	44,976 Da	60%	1-414	是

[0358]	FGF21 样品	观察的主要质量	总百分比	片段	完整 N-末端?
	48 小时	43,019 Da	40%	1-394	
	FGF21-(L15)-Fc 标准品	45,999 Da	100%	1-424	是
	FGF21-(L15)-Fc 6 小时	45,870 Da	100%	1-423	是
	FGF21-(L15)-Fc 24 小时	45,869 Da 45,301 Da 43,460 Da	40% 35% 25%	1-423 6-423 22-423	一些
	FGF21-(L15)-Fc 48 小时	45,870 Da 45,297 Da 43,461 Da	15% 20% 65%	1-423 6-423 22-423	一些

[0359] 如表13所示,所有的亲和纯化样品在循环仅6小时后都显示某种程度的降解。在循环24小时后,Fc-(L15)-FGF21的主要产物是由氨基酸残基1-414(85%的样品)和1-394(15%的样品)组成的片段,FGF21(L15)Fc的主要产物是由氨基酸残基1-423(40%的样品)、6-423(35%的样品)和22-423(25%的样品)组成的片段。鉴定出的Fc-(L15)-FGF21和FGF21-(L15)-Fc蛋白质的切割点分别见图10A和10B。

[0360] 实施例13

[0361] 注射后1-7天抗蛋白酶解Fc-(L15)-FGF21突变体的体内活性

[0362] 如本文所述,FGF21Fc融合蛋白的蛋白水解切割取决于Fc序列的方向,其中融合蛋白的Fc末端比融合蛋白的FGF21末端更稳定(即发现Fc-(L15)-FGF21融合蛋白的N末端部分和FGF21-(L15)-Fc融合蛋白的C末端部分更稳定)。例如,经鉴定在FGF21-(L15)Fc的5位和21位以及Fc-(L15)-FGF21的151位和171位上有切割。

[0363] 由于这些观察,因此进行了鉴定蛋白酶解抗性FGF21突变体的研究。Fc-(L15)-FGF21的LC-MS分析表明,体内蛋白酶降解先发生在氨基酸残基171-172之间,接着在氨基酸残基151-152之间降解。通过阻断171位上的蛋白酶降解,可防止在151位的切割,这就有效延长了分子的半寿期。然而,其中在151位的切割受阻的蛋白酶解抗性突变体仍可在171位具有易受蛋白酶攻击的残基,因此导致分子损失已知参与结合共同受体β-Klotho的最后10个氨基酸,所述共同受体β-Klotho是配体受体亲和力及体外和体内功效的决定因素。因此,成熟FGF21的171位附近的氨基酸残基的诱变似乎对改进分子的体内稳定性、效力和功效更

为关键。

[0364] 通过将FGF21突变体注射到ob/ob小鼠腹膜内,在注射后0、0.25、1、3、5和7天从注射小鼠中抽取血样,然后测定样品中的血糖水平,来测定特定抗蛋白酶解Fc- (L15) -FGF21突变体的体内活性。一项实验的结果见图11,其表示在注射PBS对照、Fc- (L15) -FGF21 (SEQ ID NO:49) 对照、或Fc- (L15) -FGF21突变体Fc- (L15) -FGF21G170E (SEQ ID NO:51)、Fc- (L15) -FGF21P171A (SEQ ID NO:53)、Fc- (L15) -FGF21S172L (SEQ ID NO:55)、Fc- (L15) -FGF21 (G170E,P171A,S172L) (SEQ ID NO:59)、或Fc- (L15) -FGF21G151A (SEQ ID NO:61) 的小鼠中测定的血糖水平。图12表示在该项实验中测定的血糖水平变化百分比。该项实验表明Fc- (L15) -FGF21G170E、Fc- (L15) -FGF21P171A、Fc- (L15) -FGF21S172L和Fc- (L15) -FGF21 (G170E,P171A,S172L) 突变体具有持续的血糖降低活性长达5天,这就优于野生型Fc- (L15) -FGF21的活性。与野生型Fc- (L15) -FGF21融合蛋白相比,Fc- (L15) -FGF21G151A突变体只部分改进血糖降低活性的持续时间。出人意料的是,虽然Fc- (L15) -FGF21S172L突变体不是蛋白酶解抗性突变体,因此具有与野生型Fc- (L15) -FGF21多肽同样的降解特征,但发现与野生型Fc- (L15) -FGF21多肽相比,这种突变体具有改进的体内功效。

[0365] 另一项实验的结果见图13,其表示在注射PBS对照、Fc- (L15) -FGF21对照、或Fc- (L15) -FGF21突变体Fc- (L15) -FGF21 (P150A,G151A,I152V) (SEQ ID NO:65)、Fc- (L15) -FGF21G170E (SEQ ID NO:51)、Fc- (L15) -FGF21 (G170E,P171A) (SEQ ID NO:63)、或Fc- (L15) -FGF21 (G170E,S172L) (SEQ ID NO:67) 的小鼠中测定的血糖水平。图14表示在该项实验中测定的血糖水平变化百分比。同上述实验一样,野生型Fc-FGF21融合蛋白和Fc- (L15) -FGF21 (P150A,G151A,I152V) 突变体不具有持续的血糖降低活性,可能是因为171位上的降解仍可发生,并且注射这些蛋白质的动物的血糖水平在注射后24小时回到基线。然而,Fc- (L15) -FGF21G170E、Fc- (L15) -FGF21 (G170E,P171A)、或Fc- (L15) -FGF21 (G170E,S172L) 在注射后长达5天具有最大血糖降低活性,这优于野生型Fc- (L15) -FGF21融合蛋白和Fc- (L15) -FGF21 (P150A,G151A,I152V) 突变体。

[0366] 另一项实验的结果见图15,其表示在注射PBS对照或者Fc- (L15) -FGF21突变体Fc- (L15) -FGF21G170E (SEQ ID NO:51)、Fc- (L15) -FGF21G170A (SEQ ID NO:69)、Fc- (L15) -FGF21G170C (SEQ ID NO:71)、Fc- (L15) -FGF21G170D (SEQ ID NO:73)、Fc- (L15) -FGF21G170N (SEQ ID NO:75)、或Fc- (L15) -FGF21G170S (SEQ ID NO:77) 的小鼠中测定的血糖水平。图16表示在该项实验中测定的血糖水平变化百分比。所有在该项实验中测定的FGF21突变体都在注射后长达5天具有血糖降低活性。

[0367] 另一项实验的结果见图17,其表示在注射PBS或者Fc- (L15) -FGF21突变体Fc- (L15) -FGF21G170E (SEQ ID NO:51)、Fc- (L15) -FGF21P171E (SEQ ID NO:79)、Fc- (L15) -FGF21P171H (SEQ ID NO:81)、Fc- (L15) -FGF21P171Q (SEQ ID NO:83)、Fc- (L15) -FGF21P171T (SEQ ID NO:85)、或Fc- (L15) -FGF21P171Y (SEQ ID NO:87) 的小鼠中测定的血糖水平。图18表示在该项实验中测定的血糖水平变化百分比。当与野生型Fc-FGF21相比时,所有在该项实验中测试的FGF21突变体都具有改进的血糖降低活性。

[0368] 实施例14

[0369] 在注射后6至120小时抗蛋白酶解Fc- (L15) -FGF21突变体的体内降解

[0370] 通过给小鼠注射FGF21突变体,在不同时间点抽取小鼠血液,通过LC-MS分析血清,

来分析选定FGF21突变体的体内稳定性。具体地讲,给小鼠注射Fc-(L15)-FGF21G170E、Fc-(L15)-FGF21P171A、或Fc-(L15)-FGF21S172L突变体(按实施例2中所述方法获自大肠杆菌),每种在注射前用约180 μ L 10mM HCl稀释,在6小时、24小时、48小时、72小时和120小时抽血。FGF21蛋白使用抗人-Fc琼脂糖树脂柱从抽取的血液中亲和纯化出来。样品用10mM HCl从柱中洗脱。所有FGF21构建体都在FGF21蛋白的氨基末端包含Fc区和15氨基酸接头。还给小鼠注射了野生型FGF21对照。

[0371] 在通过LC-MS分析亲和纯化样品前,对未治疗的野生型FGF21和未治疗的FGF21突变体进行了分析作为参比。所有标准品和时间点样品用TCEP还原,然后通过LC-MS使用ACE cyano 0.3mm x 30cm柱将柱流出液喷雾至LCQ Classic离子阱质谱仪来进行分析。亲和纯化样品用乙酸铵稀释,用TCEP还原,然后如上所述通过LC-MS进行了分析。

[0372] 在注射后0小时、6小时、24小时和48小时观察到的野生型Fc-(L15)-FGF21的质量分别见图19A-19D。在注射后0小时、6小时、24小时和48小时观察到的Fc-(L15)-FGF21G170E的质量分别见图20A-20D。在注射后0小时、6小时、24小时和48小时观察到的Fc-(L15)-FGF21P171A的质量分别见图21A-21D。在注射后0小时、6小时、24小时和48小时观察到的Fc-(L15)-FGF21S172L的质量分别见图22A-22D。

[0373] 发现在72小时和120小时抽取的所有样品都含有血纤蛋白原的高分子量(>200kDa,非还原SDS-PAGE)组分,比其余Fc-(L15)-FGF21融合蛋白的丰富得多。其它标准品和样品的LC-MS分析结果见表14。

[0374] 表14

[0375] LC-MS分析结果和预测片段

[0376]

FGF21 样品	观察的主要质量	总百分比	片段	Edman
Fc-(L15)-FGF21 WT 标准品	45,994 Da	100%	1-424	—
Fc-(L15)-FGF21 WT 6 小时	46,001 Da 44,987 Da	80% 20%	1-424 1-414	否
Fc-(L15)-FGF21 WT 24 小时	44,979 Da	~100%	1-414	否
Fc-(L15)-FGF21 WT 48 小时	44,980 Da	~100%	1-414	—
Fc-(L15)-FGF21 G170E	46,068 Da	100%	1-424	—

[0377]

FGF21 样品	观察的主要质量	总百分比	片段	Edman
标准品				
Fc-(L15)-FGF21 G170E 6 小时	46,078 Da	100%	1-424	否
Fc-(L15)-FGF21 G170E 24 小时	46,074 Da 45,761 Da	80% 20%	1-424 1-421	否
Fc-(L15)-FGF21 G170E 48 小时	46,072 Da 45,760 Da	~60% ~40%	1-424 1-421	否
Fc-(L15)-FGF21 P171A 标准品	45,970 Da	100%	1-424	—
Fc-(L15)-FGF21 P171A 6 小时	45,980 Da	100%	1-424	否
Fc-(L15)-FGF21 P171A 24 小时	45,973 Da 45,657 Da	~70% ~30%	1-424 1-421	否
Fc-(L15)-FGF21 P171A 48 小时	45,992 Da 45,673 Da	~50% ~50%	1-424 1-421	否
Fc-(L15)-FGF21 S172L 标准品	46,022 Da	100%	1-424	—
Fc-(L15)-FGF21 S172L 6 小时	46,027 Da	100%	1-424	否
Fc-(L15)-FGF21 S172L 24 小时	44,984 Da	100%	1-414	否
Fc-(L15)-FGF21 S172L 48 小时	44,985 Da	100%	1-414	否

[0378] 如表14所示,野生型Fc-(L15)-FGF21和S172L突变体的降解看起来相似,因为在循环24小时后,融合蛋白的主要产物是由氨基酸残基1-414组成的片段。Fc-(L15)-FGF21G170E和Fc-(L15)-FGF21P171A突变体的降解产物也显得相似,因为在循环24小时后抽取的样品含有70-80%完整蛋白质(氨基酸1-424)和20-30%由氨基酸残基1-421组成的片段。甚至在48小时后,Fc-(L15)-FGF21G170E和Fc-(L15)-FGF21P171A突变体仍保持完整蛋白质,同时显示由氨基酸残基1-421组成的片段的量增加。正如之前分析FC-FGF21构建体所观察到的一样,观察到融合蛋白的FGF21部分降解,而发现FC部分则保持稳定。所鉴定的野生型、Fc-(L15)-FGF21G170E、Fc-(L15)-FGF21P171A和Fc-(L15)-FGF21S172L的切割位点分别见图23A-23D。

[0379] 实施例15

[0380] 突变体聚集减少FGF21突变体的鉴定

[0381] 野生型FGF21的一个性质是其聚集倾向。由于该性质,需要产生聚集减少FGF21突变体。根据两个假设来鉴定聚集减少FGF21突变体。第一个假设是,对于FGF21,聚集(或二聚化)由暴露于亲水水基溶剂环境的疏水残基引起FGF21分子之间的疏水相互作用和范德瓦尔斯相互作用而触发。第二个假设是这些暴露的疏水残基可被取代以在FGF21氨基酸序列中产生减少聚集的点突变而不损失FGF21活性。

[0382] 应用系统性合理蛋白质工程方法来鉴定FGF21中暴露的疏水残基。由于没有已知的可用于鉴定暴露的疏水残基的FGF21的X射线或NMR结构,因此运用MOE (Molecular Operating Environment;Chemical Computing Group;Montreal,Quebec,Canada)建模软件,利用由蛋白质数据库(PDB)获得的FGF19 (1PWA)的高清晰度(1.3 Å)X射线晶体结构来创建FGF21的3D同源性模型。选择FGF19作为模板,因为就氨基酸序列同源性而言,在保存于PDB的蛋白质中,FGF19是与FGF21最密切相关的蛋白质。

[0383] 通过下列方法运用MOE计算溶剂可及性。首次测量的表面面积(SA1)定义为残基的可接近表面的面积,单位为Å²。虽然特定的氨基酸残基在蛋白质的一级序列中多次出现,但是残基的每次出现尤其由于残基与蛋白质表面的接近程度、残基侧链的方向和相邻氨基酸残基的空间位置的差异而可能具有不同的表面面积。因此,进行了表面面积(SA2)的第二次测量,其中从蛋白质结构中提取了目标残基以及该残基的相邻或邻近残基。在计算机芯片上,使这些空间上邻近的残基突变为甘氨酸以除去其侧链,然后计算目标残基的SA2,得到该残基在其特定构象中可能的总表面面积的测量值。然后,SA1SA2之比(SA1/SA2)可得到该残基实际暴露的可能的表面面积百分比的测量值。

[0384] 选择高度暴露于溶剂的若干疏水残基用于进一步的分析,在计算机芯片上进行点突变以用其它天然存在的氨基酸残基置换这些所选残基。按照CUPSAT网址提供的说明书,利用FGF21模型和交互式网上程序CUPSAT(Cologne University Protein Stability Analysis Tools(科隆大学蛋白质稳定性分析工具)),计算因不同取代产生的蛋白质热稳定性的变化。参见Parthiban等,2006,NucleicAcidsRes.34:W239-42;Parthiban等,2007,BMCStruct.Biol.7:54。在设计聚集减少点突变FGF21突变体时不包括明显的去稳定化或疏水突变。引入亲水和/或离子特征得到改进的稳定化(或在少有的情况下略去稳定化)取代被视作聚集减少FGF21突变体的候选突变体。

[0385] 通过这种理性蛋白质工程方法形成的数据概括于表15中,表中还列出预期蛋白质聚集减少和稳定性改进的示例性FGF21突变体。表15计算得到FGF21突变体对稳定性的影响。

[0386] 表15

[0387] 计算得到FGF21突变体对稳定性的影响

[0388]

残基 #	WT 残基	突变	稳定性 (Kcal/mol)
26	A	K E R	1.25 1.54 2.016
45	A	T Q K E R	0.66 0.71 1.8 2.34 1.59
52	L	T	-0.33
58	L	G S C E	0.16 -0.15 1.0 0.08
60	P	A K E R	1.3 1.51 0.66 1.31
78	P	A C R H	0.14 2.48 0.08 0.13

[0389]

残基 #	WT 残基	突变	稳定性 (Kcal/mol)
86	L	T	0.18
		C	4.1
88	F	A	2.52
		S	3.08
		K	2.88
		E	1.48
98	L	T	0.49
		Q	0.17
		K	-0.19
		C	3.08
		E	0.84
		R	3.4
99	L	C	7.34
		E	2.0
		D	1.01
		R	1.61
111	A	T	0.47
		K	-0.12
129	A	Q	3.93
		K	1.02
		N	3.76
		E	3.01
		D	3.76
		R	1.68
		H	2.9
134	A	K	5.37
		Y	4.32
		E	5.13
		R	6.18
		H	2.86

[0390] 实施例16

[0391] 聚集减少FGF21突变体和融合蛋白的制备和表达

[0392] 按照实施例11中所述方法通过野生型FGF21表达载体,来制备表16所列的编码FGF21突变体的构建体(野生型FGF21表达载体的构建见实施例1)。按照本文(例如实施例6)所述方法制备融合蛋白。当使用接头时,它是GGGGSGGGSGGGGS(“L15,”SEQ ID NO:28)。

[0393] 表16

[0394] 聚集减少FGF21突变体

[0395]

突变(s)	Fc	接头
A26E		
A26K		
A26R		
A45E		
A45K		
A45K	-NH ₂	L15
A45R	-NH ₂	L15
A45Q	-NH ₂	L15
A45T	-NH ₂	L15
A45K, L98R	-NH ₂	L15
L52T		
L58C		
L58E		
L58G		
L58S		
P60A		
P60E		
P60K		
P60R		
P78A		
P78C		
P78H		
P78R		
L86C		
L86T		
F88A		
F88E		
F88K		
F88R		
F88S		
L98C		
L98E	-NH ₂	L15
L98K	-NH ₂	L15
L98Q	-NH ₂	L15
L98R		
L98R	-NH ₂	L15
L99C		
L99D		
L99E		

[0396]	突变(s)	Fc	接头
	L99R		
	A111K	-NH ₂	L15
	A111T		
	A129D		
	A129E	-NH ₂	L15
	A129H	-NH ₂	L15
	A129K		
	A129N	-NH ₂	L15
	A129R	-NH ₂	L15
	A129Q		
	A134E		
	A134H	-NH ₂	L15
	A134K		
	A134Y		

[0397] 通过大小排阻层析法 (SEC) 测定的包括野生型FGF21、截短FGF21多肽、FGF21突变体和FGF21融合蛋白在内的各种FGF21蛋白的聚集。将待分析的样品在4℃、室温或37℃下温育至不同的时间点,然后进行了SEC分析。用配备SEC柱的Beckman HPLC系统进行实验。对于野生型FGF21,使用以含有2%异丙醇的2x PBS作为流动相的TOSOHAAS TSK-Ge1 G2000SEC柱。对于FGF21Fc融合蛋白和FGF21突变体多肽,使用以2x PBS作为流动相的TOSOHAAS TSK-Ge1 G3000SEC柱。

[0398] 实施例17

[0399] 聚集减少FGF21突变体的体外活性

[0400] 在ELK-萤光素酶体外测定法中进行了鉴定保持野生型FGF21活性的聚集减少突变体的实验。按照实施例4所述方法进行了ELK-萤光素酶测定法。图24A-24C表示FGF21突变体FGF21L99R (SEQ ID NO:109)、FGF21L99D (SEQ ID NO:111) 和FGF21A111T (SEQ ID NO:113) (图24A); FGF21突变体FGF21A129D (SEQ ID NO:115)、FGF21A129Q (SEQ ID NO:117) 和FGF21A134K (SEQ ID NO:119) (图24B); 和FGF21突变体FGF21A134Y (SEQ ID NO:121)、FGF21A134E (SEQ ID NO:123) 和FGF21A129K (SEQ ID NO:125) (图24C) 的ELK-萤光素酶活性测定结果。这些实验的结果表明,按照LK-萤光素酶测定法的测定,一些聚集减少突变不会给FGF21活性造成不利影响。

[0401] 实施例18

[0402] 具有较长半寿期和较低聚集水平的Fc- (L15) -FGF21组合突变体的制备和表达

[0403] 制备了含有显示通过减少聚集以及破坏蛋白酶降解而延长半寿期的突变的多种FGF21组合突变体,并使之与IgG1 Fc分子 (SEQ ID NO:11) 缀合。这些FGF21突变体基本按实施例11所述方法制备。

[0404] 实施例19

[0405] 具有较长半寿期和较低聚集水平的Fc- (L15) -FGF21突变体的体外研究

[0406] 在ELK-萤光素酶体外测定法中,进行了鉴定保持野生型FGF21活性的FGF21组合突

变体的实验。ELK-萤光素酶测定法按实施例4所述方法进行。

[0407] 图25A-25D表示Fc-(L15)-FGF21突变体Fc-(L15)-FGF21P171G、Fc-(L15)-FGF21P171S和Fc-(L15)-FGF21P171T(图25A);Fc-(L15)-FGF21突变体Fc-(L15)-FGF21P171Y、Fc-(L15)-FGF21P171W和Fc-(L15)-FGF21P171C(图25B);Fc-(L15)-FGF21、Fc-(L15)-FGF21(A45K,G170E)和FGF21A45K(图25C);和Fc-(L15)-FGF21、Fc-(L15)-FGF21P171E和Fc-(L15)-FGF21(A45K,G170E)(图25D)的ELK-萤光素酶活性测定结果。这些实验的结果表明,与野生型Fc-(L15)-FGF21相比,突变的目的在于改进稳定性,或者稳定性和溶解度两者,而不会损害体外活性。有趣的是,FGF21A45K突变体具有相对于野生型Fc-(L15)-FGF21的改进功效。

[0408] 图26A表示将65mg/mL蛋白质在4℃下温育1天、2天和4天后,FGF21对照(WT)和FGF21A45K的聚集变化百分比。数据表明,与野生型蛋白质相比,A45K突变导致蛋白质的聚集减少。

[0409] 图26B表示将65mg/mL蛋白质在4℃下温育1天、6天和10天后,FGF21对照(WT)以及FGF21P78C、FGF21P78R、FGF21L86T、FGF21L86C、FGF21L98C、FGF21L98R、FGF21A111T、FGF21A129D、FGF21A129Q、FGF21A129K、FGF21A134K、FGF21A134Y和FGF21A134E的聚集变化百分比。数据表明,与野生型蛋白质相比,FGF21L86C、FGF21L98C、FGF21L98R、FGF21A111T、FGF21A129Q和FGF21A129K导致蛋白质的聚集减少。

[0410] 图27表示人FGF21对照和FGF21突变体FGF21A45K、FGF21L52T和FGF21L58E的ELK-萤光素酶活性测定结果。该项实验表明FGF21A45K突变体保持野生型FGF21的全部功效,甚至效力比野生型FGF21更大。然而,与野生型FGF21相比,FGF21L52T和FGF21L58E突变体的效力和功效降低。

[0411] 图28A-28B表示在4℃下温育1天、4天和8天后,Fc-(L15)-FGF21突变体Fc-(L15)-FGF21(6-181,G170E)、Fc-(L15)-FGF21(A45K,G170E)、Fc-(L15)-FGF21P171E、Fc-(L15)-FGF21P171A、Fc-(L15)-FGF21G170E和FGF21对照的聚集水平的变化。该项实验表明,在8天时间内,Fc-(L15)-FGF21(A45K,G170E)突变体的聚集比Fc-(L15)-FGF21G170E或Fc-(L15)-FGF21P171E突变体的低,但所有三种突变体的聚集都比Fc-(L15)-FGF21对照的低。表17表示在4℃或室温下孵育第0天、第2天、第3天、第4天或第7天后得到的Fc-(L15)-FGF21对照和Fc-(L15)-FGF21(A45K,G170E)突变体的聚集百分比。

[0412] 表17

[0413] Fc-FGF21和Fc-FGF21突变体的聚集百分比

[0414]	样品		0天	2天	3天	4天	7天
	Fc-(L15)-FGF21 WT	4℃	1.12	1.71	1.89	2.14	2.32
	32 mg/mL	RT	1.12	6.09	7.94	9.57	12.59
	Fc-(L15)-FGF21 (A45K, G170E)	4℃	0.45	0.77	0.88	1.03	1.24
	33 mg/mL	RT	0.45	3.86	5.22	6.62	8.60

[0415] 实施例20

[0416] Fc-FGF21融合组合突变体的制备和表达

[0417] 如上所述,可通过引入特定的截短和氨基酸取代来调节FGF21的稳定性和溶解度。另外,可通过将这类修饰FGF21蛋白与人免疫球蛋白IgG1基因的Fc部分融合来进一步提高

FGF21稳定性。此外,通过引入上述修饰的组合,可以产生具有稳定性和溶解度两者均提高的FGF21分子。应用上述技术来制备编码表18所列的FGF21组合突变体的核酸序列。使用的接头是L15接头GGGGSGGGSGGGGS (SEQ ID NO:28)。

[0418] 表18

[0419] FGF21组合突变体

[0420]

氨基酸残基 残基	蛋白酶解 突变	聚集 突变	Fc	接头
1-181	G170E	A45K	-NH ₂	L15
1-181	G170E	L98R	-NH ₂	L15
1-181	G170E	A45K, L98R	-NH ₂	L15
1-181	P171G	A45K	-NH ₂	L15
1-181	P171S	A45K	-NH ₂	L15
1-181	P171G	L98R	-NH ₂	L15
1-181	P171S	L98R	-NH ₂	L15
1-181	P171G	A45K, L98R	-NH ₂	L15
1-178	G170E		-NH ₂	L15
6-181	G170E		-NH ₂	L15
6-181	G170E	A45K	-NH ₂	L15
6-181	G170E	L98R	-NH ₂	L15
6-181	P171G		-NH ₂	L15
6-181	P171G	L98R	-NH ₂	L15
7-181	G170E		-NH ₂	L15

[0421] 图29表示在注射Fc- (L15) -FGF21组合突变体Fc- (L15) -FGF21 (A45K, G170E)、Fc- (L15) -FGF21 (A45K, P171G)、或Fc- (L15) -FGF21 (L98R, P171G) 的小鼠中测定的血糖水平。

[0422] 在另一项实验中,与野生型成熟FGF21和Fc-FGF21并行研究了FGF21突变体Fc- (L15) -FGF21 (L98R, P171G)。在一项实验中,将重组293T细胞系在不同浓度的FGF21、Fc- (L15) -FGF21、或Fc- (L15) FGF21 (L98R, P171G) 存在下培养6小时。然后分析细胞裂解物的荧光素酶活性。如图30所示, Fc- (L15) -FGF21 (L98R, P171G) 具有与Fc- (L15) -FGF21有类似的活性,这就表明引入两个点突变不改变分子的体外活性。

[0423] 在又一项实验中,在两种不同的温度(即室温和4℃)下,与FGF21和Fc- (L15) -FGF21一起,对65mg/mL下的Fc- (L15) -FGF21 (L98R, P171G) 的稳定性进行了评价达9天。在温育期后,用SEC-HPLC对细胞裂解物进行了分析以确定在不同温度下相对于时间进程的聚集。图31A和31B所示数据表明在室温下(图31A的实心三角、虚线)和在4℃下(图31B的实心三角、虚线), Fc- (L15) -FGF21 (L98R, P171G) 的聚集形成速率显著降低。

[0424] 实施例21

[0425] 包含C末端突变的蛋白酶解抗性FGF21突变体

[0426] 还研究了组合突变体的体内稳定性。准确地讲,在鼠和食蟹猴模型中,将Fc- (L15) -FGF21 (L98R, P171G) 的体内稳定性与Fc- (L15) -FGF21的稳定性进行了比较。发现在两个物种中结果相似。在食蟹猴研究中,以23.5mg/kg经静脉内注射Fc- (L15) -FGF21 (L98R, P171G) 和Fc- (L15) -FGF21,在给药后长达840小时的时间点收集等分量的血清和血浆。对长达168小时的时间点进行了分析。各时间点样品使用抗Fc试剂进行亲和纯化,然后使用

MALDI质谱法进行了分析。在两项分析中结果有极好的关联性。

[0427] 使用免疫亲和MALDI得到的分析数据,观察到由于P171至P171G的突变,消除了Fc-(L15)-FGF21(L98R,P171G)分子中P171位的剪切。然而,观察到Fc-(L15)-FGF21(L98R,P171G)导致损失达3个C末端残基的次要和缓慢的降解(图32)。在氨基酸残基171和172之间更容易受影响的切割位点被封闭后,用其它FGF21突变体还观察到在3个C末端残基上的次要切割,见图20和图21。3个C末端残基切割可能代表被羧肽酶以相继的残基接残基方式从分子C末端切割的终止,或在氨基酸残基178和179的特异性蛋白酶攻击与在氨基酸残基179-180和180-181上非特异性剪切。在C末端损失2-3个氨基酸可能引起 β -Klotho结合降低,并最终降低分子的效力和体内活性,参见例如Yie等,2009,FEBS Lett. 583:19-24。为了克服C末端明显的羧肽酶降解,对将氨基酸残基“帽(cap)”加到各种FGF21突变体多肽上产生的影响进行了研究。采用本文所述技术,制备了包括表19所示构建体在内的各种构建体并进行了测定。表19概括了体外ELK荧光素酶测定法的结果。

[0428] 合适的氨基酸帽的长度可介于1和15个氨基酸之间,例如长度为1、2、3、4、5、10或15个氨基酸。任何数目和类型的氨基酸都可用作帽,例如单个脯氨酸残基和单个甘氨酸残基、两个甘氨酸残基、五个甘氨酸残基以及其它组合。在本实施例和表19中提供了帽的其它实例。

[0429] 另外,为了克服在氨基酸残基178和179上的明显蛋白酶攻击,对在179、180和181位上的氨基酸残基的突变进行了研究。此外,采用本文技术,制备包括表19所列构建体在内的各种构建体,并进行了研究。还研究了帽和这些位点上的突变的组合的影响。表19概括了制备的示例性构建体,并且在按本文所述方法进行的体外ELK $\rightarrow$ 荧光素酶测定法中进行了研究。与本文使用的术语一致,hFc是指人Fc序列(即SEQ ID NO:11),L15是指L15接头(即GGGGSGGGSGGGGS,SEQ ID NO:28)。

[0430] 表19

[0431] 包含C末端修饰的FGF21多肽的功效和EC50值

	构建体	EC50(nM)	功效
[0432]	huFGF21	0.4	100.0%
	hFc-(L15)-hFGF21(L98R, P171G)	2.5	76.1%
	hFc-(L15)-hFGF21(L98R, P171G, Y179F)	2.6	78.3%
	hFc-(L15)-hFGF21(L98R, P171G, 1-180)		
	hFc-(L15)-hFGF21(L98R, P171G, 1-179)	7.8	77.4%
	hFc-(L15)-hFGF21(L98R, P171G, A180E)	1.9	79.6%
	hFc-(L15)-hFGF21(L98R, P171G, S181K)	130	87.9%
	GSGSGSGSGS-hFGF21 -(L15)-hFc		
	MKEDD-hFGF21-(L15)-hFc	834	83.1%
	hFc-(L15)-hFGF21(L98R, P171G, S181P, P182)	272	69.9%
	hFc-(L15)-hFGF21(L98R, P171G, A180G)	3.25	76.9%
	hFc-(L15)-hFGF21(L98R, P171G, S181G)	3.43	77.3%
	hFc-(L15)-hFGF21(L98R, P171G, L182)		
	hFGF21(L98R, P171G, G182)		
	hFc-(L15)-hFGF21(L98R, P171G, Y179P)	428	44.4%
	hFc-(L15)-hFGF21(L98R, P171G, Y179G)	61	82.6%
	hFc-(L15)-hFGF21(L98R, P171G, Y179S)	25.3	74.8%
[0433]	构建体	EC50(nM)	功效
	hFc-(L15)-hFGF21(L98R, P171G, Y179A)	43.2	79.6%
	hFc-(L15)-hFGF21(L98R, P171G, S181T)	3.07	77.6%
	hFc-(L15)-hFGF21(L98R, P171G, S181A)	2.66	73.5%
	hFc-(L15)-hFGF21(L98R, P171G, S181L)	3.46	72.6%
	hFc-(L15)-hFGF21(L98R, P171G, S181P)	33.8	79.5%
	hFc-(L15)-hFGF21(L98R, P171G, A180P)	617	77.1%
	hFc-(L15)-hFGF21(L98R, P171G, A180S)	2.18	84.7%
	hFGF21(L98R, P171G, GGGGG182-6)		
	hFc-(L15)-hFGF21(L98R, P171G, P182)	6.1	85.9%
	hFc-(L15)-hFGF21(L98R, P171G, G182)	6.5	71.1%
	hFc-(L15)-hFGF21(1-178, L98R, P171G)	167	63.9%
	hFc-(L15)-hFGF21(L98R, P171G, GG182-3)	1941	84.2%
	hFc-(L15)-hFGF21(L98R, P171G, GGGGG182-6)	4307	99.7%

[0434] 图33表示在注射PBS对照、天然野生型FGF21、Fc-(L15)-FGF21(L98R, P171G)以及在C末端加入了脯氨酸或甘氨酸残基的两个加帽分子即Fc-(L15)-FGF21(L98R, P171G, 182P)和Fc-(L15)-FGF21(L98R, P171G, 182G)的糖尿病db/db小鼠(C57B6背景)中观察到的血糖水平变化百分比。当将残基加到野生型或突变体FGF21多肽的C末端时,用该残基通过其在所得蛋白质中的位置来表示。因此,“182G”表示甘氨酸残基被加至成熟181残基野生型或突变体蛋白质的C末端。图33表示天然FGF21降低血糖水平达6小时,而研究的所有三种Fc-FGF21突变体显示持续的血糖降低活性达至少120小时。与Fc-(L15)-FGF21(L98R, P171G)和Fc-(L15)-FGF21(L98R, P171G, 182G)相比,Fc-(L15)-FGF21(L98R, P171G, 182P),即包含添加在融合分子的FGF21组分C末端的脯氨酸残基的分子似乎最有效,并引起最低的血糖水平。

[0435] 在后续实验中,研究了Fc- (L15) -FGF21 (L98R,P171G,182G) 和Fc- (L15) -FGF21 (L98R,P171G,182P) 的体内活性,并与包含添加在C末端两个甘氨酸的加帽分子(即Fc- (L15) -FGF21 (L98R,P171G,182G,183G)) 的体内活性进行了比较。图34表示在注射PBS对照、Fc- (L15) -FGF21 (L98R,P171G) 、Fc- (L15) -FGF21 (L98R,P171G,182G,183G) 、Fc- (L15) -FGF21 (L98R,P171G,182G) 和Fc- (L15) -FGF21 (L98R,P171G,182P) 的ob/ob小鼠中观察到的血糖水平变化百分比。

[0436] 如图34所示,与PBS对照相比,被研究的所有分子都具有持续的葡萄糖降低活性。该项实验证实了之前的结果(图33),即与无脯氨酸帽的分子(例如Fc- (L15) -FGF21 (L98R,P171G)) 相比,在C末端添加脯氨酸的Fc- (L15) -FGF21 (L98R,P171G,182P) 具有略提高的葡萄糖降低功效。然而,在C末端添加两个甘氨酸残基,例如Fc- (L15) -FGF21 (L98R,P171G,182G 183G),似乎降低分子的体内效力,并缩短体内葡萄糖降低效果的持续时间。

[0437] 图35表示在注射PBS对照或FGF21突变体多肽Fc- (L15) -FGF21 (L98R,P171G) 、Fc- (L15) -FGF21 (L98R,P171G,Y179S) 、Fc- (L15) -FGF21 (L98R,P171G,Y179A) 、Fc- (L15) -FGF21 (L98R,P171G,A180S) 和Fc- (L15) -FGF21 (L98R,P171G,A180G) 的糖尿病db/db小鼠(C57B6背景)中观察到的血糖水平变化百分比。所有突变体都具有相似的葡萄糖降低活性与相似的持续作用。

[0438] 图36表示在注射溶媒对照、Fc- (L15) -FGF21 (L98R,P171G) 、Fc- (L15) -FGF21 (L98R,P171G,Y179F) 和Fc- (L15) -FGF21 (L98R,P171G,A180E) 的糖尿病db/db小鼠(C57B6背景)中观察到的血糖水平变化百分比。与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (L15) -FGF21 (L98R,P171G,Y179F) 在降低血糖时不太有效。然而,其中在氨基酸180位的丙氨酸突变成谷氨酸的Fc- (L15) -FGF21 (L98R,P171G,A180E) 比Fc- (L15) -FGF21 (L98R,P171G) 更有效,与Fc- (L15) -FGF21 (L98R,P171G) 相比,引起血糖水平额外降低20%。这些数据表明,A180E突变可能降低体内C末端降解,从而改进分子的体内效力和功效。

[0439] 实施例22

[0440] 猕猴研究

[0441] 采用本文所述方法制备Fc-接头-FGF21构建体。构建体包含IgG1 Fc序列(SEQ ID NO:11)在C末端与L15 (Gly)₅-Ser- (Gly)₃-Ser- (Gly)₄-Ser接头序列(SEQ ID NO:28)融合,接头序列然后在C末端与成熟FGF21序列(SEQ ID NO:4)的N末端融合,在成熟FGF21序列中引入了两个突变,即L98R和P171G。按本文所述方法表达和纯化这种构建体。将蛋白质的二聚体形式分离,其通过分子间二硫键在各单体的Fc区之间连接。这个分子在本实施例22中亦称为“Fc- (L15) -FGF21 (L98R,P171G)”,其具有SEQ ID NO:43的氨基酸序列,由SEQ ID NO:42编码。在该实施例中,FGF21是指FGF21的成熟形式,即SEQ ID NO:4。

[0442] 22.1研究设计

[0443] 缓慢地经皮下(“SC”)将Fc- (L15) -FGF21 (L98R,P171G) 构建体给予BMI>35的无糖尿病雄性猕猴。其它两组猴(n=10只/组)用成熟FGF21(即SEQ ID NO:4)或溶媒对照治疗。

[0444] 在给予任何试验化合物前42天使动物适应环境,然后分组,每组10只,按图37所示,按盲法多次皮下注射给予试验化合物或对照品。简单地说,每天给每只动物注射一次化合物或溶媒。FGF21每日给予,而Fc- (L15) -FGF21 (L98R,P171G) 每周给予。每两周逐步增加Fc- (L15) -FGF21 (L98R,P171G) 和FGF21的剂量,见图37。在整个研究中监测体重和食物摄

取。CRO对治疗不知情。

[0445] 在开始治疗前,进行了两次口服葡萄糖耐量试验(OGTT)。OGTT1用来将动物分到3个等同的组中,各组具有相似的基于曲线下面积(AUC)和体重的动物分布。第二次OGTT(OGTT2)的结果用来证实第一次OGTT(OGTT1)的分选。一次试验(OGTT1)的OGTT分布图与下次试验(OGTT2)的不一致的猴被排除。OGTT1和OGTT2的结果见图38A和图38B,其AUC测量值见图38C。基线体重见图38D和表20。

[0446] 在低、中和高剂量的各剂量治疗结束时,每两周进行了OGTT 3、OGTT 4和OGTT 5。每周从空腹动物中采集血样,并用来测量葡萄糖、胰岛素、甘油三酯水平以及试验化合物的水平。在3周洗净期内,同样每周采集血样。

[0447] 基线OGTT1和OGTT2显示出与在正常动物中观察一致的预期葡萄糖分布,在30分钟内达到最大血浆葡萄糖,并表明3个不同组的稳定AUC。

[0448] 血浆化学成分的空腹基线值见表20。对在开始治疗前所采集的血样进行了血浆化学成分的测量测定。

[0449] 表20

[0450] 3组猕猴的体重、空腹血浆葡萄糖、胰岛素和甘油三酯水平的基线值

	溶媒	FGF21	Fc-(L15)-FGF21 (L98R, P171G)
N	10	10	10
体重(kg)	8.5 ± 0.5	8.7 ± 0.4	8.5 ± 0.4
血浆葡萄糖(mg/dL)	91.9 ± 4.8	94.8 ± 5.3	82.2 ± 3.7
胰岛素(pg/mL)	942.6 ± 121.4	976.1 ± 107.7	1023.4 ± 205.1
甘油三酯(mg/dL)	44.4 ± 4.8	58.6 ± 5.2	71.7 ± 9.8

[0452] 选择了3种不同的剂量水平,对于FGF21和Fc-(L15)-FGF21(L98R,P171G),低剂量分别为0.1mg/kg和0.3mg/kg,中等剂量分别为0.3mg/kg和1mg/kg,高剂量为分别1mg/kg和5mg/kg。根据在小鼠中所观察到的剂量反应与基于人的预期注射频率的剂量方案来选择剂量水平。对于低剂量和中等剂量,采用等摩尔剂量的FGF21,将Fc-(L15)-FGF21(L98R,P171G)高剂量升至5mg/kg(即不是3mg/kg,这可与1mg/kg FGF21剂量等摩尔)。

[0453] 22.2 试验化合物对体重的作用

[0454] 在本项实验中,为了测定试验化合物对每周测量的体重的影响,每周计算出3个不同的猕猴组中相对于基线的体重变化百分比。还测定了在3周洗净期内的体重。各组的基线体重值见表20。

[0455] 在整个研究中密切注意给予试验化合物前后的体重。相对于溶媒动物基线的体重变化百分比随着时间而增加,而用Fc-(L15)-FGF21(L98R,P171G)和FGF21治疗的动物体重在6周治疗期的进程中以剂量依赖性方式减轻,见图39。正如之前在啮齿动物中所观察到的一样(Xu等,Diabetes 58(1):250-9(2009)),用FGF21治疗统计显著性地减轻体重。Fc-(L15)-FGF21(L98R,P171G)比FGF21具有较大的暴露量(分别见图48和图47),这就为Fc-(L15)-FGF21(L98R,P171G)比FGF21更明显地减轻体重提供了可能的解释。

[0456] 22.3. 试验化合物对胰岛素水平的作用

[0457] 测定了在空腹过夜后或在午后进餐后采集的血样的胰岛素水平。

[0458] 在用溶媒、FGF21或Fc- (L15) -FGF21 (L98R,P171G) 治疗和在3周洗净期内的动物中,每周测定猕猴的空腹血浆胰岛素水平。在最后一次Fc- (L15) -FGF21 (L98R,P171G) 注射后5天和在最后一次FGF21注射后约21小时抽取空腹血样。

[0459] 在高剂量治疗期间,在用溶媒或FGF21治疗的第5周和第6周内测定了猕猴的餐后血浆胰岛素水平。在Fc- (L15) -FGF21 (L98R,P171G) 注射后约3天和在最后一次FGF21注射后约2小时抽取餐后血样。图40表示在整个9周研究期内溶媒、FGF21和Fc- (L15) -FGF21 (L98R,P171G) 对空腹胰岛素水平的影响,而图41表示在第5和6周采集样品的餐后胰岛素水平。

[0460] 概括地说,在两个高剂量下,FGF21和Fc- (L15) -FGF21 (L98R,P171G) 两者都统计显著性地降低空腹和餐后血浆胰岛素水平。观察到用FGF21和Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物的胰岛素水平降低而未观察到葡萄糖水平升高表明胰岛素敏感性得到提高。

[0461] 22.4试验化合物对OGTT(葡萄糖和胰岛素)的作用

[0462] 在开始治疗后,进行了三次OGTT(OGTT 3、4和5)。在用溶媒、FGF21或Fc- FGF21 (L98R,P171G) 治疗6周动物中,测定了OGTT5葡萄糖和胰岛素水平分布,对应于最后两周的高剂量递增方案。在最后一次Fc- (L15) -FGF21 (L98R,P171G) 注射后约7天,以及在最后一次FGF21注射后约21小时进行了OGTT5。OGTT5葡萄糖和胰岛素分布分别见图42和图43。与只用最高剂量的溶媒治疗和在最后时间点测定的动物相比,用Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物具有改进的葡萄糖清除率,见图42。在最后一次剂量结束时,Fc- (L15) -FGF21 (L98R,P171G) 具有最强改进的葡萄糖清除率。FGF21显示葡萄糖清除率无改进。Fc- (L15) -FGF21 (L98R,P171G) 具有比FGF21大的暴露量(分别见图48和图47),为在葡萄糖清除率方面Fc- (L15) -FGF21 (L98R,P171G) 具有更明显的作用的观察提供了可能的解释。与用溶媒治疗的动物相比,在用Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物中,在最后时间点测定的OGTT5期间的胰岛素水平呈统计显著性地降低。

[0463] 如图44所示,在3组不同的猕猴组中,计算出在每个低、中和高剂量结束时进行的3次OGTT(OGTT 3、4和5)的相对于基线的葡萄糖AUC变化百分比。在最后一次Fc- (L15) -FGF21 (L98R,P171G) 注射后约7天和在最后一次FGF21注射后21小时进行了OGTT5,结果显示Fc- (L15) -FGF21 (L98R,P171G) 统计显著性地降低AUC5。各组的基线OGTT值见图38C。

[0464] 在不进行OGTT的当天测定了空腹血浆葡萄糖水平。在3组动物中检测的空腹血浆葡萄糖水平中没有观察到有意义的统计上的差异。

[0465] 22.5试验化合物对甘油三酯水平的作用

[0466] 在用溶媒、FGF21或Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物中和在3周洗净期内,每周计算出在猕猴中空腹血浆甘油三酯水平的变化百分比。在最后一次Fc- (L15) -FGF21 (L98R,P171G) 注射后约5天和在最后一次FGF21注射后约21小时抽取空腹血样。在开始治疗后每周测定了甘油三酯水平,相对于基线的变化百分比见图45,空腹基线值见表20。

[0467] 如图45所示,用Fc- (L15) -FGF21 (L98R,P171G) 或FGF21治疗的动物显示甘油三酯水平剂量依赖性地降低,其中与FGF21相比,Fc- (L15) -FGF21 (L98R,P171G) 具有最大降低效果。

[0468] 图46表示在用溶媒或Fc- (L15) -FGF21 (L98R,P171G) 或FGF21治疗的第5和6周期间从进食状态下的猕猴中获取的样品的血浆甘油三酯水平。在Fc- (L15) -FGF21 (L98R,P171G)

注射后约3天和在最后一次FGF21注射后约2小时抽取餐后血样。与用溶媒治疗的动物的甘油三酯水平相比,用FGF21和Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物的餐后血浆甘油三酯水平统计显著性的降低(图46)。

[0469] 22.6试验化合物的浓度

[0470] 在整个研究期间,对以约等摩尔剂量水平给予的试验化合物的暴露量进行了评价。在给药前和最后一次注射后约5天,测定了Fc- (L15) -FGF21 (L98R,P171G) 的浓度。在给药前和在第5、12、19和26天测定了FGF21水平。在最后一次注射后约21小时抽取血样。

[0471] 每只猴的试验化合物的各个浓度见图47和48。如图47所示,FGF21治疗组中,多数动物的浓度低于定量限。图48表示在各给药期内(以相同的剂量强度每周两次给药),Fc- (L15) -FGF21 (L98R,P171G) 治疗组中的动物具有可检测的Fc- (L15) -FGF21 (L98R,P171G) 水平。对于Fc- (L15) -FGF21 (L98R,P171G),各给药期的平均浓度大致与剂量成比例地从0.3mg/kg提高至5mg/kg。在两种化合物的各个剂量递增期内,存在最小的蓄积,正如在每周第一和第二剂量后稳定的浓度所表明的一样。在无治疗期(洗净期),Fc- (L15) -FGF21 (L98R,P171G) 水平直到约第47天(最后一次剂量后12天)仍可检出,且在此后低于定量下限(LL0Q)。

[0472] 在各OGTT期间还对试验化合物的暴露量进行了监测。在FGF21低、中剂量治疗后,在OGTT 3和4期间,未检出FGF21。然而,在高剂量治疗后,在OGTT5期间观察到可测量水平。在以递增剂量水平的第三与第五OGTT期间,观察到Fc- (L15) -FGF21 (L98R,P171G) 水平的剂量成比例地增加,见图49。

[0473] 化合物水平数据证实,动物以剂量递增方式的暴露于预期量的各种化合物即FGF21和Fc- (L15) -FGF21 (L98R,P171G) 中。在所测定的FGF21量中观察到大的差异性,鉴于在最后一次剂量后约21小时采样,并且FGF21的半寿期为约1小时,因此这也是预期中的结果。

[0474] 22.7结论

[0475] FGF21降低空腹和餐后血浆甘油三酯及胰岛素水平,并在最高剂量下减轻体重。Fc- (L15) -FGF21 (L98R,P171G) 改进OGTT,并在最高剂量下降低胰岛素水平,而且剂量依赖性地降低空腹和餐后血浆甘油三酯水平以及体重。FGF21和Fc- (L15) -FGF21 (L98R,P171G) 两者均在无糖尿病猕猴中降低多个代谢参数。当在进食条件下循环化合物水平处于相似范围中时,FGF21和Fc- (L15) -FGF21 (L98R,P171G) 之间胰岛素和甘油三酯水平的降低相同。由于其改进性质,在测量的多数参数中Fc- (L15) -FGF21 (L98R,P171G) 优于FGF21,并且可一周一次给药以观察对代谢参数的功效。

[0476] 实施例23

[0477] Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) Fc融合分子

[0478] 产生包含FGF21突变体的Fc融合物,该突变体通过接头连接至IgG1 Fc组分。Fc融合物的FGF21组分包含三个在FGF21的多肽序列中工程改造的点突变,即L98R、P171G、A180E(基于作为SEQ ID NO:4提供的FGF21的成熟形式编号)。通过将人Fc(SEQ ID NO:11)经由包含GGGGSGGGSGGGGS(SEQ ID NO:31)序列的15-氨基酸接头与L98R,P171G,A180E突变体FGF21(SEQ ID NO:39)的N-末端缀合,来构建该分子。该分子命名为Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)",它的全长氨基酸序列显示在图50和在SEQ ID NO:47中;通过SEQ ID

N0:46的核酸编码它。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)的体外测试显示:它在过量表达 β -Klotho的重组细胞系中是Erk磷酸化的有效刺激物。与野生型FGF21的Fc融合物或FGF21- (G4S) 3-FGF21 (L98R,P171G) (SEQ ID N0:45)的Fc融合物相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)也显示增强的 β -Klotho结合亲和力。当将其注射入糖尿病动物模型时,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)降低血糖水平,减少体重,并且其是适合于两周一次注射。

[0479] 23.1

[0480] Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)的体外活性

[0481] 进行实验以检查在ELK-萤光素酶体外测定中,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)是否保留与野生型FGF21的Fc融合物或野生型天然FGF21类似的活性

[0482] 使用重组人293T肾细胞体系进行ELK-萤光素酶测定,其中293T过量表达 β -Klotho和萤光素酶报道分子构建体。 β -Klotho是FGF21激活FGF受体和诱导包括Erk磷酸化在内的细胞内信号传导所需的共同受体。Erk-萤光素酶报道分子构建体包含编码GAL4-ELK1和5xUAS-萤光素酶报道分子的序列。通过含有五个Gal4结合位点的串联拷贝的启动子驱动5xUAS-萤光素酶报道分子。通过磷酸化Erk的水平调节报道分子活性,并且将报道分子活性用来间接监测和定量FGF21活性。

[0483] 如下进行ELK-萤光素酶测定:通过在不同浓度的野生型FGF21、野生型FGF21的Fc融合物Fc-L15-FGF21 (L98R,P171G,A180E)和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)存在下,培养293T细胞6小时,然后测定细胞裂解物的萤光素酶活性。各FGF21构建体在ELK-萤光素酶测定中获得的发光在y-轴表示,化合物浓度在x-轴表示。

[0484] 图51显示在Erk-萤光素酶测定中试验化合物的剂量反应。相比于FGF21野生型的Fc融合物,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)保留类似的活性,这表明含L98R、P171G和A180E的突变的组合没有改变FGF21的生物活性。与天然野生型FGF21相比,在过量表达共同受体 β -Klotho的这种基于细胞的测定中,Fc融合构建体显示稍微减少的效能和最大活性。

[0485] 23.2

[0486] 包含不同接头序列的Fc-FGF21 (L98R,P171G,A180E)融合物的体外活性

[0487] 通过经由不同的接头序列GGGGSGGGSGGGGS (SEQ ID N0:28)将人IgG1 Fc与FGF21 (L98R,P171G,A180E)融合,产生类似的Fc融合类似物。将该接头命名为L15,以及所得的融合分子命名为Fc-L15-FGF21 (L98R,P171G,A180E) (SEQ ID N0:57)。在该实验中,研究不同的接头序列对Fc-FGF21 (L98R,P171G,A180E)融合物的活性的作用。

[0488] 如下进行ELK-萤光素酶测定:通过在不同浓度的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)和Fc-L15-FGF21 (L98R,P171G,A180E)存在下,培养293T细胞6小时,然后测定细胞裂解物的萤光素酶活性。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)显示与Fc-L15-FGF21 (L98R,P171G,A180E)类似的活性,这表明不同的接头序列(例如(G4S) 3或L15接头)对Fc-FGF21融合物的生物活性没有显著影响。

[0489] 23.3

[0490] 在结合测定法中Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)对 β -Klotho的体外结合亲和力

[0491] 在Biacore溶液平衡结合测定法中测试Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)与

人和食蟹猴 β -Klotho的结合。还比较Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 和只有L98R和P171G突变的Fc融合FGF21类似物(即Fc-L15-FGF21 (L98R,P171G) (SEQ ID NO:43)) 的亲合力。

[0492] 在CM5芯片上利用胺偶联将Neutravidin固定化。生物素-FGF21在第二流通池(flow cell)上捕捉至至1500RU。将第一流通池用作背景对照。将5x稀释的FGF21突变体(0.03~2000nM) 与PBS中的10nM人或25nM食蟹猴 β -Klotho和0.1mg/ml BSA、0.005%P20在室温下温育1小时。通过注射到生物素-FGF21表面上来测定混合溶液中游离 β -Klotho的结合。在没有FGF21突变体的溶液中测定100% β -Klotho结合信号。随着FGF21突变体的浓度的增加, β -Klotho结合反应减少表明: β -Klotho在溶液中与FGF21突变体结合,这阻断 β -Klotho与固定化的生物素-FGF21表面结合。使用GraphPad Prism 5将混合物的相对结合对FGF21的摩尔浓度绘图。使用单位点竞争非线性拟合(one site competition nonlinear fit) 在相同的软件中计算EC₅₀。

[0493] 图52显示Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 和Fc-L15-FGF21 (L98R,P171G) 与人(右) 和食蟹猴 β -Klotho(左) 的Biacore溶液平衡结合测定法的结果。与Fc-L15-FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 显示与人和食蟹猴 β -Klotho两者至少2x改善的结合活性。

[0494] 23.4

[0495] 在糖尿病db/db小鼠中Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 的体内功效

[0496] 研究在糖尿病db/db小鼠中,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 是否可发挥代谢有益作用例如降低血糖和减少体重的问题。研究还旨在检查单次注射后Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 的持续时间和剂量反应。将Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 以剂量为0.1、0.3、1和3mg/kg腹膜内注射至糖尿病db/db小鼠。溶媒(10mM Tris, 2.2%蔗糖,3.3%山梨醇,pH8.5) 治疗的组也包括在研究中。在基线(注射前) 和注射后6、24、72、120和168小时获取每只动物(n=10/组) 的血液样品。用OneTouchGlucometer (LifeScan,Inc.Milpitas,CA) 测定血糖水平。在基线(0时)、注射后24、72、120和168小时测定体重。

[0497] 图53A显示在注射溶媒或Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 后在各个时间点db/db小鼠的血糖水平。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 导致在db/db小鼠中血糖水平的剂量依赖性减少。自基线或与溶媒治疗组相比,最大葡萄糖减少约50%。最大作用在注射后6小时内达到并且维持达注射后120小时。在约168小时内血糖水平开始返回基线。估算的ED₅₀(达到最大作用的一半需要的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 的剂量) 在db/db小鼠中约为1mg/kg。

[0498] 图53B显示在单次注射至db/db小鼠后Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 对体重的作用。结果用从0时(注射前) 起的体重变化表示。溶媒治疗的小鼠在7天研究期间显示进行性的稳定体重增加。然而,在用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 治疗的小鼠中以剂量依赖性方式抑制体重增长的速率。剂量越大,对增长的抑制越久。在一个实例中,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 在3mg/kg下减弱体重增加达5天,1mg/kg下减弱体重增加达3天,或0.3mg/kg下减弱体重增加达1天。随后恢复增长速率。在该实验中,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 对体重减少的估算的ED₅₀约为1mg/kg。

[0499] 23.5

[0500] 在不同注射频率的DIO小鼠中Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 和Fc- (L15) - FGF21 (L98R,P171G) 的功效比较

[0501] 本研究是为了确定Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 是否可比Fc- (L15) - FGF21 (L98R,P171G) 更低频率注射但获得相类似的功效。本研究用每周给予一次 (Q7D) 或每两周给予一次 (Q14D) 的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或者每周给予两次 (BIW)、Q7D或Q14D的Fc-L15-FGF21 (L98R,P171G) 在DIO小鼠中进行。

[0502] 通过向4周大雄性C57BL/6小鼠喂饲含有60%来自富含饱和脂肪酸的脂肪 (D12492,Research Diets,Inc.,New Brunswick,NJ) 的能量的高脂肪饮食,来准备DIO小鼠。在喂饲12周的高脂肪饮食后,测定体重和血糖水平。然后将DIO小鼠随机分成溶媒组或治疗组,从而达到类似的基线平均血糖水平和体重。在研究中包括了总共7个组:以Q7D给予的溶媒;以Q7D或Q14D给予的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E);或以BIW、Q7D或Q14D给予的Fc- (L15) - FGF21 (L98R,P171G)。腹膜内注射以及将研究进行31天。每周测定体重。在研究第28天时进行GTT并且在31天时结束研究。研究设计图示在图54中。

[0503] 图55显示在以不同的给药频率用溶媒、Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) - FGF21 (L98R,P171G) 治疗的小鼠的GTT分布图。当与溶媒相比时,在以Q7D或Q14D给药用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 治疗的小鼠中,葡萄糖耐量统计学上显著地改善,这表明Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 是有效的以及适合用于在DIO小鼠中按Q14D给予。当按BIW或Q7D,而不是Q14D给予时,Fc- (L15) - FGF21 (L98R,P171G) 改善葡萄糖耐量,这表明Fc- (L15) - FGF21 (L98R,P171G) 在小鼠中可能较不适于Q14D注射。按Q7D或Q14D的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 的功效分别相当于按BIW或Q7D的Fc- (L15) - FGF21 (L98R,P171G) 的功效,这表明可将Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 以Fc- (L15) - FGF21 (L98R,P171G) 的1/2频率给予。

[0504] 图56显示以不同的给药频率用溶媒、Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) - FGF21 (L98R,P171G) 治疗的小鼠中从基线 (0天) 起的体重变化。与用Fc- (L15) - FGF21 (L98R,P171G) 按BIW治疗的小鼠一样,用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 按Q7D治疗的小鼠体重显著性减轻。在用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 按Q14D或用Fc- (L15) - FGF21 (L98R,P171G) 按Q7D治疗的小鼠中,体重适当地减轻。在用Fc- (L15) - FGF21 (L98R,P171G) 按Q14D治疗的小鼠中,没有观察到显著的体重作用。对体重的作用如上述对GTT的作用一致,这表明:按Q14D给药时,Fc- (G4S) 4-FGF21 (L98R,P171G,A180E) 是有效的,并且为达到相同的作用,Fc- (G4S) 4-FGF21 (L98R,P171G,A180E) 需要以Fc- (L15) - FGF21 (L98R,P171G) 的约1/2频率注射。

[0505] 实施例24

[0506] 包含FGF21突变体的水凝胶制剂

[0507] 作为用于基于蛋白质的治疗剂的配制剂,水凝胶提供大量期望的性质。例如,水凝胶保留掺入水凝胶的蛋白质的天然结构和功能。而且,它们良好耐受并取决于交联的聚合物和类型,它们可以是生物可降解的。此外,以前已成功将水凝胶用于蛋白质的持续释放。因此,研究水凝胶作为本文中公开的FGF21突变体的可能的递送方法。

[0508] 对于本实施例中描述的所有实验,水凝胶如下制备。制备1.25%牛明胶 (Sigma)

PBS溶液。将交联剂甲基丙烯酸酐加至使得摩尔比率(MA:明胶)为16:1、24:1或32:1。将所得的溶液对水透析以移除任何的非聚合的甲基丙烯酰胺,从而制备水凝胶载体。最后将水凝胶载体冻干并储存在4℃下直至准备制备包含FGF21突变体的水凝胶。可将该制备方法用于制备基于明胶的水凝胶载体,其可随后适用于包含任何本文中公开的FGF21突变体。

[0509] 然后制备含特定FGF21突变体的水凝胶。首先制备含10%冻干的甲基丙烯酸明胶水凝胶载体的溶液。将水凝胶载体升温,然后离心使冻干的MA明胶水凝胶载体溶解和液化。然后将选择的FGF21蛋白质(本实施例中的FGF21(L98R,P171G), (SEQ ID NO:37))加入至液化的明胶溶液中至预定的浓度。然后将TEMED储液加入。然后将KPS储液加入并轻轻地混合溶液。将1ml的注射器填充至200μl,并使之在室温下静置1.5至2小时。将注射器储存在-20℃下,在使用前在4℃解冻过夜。将包含pH8.5 10mM Tris、9%蔗糖和未加入FGF21突变体的水凝胶载体用作对照。

[0510] 对于体内实验,在注射至动物前将注射器放置在37℃的加热垫上约10分钟。

[0511] 24.1

[0512] 从各种交联比率的10%水凝胶释放的FGF21(L98R,P171G)的体外活性

[0513] 本实验的目的是为了测试在ELK-萤光素酶体外测定中,与FGF21(L98R,P171G)的天然形式相比,从水凝胶释放的FGF21(L98R,P171G)是否为生物活性的。

[0514] 制备FGF21(L98R,P171G)并将其掺入至如上述的甲基丙烯酸明胶交联比率为16:1、24:1和32:1的10%甲基丙烯酸明胶溶液中。然后将水凝胶分散成体外缓冲溶液使FGF21(L98R,P171G)释放。在100或150小时后收集介质,并使其经历FGF21(L98R,P171G)活性的体外测定。分析测定(例如,SDS-PAGE、尺寸排阻HPLC和反相HPLC)显示释放的FGF21(L98R,P171G)在所有时间点是完整的。

[0515] 使用重组人293T肾细胞体系进行ELK-萤光素酶测定,其中293T细胞过量表达β-Klotho和萤光素酶报道分子构建体。β-Klotho是FGF21激活其FGF受体的所需要的共同受体。在该测定中使用的FGF受体是293T肾细胞中表达的内源性FGF受体。萤光素酶报道分子构建体含有含有编码GAL4-ELK1和萤光素酶报道分子的序列,其由含有Gal4结合位点的五个串联拷贝(5xUAS-Luc)的启动子驱动。萤光素酶活性受磷酸化Erk/ELK1的水平调节,用于间接监测和定量FGF21活性。

