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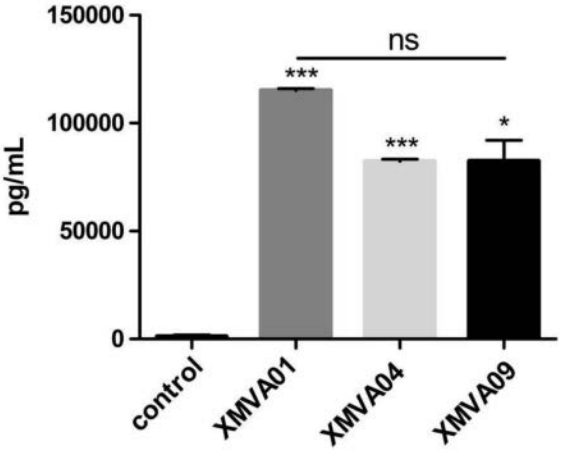
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(54)发明名称

一种编码抗VEGF-A和ANG-2双特异性抗体的AAV载体

(57)摘要

本公开提供了用于治疗受试者的湿性年龄相关性黄斑变性或糖尿病性黄斑水肿的药物组合物和方法。提供了一种双特异性抗体、核酸、以及AAV病毒载体和病毒颗粒。双特异性抗体表达盒包括编码启动子、可操作地连接至双特异性抗体的可选择的信号肽,其中所述双特异性抗体包含特异于VEGF-A和ANG-2的结合结构域。



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1.一种双特异性抗体,其包括抗VEGF-A和ANG-2的结合结构域,所述双特异性抗体重链可变区(VH)和轻链可变区(VL)从N-末端到C-末端按照如下顺序排列:

$VH_{抗VEGF}$-A-$VL_{抗VEGF}$-A-$VH_{抗ANG-2}$-$VL_{抗ANG-2}$;

其中,所述$VH_{抗VEGF-A}$包括SEQ ID NO:1所示的CDR1,SEQ ID NO:2所示的CDR2;SEQ ID NO:3所示的CDR3;

所述$VL_{抗VEGF-A}$包括SEQ ID NO:4所示的CDR1,SEQ ID NO:5所示的CDR2;SEQ ID NO:6所示的CDR3;

所述$VH_{抗ANG-2}$包括SEQ ID NO:7所示的CDR1,SEQ ID NO:8所示的CDR2;SEQ ID NO:9所示的CDR3;

所述$VL_{抗ANG-2}$包括SEQ ID NO:10所示的CDR1,SEQ ID NO:11所示的CDR2;SEQ ID NO:12所示的CDR3。

2.如权利要求1所述的双特异性抗体,其中

所述$VH_{抗VEGF-A}$包括SEQ ID NO:13所示的序列或与SEQ ID NO:13序列同一性为70%、80%、90%、95%、或99%的序列;

所述$VL_{抗VEGF-A}$包括SEQ ID NO:14所示的序列或与SEQ ID NO:14或SEQ ID NO:48序列同一性为70%、80%、90%、95%、或99%的序列;

所述$VH_{抗ANG-2}$包括SEQ ID NO:15所示的序列或与SEQ ID NO:15序列同一性为70%、80%、90%、95%、或99%的序列;

所述$VL_{抗ANG-2}$包括SEQ ID NO:16所示的序列或与SEQ ID NO:16序列同一性为70%、80%、90%、95%、或99%的序列。

3. 如权利要求1所述的双特异性抗体,其中所述抗体包括SEQ ID NO:17所示的序列或与SEQ ID NO:17序列同一性为70%、80%、90%、95%、或99%的序列。

4.如权利要求1所述的双特异性抗体,所述双特异性抗体的N-末端包含信号肽序列或标签序列。

5. 如权利要求4所述的双特异性抗体,所述信号肽序列为如SEQ ID NO:23所示的CD5-sp信号肽。

6. 如权利要求5所述的双特异性抗体,其中所述抗体包括SEQ ID NO:20所示的序列或与SEQ ID NO:20序列同一性为70%、80%、90%、95%、或99%的序列。

7.如权利要求1所述的双特异性抗体,其中所述重链可变区(VH)和轻链可变区(VL)之间由$(G_4S)n$链接,其中n=1至4间任意整数。

8.如权利要求1所述的双特异性抗体,其中所述双特异性抗体的结构为:

$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$;

CD5-sp-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$。

9.一种核酸,其编码如权利要求1-8中任一项所述的双特异性抗体。

10.一种载体,其包括编码如权利要求1-8中任一项所述的双特异性抗体的核酸,所述载体为AAV病毒载体。

11. 如权利要求10所述的AAV病毒载体,进一步包括:5’ ITR和3’ ITR、启动子、polyA序列。

12.一种AAV病毒颗粒,包括如权利要求10或11所述的AAV病毒载体和衣壳蛋白。

13.如权利要求12所述的AAV病毒颗粒,其中所述衣壳蛋白的血清型为AAV1、AAV2、AAV4、AAV5、AAV6、AAV7、AAV8或AAV9。

14.一种药物组合物,包括如权利要求1-8中任一项所述的双特异性抗体、如权利要求9所述的核酸、如权利要求10或11所述的载体、如权利要求12或13所述的AAV病毒颗粒中的至少一种,以及药学上可接受的载体。

15.如权利要求1-8中任一项所述的双特异性抗体、如权利要求9所述的核酸、如权利要求10或11所述的载体、如权利要求12或13所述的AAV病毒颗粒或如权利要求14所述的药物组合物在制备用于治疗眼内新生血管综合征、增殖性视网膜病变、年龄相关性黄斑变性或糖尿病性黄斑水肿的药物中的用途。

