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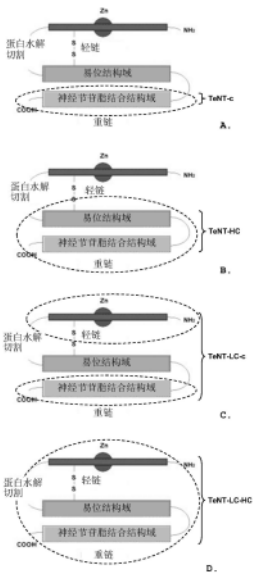
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(54)发明名称

聚乙二醇化的破伤风神经毒素和张力减退的治疗

(57)摘要

本发明涉及一种组合物,所述组合物包含:第一聚乙二醇化的破伤风神经毒素(PEG-TeNT)和第二破伤风神经毒素(TeNT),所述PEG-TeNT包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)。本发明还涉及各种PEG-TeNT。本发明还涉及一种使用所述组合物或各种PEG-TeNT治疗张力减退的方法和一种包含所述组合物或各种PEG-TeNT的试剂盒。在一个实施方案中,所述张力减退是阻塞性睡眠呼吸暂停。



CN 112638937 B

1.一种破伤风神经毒素(TeNT),所述破伤风神经毒素相对于SEQ ID NO: 1的破伤风神经毒素含有氨基酸取代R1225E和W1288A,其中所述TeNT是无活性的。

2.一种组合物,其包含:

(i)聚乙二醇化的破伤风神经毒素(PEG-TeNT),其中所述PEG-TeNT 相对于SEQ ID NO: 1的破伤风神经毒素(TeNT)包含以下表面丝氨酸→半胱氨酸的氨基酸取代:

S963C、S1041C、S1155C和S1187C;

S600C、S963C、S1041C、S1155C和 S1187C;

S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C;或

S81C、S120C、S144C、S248C、S335C、S428C、S600C、S963C、S1041C、S1155C和S1187C;

并且其中取代的半胱氨酸与所述PEG缀合;和

(ii)根据权利要求1所述的TeNT。

3.根据权利要求2所述的组合物,其中所述PEG的分子量是2 kDa、5 kDa、10 kDa或20 kDa。

4.根据权利要求2所述的组合物,其中所述PEG是直链的或支链的。

5.根据权利要求2所述的组合物,其中所述PEG-TeNT包含聚乙二醇化的TeNT轻链(LC)、聚乙二醇化的TeNT重链(HC)或聚乙二醇化的TeNT片段c (c)。

6.根据权利要求2所述的组合物,其中所述PEG-TeNT是包含聚乙二醇化的HC的PEG-TeNT-HC,或是包含聚乙二醇化的LC和聚乙二醇化的c的PEG-TeNT-LC-c。

7.根据权利要求2所述的组合物,其中所述PEG-TeNT是PEG-TeNT-HC,并且所述组合物还包含PEG-TeNT-LC-c。

8.根据权利要求2所述的组合物,其中所述组合物是治疗组合物。

9.TeNT或包含TeNT的组合物在制备用于治疗选自阻塞性睡眠呼吸暂停、呼吸暂停和打鼾的张力减退的药物中的用途,其中所述TeNT或组合物包含:

(i)聚乙二醇化的破伤风神经毒素(PEG-TeNT),其中所述PEG-TeNT相对于SEQ ID NO: 1的破伤风神经毒素(TeNT)包含以下表面丝氨酸→半胱氨酸的氨基酸取代:

S963C、S1041C、S1155C和S1187C;

S600C、S963C、S1041C、S1155C和 S1187C;

S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C;或

S81C、S120C、S144C、S248C、S335C、S428C、S600C、S963C、S1041C、S1155C和S1187C;

并且其中取代的半胱氨酸与所述PEG缀合;以及

(ii)根据权利要求1所述的TeNT。

10.根据权利要求9所述的用途,其中所述药物包含:

包含聚乙二醇化的c的PEG-TeNT (PEG-TeNT-c);和/或

包含聚乙二醇化的HC的PEG-TeNT (PEG-TeNT-HC)和包含聚乙二醇化的LC-c的PEG-TeNT (PEG-TeNT-LC-c);和/或

包含聚乙二醇化的HC和聚乙二醇化的LC的PEG-TeNT (PEG-TeNT-LC-HC)。

11.根据权利要求9所述的用途,其中所述张力减退是阻塞性睡眠呼吸暂停。

12.一种试剂盒,其包含根据权利要求1所述的TeNT或根据权利要求2至8中任一项所述的组合物。

聚乙二醇化的破伤风神经毒素和张力减退的治疗

技术领域

[0001] 本发明涉及一种组合物,所述组合物包含:包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)的第一聚乙二醇化的破伤风神经毒素(PEG-TeNT)和第二TeNT。本发明还涉及一种使用所述组合物治疗张力减退的方法。

背景技术

[0002] 破伤风神经毒素(TeNT)是由破伤风梭菌(Clostridium tetani)产生的。TeNT作用于脊髓并且阻断作为抑制性神经递质的γ-氨基丁酸(GABA)和甘氨酸在脊髓抑制性中间神经元处的释放。因而,TeNT会导致痉挛性麻痹。TeNT不存在多种血清型。

[0003] 已经提出了利用TeNT或至少TeNT片段的生物学特性进行治疗。然而,使用蛋白质治疗剂进行长期治疗往往会导致靶向免疫应答。由于仅已知TeNT的一种血清型,因此基于TeNT的治疗不能选择血清型转换来规避免疫。此外,许多人群针对TeNT接受过疫苗接种,从而排除了基于TeNT的治疗。

[0004] US 2002/0197278 A1公开了聚乙二醇化的肉毒杆菌毒素用于治疗不适当的肌肉收缩病症的用途。US 2002/0197278 A1还提出了聚乙二醇化的TeNT用于治疗不适当的肌肉收缩病症,例如迁移性头痛或斜视的用途。然而,如上所述,TeNT会引起肌肉收缩,从而排除了其在被聚乙二醇化或未被聚乙二醇化的情况下用于治疗不适当的肌肉收缩病症的用途。

[0005] Wan等,Process Biochemistry(2017)52:183-191公开了聚乙二醇化对由施用聚乙二醇化的蛋白质而产生的抗PEG免疫应答的影响,但是没有利用其发现用于任何治疗。

[0006] WO 2016/001762 A1公开了聚乙二醇化的TeNT片段c(c)用于增加肌肉质量的用途。当通过木瓜蛋白酶对TeNT进行酶切时,产生片段c(50kDa),并且该片段c对应于TeNT重链的C末端处的451个氨基酸。片段c保留了未消化的TeNT的结合、内化和跨突触转运能力,但是不会破坏任何神经元过程,并且因此是无毒的。

[0007] 需要一种基于TeNT的治疗,所述治疗在接受过破伤风类毒素免疫接种的受试者中避免了预先存在的抗TeNT免疫应答。

[0008] 应当了解的是,如果在本文中引用了任何现有技术出版物,那么这样的引用并不构成承认所述出版物形成了澳大利亚或任何其它国家的本领域公知常识的一部分。

发明内容

[0009] 本申请的发明人已经认识到,由于适应性免疫系统,因此对TeNT的利用尚未完全实现,在施用蛋白质治疗剂时,所述适应性免疫系统会产生抗体应答,从而降低了该蛋白质治疗剂的功效。作为疫苗接种的结果,所述适应性免疫应答可能是有意的,如由已经针对TeNT接受过免疫接种的许多人群所表现的那样。或者,适应性免疫应答可能是无意的,由反复暴露于蛋白质治疗剂而产生。

[0010] 本申请的发明人已经产生了解决这些问题的修饰的TeNT的家族和治疗方案。具体地,本发明提供了各自逃避免疫系统的聚乙二醇化的TeNT(PEG-TeNT)的家族和分级的治疗

方案,其中当先前施用的PEG-TeNT的功效降低时或当患者的免疫学特征排除使用另一种PEG-TeNT时,使用不同的替代性PEG-TeNT进行治疗。

[0011] 第一个方面提供了一种破伤风神经毒素(TeNT)或其片段,其相对于SEQ ID NO:1包含一个或多个表面丝氨酸→半胱氨酸的氨基酸取代。

[0012] 在第一个方面的一个实施方案中,取代的半胱氨酸与聚乙二醇(PEG)缀合。

[0013] 第二个方面提供了一种TeNT或其片段,其相对于SEQ ID NO:1包含:R1225K;R1225E;W1288A;W1288Y;W1288F;W1288L;R1225K和W1288A;R1225E和W1288A;R1225K和W1288Y;R1225E和W1288Y;R1225K和W1288F;R1225E和W1288F;R1225K和W1288L;R1225E和W1288L;R1225del;W1288del;或R1225del和W1288del;E270A;Y374A;E270A和Y374;G270del;Y374del;或其组合,其中所述TeNT或片段是无活性的。

[0014] 第三个方面提供了一种组合物,其包含:(i)第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT);和(ii)第二TeNT,其中所述第一PEG-TeNT不与所述第二TeNT缀合。

[0015] 第四个方面提供了一种用于治疗张力减退的方法,所述方法包括向受试者施用:(i)第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT);和(ii)第二TeNT。

[0016] 第四个方面还提供了包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)的第一聚乙二醇化的破伤风神经毒素(PEG-TeNT)在制造用于治疗在被施用了第二TeNT的受试者中张力减退的药物中的用途。

[0017] 第四个方面还提供了第二破伤风神经毒素(TeNT)在制造用于治疗在接受了第一聚乙二醇化的破伤风神经毒素(PEG-TeNT)的受试者中张力减退的药物中的用途,所述第一聚乙二醇化的破伤风神经毒素包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)。

[0018] 第四个方面还提供了以下各项在制造用于治疗张力减退的药物中的用途:(i)第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT);和(ii)第二TeNT。

[0019] 第四个方面还提供了一种包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)的第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其用于在被施用了第二TeNT的受试者中治疗张力减退的方法中。

[0020] 第四个方面还提供了一种第二破伤风神经毒素(TeNT),其用于治疗在被施用了第一聚乙二醇化的破伤风神经毒素(PEG-TeNT)的受试者中张力减退的方法中,所述第一聚乙二醇化的破伤风神经毒素包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)。

[0021] 第四个方面还提供了:(i)第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT);和(ii)第二TeNT;所述组合物用于治疗张力减退的方法中。

[0022] 在第四个方面的实施方案中,组合物可以包含所述第一PEG-TeNT和第二TeNT。

[0023] 第四个方面还提供了一种组合物,其包含:(i)第一聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT);和(ii)第二TeNT,所述组合物用于治疗张力减退的方法中。

[0024] 在一个实施方案中,所述第一PEG-TeNT或所述第二TeNT包含聚乙二醇化的TeNT轻

链(LC)、聚乙二醇化的TeNT重链(HC)、聚乙二醇化的TeNT重链(HC)和聚乙二醇化的TeNT轻链(LC),或聚乙二醇化的TeNT片段c(c)。在一个实施方案中,所述第一PEG-TeNT或所述第二TeNT包含PEG-TeNT-LC-HC。

[0025] 在另一个实施方案中,所述第一PEG-TeNT或所述第二TeNT是包含聚乙二醇化的HC的PEG-TeNT-HC。在该实施方案中,LC未被聚乙二醇化。在另一个实施方案中,所述第一PEG-TeNT或所述第二TeNT是包含聚乙二醇化的LC和聚乙二醇化的c的PEG-TeNT-LC-c。在该实施方案中,HN未被聚乙二醇化。

[0026] 在另一个实施方案中,所述第一PEG-TeNT是PEG-TeNT-HC,并且所述第二TeNT是PEG-TeNT-LC-c。

[0027] 在一个实施方案中,所述第二TeNT包含灭活的TeNT。相对于SEQ ID NO:1,所述灭活的TeNT可以包含:R1225K;R1225E;W1288A;W1288Y;W1288F;W1288L;R1225K和W1288A;R1225E和W1288A;R1225K和W1288Y;R1225E和W1288Y;R1225K和W1288F;R1225E和W1288F;R1225K和W1288L;R1225E和W1288L;R1225del;W1288del;R1225del或W1288del;E270A;Y374A;E270A和Y374A;G270del;Y374del;或其组合。在一个实施方案中,所述第二TeNT包含灭活的TeNT,所述灭活的TeNT包含R1225E和W1288A。

[0028] 在一个实施方案中,向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c)直到功效降低为止;然后施用包含PEG-TeNT-HC和PEG-TeNT-LC-c的组合物直到功效降低为止;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC)。

[0029] 在一个实施方案中,治疗包括向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c);然后施用包含PEG-TeNT-HC和PEG-TeNT-LC-c的组合物;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC),以确定所述受试者的抗TeNT抗体的免疫学特征并且基于该特征确定PEG-TeNT的有效组合物。

[0030] 在一个实施方案中,所述张力减退是阻塞性睡眠呼吸暂停。

[0031] 在另一个实施方案中,所述组合物是治疗组合物。在另一个实施方案中,所述组合物是美容组合物。

[0032] 还公开了一种用于制备由TeNT LC和TeNT HN组成的蛋白质(LC-HN)的方法,所述方法包括在宿主细胞中表达编码包含SEQ ID NO:6的氨基酸序列的核酸分子。

[0033] 第五个方面提供了一种聚乙二醇化的破伤风神经毒素(PEG-TeNT),其包含与聚乙二醇(PEG)缀合的破伤风神经毒素(TeNT)。

[0034] 在一个实施方案中,TeNT轻链(LC)被聚乙二醇化,TeNT重链(HC)被聚乙二醇化,或TeNT片段c(c)被聚乙二醇化。在一个实施方案中,LC被聚乙二醇化并且HC被聚乙二醇化(PEG-TeNT-LC-HC),或LC被聚乙二醇化并且c被聚乙二醇化(PEG-TeNT-LC-c)。

[0035] 在另一个实施方案中,PEG与TeNT的赖氨酸残基缀合。在另一个实施方案中,PEG与TeNT的半胱氨酸残基缀合。在一个实施方案中,PEG与TeNT的半胱氨酸残基缀合,其中相对于SEQ ID NO:1,所述半胱氨酸残基是天然的或是对丝氨酸残基的取代。

[0036] 在一个实施方案中,PEG具有约2kDa、约5kDa、约10kDa或约20kDa或约30kDa的分子量。

[0037] 第六个方面提供了一种用于治疗张力减退的方法,所述方法包括向受试者施用第

五个方面的PEG-TeNT,其中所述PEG-TeNT不与第二TeNT缀合。

[0038] 第六个方面还提供了第五个方面的PEG-TeNT在制造用于治疗张力减退的药物中的用途,其中所述PEG-TeNT不与第二TeNT缀合。

[0039] 或者,第六个方面提供了第五个方面的PEG-TeNT,其用于治疗张力减退的方法中,所述方法包括向受试者施用所述PEG-TeNT,其中所述PEG-TeNT不与第二TeNT缀合。

[0040] 在一个实施方案中,向所述受试者施用包含聚乙二醇化的HC的第一PEG-TeNT(PEG-TeNT-HC)和包含聚乙二醇化的LC和聚乙二醇化的c的第二PEG-TeNT(PEG-TeNT-LC-c)。