[0516] 如下进行ELK-萤光素酶测定:通过在不同浓度的FGF21(L98R,P171G)的天然形式或水凝胶释放的FGF21(L98R,P171G)存在下,培养293T细胞6小时,然后测定细胞裂解物的萤光素酶活性。图57显示ELK-萤光素酶测定的体外结果。自甲基丙烯酸明胶交联比率为16:1、24:1和32:1的水凝胶中释放的FGF21(L98R,P171G)是生物活性的,其与FGF21(L98R,P171G)的天然形式有相等的活性。数据证实:水凝胶保留掺入的蛋白质的结构和功能,并且释放的FGF21(L98R,P171G)在介质中甚至在10-15小时后是活性和稳定的。

[0517] 24.2

[0518] 在ob/ob小鼠中在不同的交联比率下水凝胶FGF21(L98R,P171G)的体内

[0519] 功效

[0520] 本实验的目的是为了确定:与FGF21(L98R,P171G)的天然形式相比,用甲基丙烯酸明胶交联比率为24:1和32:1制备的FGF21(L98R,P171G)水凝胶是否提供生物活性的FGF21(L98R,P171G)在体内的持续释放,并最终导致更久的体内功效。此外,基于体外释放速率的

评估,确定更高交联比率的甲基丙烯酸明胶产生更好的掺入的FGF21 (L98R,P171G)的持续释放。因此,本实验的另一目的是比较两种用甲基丙烯酸明胶交联比率为24:1和32:1制备的FGF21 (L98R,P171G)水凝胶。

[0521] FGF21具有多种生物活性,包括降低血糖、胰岛素、甘油三酯或胆固醇水平的能力;减轻体重的能力;或改善葡萄糖耐量的能力、能量消耗或胰岛素敏感性的能力。将FGF21 (L98R,P171G)水凝胶引入胰岛素抵抗ob/ob小鼠,然后测定FGF21 (L98R,P171G)水凝胶降低血糖和减轻体重的能力。体内操作程序如下:

[0522] 使用上述程序制备水凝胶。将8周大ob/ob小鼠 (Jackson Laboratory) 在注射位置剃毛并刚好在注射前用异氟烷和O₂麻醉。将水凝胶 (0.2ml) 缓慢地在皮下注射以及在注射后将Vetbond施用在注射位置上。溶媒 (10mM Tris, 9%蔗糖pH8.5) 或天然FGF21 (L98R, P171G) 也包括在实验中并与水凝胶类似地注射。将自麻醉中醒来后的动物放回它们的笼子。在注射前和注射后的各个时间点获取血液样品,例如,在注射后0、3、6、24、72、120、192和264小时。用OneTouch Glucometer (LifeScan, Inc. Milpitas, CA) 测定血糖水平。还监测体重。

[0523] 图58和59概述实验的结果。与溶媒或对照水凝胶相比,FGF21 (L98R,P171G)的天然形式在注射后3和6小时迅速地降低血糖水平。然而,FGF21 (L98R,P171G)的天然形式的体内活性减少并且在注射后24小时血糖水平回落至基线。FGF21 (L98R,P171G)水凝胶导致血糖在注射后早至3小时降低并且活性持续至多8天。交联比为24:1或32:1之间没有显著性差异。与单独用溶媒或水凝胶治疗的小鼠相比,FGF21 (L98R,P171G)水凝胶组也显示更慢的体重增加。这些结果证实:与FGF21 (L98R,P171G)的天然形式相比,用甲基丙烯酸明胶交联比率为24:1和32:1制备的FGF21 (L98R,P171G)水凝胶能够提供生物活性的FGF21 (L98R, P171G)在体内的持续释放,并最终导致更久的体内功效。

[0524] 24.3

[0525] 在db/B6小鼠中在不同的交联比率下水凝胶FGF21 (L98R,P171G)和FGF21 (L98R, P171G,A180E)的体内功效

[0526] 使用牛明胶 (Sigma) 和若干FGF21突变体与构建体 (即FGF21 (L98R,P171G) 和Fc-(G4S) 3-FGF21 (L98R,P171G,A180E)) 制备水凝胶制剂。还制备水凝胶对照。将0.2mL水凝胶放置在具有21G针头的1ml注射器中。

[0527] 如上所述制备包含FGF21突变体的水凝胶对照和水凝胶。将8周大db/B6小鼠 (Jackson Laboratory) 在注射位置剃毛并正好在注射前用异氟烷和O₂麻醉。将水凝胶 (0.2ml) 缓慢地在皮下注射以及在注射后将Vetbond施用在注射位置上。溶媒 (10mM Tris, 9%蔗糖pH8.5) 或天然FGF21 (L98R,P171G) 也包括在实验中并与水凝胶类似地注射。将自麻醉中醒来后的动物放回它们的笼子。在注射前和注射后的各个时间点获取血液样品,例如,在注射后0、24、96、168、240、312小时。用OneTouch Glucometer (LifeScan, Inc. Milpitas, CA) 测定血糖水平。还监测体重。

[0528] 实验设计如下:

[0529] 动物组 (n=9/组)

[0530] A.对照水凝胶32:1 (10%) MA:HU4 200μl

[0531] B.FGF21 (L98R,P171G)水凝胶32:1 (10%) MA:HU4 0.5mg/小鼠

[0532] (200 μ l, 约10mg/kg)

[0533] C.FGF21 (L98R,P171G) 水凝胶32:1 (10%) MA:HU4 1.5mg/小鼠

[0534] (200 μ l, 约30mg/kg)

[0535] D.Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (无水凝胶)

[0536] 3mg/kg

[0537] 测定各种参数,实验结果显示在图60-63中。图60显示在14天实验过程中的血糖变化,而图61显示在相同时期内的血糖变化百分比。图62显示在14天实验过程中的体重变化,而图63显示在相同时期内的体重变化百分比。

[0538] 图60-63中图示的实验结果可概述如下:

[0539] 10mg/kg的FGF21 (L98R,P171G) 32:1 (10%) MA:HU4在注射后24小时在降低血糖方面是有效的,在4-7天间血糖水平恢复至基线。

[0540] 与10mg/kg的剂量相比,30mg/kg的FGF21 (L98R,P171G) 32:1 (10%) MA:HU4在降低血糖方面更有效,并且可看到血糖水平在7-10天间恢复至基线。

[0541] 3mg/kg的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 自身在注射后24小时降低血糖的程度与来自水凝胶的30mg/kg的FGF21 (L98R,P171G) 相类似。

[0542] 水凝胶对照(其不包含FGF21突变体)不具有任何降低血糖的作用。

[0543] 相对于用水凝胶对照治疗的小鼠,FGF21 (L98R,P171G) 水凝胶组和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (其在水凝胶中不存在) 显示减少的体重增加。

[0544] 实施例25

[0545] 食蟹猴研究

[0546] 采用本文所述方法制备两种Fc-接头-FGF21构建体。一种构建体包含IgG1 Fc序列 (SEQ ID NO:11),其在C末端与(Gly)₅-Ser-(Gly)₃-Ser-(Gly)₄-Ser接头序列 (SEQ ID NO:28) 融合,接头序列然后与成熟FGF21序列 (SEQ ID NO:4) 的N末端融合,在成熟FGF21序列中引入了两个突变,即L98R和P171G。该分子在本实施例中称为“Fc- (L15) -FGF21 (L98R,P171G)” (SEQ ID NO:43)。第二种构建体包含IgG1 Fc序列 (SEQ ID NO:11),其在C末端与(Gly)₄-Ser-(Gly)₄-Ser-(Gly)₄-Ser接头序列 (SEQ ID NO:31) 融合,接头序列然后与成熟FGF21序列 (SEQ ID NO:4) 的N末端融合,其中引入三个突变,即L98R、P171G和A180E。该分子在本实施例中称为“Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)” (SEQ ID NO:47)。然后将这些构建体如本文所述表达和纯化,并分离为蛋白质的二聚体形式,二聚体的各单体经由在各单体的Fc区之间的分子间二硫键连接。

[0547] 25.1研究设计

[0548] 在有葡萄糖耐量降低 (IGT) 的特征的食蟹猴中进行研究。猴子为8-18岁大。它们的体重范围为5-15kg以及BMI范围为32-70kg/m²。在化合物给予开始前6周使44只猴子适应环境。在适应环境期间,在4周内每周训练猴子训练4次,使其熟悉程序,包括椅子束缚、皮下注射 (PBS, 0.1ml/kg)、管饲法 (水, 10ml/kg)、抽取用于非OGTT和OGTT样品的血液。在经过4周的训练后,测定基线OGTT和血浆代谢参数。从44只猴子中选出40只,并随机分至三个治疗组中以达到体重、OGTTAUC反应和血浆葡萄糖与甘油三酯水平的类似基线水平。

[0549] 用盲法进行研究。将溶媒 (n=14)、Fc- (L15) -FGF21 (L98R,P171G) (n=13) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) (n=13) 标记为化合物A、B和C,并经由皮下注射每周给

予一次。将化合物以剂量逐步增加的方式从低 (0.3mg/kg)、中 (1mg/kg) 至高 (3mg/kg) 水平给予,并且每三周增加剂量。在化合物治疗9周后,监测动物另外3周用于化合物洗净和治疗复原。在整个研究中监测食物摄入、体重、临床化学和OGTT。每餐测定食物摄入。每周测定体重。每周在每次注射后5天收集血液样品以测定葡萄糖、甘油三酯、总胆固醇、HDL胆固醇和LDL胆固醇水平。在治疗开始后每三周 (在每个剂量水平结束时) 进行OGTT。开始治疗的天数指定为0,详细的研究计划显示在图64中。

[0550] 显示在本实施例中的结果是在9周治疗结束时收集的数据。

[0551] 25.2 试验化合物对食物摄入的作用

[0552] 在适应环境期间将动物每天喂食两次,其中每只动物接受120g的已配制的确立食物。在每餐后移走剩余的食物并称重以计算食物摄入。喂食时间是从8:00AM至8:30AM (±30分钟) 和然后从4:30PM至5:00PM (±30分钟)。为产生乐事 (treat),每天将苹果 (150g) 在11:30至12:30PM (±30分钟) 供应给每只动物。

[0553] 与溶媒相比,Fc- (L15) -FGF21 (L98R,P171G) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 都减少猴子的食物摄入 (图65、66和67)。0.3mg/kg剂量的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 抑制每餐的食物摄入,包括AM、水果和PM餐。然而,当剂量增加至1mg/kg时,作用消失了并且在约30天的治疗后食物摄入恢复接近基线或对照水平。Fc- (L15) -FGF21 (L98R,P171G) 对AM食物摄入没有显著的作用,以及当剂量增加至1和3mg/kg时,仅适度地减少PM餐的食物摄入。然而,Fc- (L15) -FGF21 (L98R,P171G) 减少水果摄入,类似于Fc- (G4S) 3-FGF21 (L98R,P171G,A180E)。总的来说,与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 对抑制食物摄入显示更强的作用。对食物摄入的作用似乎是短期的,食物摄入在约30天的治疗后恢复。

[0554] 25.3. 试验化合物对体重的作用

[0555] 在整个研究中每周监测体重。在9周治疗的过程中,用溶媒治疗的动物的体重保持恒定,而用Fc- (L15) -FGF21 (L98R,P171G) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 治疗的动物体重渐进减少。如图68所示,与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 导致更显著的体重减少。

[0556] 25.4. 试验化合物对体重指数 (BMI)、皮褶厚度 (SFT) 和腹围 (AC) 的作用

[0557] 当测定体重时,在整个研究中 (在试验化合物的给予前后) 每周监测BMI、SFT和AC。BMI定义为个体体重除以他或她高度的平方。SFT是双层皮肤和其下方有特定尺寸 (caliber) 的脂肪的厚度,该脂肪对该部位施加恒定的张力。BMI、SFT和AC是相对准确、简单和便宜的身体组成的衡量,尤其表征皮下脂肪。在整个研究中,用溶媒治疗的动物显示相对稳定的BMI、SFT和AC。在9周的研究过程中,用Fc- (L15) -FGF21 (L98R,P171G) 和Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 治疗的动物显示BMI、SFT和AC的水平减少,这表明两种化合物都导致脂肪质量减少。与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 更有效,并导致BMI、SFT和AC更显著地减少。结果分别显示在图69、70和71中。

[0558] 25.5 试验化合物对空腹血糖水平的作用

[0559] 收集空腹过夜动物的血液。每周在每次注射后5天进行抽血。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 和Fc- (L15) -FGF21 (L98R,P171G) 都降低空腹血糖水平。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 在剂量为0.3mg/kg时降低空腹血糖水平,并且当剂量逐步增加

至1mg/kg时,达到最大葡萄糖降低。然而,Fc- (L15) -FGF21 (L98R,P171G) 在测试的最高剂量(3mg/kg) 下仅导致血糖水平的适度降低。因此,与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 更有效且产生更显著的血糖降低。在任何用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) -FGF21 (L98R,P171G) 治疗的猴子中均未观察到低血糖。图72显示在研究期间空腹血浆葡萄糖的水平。

[0560] 25.6试验化合物对口服葡萄糖耐量试验(OGTT)的作用

[0561] 在开始治疗前后进行OGTT。每三周进行给药后OGTT以测试化合物在各剂量水平的作用。Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 在从0.3至3mg/kg的所有测试剂量下都改善葡萄糖耐量。响应Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 治疗,葡萄糖水平降低并且在葡萄糖攻击丸剂后,葡萄糖波动增加。未观察到剂量反应,这表明Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 在0.3mg/kg的剂量时达到其最大作用。Fc- (L15) -FGF21 (L98R,P171G) 仅在1mg/kg剂量时导致葡萄糖耐量的改善,并且不清楚当剂量逐步增加至3mg/kg时,作用为什么会消失。图73显示OGTT前后曲线分布图和OGTT曲线下面积。

[0562] 25.7试验化合物对甘油三酯水平的作用

[0563] 从空腹过夜的动物中收集血液。每周在每次注射后5天进行抽血。在用Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) -FGF21 (L98R,P171G) 治疗的动物中,甘油三酯水平显著减少。然而,与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 更加有效。0.3mg/kg的Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 导致血浆甘油三酯水平最大减少,而用最高测试剂量(3mg/kg) 的Fc- (L15) -FGF21 (L98R,P171G) 仅导致甘油三酯水平的中度减少。图74显示在研究过程中空腹血浆甘油三酯的水平。

[0564] 25.8试验化合物对总胆固醇和HDL-胆固醇水平的作用

[0565] 从空腹过夜的动物中收集血液。每周在每次注射后5天进行抽血。在Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) -FGF21 (L98R,P171G) 治疗后,血浆总胆固醇和HDL-胆固醇水平趋向于减少。图75和76显示在研究过程中总胆固醇和HDL-胆固醇的水平。

[0566] 结论

[0567] 在雄性IGT食蟹猴中进行的剂量逐步增加研究中,用Fc缀合的FGF21突变体(即Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 和Fc- (L15) -FGF21 (L98R,P171G)) 治疗的动物显示改善的代谢参数。减少体重并且改善身体组成。观察到食物摄入的短期减少并且在研究中食物摄入恢复至基线或对照水平。两种化合物(Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 或Fc- (L15) -FGF21 (L98R,P171G)) 也减少空腹血糖水平和甘油三酯水平。改善OGTT并且HDL-胆固醇水平稍微提高。与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 在任何测试剂量下测定的所有参数似乎都优于Fc- (L15) -FGF21 (L98R,P171G)。当以0.3mg/kg给予时,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 对大部分测定的参数达到其最大作用。因此在高等物种中,Fc- (G4S) 3-FGF21 (L98R,P171G,A180E) 的治疗有效剂量可低于0.3mg/kg。

[0568] 实施例26

[0569] 食蟹猴稳定性研究

[0570] 设计本研究以确定Fc- (L15) -FGF21 (L98R,P171G,A180E) (SEQ ID NO:57) 是否比Fc- (L15) -FGF21 (L98R,P171G) (SEQ ID NO:43) 更加抵抗蛋白酶。在将Fc- (L15) -FGF21

(L98R,P171G)注射至如实施例21所示的小鼠或猴子后,观察羧酸末端处理。降解导致从C-末端连续损失1至3个氨基酸残基。通过给C-末端加帽或引入另外的突变至Fc-(L15)-FGF21(L98R,P171G)的C-末端的尝试产生更优越的分子Fc-(L15)-FGF21(L98R,P171G,A180E)。设计本研究以评估Fc-(L15)-FGF21(L98R,P171G,A180E)与Fc-(L15)-FGF21(L98R,P171G)相比是否具有改善的体内稳定性。

[0571] 产生Fc-(L15)-FGF21(L98R,P171G,A180E)和Fc-(L15)-FGF21(L98R,P171G)构建体。这些构建体包含IgG1 Fc序列(SEQ ID NO:11),其在C末端与(Gly)5-Ser-(Gly)3-Ser-(Gly)4-Ser接头序列(SEQ ID NO:28)融合,接头序列然后与成熟FGF21序列(SEQ ID NO:4)的N末端融合,其中引入了两个突变即L98R和P171G,或三个突变即L98R、P171G和A180E。然后将这些构建体如本文所述表达和纯化,并分离为蛋白质的二聚体形式,二聚体的各单体经由在各单体的Fc区之间的分子间二硫键连接。

[0572] 比较雄性食蟹猴中Fc-(L15)-FGF21(L98R,P171G)和Fc-(L15)-FGF21(L98R,P171G,A180E)的体内稳定性。将Fc-(L15)-FGF21(L98R,P171G)和Fc-(L15)-FGF21(L98R,P171G,A180E)以23.5mg/kg静脉注射至食蟹猴中。在单次iv注射后收集各时间点的血液样品。将免疫亲和性-MALDI-TOF质谱测定法用于监测在注射后各时间点的代谢物。结果显示在图77中。

[0573] 与Fc-(L15)-FGF21(L98R,P171G)相比,Fc-(L15)-FGF21(L98R,P171G,A180E)显示C-末端降解显著减少,更少可检测的临近完整分子母峰的质量峰,这表明A180E突变减缓C-末端肽酶降解。也观察到估计在[1-376]、[1-394]和[1-401]有质量损失的更大的截短,该位点与FGF21多肽序列中的133-134、153-154和158-159相对应。内部的内肽酶切割有助于Fc-(L15)-FGF21(L98R,P171G)和Fc-(L15)-FGF21(L98R,P171G,A180E)两者的整体代谢,并且A180E突变似乎没有显著影响内部的内肽酶降解的速率。

[0574] 为了增加分辨率和提供降解混合物的细节,还进行MRM(多反应监测)LC-MS质谱分析法以监测C-末端降解片段的各种形式。猴子样品是亲和力和纯化的,然后将该样品经过Asp-N消化。然后通过MRM监测C-末端消化的多肽。C-末端降解片段的各种形式的结果用显示在图78中的全长肽种类的相对量(%)表示。与MALDI谱一致,与Fc-(L15)-FGF21(L98R,P171G)相比,在给予Fc-(L15)-FGF21(L98R,P171G,A180E)的猴子中,C-末端片段的MRM半定量分析也显示从C-末端丢失1-3个氨基酸的肽片段的相对丰度减少和完整分子的相对丰度增加。

[0575] 总之,在食蟹猴中,与Fc-(L15)-FGF21(L98R,P171G)相比,Fc-(L15)-FGF21(L98R,P171G,A180E)显示C-末端降解减少和体内稳定性提高。

[0576] 实施例27

[0577] 小鼠中Fc-(L15)-FGF21(L98R,P171G,A180E)和Fc-(L15)-FGF21(L98R,P171G)的药代动力学

[0578] 设计本研究以评估在单次静脉给药至雄性C57BL/6小鼠后,Fc-(L15)-FGF21(L98R,P171G,A180E)(SEQ ID NO:57)和Fc-(L15)-FGF21(L98R,P171G)(SEQ ID NO:43)的药代动力学。

[0579] 通过静脉内注射后给予20mg/kg的Fc-(L15)-FGF21(L98R,P171G,A180E)和Fc-(L15)-FGF21(L98R,P171G)。在给药后0.083(5分钟)、1、4、8、16、24、48、72、96、168和240小

时收集血液样品。为了确定完整全长分子的血浆浓度,开发具有针对N-末端和C-末端FGF21的免疫反应性的ELISA测定法。测定法从其它的降解产物中跟踪有微小污染的全长完整分子。在小鼠中,完整Fc- (L15) -FGF21 (L98R,P171G,A180E) 和Fc- (L15) -FGF21 (L98R,P171G) 在静脉内注射后240小时期间的血浆浓度显示在图79中。

[0580] 在注射后24-168小时,Fc- (L15) -FGF21 (L98R,P171G,A180E) 的血浆浓度显著高于以相同剂量水平给予的Fc- (L15) -FGF21 (L98R,P171G) 的血浆浓度。在小鼠中注射后168小时可测量到显著量的Fc- (L15) -FGF21 (L98R,P171G,A180E)。因此,在小鼠中,与Fc- (L15) -FGF21 (L98R,P171G) 相比,Fc- (L15) -FGF21 (L98R,P171G,A180E) 显示AUC面积和血浆循环半寿期增加至2倍。Fc- (L15) -FGF21 (L98R,P171G,A180E) 的半寿期是16.6小时,Fc- (L15) -FGF21 (L98R,P171G) 的半寿期是9.4小时。在给药后240小时两种化合物都低于可检测水平。

[0581] 实施例28

[0582] 为改进溶解度或减少C-末端切割以增加半寿期的N联糖基化突变体的产生

[0583] 设计和产生FGF21突变体以产生潜在的N联糖基化位点用于以最少破坏天然氨基酸序列进行哺乳动物表达。构建的突变体包括FGF21 (Y179N,S181T) (SEQ ID NO:161)、FGF21Y179N (SEQ ID NO:163) 和FGF21P124S (SEQ ID NO:165)。

[0584] 突变体的表达在293-6E细胞中瞬时进行,在ELK-萤光素酶体外测定中检测条件培养基的活性。如实施例4所述进行ELK-萤光素酶测定,除了使用连续稀释的条件培养基,而不是不同浓度的纯化蛋白。

[0585] 条件培养基的分析揭示:在瞬时表达体系中与野生型相比,未达到糖基化增加。图80显示ELK-萤光素酶活性测定结果。在图80中显示的结果表明:FGF21P124S突变体没有不利地影响FGF21活性,但是在糖基化存在下,FGF21Y179N和FGF21 (Y179N,S181T) 突变体导致在ELK-萤光素酶测定中测定的活性减少。

[0586] 虽然已根据多个实施方案对本发明进行了描述,但要理解的是,本领域技术人员可进行变动和修改。因此,预期随附权利要求书涵盖属于所要求保护的本发明范围的所有这类等同变化。另外,本文使用的小节标题只用于组织目的,不得解释为限制所描述的主题。

[0587] 本申请中引用的全部参考文献都通过引用明确并入本文用于任何目的。

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[0266]	Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln		
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[0307]	Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg			
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[0309]	Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His			
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[0809]	Pro Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro	
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[0815]	Val Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg	
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[0946]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu	
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[1204]	Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly	
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[1257]	85	90	95	
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[1259]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro			
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[1261]	atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag	384		
[1262]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
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[1912]	Ser Phe Arg Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser	
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[1921]	Leu Pro Pro Ala Pro Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro	
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[1924]	Pro Asp Val Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Leu Gln	
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[2010]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu	
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[2012]	gtg cat aat gcc aag aca aag ccg cgt gag gag cag tac aac agc acg	240
[2013]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr	
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[2015]	tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat	288
[2016]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn	
[2017]	85 90 95	
[2018]	ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc	336
[2019]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro	
[2020]	100 105 110	
[2021]	atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag	384
[2022]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln	
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[2024]	gtg tac acc ctg ccc cca tcc cgt gat gag ctg acc aag aac cag gtc	432
[2025]	Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val	
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[2061]	Pro	Asp	Gly	Ala	Leu	Tyr	Gly	Ser	Leu	His	Phe	Asp	Pro	Glu	Ala	Cys	
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[2063]	agc	ttc	cgt	gag	cgt	ctt	ctt	gag	gac	ggt	tac	aat	gtt	tac	cag	tcc	1056
[2064]	Ser	Phe	Arg	Glu	Arg	Leu	Leu	Glu	Asp	Gly	Tyr	Asn	Val	Tyr	Gln	Ser	
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[2070]	Arg Asp Pro Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly	
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[2128]	Pro Asp Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys		
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[2155]	ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc	96	
[2156]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
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[2469]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	
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[2472]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	
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[2528]	ctg ccc ccc gca ccc ccg gag cca ccc gga atc ctg gcc ccc cag ccc	1200
[2529]	Leu Pro Pro Ala Pro Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro	
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[3944]	Gly Gln Val Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr			
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[3946]	Glu Ala His Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala			
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[3948]	Asp Gln Ser Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly			
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[3952]	Pro Asp Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys			
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[3992]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	
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[3995]	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	
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[5670]	Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser Pro Glu Ser Leu		
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[5678]	Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His Gly Leu Pro Leu		
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[5704]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys	
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[5743]	tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat			288
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[5750]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
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[5765]	Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val			
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[5771]	Ser Pro Gly Lys Gly Gly Gly Gly Gly His Pro Ile Pro Asp Ser Ser			

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[5783]	Lys Ala Leu Lys Pro Gly Val Ile Gln Ile Leu Gly Val Lys Thr Ser				
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227

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[6424]	Ser Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile	
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[6581]	Gln Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Cys Asp	
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[6584]	Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe	
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[6586]	cgg gag ctg ctt ctt gag gac gga tac aat gtt tac cag tcc gaa gcc	336
[6587]	Arg Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala	
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[6589]	cac ggc ctc ccg ctg cac ctg cca ggg aac aag tcc cca cac cgg gac	384
[6590]	His Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp	

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[6661]	Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe			
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[7531]	Ser Pro Gly Lys Gly Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly	
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[7809]	85	90	95	
[7810]	ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc	336		
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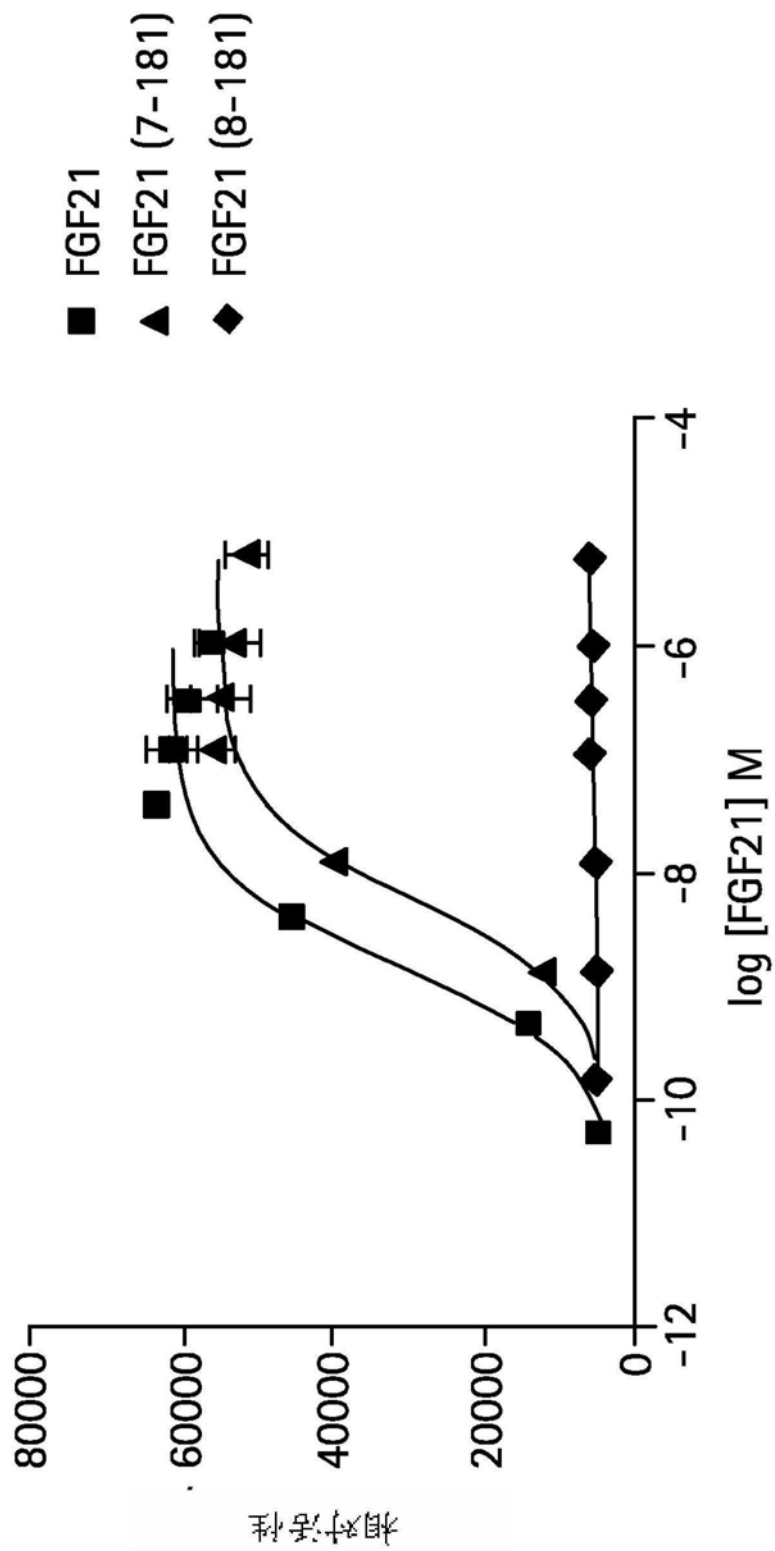


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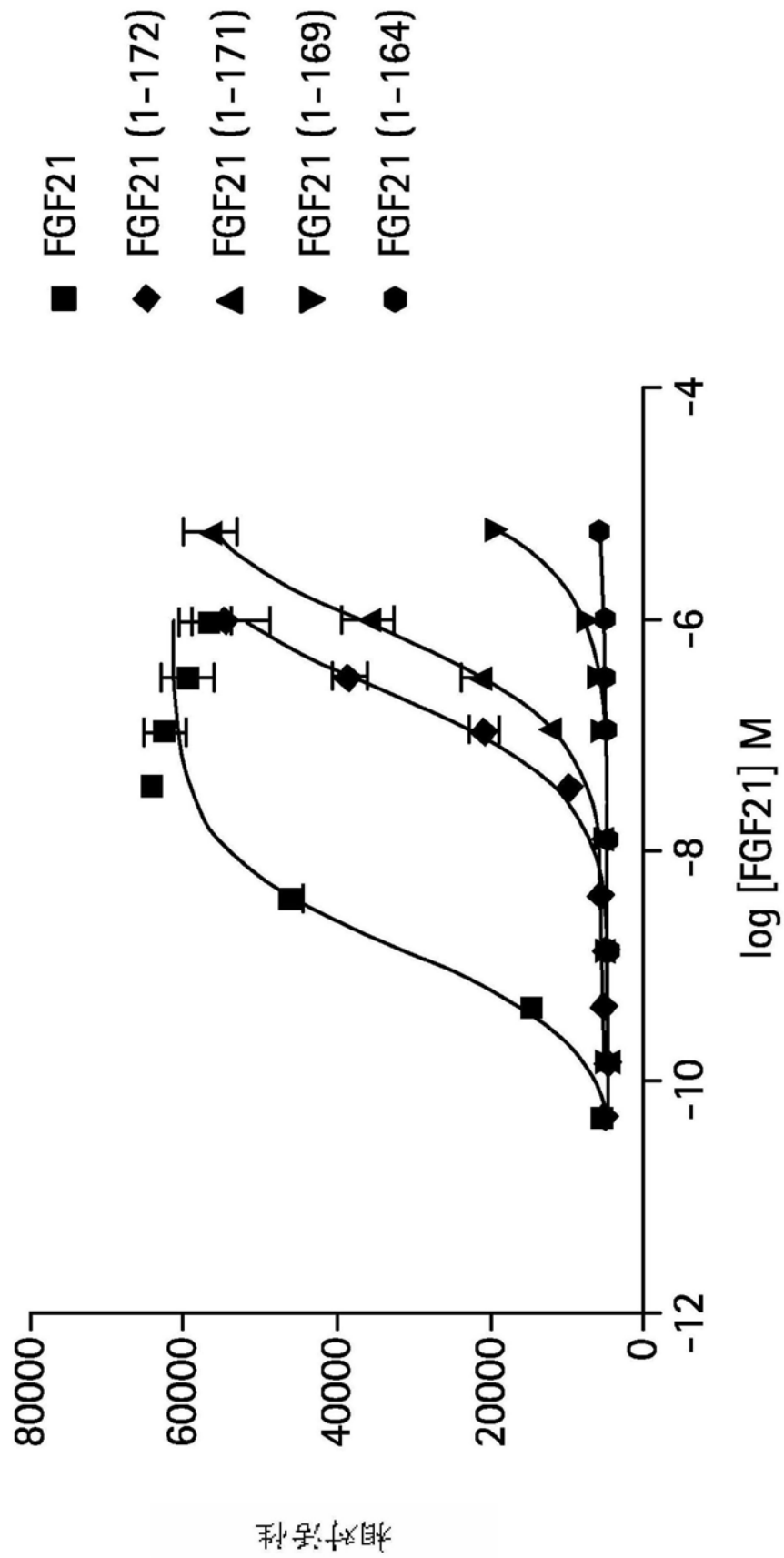


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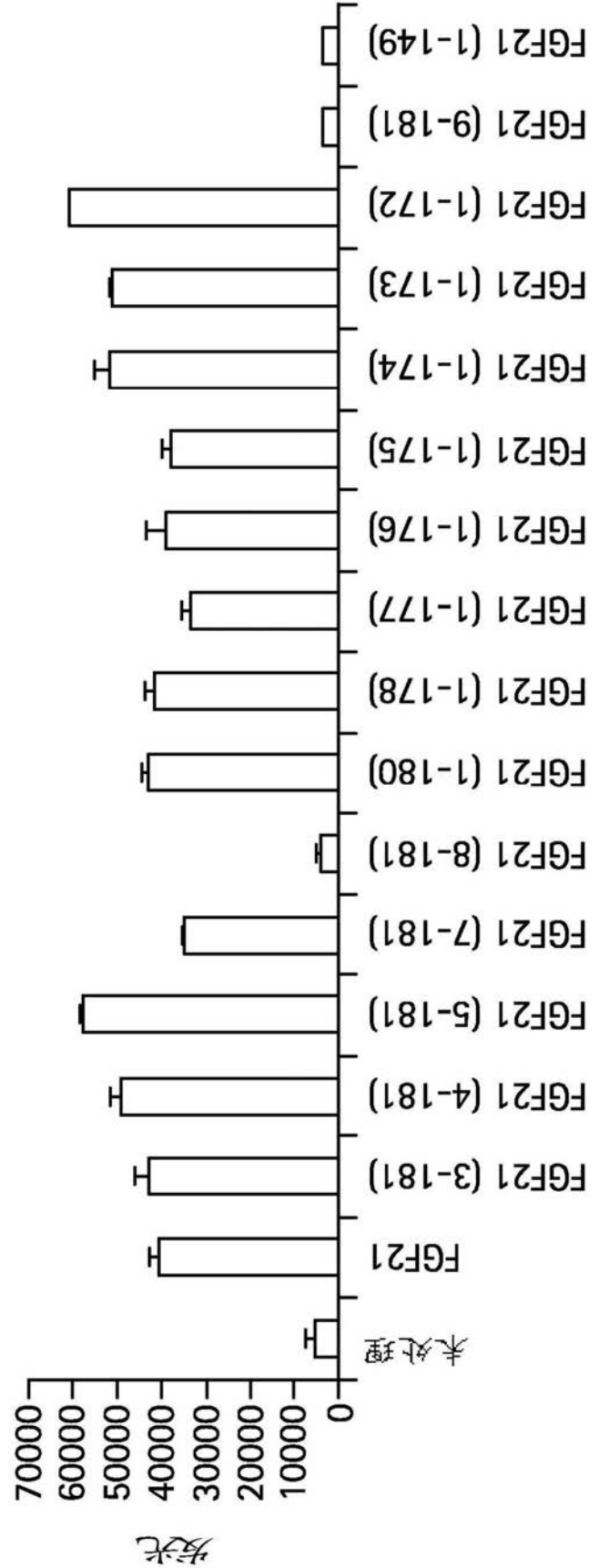


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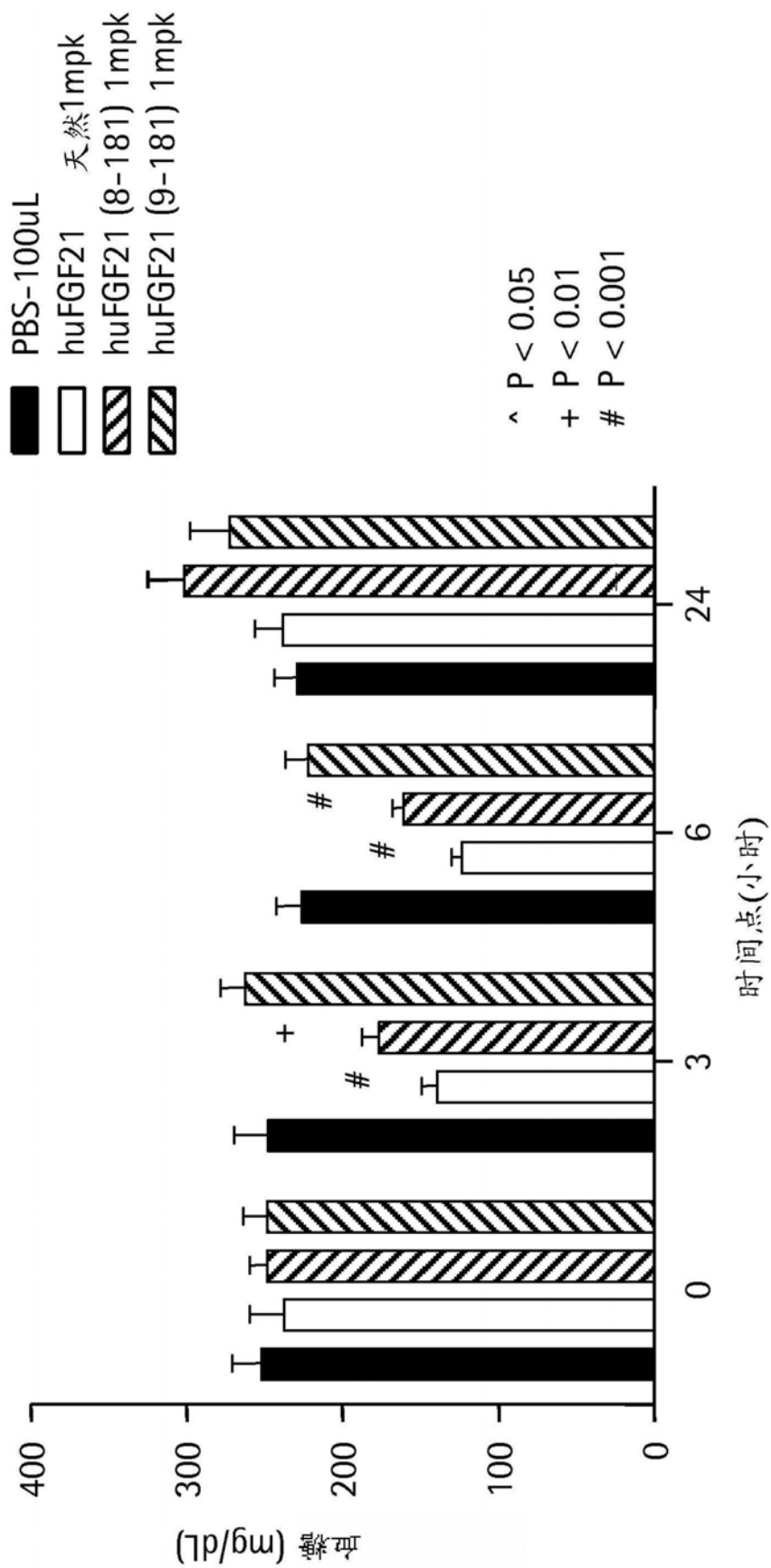


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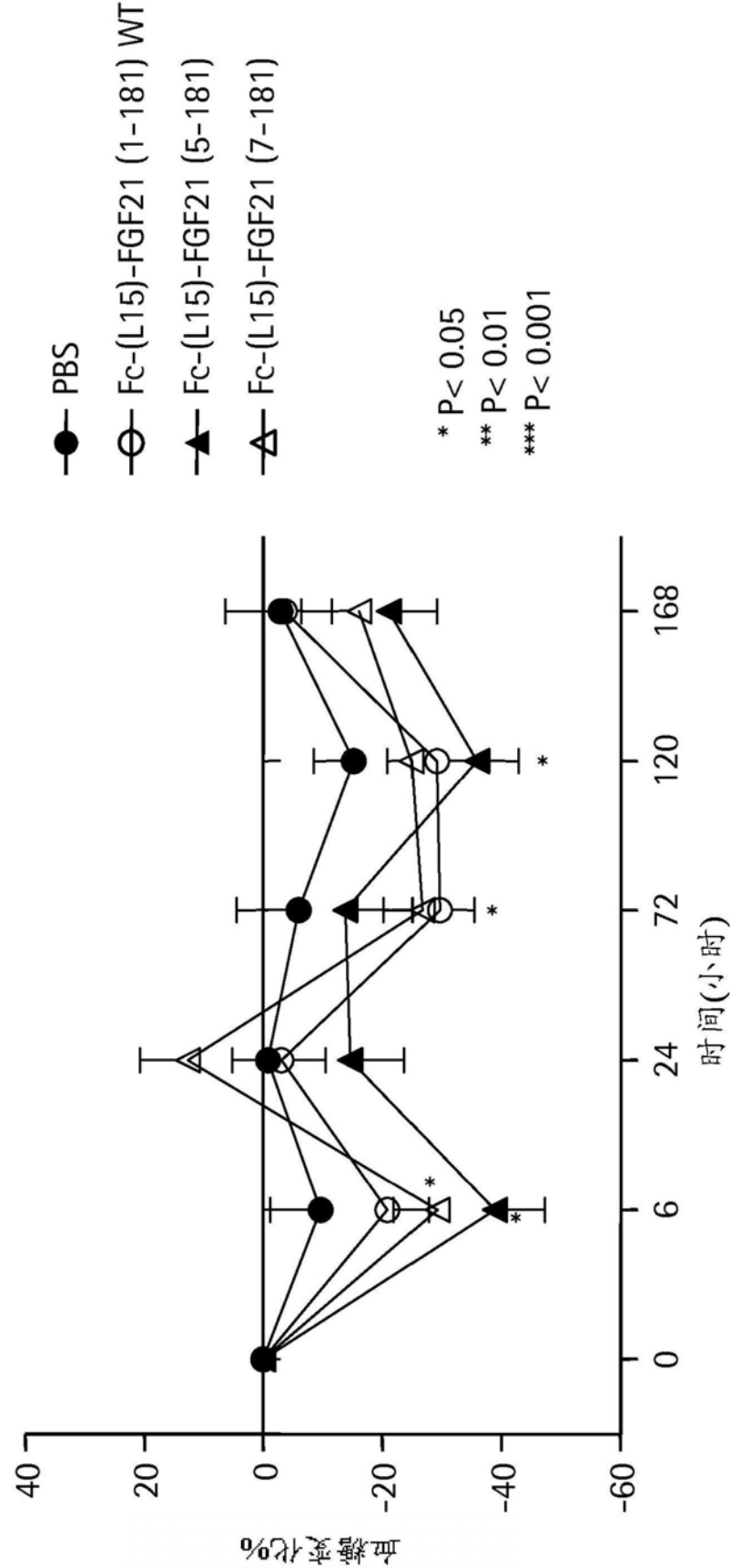


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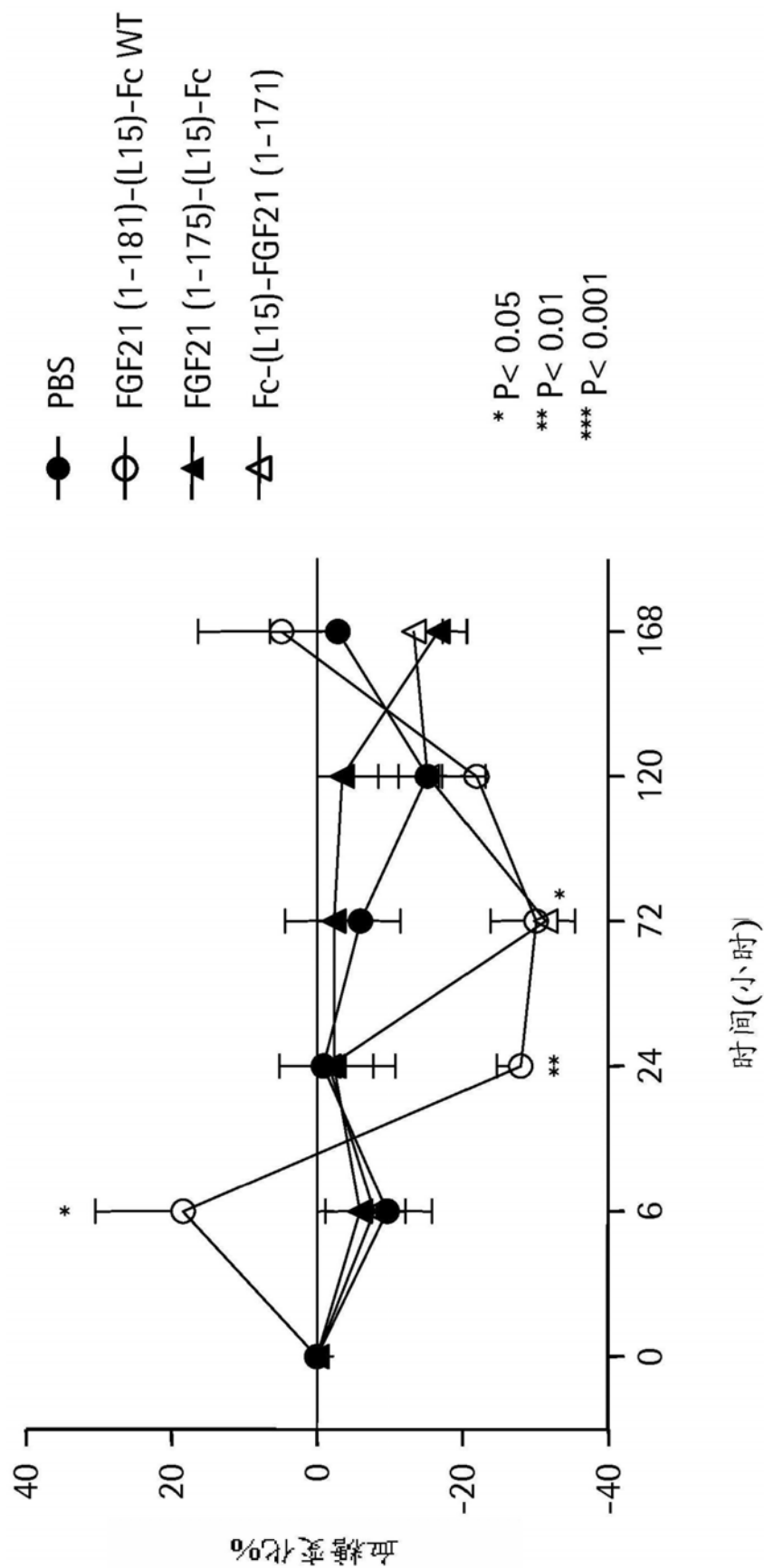


图5

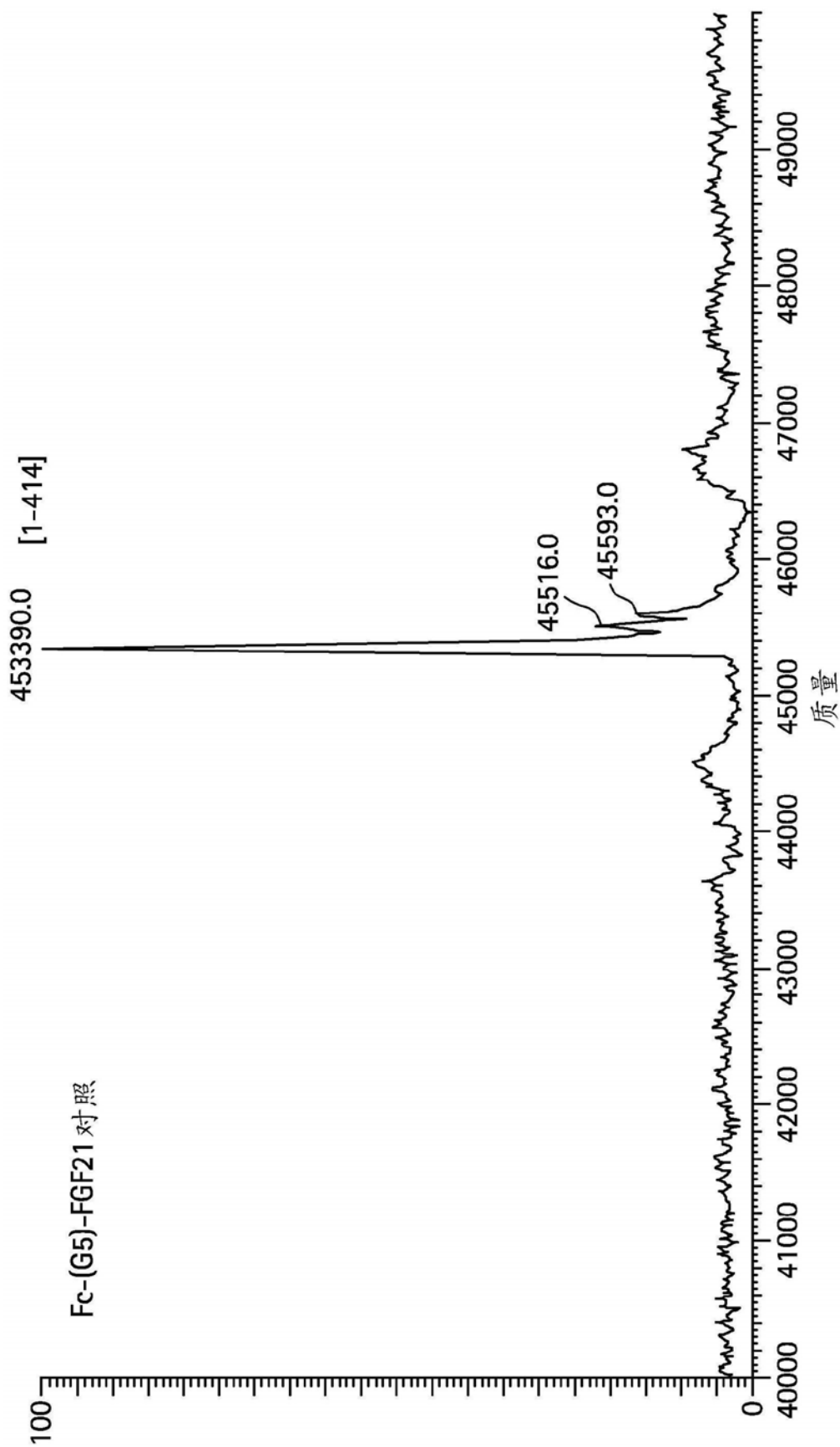


图6A

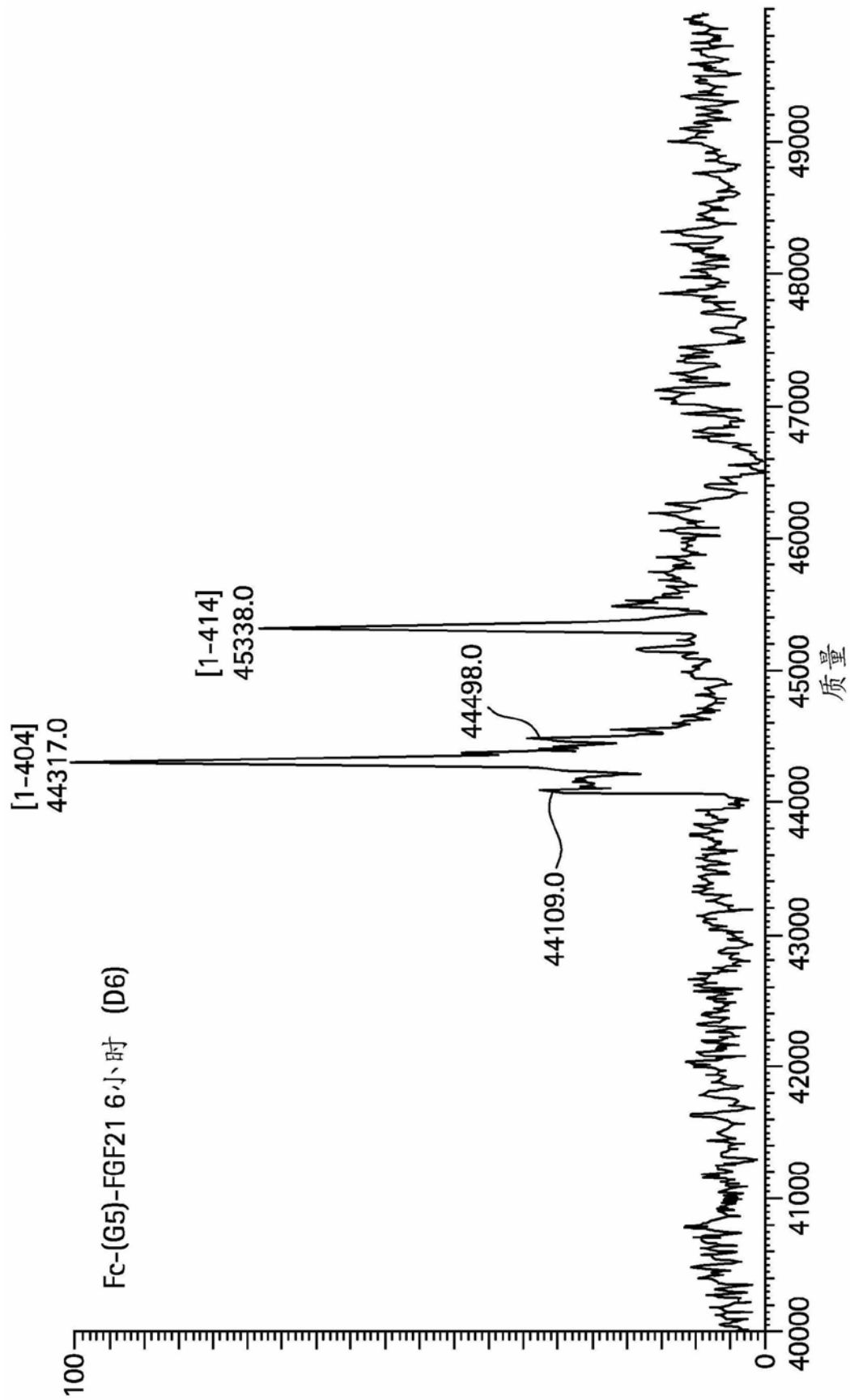


图6B

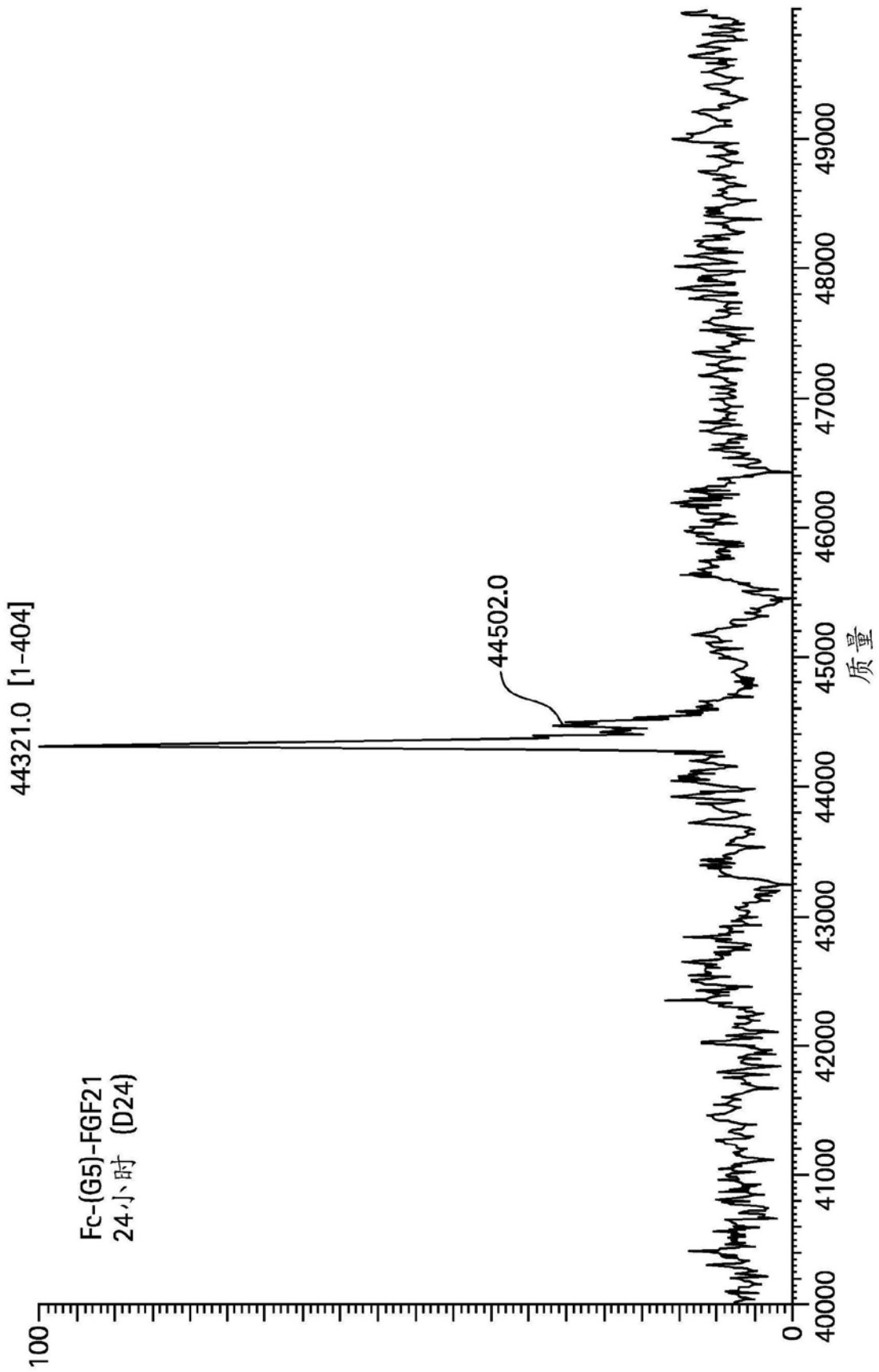


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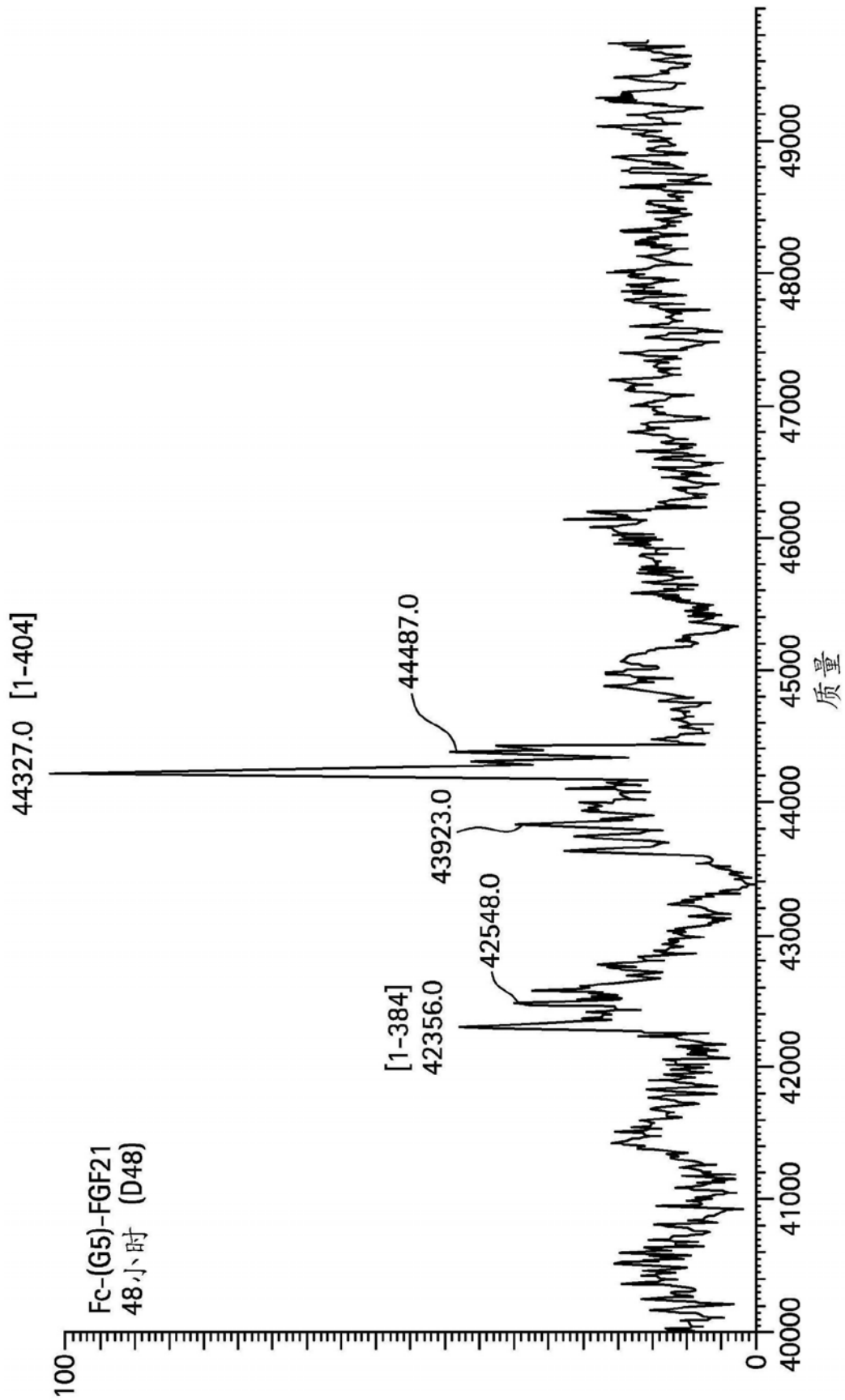