[0041] 在另一个实施方案中,向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c);和/或包含聚乙二醇化的HC的第一PEG-TeNT(PEG-TeNT-HC)和包含聚乙二醇化的LC-c的第二PEG-TeNT(PEG-TeNT-LC-c);和/或包含聚乙二醇化的HC和聚乙二醇化的LC的PEG-TeNT(PEG-TeNT-LC-HC)。

[0042] 在一个实施方案中,治疗包括向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c)直到功效降低为止。之后,治疗可以包括向所述受试者施用:PEG-TeNT-HC和PEG-TeNT-LC-c直到功效降低为止。之后,治疗可以包括向所述受试者施用:包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC)。

[0043] 在一个实施方案中,治疗包括向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c)直到功效降低为止;然后施用PEG-TeNT-HC和PEG-TeNT-LC-c直到功效降低为止;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC)。

[0044] 在一个实施方案中,治疗包括向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c),其包含具有约5kDa的分子量的PEG,直到功效降低为止;然后施用包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c),其包含具有约10kDa的分子量的PEG,直到功效降低为止;然后施用包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c),其包含具有约20kDa的分子量的PEG,直到功效降低为止。之后,治疗可以包括向所述受试者施用:PEG-TeNT-HC和PEG-TeNT-LC-c,其中任一者或两者包含具有5kDa的分子量的PEG,直到功效降低为止;然后施用PEG-TeNT-HC和PEG-TeNT-LC-c,其中任一者或两者包含具有10kDa的分子量的PEG,直到功效降低为止;然后施用PEG-TeNT-HC和PEG-TeNT-LC-c,其中任一者或两者包含具有20kDa的分子量的PEG,直到功效降低为止。之后,治疗可以包括向所述受试者施用:包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC),其中任一者或两者包含具有5kDa的分子量的PEG,直到功效降低为止;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC),其中任一者或两者包含具有10kDa的分子量的PEG,直到功效降低为止;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC),其中任一者或两者包含具有20kDa的分子量的PEG。

[0045] 在一个实施方案中,治疗包括向所述受试者施用:包含聚乙二醇化的c的PEG-TeNT(PEG-TeNT-c);然后施用包含PEG-TeNT-HC和PEG-TeNT-LC-c的组合物;然后施用包含聚乙二醇化的LC和聚乙二醇化的HC的PEG-TeNT(PEG-TeNT-LC-HC),以确定所述受试者的抗TeNT抗体的免疫学特征并且基于该特征确定PEG-TeNT的有效组合物。

[0046] 在另一个实施方案中,用TeNT治疗还包括施用灭活的TeNT。相对于SEQ ID NO:1,所述灭活的TeNT可以包含:R1225K;R1225E;W1228A;W1288Y;W1288F;W1288L;R1225K和

W1288A;R1225E和W1288A;R1225K和W1288Y;R1225E和W1288Y;R1225K和W1288F;R1225E和W1288F;R1225K和W1288L;R1225E和W1288L;R1225del;W1288del;R1225del或W1288del。在一个实施方案中,所述第二TeNT包含灭活的TeNT,所述灭活的TeNT包含R1225E和W1288A;E270A;Y374A;E270A和Y374A;G270del;Y374del;或其组合。

[0047] 在一个实施方案中,所述张力减退是阻塞性睡眠呼吸暂停。

[0048] 第七个方面提供了一种试剂盒,所述试剂盒包含第一个方面的TeNT、第二个方面的组合物或第五个方面的PEG-TeNT。

[0049] 在一个实施方案中,分别根据第三个方面或第六个方面的方法使用所述组合物或PEG-TeNT。

附图说明

[0050] 图1是本发明的示例性PEG-TeNT的示意图:A为PEG-TeNT-c;B为PEG-TeNT-HC;C为PEG-TeNT-LC-c;D为PEG-TeNT-LC-HC,其中所述TeNT是完整的并且具有活性,即TeNT包含两条链,并且聚乙二醇化分别存在于特定区域上,即c、HC、LC-c或LC-HC。

[0051] 图2是包含1314个氨基酸的成熟TeNT的氨基酸序列(SEQ ID NO:1)。

[0052] 图3是编码TeNT的载体pRSET-TeNT的核酸序列(SEQ ID NO:2)。

[0053] 图4是编码TeNT的载体pRSET-TeNT的图。TeNT被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0054] 图5是包含SEQ ID NO:1的氨基酸457至1314的HC的氨基酸序列(SEQ ID NO:3)。

[0055] 图6是包含SEQ ID NO:1的氨基酸864至1314的c的氨基酸序列(SEQ ID NO:4)。

[0056] 图7是编码c的载体pRSET-TeNT-c的核酸序列(SEQ ID NO:5)。

[0057] 图8是编码c的载体pRSET-TeNT-c的图。c被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0058] 图9是包含SEQ ID NO:1的氨基酸1至863的LC-HN的氨基酸序列(SEQ ID NO:6)。

[0059] 图10是编码LC-HN的载体pRSET-TeNT-LC-HN的核酸序列(SEQ ID NO:7)。

[0060] 图11是编码LC-HN的载体pRSET-TeNT-LC-HN的图。LC-HN被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0061] 图12是相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的非功能性c的氨基酸序列(SEQ ID NO:8)。

[0062] 图13是编码相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的图12的非功能性c(SEQ ID NO:8)的载体pRSET-TeNT-c的核酸序列(SEQ ID NO:9)。

[0063] 图14是编码相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的图12的非功能性c(SEQ ID NO:8)的载体pRSET-TeNT-c的图。相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的c被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0064] 图15是相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的非功能性TeNT的氨基酸序列(SEQ ID NO:10)。

[0065] 图16是编码相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的图15的非功能性TeNT(SEQ ID NO:10)的载体pRSET-TeNT的核酸序列(SEQ ID NO:11)。

[0066] 图17是编码相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的图15的非功能性TeNT(SEQ ID NO:10)的载体pRSET-TeNT的图。相对于SEQ ID NO:1包含氨基酸取代W1288A和R1225E的TeNT被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0067] 图18是具有1314个氨基酸的成熟TeNT的氨基酸序列(SEQ ID NO:12),相对于SEQ ID NO:1,所述成熟TeNT包含表面丝氨酸→半胱氨酸的氨基酸取代S81C、S120C、S144C、S248C、S335C、S428C、S600C、S963C、S1041C、S1155C和S1187C。

[0068] 图19是编码图18的表面丝氨酸被半胱氨酸取代的成熟TeNT(SEQ ID NO:12)的载体pRSET-TeNT的核酸序列(SEQ ID NO:13)。

[0069] 图20是编码图18的表面丝氨酸被半胱氨酸取代的成熟TeNT(SEQ ID NO:12)的图19的载体pRSET-TeNT(SEQ ID NO:13)的图。表面丝氨酸被半胱氨酸取代的TeNT被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0070] 图21是具有1314个氨基酸的成熟TeNT的氨基酸序列(SEQ ID NO:14),相对于SEQ ID NO:1,所述成熟TeNT在LC区域和c区域中包含表面丝氨酸→半胱氨酸的氨基酸取代S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C。

[0071] 图22是编码图21的表面丝氨酸被半胱氨酸取代的成熟TeNT(SEQ ID NO:14)的载体pRSET-TeNT的核酸序列(SEQ ID NO:15)。

[0072] 图23是编码图21的表面丝氨酸被半胱氨酸取代的成熟TeNT(SEQ ID NO:14)的图22的载体pRSET-TeNT(SEQ ID NO:15)的图。表面丝氨酸被半胱氨酸取代的TeNT被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0073] 图24是相对于SEQ ID NO:1包含HC表面丝氨酸→半胱氨酸的氨基酸取代S600C、S963C、S1041C、S1155C和S1187C的TeNT的氨基酸序列(SEQ ID NO:16)。

[0074] 图25是编码图24的表面丝氨酸被半胱氨酸取代的成熟TeNT(SEQ ID NO:16)的载体pRSET-TeNT的核酸序列(SEQ ID NO:17)。

[0075] 图26是编码图24的表面丝氨酸被半胱氨酸取代的TeNT(SEQ ID NO:16)的图25的载体pRSET-TeNT(SEQ ID NO:17)的图。表面丝氨酸被半胱氨酸取代的TeNT被表达为具有N末端His_6标签。该核酸插入于pRSET-A载体的MCS内并且在T7启动子的控制下表达。

[0076] 图27是源自于存储在蛋白质数据库(登录ID PDB:5N0B)中的晶体学数据的TeNT的3维蛋白质结构模型,其使用Discovery Studio将由主要人类抗体克隆型识别的表位(如由da Silva Antunes等(2017)和Palermo等(2017)所鉴定出)定位到所述模型上。选择所鉴定的表位中或附近的表面丝氨酸残基来将其突变为半胱氨酸以用于后续的聚乙二醇化。

[0077] 图28包括PEG-TeNT的SDS-PAGE分析的两张照片,PEG-TeNT包含具有递增分子量的PEG,其中(A)使用考马斯蓝进行检测和(B)使用多克隆抗TeNT抗体通过蛋白质印迹进行检测。(B)示出了免疫原性与PEG分子量成比例。左边缘具有以kDa为单位的分子量标记泳道1;TeNT泳道2;2kDa PEG-TeNT-HC-LC泳道3;5kDa PEG-TeNT-LC-HC泳道4;10kDa PEG-TeNT-LC-HC泳道5;20kDa PEG-TeNT-LC-HC泳道6。

[0078] 图29包括代表竞争性ELISA测定的四个线图。使用多克隆抗TeNT抗体针对TeNT测定了各自包含不同分子量的PEG(2kDa、5kDa、10kDa和20kDa)的四种PEG-TeNT和四种PEG-TeNT-LC-c丝氨酸突变体。(A)将TeNT吸附到ELISA板上,然后使用与四种浓度(10μg/mL、1μ

g/mL、0.1μg/mL和0.01μg/mL)的四种PEG-TeNT抗原(2kDa、5kDa、10kDa和20kDa)中的每一种一起预孵育的多克隆抗TeNT抗体进行探测。(B)将每一种PEG-TeNT(2kDa、5kDa、10kDa和20kDa)吸附到单独的ELISA板上,然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的TeNT抗原中的每一种一起预孵育的多克隆抗TeNT抗体进行探测。(C)将TeNT-LC-c丝氨酸突变体吸附到ELISA板上,然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的四种PEG-TeNT-LC-c丝氨酸突变体抗原(2kDa、5kDa、10kDa和20kDa)中的每一种一起预孵育的多克隆抗TeNT抗体进行探测。(D)将每一种PEG-TeNT-LC-c丝氨酸突变体(2kDa、5kDa、10kDa和20kDa)吸附到单独的ELISA板上,然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的TeNT-LC-c丝氨酸突变体抗原中的每一种一起预孵育的多克隆抗TeNT抗体进行探测。

[0079] 图30包括示出了接受PEG-TeNT-LC-HC注射的雌性C57BL/6小鼠的后肢中的局部肢体抽搐的四张照片。A和B示出了未接受过实验的小鼠中的局部肢体抽搐。C示出了在接种过破伤风类毒素疫苗的小鼠中注射100单位的TeNT之后没有肢体抽搐,而D示出了在接种过破伤风类毒素疫苗的小鼠中注射80单位的PEG-TeNT LC-HC 20kDa之后有持续的肢体抽搐。

[0080] 图31包括两个点图,示出了在注射了限定数量的单位的TeNT、PEG-TeNT-LC-HC 20kDa、TeNT-LC-c丝氨酸突变体、PEG-TeNT-LC-c丝氨酸突变体2kDa或PEG-TeNT-LC-c丝氨酸突变体20kDa之后在雌性C57BL/6小鼠的后肢中表现出的临床破伤风水平。A)向小鼠注射TeNT或PEG-TeNT-LC-HC 20kDa。B)向小鼠注射TeNT、TeNT-LC-c丝氨酸突变体、PEG-TeNT-LC-c丝氨酸突变体2kDa或PEG-TeNT-LC-c丝氨酸突变体20kDa。1单位是在未接受过实验的小鼠中在24小时内产生第四阶段抽搐所需的毒素的最小量。

[0081] 图32包括两个线图,示出了在接种过破伤风类毒素疫苗的小鼠中临床抽搐的进展。A示出了在存在或不存在灭活的TeNT诱饵的情况下注射4000单位的TeNT之后抽搐的进展。B示出了在存在或不存在灭活的TeNT诱饵的情况下注射40单位的TeNT-PEG 20kDa之后抽搐的进展。在这两种情况下,诱饵的存在都明显促进了进展。

[0082] 图33是箱线图,其示出了增加破伤风毒素的剂量对根据实施例23处理的英国牛头犬的呼吸紊乱指数(RDI)的影响。黑色条柱代表在每一种破伤风毒素剂量下进行的六次研究的中值RDI。阴影箱代表四分位数间距并且括号代表在每一种剂量下的最小和最大RDI样品。与在施用安慰剂后的RDI相比,在施用10IU/kg后,增加破伤风毒素与RDI降低有关(P=0.043;威氏符号秩次检验(Wilcoxon Signed Ranks test))。安慰剂和10IU/kg的中值另外分别由○和*表示。

具体实施方式

[0083] 本发明涉及逃避免疫的TeNT和PEG-TeNT分子(图1)、其组合物以及它们的治疗和美容用途。在一个实施方案中,本发明涉及治疗张力减退,任选地阻塞性睡眠呼吸暂停。

[0084] 本文描述了特定修饰的TeNT以及TeNT和诱饵(无活性的TeNT)的组合物在有针对破伤风类毒素的保护性免疫应答的受试者中治疗张力减退的用途。为了实现该目的,通过添加PEG、引入特定的突变或其组合来修饰活性TeNT,以用于在破伤风免疫患者中递送能够增加肌张力的生物活性化合物。

[0085] 所述活性可以通过施用单位确定剂量的修饰的毒素或制剂来证实,其中在相同的

单位剂量下,TeNT在接受过疫苗接种的受试者中将不表现出活性。基于对TeNT的三维结构的分析,引入特定表面突变以定向连接PEG分子允许掩蔽已知在接受过疫苗接种的受试者中被保护性抗体应答靶向的特定TeNT表位。相对于所施用的等效单位的TeNT,聚乙二醇化、定点突变和诱饵分子制剂的组合极大地提高了分子在接受过疫苗接种的哺乳动物模型中增加肌张力的作用。

[0086] US 2002/0197278公开了用于治疗不适当的肌肉收缩病症的一系列聚乙二醇化的肉毒杆菌毒素并且表明TeNT可以用作肉毒杆菌毒素的替代物。然而,TeNT不能用于治疗肌肉收缩。此外,由于所公开的方法不包括表位的定点掩蔽,因此US 2002/0197278的所谓的发明似乎无法实现,并且就本申请的发明人所知,有意掩蔽TeNT表位所需的三维结构和表位鉴定在US 2002/0197278的优先权日是未知的。

[0087] Wan等涉及聚乙二醇化对由施用聚乙二醇化的蛋白质而产生的抗PEG免疫应答的影响,但是并未利用其发现用于任何治疗。尽管Wan等公开了聚乙二醇化的破伤风类毒素相对于非聚乙二醇化的破伤风类毒素表现出降低的免疫原性,但是Wan等并未提出治疗相关的分子或制剂。此外,破伤风类毒素的聚乙二醇化与活性TeNT的修饰无关,这是因为破伤风类毒素是用于疫苗接种的无生物活性的TeNT,其可以通过TeNT的甲醛交联而产生。也就是说,聚乙二醇化或未聚乙二醇化的破伤风类毒素不具有活性TeNT的酶活性、结合活性和易位活性的组合。