图6D

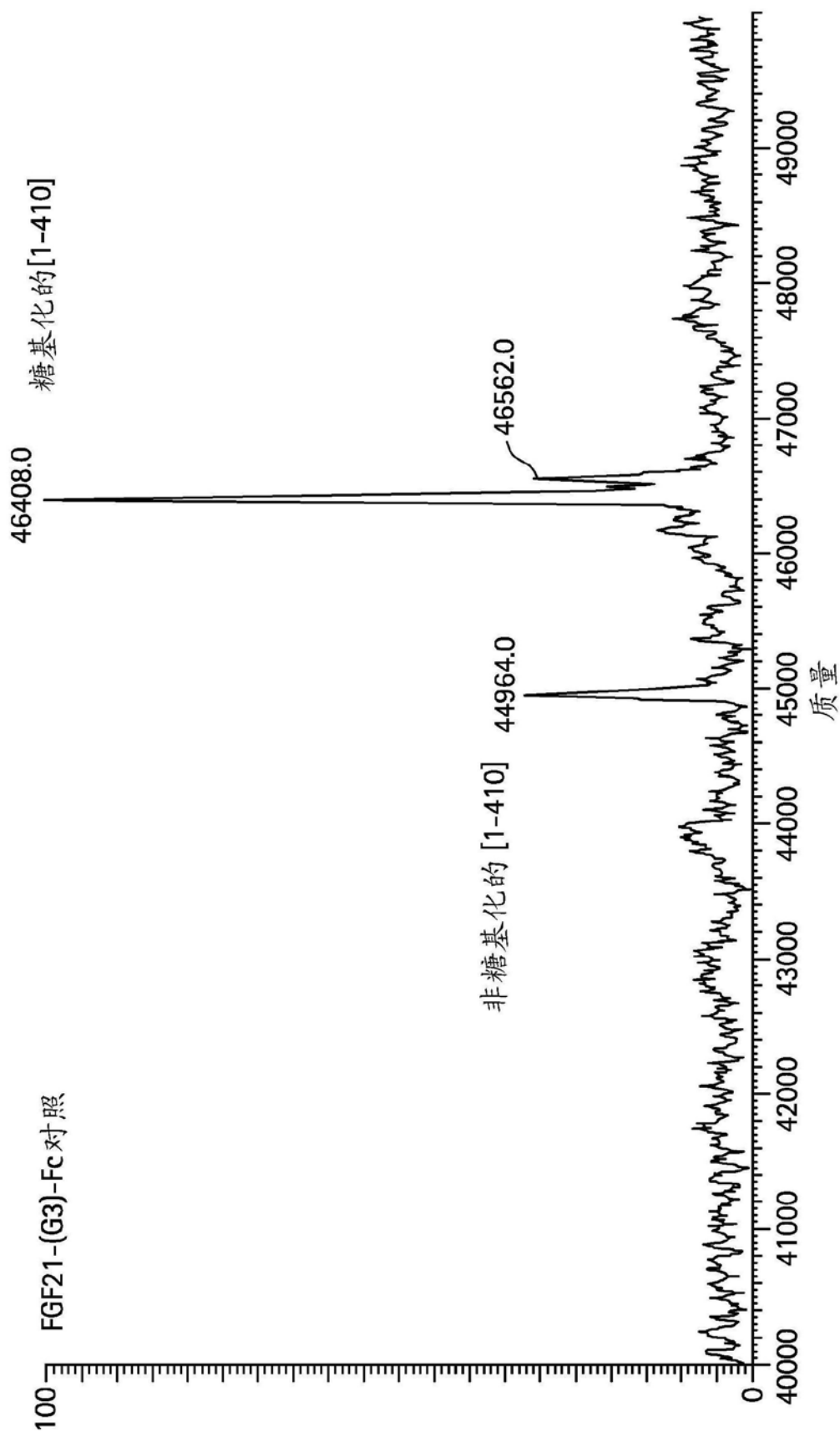


图7A

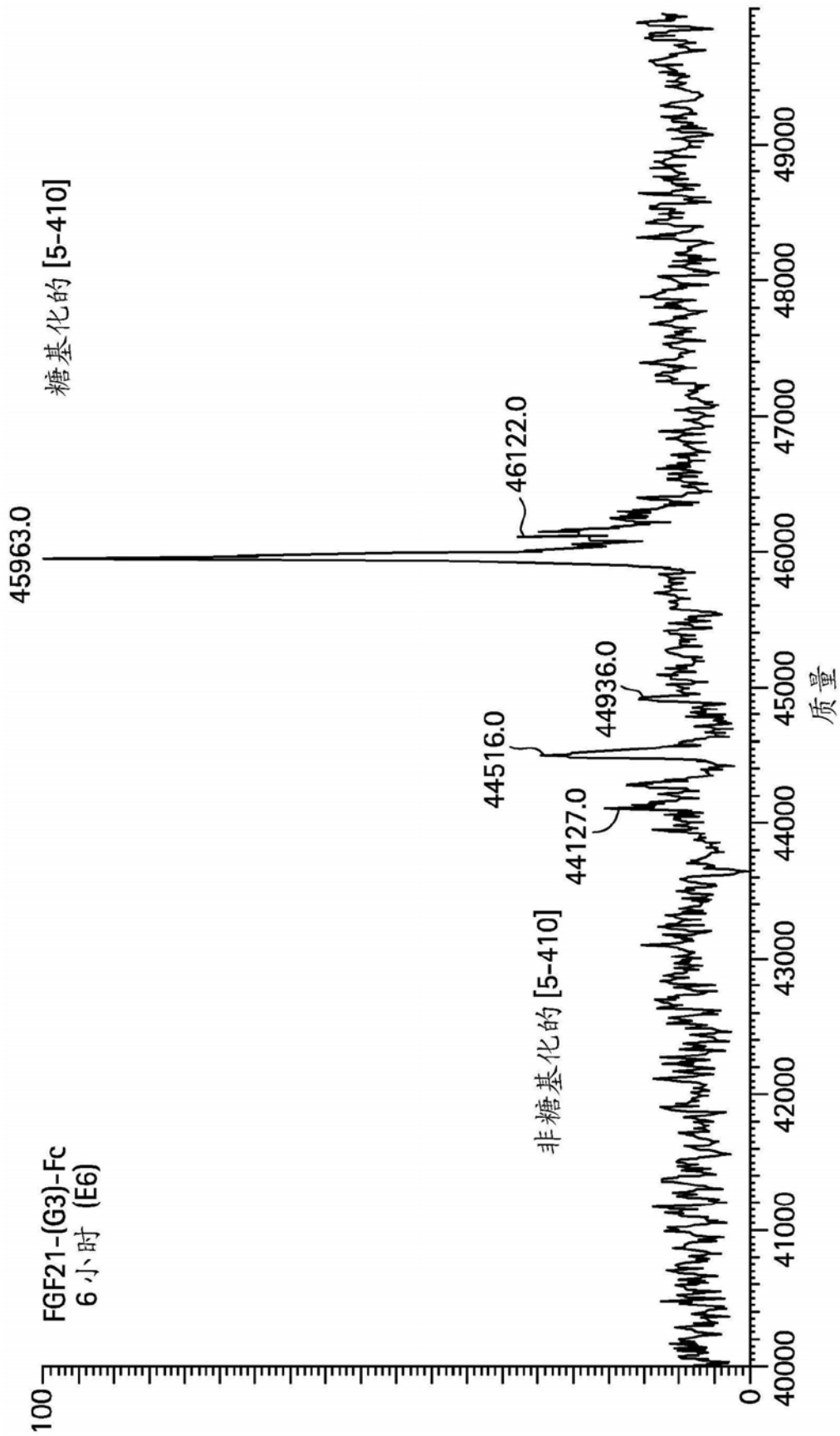


图7B

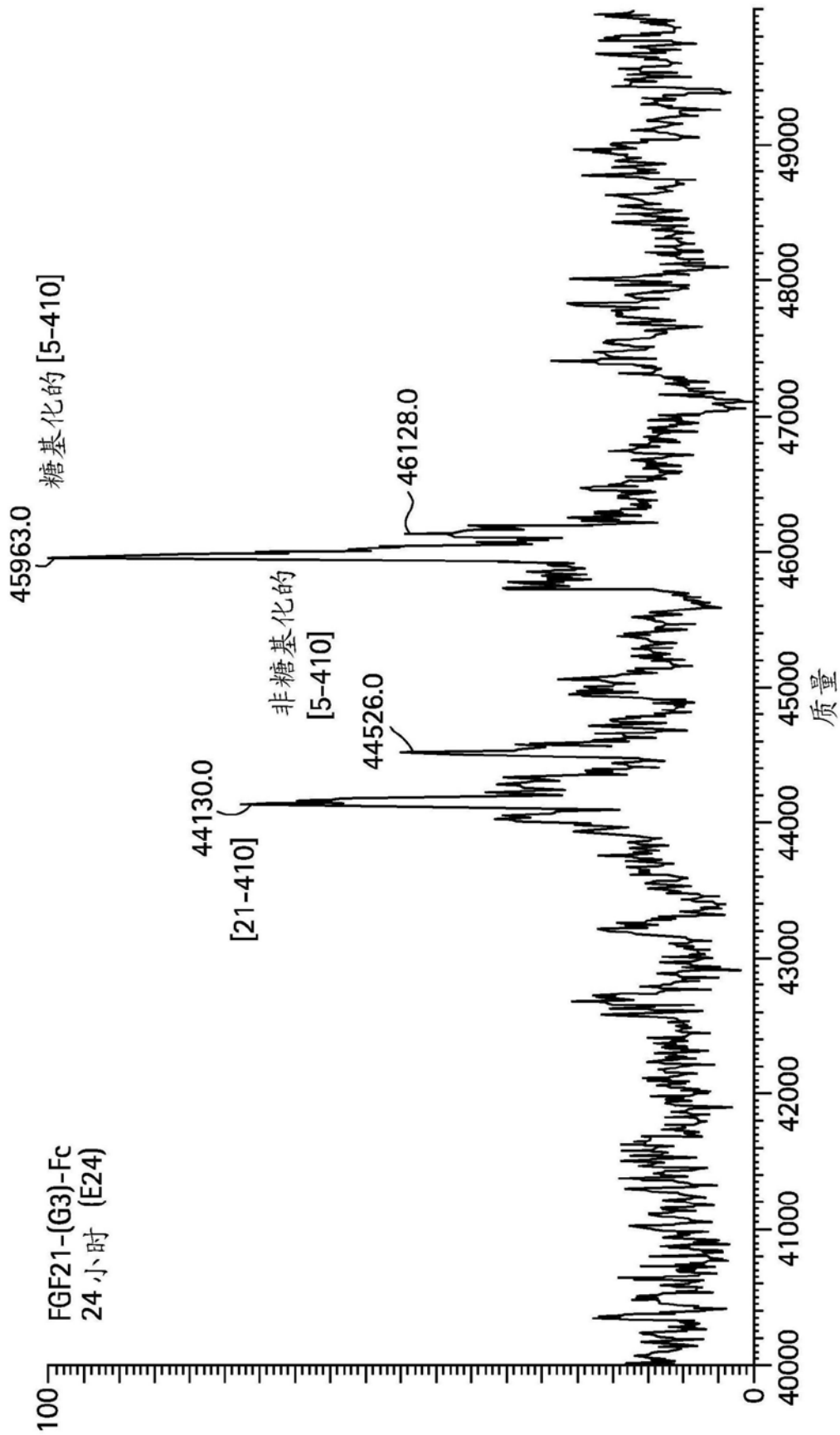


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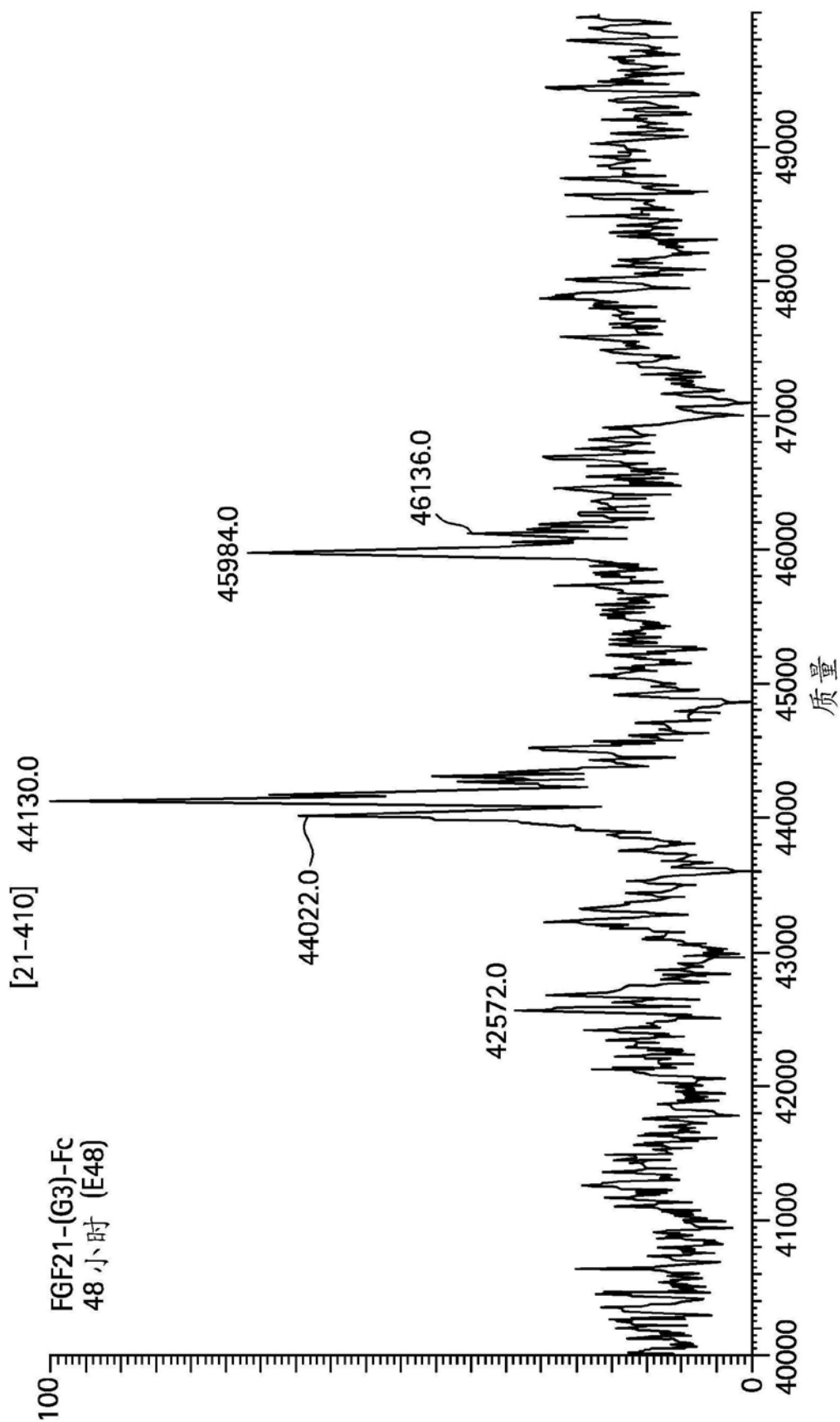


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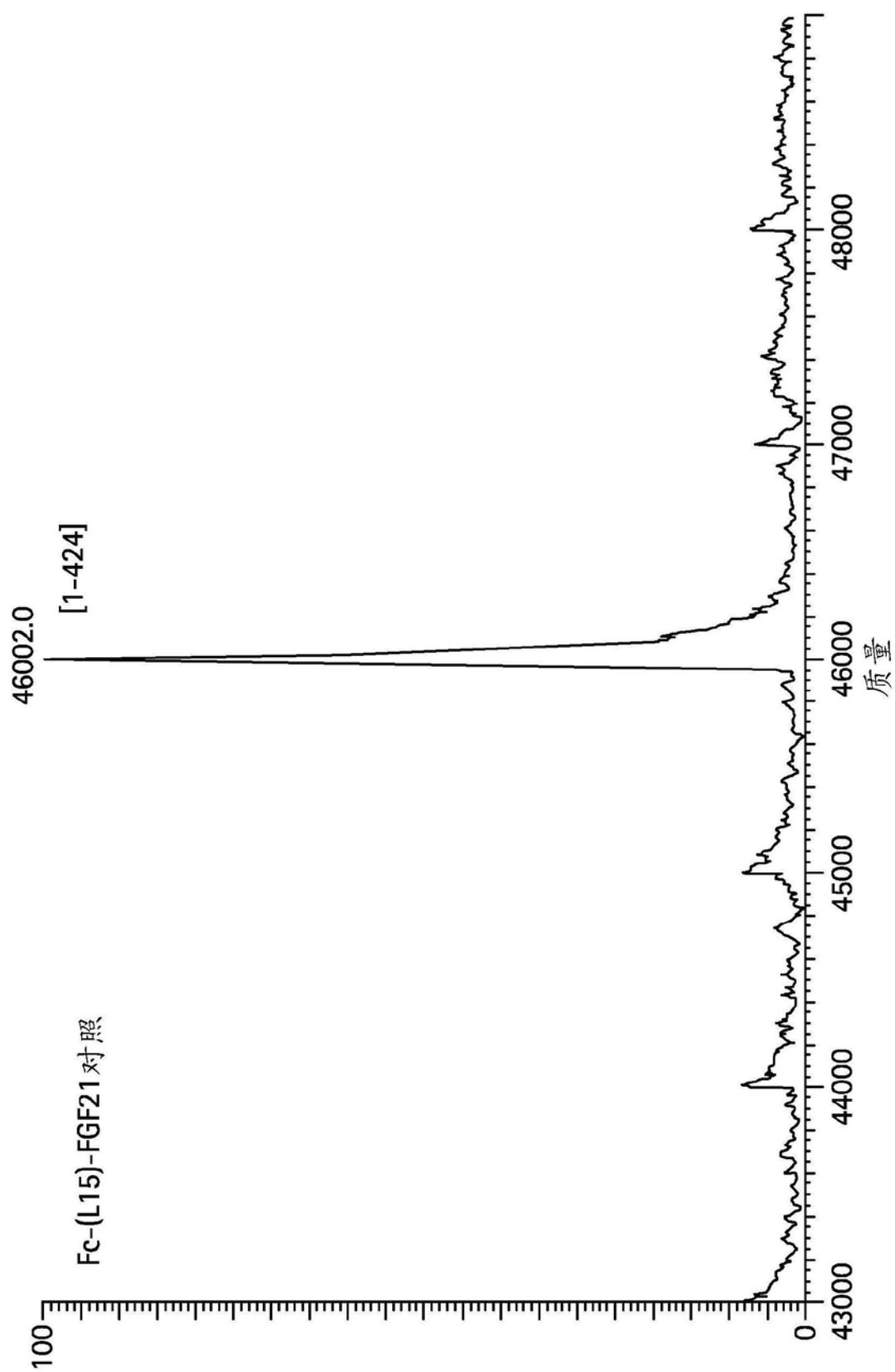


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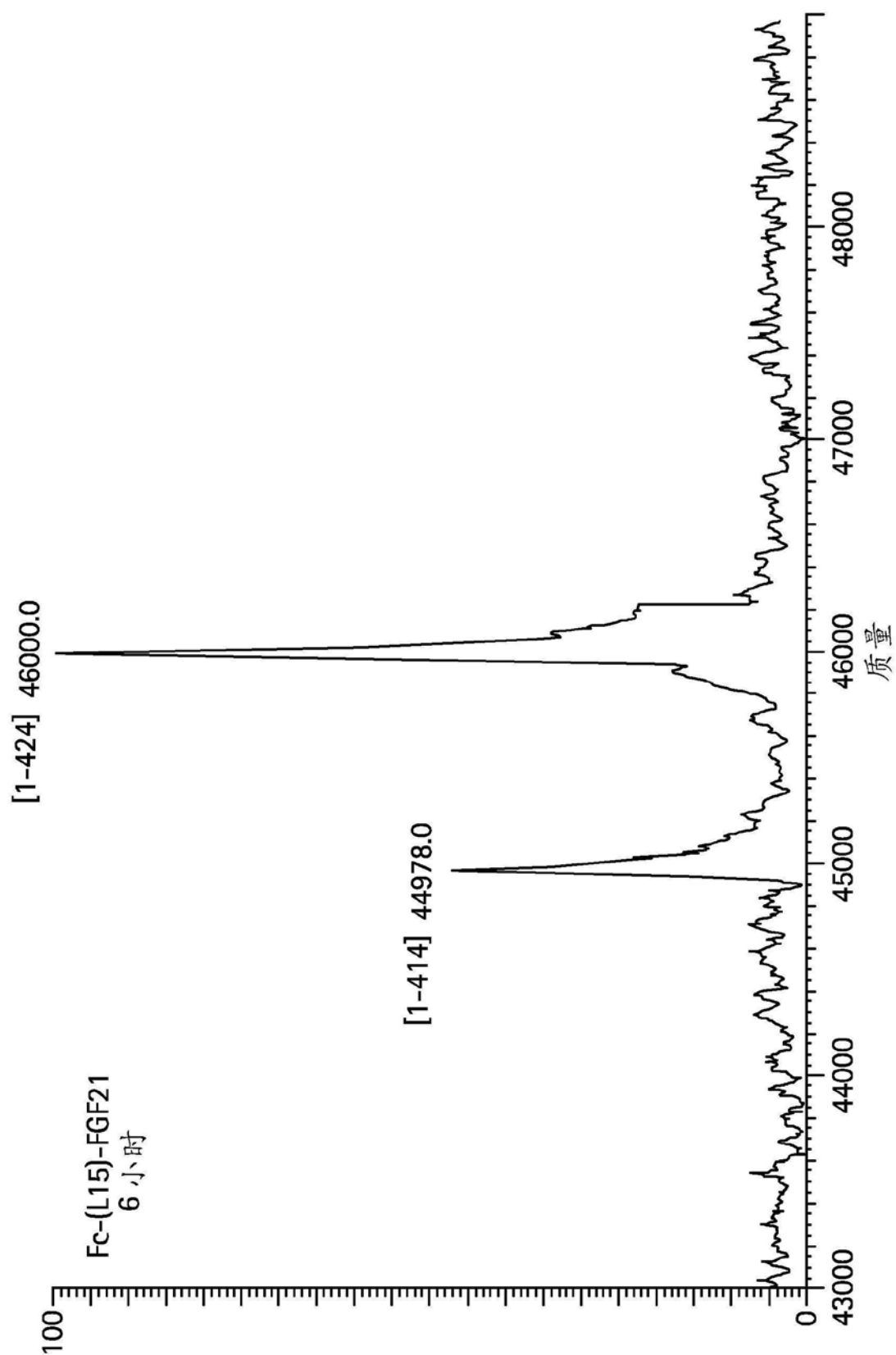


图8B

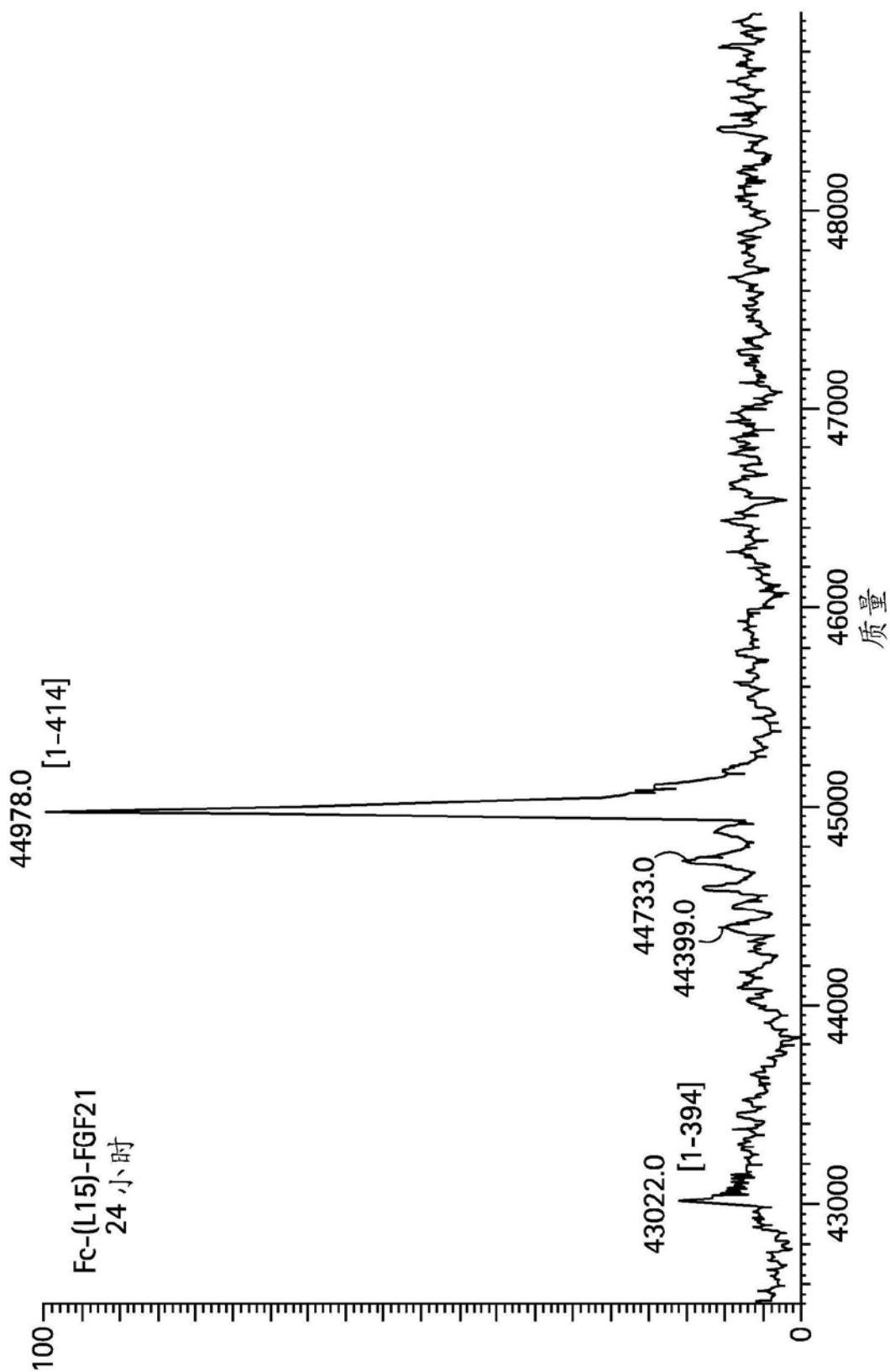


图8C

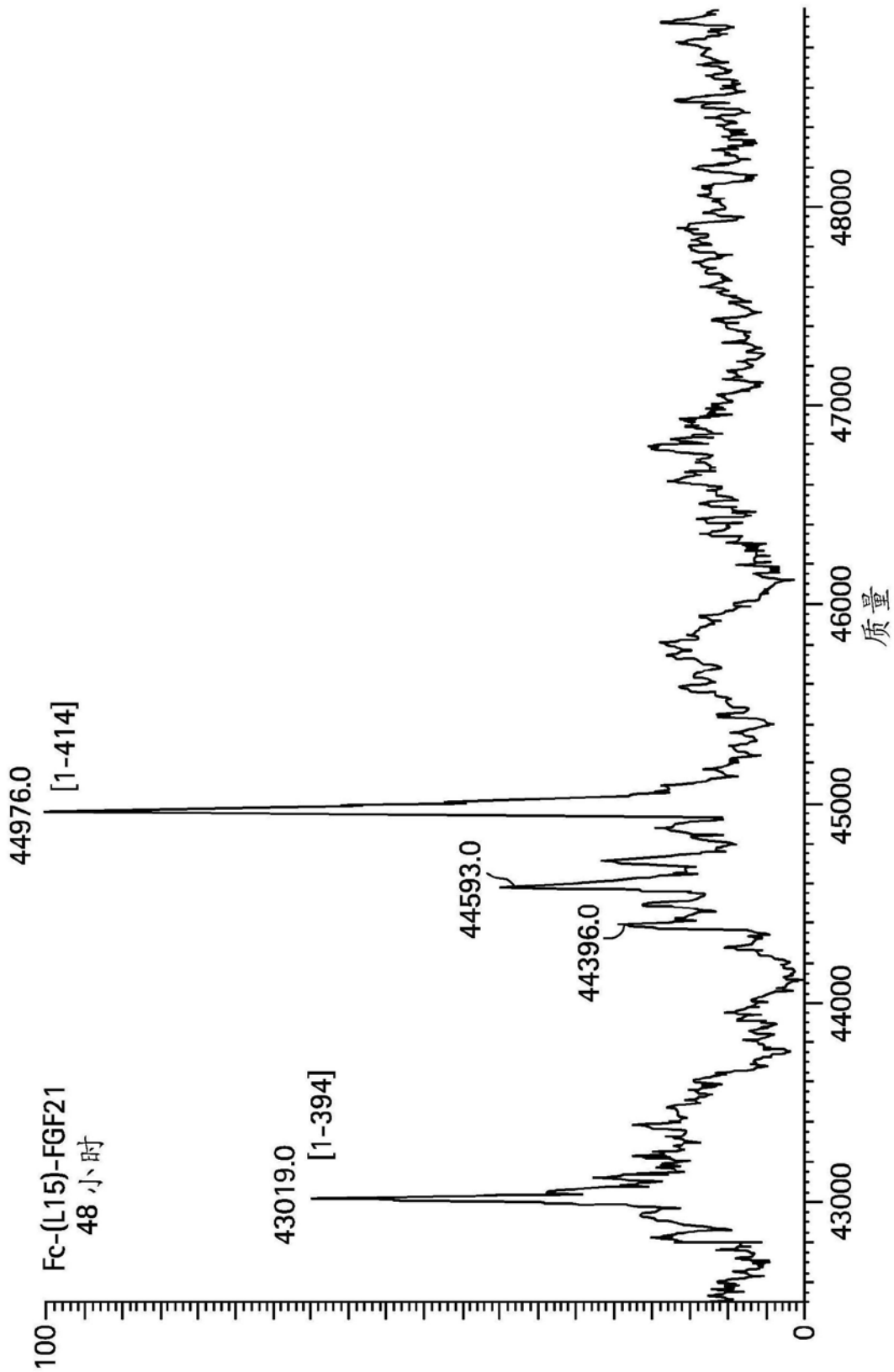


图8D

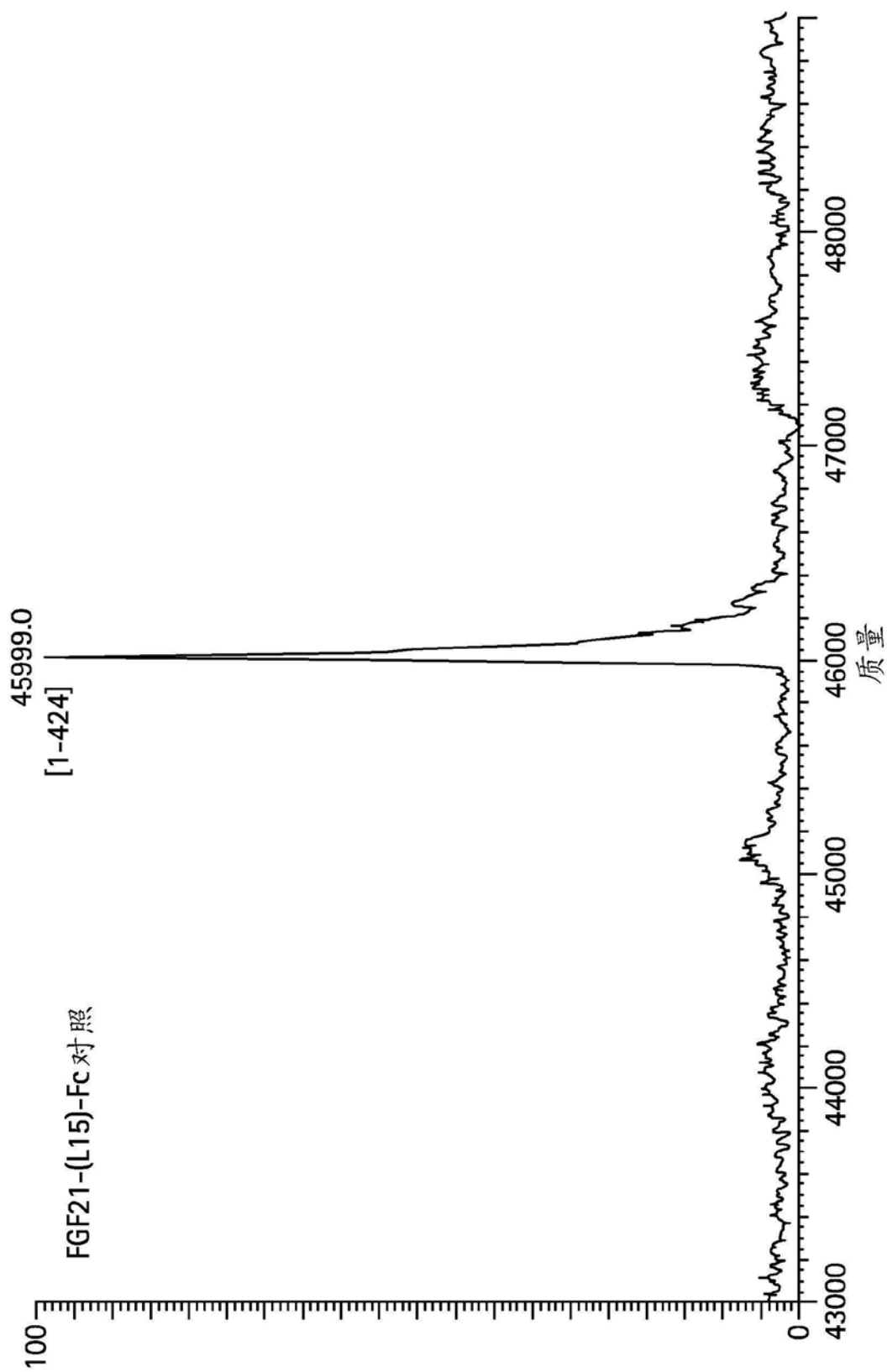


图9A

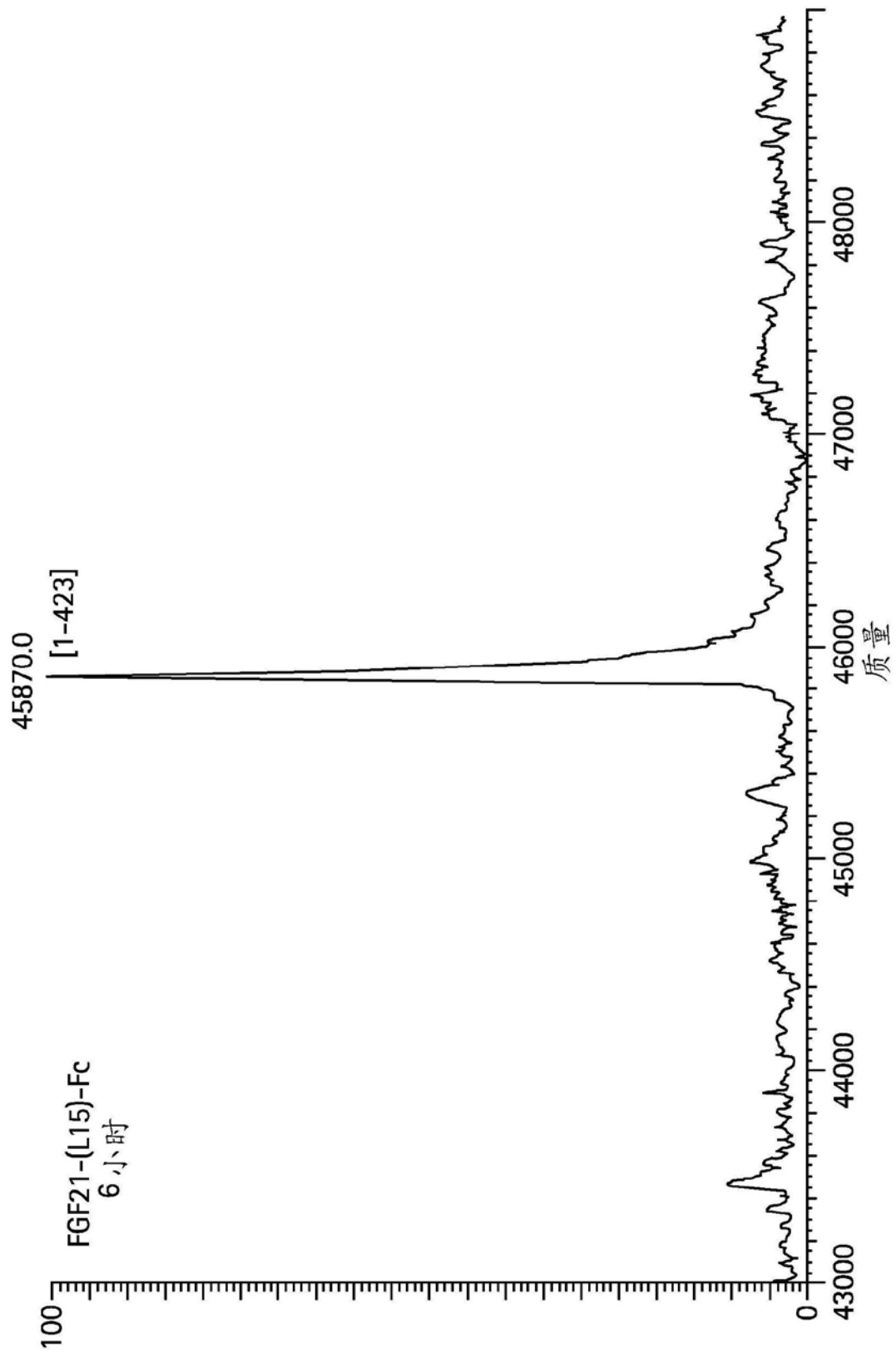


图9B

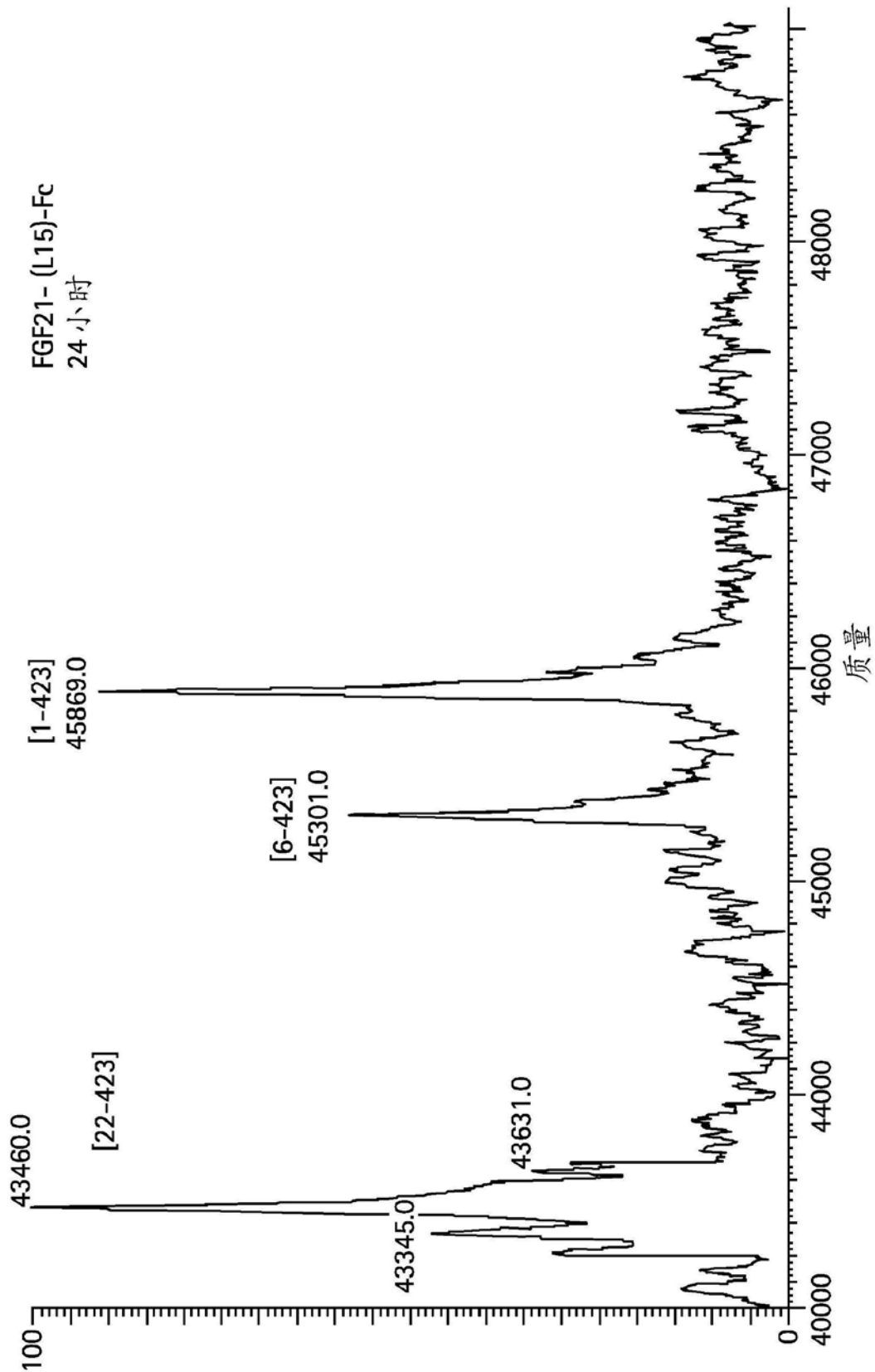


图9C

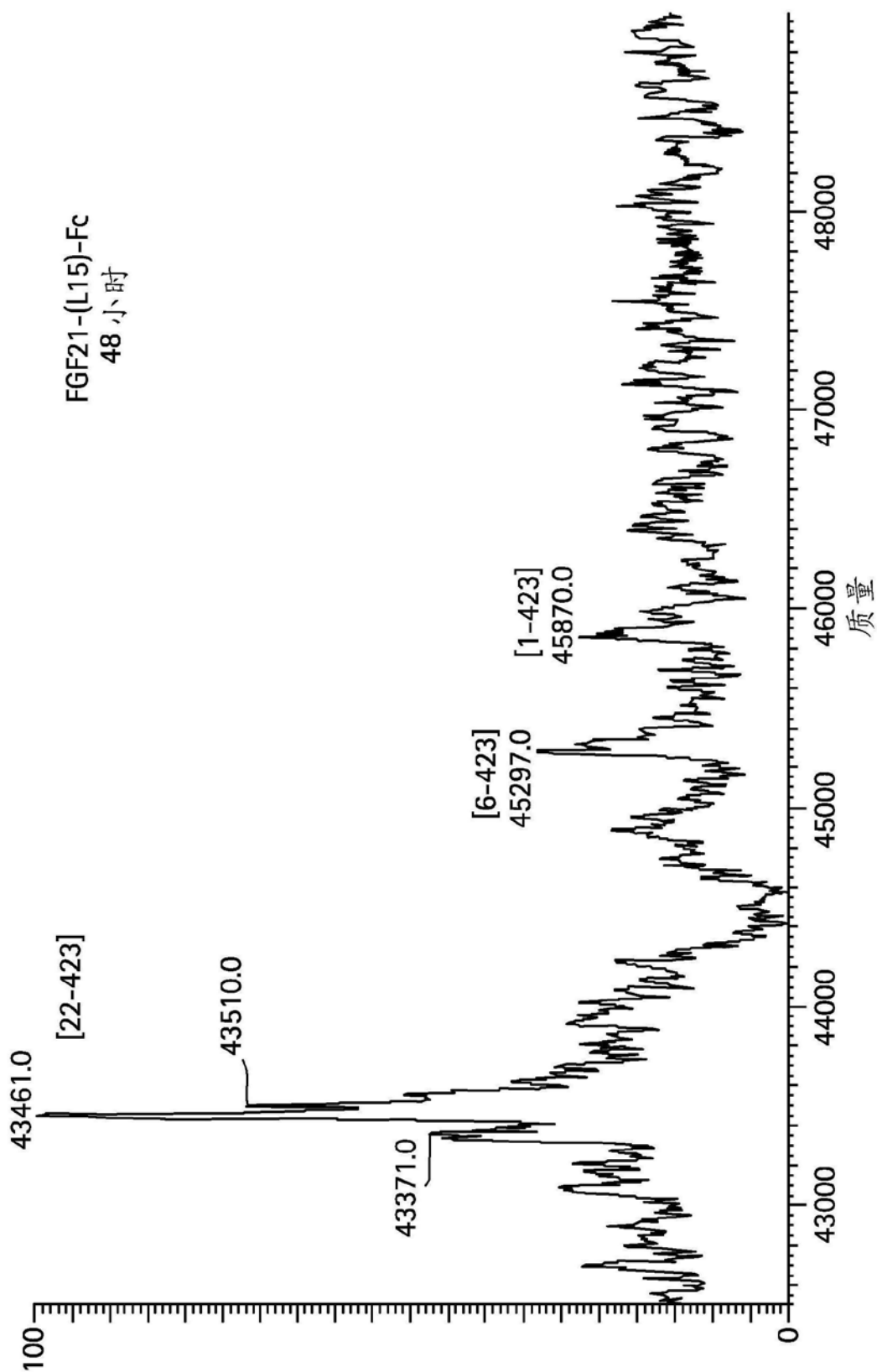


图9D

Fc-(L15)-FGF21



图10A



图10B

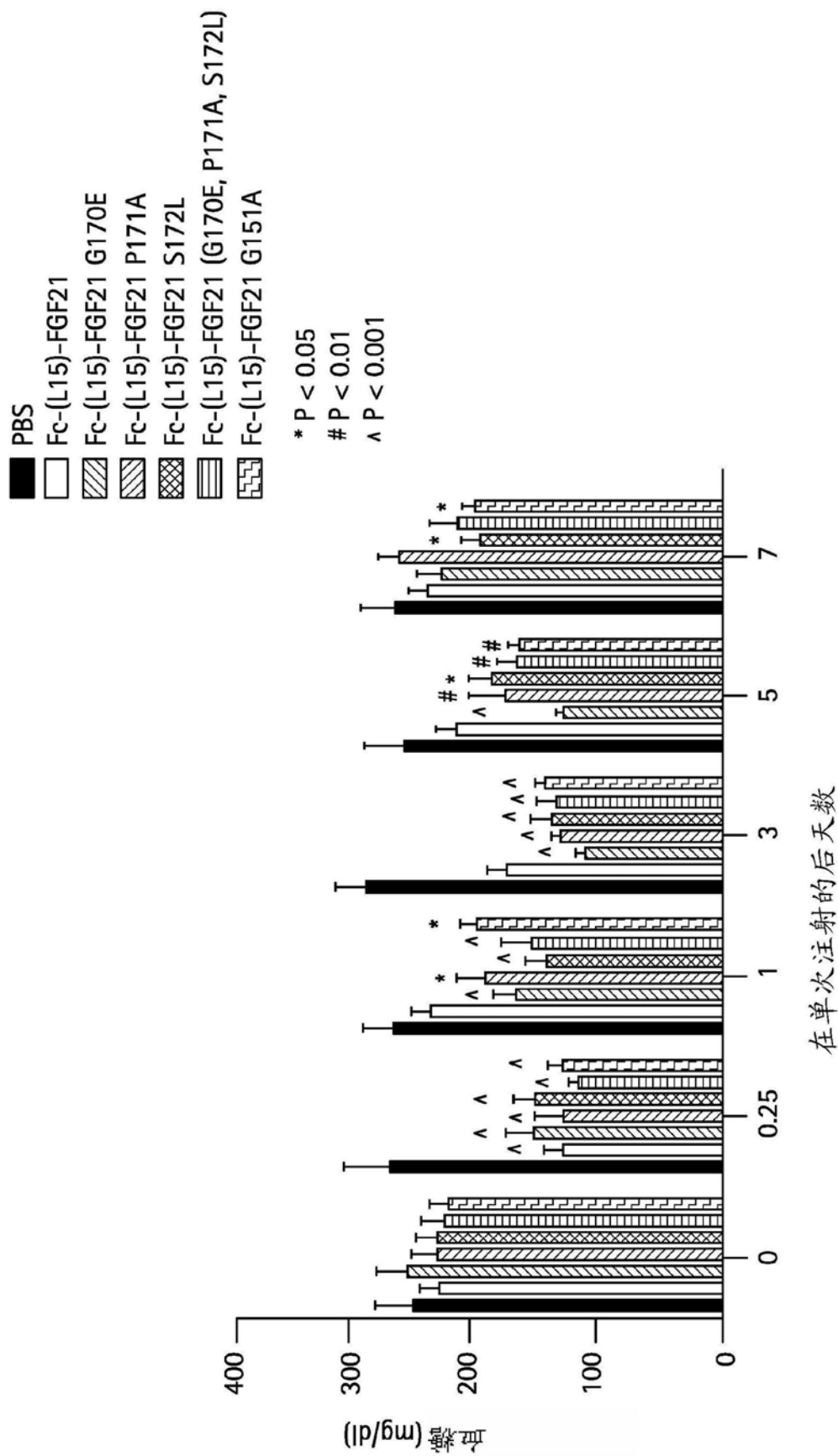


图11

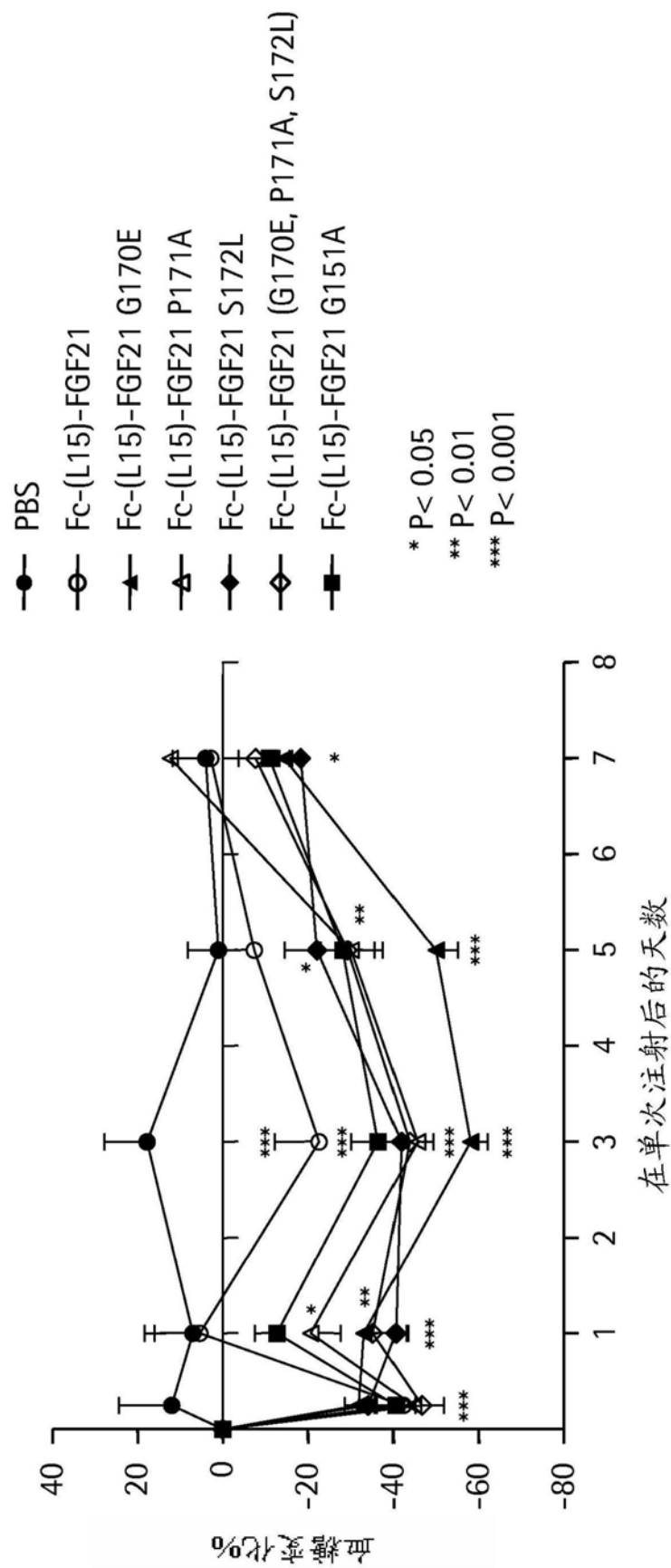


图12

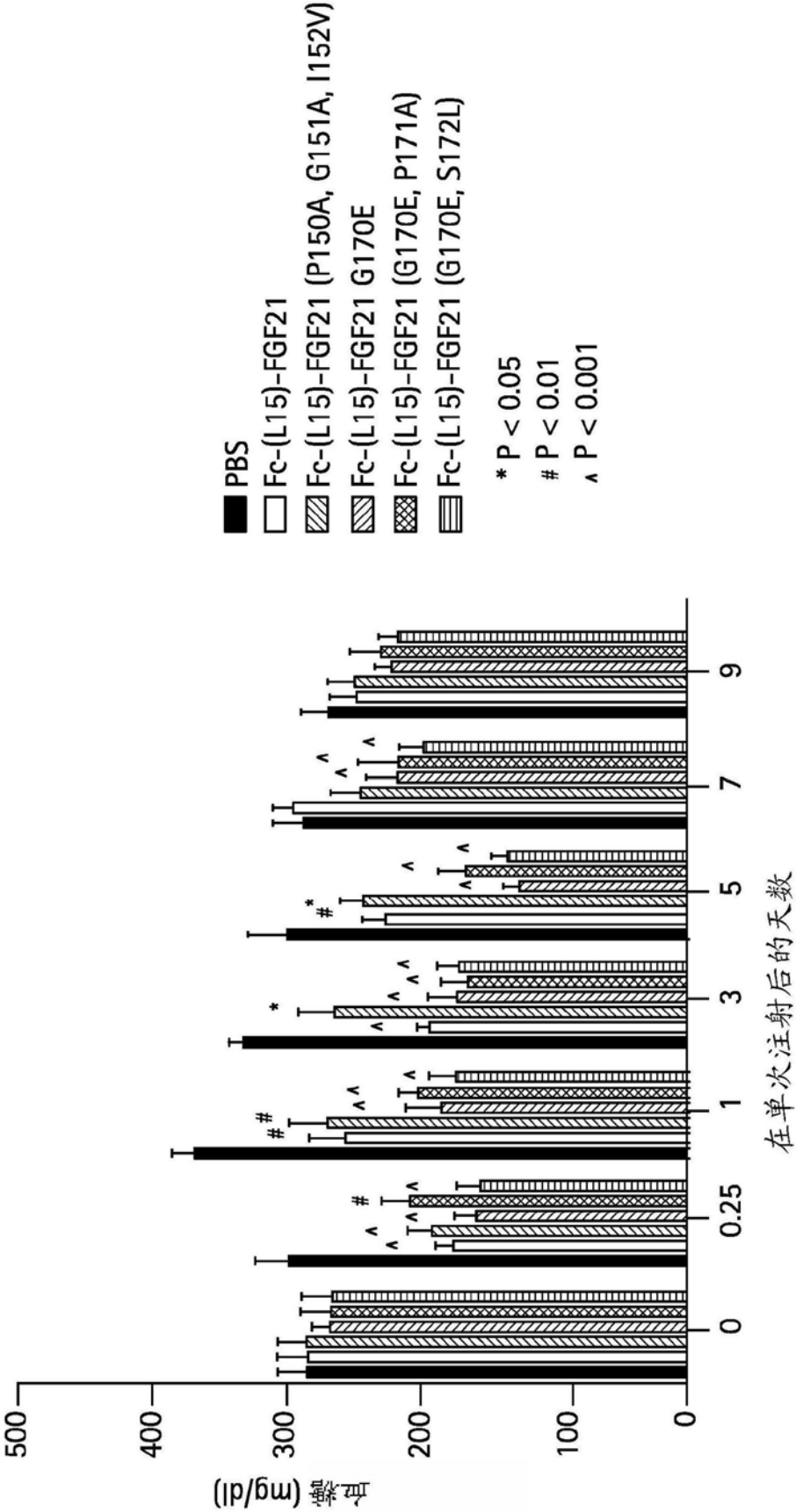


图13

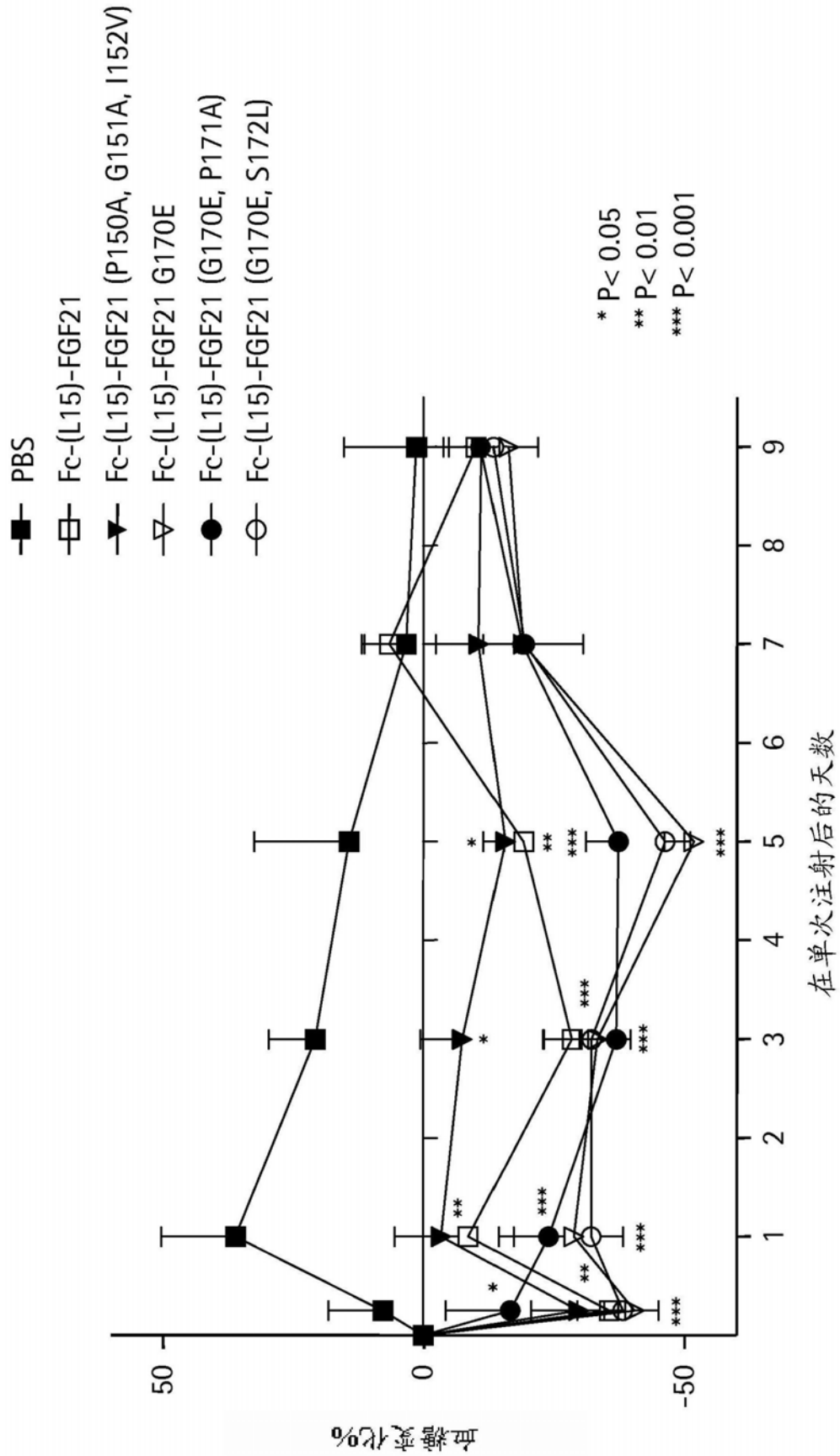


图14

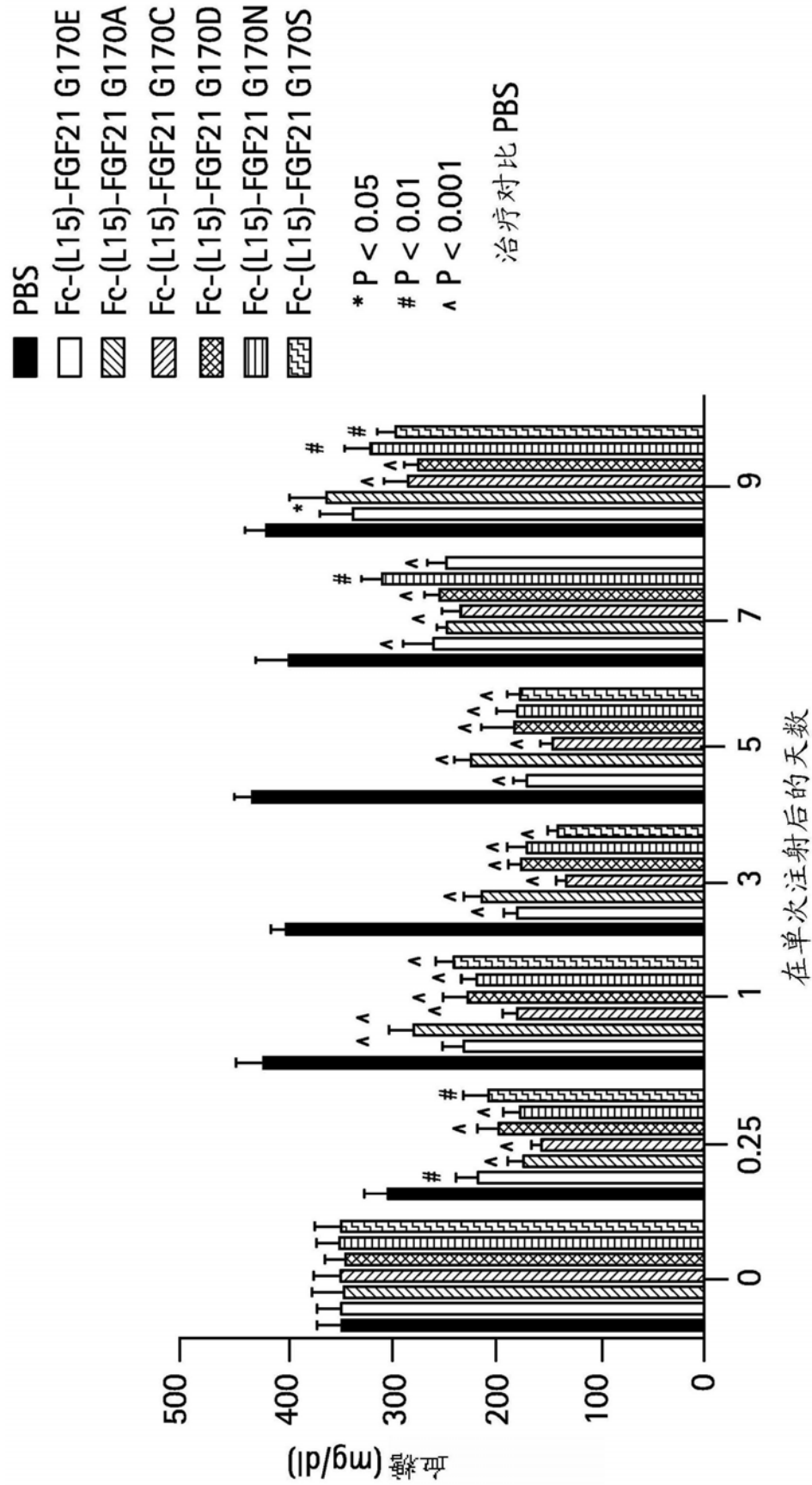


图15

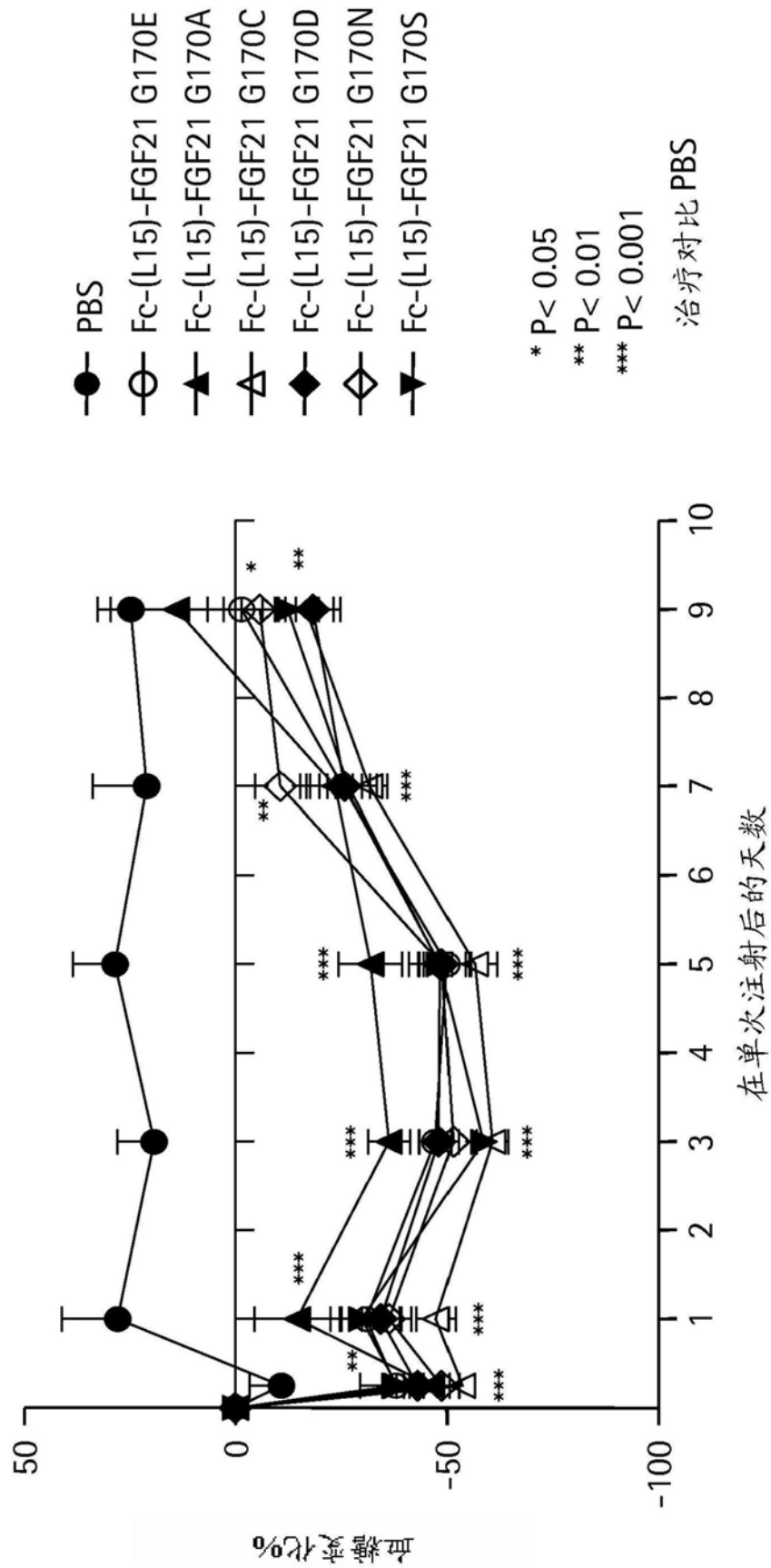


图16

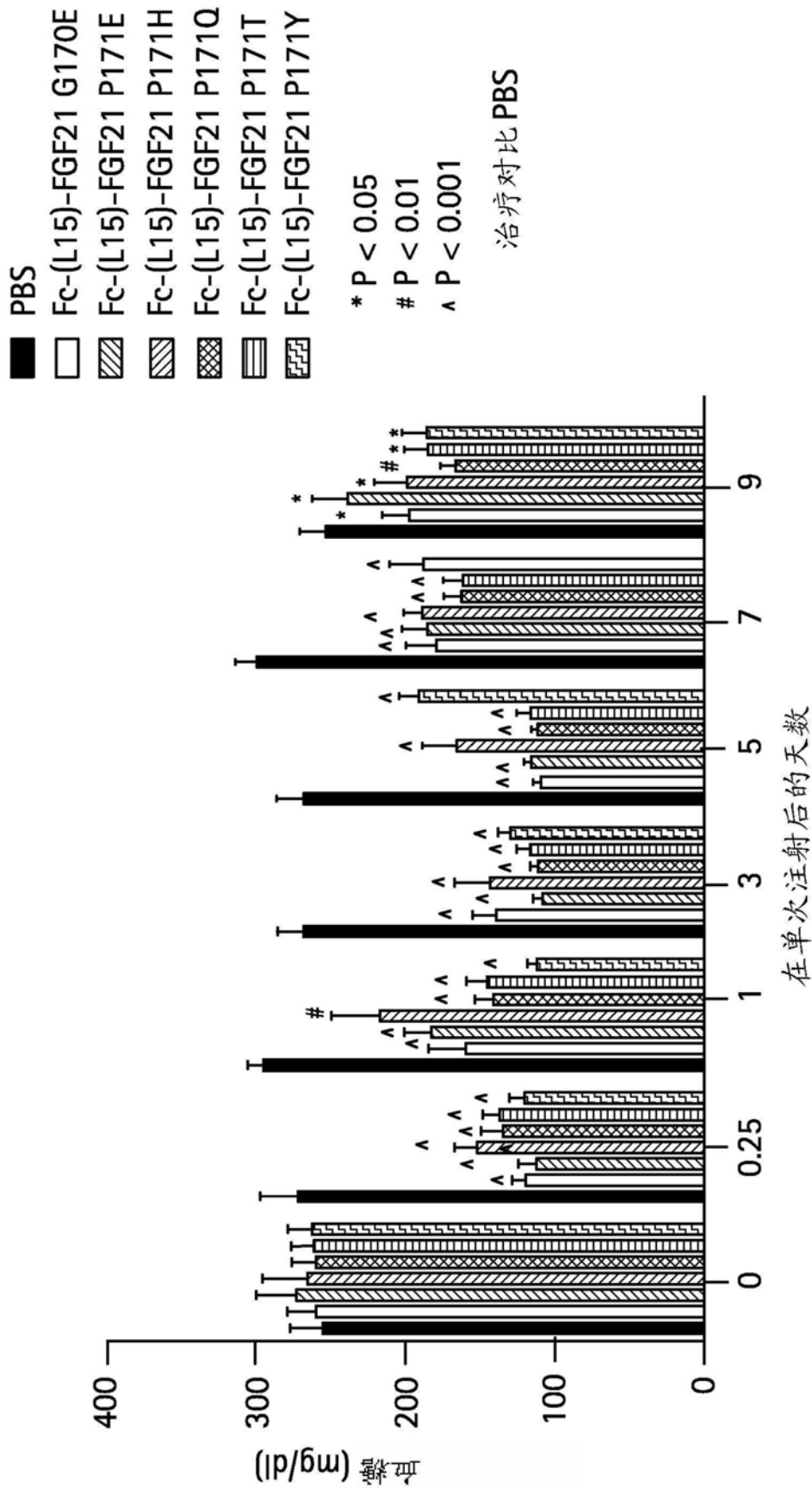


图17

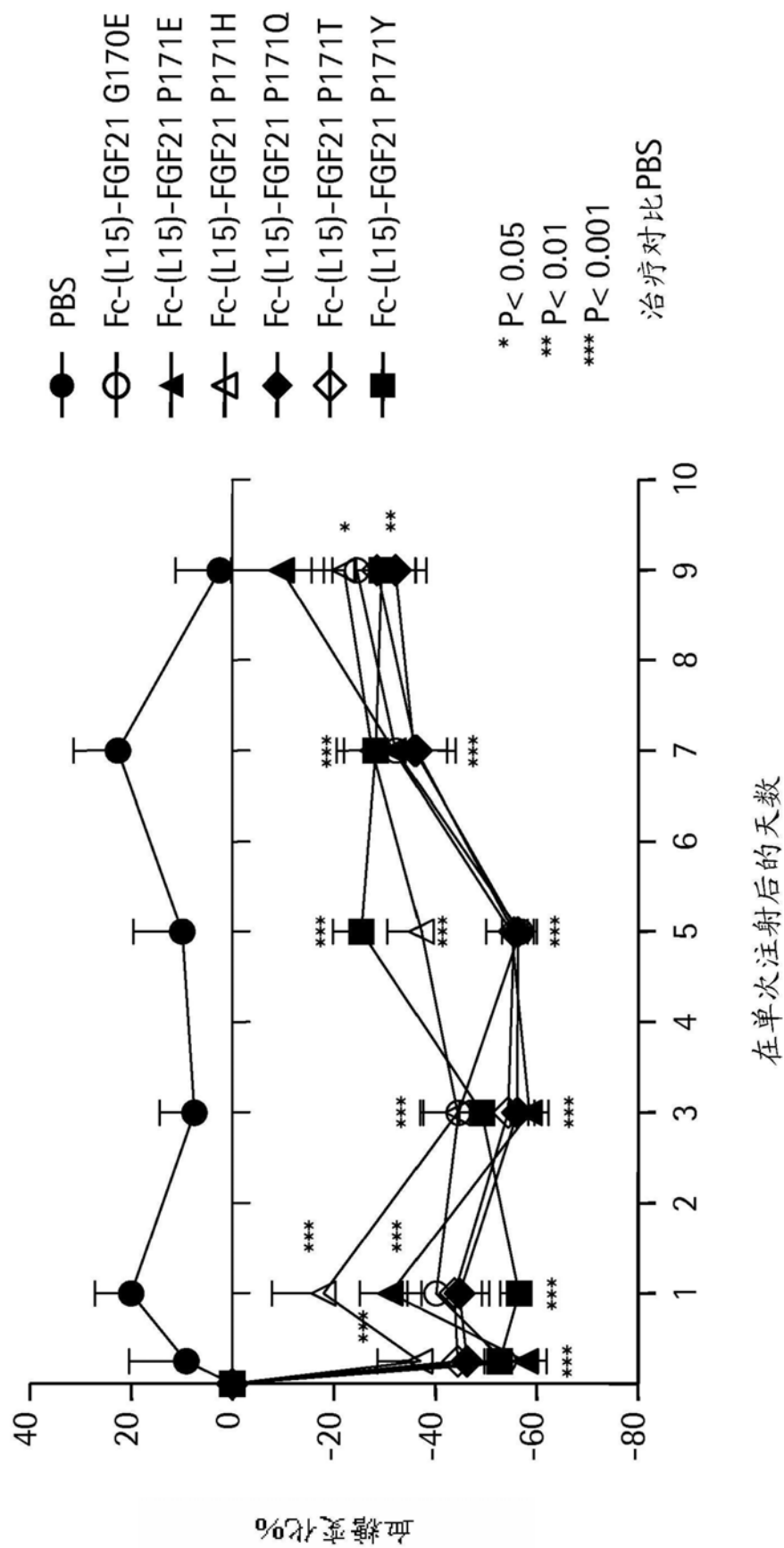


图18

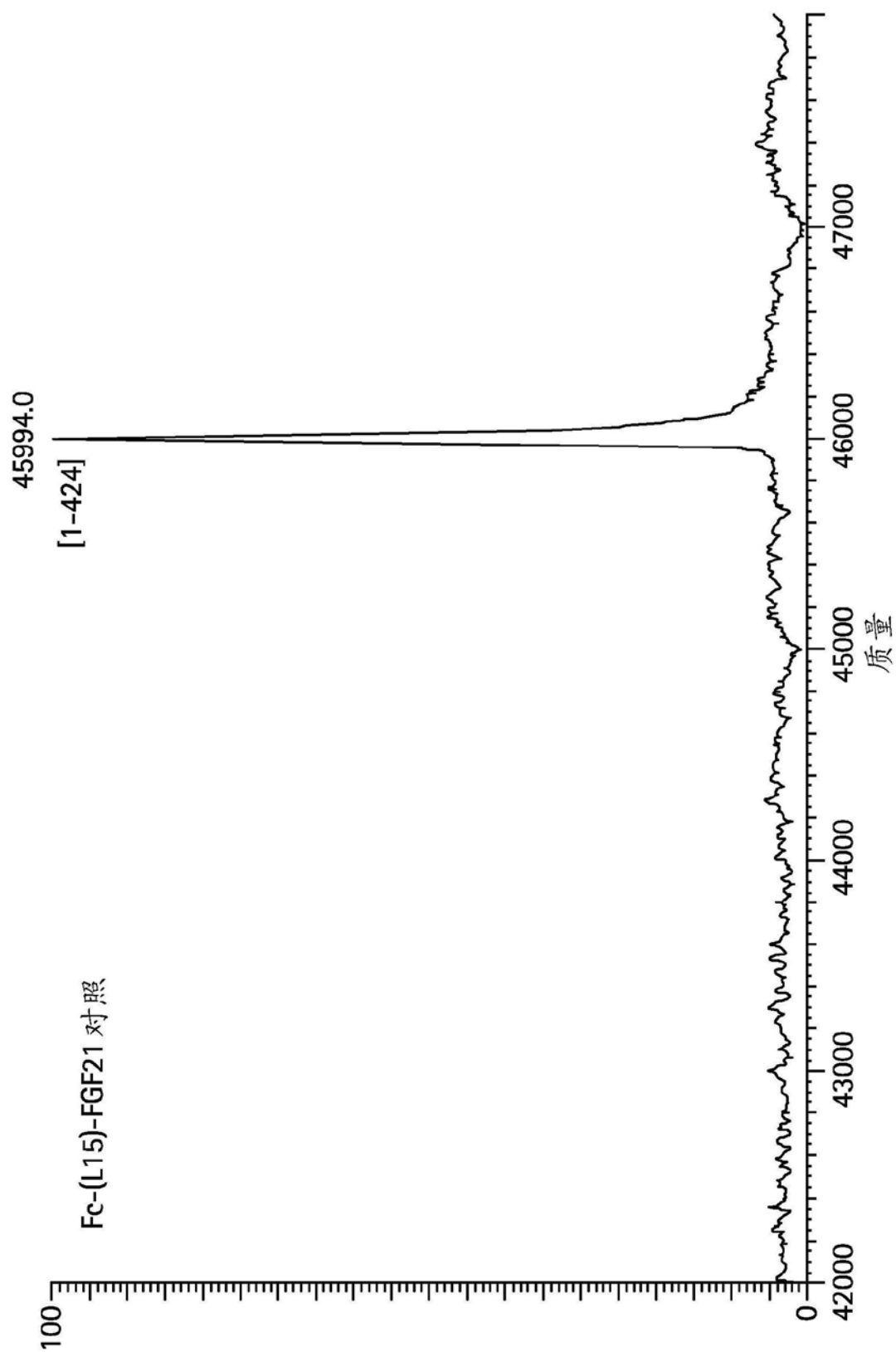


图19A

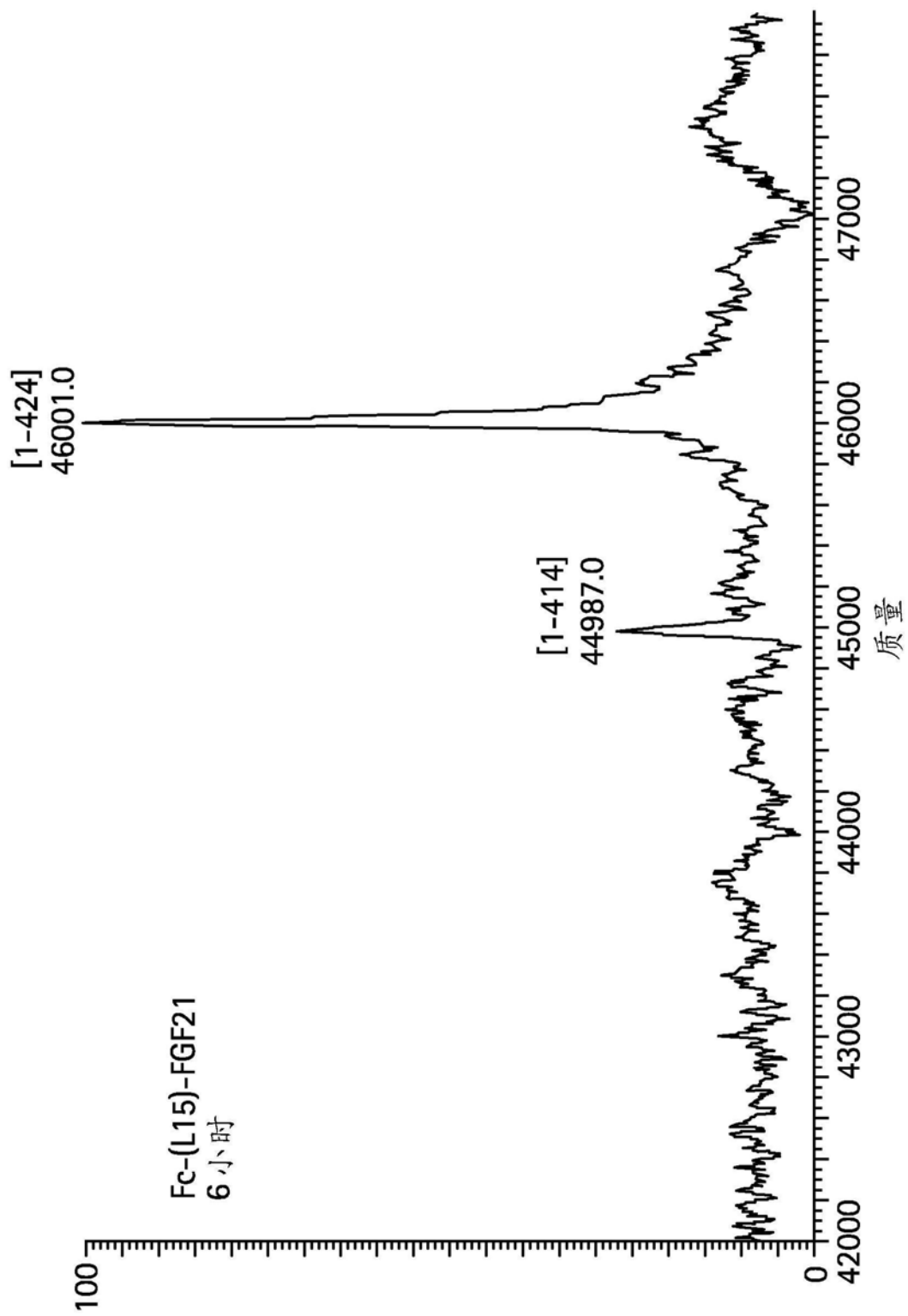


图19B

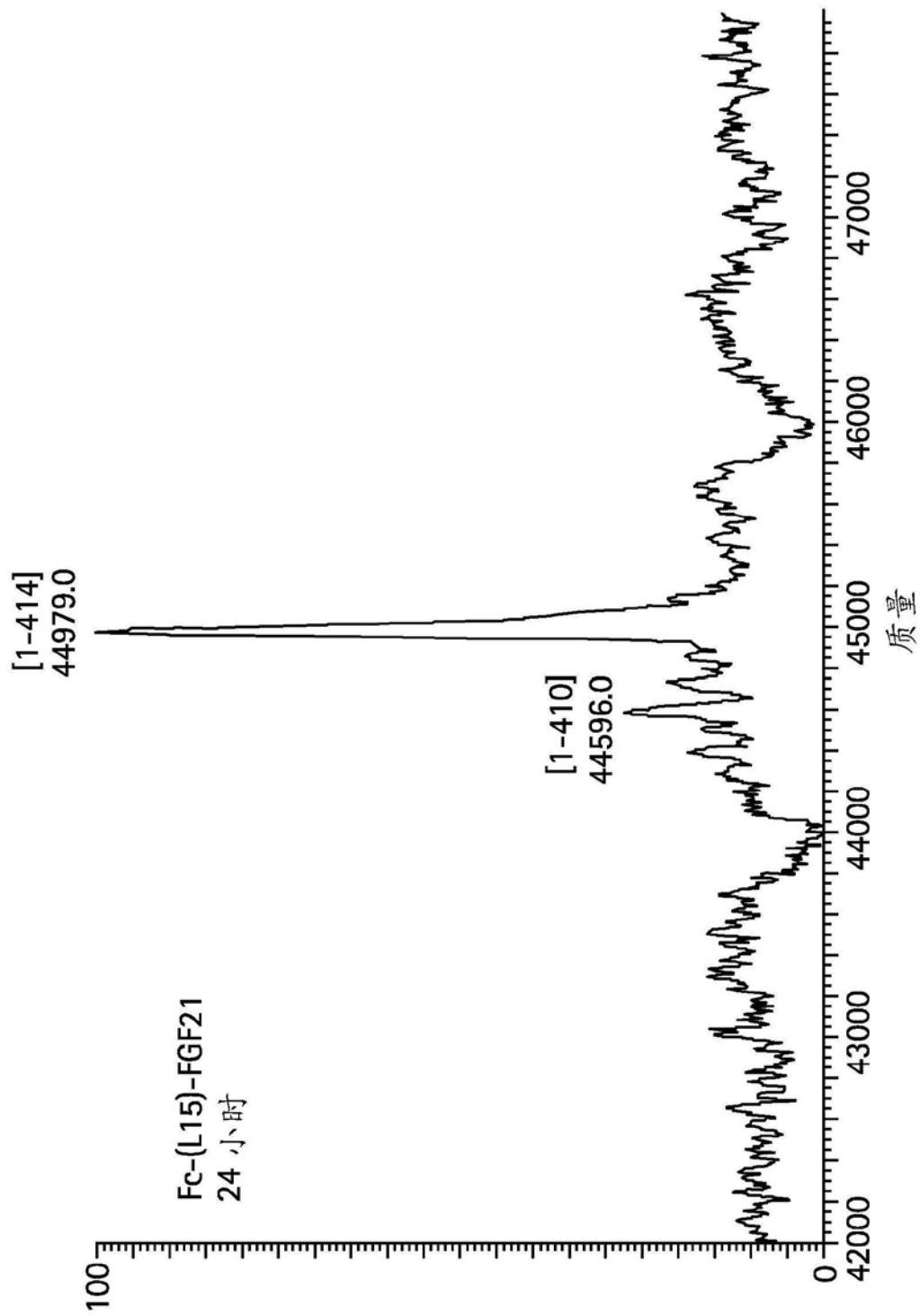


图19C

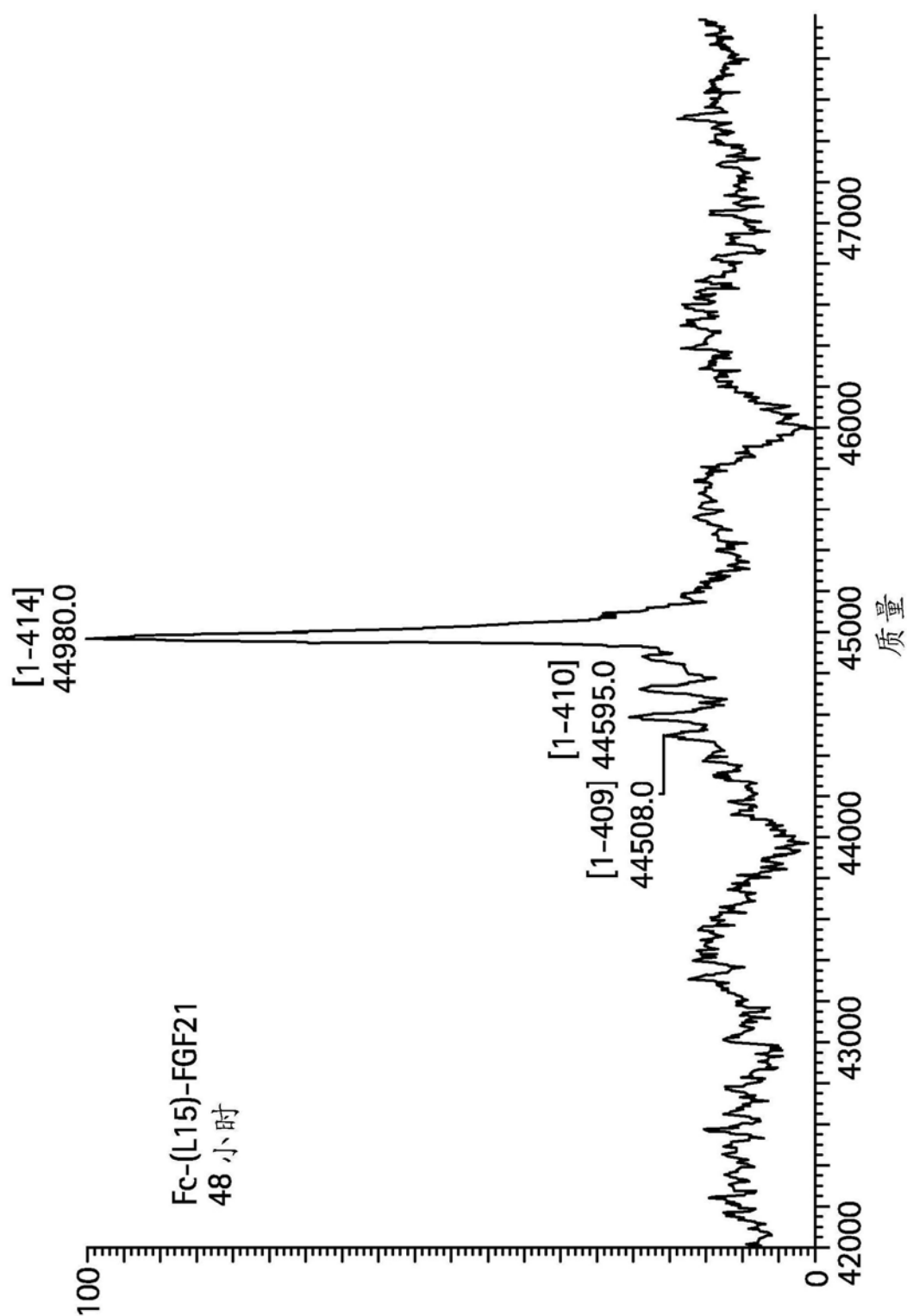


图19D

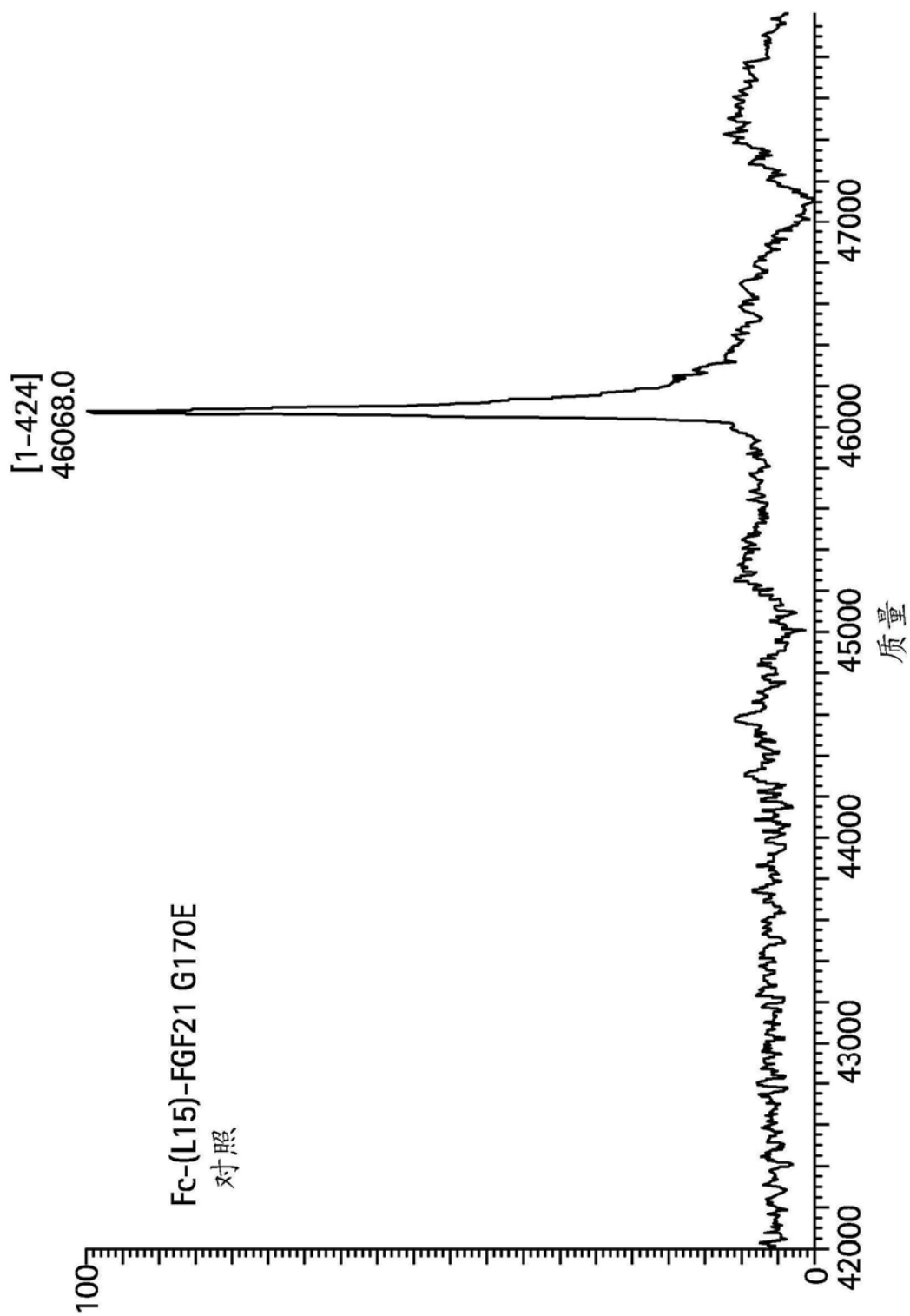


图20A

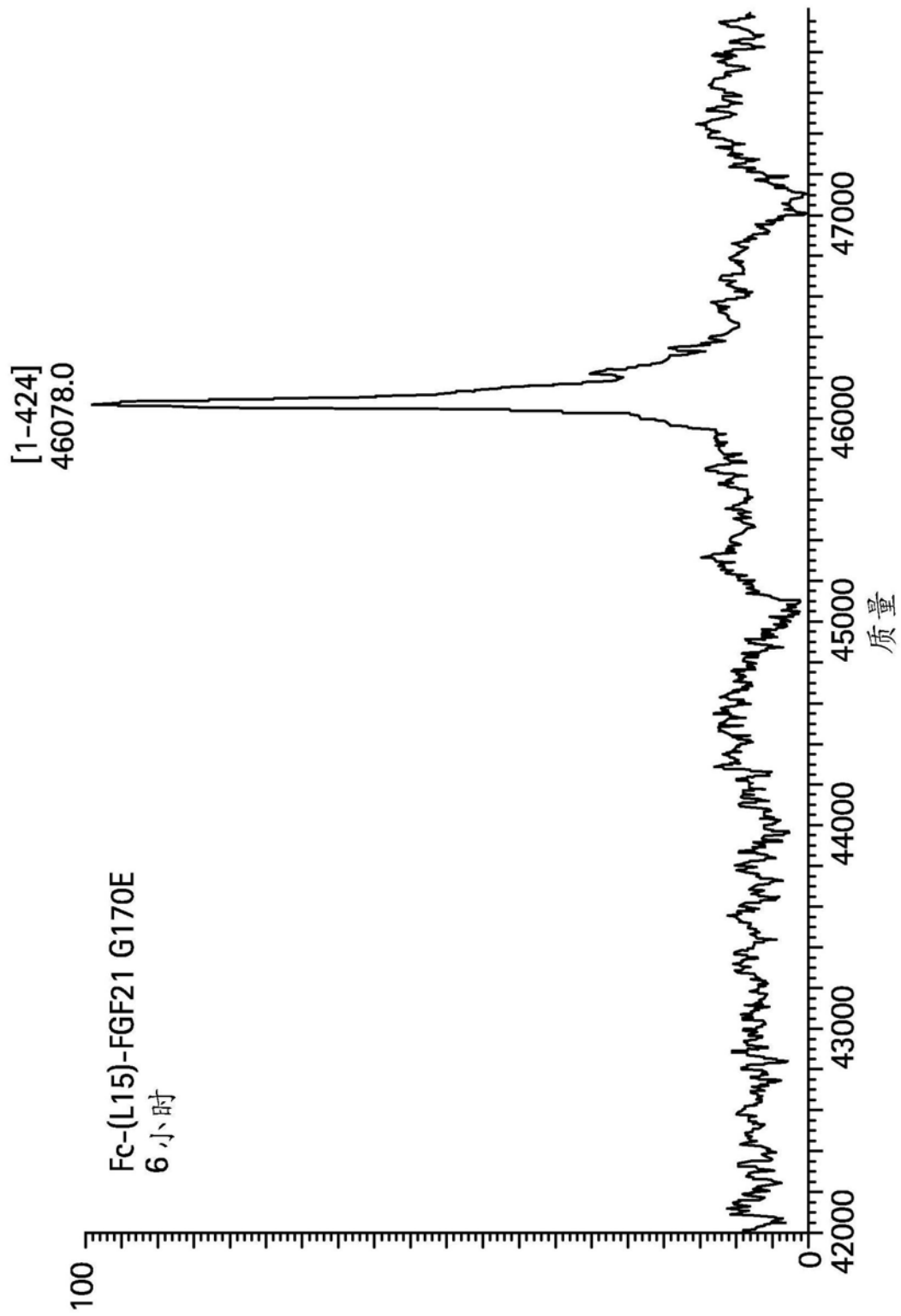


图20B

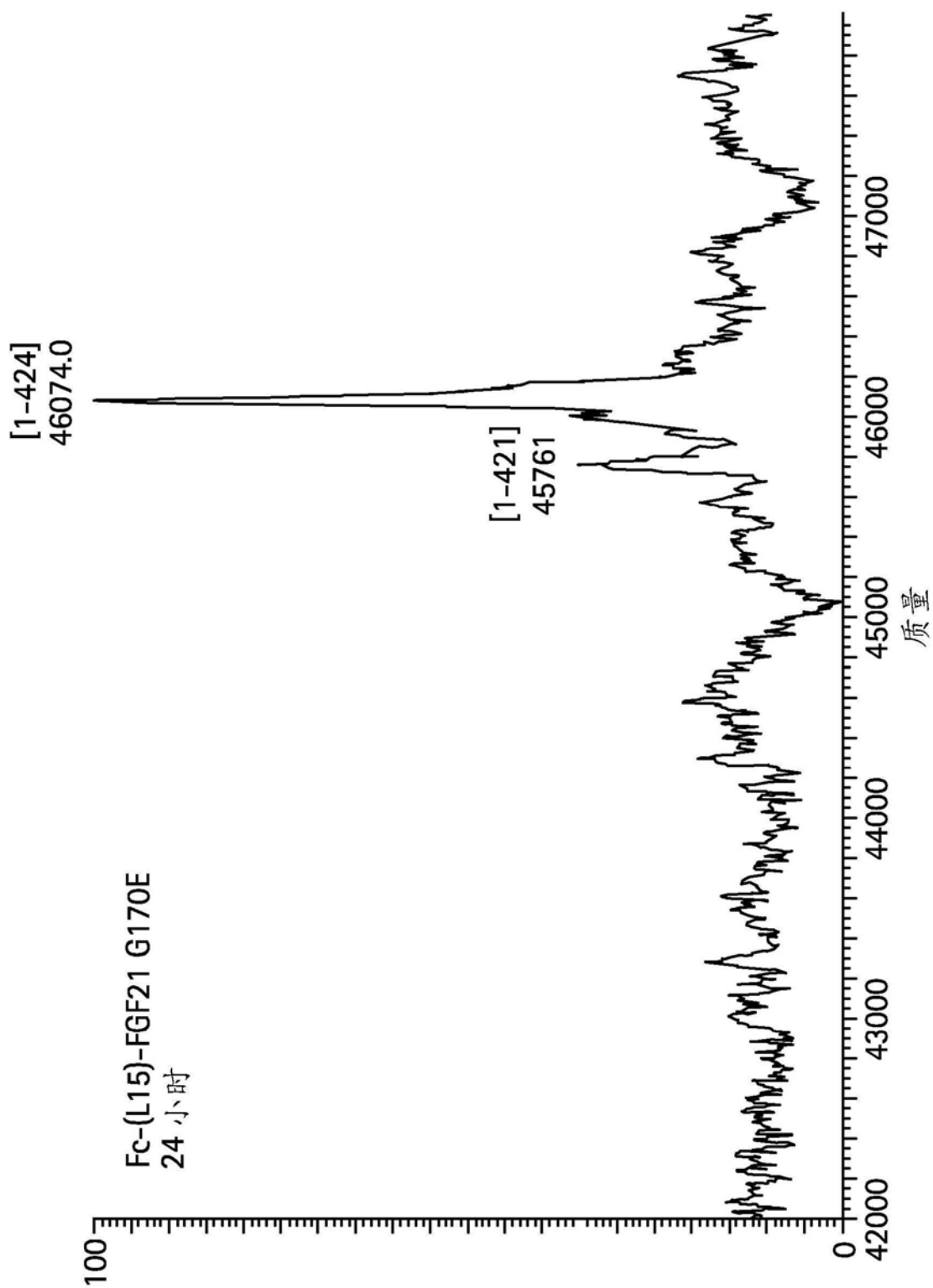


图20C

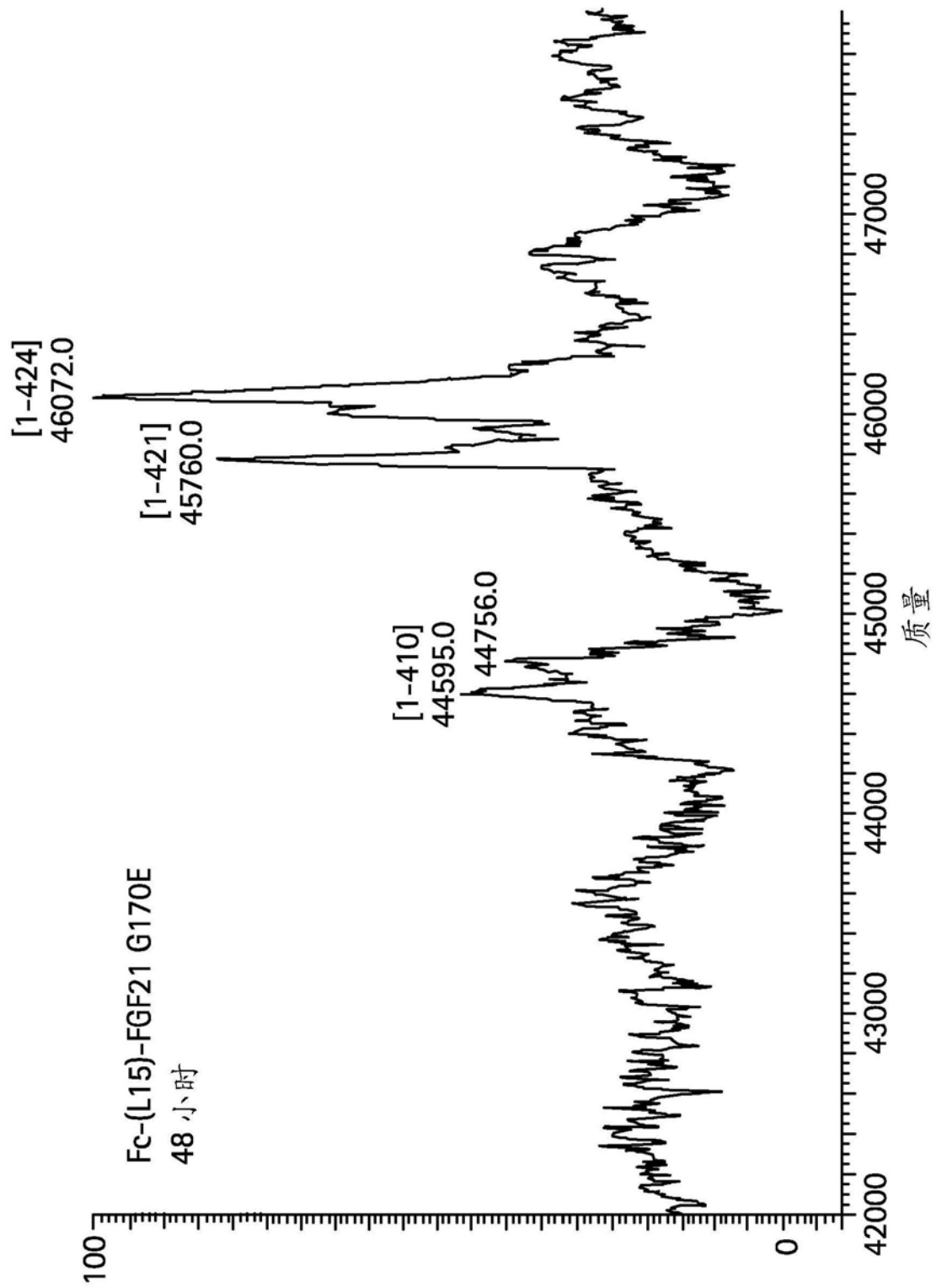


图20D

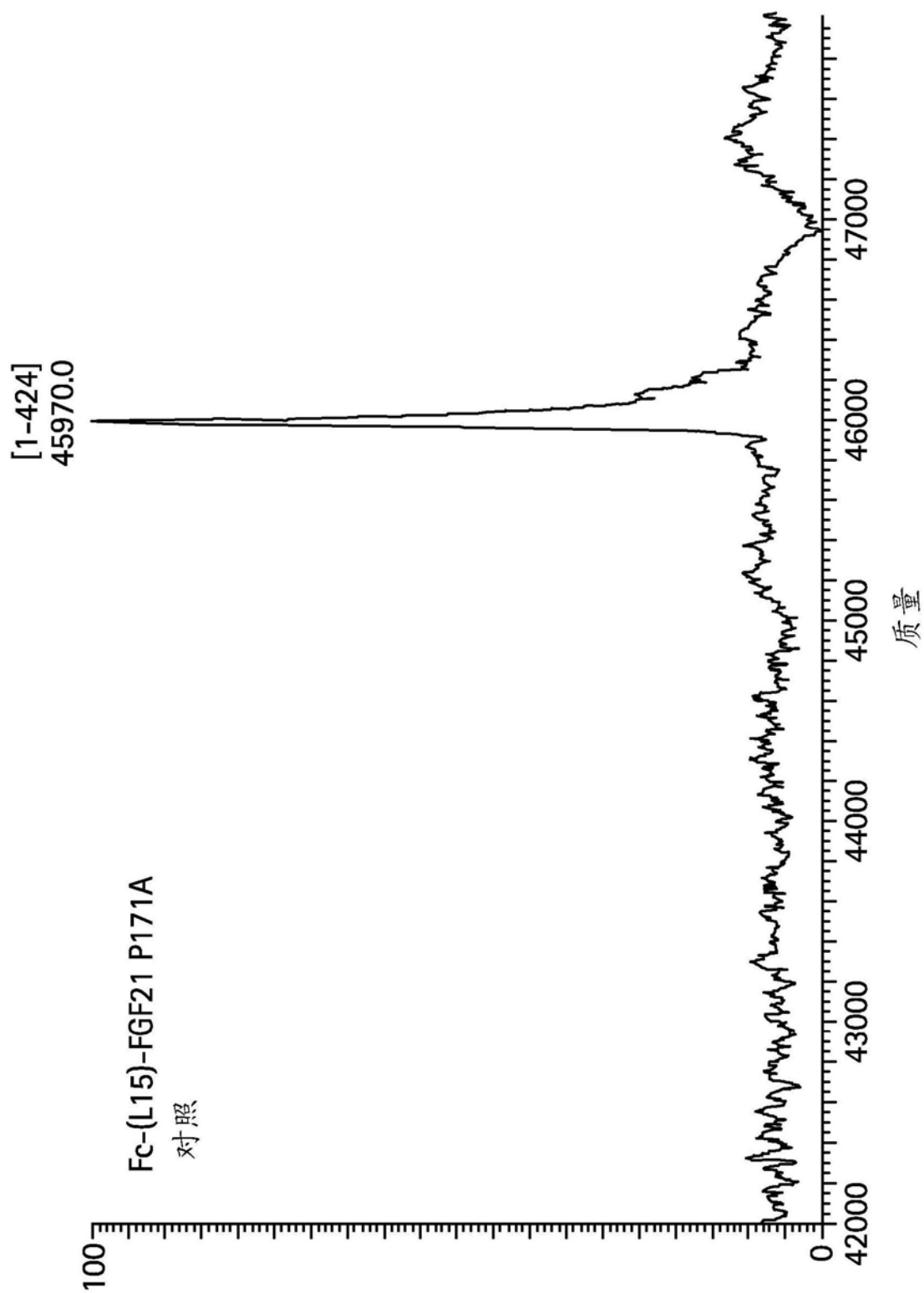


图21A

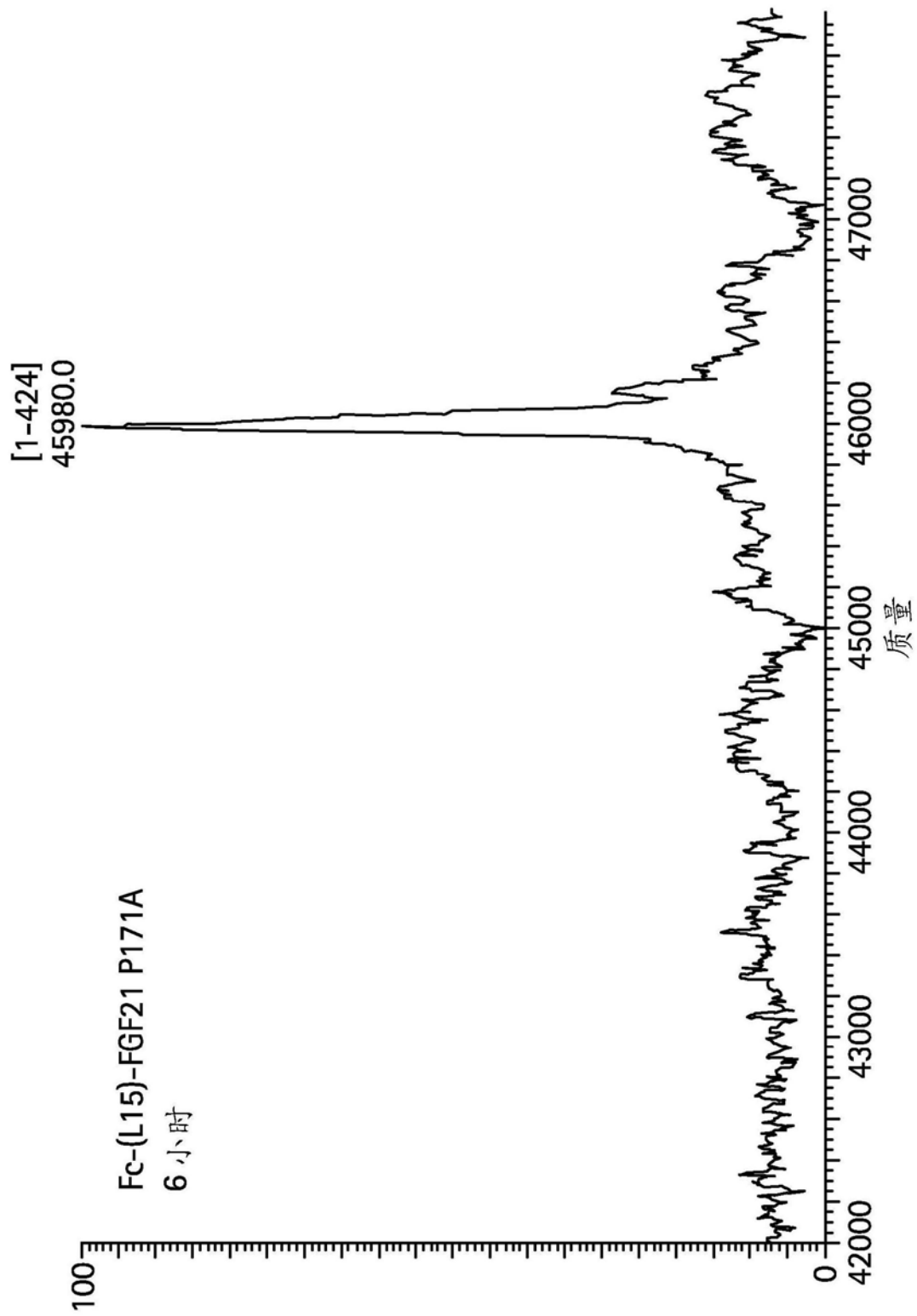


图21B

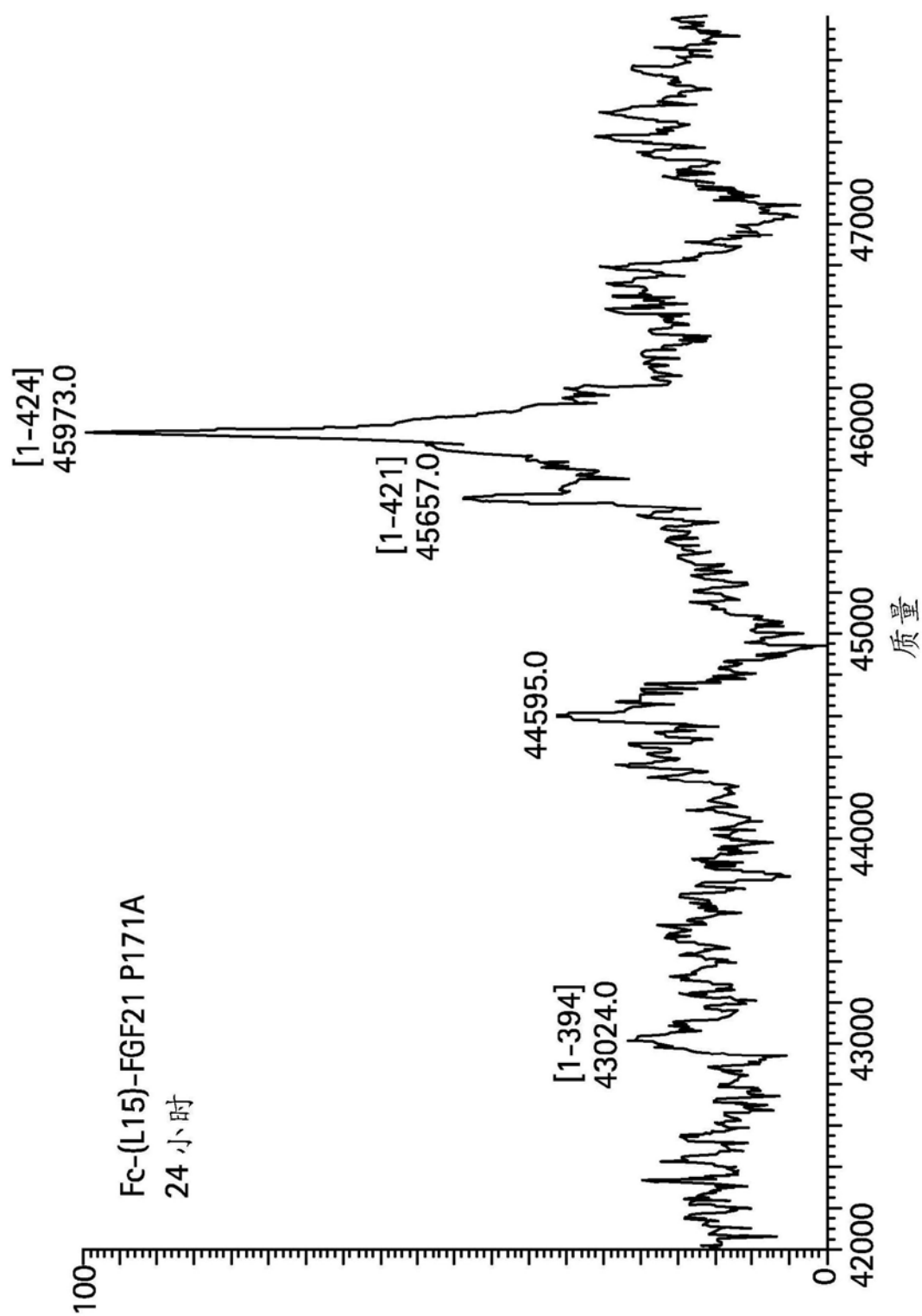


图21C

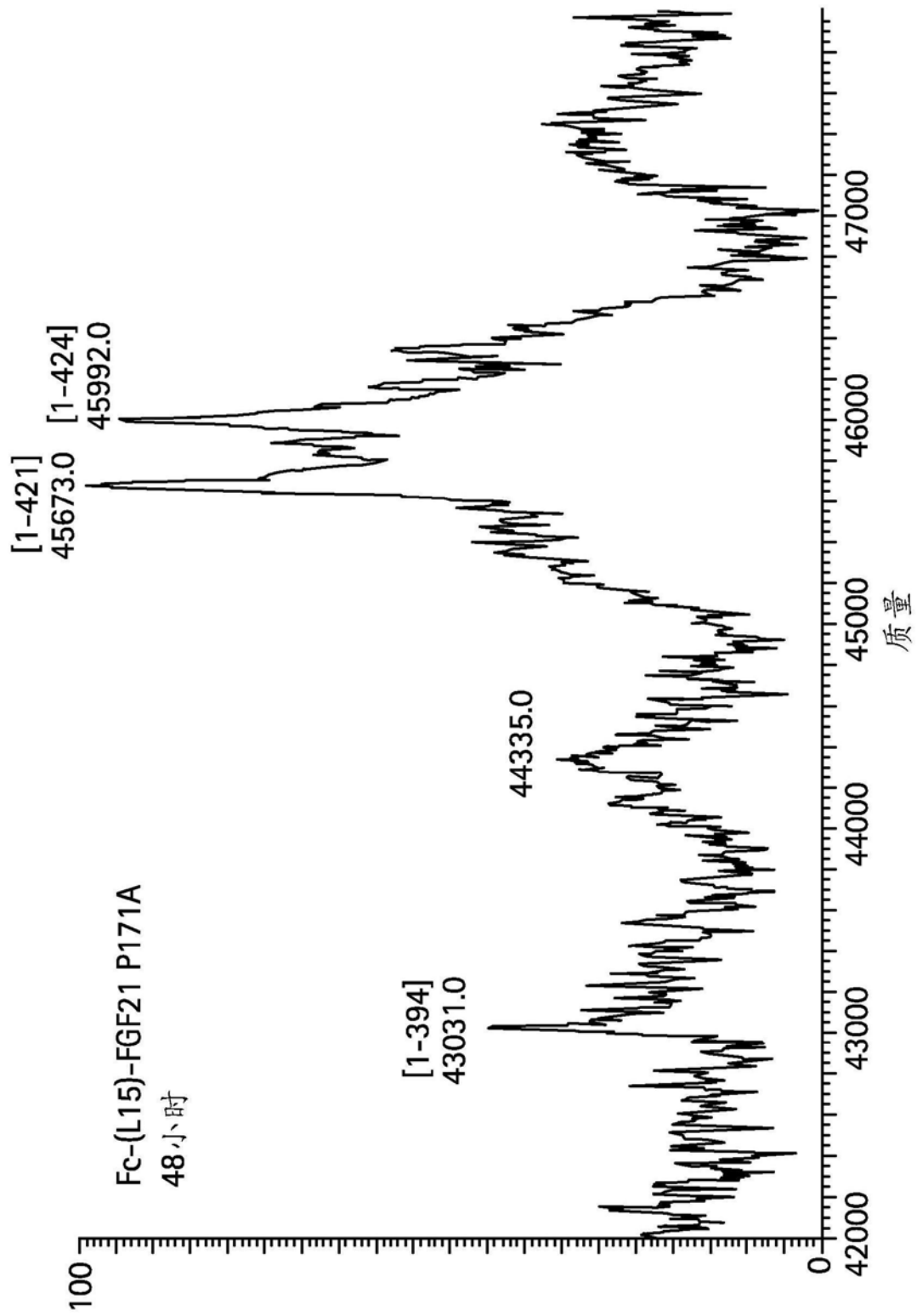


图21D

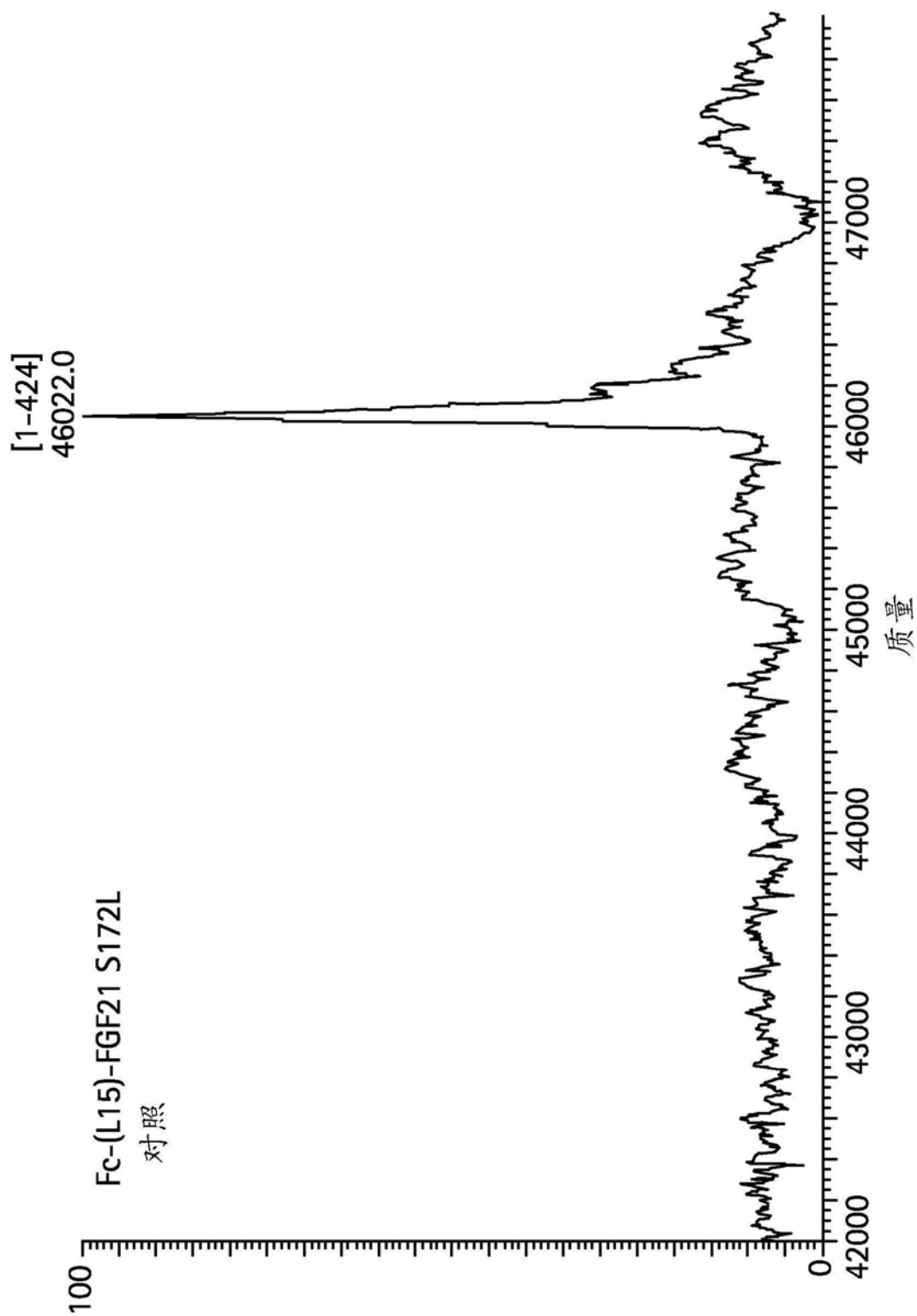


图22A

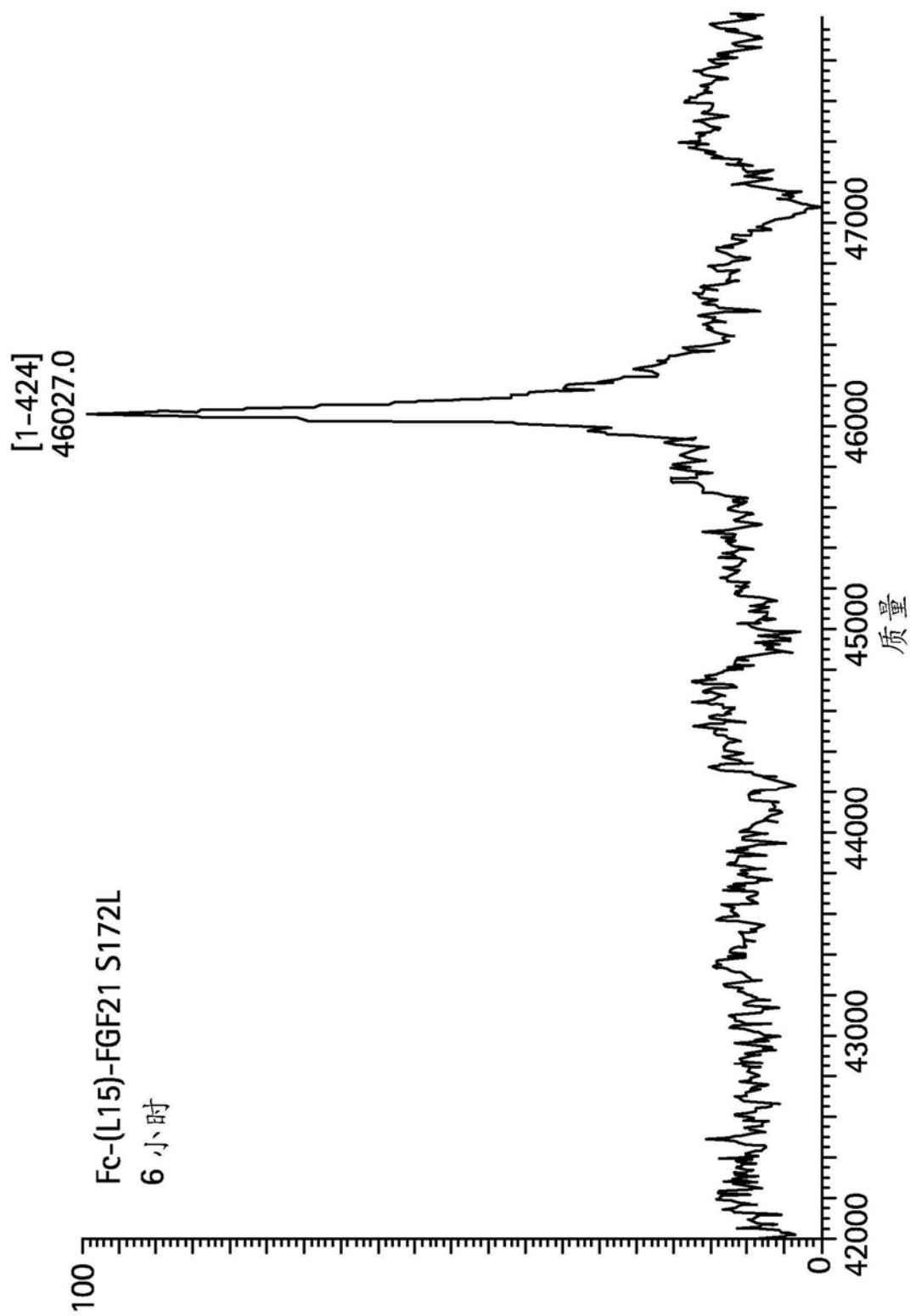


图22B

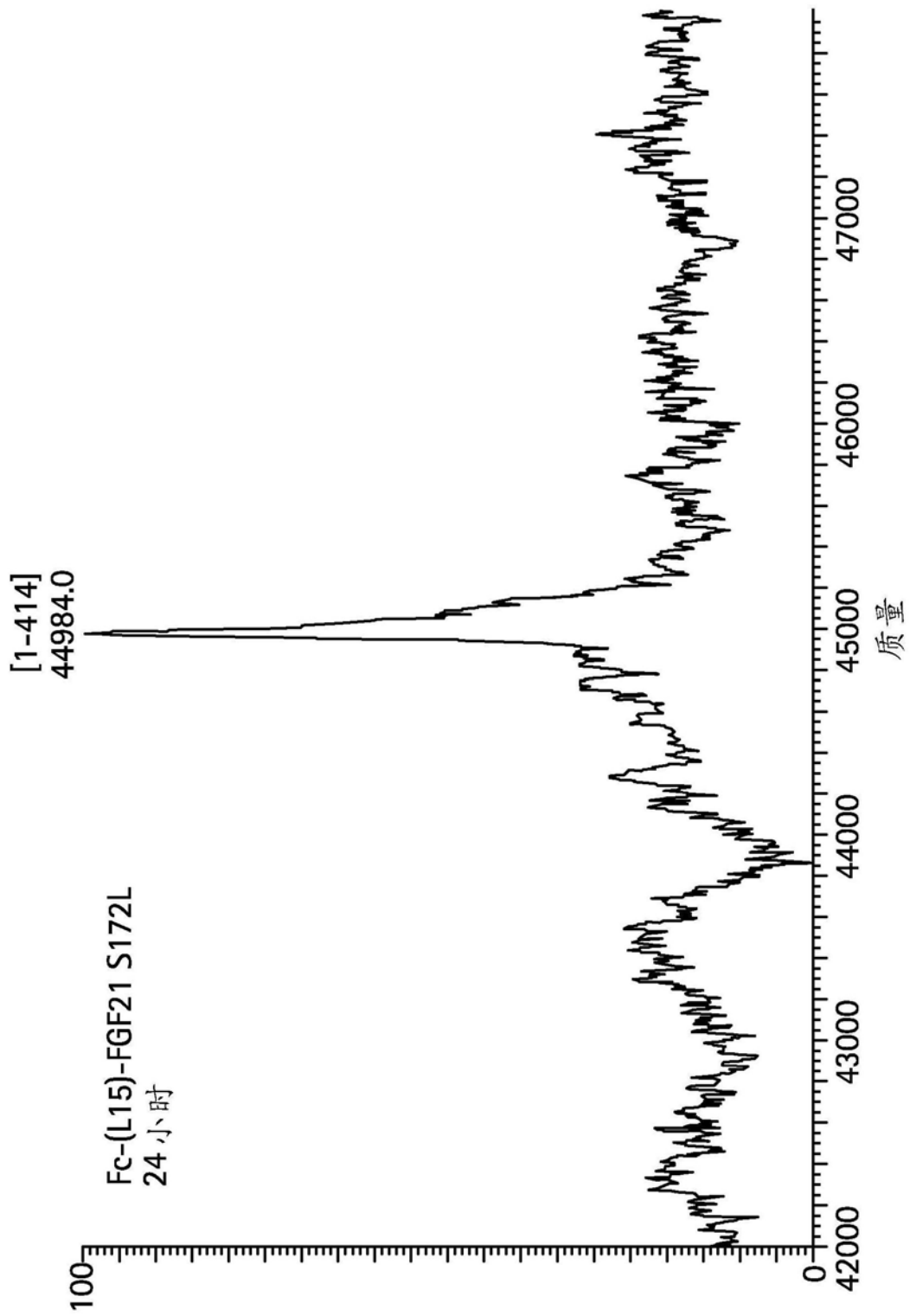


图22C

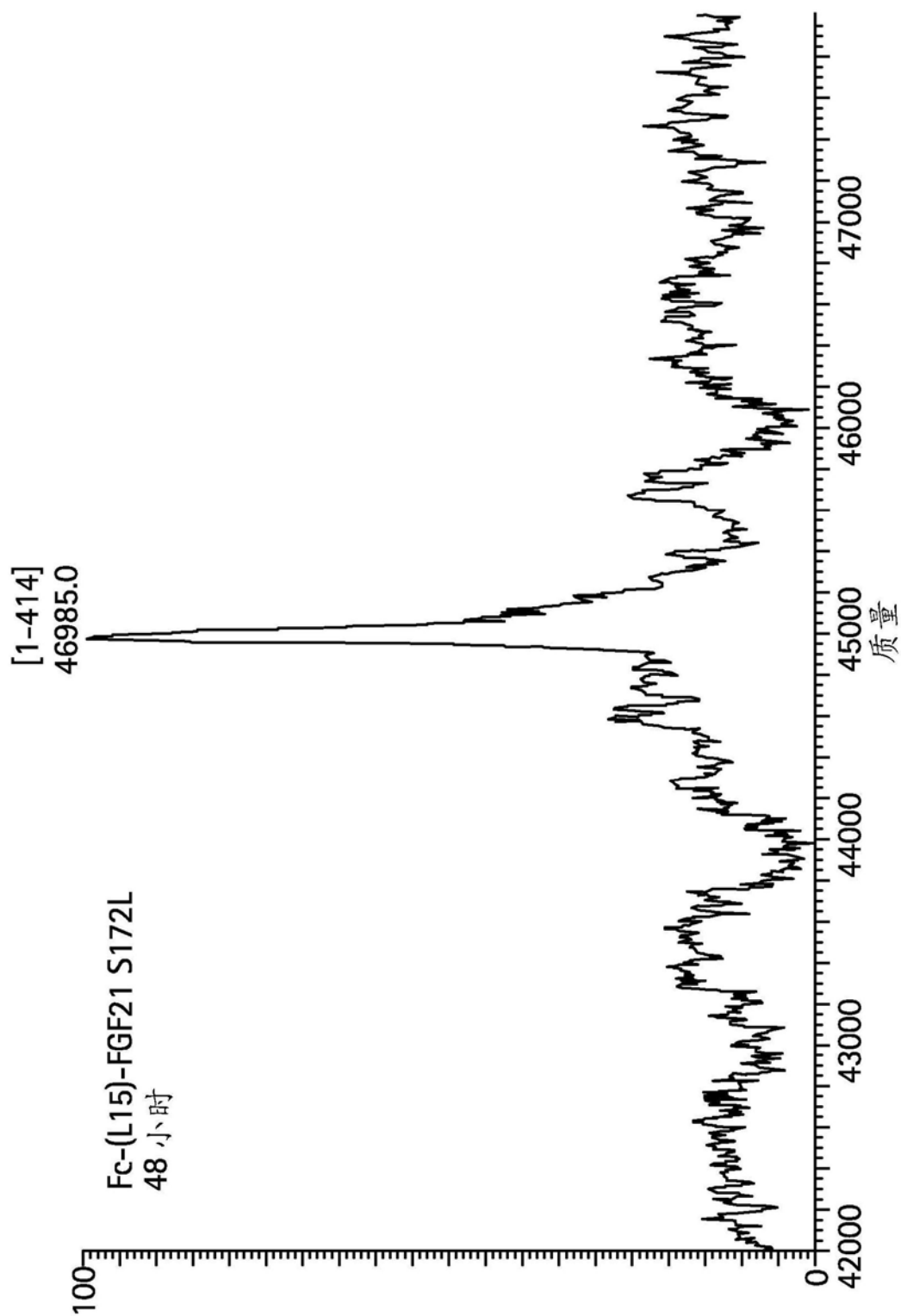