[0088] WO 2016/001762 A1仅涉及TeNT c片段,其是除了结合神经递质和进入神经元之外没有特定活性的分子。

[0089] 因此,需要一种基于TeNT的治疗,其在接受过破伤风类毒素免疫接种的受试者中避免预先存在的抗TeNT免疫力。本文公开了该问题的解决方案,其部分地由掩蔽的活性的和治疗相关的聚乙二醇化的TeNT提供。

[0090] 破伤风神经毒素(TeNT)

[0091] TeNT为约150kDa并且由tetX基因表达。对应于tetX的编码区,但是缺少起始甲硫氨酸密码子的密码子优化的核酸序列提供于图3的载体序列(SEQ ID NO:2)中。TeNT被表达为一个蛋白质,所述蛋白质被翻译后切割,即首先去除起始甲硫氨酸,然后切割成两部分:源自于未切割的蛋白质的N末端的50kDa轻链(LC或A链)和源自于未切割的蛋白质的C末端的100kDa重链(HC或B链)。这两条链通过链间二硫键连接,这对于神经毒性来说至关重要。成熟TeNT的1314氨基酸序列提供于图2中(SEQ ID NO:1)。

[0092] LC具有锌内肽酶活性并且攻击囊泡与膜融合所必需的囊泡相关膜蛋白(VAMP),从而阻止了神经递质的释放。

[0093] 在用木瓜蛋白酶消化后,HC可以被切割成各自50kDa的两个结构域:被命名为HN的N末端易位结构域;和被命名为片段c(c)的C末端神经节苷脂(膜)结合结构域。缺少c的TeNT在本文被称为LC-HN。

[0094] c带有两个多唾液酸神经节苷脂结合位点并且与神经元膜上的多唾液酸神经节苷脂(GD2 GD1b和GT1b)结合。因此,c介导TeNT与周围运动轴突的突触前膜的结合并且帮助TeNT移动穿过该膜进入神经元。

[0095] 氨基酸序列:

[0096] 缺少起始甲硫氨酸的TeNT的氨基酸序列提供于图2中(SEQ ID NO:1);

[0097] HC的氨基酸序列提供于图5中(SEQ ID NO:3);

[0098] c的氨基酸序列提供于图6中(SEQ ID NO:4);并且

[0099] LC-HN的氨基酸序列提供于图9中(SEQ ID NO:6)。

[0100] 编码以下各项的载体的密码子优化的核酸序列和载体图:

[0101] c提供于图7(SEQ ID NO:5)和图8中;并且

[0102] LC-HN提供于图10(SEQ ID NO:7)和图11中。

[0103] 如本文所用的"TeNT"用于指由重链和轻链组成的完整TeNT分子。亚结构域和片段在本文中由它们的缩写指代:轻链"LC";重链"HC";重链N末端结构域"HN";重链片段c"c";轻链加重链N末端结构域"LC-HN"(即缺少c的TeNT分子)。在任何亚结构域或片段被聚乙二醇化的情况下,使用前缀PEG:PEG-LC;PEG-HC;PEG-HN;PEG-c;PEG-LC-HN。在包含聚乙二醇化的片段或亚结构域的完整TeNT分子中,使用前缀PEG并且指示聚乙二醇化的亚结构域或片段:PEG-TeNT-LC;PEG-TeNT-HC;PEG-TeNT-LC-HC;PEG-TeNT-HN;PEG-TeNT-c;PEG-TeNT-LC-c;PEG-TeNT-LC-HN等。

[0104] 应当了解的是,由于亚结构域和片段具有特定功能,因此亚结构域和片段对于完整TeNT来说是不可互换的。

[0105] 本文公开的TeNT可以具有活性或无活性。活性TeNT具有与天然TeNT相同的生物活性。无活性的TeNT缺少天然TeNT的一种或多种活性。在一个实施方案中,无活性的TeNT不阻断抑制性神经递质的释放。本公开的无活性的TeNT也可以被称为"诱饵"。无活性的TeNT包括破伤风类毒素。在一个实施方案中,无活性的TeNT是如本文所公开的无活性的TeNT。

[0106] 在一个实施方案中,两种或更多种TeNT可以缀合。

[0107] 在另一个实施方案中,TeNT不缀合。在本文公开的组合物、方法和用途的一个实施方案中,第一PEG-TeNT不与第二TeNT缀合。

[0108] 本文公开并且在图1中描绘的逃避免疫的PEG-TeNT包括:

[0109] 具有聚乙二醇化的片段c的TeNT(PEG-TeNT-c)(图1A);

[0110] 具有聚乙二醇化的重链的TeNT(PEG-TeNT-HC)(图1B);

[0111] 具有聚乙二醇化的轻链和聚乙二醇化的片段c的TeNT(PEG-TeNT-LC-c)(图1C);和

[0112] 完全聚乙二醇化的TeNT(PEG-TeNT-LC-HC)(图1D)。

[0113] PEG-TeNT-c在接受过疫苗接种的受试者中有利地逃避了适应性免疫系统的预先存在的免疫应答。在一个实施方案中,PEG-TeNT-c提供了第一级治疗以被使用直到功效降低为止。

[0114] PEG-TeNT-HC和PEG-TeNT-LC-c在接受过疫苗接种的受试者中有利地逃避了适应性免疫系统的预先存在的免疫应答并且还逃避了由反复暴露于PEG-TeNT-c而引发的适应性免疫系统的免疫应答。

[0115] 在一个实施方案中,PEG-TeNT-HC和PEG-TeNT-LC-c一起提供第二级治疗以被使用直到它们的功效降低为止。

[0116] PEG-TeNT-LC-HC在接受过疫苗接种的受试者中有利地逃避了适应性免疫系统的预先存在的免疫应答并且还逃避了由反复暴露于PEG-TeNT-c和暴露于PEG-TeNT-HC加PEG-TeNT-LC-c而引发的适应性免疫系统的免疫应答。

[0117] 在一个实施方案中,PEG-TeNT-LC-HC提供了第三级治疗以被使用直到它的功效降

低为止。

[0118] 还公开了具有聚乙二醇化的轻链的TeNT(PEG-TeNT-LC)、具有聚乙二醇化的LC和HN的TeNT(PEG-TeNT-LC-HN)和具有聚乙二醇化的HN的TeNT(PEG-TeNT-HN)。

[0119] 本领域技术人员将了解的是,PEG-TeNT的具体组合以及使用那些PEG-TeNT组合进行治疗的顺序可以改变。

[0120] 聚乙二醇(PEG)

[0121] PEG可以例如与TeNT中的以下氨基酸残基缀合:赖氨酸(例如氨基-聚乙二醇化)、半胱氨酸(例如硫醇-聚乙二醇化和桥联聚乙二醇化)、组氨酸、精氨酸、天冬氨酸、天冬酰胺(例如N-糖基-聚乙二醇化)、谷氨酸、谷氨酰胺(例如转谷氨酰胺酶介导的聚乙二醇化)、丝氨酸(例如O-糖基-聚乙二醇化)、苏氨酸(例如O-糖基-聚乙二醇化)或酪氨酸残基。聚乙二醇化的实例还包括N末端聚乙二醇化和C末端聚乙二醇化。

[0122] 聚乙二醇化可以通过使PEG与具有羟基反应性的官能团,例如酐、酰氯、氯甲酸盐和碳酸盐反应来实现。或者,聚乙二醇化可以用诸如醛、酯和酰胺的官能团来实现。

[0123] PEG可以是线性的或支化的。

[0124] PEG可以是改性的PEG,例如聚[低聚(乙二醇)甲基醚甲基丙烯酸酯](POEGMA)。

[0125] 聚乙二醇化可以是位点特异性聚乙二醇化。

[0126] 在一个实施方案中,将TeNT或TeNT片段的表面丝氨酸残基突变为表面半胱氨酸残基以促进在免疫原性表位处的定向PEG缀合。在这种背景下,突变与取代同义,例如丝氨酸被半胱氨酸取代。这样的突变或取代包括以下各项中的一个或多个的任意组合:S81C;S120C;S144C;S248C;S335C;S428C;S600C;S963C;S1041C;S1155C;和S1187C。

[0127] 用于异双官能PEG的官能团包括顺丁烯二酰亚胺、乙烯砜、吡啶基二硫化物、胺、羧酸和NHS酯。

[0128] 在一个实施方案中,使用碳二亚胺-EDC和磺基-NHS,用羧基-胺交联来将PEG与TeNT缀合。

[0129] 本发明还考虑了包含与TeNT的不同亚结构域或片段缀合的不同分子量的PEG的PEG-TeNT。

[0130] 例如可以在4℃至25℃将PEG与本公开的TeNT缀合或连接2小时至6小时。在一个实施方案中,在室温下将PEG与TeNT缀合6小时。

[0131] 适应症

[0132] 如本文所用的“张力减退”指的是可以通过抑制例如GABA或甘氨酸的抑制性神经递质来治疗的包括不随意肌无力的任何病症。因而,“张力减退”包括继发于神经系统驱动力降低或肌张力、强度或神经系统驱动力降低或不足的其它病因和疾患的肌张力降低。因此,在一个实施方案中,张力减退可以是神经性张力减退。

[0133] 可以用根据本公开的PEG-TeNT、组合物或方法治疗的张力减退病症包括阻塞性睡眠呼吸暂停、呼吸暂停、打鼾、上睑下垂、霍纳氏综合征(Horner’s syndrome)、肌肉萎缩、肌肉神经功能受损、肌萎缩性侧索硬化(ALS)、运动神经元病、任何肌病、多发性硬化症、重症肌无力、面部肌张力降低、任选的睑外翻、任何骨骼肌或平滑肌的任何病因引起的弛缓性麻痹或无力、任何病因引起的呼吸肌无力,包括呼吸机后无力;创伤引起的肌无力或由肌肉松弛引起的姿势不良、骨盆底肌松弛或无力或鼻或上呼吸道松弛。

[0134] 可以用根据本公开的PEG-TeNT、组合物或方法治疗的其它病症包括肌肉萎缩、肌营养不良或肌肉质量下降。

[0135] 在要根据本公开治疗的病症本身不是张力减退病症的情况下,通过用本公开的TeNT治疗来增加肌张力可以减轻所述病症的症状。

[0136] PEG-TeNT的美容应用可以包括收紧腹肌、收紧胸肌、收紧臀大肌、收紧骨骼肌或治疗由肌肉松弛引起的面部下垂。

[0137] 可以用根据本公开的PEG-TeNT、组合物或方法治疗的平滑肌、骨骼肌、组织或器官包括上食道、食道壁、食道括约肌、下食道括约肌、肛门括约肌、膀胱、膀胱括约肌、阴道括约肌、幽门括约肌、奥迪括约肌、回盲括约肌、骨盆底肌、阴道壁肌、前列腺、下颌下腺、腮腺、舌下腺、口腔粘膜的小唾液腺、声带、面部肌肉、咀嚼肌、头皮肌、胸肌、背肌、上肢肌肉、前臂肌肉、下肢肌肉、手部肌肉、足部肌肉、胃壁肌肉、结肠壁肌肉、颈部肌肉、咽喉扩张肌、咬肌、翼内肌、翼外肌、颏舌骨肌、颏舌肌、腭帆张肌、腭帆提肌、茎突咽肌、茎突舌肌、下颌舌骨肌、茎突舌骨肌、舌骨舌肌、二腹肌、胸锁乳突肌、斜方肌、颞肌、环咽肌、子宫肌和子宫颈、胃神经分布、鼻内粘膜、肺粘膜、皮肤、胸腺、骨骼、冠状动脉、肺平滑肌和心肌。

[0138] 组合物和施用

[0139] 本公开的组合物可以是治疗组合物或美容组合物。也就是说,所述组合物可以用于治疗或美容目的。

[0140] 如本文所用的术语“治疗组合物”或“美容组合物”指的是包含如本文所述的在受试者中抑制或治疗张力减退的TeNT的组合物。所述组合物已经被配制用于向受试者施用。在一个实施方案中,所述组合物是无菌的。在一个实施方案中,所述组合物是无热原的。所述组合物可以包含药学上可接受的载体。优选地,所述组合物是根据优良实验室规范(GLP)或优良制造规范(GMP)制造的。

[0141] 本公开的TeNT可以高达10mg/kg或更高的剂量施用。本公开的TeNT可以如下剂量施用:约1fg/kg、约5fg/kg、约10fg/kg、约50fg/kg、约100fg/kg、约500fg/kg、约1pg/kg、约5pg/kg、约10pg/kg、约50pg/kg、约100pg/kg、约500pg/kg、约1ng/kg、约2ng/kg、约3ng/kg、约4ng/kg、约5ng/kg、约6ng/kg、约7ng/kg、约8ng/kg、约9ng/kg、约10ng/kg、约11ng/kg、约12ng/kg、约13ng/kg、约14ng/kg、约15ng/kg、约16ng/kg、约17ng/kg、约18ng/kg、约19ng/kg、约20ng/kg、约30ng/kg、约40ng/kg、约50ng/kg、约60ng/kg、约70ng/kg、约80ng/kg、约90ng/kg、约100ng/kg、约200ng/kg、约300ng/kg、约400ng/kg、约500ng/kg、约600ng/kg、约700ng/kg、约800ng/kg、约900ng/kg、约1μg/kg、约5μg/kg、约10μg/kg、约50μg/kg、约100μg/kg、约500μg/kg、约1mg/kg或约10mg/kg。本公开的TeNT可以在以上列出的任何剂量的任何范围内施用。

[0142] 本公开的TeNT可以高达1000IU/kg或更高的剂量施用。本公开的TeNT可以如下剂量施用:约0.1IU/kg、约0.2IU/kg、约0.3IU/kg、约0.4IU/kg、约0.5IU/kg、约0.6IU/kg、约0.7IU/kg、约0.8IU/kg、约0.9IU/kg、约1IU/kg、约2IU/kg、约3IU/kg、约4IU/kg、约5IU/kg、约6IU/kg、约7IU/kg、约8IU/kg、约9IU/kg、约10IU/kg、约11IU/kg、约12IU/kg、约13IU/kg、约14IU/kg、约15IU/kg、约16IU/kg、约17IU/kg、约18IU/kg、约19IU/kg、约20IU/kg、约30IU/kg、约40IU/kg、约50IU/kg、约60IU/kg、约70IU/kg、约80IU/kg、约90IU/kg、约100IU/kg、约200IU/kg、约300IU/kg、约400IU/kg、约500IU/kg、约600IU/kg、约700IU/kg、约800IU/kg、约

900IU/kg、约1000IU/kg。本公开的TeNT可以在以上列出的任何剂量的任何范围内施用。

[0143] 在包含两种PEG-TeNT的组合物,例如包含其中TeNT-HC被聚乙二醇化的第一PEG-TeNT(PEG-TeNT-HC)和其中TeNT-LC被聚乙二醇化并且TeNT-c被聚乙二醇化的第二PEG-TeNT(PEG-TeNT-LC-c)的组合物中,所述第一PEG-TeNT与所述第二PEG-TeNT的比例可以变化。例如,第一PEG-TeNT与第二PEG-TeNT的比例可以是约1000:1、约500:1、约100:1、约50:1、约10:1、约5:1、约4:1、约3:1、约2:1、约1:1、约1:2、约1:3、约1:4、约1:5、约1:10、约1:50、约1:100、约1:500或约1:1000。