图22D

Fc-(L15)-FGF21

MDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMISRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGSGG
 GGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTVGGAADQSPESLLQLKALKPGVVIQILGVKTSRFLCQR
 PDGALYGSLSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPAPRFLPLPGLPPAPPEPPGILAPQP
 PDVGSSDPLSMVGPSQGRSPSYAS



6小时 (20%)
 24小时 (100%) [1-414]
 48小时 (~100%)

图23A

Fc-(L15)-FGF21 G170E

MDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHAEALHNHYTQKSLSLSPGKGGGGSGGGSGG
 GGSHPIDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQR
 PDGALYGSLHFDPEACSFRELLEDDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQP
 PDVGSSDPLSMVEPSQGRSPSYAS



6小时 (0%)
 24小时 (20%) [1-442]
 48小时 (~40%)

图23B

Fc-(L15)-FGF21 P171A

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGSGSGG
 GGSHPIDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQR
 PDGALYGSLSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQP
 PDVGSSDPLSMVGASQGRSPSYAS



6小时 (0%)
 24小时 (~30%) [1-421]
 48小时 (~50%)

图23C

Fc-(L15)-FGF21 S172L

MDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMISRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELYKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
 GGSHPIDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQR
 PDGALYGSLSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPAPRFLPLPGLPPAPPEPPGILAPQP
 PDVGSSDPLSMVGPIQGRSPSYAS



6小时 (0%)
 24小时 (100%) [1-414]
 48小时 (100%)

图23D

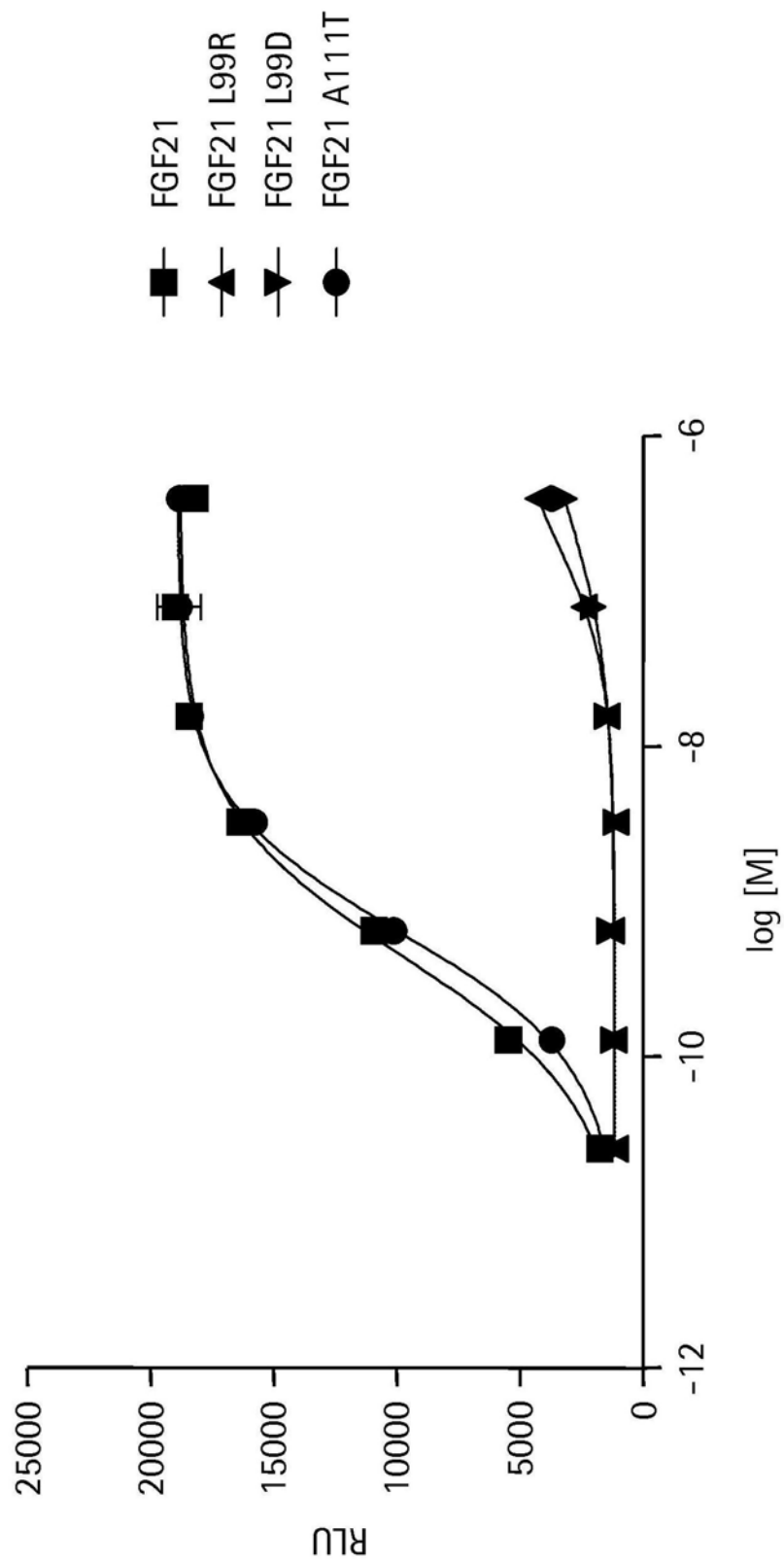


图24A

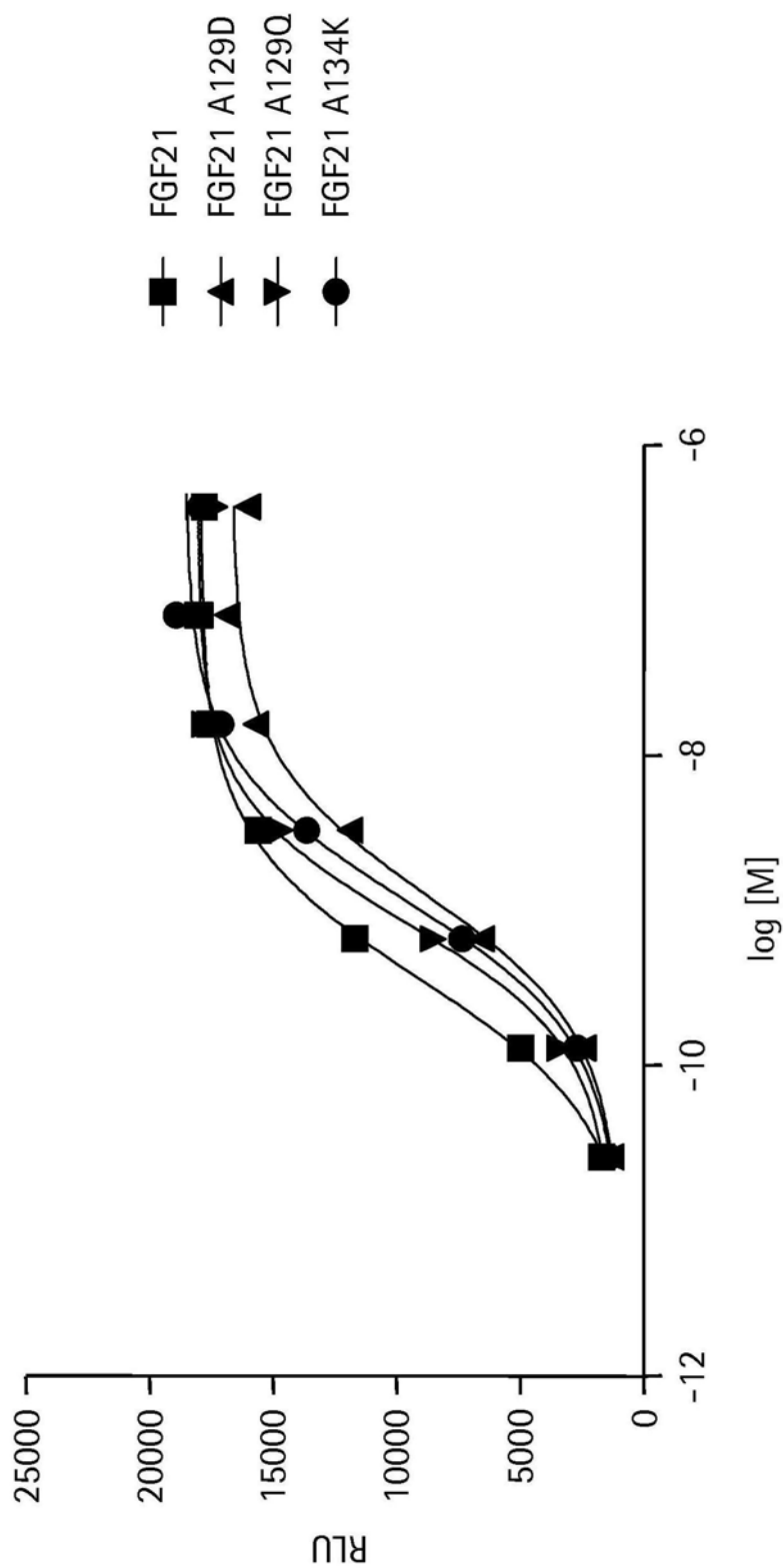


图24B

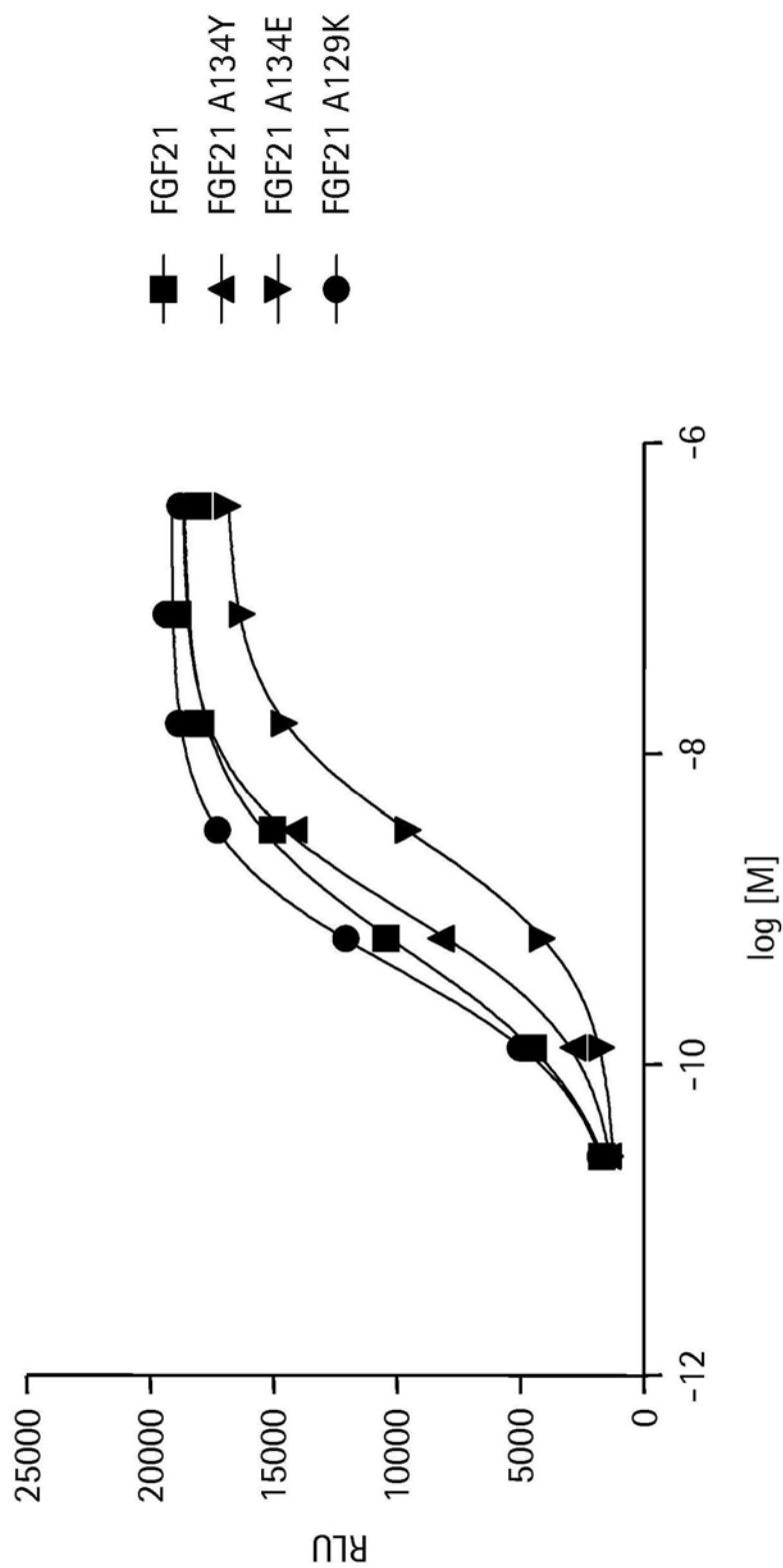


图24C

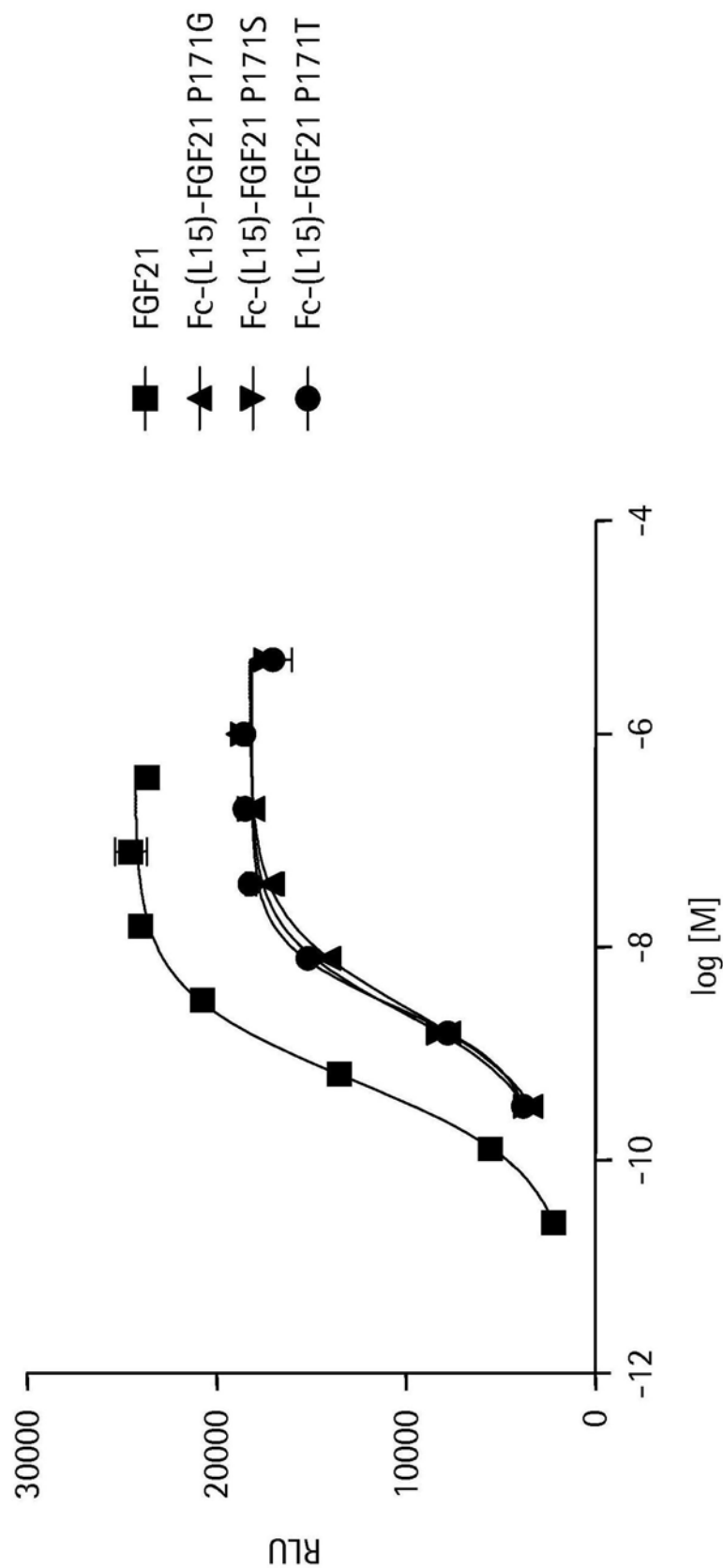


图25A

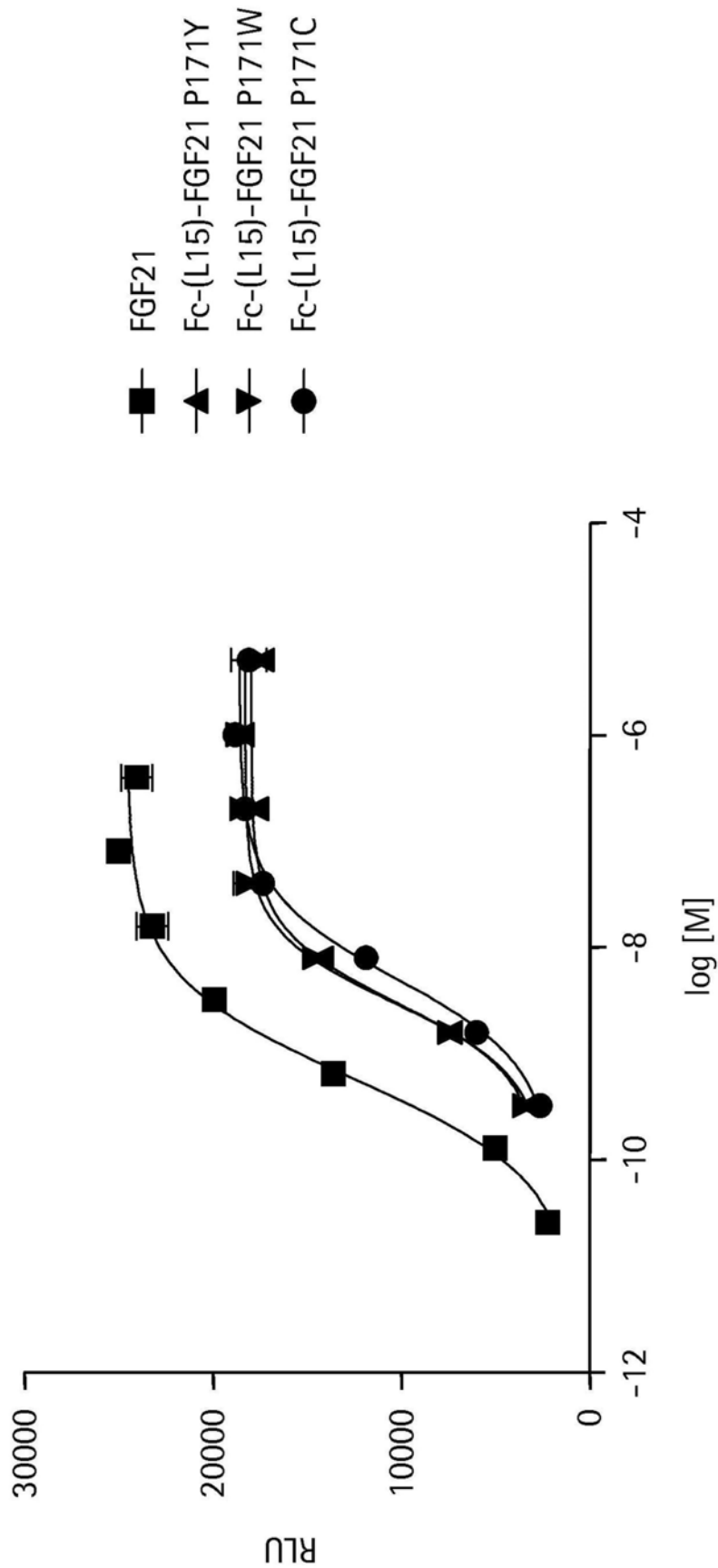


图25B

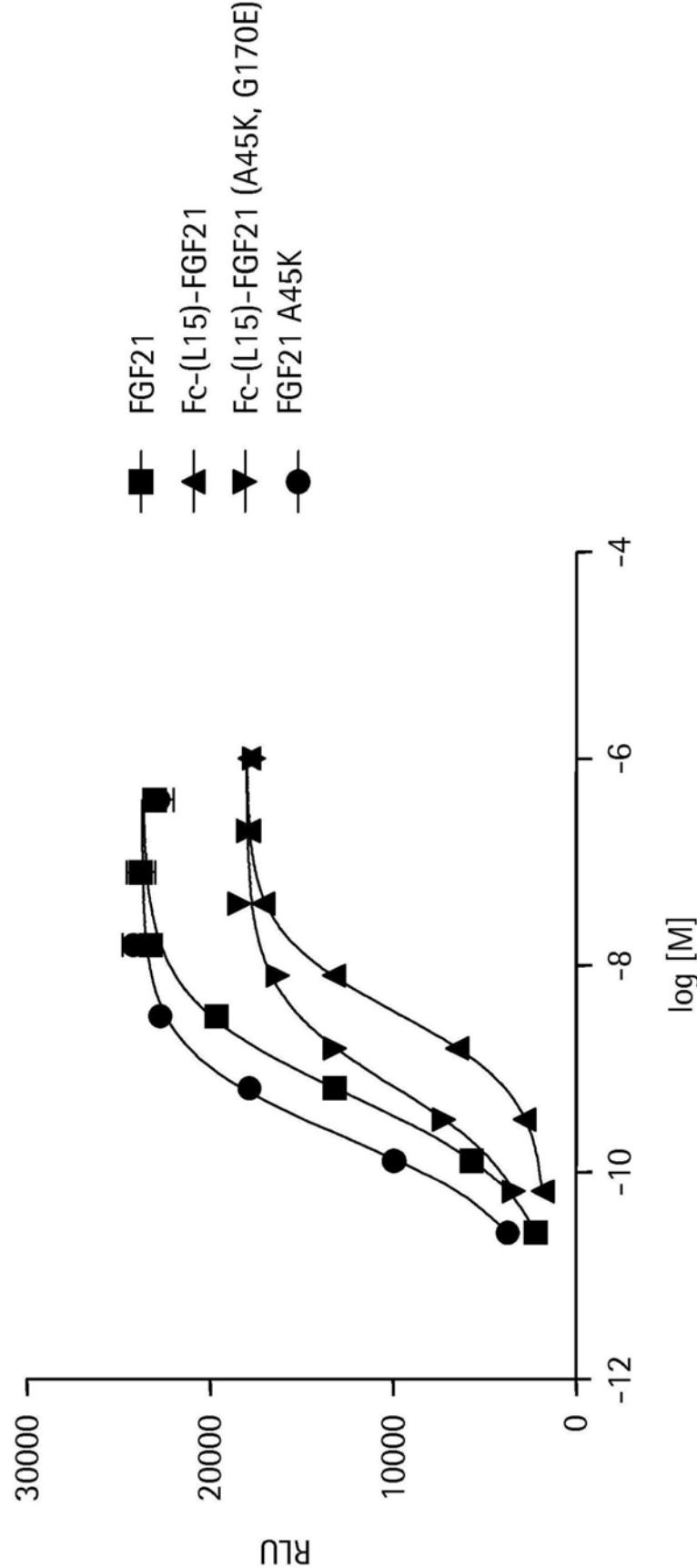


图25C

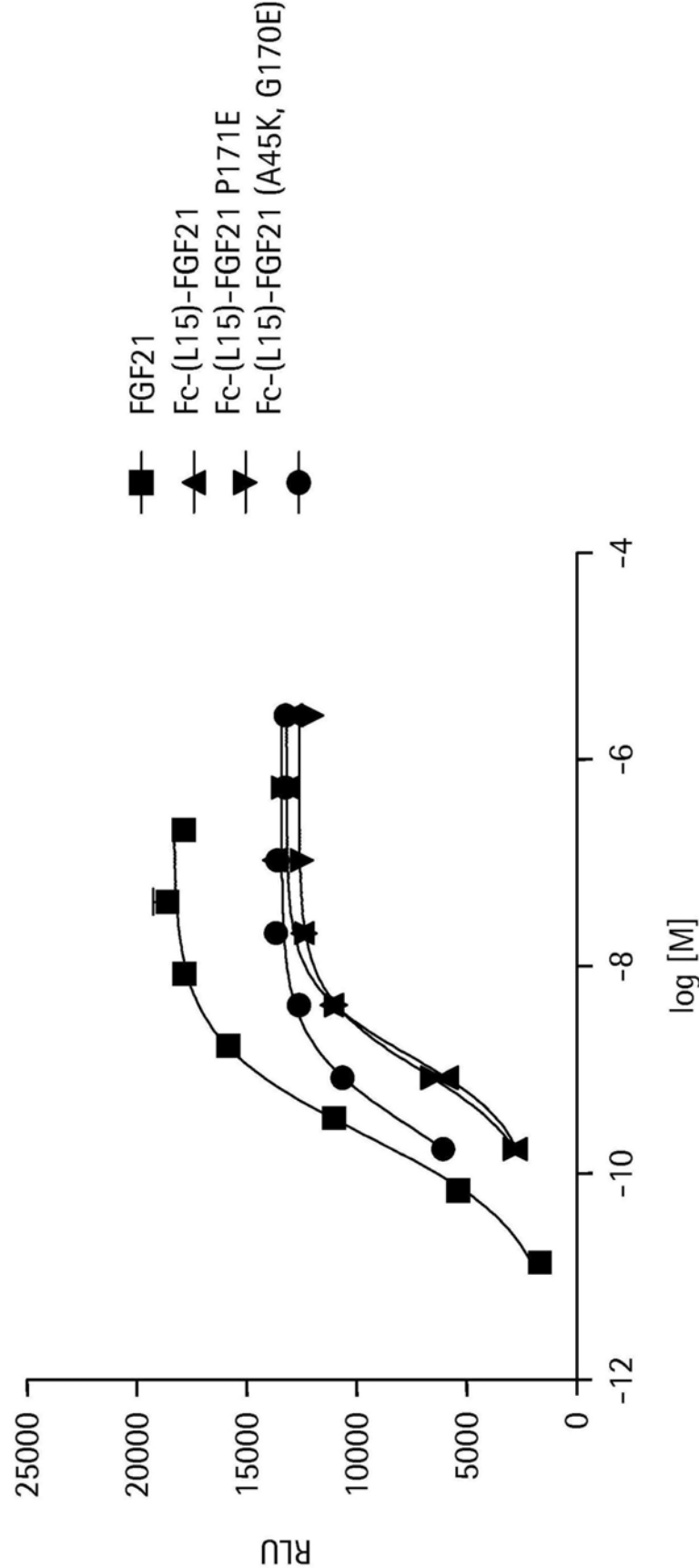


图25D

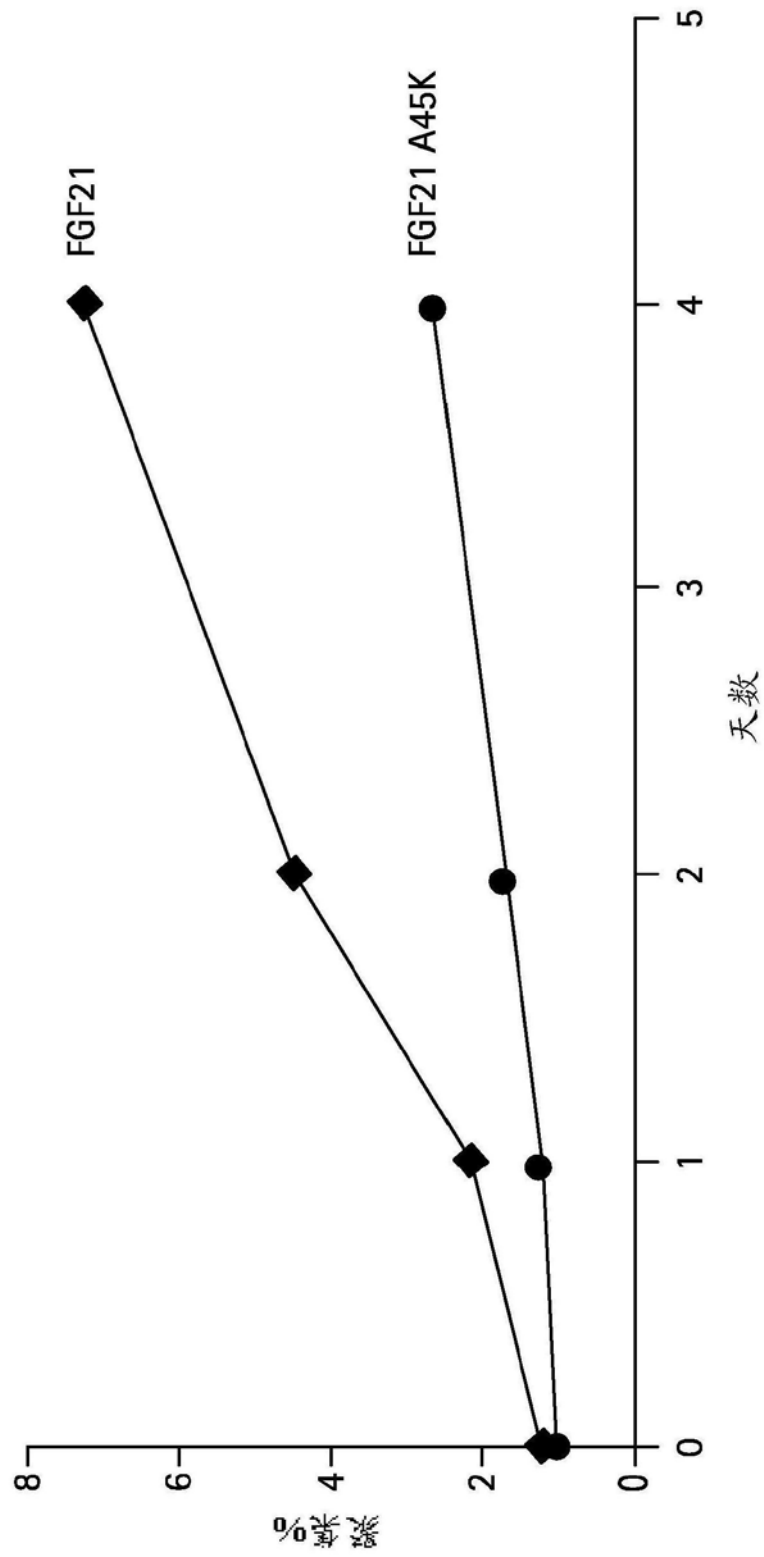


图26A

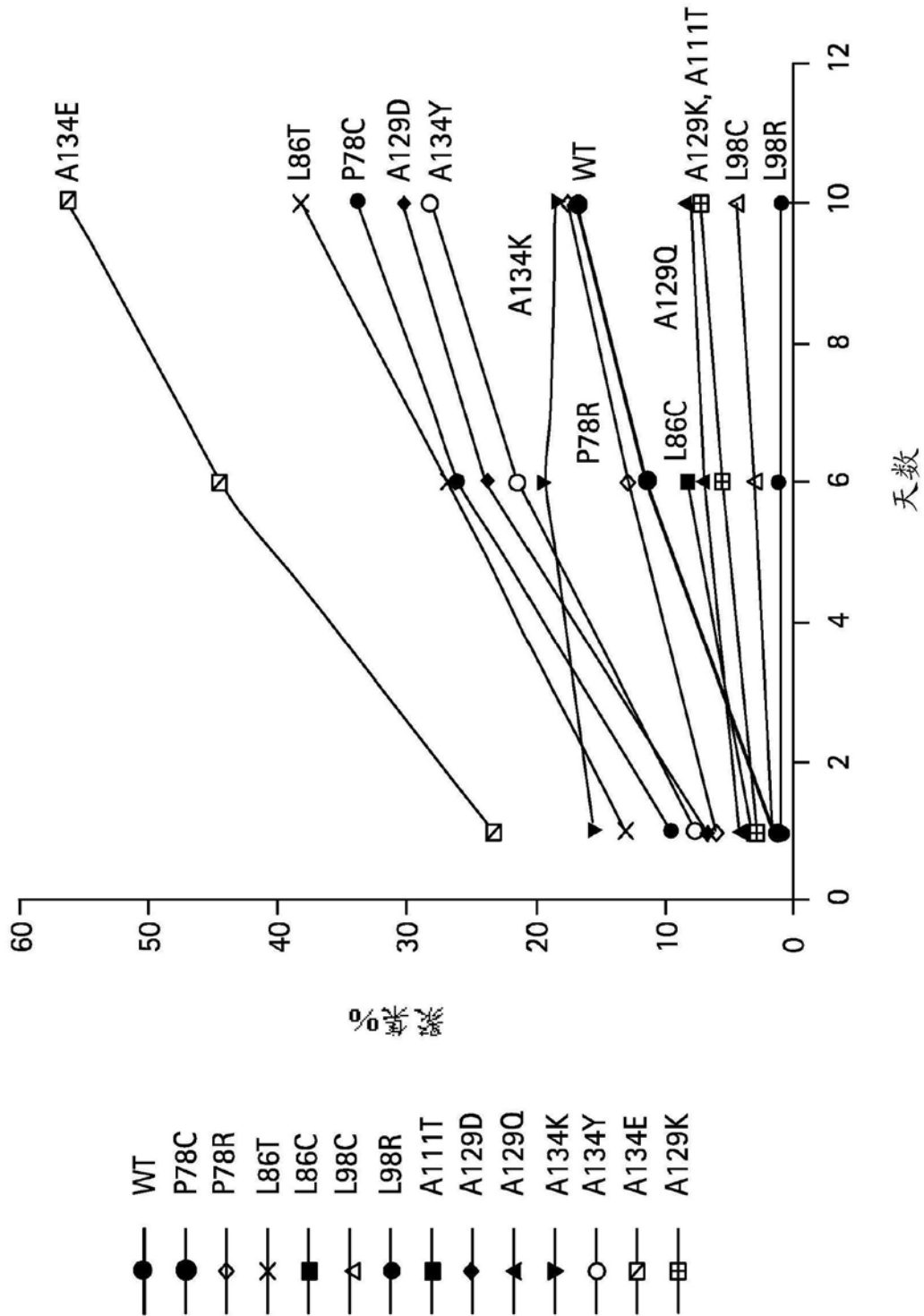


图26B

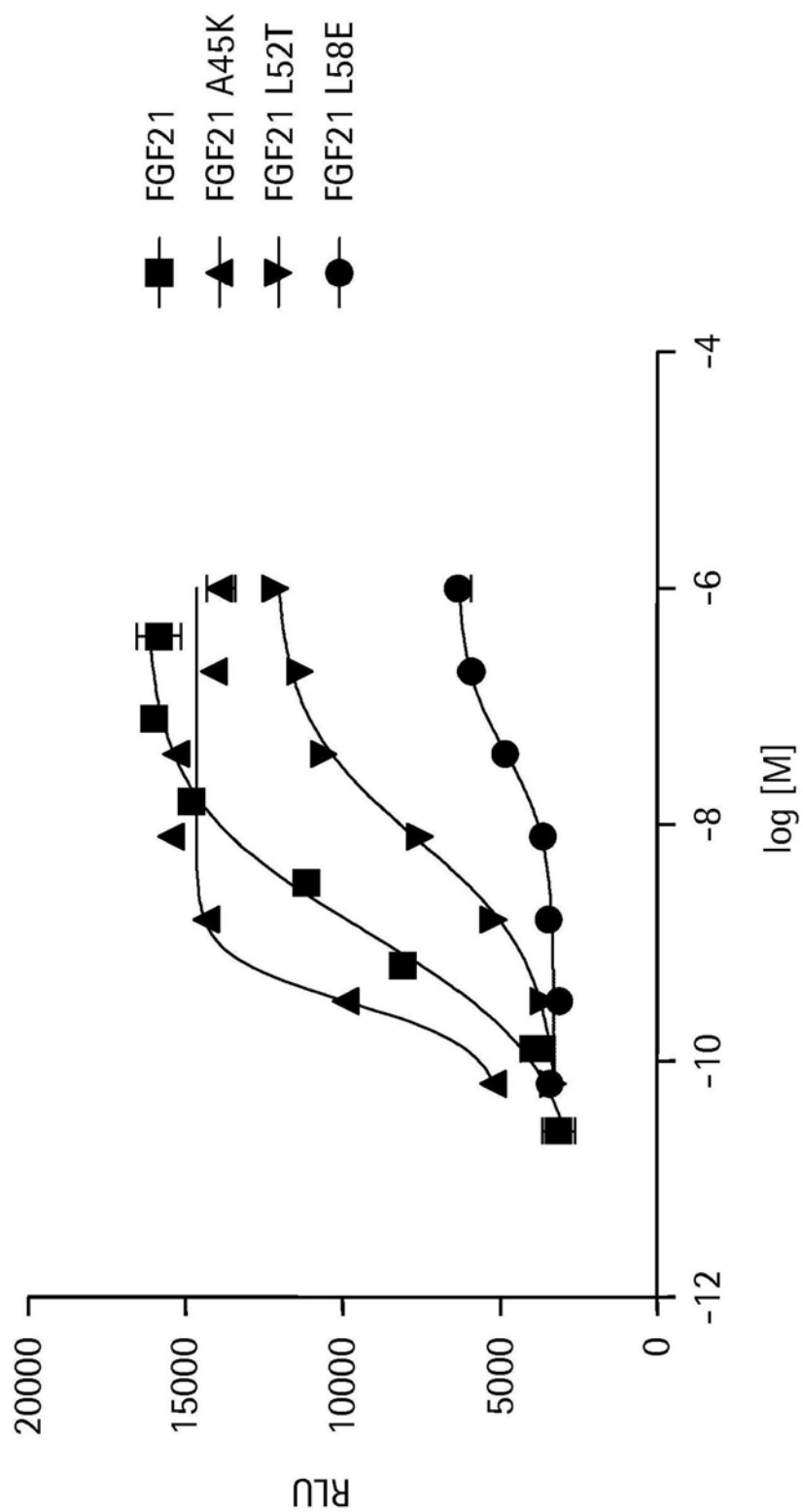


图27

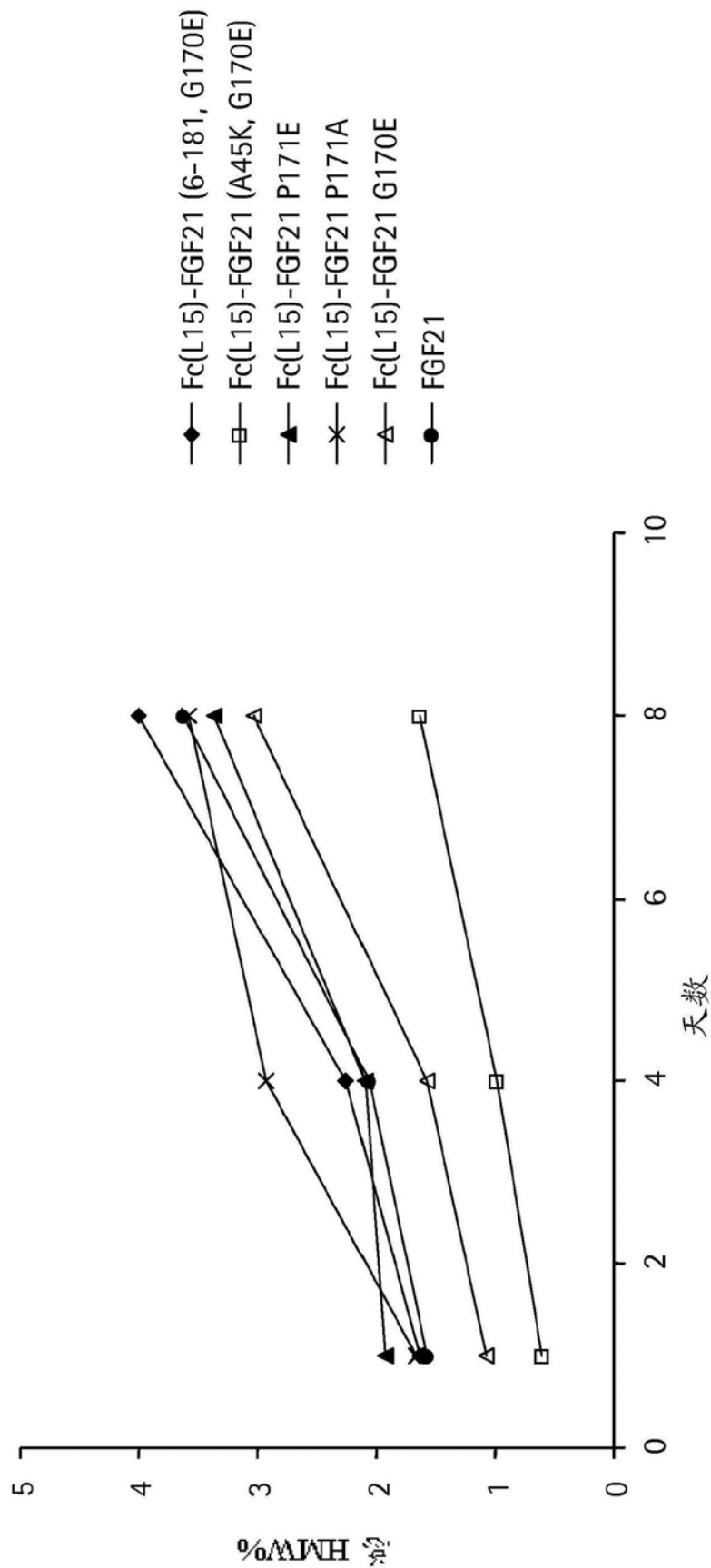


图28A

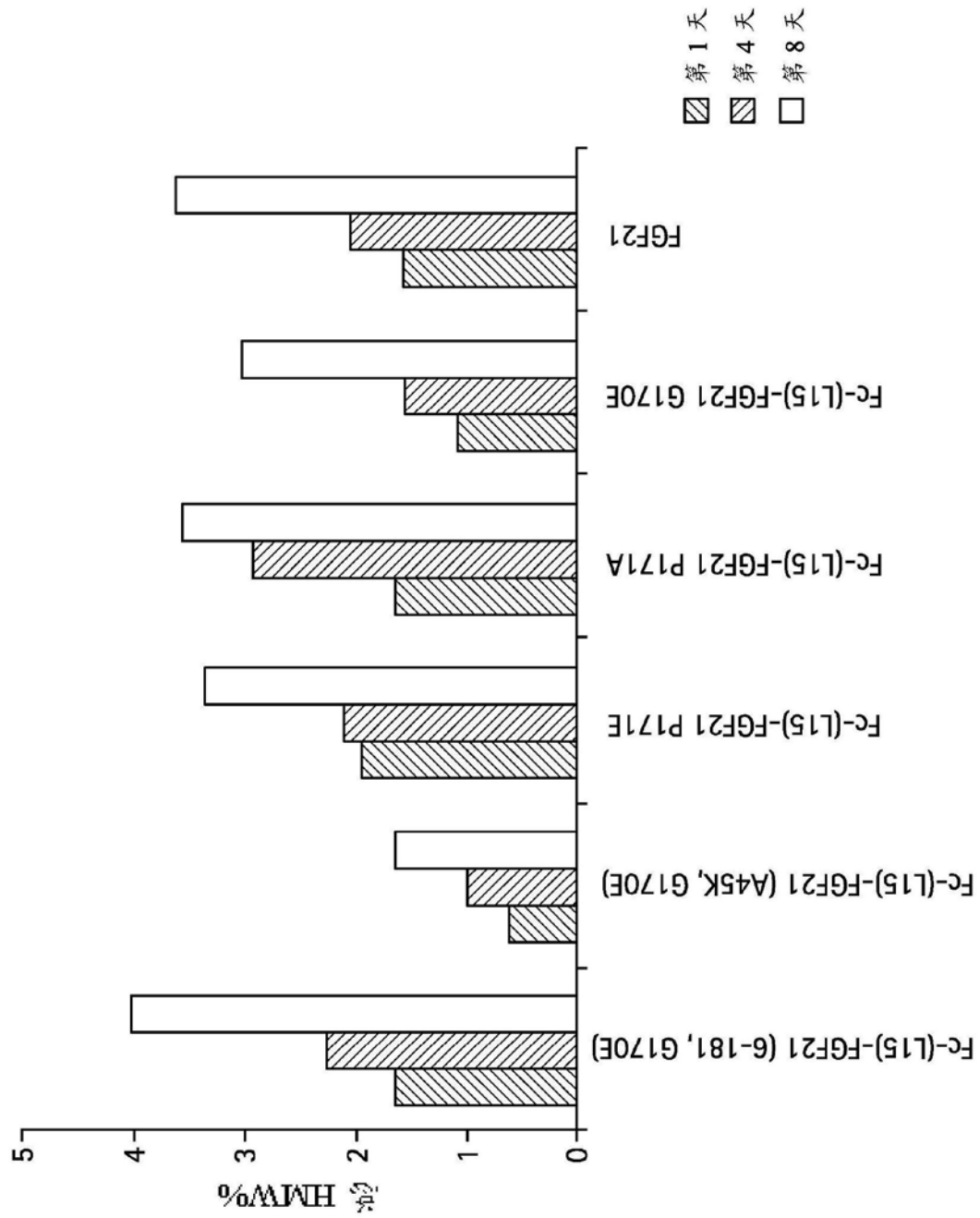


图28B

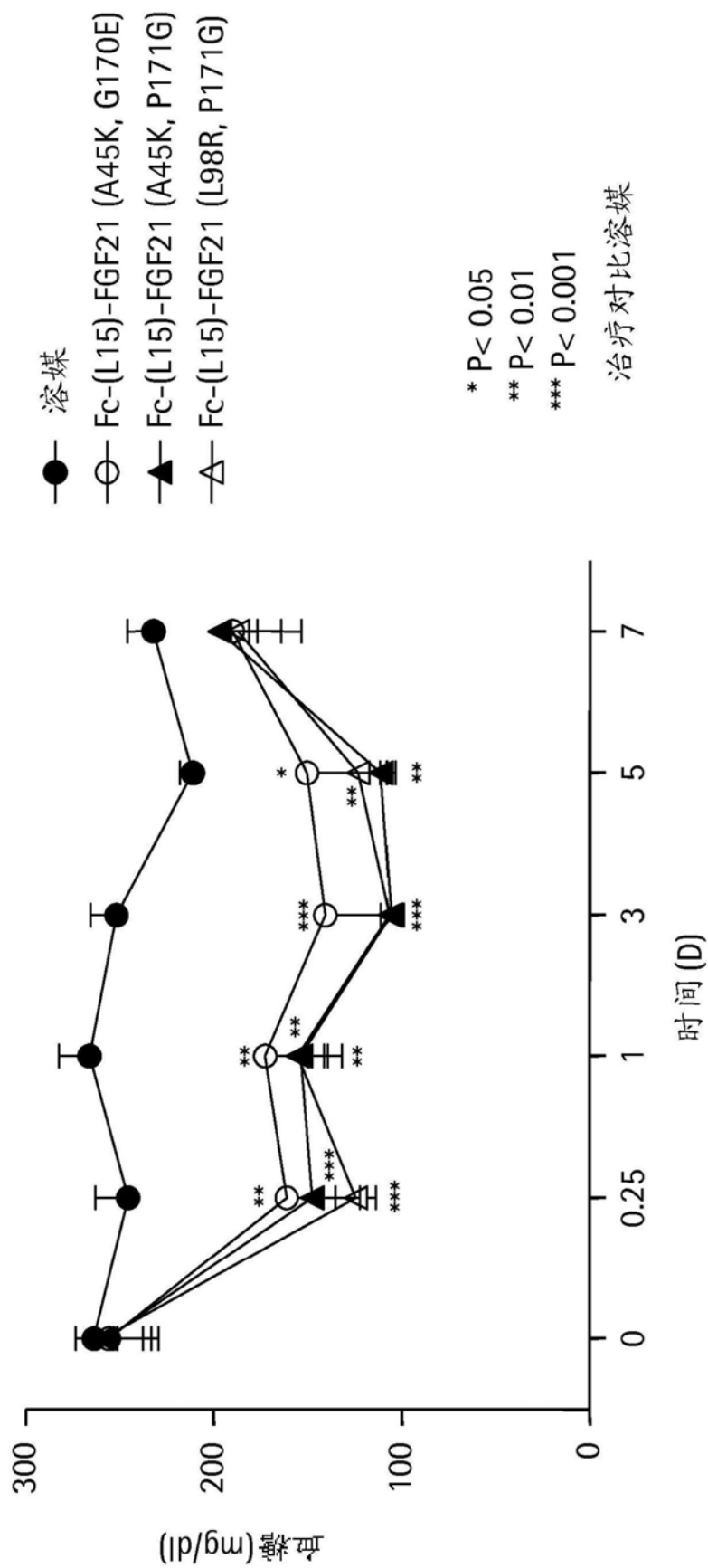


图29

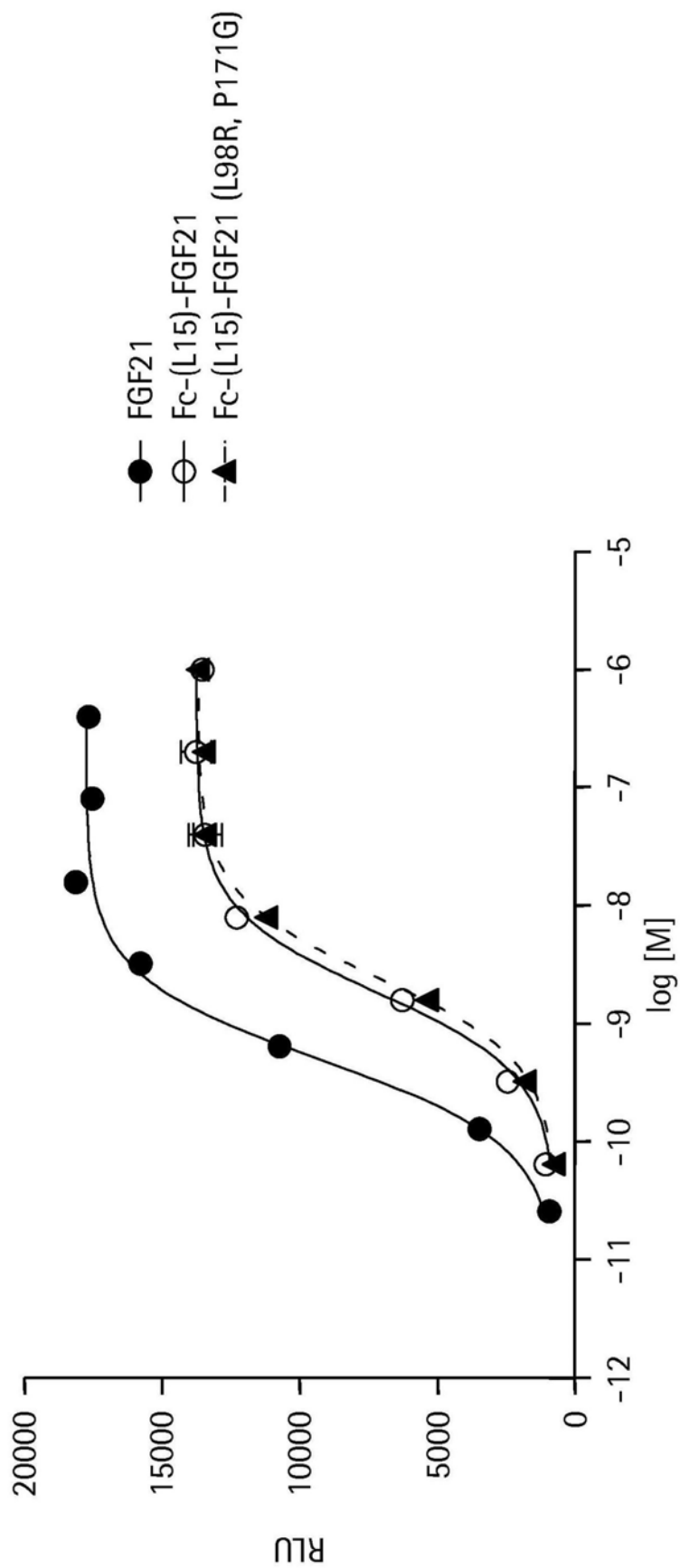


图30

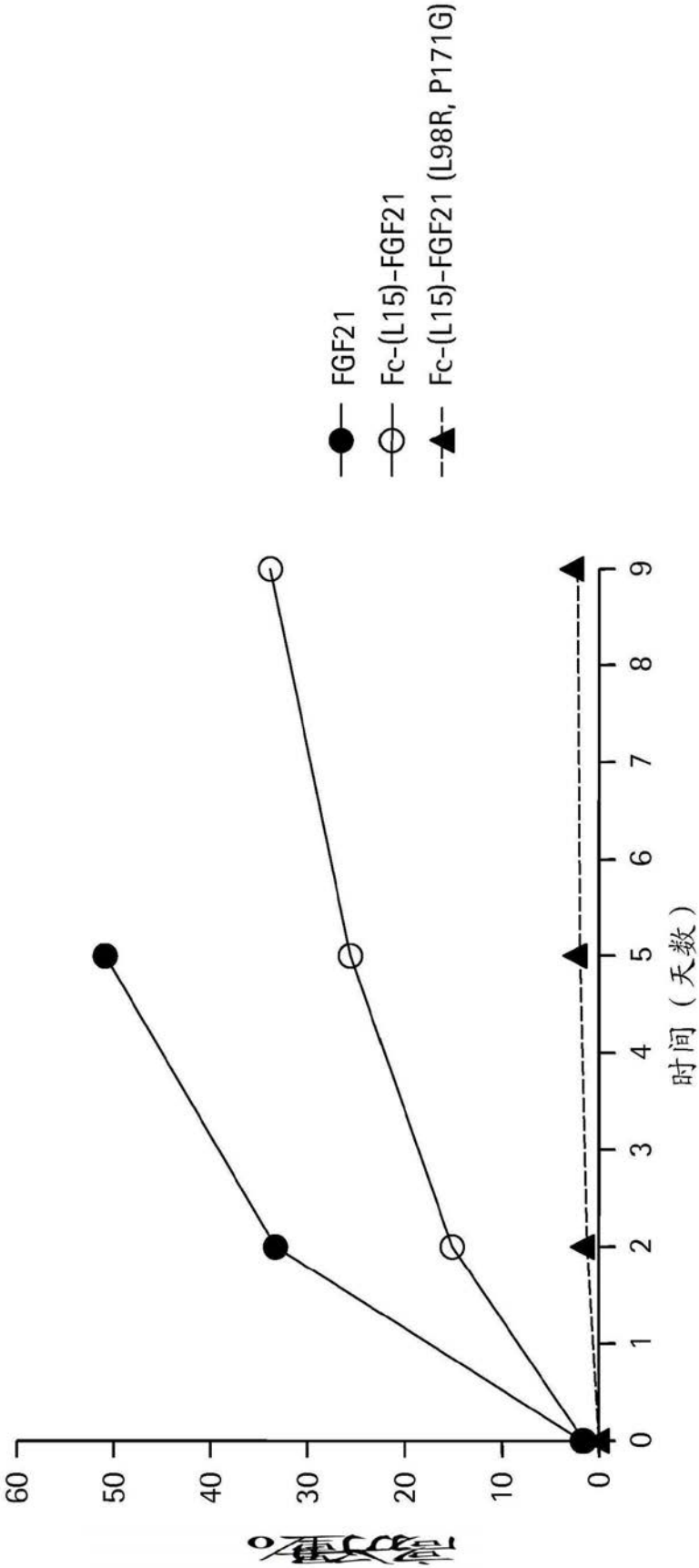


图31A

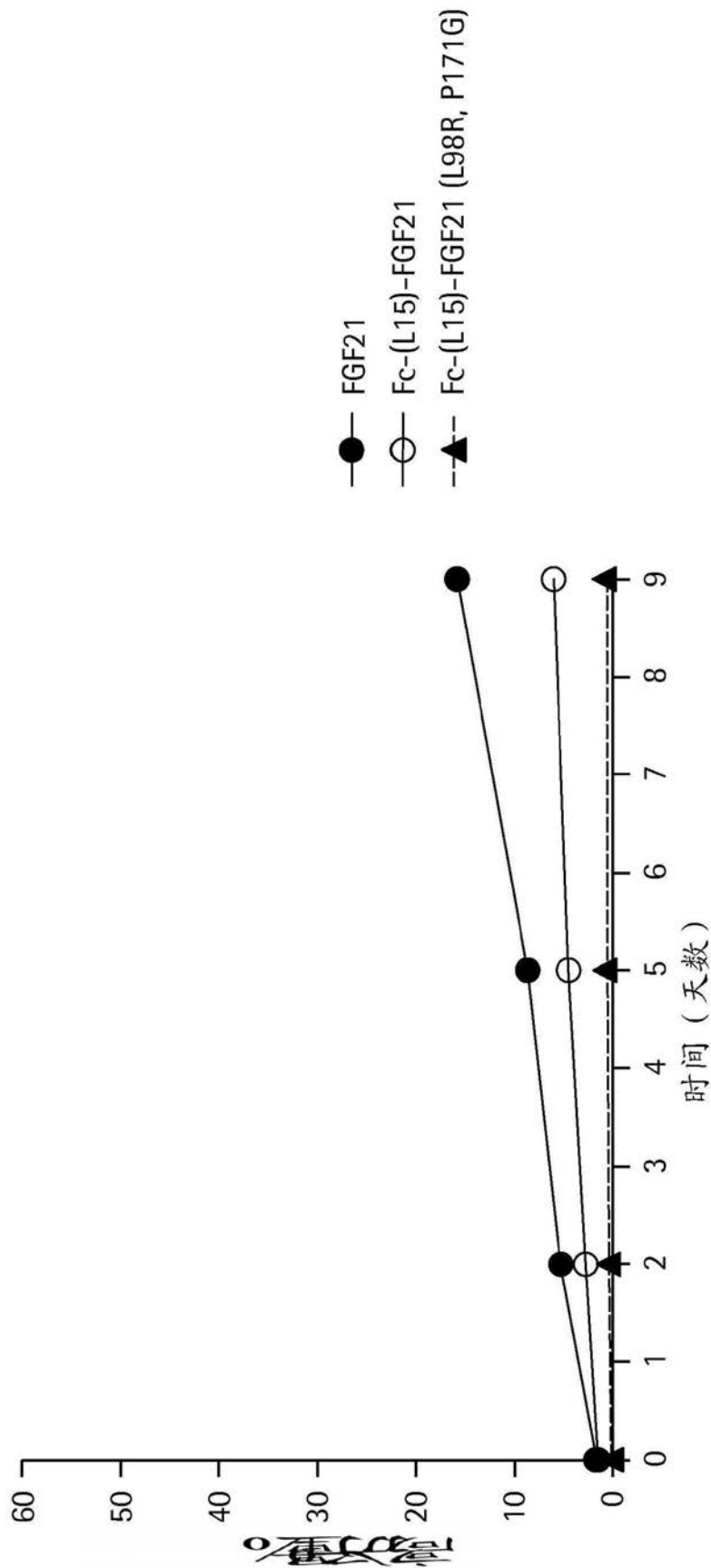


图31B

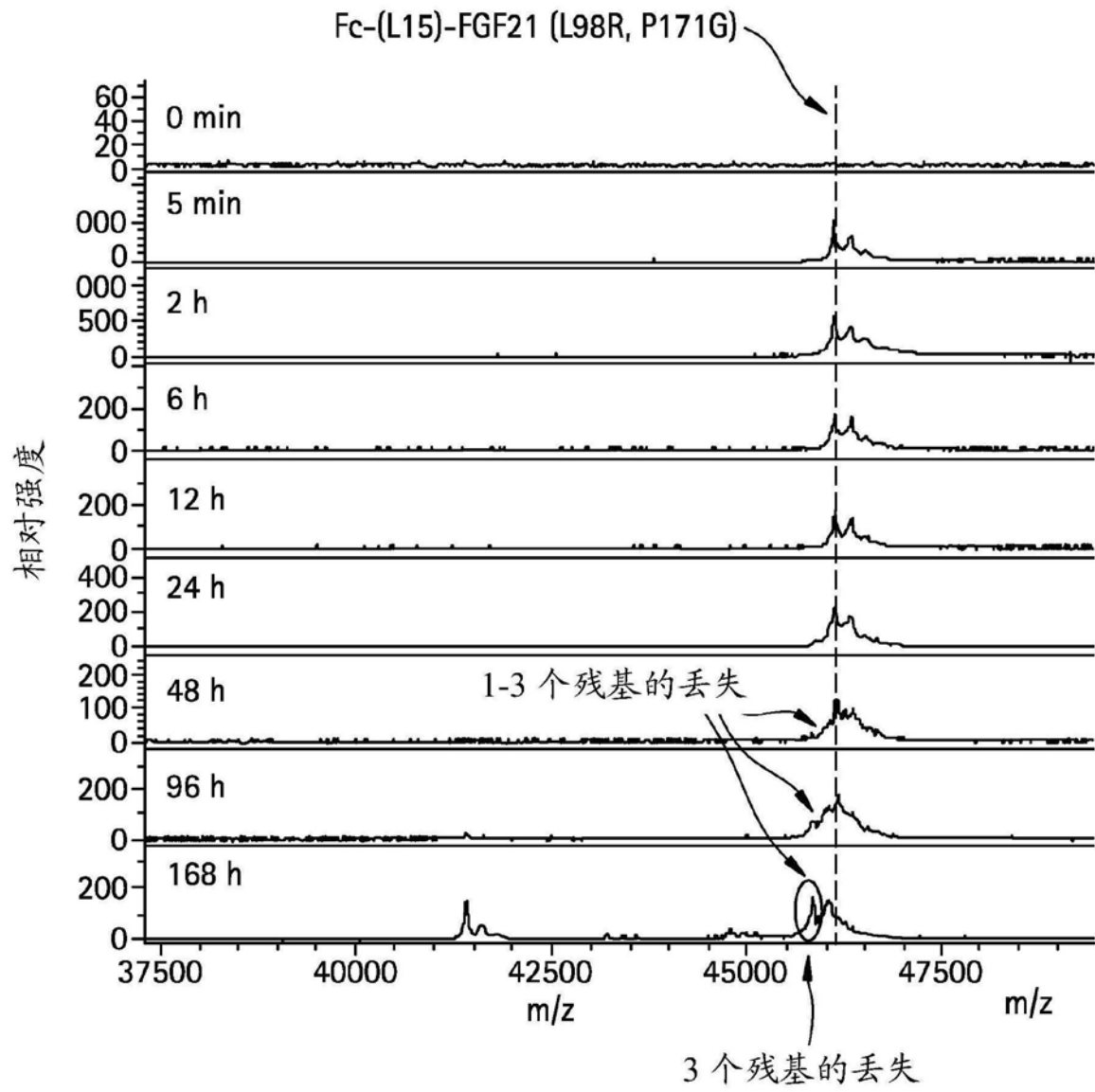


图32

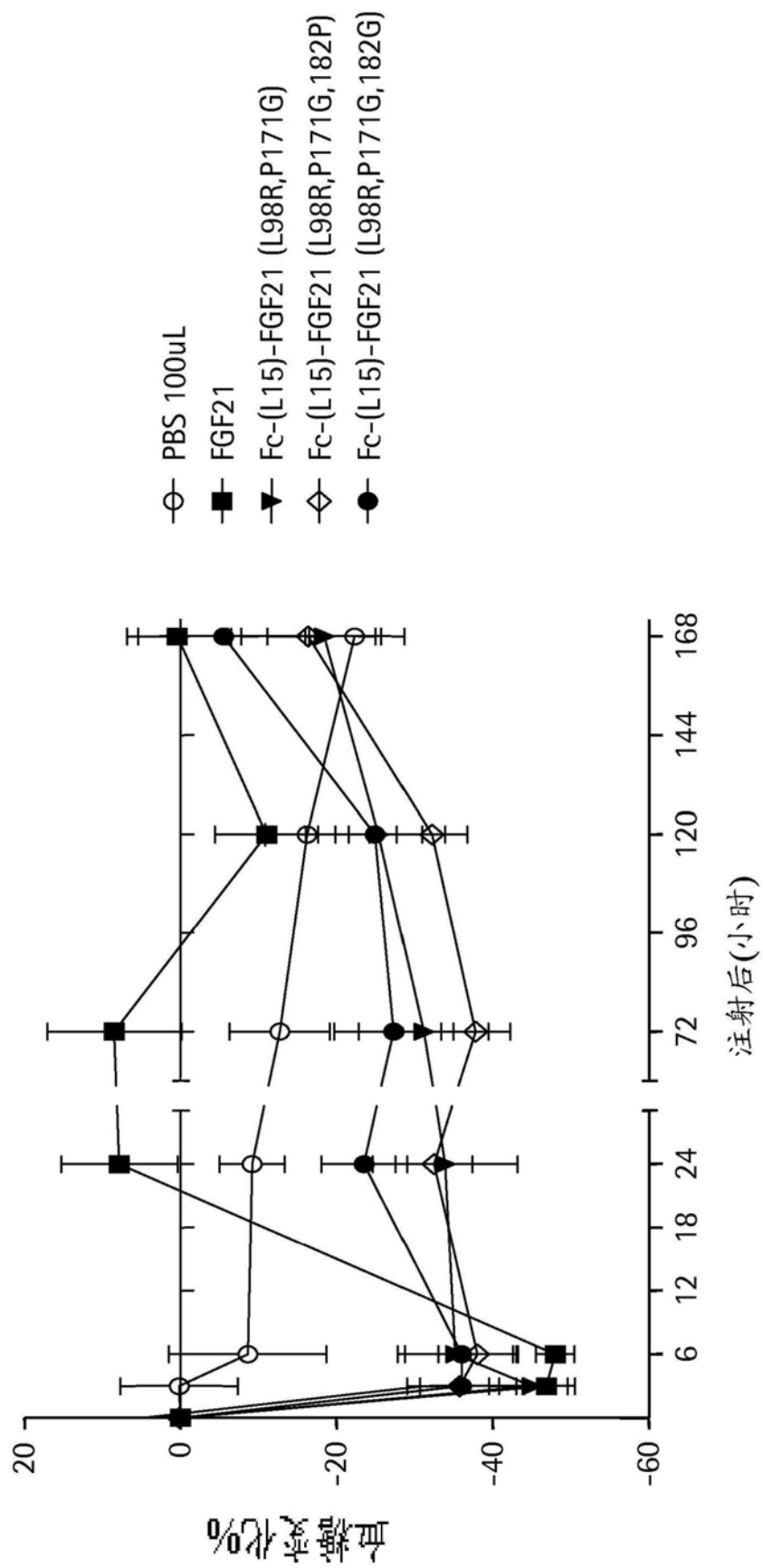


图33

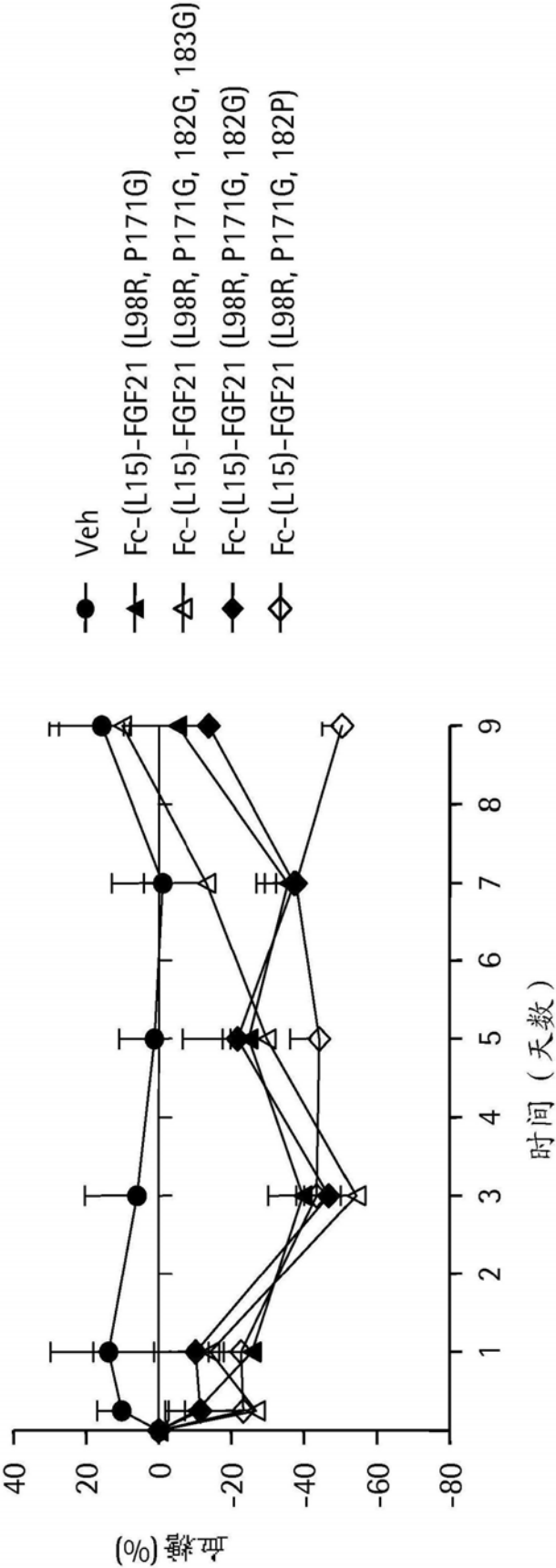


图34

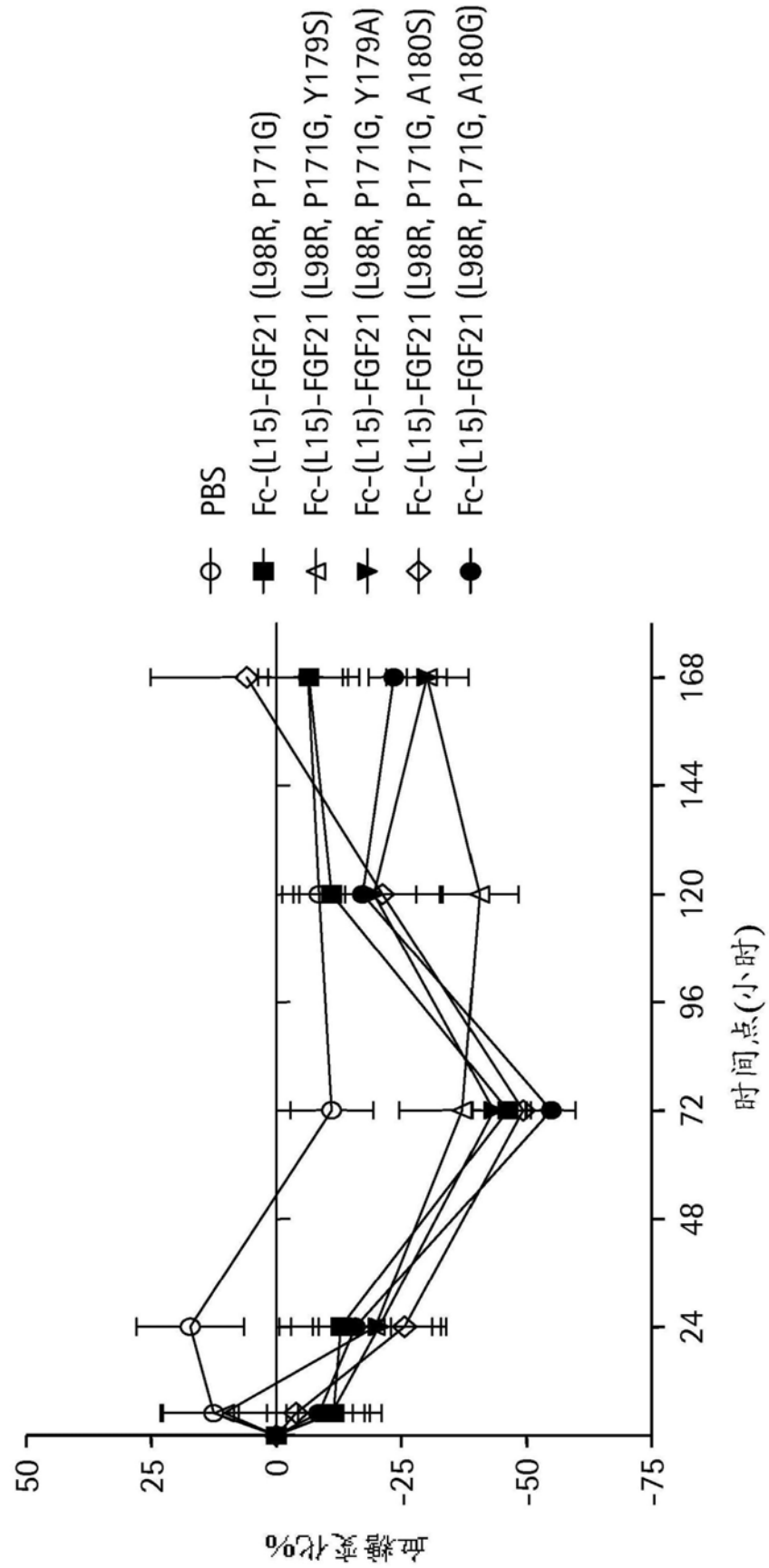


图35

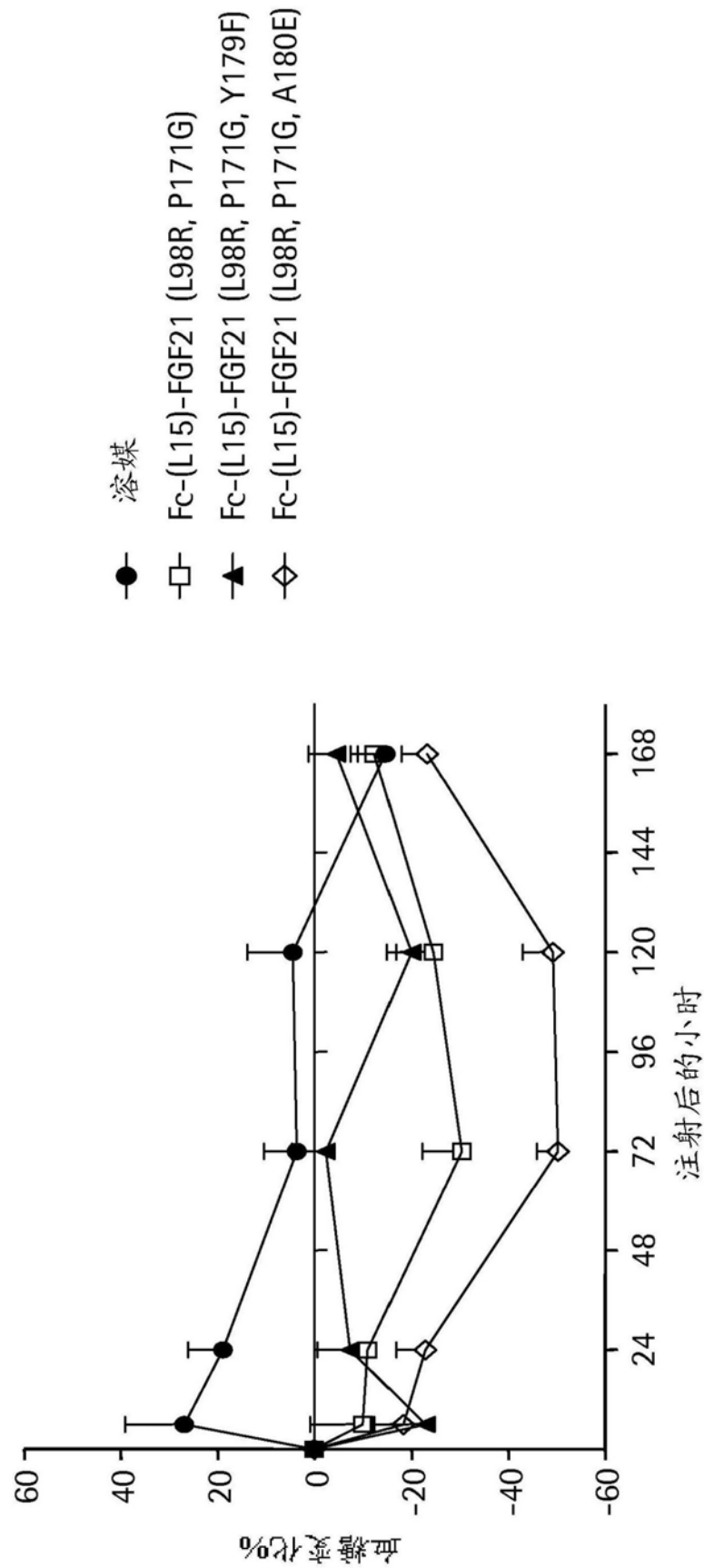


图36

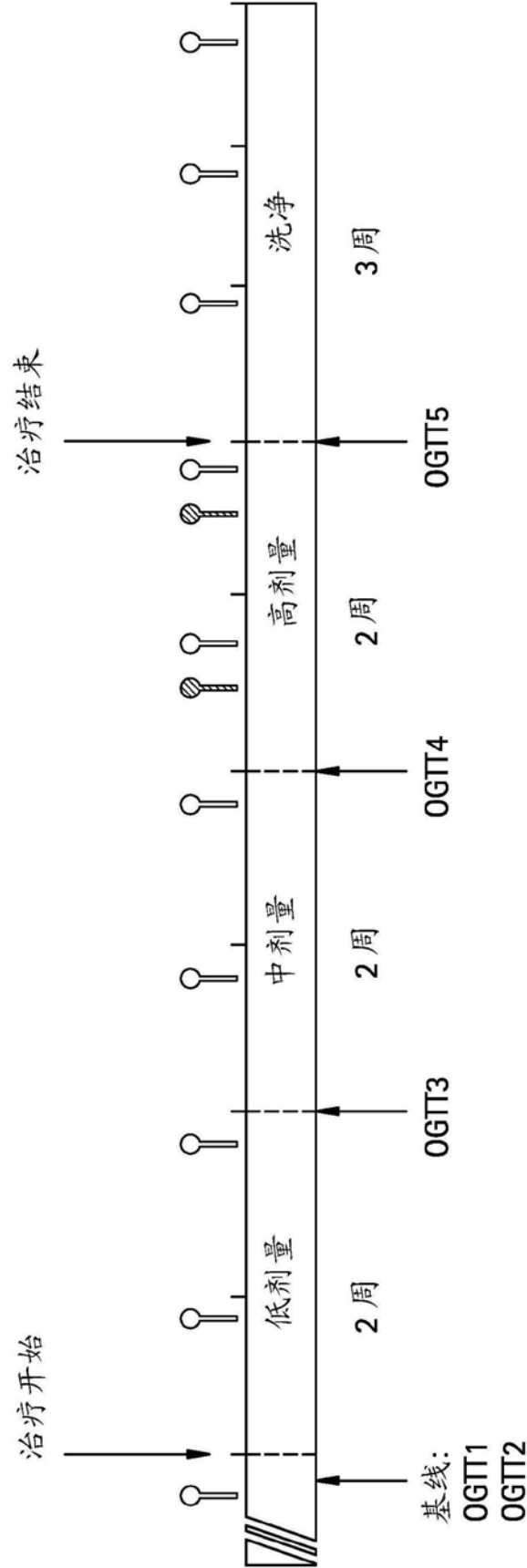


图37

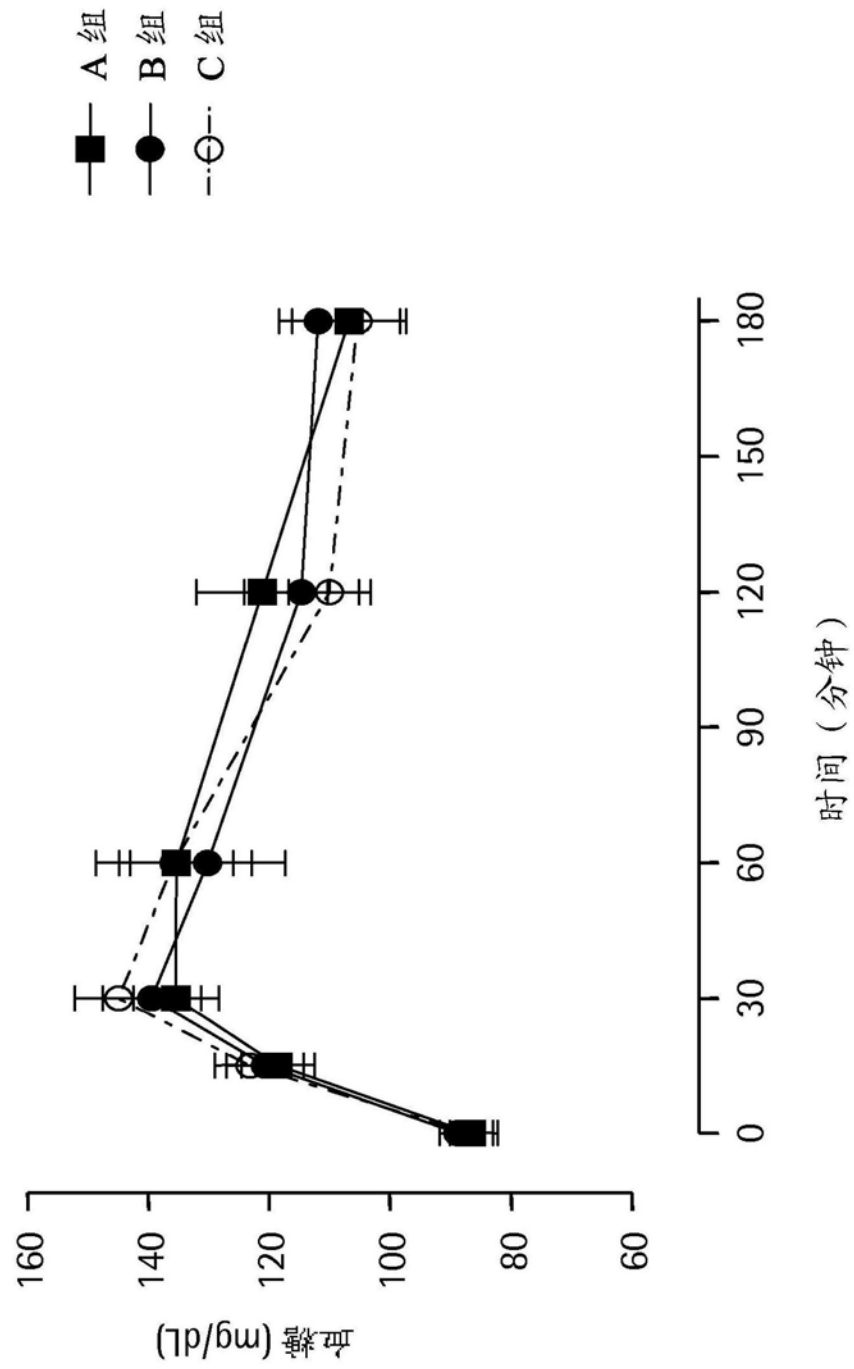


图38A

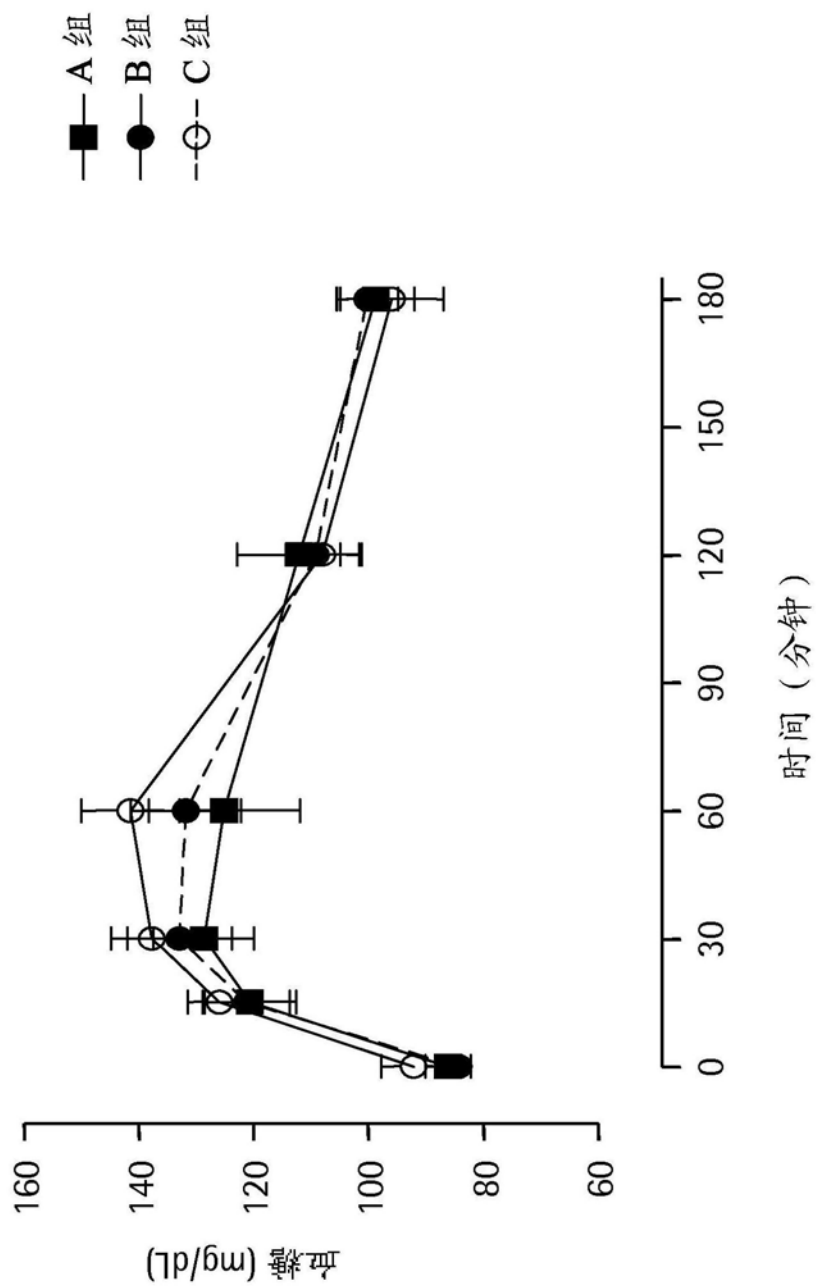


图38B

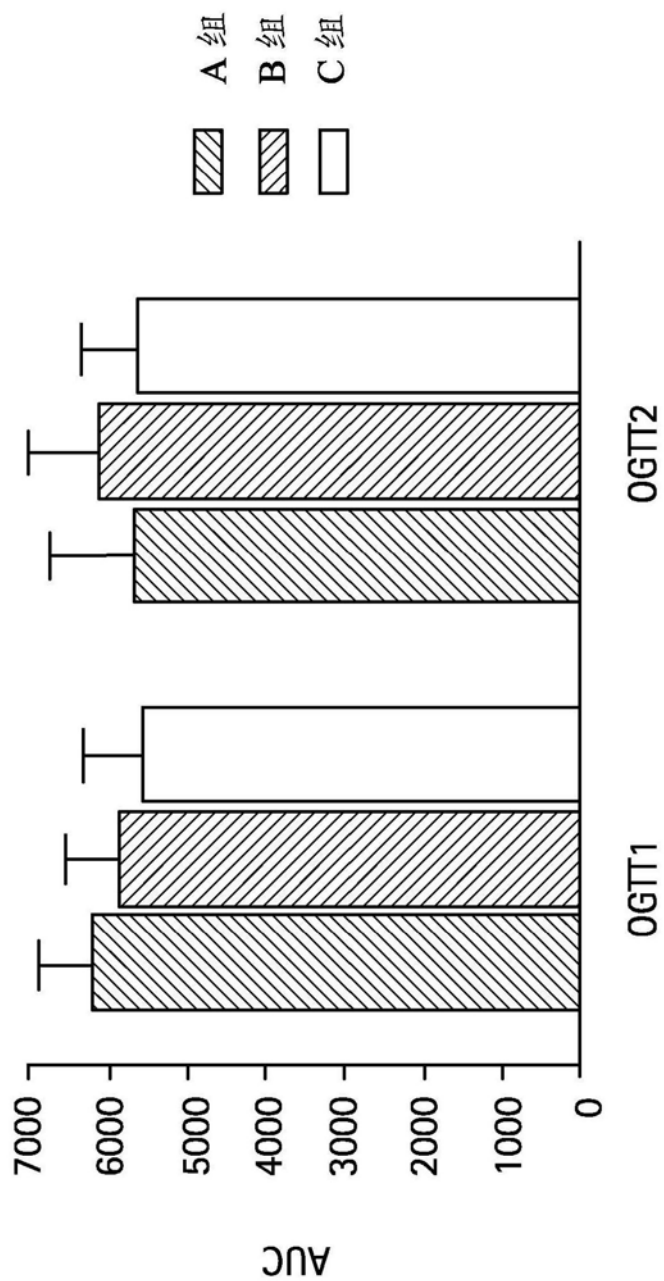


图38C

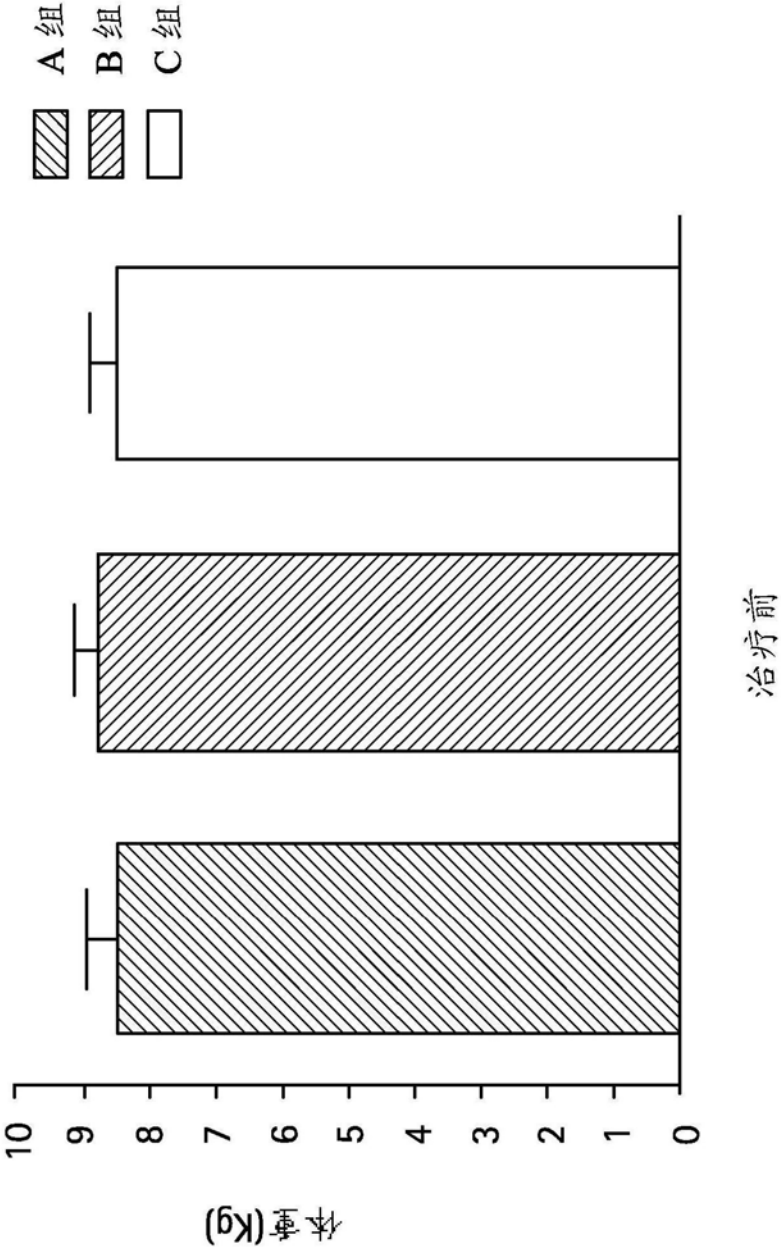


图38D

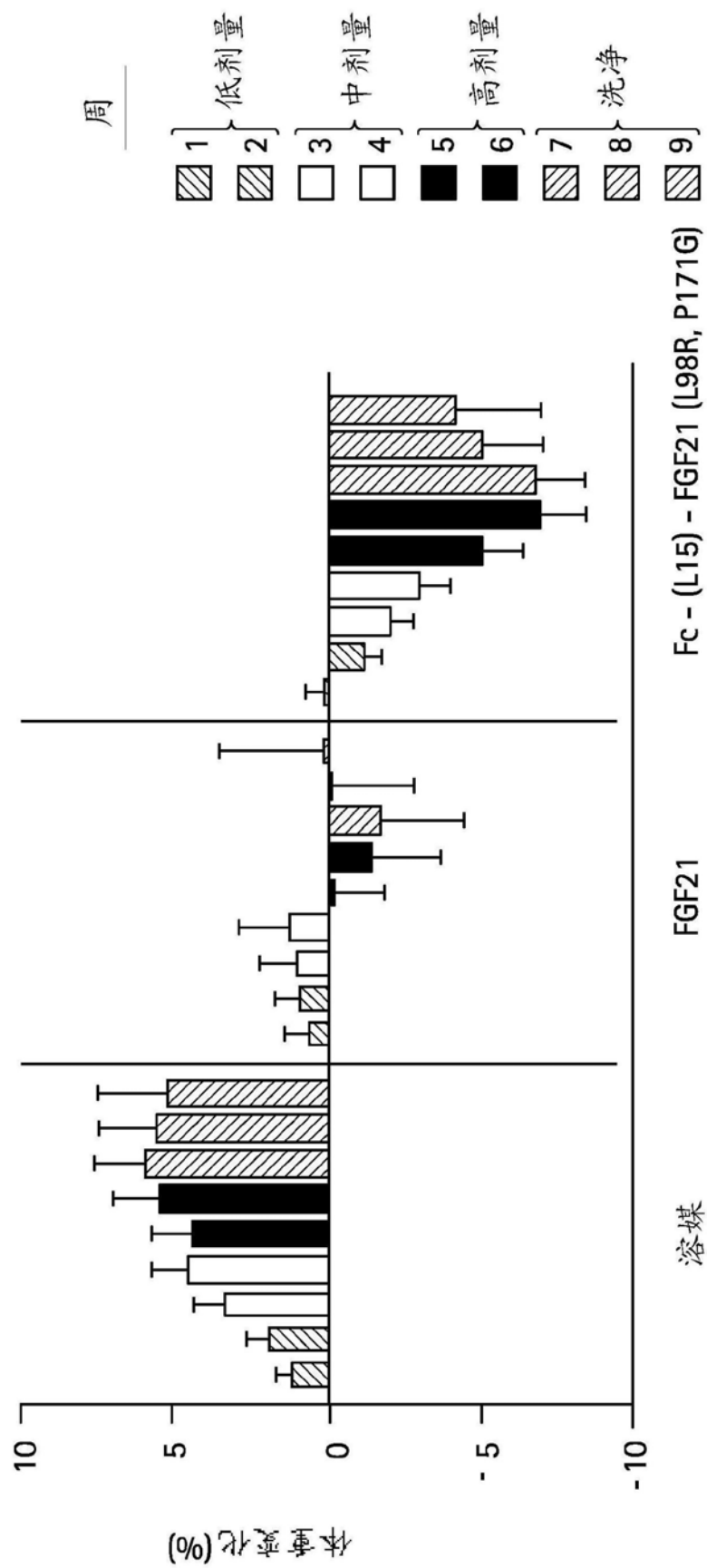


图39