[0144] 组合物可以包含TeNT的任何组合并且不限于PEG-TeNT-HC和PEG-TeNT-LC-c的组合。组合物可以包含:PEG-TeNT-c和PEG-TeNT-HC;PEG-TeNT-c和PEG-TeNT-LC-c;PEG-TeNT-c和PEG-TeNT-LC-HC;PEG-TeNT-HC和PEG-TeNT-LC-HC;以及PEG-TeNT-LC-c和PEG-TeNT-LC-HC。还公开了一种组合物,所述组合物包含:PEG-TeNT-c、PEG-TeNT-HC和PEG-TeNT-LC-c;PEG-TeNT-c、PEG-TeNT-HC和PEG-TeNT-LC-HC;PEG-TeNT-c、PEG-TeNT-LC-c和PEG-TeNT-LC-HC;PEG-TeNT-HC、PEG-TeNT-LC-c和PEG-TeNT-LC-HC;以及PEG-TeNT-c、PEG-TeNT-HC、PEG-TeNT-LC-c和PEG-TeNT-LC-HC。在组合物中,可以替换任何TeNT,并且任何组合物还可以包含PEG-TeNT-LC、PEG-TeNT-LC-HN和/或PEG-TeNT-HN。

[0145] 在一个实施方案中,所述组合物还包含灭活的TeNT,所述灭活的TeNT用作由先前暴露于TeNT,例如由疫苗接种而产生的抗TeNT抗体的诱饵。相对于SEQ ID NO:1,所述灭活的TeNT可以包含:R1225K;R1225E;W1228A;W1288Y;W1288F;W1288L;R1225K和W1288A;R1225K和W1288Y;R1225E和W1288Y;R1225K和W1288F;R1225E和W1288F;R1225K和W1288L;R1225E和W1288L;R1225del;W1288del;或R1225del和W1288del;E270A;Y374A;E270A和Y374A;E270del;Y374del或其组合。在一个实施方案中,所述第二TeNT包含灭活的TeNT,所述灭活的TeNT包含R1225E、W1288A、E270A和Y374A。

[0146] 在包含至少一种PEG-TeNT和诱饵TeNT的组合物中,所述诱饵TeNT相对于所述PEG-TeNT将是摩尔过量的。例如,诱饵TeNT与PEG-TeNT的比例可以是约10^6:1;10^5:1、10^4:1、1000:1、约500:1、约400:1、约300:1、约200:1、约100:1、约90:1、约80:1、约70:1、约60:1、约50:1、约40:1、约30:1、约20:1、约10:1、约9:1、约8:1、约7:1、约6:1、约5:1、约4:1、约3:1、约2:1或约1:1。

[0147] 本公开的PEG-TeNT可以每周施用一次、两次或三次;每月施用一次、两次或三次;每季度施用一次、两次或三次;每6个月施用一次、两次或三次;或每年施用一次、两次或三次。

[0148] PEG-TeNT可以单次剂量、分次剂量或多次剂量施用。在肌肉成对存在的情况下,可以将PEG-TeNT单侧施用于该对肌肉中的一个肌肉或双侧施用于该对肌肉中的两个肌肉。

[0149] 作为包含本公开的两种或更多种PEG-TeNT的组合的替代,可以依次或同时组合施用所述两种或更多种PEG-TeNT。

[0150] 可以通过任何合适的方法,例如通过注射、手术植入、局部施用或鼻内施用向受试者局部施用PEG-TeNT。在一个实施方案中,通过注射到受影响的肌肉内来肌内施用TeNT。

[0151] PEG-TeNT将按照与优良医学规范一致的方式进行配制、给药和施用。在这种背景下考虑的因素包括所治疗的张力减退的具体类型、所治疗的具体受试者、受试者的临床状况、施用部位、施用方法、施用时间安排和包括牙科医生的医生已知的其它因素。要施用的

PEG-TeNT的治疗有效量将取决于这些考虑因素。

[0152] 药学上可接受的载体包括水、缓冲水、盐水溶液,例如生理盐水或平衡盐水溶液,如汉克氏平衡溶液(Hank's balanced solution)或厄尔氏平衡溶液(Earle's balanced solution)、甘氨酸和透明质酸。

[0153] 所述组合物可以被配制用于肌内施用。用于肌内施用的组合物可以包含药学上可接受的无菌水性或非水性溶液、分散液、悬浮液或乳液以及用于复原成无菌可注射溶液或分散液的无菌粉末。合适的水性和非水性载体、溶剂、稀释剂或媒介物的实例包括水、乙醇、多元醇(如甘油、丙二醇、聚乙二醇)、羧甲基纤维素和其混合物、植物油(如橄榄油)、可注射的有机酯(例如油酸乙酯)。

[0154] 所述组合物可以包含渗透促进剂以促进它们的TeNT递送。渗透促进剂可以包括脂肪酸,如油酸、月桂酸、癸酸、肉豆蔻酸、棕榈酸、硬脂酸、亚油酸、亚麻酸、二癸酸酯、reclineate、甘油一油酸酯、甘油二月桂酸酯、辛酸、花生四烯酸、1-单癸酸甘油酯、单酸甘油酯和二酸甘油酯以及其生理学上可接受的盐。

[0155] 所述组合物还可以包括螯合剂,例如乙二胺四乙酸(EDTA)、柠檬酸、水杨酸盐(例如水杨酸钠、5-甲氧基水杨酸盐、高香草酸盐)。

[0156] 还提供了一种制品和/或试剂盒,其包括包含PEG-TeNT或包含PEG-TeNT的组合物的容器。所述容器可以是包含PEG-TeNT或组合物(任选地为单位剂型)的瓶子、小瓶或注射器。例如,所述PEG-TeNT或组合物可以是在一次性容器,任选地注射器中的可注射溶液的形式。所述制品和/或试剂盒还可以包含印刷的说明书和/或标签等,指示根据本文公开的方法治疗受试者。

[0157] 术语"治疗有效量"指的是有效治疗受试者的张力减退的PEG-TeNT的量。

[0158] 术语"治疗(treat)"、"治疗(treating)"或"治疗(treatment)"指的是治疗性治疗和防范或预防性措施,其中目的在于在受试者中预防、减少或改善张力减退或减慢(减轻)受试者的张力减退的进展。需要治疗的受试者包括已经患有张力减退的受试者以及要预防或改善张力减退的受试者。

[0159] 术语"预防(preventing)"、"预防(prevention)"、"预防性"或"防范性"指的是避免发生张力减退或阻碍、防御或防止张力减退的发生。需要预防的受试者可能容易患上张力减退。

[0160] 术语"改善(ameliorate)"或"改善(amelioration)"指的是减轻、减少或消除张力减退。

[0161] 张力减退可以被定量。张力减退可以在半定量量表上定量,例如0至5,其中0代表不存在,1至4代表严重程度的可辨识的增加,并且5代表最大严重程度。或者,张力减退可以作为二元事件定量,即存在或不存在(0或1)。其它半定量量表对于本领域技术人员来说将是显而易见的。在另一个实施方案中,张力减退可以在定量量表上定量,例如使用测力计。

[0162] 张力减退的任何定量可以与对照进行比较,例如没有接受PEG-TeNT的健康对照受试者、接受张力减退的治疗,但是没有用PEG-TeNT治疗的患病对照受试者,或人群。

[0163] 通过施用PEG-TeNT治疗张力减退可以是使张力减退减少约1%、减少约2%、减少约3%、减少约4%、减少约5%、减少约6%、减少约7%、减少约8%、减少约9%、减少约10%、减少约20%、减少约30%、减少约40%、减少约50%、减少约60%、减少约70%、减少约80%、

减少约90％或减少约100％。

[0164] 如本文所用的术语“受试者”可以指的是哺乳动物。所述哺乳动物可以是灵长类动物,特别是人类,或可以是家畜、动物园动物或伴侣动物。尽管特别考虑了本文公开的PEG-TeNT、组合物和方法适用于人类的医学治疗,但是它也适用于兽医学治疗,包括治疗家畜,如马、牛和羊;伴侣动物,如狗和猫;或动物园动物,如猫科动物、犬科动物、牛科动物和有蹄类动物。

[0165] 除非在本说明书中另有定义,否则本文使用的技术术语和科学术语具有与本发明所属领域的技术人员通过参考公开文本通常所理解的含义相同的含义。

[0166] 要指出的是,术语“一个/种(a/an)”指的是一个/种或多个/种,例如“一种TeNT”应当被理解为表示一种或多种TeNT。因而,术语“一个/种(a/an)”、“一个/种或多个/种”和“至少一个/种”在本文中可互换使用。

[0167] 在所附权利要求和本发明的说明书中,除非上下文由于表达语言或必要的暗示而另外需要,否则词语“包含(comprise)”或诸如“包含(comprises)”或“包含(comprising)”的变体以包括性含义使用,即指定所述特征的存在,但不排除在本发明的各种实施方案中存在或添加另外的特征。

[0168] 如本文所用的术语“约”涵盖了给定数量的与该数量的量值相差±25％的值的范围。在其它实施方案中,术语“约”涵盖了给定数量的与该数量的量值相差±20％、±15％、±10％、±5％、±4％、±3％、±2％或±1％的值的范围。例如,在一个实施方案中,“约3克”表示2.7克至3.3克的值(即3克±10％)等。

[0169] 类似地,事件的时间或持续时间可以变化至少25％。例如,尽管具体事件在一个实施方案中可以被公开为持续一天,但是所述事件可以持续多于一天或少于一天。例如,“一天”可以包括约18小时至约30小时的时间段。在其它实施方案中,时间段可以变化该时间段的±20％、±15％、±10％、±5％、±4％、±3％、±2％或±1％。

[0170] 实施例

[0171] 实施例1:PEG-TeNT-c的制备(图1A)

[0172] 在本实施例中,将TeNT-c的表面丝氨酸残基突变为表面半胱氨酸残基以促进在免疫原性表位处的定向PEG缀合而产生图1A的分子。所述突变将是:S963C、S1041C、S1155C和S1187C。

[0173] 具有表面丝氨酸→半胱氨酸取代S963C、S1041C、S1155C和S1187C的TeNT的基因将由商业提供商(例如Integrated DNA Technologies公司)合成。通过限制性酶切消化将所述基因亚克隆到pRSET-A表达载体中以将来自所述载体的6×组氨酸标签添加到突变蛋白的N末端。

[0174] 将根据实施例5将包含S963C、S1041C、S1155C和S1187C的TeNT表达、聚乙二醇化和纯化以产生PEG-TeNT-c。

[0175] 实施例2:PEG-TeNT-HC的制备(图1B)

[0176] 在本实施例中,将TeNT-HC的表面丝氨酸残基突变为表面半胱氨酸残基以促进在免疫原性表位处的定向PEG缀合而产生图1B的分子。突变将是:S600C、S963C、S1041C、S1155C和S1187C(图24,SEQ ID NO:16)。

[0177] 具有表面丝氨酸→半胱氨酸取代S600C、S963C、S1041C、S1155C和S1187C的TeNT的

基因将由商业提供商(例如Integrated DNA Technologies公司)合成。通过限制性酶切消化将所述基因亚克隆到pRSET-A表达载体(图25,SEQ ID NO:17,图26)中以将来自所述载体的6×组氨酸标签添加到突变蛋白的N末端。

[0178] 将根据实施例5将包含S600C、S963C、S1041C、S1155C和S1187C的TeNT表达、聚乙二醇化和纯化以产生PEG-TeNT-HC。

[0179] 实施例3:PEG-TeNT-LC-c的制备(图1C)

[0180] 在本实施例中,将LC和c的表面丝氨酸残基突变为表面半胱氨酸残基以促进在免疫原性表位处的定向PEG缀合而产生图1C的分子。突变是:S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C(图21,SEQ ID NO:14)。

[0181] 在LC和c中具有表面丝氨酸→半胱氨酸取代S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C的TeNT的基因由商业提供商(Integrated DNA Technologies公司)合成。通过限制性酶切消化将所述基因亚克隆到pRSET-A表达载体(图22,SEQ ID NO:15,图23)中以将来自所述载体的6×组氨酸标签添加到突变蛋白的N末端。

[0182] 根据实施例5将包含S81C、S120C、S144C、S248C、S335C、S428C、S963C、S1041C、S1155C和S1187C的TeNT表达、聚乙二醇化和纯化以产生PEG-TeNT-LC-c。

[0183] 内毒素去除

[0184] 根据实施例4从TeNT-LC-c丝氨酸突变体中去除内毒素。

[0185] PEG与半胱氨酸残基的连接。

[0186] 1.将摩尔过量的PEG-顺丁烯二酰亚胺与丝氨酸突变体TeNT-LC-c(0.5mg/mL-2mg/mL)在pH 6.5-7.5的PBS中组合,其中PEG具有约2kDa、约5kDa、约10kDa或约20kDa。

[0187] 2.在室温下进行连接6小时。

[0188] 3.通过尺寸排阻色谱法去除过量的PEG。

[0189] 蛋白质的胰蛋白酶消化激活

[0190] 根据实施例4进行胰蛋白酶消化以激活TeNT-LC-c丝氨酸突变体。

[0191] 实施例4:PEG-TeNT-LC-HC的制备(图1D)(方法1)

[0192] TeNT的制备

[0193] 1.用pRSET-TeNT载体(图3和图4)对大肠杆菌BL21 DE3 pLysS菌株进行电转化并且使其在具有选择抗生素(氨苄西林和氯霉素)的LB琼脂上在37℃生长过夜。

[0194] 2.用来自选择平板的1个菌落接种200mL的预诱导肉汤。pH 7.2-7.4的预诱导肉汤包含:1.2%的胰蛋白胨;2.4%的酵母提取物;2%的葡萄糖;0.4%的甘油;17mM KH_2PO_4;72mM K_2HPO_4;和选择抗生素(氨苄西林和氯霉素)。

[0195] 3.将培养物在30℃在快速振荡下孵育过夜。

[0196] 4.通过以4000g离心10分钟来收获过夜培养物。

[0197] 5.将沉淀物重悬在200mL的表达肉汤(pH 7.2-7.4)中,所述表达肉汤包含:1.2%的胰蛋白胨;2.4%的酵母提取物;0.4%的甘油;1mM IPTG;17mM KH_2PO_4;72mM K_2HPO_4;100μg/mL氨苄西林;和10μM $ZnCl_2$。

[0198] 6.在30℃在快速振荡下使蛋白质表达6小时。

[0199] 7.通过以4500g离心15分钟来收获细胞并且将沉淀物重悬在含有20mM咪唑的30mL TBS(pH 8)中。

[0200] 8.通过超声处理将细胞裂解。

[0201] 9.通过以4500g离心20分钟来澄清细胞裂解液并且通过0.45μm过滤器过滤。

[0202] 10.使用AKTA纯25FPLC系统(通用电气公司(GE))通过His标签亲和色谱法纯化蛋白质。

[0203] 11.使用尺寸排阻色谱法将纯化的蛋白质与PBS进行缓冲液交换,继而使用AKTA纯25FPLC和Superdex 200增加10/300GL柱通过凝胶过滤进行第二阶段纯化。