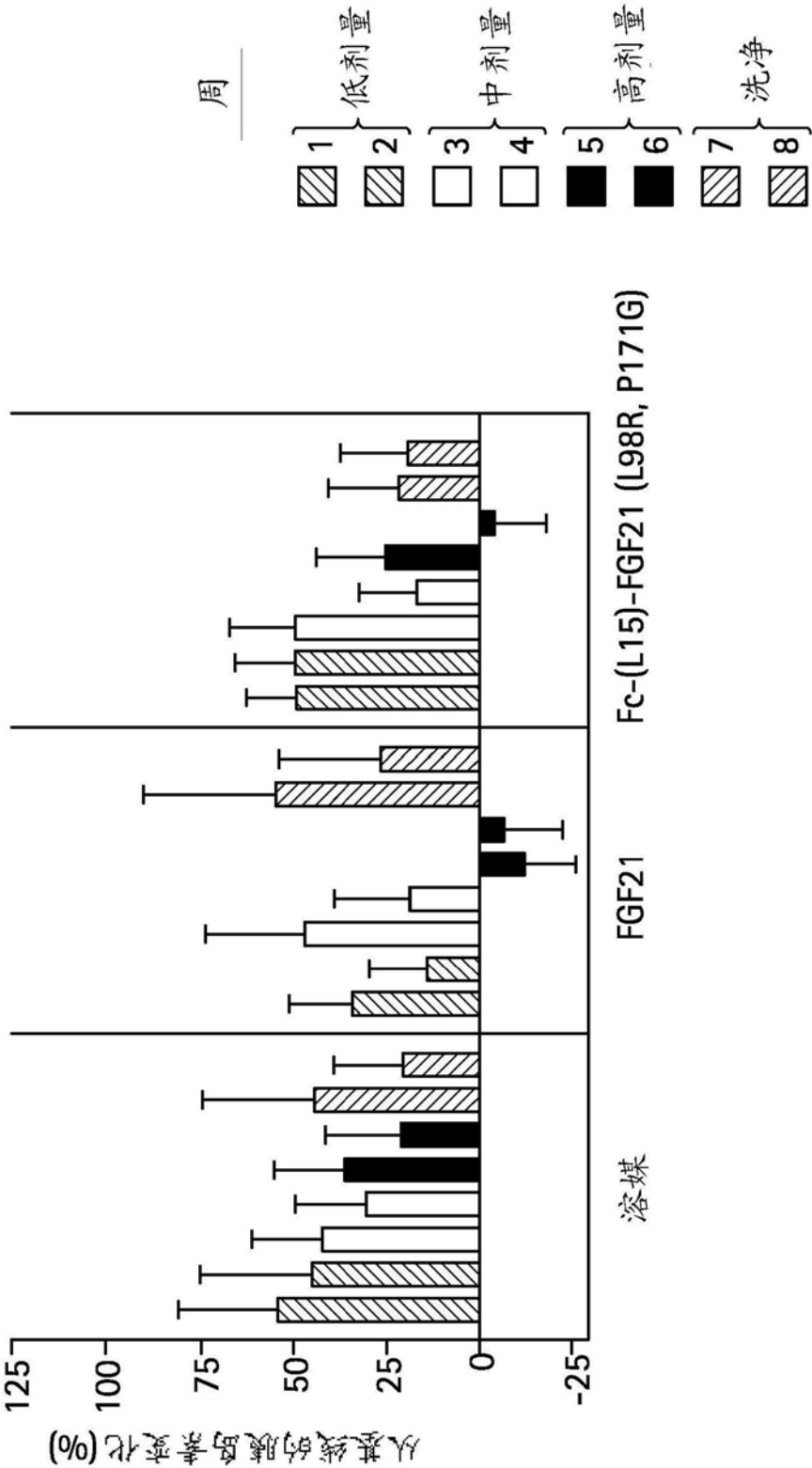


图40

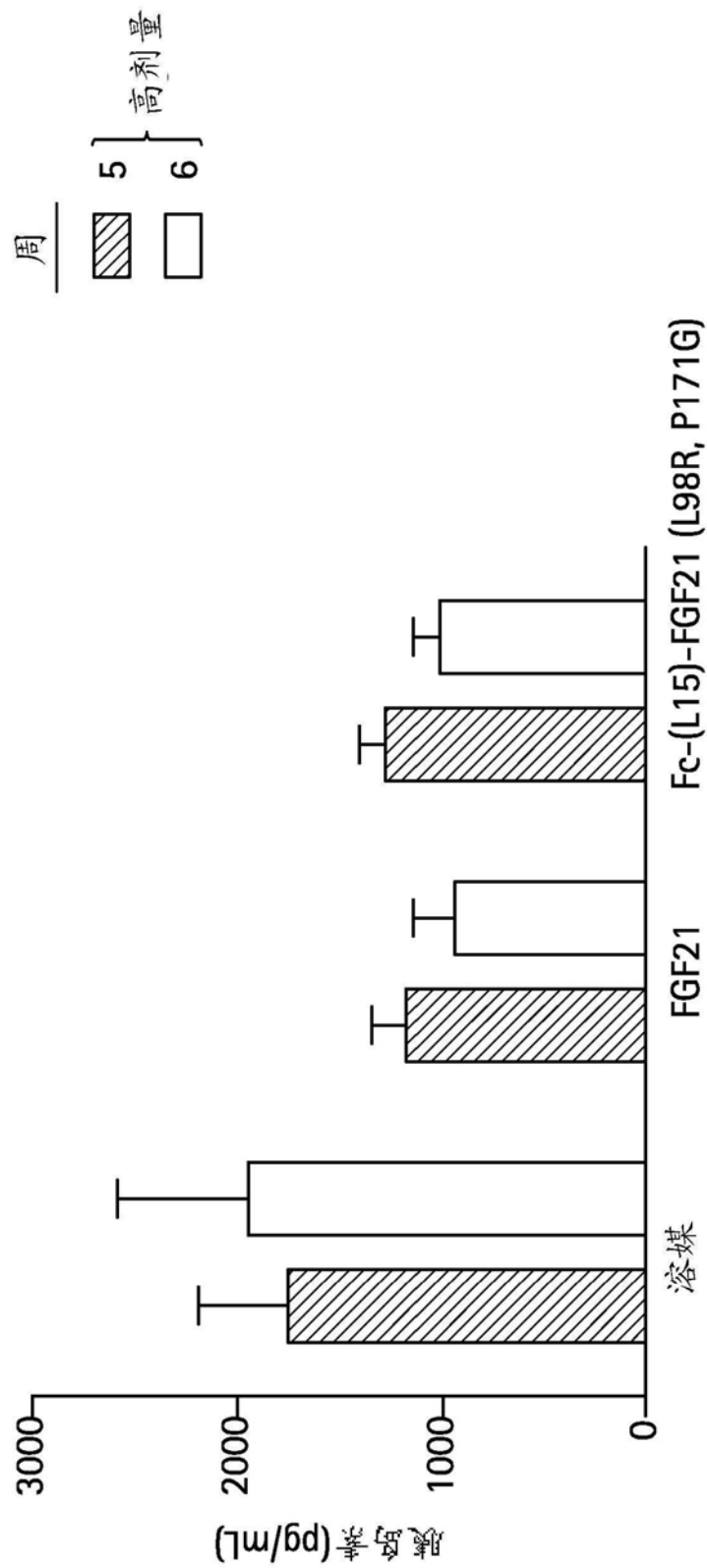


图41

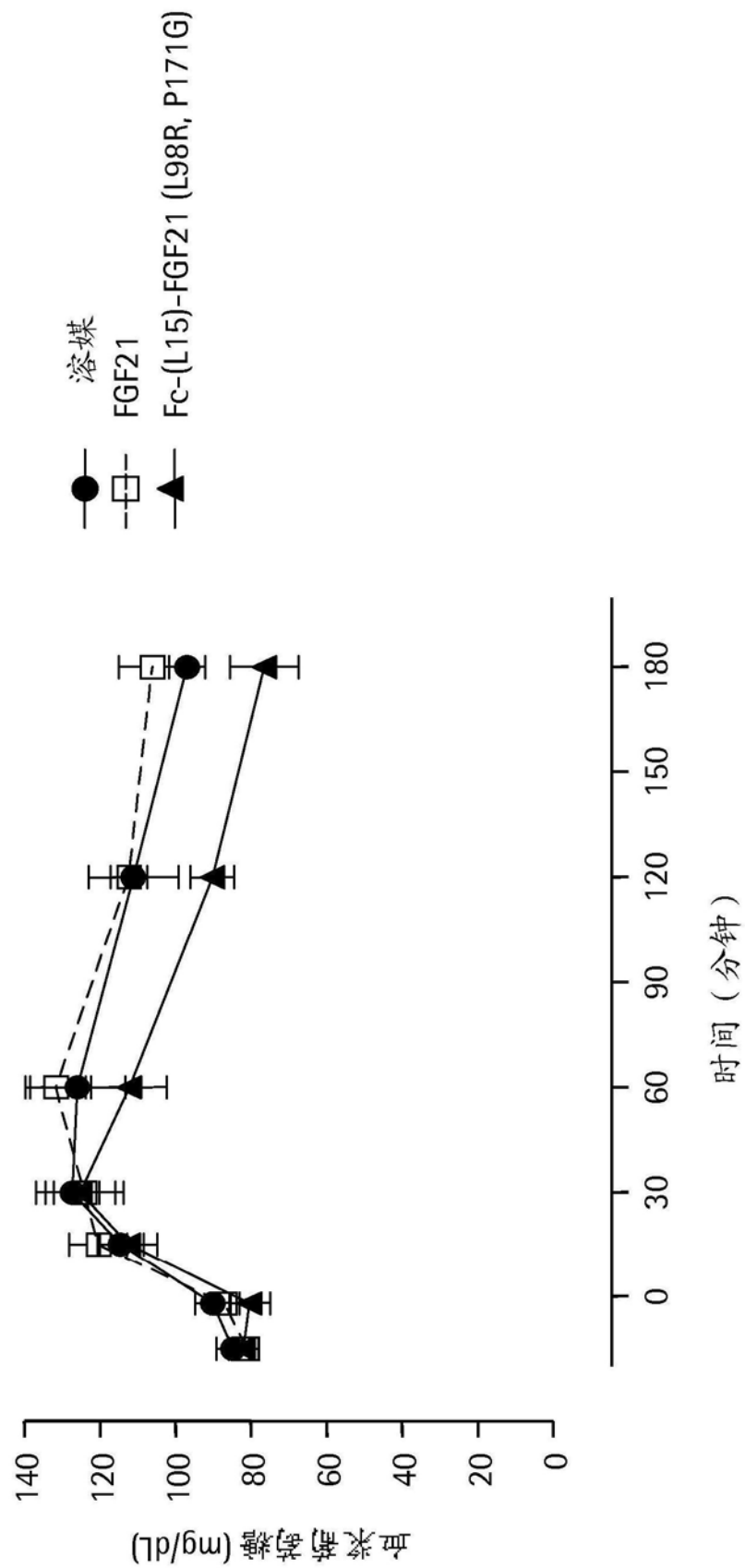


图42

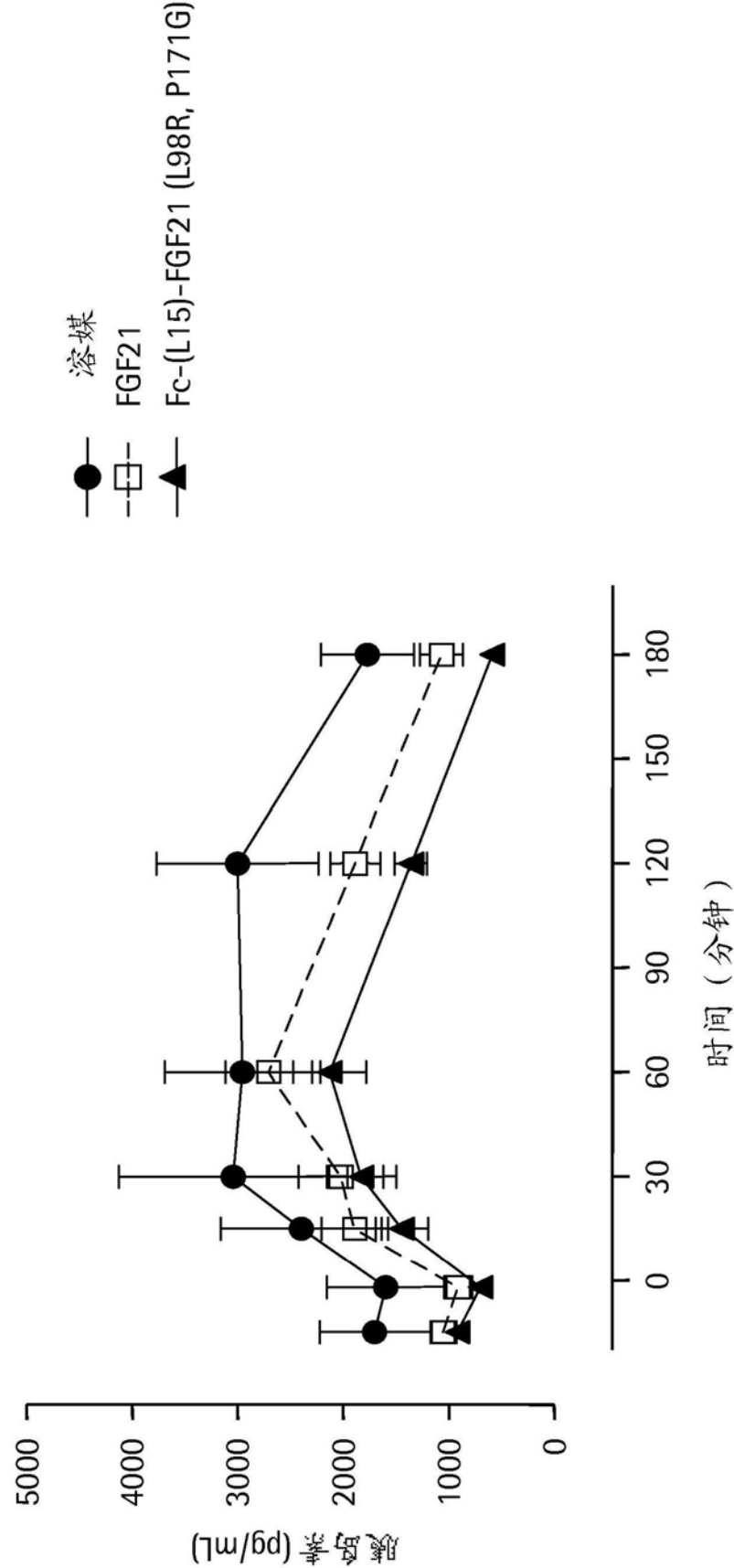


图43

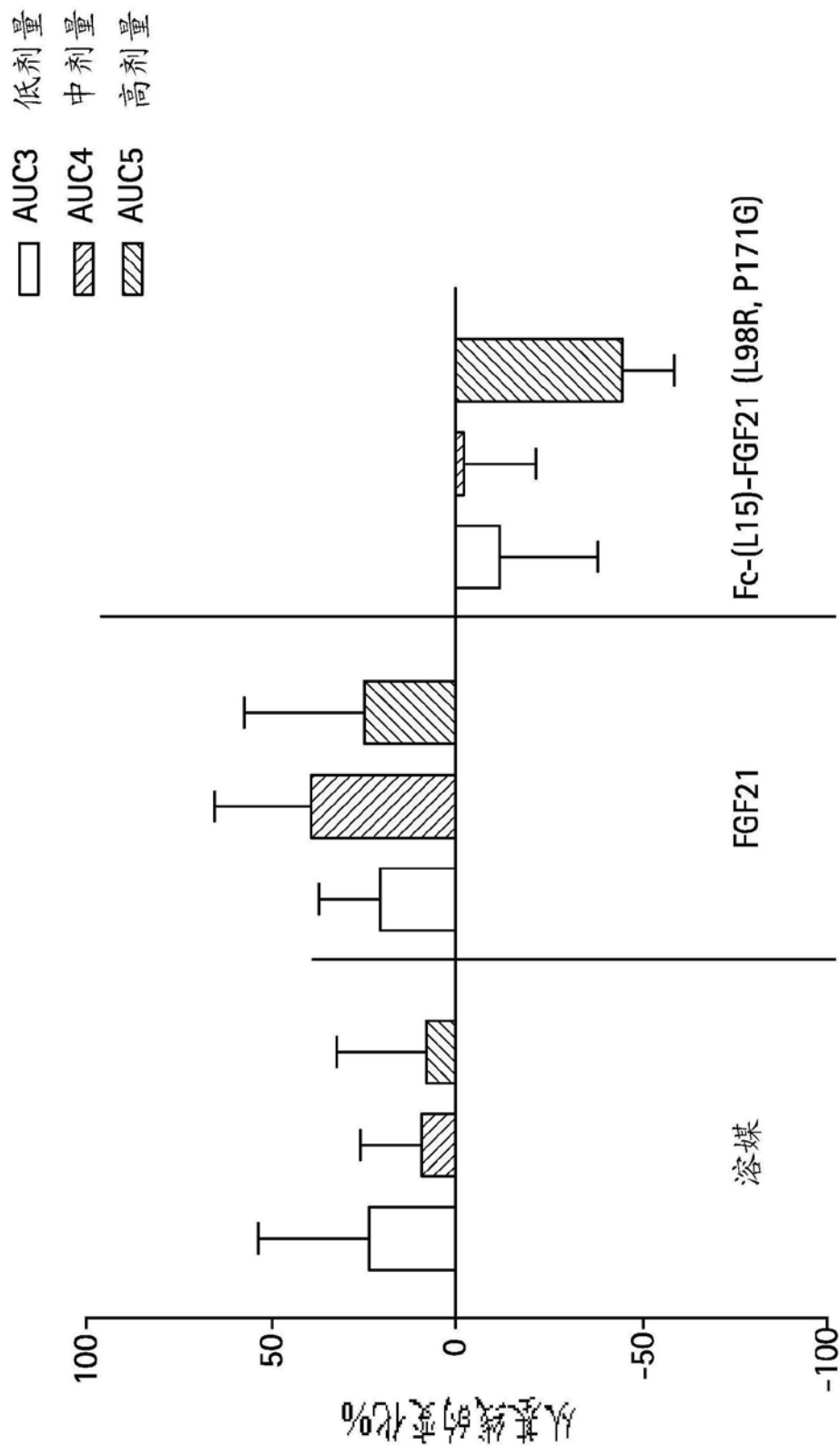


图44

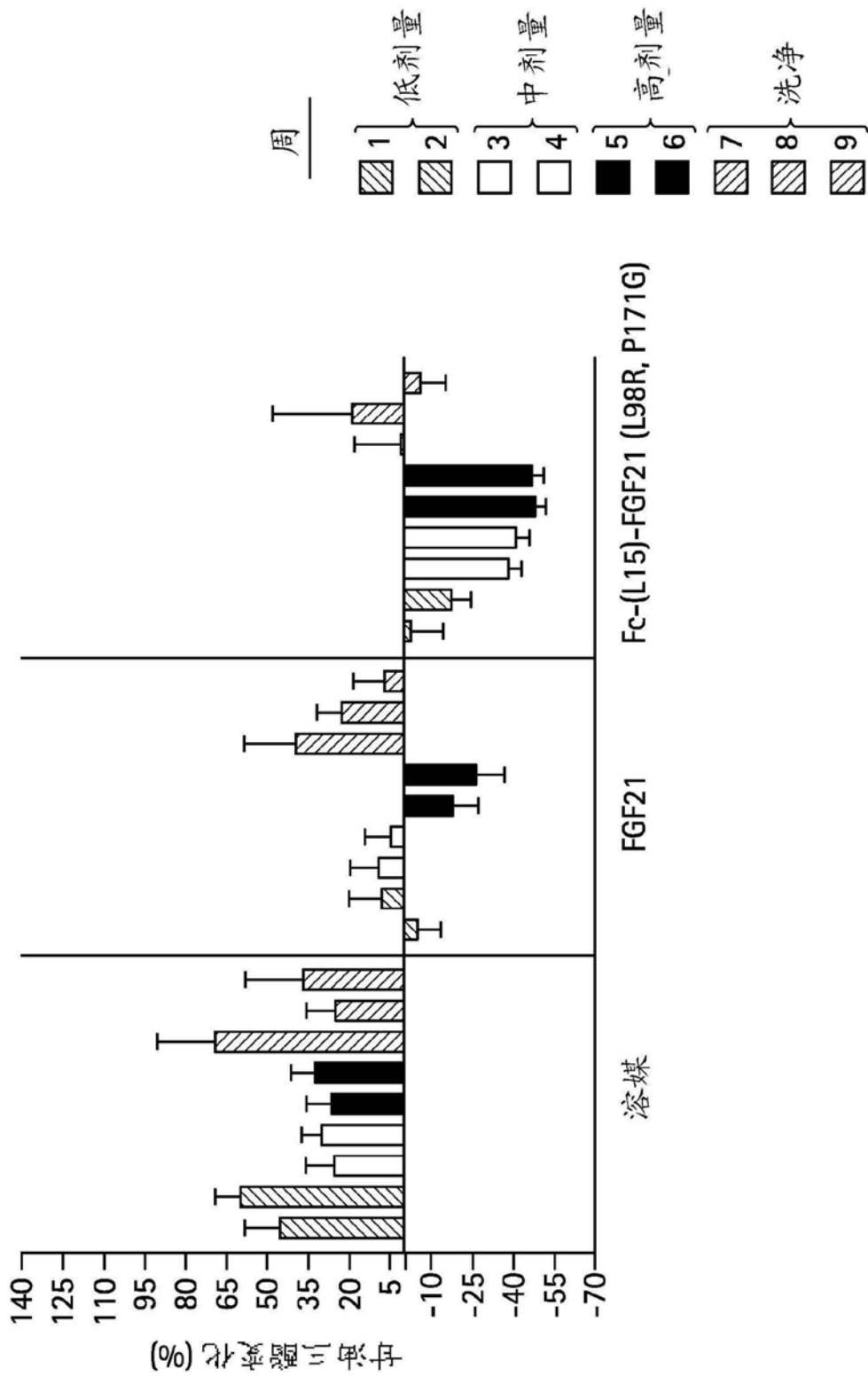


图45

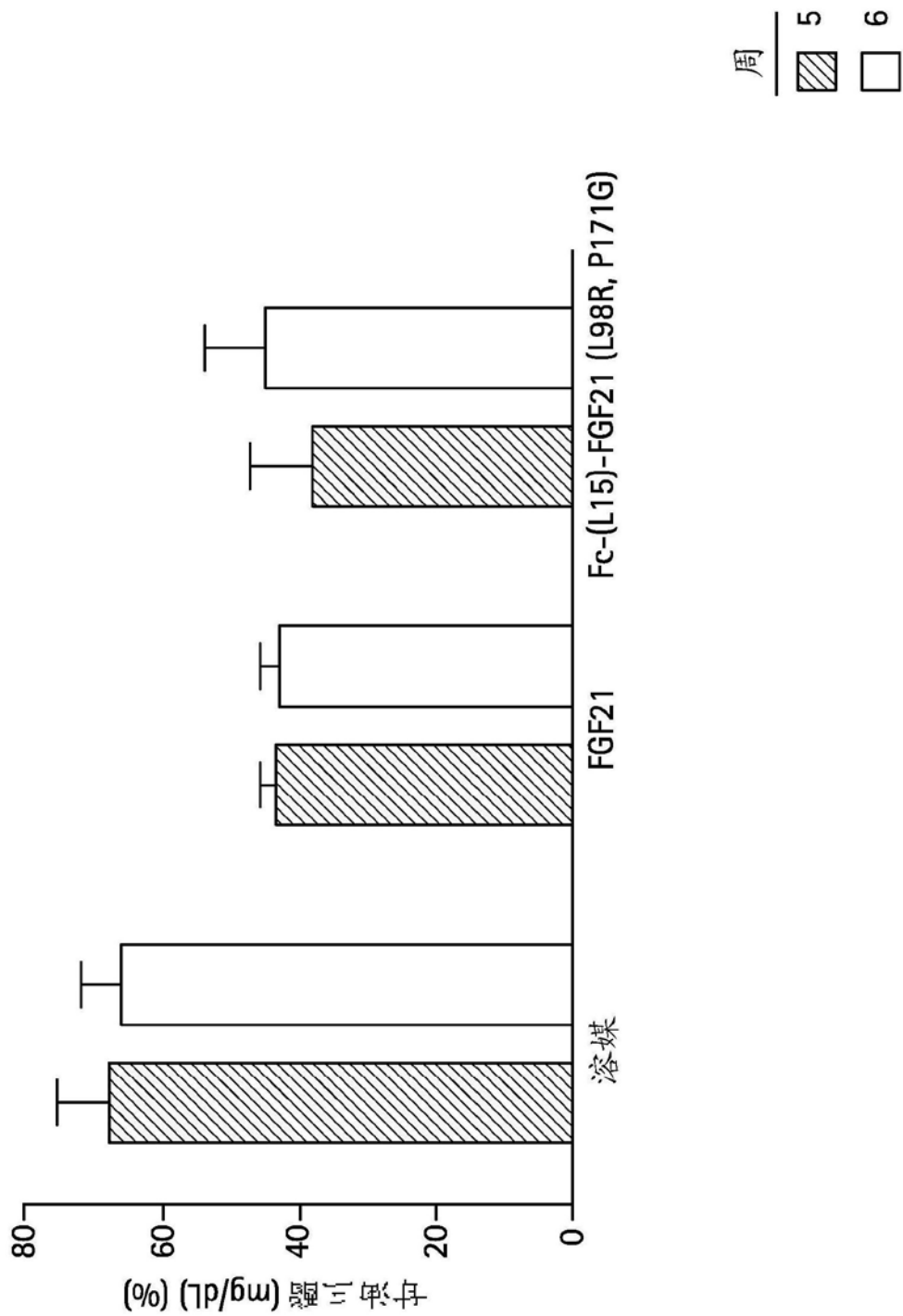


图46

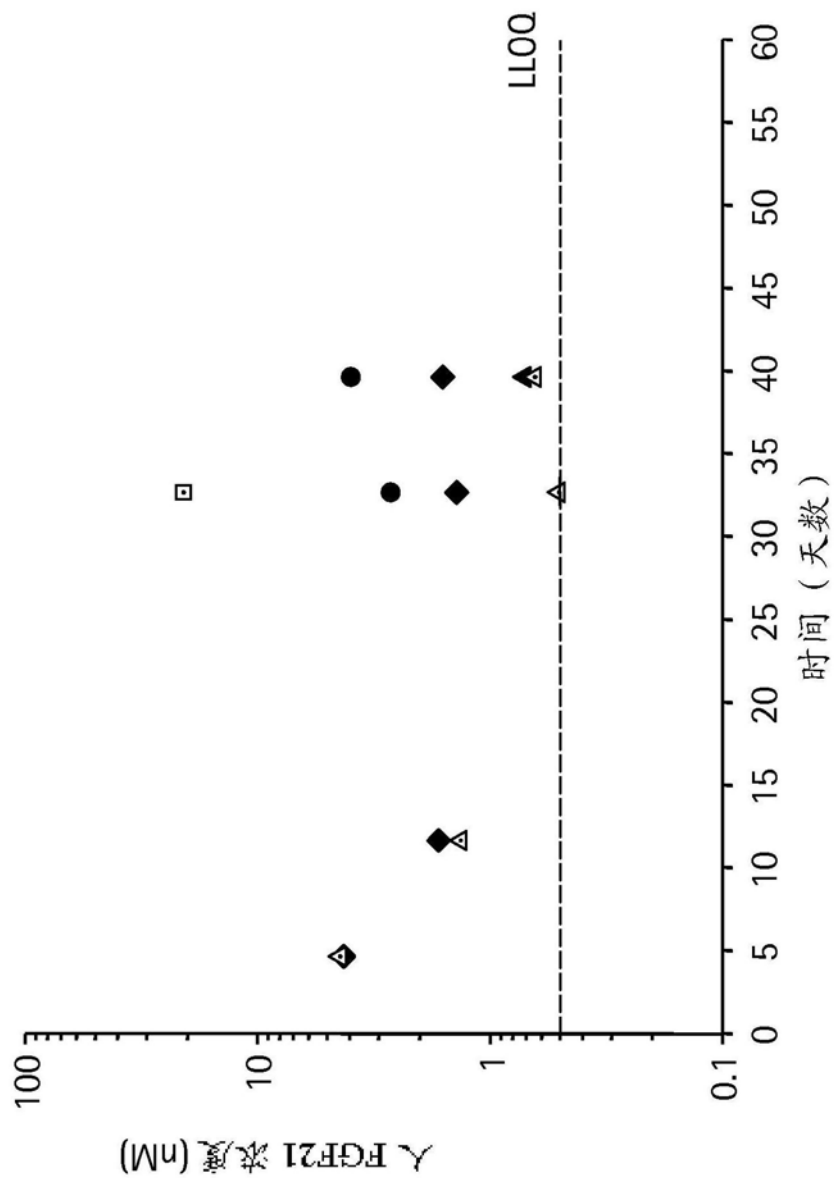


图47

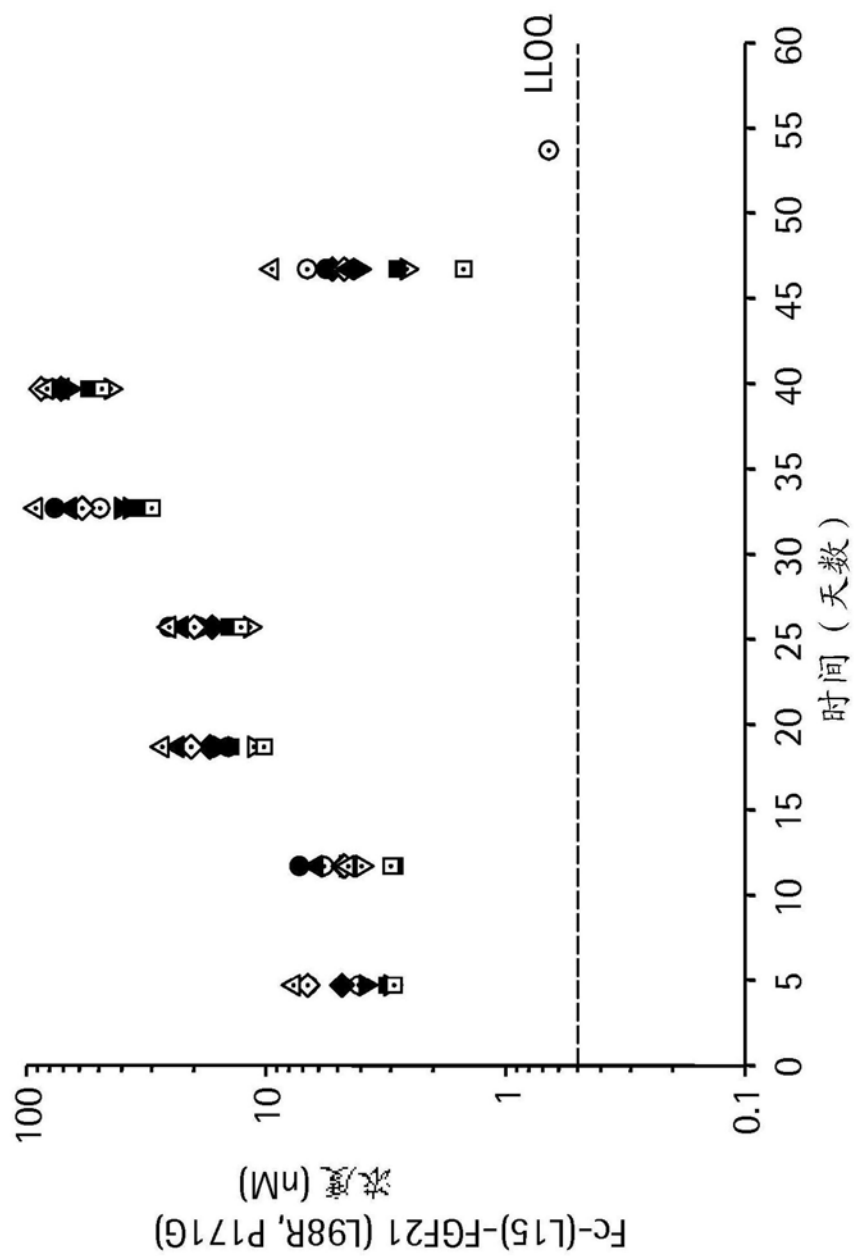


图48

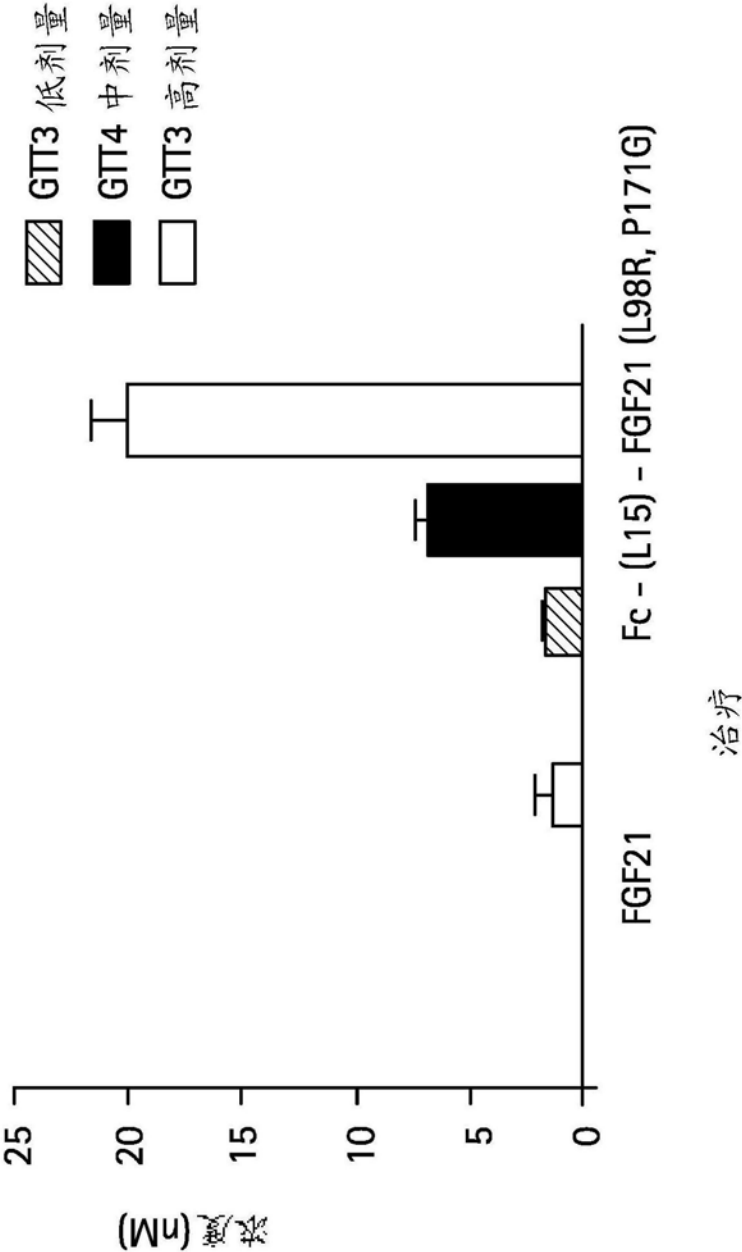


图49

Fc-(G4S)3-FGF21 (L98R, P171G, A190E)

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVQLHQLDNLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
GGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQR
PDGALYGSLHFDPEACSFRE¹RLLEDGYNVYQSEAHGLPLELPGNKSPHRDPAPRGPAPRFLPLPGLPPAPPEPPGILAPQP
PDVGSSDPLSMVG²SSQGRSPSY³E⁴

图50

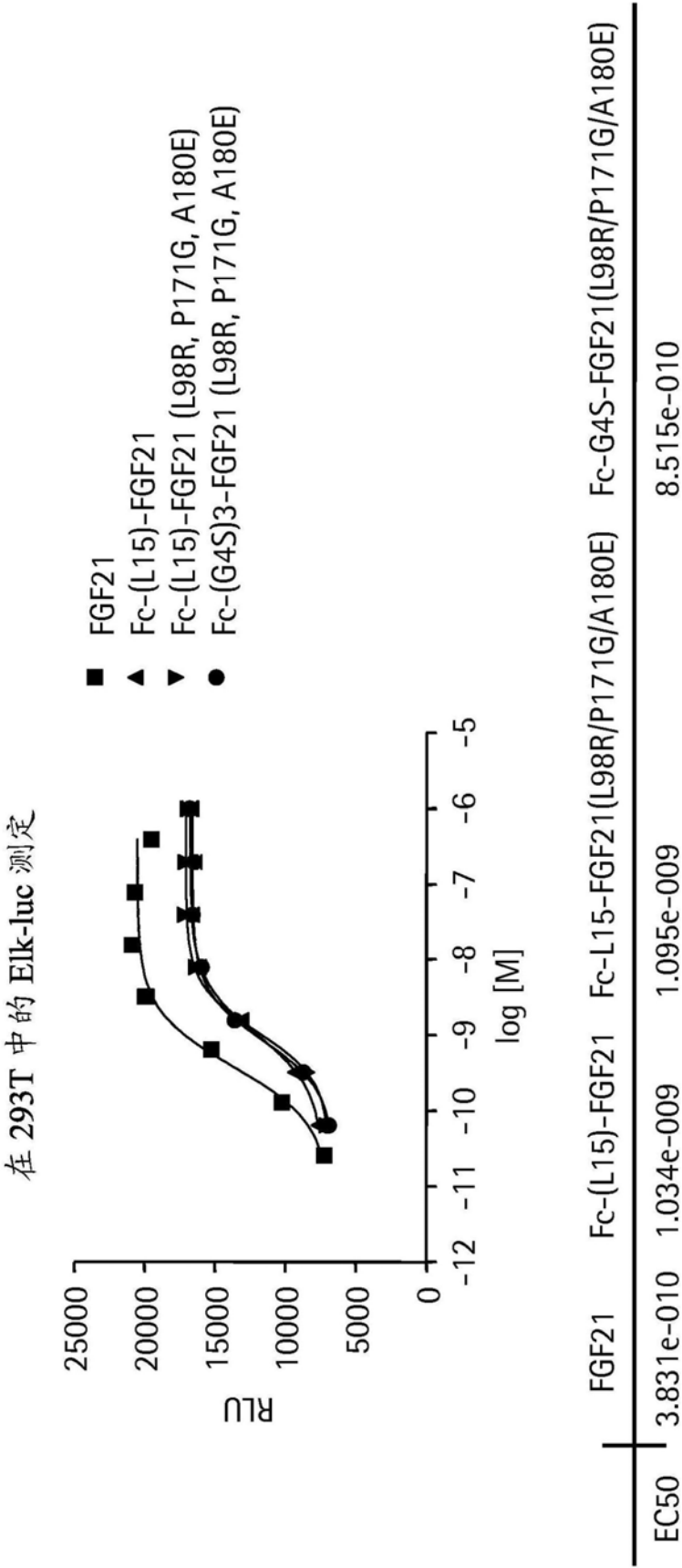


图51

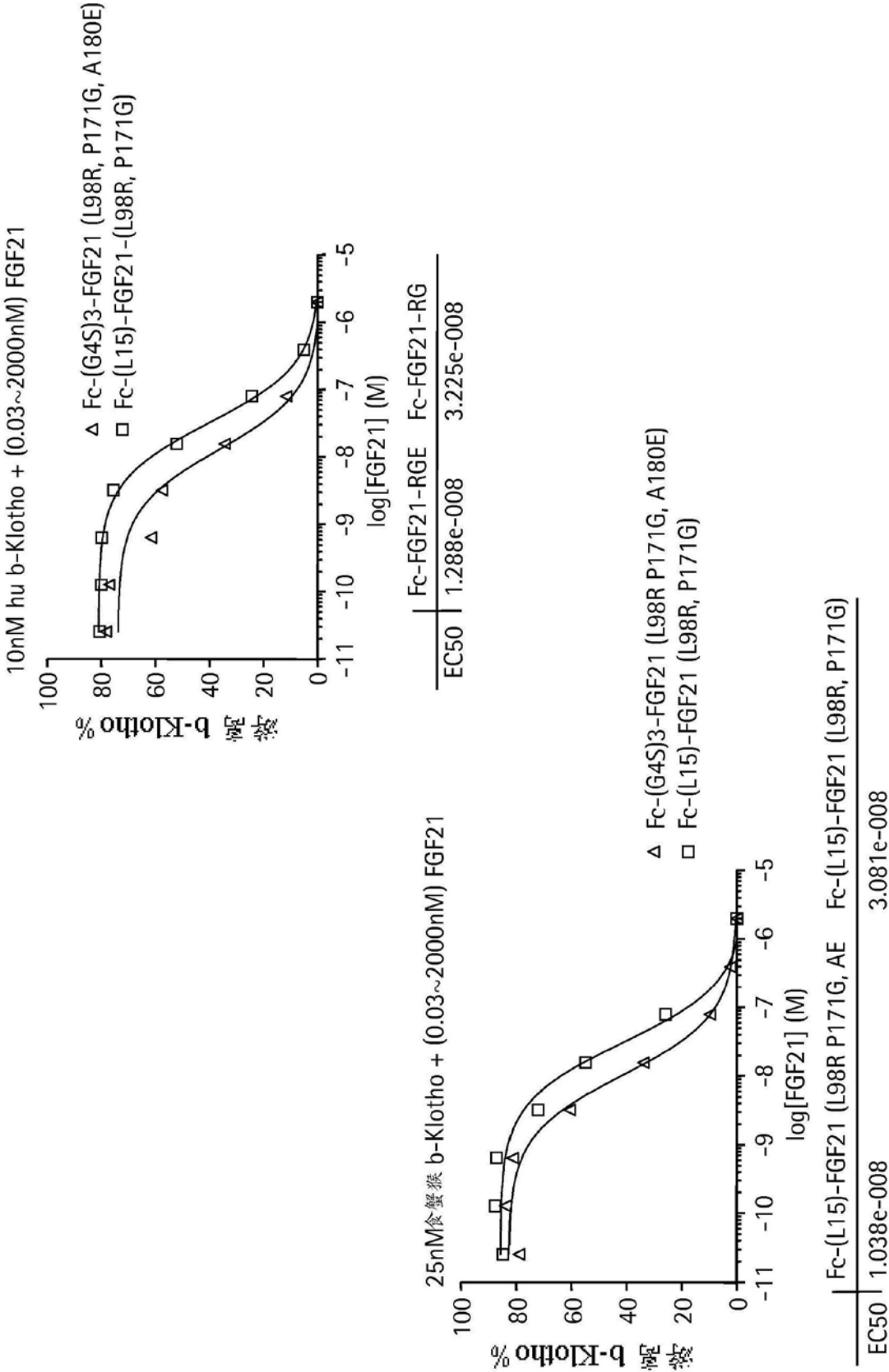


图52

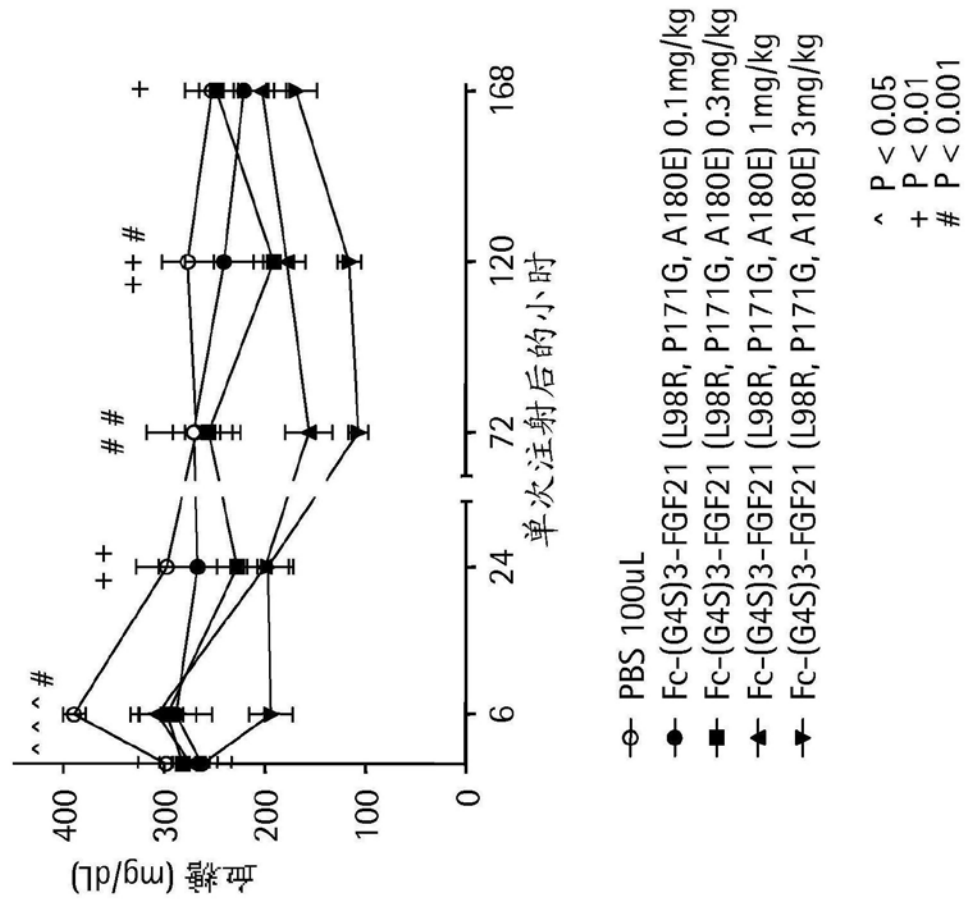


图53A

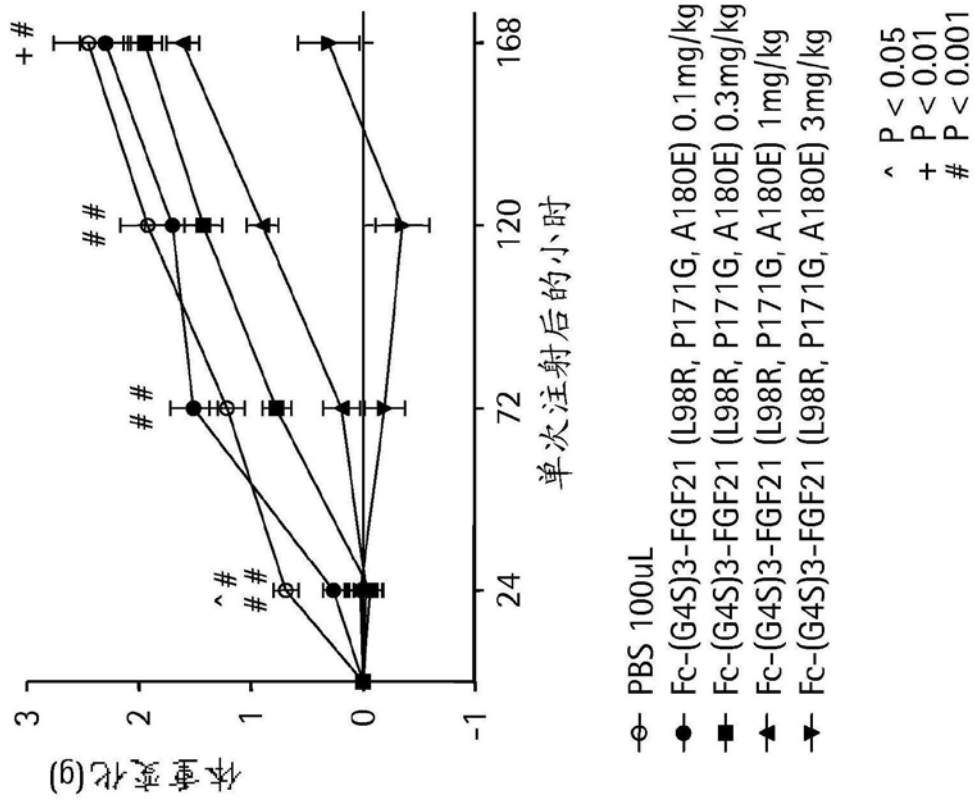
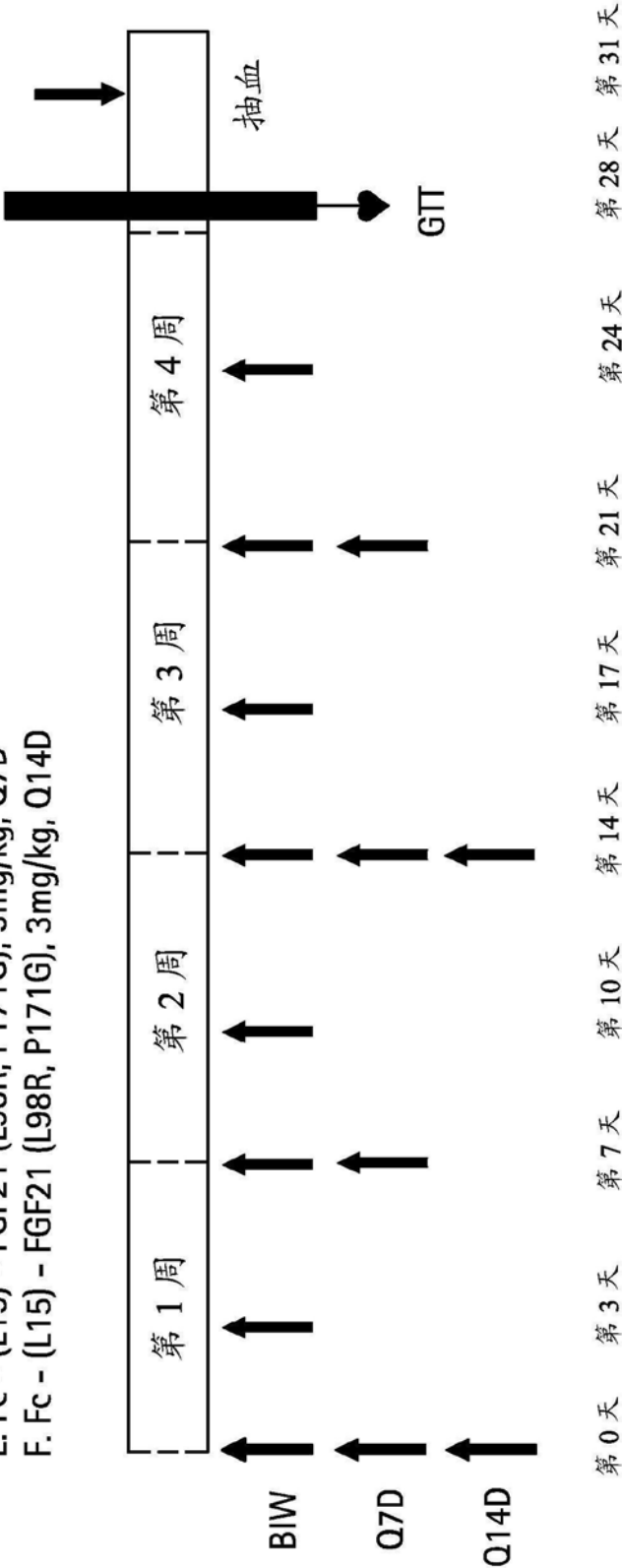


图53B

- A. 溶媒 Q7D
- B. Fc - (G4S)3 - FGF21 (L98R, P171G, A180E), 3mg/kg, Q7D
- C. Fc - (G4S)3 - FGF21 (L98R, P171G, A180E), 3mg/kg, Q14D
- D. Fc - (L15) - FGF21 (L98R, P171G), 3mg/kg, BIW
- E. Fc - (L15) - FGF21 (L98R, P171G), 3mg/kg, Q7D
- F. Fc - (L15) - FGF21 (L98R, P171G), 3mg/kg, Q14D



缓冲剂: 10mM Tris, 2.2% 蔗糖, 3.3% 山梨醇; pH 8.5

图54

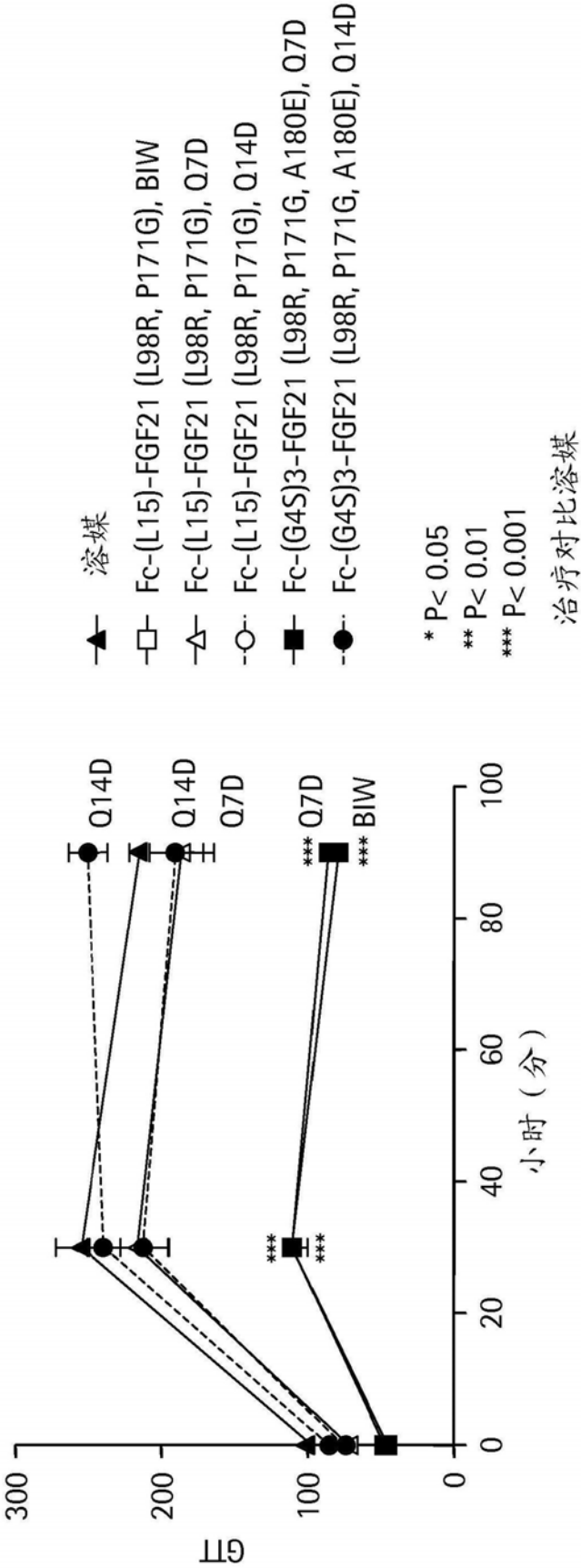


图55

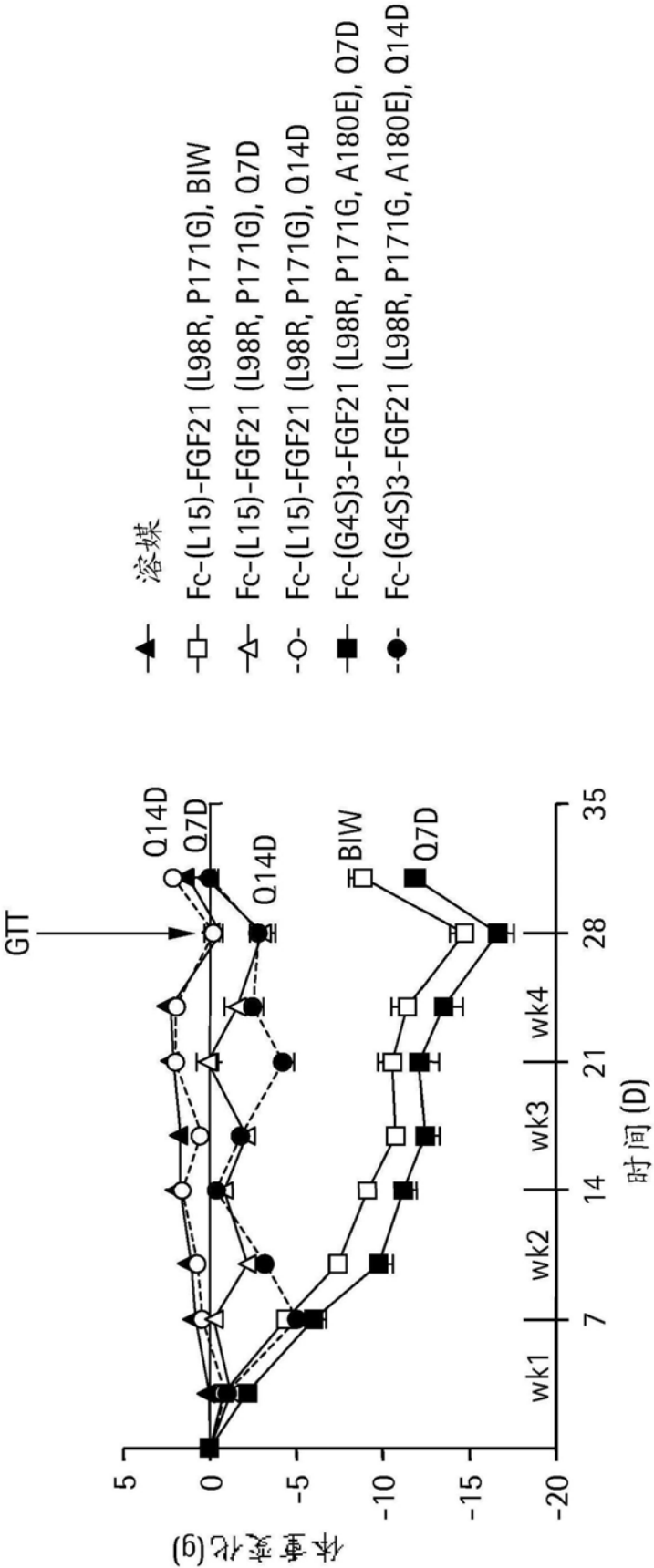


图56

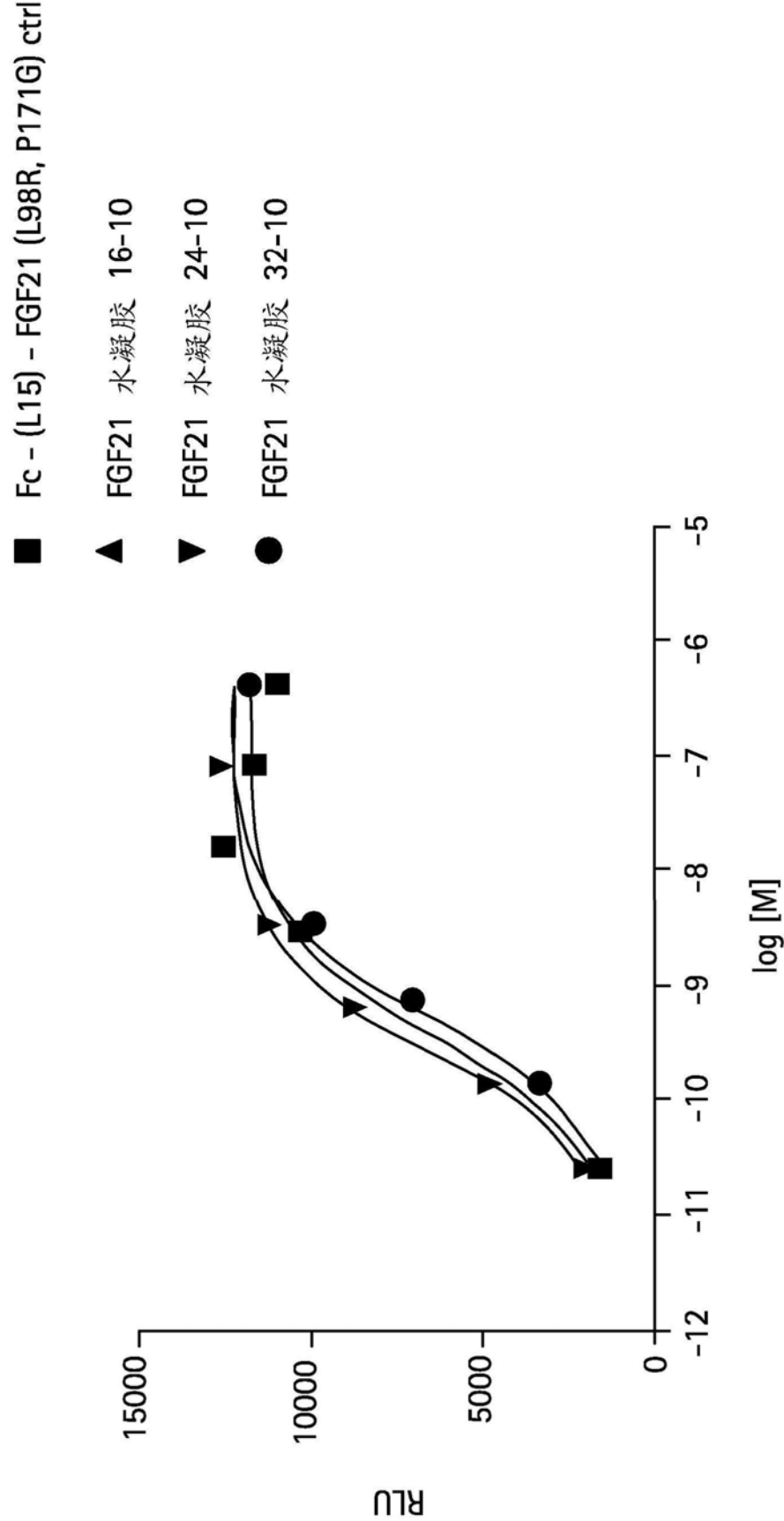


图57

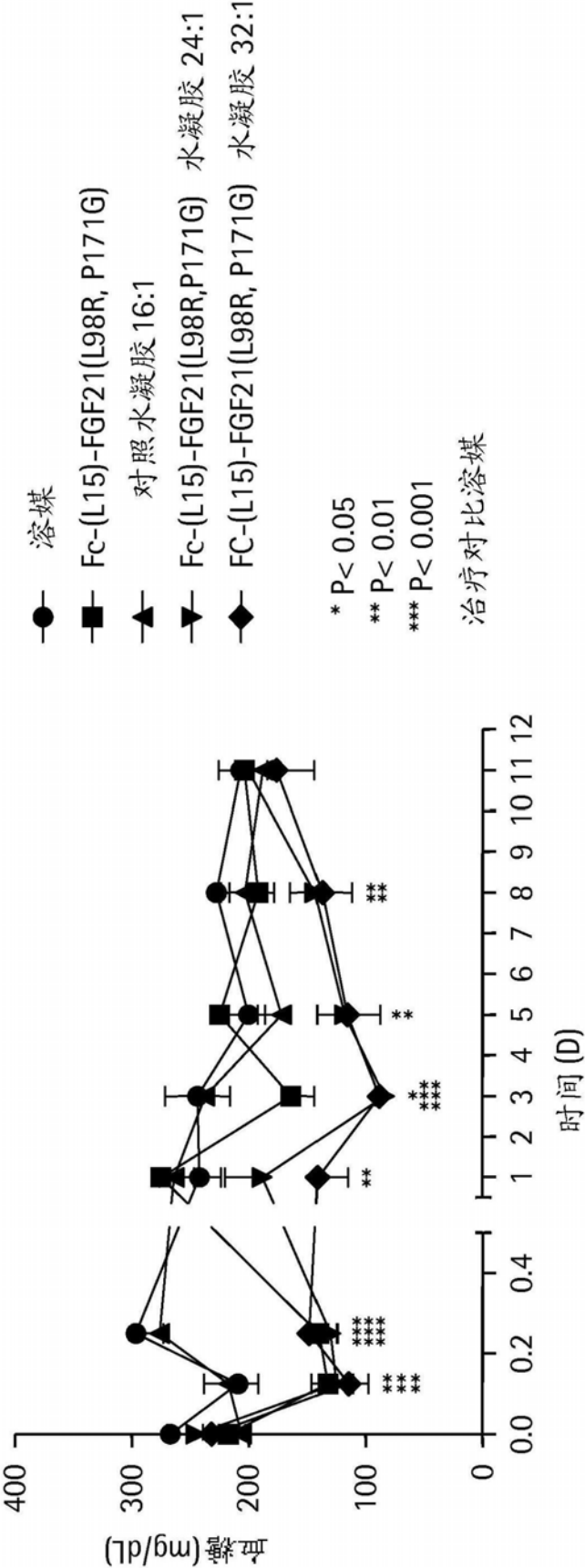


图58

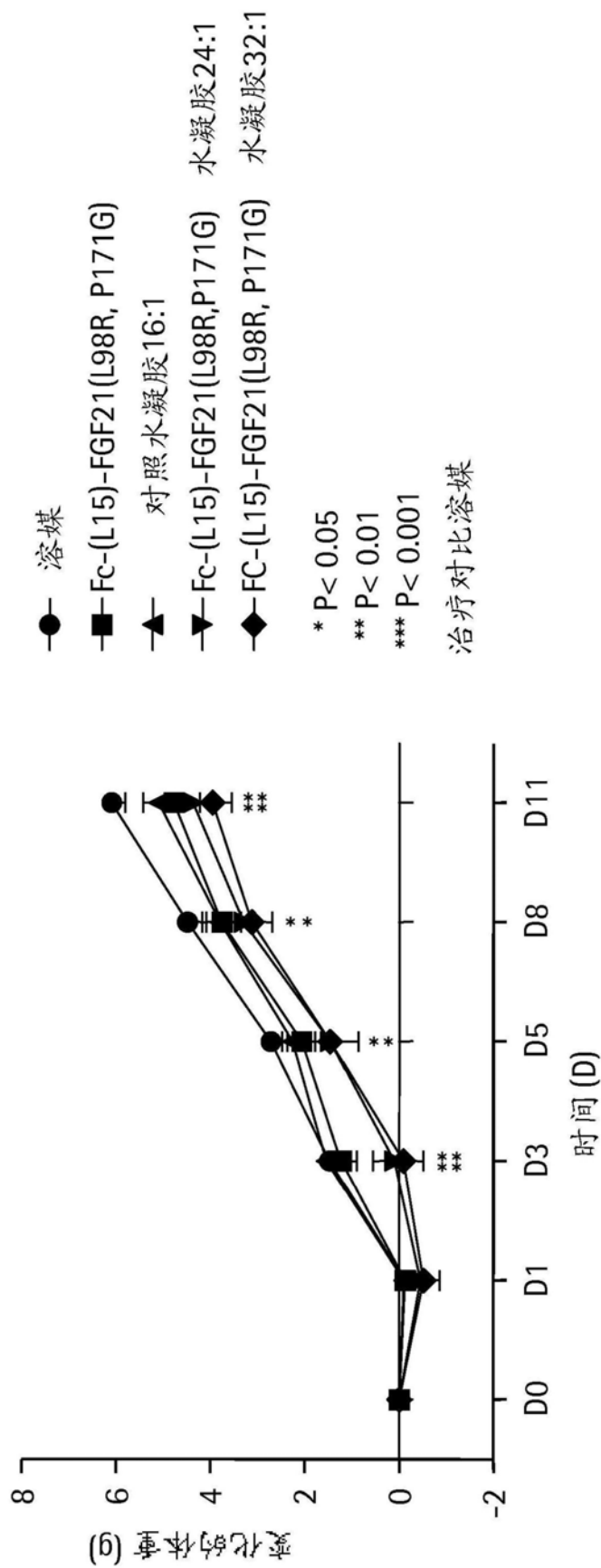


图59

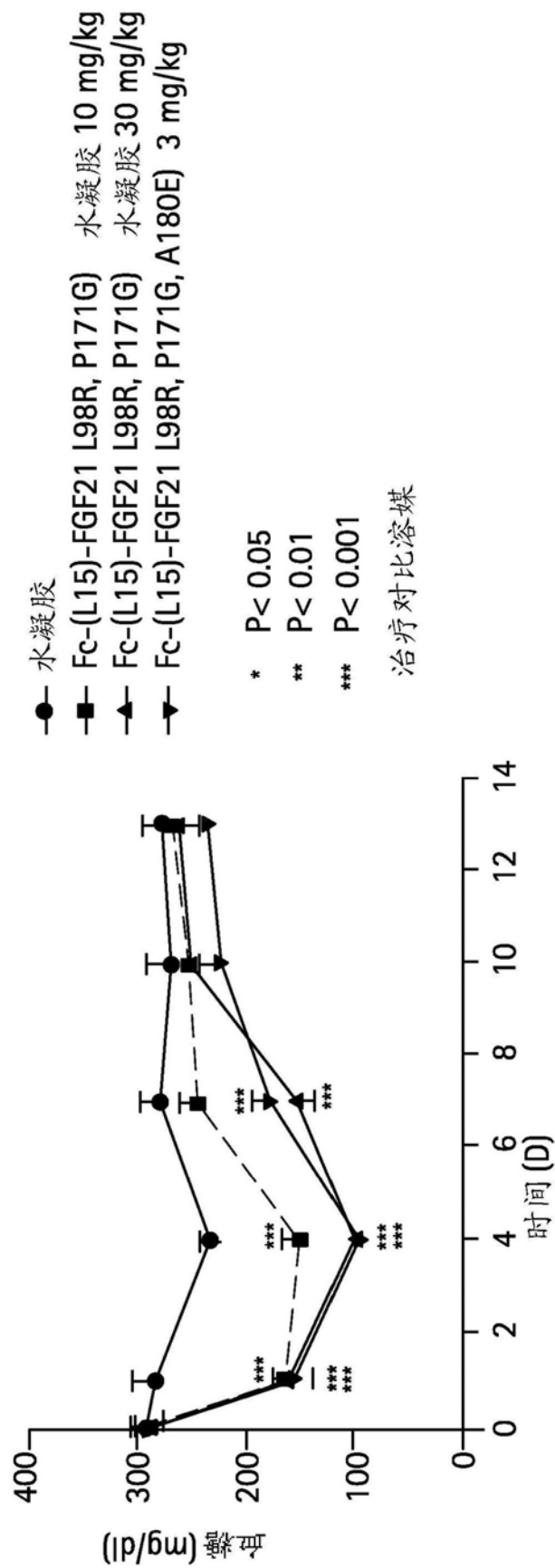


图60

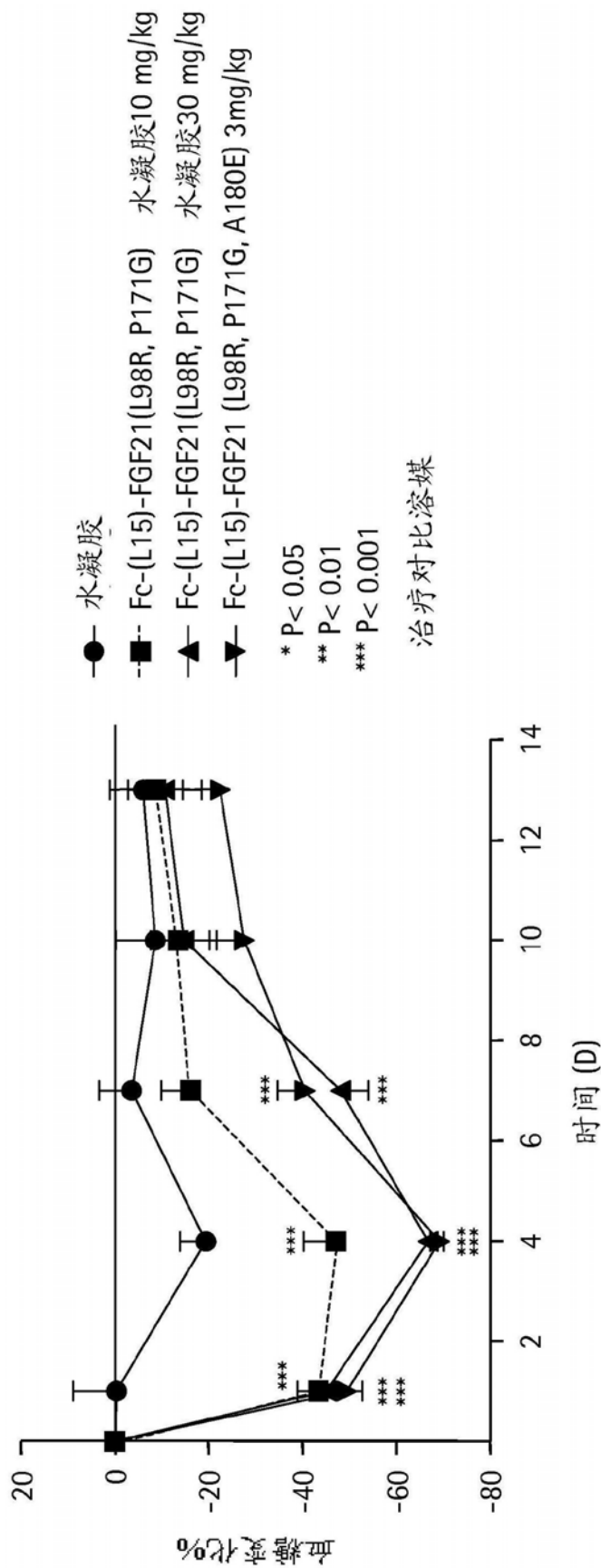


图61

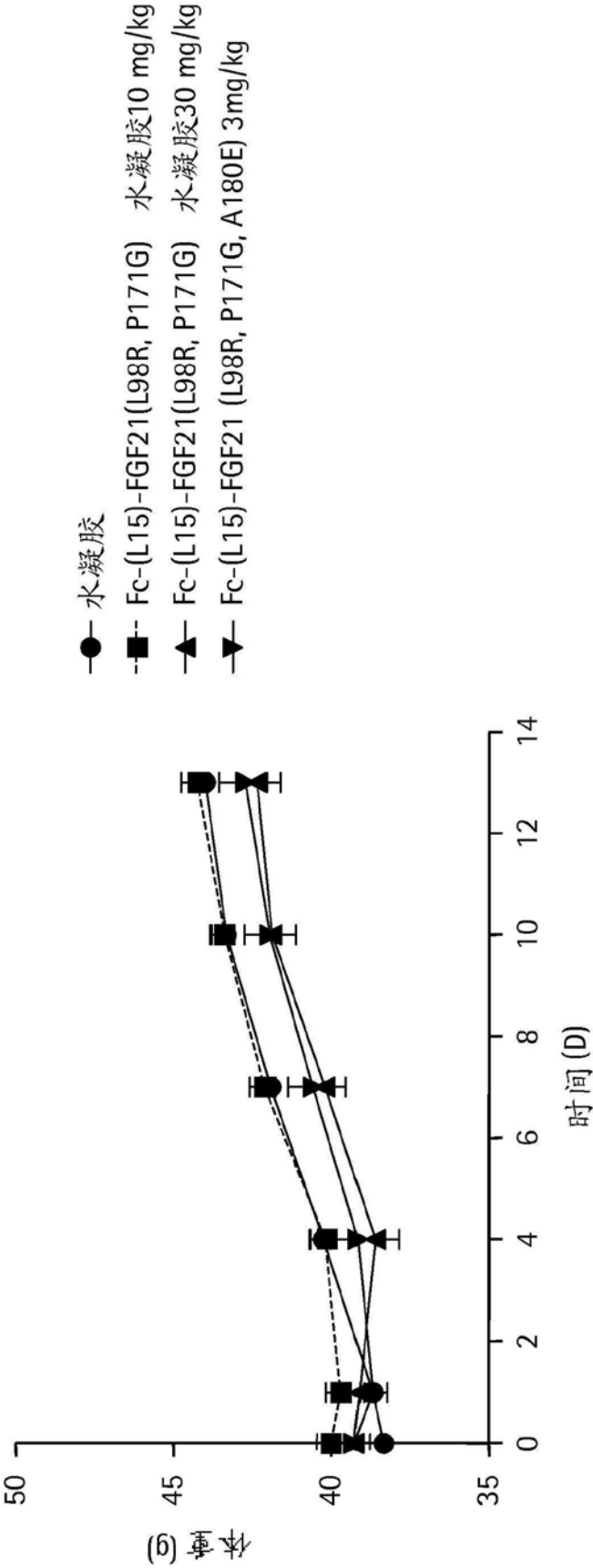


图62

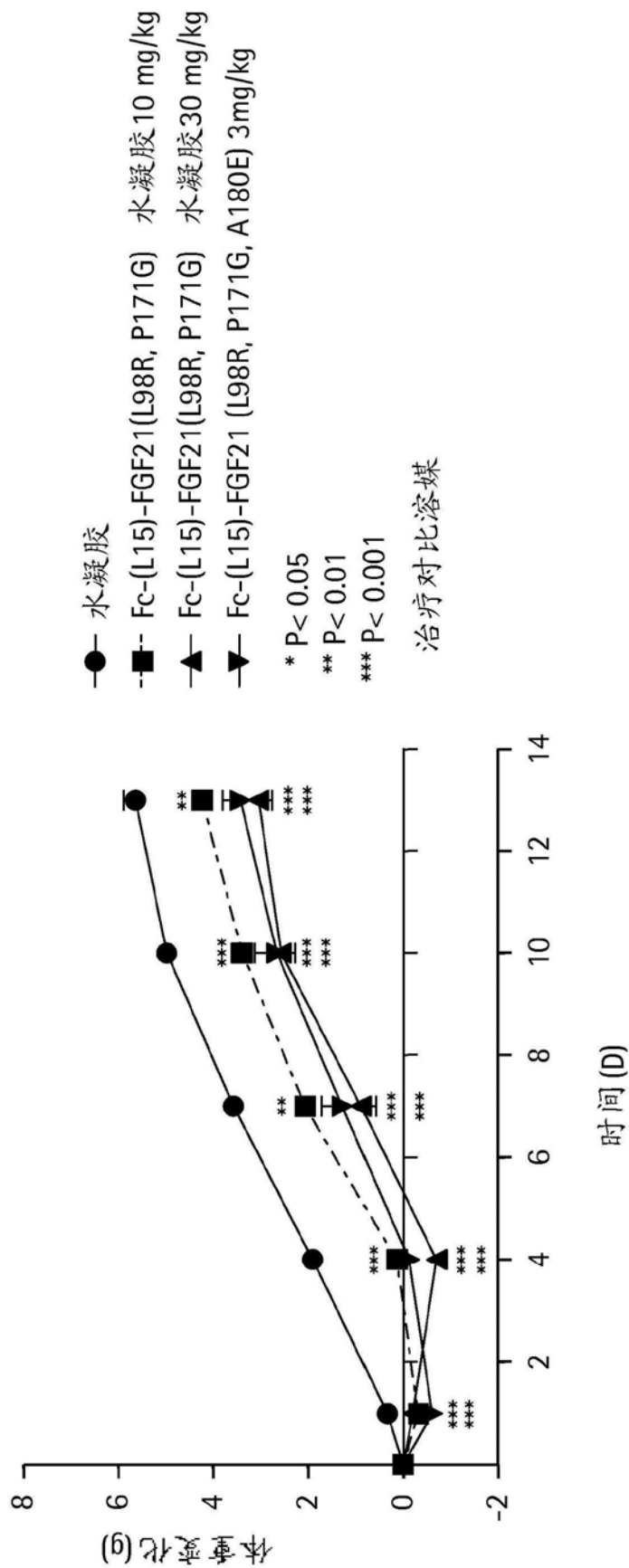


图63

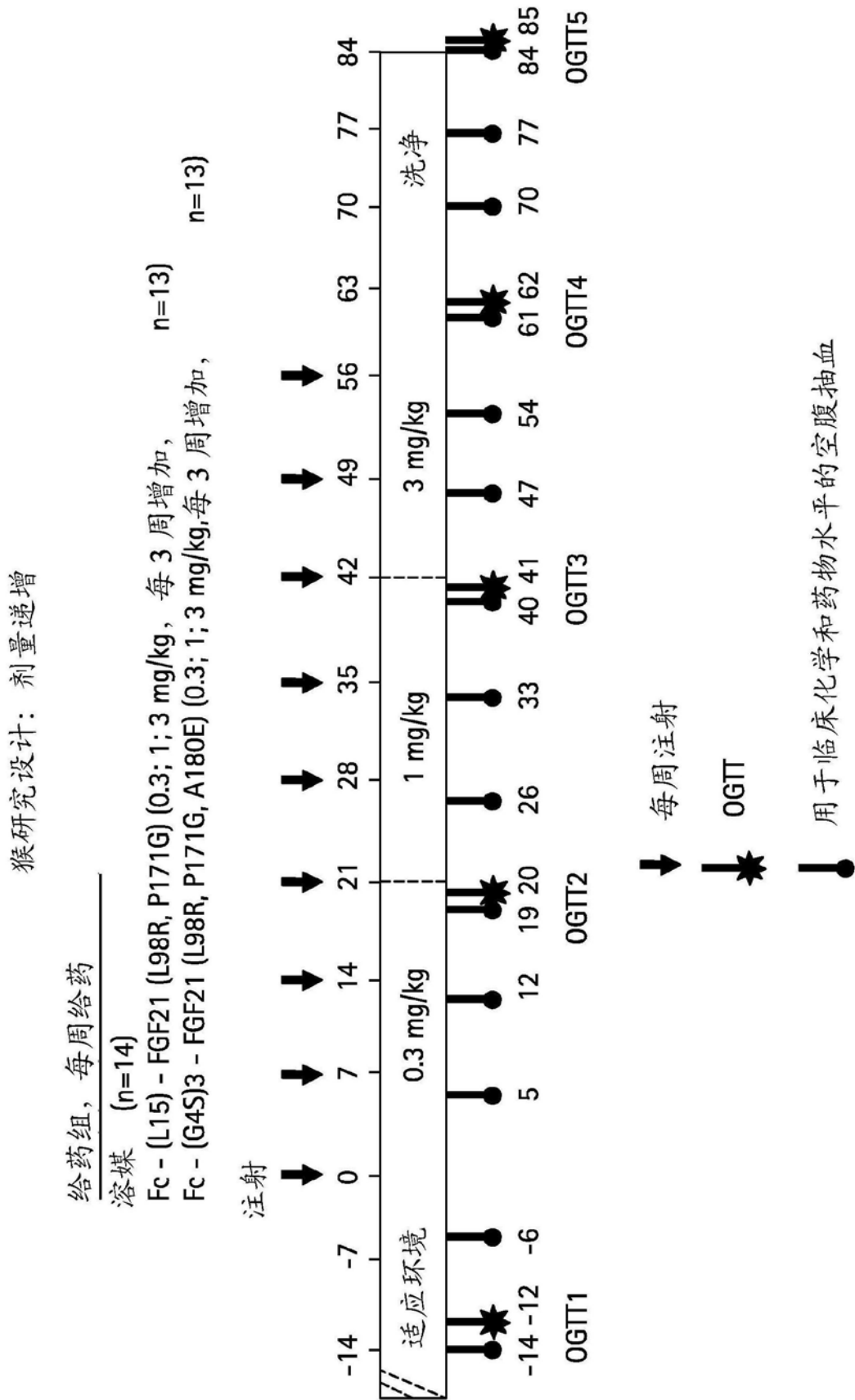


图64

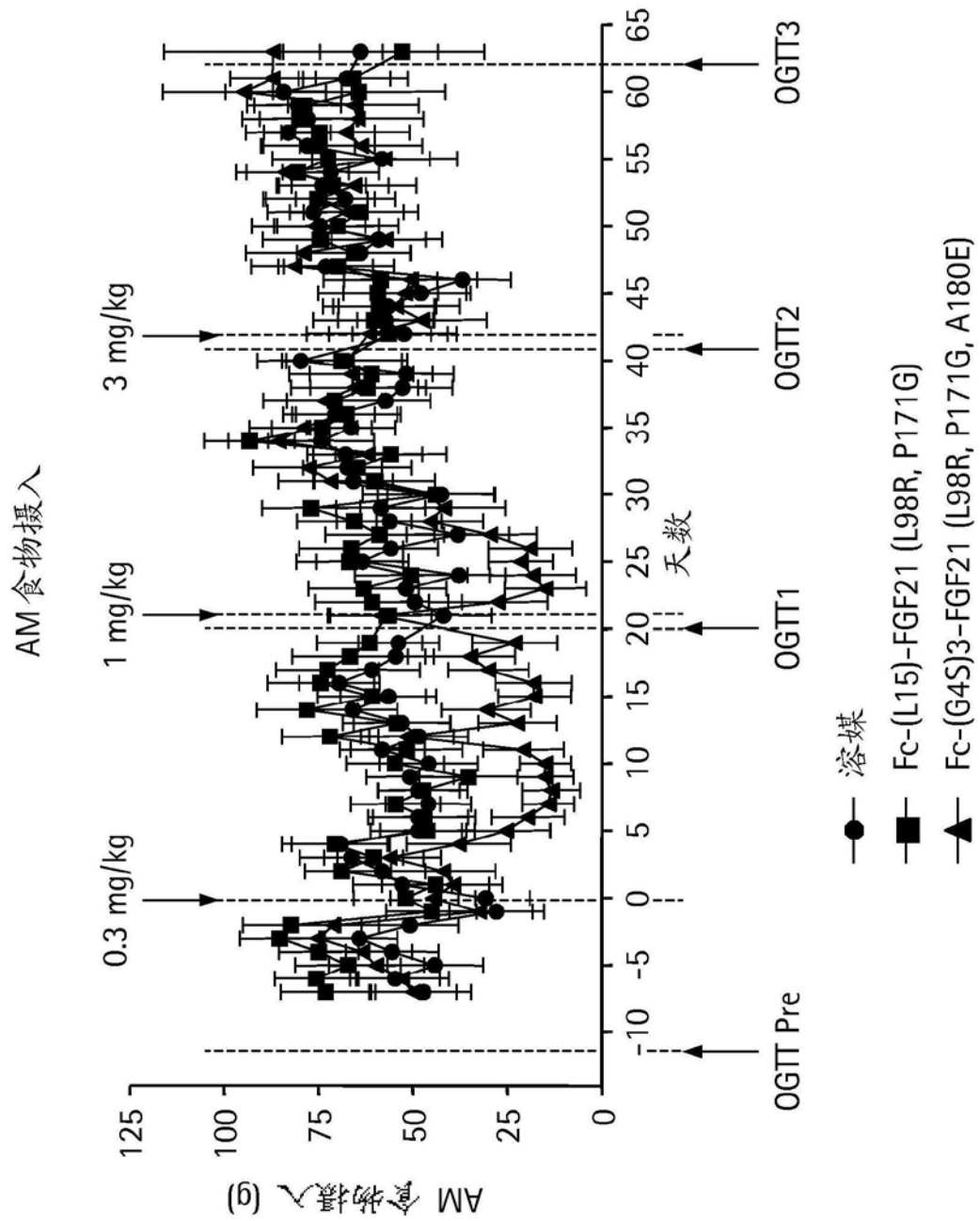


图65

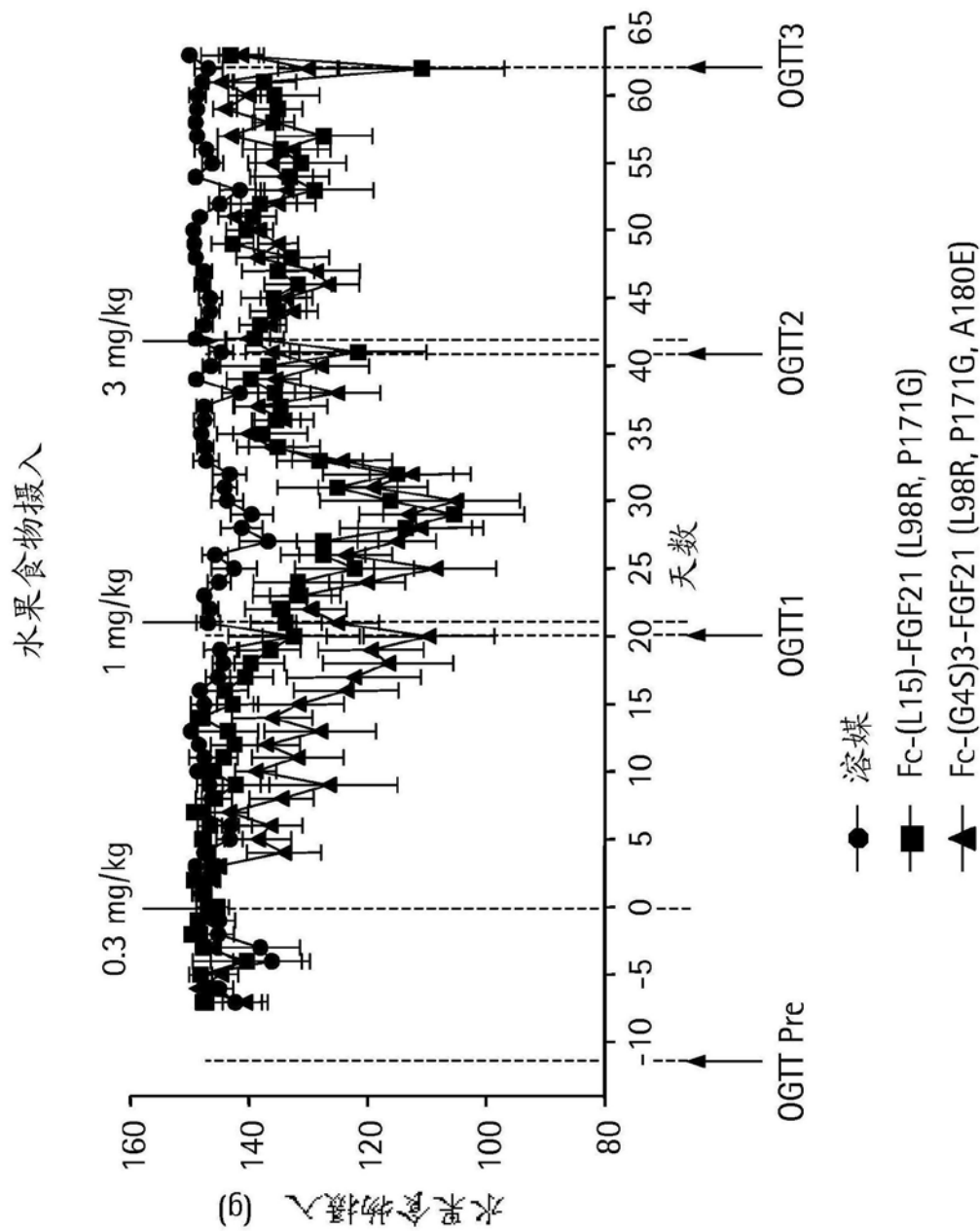


图66

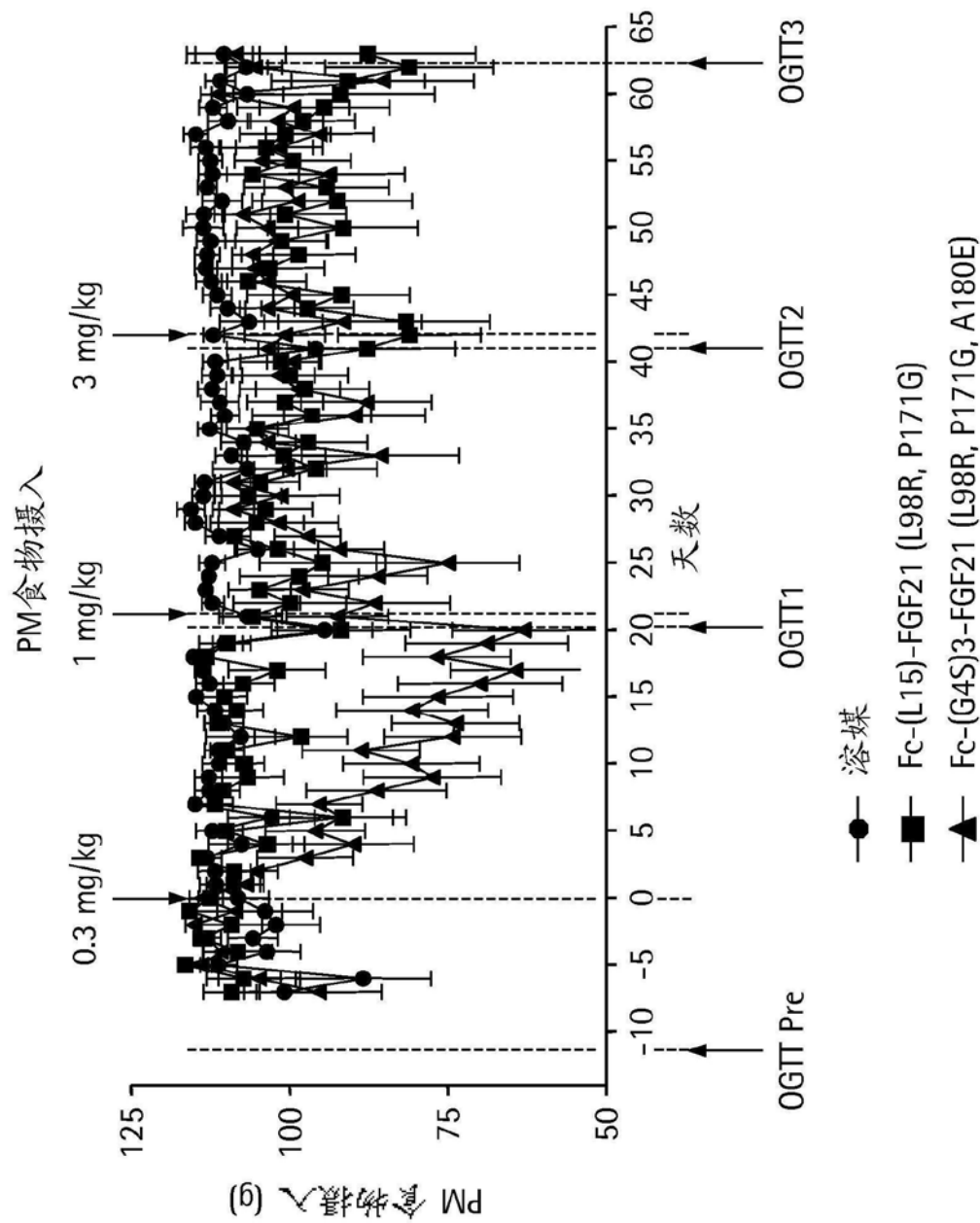


图67

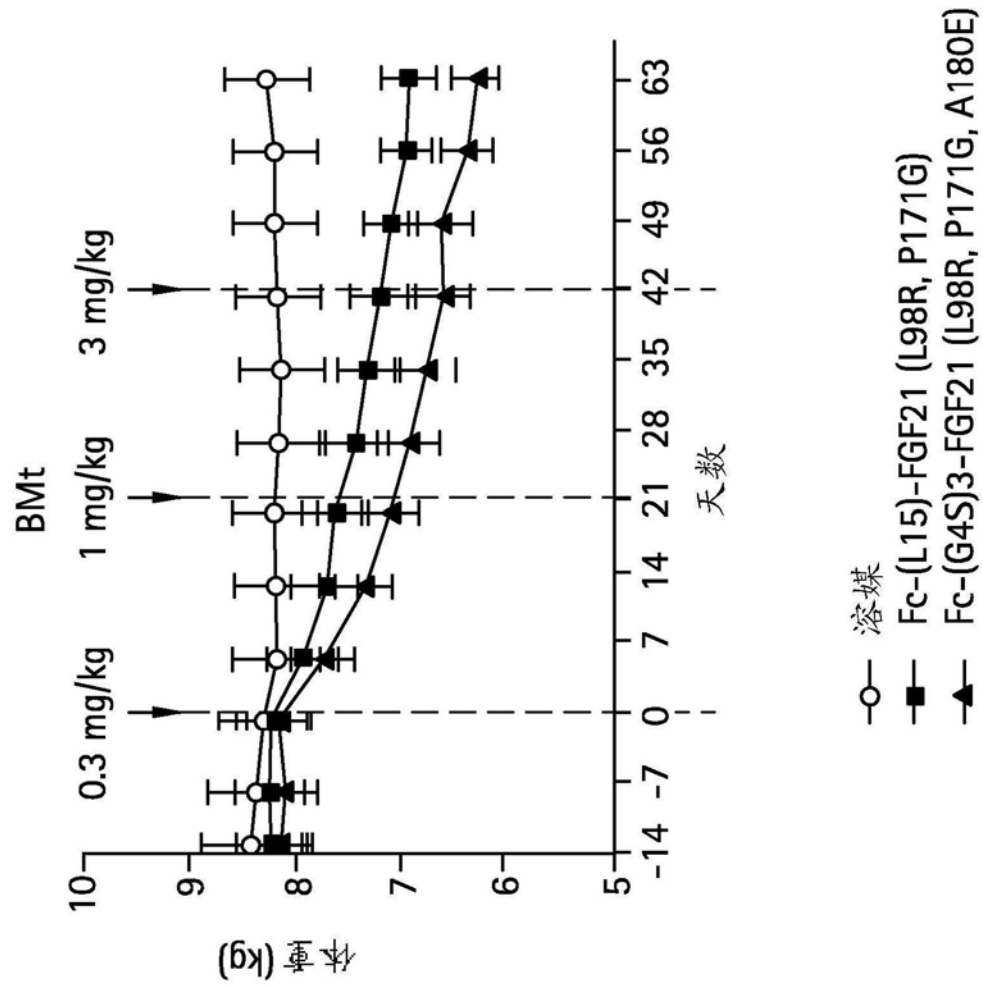


图68

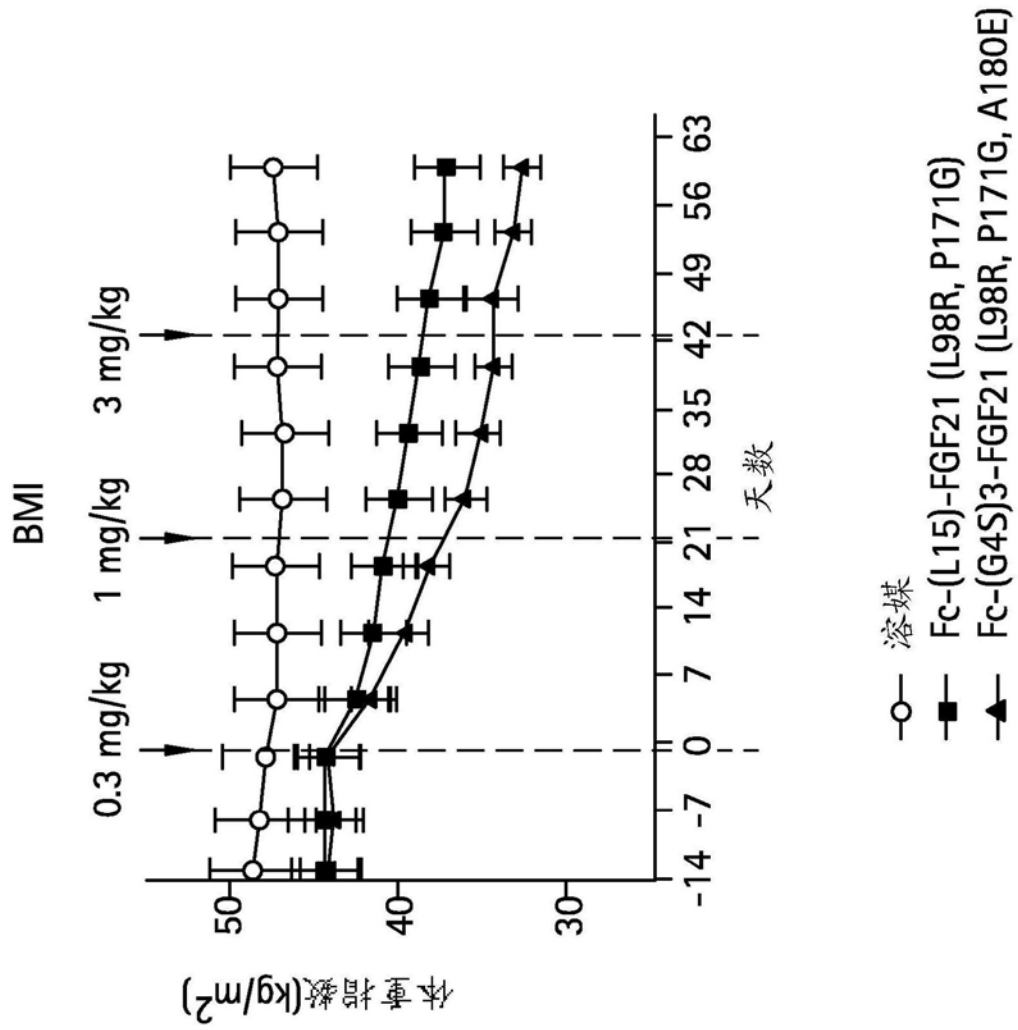


图69

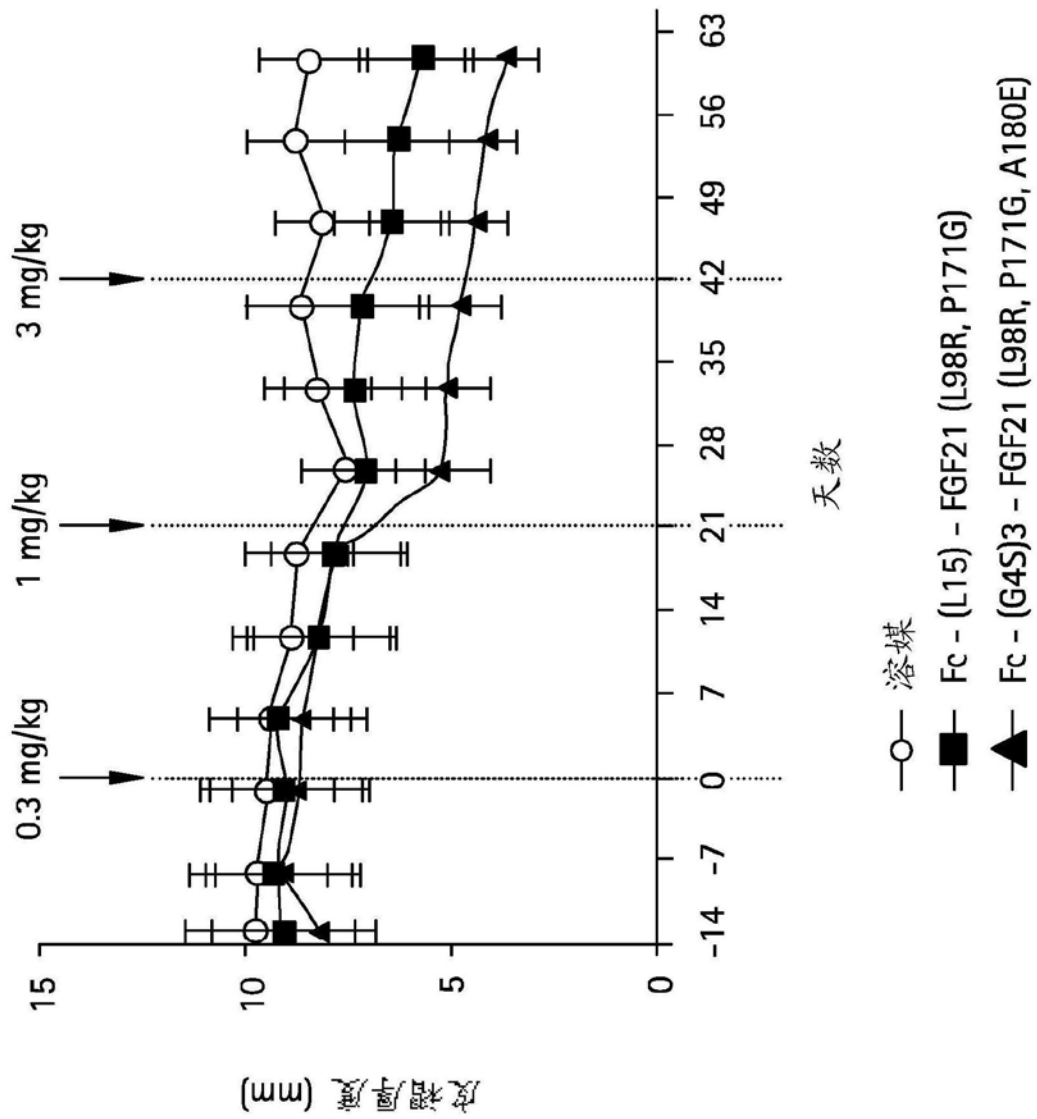


图70

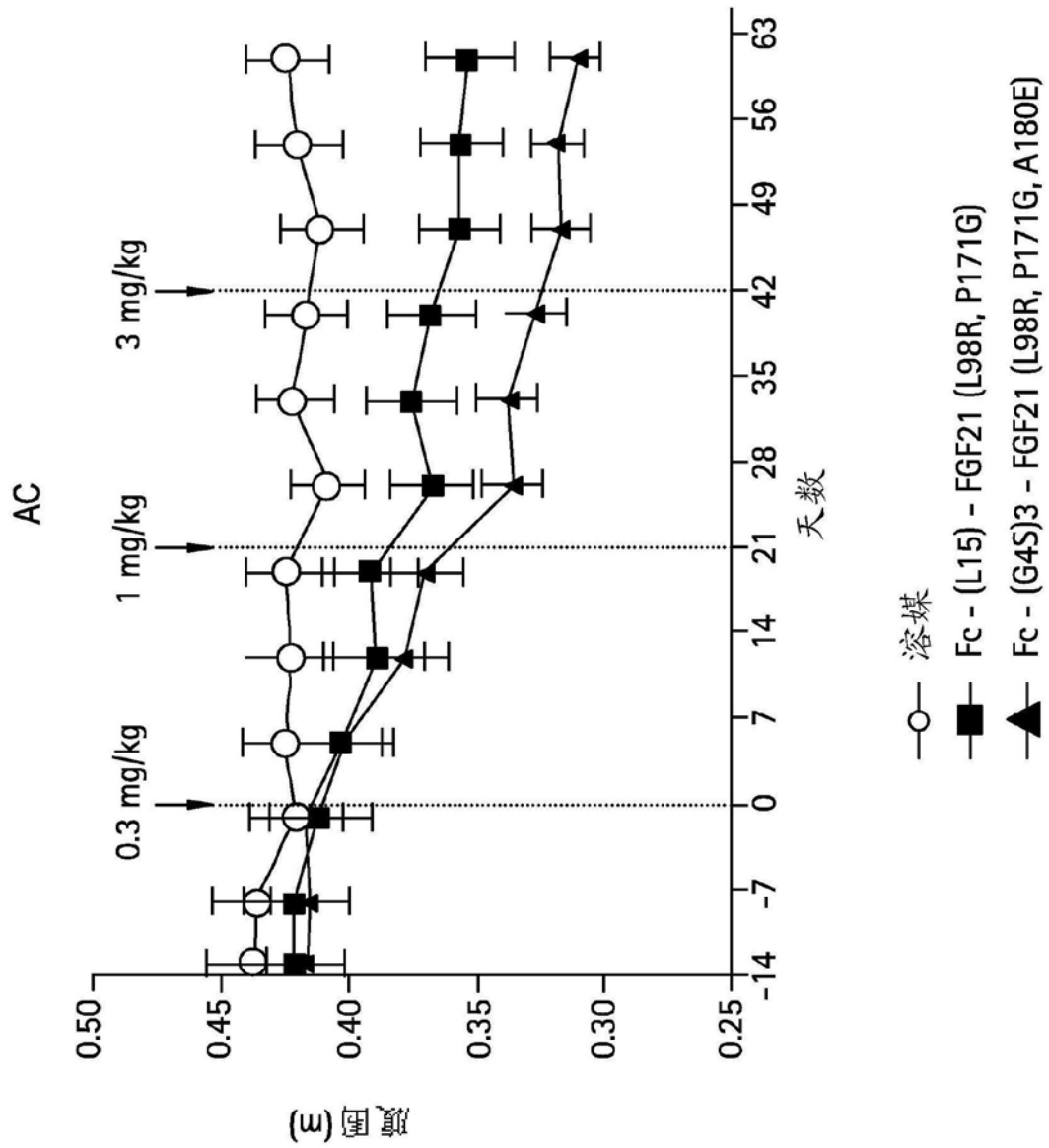


图71

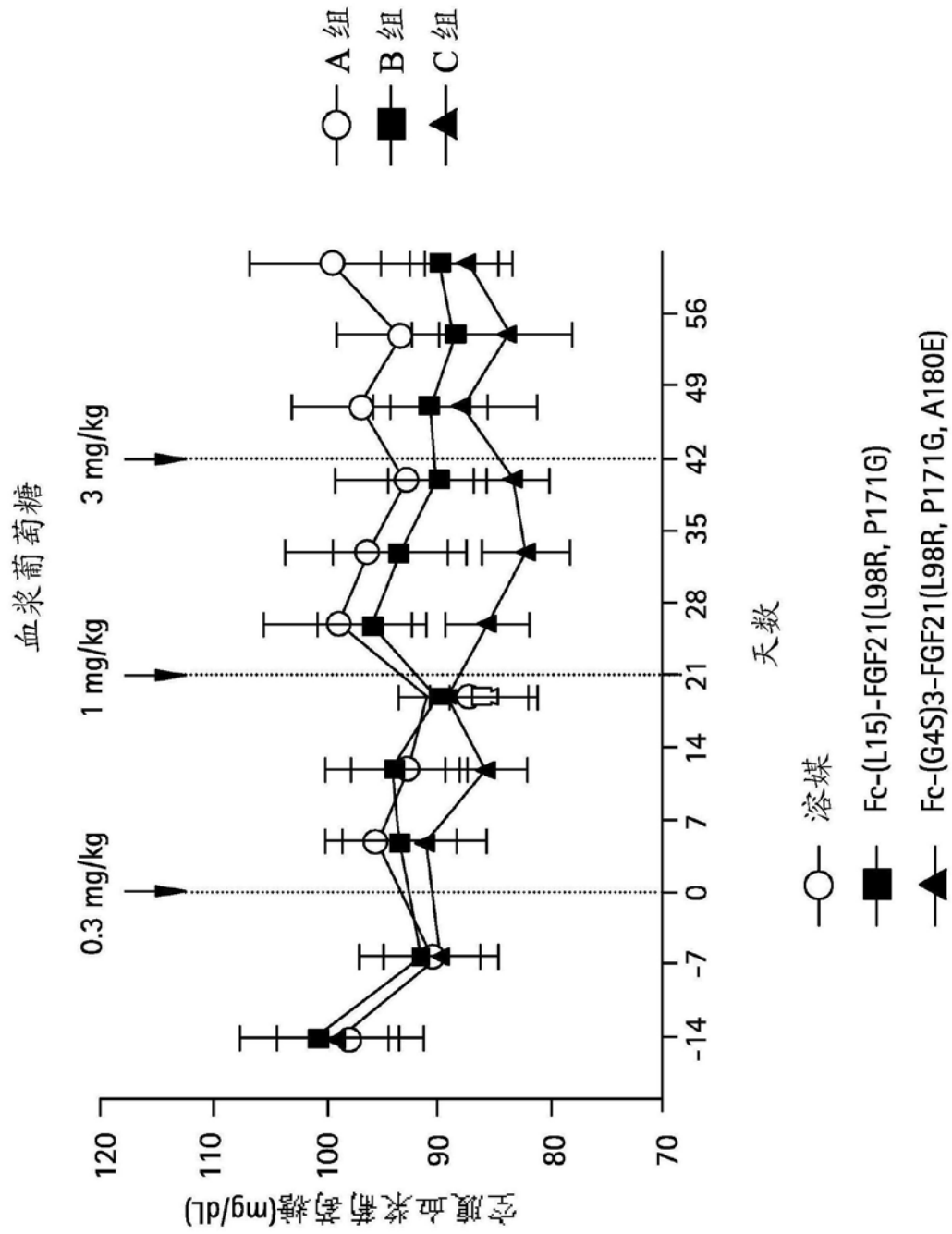


图72

图 73

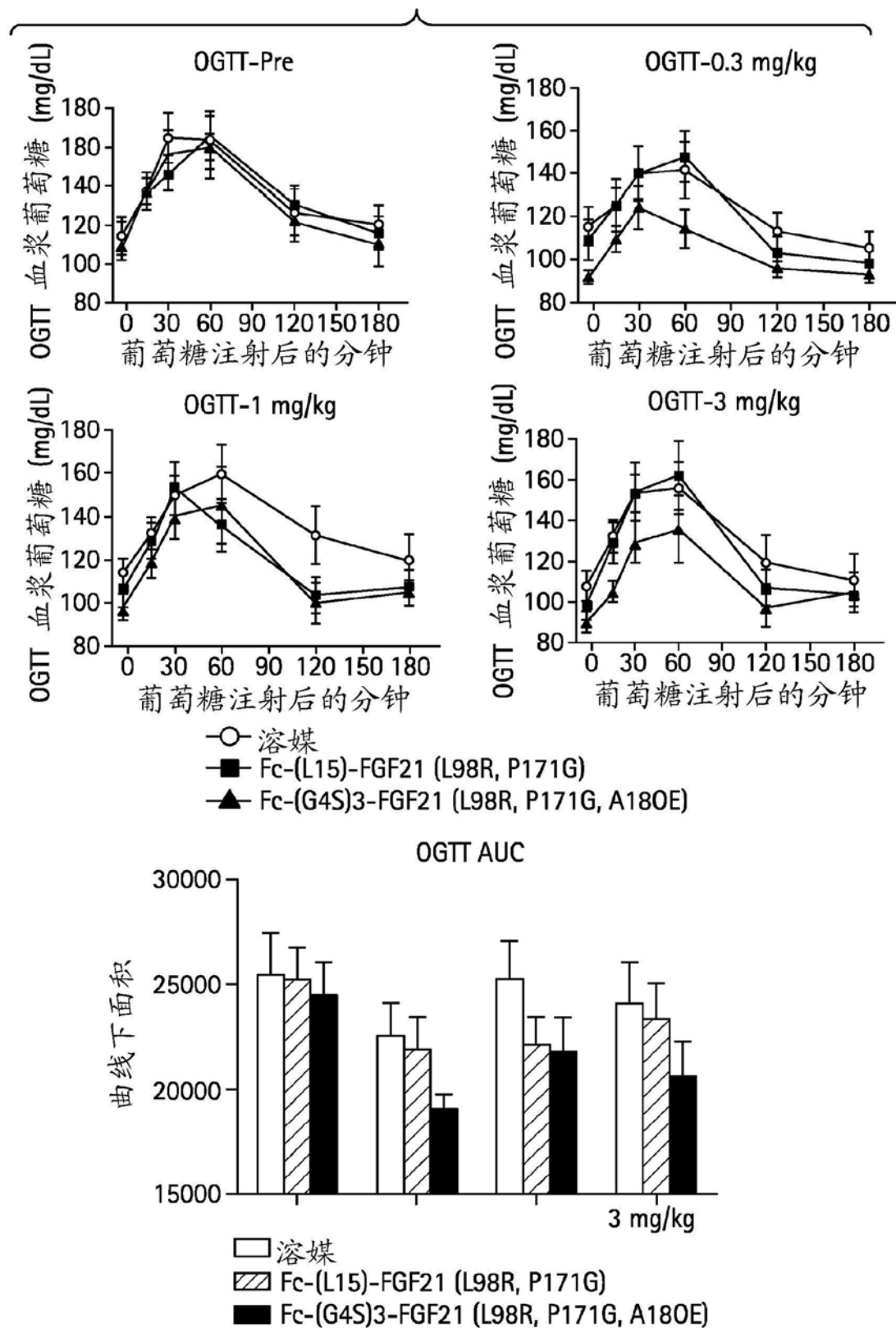


图73

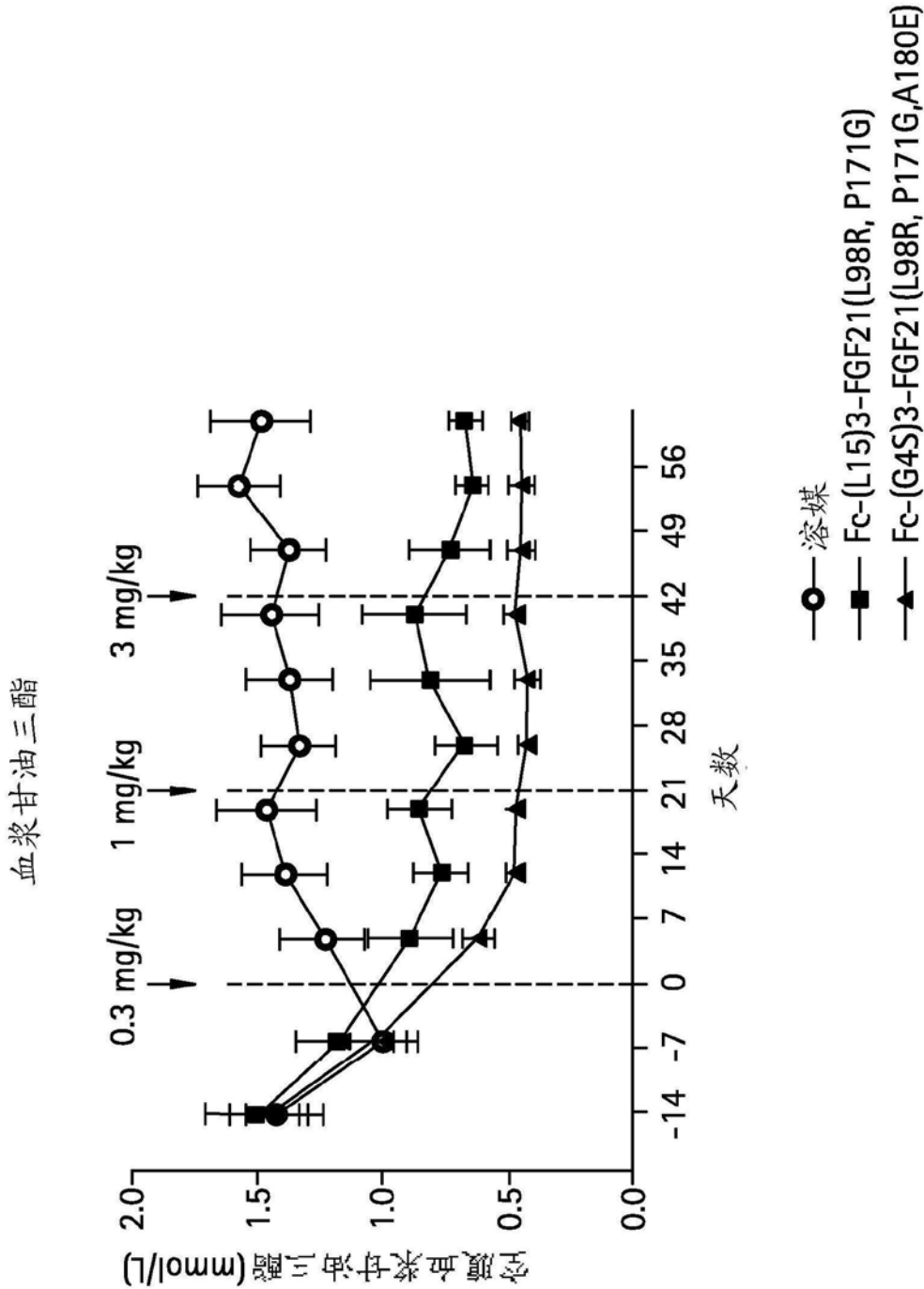


图74

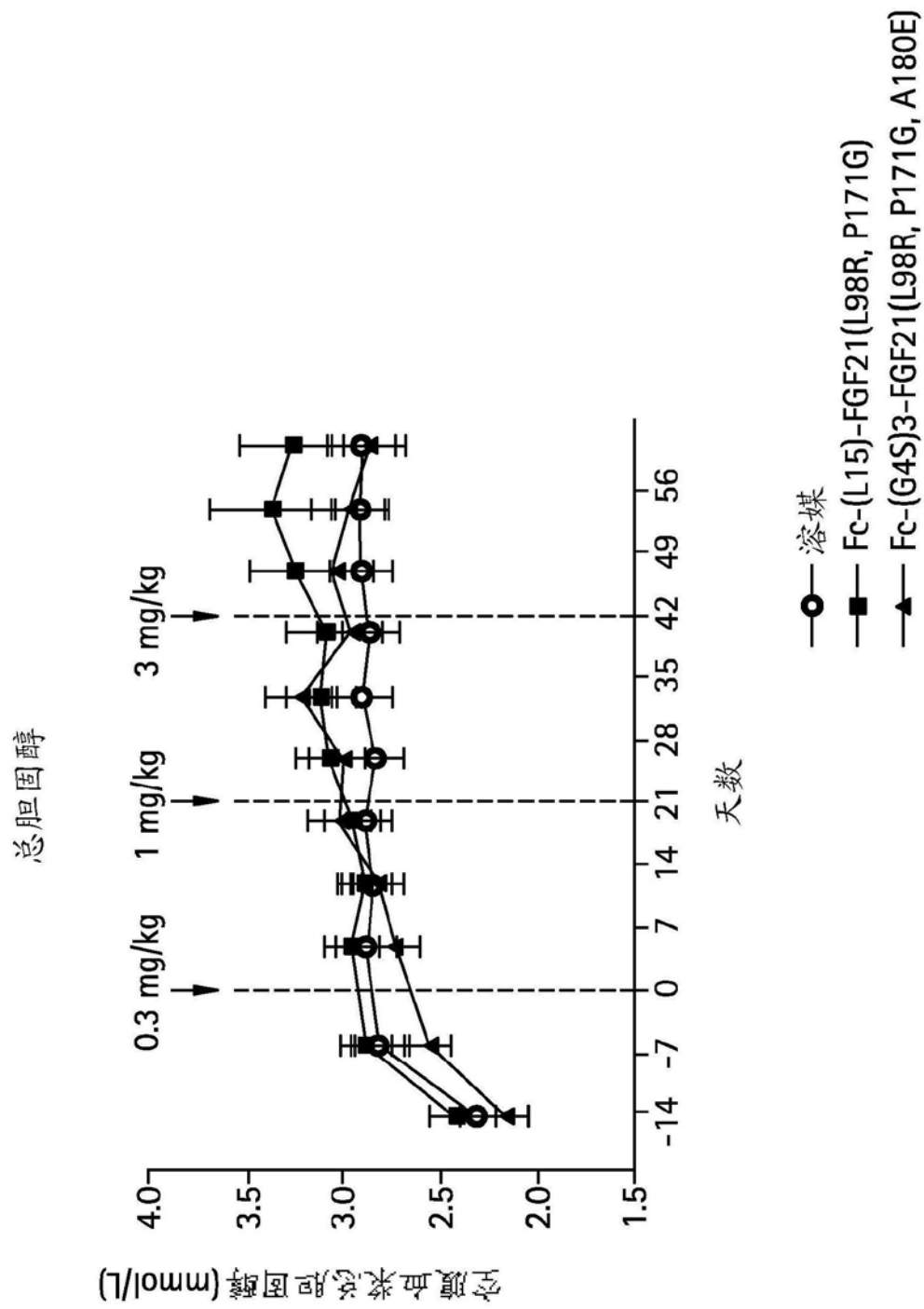


图75

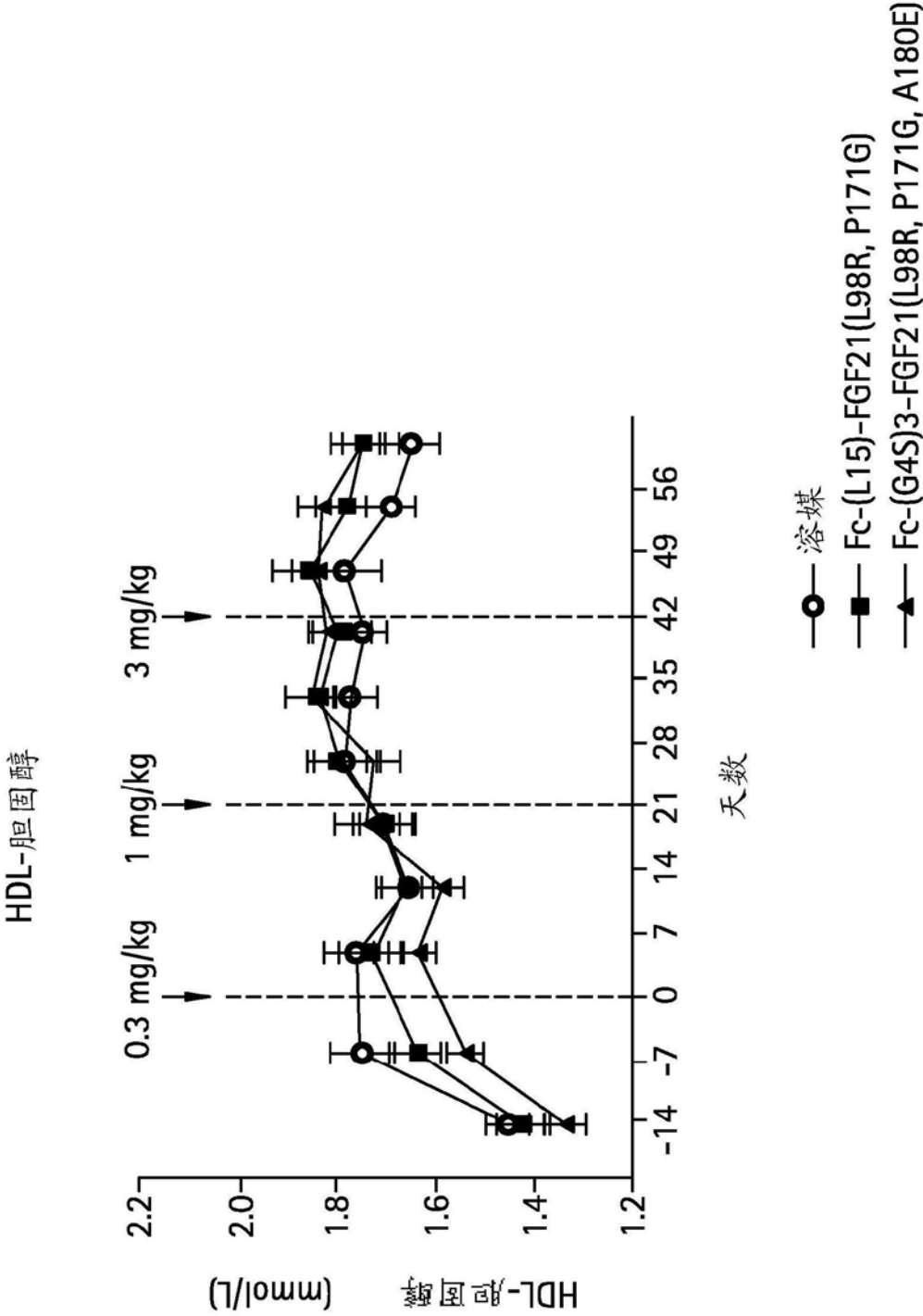


图76

图 77

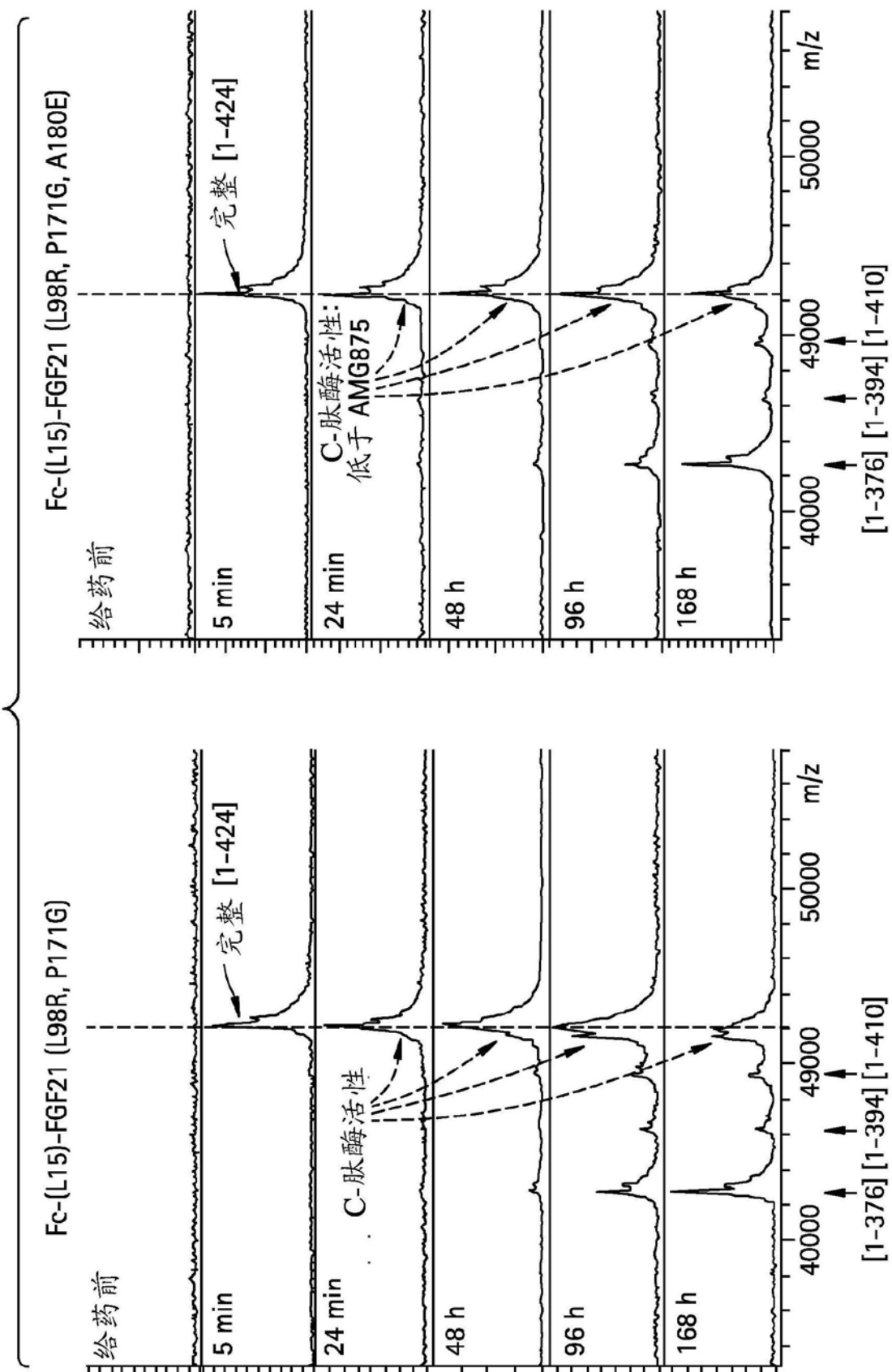


图77

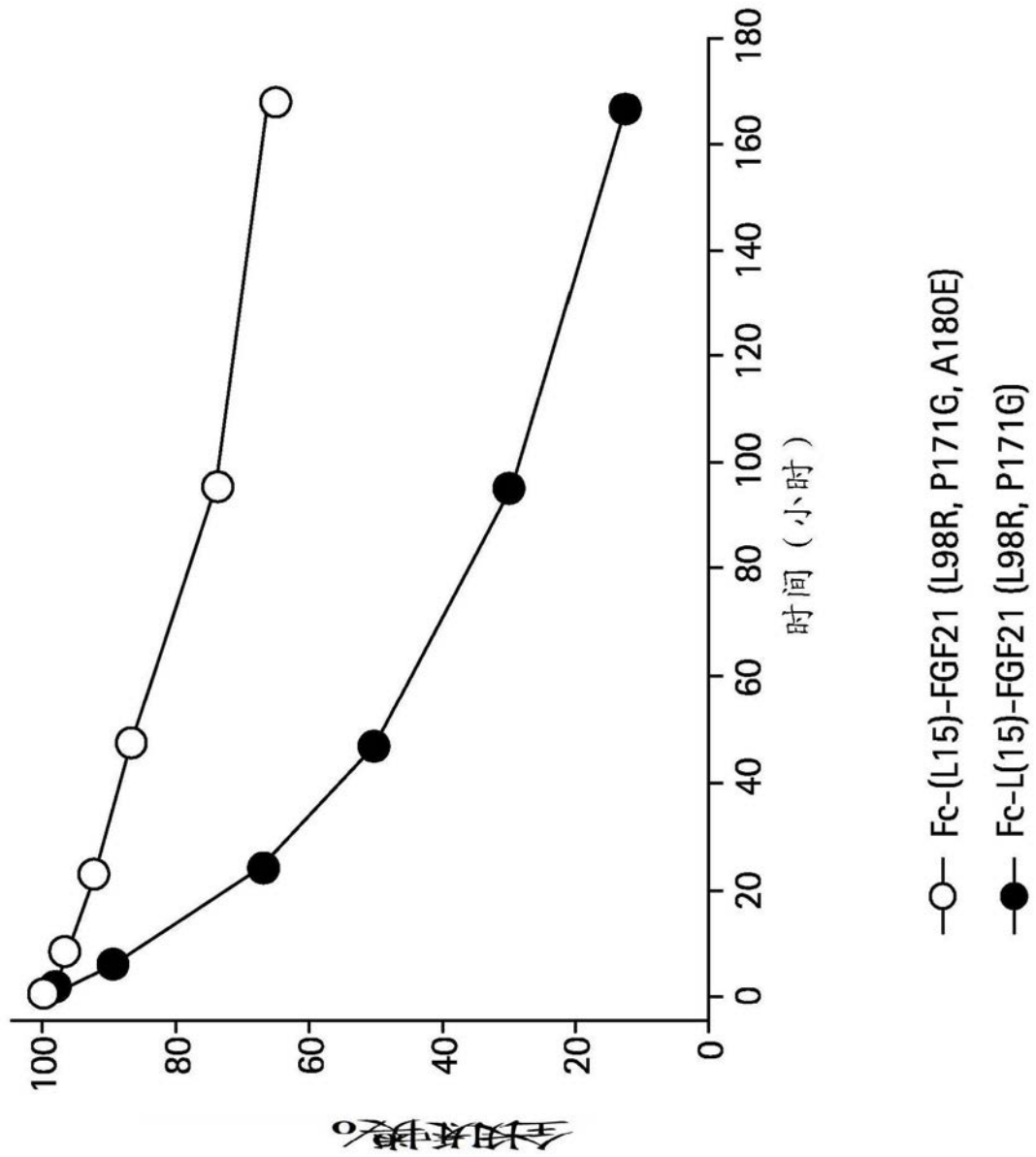


图78

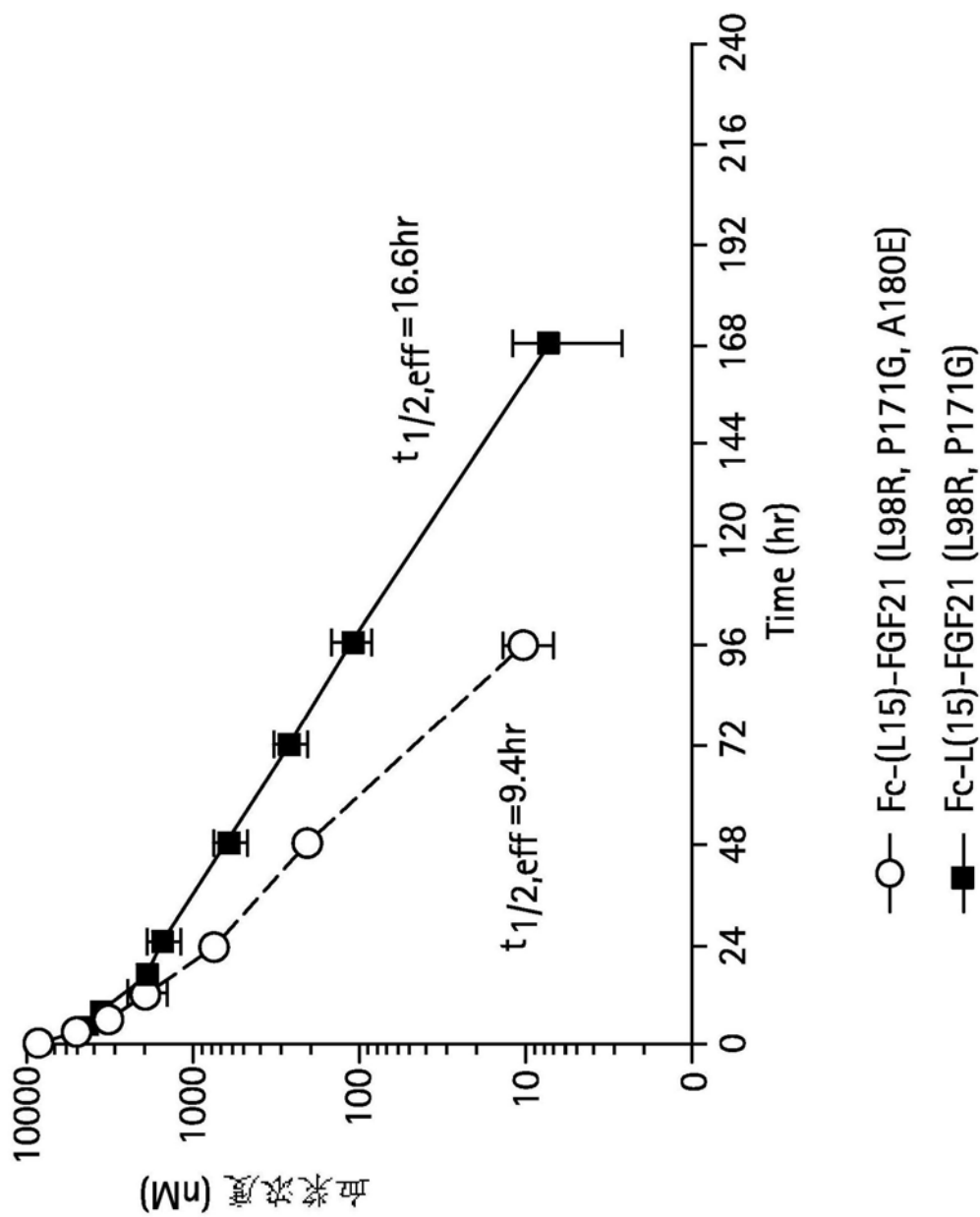


图79

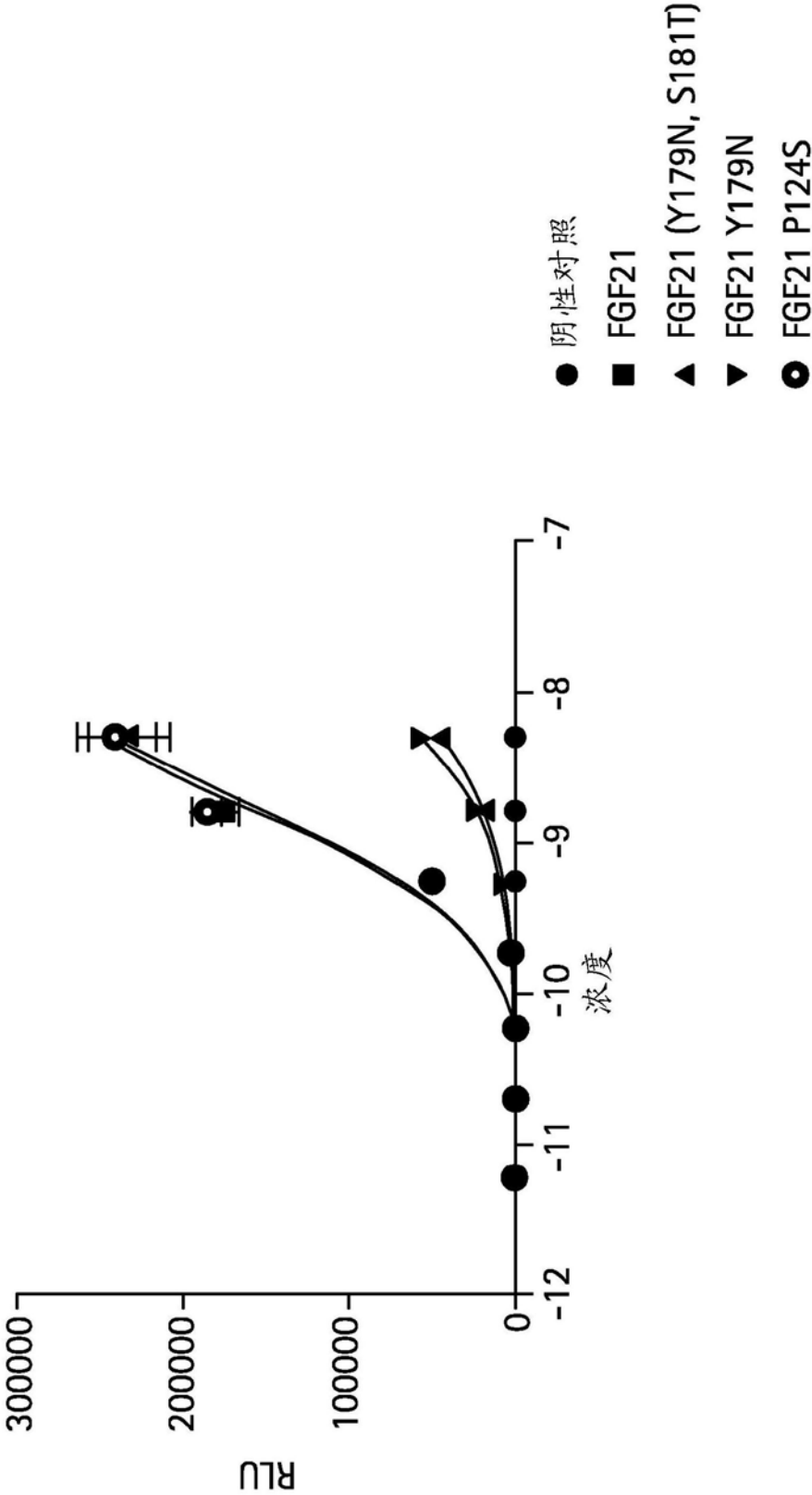


图80