[0204] 内毒素去除

[0205] 1.将0.5mL内毒素去除旋转柱平衡到室温。

[0206] 2.去除柱底塞,松开柱帽,将柱放置在15mL管中,然后以500g离心1分钟以从柱中去除溶液。丢弃溶液。

[0207] 3.更换柱底塞,去除柱帽,将于95%乙醇中0.2N的NaOH添加到树脂中,更换柱帽,将柱翻转几次以重悬树脂,然后在室温下孵育1小时-2小时。

[0208] 4.去除柱底塞,松开柱帽,将柱放置在15mL管中,然后以500g离心1分钟以从柱中去除溶液。丢弃溶液。

[0209] 5.更换柱底塞,去除柱帽,将无内毒素的2M NaCl添加到树脂中,更换柱帽,并且将柱翻转几次以重悬树脂。

[0210] 6.去除柱底塞,松开柱帽,将柱放置在15mL管中,然后以500g离心1分钟以从柱中去除溶液。丢弃溶液。

[0211] 7.更换柱底塞,去除柱帽,将无内毒素的超纯水添加到树脂中,更换柱帽,并且将柱翻转几次以重悬树脂。

[0212] 8.去除柱底塞,松开柱帽,将柱放置在15mL管中,并且以500g离心1分钟以从柱中去除溶液。丢弃溶液。

[0213] 9.更换柱底塞,去除柱帽,将无内毒素的磷酸盐缓冲液添加到树脂中,更换柱帽,并且将柱翻转几次以重悬树脂。

[0214] 10.去除柱底塞,松开柱帽,将柱放置在15mL管中,并且以500g离心1分钟以从柱中去除溶液。丢弃溶液。

[0215] 11.用磷酸盐缓冲液将柱再冲洗两次并且丢弃洗脱液。

[0216] 12.更换柱底塞,去除柱帽,将样品施加到树脂中,更换柱帽,并且将柱翻转几次以重悬树脂。

[0217] 13.将柱在4℃在颠倒混合下孵育至少1小时。

[0218] 14.去除柱底塞,松开柱帽,将柱放置在无内毒素的15mL管中,并且以500g离心1分钟以从柱中去除溶液。保留样品。

[0219] 15.使用再生的旋转柱重复内毒素去除程序直到样品中的内毒素水平在等同或更低的水平为止以使得所有剂量均将含有每公斤受试者少于5EU单位的内毒素。

[0220] PEG-TeNT-LC-HC的制备

[0221] 1.在总体积500μL的PBS(pH 7.4)中,将3μmol纯化的TeNT和0.5mmol mpeg-NHS(SC)(Nanocs公司)与2kDa、5kDa、10kDa、20kDa或30kDa PEG中的一种组合。

[0222] 2.将样品在室温下混合3小时。

[0223] 3.通过尺寸排阻色谱法去除过量的PEG。

[0224] 胰蛋白酶将蛋白质消化成活性形式

[0225] 1.将1mg的蛋白质溶解在0.5mL消化缓冲液中,所述消化缓冲液包含0.1M NH_4HCO_3缓冲液(pH 8.0)或0.1M Tris缓冲液(pH 8.5)。

[0226] 2.用3×500μL消化缓冲液洗涤0.10mL至0.25mL固定的TPCK胰蛋白酶。在每一次洗涤后通过离心将凝胶与缓冲液分离。

[0227] 3.将凝胶重悬在约0.2mL消化缓冲液中。

[0228] 4.将固定的TPCK胰蛋白酶添加到蛋白质样品中。

[0229] 5.将反应混合物在快速振荡孵育箱中在37℃孵育2小时至18小时。

[0230] 6.通过离心分离固定的TPCK胰蛋白酶。

[0231] 实施例5:PEG-TeNT-LC-HC的制备(图1D)(方法2)

[0232] 在本实施例中,将TeNT-LC-HC的表面丝氨酸残基突变为表面半胱氨酸残基(S→C突变体)以促进在免疫原性表位处的定向PEG缀合。相对于SEQ ID NO:1,TeNT突变是:S81C;S120C;S144C;S248C;S335C;S428C;S600C;S963C;S1041C;S1155C;和S1187C。

[0233] 丝氨酸突变体TeNT-LC-HC的制备

[0234] 用编码包含S→C突变的图18的氨基酸序列(SEQ ID NO:12)的载体pRSET-TeNT(图19和图20)对大肠杆菌BL21(DE3)pLysS菌株进行电转化。根据实施例4表达和纯化包含S→C突变的TeNT-LC-HC,其中在步骤10与步骤11之间增加了用0.5mM DTT处理15分钟。

[0235] 内毒素去除

[0236] 根据实施例4从TeNT-LC-HC丝氨酸突变体中去除内毒素。PEG与半胱氨酸残基的连接。

[0237] 1.将摩尔过量的PEG-顺丁烯二酰亚胺与丝氨酸突变体TeNT-LC-HC(0.5mg/mL-2mg/mL)在pH 6.5-7.5的PBS中组合,其中PEG具有约2kDa、约5kDa、约10kDa或约20kDa。

[0238] 2.在室温下进行连接6小时。

[0239] 3.通过尺寸排阻色谱法去除过量的PEG。

[0240] 蛋白质的胰蛋白酶消化激活

[0241] 根据实施例4进行胰蛋白酶消化以激活TeNT-LC-HC丝氨酸突变体。

[0242] 实施例6:无活性的诱饵TeNT

[0243] 在本实施例中,产生了在神经节苷脂结合区中相对于SEQ ID NO:1具有灭活性R1225E和W1288A氨基酸取代的非聚乙二醇化的重组c。将灭活的c与等摩尔量的非聚乙二醇化的LC-HN组合以产生无活性的诱饵TeNT。所得的无活性的TeNT将用作接种过破伤风类毒素疫苗的受试者中基于抗体的中和应答的诱饵。

[0244] 包含R1225E、W1288A的c的制备

[0245] 通过商业提供商(Integrated DNA Technologies公司)合成了具有R1225E和W1288A的c的基因。通过限制性酶切消化将所述基因亚克隆到pRSET-A表达载体中以将来自所述载体的6×组氨酸标签添加到突变蛋白的N末端。

[0246] 用编码包含R1225E、W1288A的c(图12,SEQ ID NO:8)的pRSET-TeNT-c载体(图13(SEQ ID NO:9)和图14)对大肠杆菌BL21(DE3)pLysS菌株进行电转化并且使其在含有选择抗生素(氨苄西林、氯霉素)的LB琼脂上在37℃生长过夜。根据实施例4表达并且纯化包含R1225E、W1288A的c。

[0247] 内毒素去除

[0248] 根据实施例4从纯化的蛋白质中去除内毒素。

[0249] LC-HN的制备

[0250] 用pRSET-TeNT-LC-HN载体(图10和图11)对大肠杆菌BL21(DE3)pLysS菌株进行电转化并且使其在含有选择抗生素(氨苄西林、氯霉素)的LB琼脂上在37℃生长过夜。根据实施例4表达并且纯化LC-HN。

[0251] 内毒素去除

[0252] 根据实施例4从纯化的蛋白质中去除内毒素。

[0253] 包含E270A、Y374A的LC-HN的制备

[0254] 用编码包含E270A、Y374A的LC-HN的pRSET-TeNT-LC-HN载体对大肠杆菌BL21(DE3)pLysS菌株进行电转化并且使其在含有选择抗生素(氨苄西林、氯霉素)的LB琼脂上在37℃生长过夜。根据实施例4表达并且纯化包含E270A、Y374A的LC-HN。

[0255] 内毒素去除

[0256] 根据实施例4从纯化的蛋白质中去除内毒素。

[0257] 实施例7:无活性的诱饵TeNT

[0258] 通过商业提供商(Integrated DNA Technologies公司)合成了包含R1225E和W1288A的TeNT的基因。通过限制性酶切消化将所述基因亚克隆到pRSET-A表达载体中以将来自所述载体的6×组氨酸标签添加到突变蛋白的N末端(图15(SEQ ID NO:10)、图16(SEQ ID NO:11)和图17)。

[0259] 根据实施例4表达并且纯化包含R1225E和W1288A的灭活的TeNT。

[0260] 内毒素去除

[0261] 根据实施例4从纯化的蛋白质中去除内毒素。

[0262] 实施例8:PEG-TeNT分析

[0263] 根据实施例4制备TeNT并且将其聚乙二醇化,然后通过SDS-PAGE分析(图28)并且(A)使用考马斯蓝和(B)使用多克隆抗TeNT抗体通过蛋白质印迹进行检测。(B)示出了免疫原性与PEG分子量成比例。

[0264] 实施例9:与TeNT相比PEG-TeNT的免疫原性降低

[0265] 根据实施例4制备各自包含不同分子量的PEG(2kDa、5kDa、10kDa和20kDa)的四种PEG-TeNT并且将其聚乙二醇化。然后通过竞争性ELISA针对TeNT测定PEG-TeNT。

[0266] 在第一测定(图29A)中,将TeNT吸附到ELISA板上。然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的四种PEG-TeNT抗原(2kDa、5kDa、10kDa和20kDa)中的每一种一起预孵育的多克隆抗TeNT抗体探测吸附的TeNT。在该测定中,更高的响应(OD 450nm)表明对TeNT的亲和力更大并且因此,PEG-TeNT的免疫原性降低。

[0267] 在第二测定(图29B)中,将每一种PEG-TeNT吸附到单独的ELISA板上。然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的TeNT抗原中的每一种一起预孵育的多克隆抗TeNT抗体探测每一种吸附的PEG-TeNT(2kDa、5kDa、10kDa和20kDa)。在该测定中,更低的响应(OD 450nm)表明对TeNT的亲和力更大并且因此,PEG-TeNT的免疫原性降低。

[0268] 本实施例表明了,抗TeNT抗体优先结合TeNT并且聚乙二醇化的TeNT相对于TeNT(即非聚乙二醇化的)具有降低的免疫原性。

[0269] 实施例10:与TeNT-LC-c丝氨酸突变体相比PEG-TeNT-LC-c丝氨酸突变体的免疫原性降低

[0270] 根据实施例5制备TeNT-LC-c丝氨酸突变体。根据实施例5将TeNT-LC-c丝氨酸突变体的四个样品进行聚乙二醇化,每一个样品包含不同分子量的PEG(2kDa、5kDa、10kDa和20kDa)。然后通过竞争性ELISA针对TeNT-LC-c丝氨酸突变体测定PEG-TeNT-LC-c丝氨酸突变体。

[0271] 在第一测定(图29C)中,将TeNT-LC-c丝氨酸突变体吸附到ELISA板上。然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的四种PEG-TeNT丝氨酸突变体抗原(2kDa、5kDa、10kDa和20kDa)中的每一种一起预孵育的多克隆抗TeNT抗体探测吸附的TeNT丝氨酸突变体。在该测定中,更高的响应(OD 450nm)表明对TeNT丝氨酸突变体的亲和力更大并且因此,PEG-TeNT丝氨酸突变体的免疫原性降低。

[0272] 在第二测定(图29D)中,将每一种PEG-TeNT-LC-c丝氨酸突变体吸附到单独的ELISA板上。然后用与四种浓度(10μg/mL、1μg/mL、0.1μg/mL和0.01μg/mL)的TeNT丝氨酸突变体抗原中的每一种一起预孵育的多克隆抗TeNT抗体探测每一种吸附的PEG-TeNT丝氨酸突变体(2kDa、5kDa、10kDa和20kDa)。在该测定中,更低的响应(OD 450nm)表明对TeNT丝氨酸突变体的亲和力更大并且因此,PEG-TeNT丝氨酸突变体的免疫原性降低。

[0273] 本实施例表明了,抗TeNT抗体优先结合TeNT-LC-c丝氨酸突变体并且相对于TeNT-LC-c丝氨酸突变体(即非聚乙二醇化的),聚乙二醇化的TeNT-LC-c丝氨酸突变体具有降低的免疫原性。

[0274] 实施例11:与TeNT相比PEG-TeNT的免疫原性降低

[0275] 将根据实施例9进行竞争性ELISA测定,不同的是将用从在先前12个月内已经接受过加强破伤风类毒素疫苗接种的一个或多个受试者收集的人类血清代替多克隆抗体。相比于对PEG-TeNT,血清中的抗体将对TeNT(即非聚乙二醇化的TeNT)显示出更大的亲和力。

[0276] 实施例12:体内模型

[0277] 根据实施例4,通过将PEG(约5kDa、约10kDa或约20kDa)与重组TeNT的表面暴露的赖氨酸残基连接来制备PEG-TeNT-LC-HC。

[0278] 将于15μL PBS中一个或多个单位的PEG-TeNT-LC-HC注射到雌性C57BL/6小鼠的后肢中。每一只动物在注射的48小时内均表现出局部肢体抽搐(图30A和图30B)。

[0279] 实施例13:体内模型

[0280] 将根据实施例4的具有与TeNT的表面赖氨酸残基连接的5kDa PEG的PEG-TeNT-LC-HC与c诱饵(即由R1225E和W1288A灭活的c)以1:10的摩尔比组合。将在PBS中含有5ng PEG-TeNT的15微升组合物注射到雌性C57BL/6小鼠的后肢肌肉中。每一只动物在48小时内均表现出局部肢体抽搐,症状发展与在不存在诱饵的情况下用PEG-TeNT-LC-HC处理的动物难以区别。

[0281] 实施例14

[0282] 将包含5kDa、10kDa或20kDa PEG的PEG-TeNT-LC-HC以50ng/kg-500000ng/kg肌内施用到先前接受过破伤风类毒素免疫接种的小鼠的后腿肌肉。在注射的肌肉中观测到肌肉收缩增加,持续长达3天,并且肌肉收缩增加大于在接受相同单位的TeNT施用的小鼠中观测到的效果。图31A报告了PEG-TeNT-LC-HC 20kDa的结果。

[0283] 实施例15

[0284] 将包含TeNT-LC-HC和10:1或100:1摩尔过量的根据实施例6产生的诱饵TeNT的组合物以50ng/kg-500000ng/kg肌内施用到先前接受过破伤风类毒素免疫接种的小鼠的后腿肌肉。在注射的肌肉中观测到肌肉收缩增加,持续长达3天,并且肌肉收缩增加大于在接受TeNT施用的小鼠中观测到的效果(图32A)。

[0285] 实施例16

[0286] 将含有包含5kDa、10kDa或20kDa PEG的PEG-TeNT-LC-HC和10:1或100:1摩尔过量的根据实施例6产生的诱饵TeNT的组合物以50ng/kg-500000ng/kg肌内施用到先前接受过破伤风类毒素免疫接种的小鼠的后腿肌肉。在注射的肌肉中观测到肌肉收缩增加,持续长达3天,并且肌肉收缩增加大于在接受TeNT施用的小鼠中观测到的效果,并且大于在仅接受PEG-TeNT施用的小鼠中观测到的效果(图32B)。

[0287] 实施例17

[0288] 将包含20kDa PEG的PEG-TeNT-LC-HC以0.01ng/kg-50000ng/kg肌内施用到先前接种过破伤风类毒素疫苗的人类受试者的左颏舌骨肌。在注射的肌肉中将观测到肌肉收缩增加,持续长达2周,并且肌肉收缩增加将大于在同一受试者的仅接受媒介物施用的右颏舌骨肌中观测到的效果。

[0289] 实施例18

[0290] 将含有包含20kDa PEG的PEG-TeNT-LC-HC和10:1-1000:1摩尔过量的根据实施例6产生的诱饵TeNT的组合物以50ng/kg肌内施用到先前接种过破伤风类毒素疫苗的人类受试者的左颏舌骨肌。将包含20kDa PEG的PEG-TeNT-LC-HC以50ng/kg肌内施用到同一人类受试者的右颏舌骨肌。

[0291] 在左颏舌骨肌和右颏舌骨肌中均将观测到肌肉收缩增加,持续长达2周,但是与单独的PEG-TeNT-LC-HC相比,在用包含PEG-TeNT-LC-HC和诱饵TeNT的组合物治疗的左颏舌骨肌中,肌肉收缩增加将更大。

[0292] 实施例19

[0293] 将向约30kg的牛头犬肌内施用25ng/kg-50000ng/kg的包含20kDa PEG的PEG-TeNT-c,其中所述剂量被双侧分开施用到左颏舌骨肌和右颏舌骨肌。在施用后,与用单独的媒介物处理的动物相比,接受PEG-TeNT处理的动物的阻塞性睡眠呼吸暂停(OSA)将减少。将每周观测一次牛头犬的OSA并且根据需要将重复PEG-TeNT-c剂量直到功效降低为止,如由与用单独的媒介物处理的动物相当的OSA的恢复所确定。

[0294] 之后,将向牛头犬施用25-50000ng/kg的PEG-TeNT-HC或25-50000ng/kg的PEG-TeNT-LC-c,其各自包含20kDa PEG,被双侧分开施用到左颏舌骨肌和右颏舌骨肌。在施用后,与用单独的媒介物处理的动物相比,接受PEG-TeNT处理的动物的OSA将减少。将每周观测一次牛头犬的OSA并且根据需要将重复PEG-TeNT-HC和PEG-TeNT-LC-c剂量直到功效降低为止,如由与用单独的媒介物处理的动物相当的OSA的恢复所确定。

[0295] 之后,将向牛头犬施用25-50000ng/kg的包含20kDa PEG的PEG-TeNT-LC-HC,被双侧分开施用到左颏舌骨肌和右颏舌骨肌。在施用后,与用单独的媒介物处理的动物相比,接受PEG-TeNT处理的动物的OSA将减少。将每周观测一次牛头犬的OSA并且根据需要将重复PEG-TeNT-LC-HC剂量直到功效降低为止,如由与用单独的媒介物处理的动物相当的OSA的

恢复所确定。

[0296] 实施例20

[0297] 使用Discovery Studio将如由da Silva Antunes等(2017)PloS One,12(1),e0169086和Palermo等(2017)Biotechnology Journal,12(10),1700197所鉴定的主要人类抗体克隆型识别的TeNT表位定位到源自于蛋白质数据库(登录ID PDB:5N0B)中存储的结晶学数据的TeNT的3维模型上。鉴定出所鉴定的表位中或周围的表面丝氨酸残基以如实施例1至实施例3和实施例5中所述突变为半胱氨酸以随后进行聚乙二醇化。

[0298] 实施例21

[0299] 将PEG-TeNT(5kDa、10kDa或20kDa支化或线性PEG与表面赖氨酸或半胱氨酸残基连接)和10-1000倍摩尔过量的诱饵TeNT的1纳克至64微克的混合物肌内注射到接种过破伤风类毒素疫苗的小鼠的后腿肌肉中。将观测到局部抽搐,持续数小时至数月的时间段,该局部抽搐大于在接受天然TeNT注射的小鼠中观测到的效果。

[0300] 实施例22

[0301] 将PEG-TeNT(5kDa、10kDa或20kDa支化或线性PEG与表面赖氨酸或半胱氨酸残基连接)和10-1000倍摩尔过量的诱饵TeNT的1纳克至64微克的混合物肌内注射到接种过破伤风类毒素疫苗的人类的颏舌骨肌中。观测到局部抽搐,持续数周至数月的时间段,该局部抽搐大于在接受天然TeNT注射的人类中观测到的效果。

[0302] 实施例23

[0303] 向有睡眠呼吸障碍的英国牛头犬肌内施用0.001-10IU/Kg的TeNT,其中所述剂量被双侧分开施用到左颏舌骨肌和右颏舌骨肌。在施用后,观测到阻塞性睡眠呼吸暂停(OSA)在最高剂量下显著减少。基线呼吸紊乱指数(RDI)评分是19.9(四分位数间距5.45),在用10IU/Kg TeNT处理后减少到13.2(四分位数间距4.45),这通过威氏符号秩次检验确定与施用安慰剂相比是显著的(P=0.043)。在试验后四个月观测到该牛头犬维持了RDI的降低;中值RDI=13.4,P=0.043;威氏符号秩次检验。

[0001] 序列表

[0002] <110> 斯诺雷托克斯私人有限公司

[0003] <120> 组合物和方法

[0004] <130> AU2018902779A

[0005] <140> 2018902779

[0006] <141> 2018-07-31

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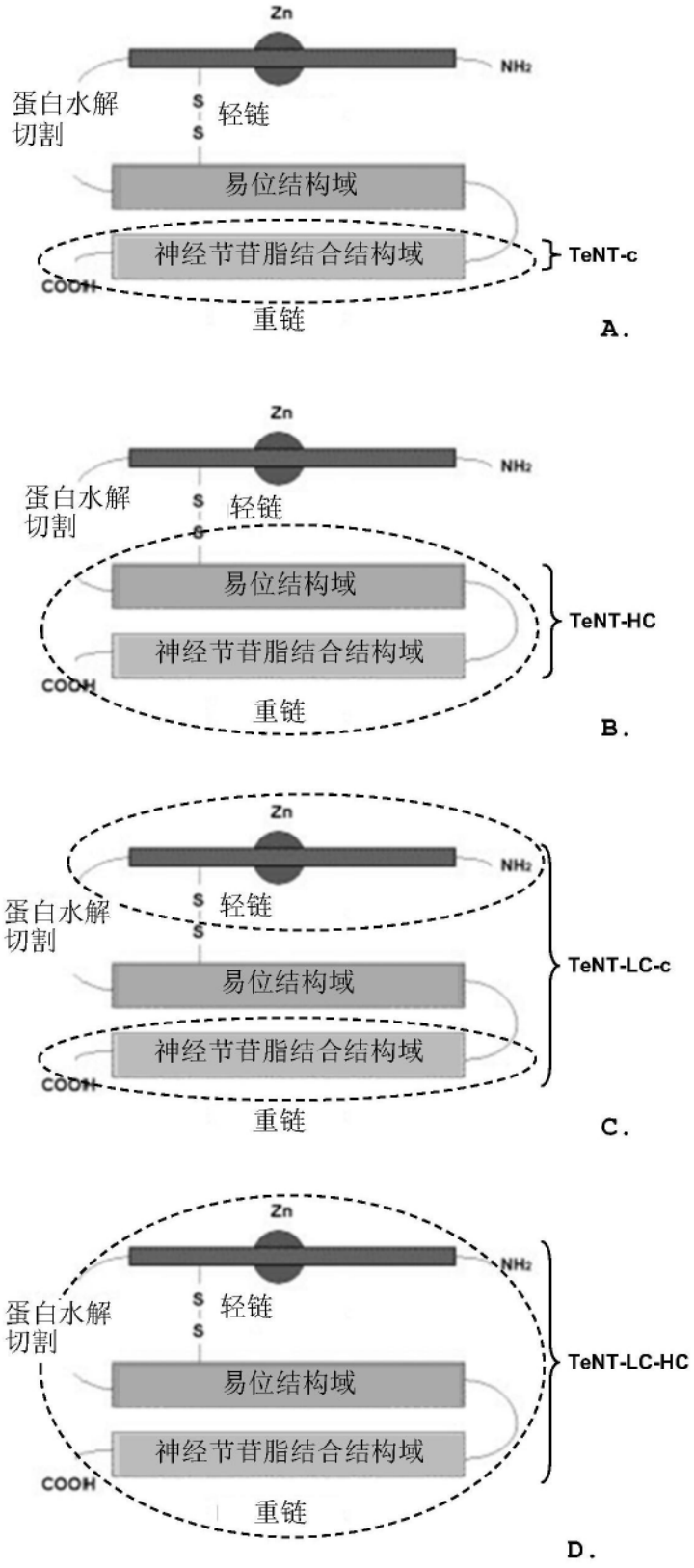

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切割
S
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轻链
易位结构域
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切割
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COOH
重链
D.

图1

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图3 SEQ ID NO:2

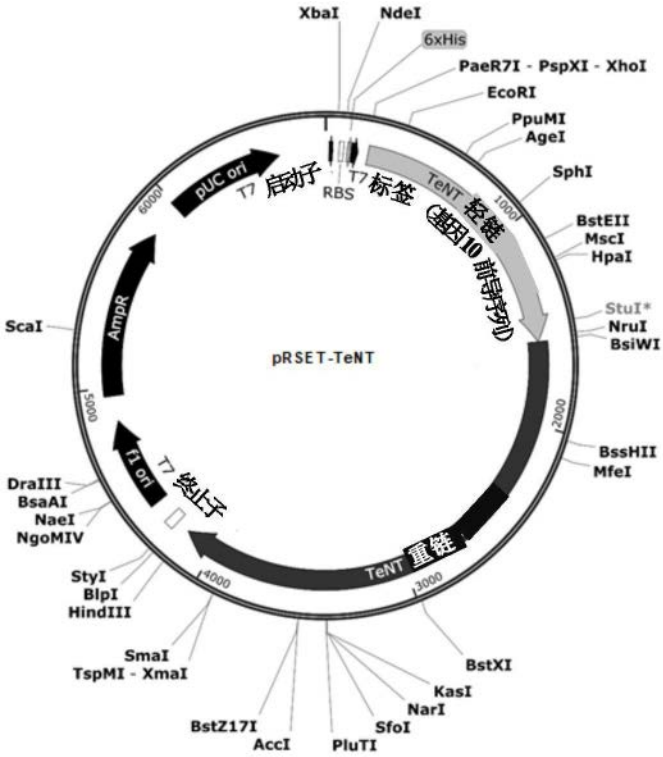


图4

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图5 SEQ ID NO:3

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图6 SEQ ID NO:4

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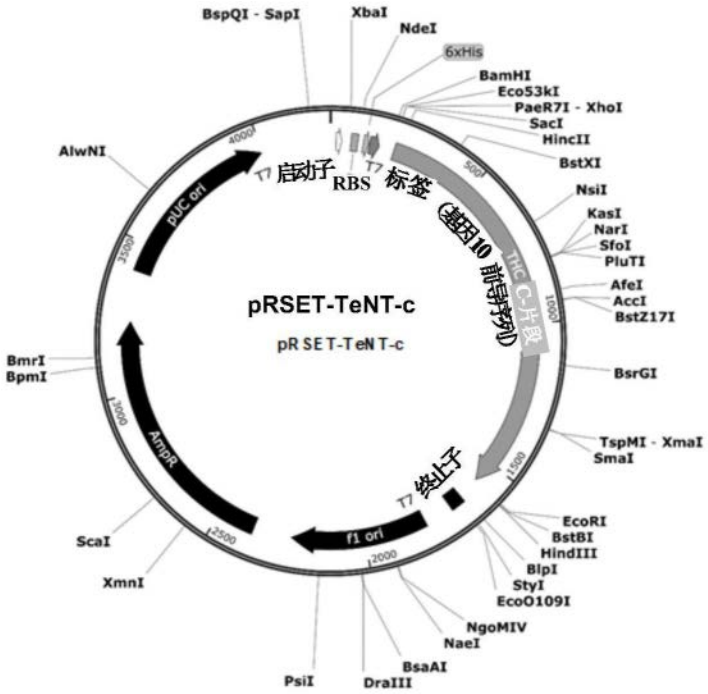


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图9 SEQ ID NO:6

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图10 SEQ ID NO:7(接下页)

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图10 SEQ ID NO:7

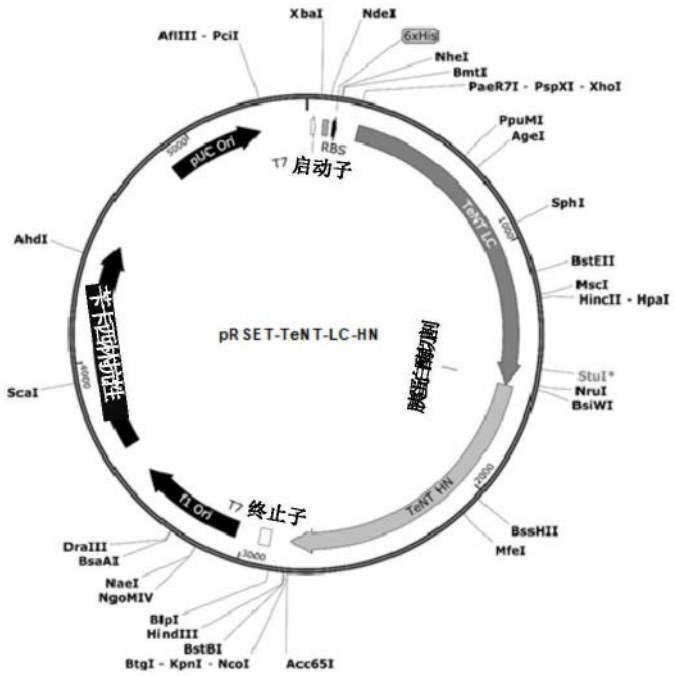


图11

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图13 SEQ ID NO:9

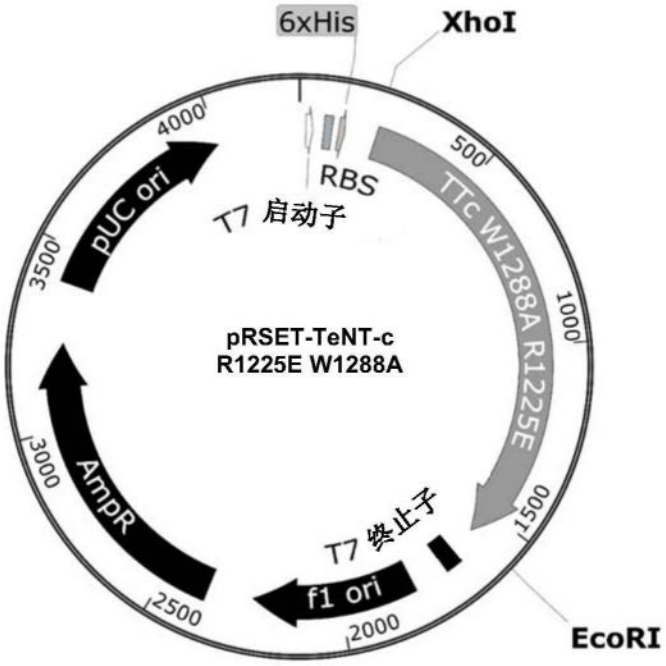


图14

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图15 SEQ ID NO:10

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图16 SEQ ID NO:11(接下页).

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图16 SEQ ID NO:11



图17

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图18 SEQ ID NO:12

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图19 SEQ ID NO:13(接下页).

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图19 SEQ ID NO:13(接下页).

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图19 SEQ ID NO:13

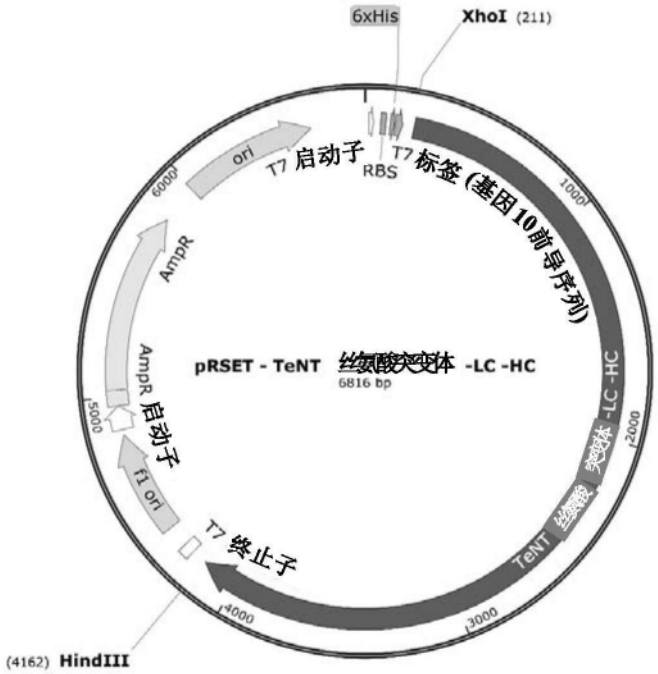


图20.

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图21 SEQ ID NO:14(接下页).

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图21 SEQ ID NO:14

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图22 SEQ ID NO:15(接下页).

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图22 SEQ ID NO:15

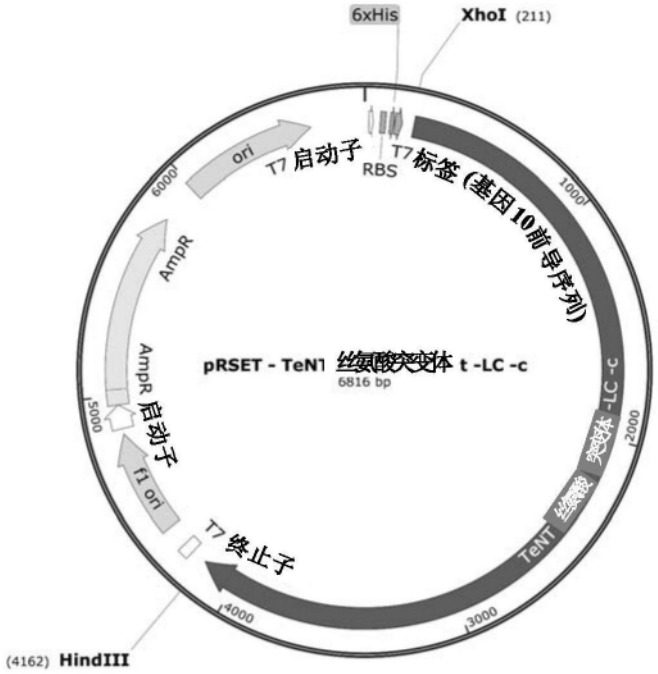


图23

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图24 SEQ ID NO:16.

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图25 SEQ ID NO:17(接下页)

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AAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTT
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GGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGT
TCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCA
GAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAG

图25 SEQ ID NO:17(接下页)

TGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAAC

CGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACC
AAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACT
TACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGC
CCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACT
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GCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGT
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GCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGG
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图25 SEQ ID NO:17.

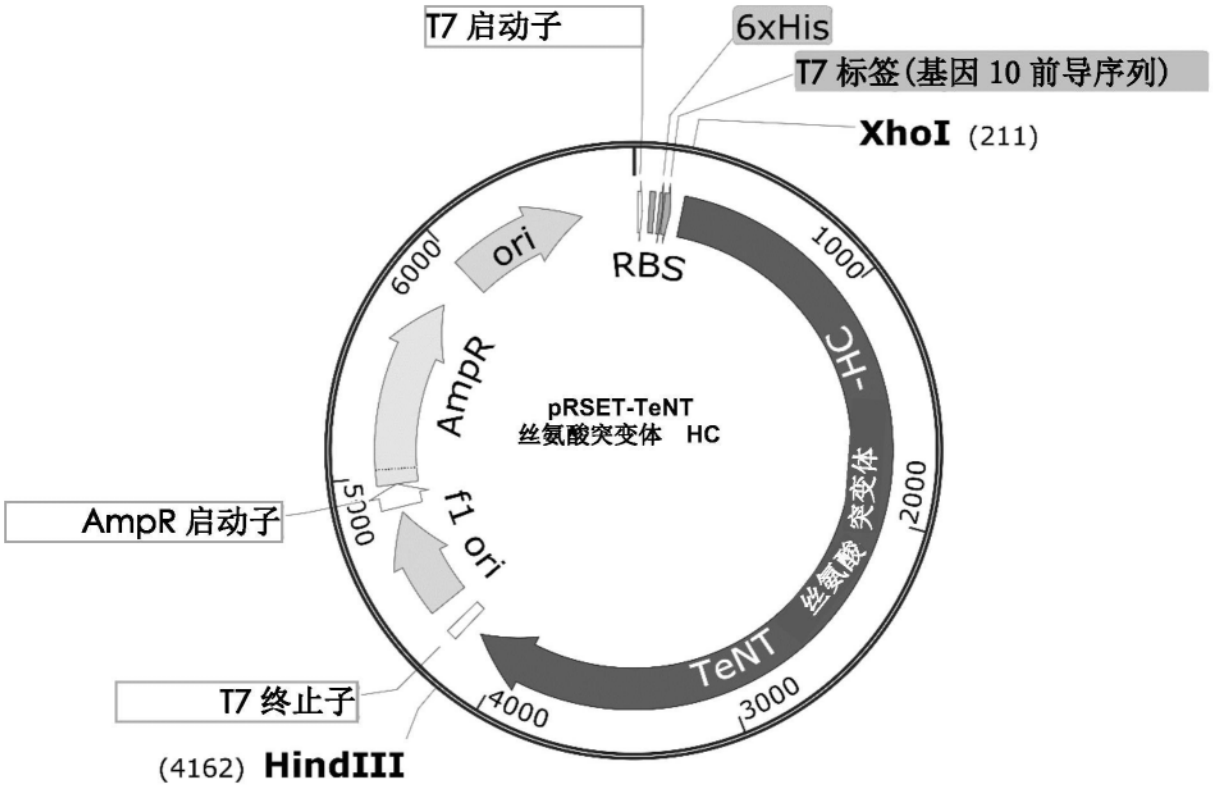


图26

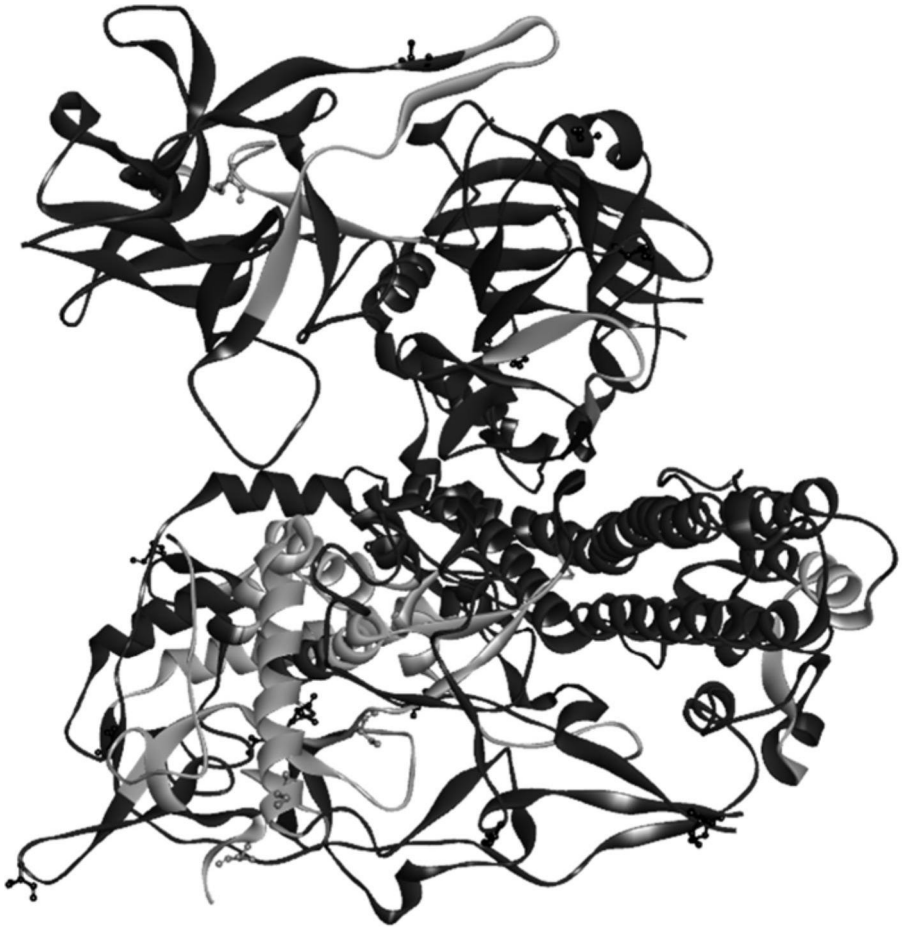


图27

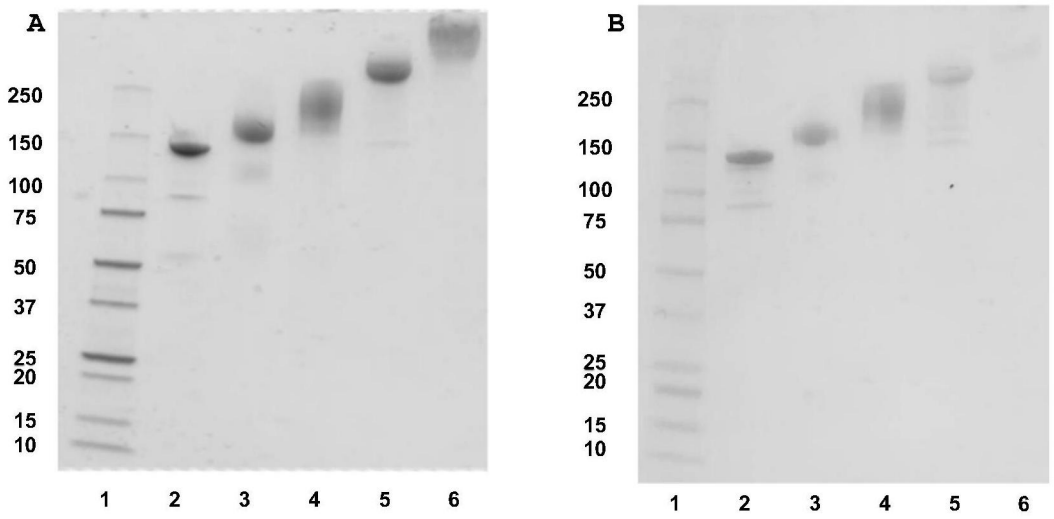

A
250
150
100
75
50
37
25
20
15
10
1
2
3
4
5
6
B
250
150
100
75
50
37
25
20
15
10
1
2
3
4
5
6

图28

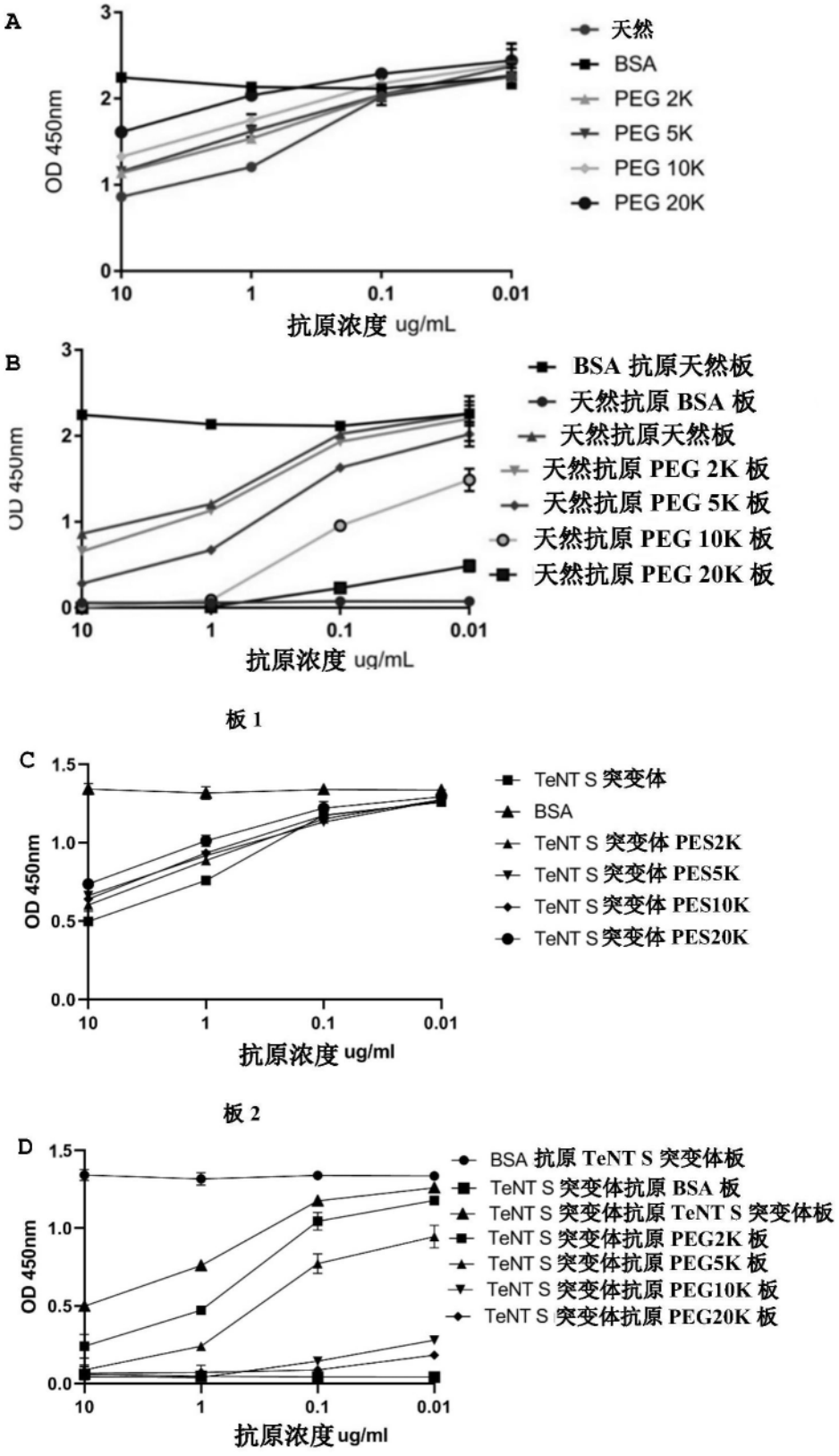
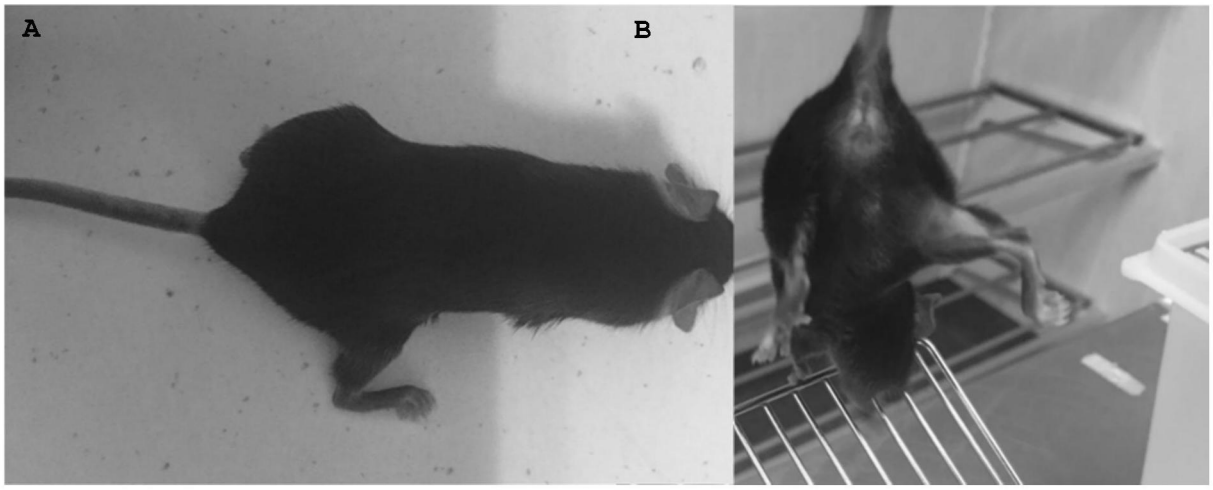

A
OD 450nm
抗原浓度 ug/mL
天然
BSA
PEG 2K
PEG 5K
PEG 10K
PEG 20K
B
OD 450nm
抗原浓度 ug/mL
BSA 抗原天然板
天然抗原 BSA 板
天然抗原天然板
天然抗原 PEG 2K 板
天然抗原 PEG 5K 板
天然抗原 PEG 10K 板
天然抗原 PEG 20K 板
板 1
C
OD 450nm
抗原浓度 ug/ml
TeNT S 突变体
BSA
TeNT S 突变体 PES2K
TeNT S 突变体 PES5K
TeNT S 突变体 PES10K
TeNT S 突变体 PES20K
板 2
D
OD 450nm
抗原浓度 ug/ml
BSA 抗原 TeNT S 突变体板
TeNT S 突变体抗原 BSA 板
TeNT S 突变体抗原 TeNT S 突变体板
TeNT S 突变体抗原 PEG2K 板
TeNT S 突变体抗原 PEG5K 板
TeNT S 突变体抗原 PEG10K 板
TeNT S 突变体抗原 PEG20K 板

图29.



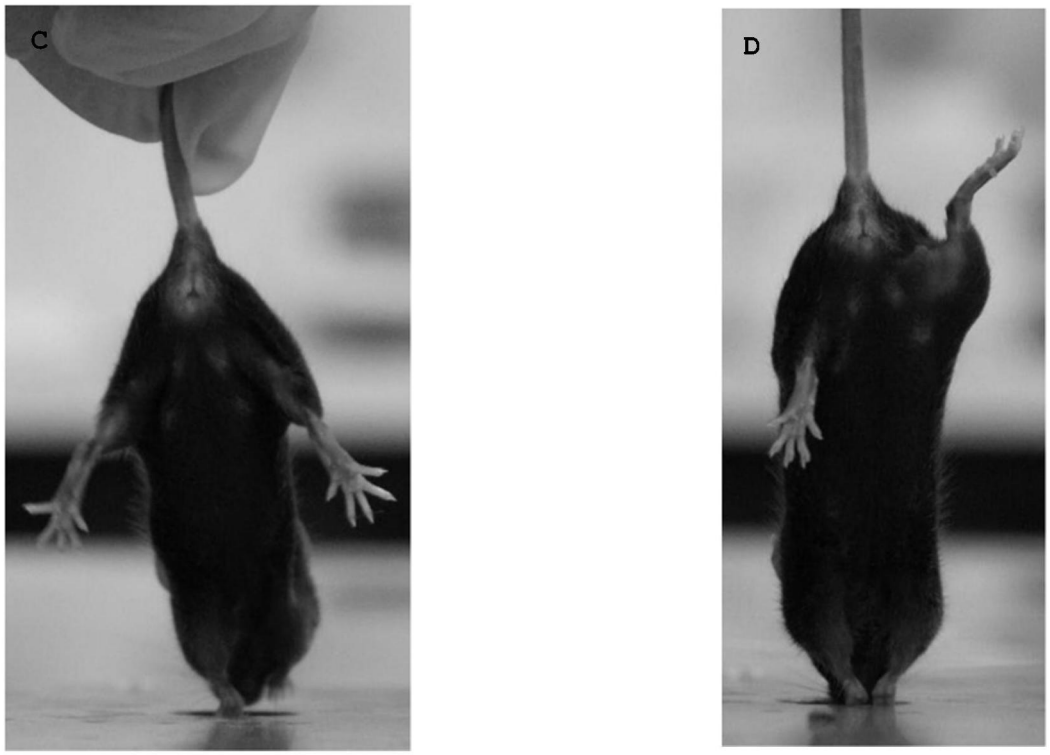


图30.

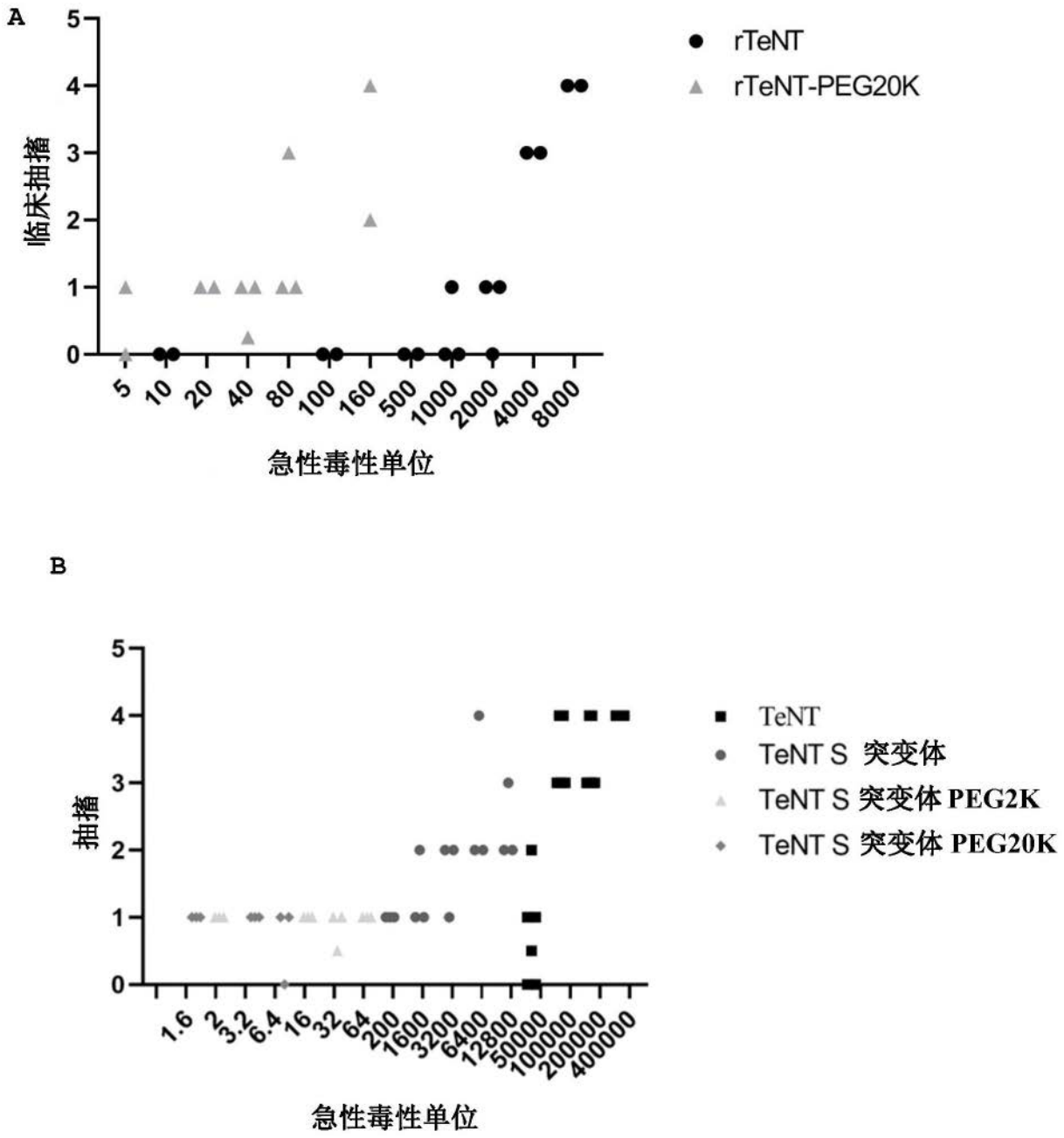

A
临床抽搐
0
1
2
3
4
5
5
10
20
40
80
100
160
500
1000
2000
4000
8000
急性毒性单位
rTeNT
rTeNT-PEG20K
B
抽搐
0
1
2
3
4
5
1.6
2
3.2
6.4
16
32
64
200
1600
3200
6400
12800
50000
100000
200000
400000
急性毒性单位
TeNT
TeNT S 突变体
TeNT S 突变体 PEG2K
TeNT S 突变体 PEG20K

图31

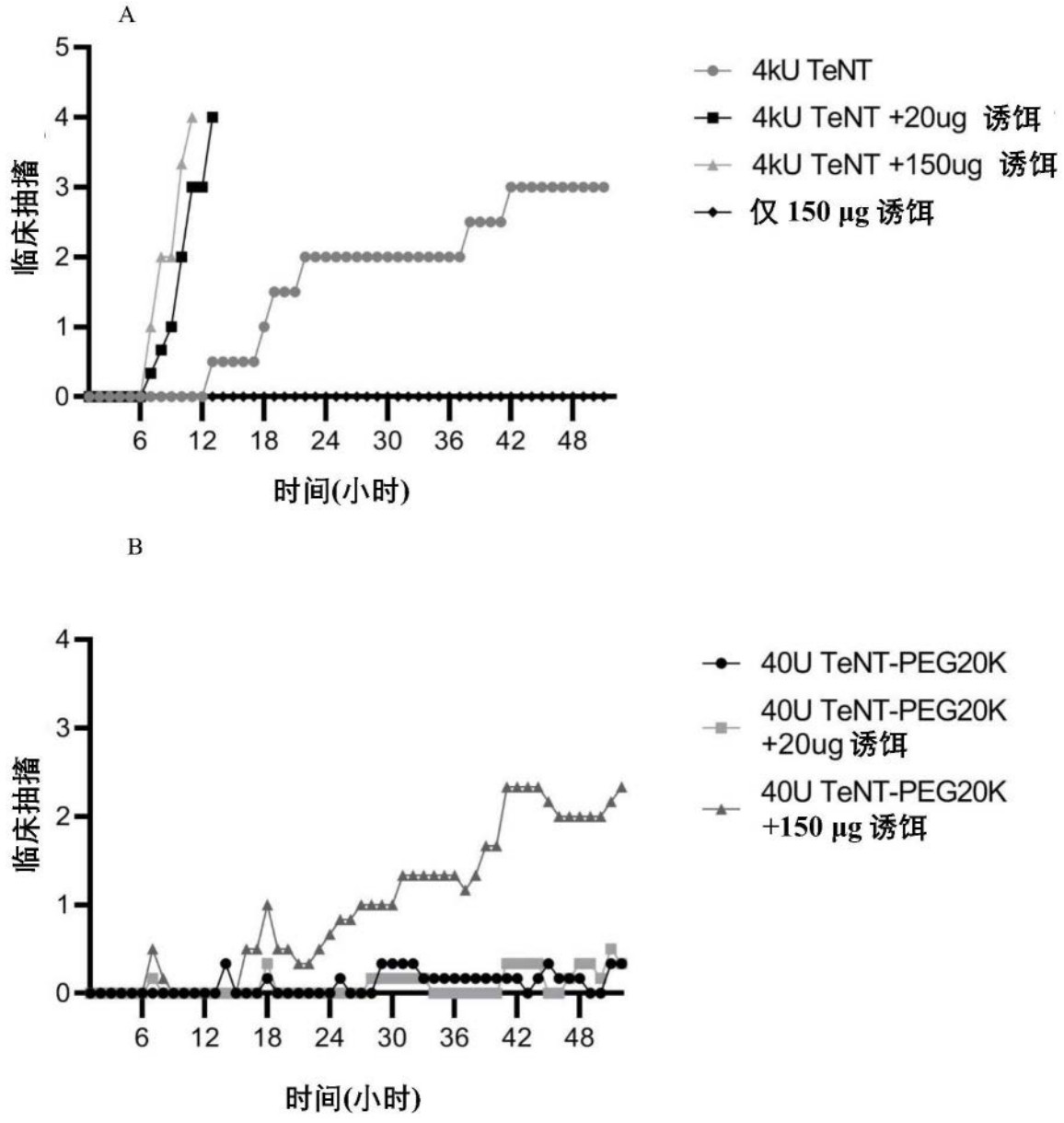

A
临床抽搐
时间(小时)
4kU TeNT
4kU TeNT +20ug 诱饵
4kU TeNT +150ug 诱饵
仅 150 μg 诱饵
B
临床抽搐
时间(小时)
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40U TeNT-PEG20K +150 μg 诱饵

图32

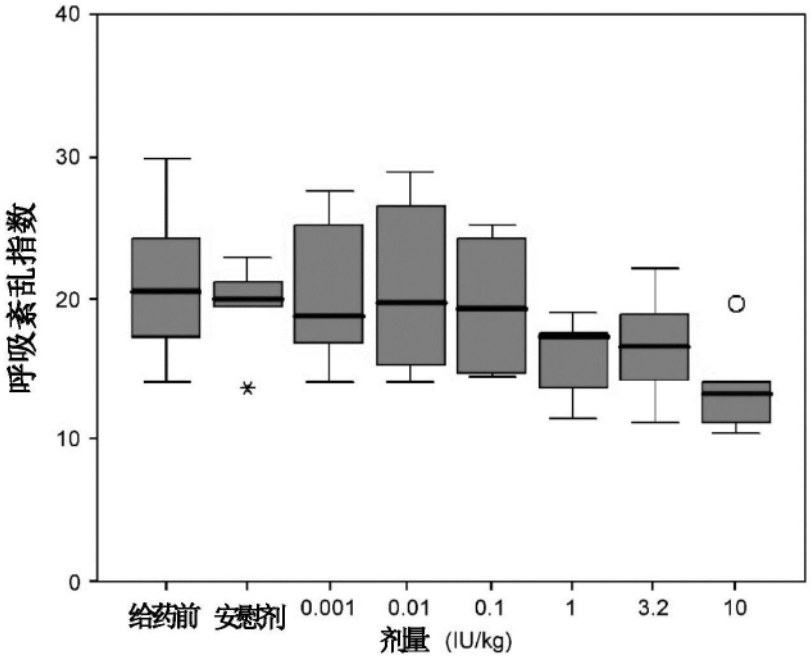


图33