16.如权利要求15所述的用途,所述年龄相关性黄斑变性为湿性年龄相关性黄斑变性。

17.如权利要求15或16所述的用途,其中所述药物通过玻璃体腔或视网膜下腔注射施用。

一种编码抗VEGF-A和ANG-2双特异性抗体的AAV载体

发明领域

[0001] 本发明涉及免疫学和基因递送领域。更具体地,本申请涉及用于生产感兴趣的蛋白诸如抗体的组合物、系统和方法。

背景技术

[0002] 年龄相关性黄斑变性(age-related macular degeneration,AMD)是由各种因素诱导并与年龄相关的一组黄斑疾病,其共同特点是黄斑部视网膜及视网膜色素上皮和脉络膜发生病变,并导致患者视功能障碍和中心视力进行性下降。我国乃至世界AMD的患病率不断上升且随着年龄增加而升高,是50岁以上人群不可逆视力损伤的主要原因之一。随着人口的老龄化,预计到2040年AMD患者将达2.88亿人。AMD临床分型没有统一标准,国内外目前均倾向于先分期再分型,晚期分成2种类型,分别为干性型(萎缩型)和新生血管性型(渗出型、湿性型),其中,新生血管性年龄相关性黄斑变性(neovascular age-related macular degeneration,nAMD)也称湿性年龄相关性黄斑变性(wet age-related macular degeneration,wAMD),是导致视力丧失的主要临床类型,其主要特点是脉络膜新生血管(choroidal neovascularization,CNV)出现在黄斑区,从而导致黄斑区发生出血、渗出。糖尿病性视网膜病变(diabetic macular edema,DME)目前是西方发达国家重要致盲的原因之一,随着我国人民生活水平的提高,人口老龄化,DME的发病率已逐渐增高,严重影响患者的视功能和生存质量。

[0003] VEGF是wAMD和DME的发病机制中最重要的因素之一,它能特异地作用于血管内皮细胞,促使血管内皮细胞的增殖,诱导新生血管的生成以及血管渗漏的增加。目前研究发现,阻断VEGF的表达可诱导血管重塑的发生,同时促使尚未成熟的新生血管回退,因此VEGF是一个有前景的wAMD和DME的治疗靶点。自2006年以雷珠单抗(Ranibizumab)为代表的抗VEGF药物应用以来,抗VEGF药物已被广泛应用于治疗wAMD和DME。在近10年间,由于同时应用多种抗VEGF治疗方法,因wAMD和DME导致的不可逆盲已有大幅减少。

[0004] 尽管靶向VEGF的药物在临床上取得了长足的进步和突破,它可以显著降低血管渗漏和水肿的程度,改善视力,并且未发现严重的并发症。但是,这些注射入体内的蛋白质药物会随着代谢而迅速清除,因此需要多次眼内注射以维持治疗效果。长期治疗增加了患者的经济负担,重复注射会增加患者的痛苦和发生不良反应的可能性,在从常规给药转变为低频给药时会出现一定程度的视力下降,一些患者在治疗后容易复发。针对wAMD和DME现有疗法的局限性,在本领域上出现了对更加经济且持续时间更长、效果更优的治疗策略的需求。

[0005] 本发明旨在提供一种抗VEGF-A和抗ANG-2基因疗法。

发明内容

[0006] 本发明提供了一种双特异性抗体,其包括抗VEGF-A和ANG-2的结合结构域,其优选为单链抗体串联分子(tandem scFv,ta-scFv),所述双特异性抗体重链可变区(VH)和轻链

可变区(VL)从N-末端到C-末端按照如下顺序排列：

[0007] 1)$VH_{抗VEGF-A}$-$VL_{抗VEGF-A}$-$VH_{抗ANG-2}$-$VL_{抗ANG-2}$；

[0008] 2)$VL_{抗ANG-2}$-$VH_{抗VEGF-A}$-$VL_{抗VEGF-A}$-$VH_{抗ANG-2}$；或

[0009] 3)$_{VL抗VEGF-A}$-$VH_{抗ANG-2}$-$VL_{抗ANG-2}$-$VH_{抗VEGF-A}$；

[0010] 其中，所述$VH_{抗VEGF-A}$包括SEQ ID NO:1所示的CDR1，SEQ ID NO:2所示的CDR2；SEQ ID NO:3所示的CDR3；

[0011] 所述$VL_{抗VEGF-A}$包括SEQ ID NO:4所示的CDR1，SEQ ID NO:5所示的CDR2；SEQ ID NO:6或SEQ ID NO:47所示的CDR3；

[0012] 所述$VH_{抗ANG-2}$包括SEQ ID NO:7所示的CDR1，SEQ ID NO:8所示的CDR2；SEQ ID NO:9所示的CDR3；

[0013] 所述$VL_{抗ANG-2}$包括SEQ ID NO:10所示的CDR1，SEQ ID NO:11所示的CDR2；SEQ ID NO:12所示的CDR3。

[0014] 在一个实施例中，所述$VH_{抗VEGF-A}$包括SEQ ID NO:13所示的序列或与SEQ ID NO:13序列同一性为70％、80％、90％、95％、或99％的序列；

[0015] 所述$VL_{抗VEGF-A}$包括SEQ ID NO:14所示的序列或与SEQ ID NO:14或SEQ ID NO:48序列同一性为70％、80％、90％、95％、或99％的序列；

[0016] 所述$VH_{抗ANG-2}$包括SEQ ID NO:15所示的序列或与SEQ ID NO:15序列同一性为70％、80％、90％、95％、或99％的序列；

[0017] 所述$VL_{抗ANG-2}$包括SEQ ID NO:16所示的序列或与SEQ ID NO:16序列同一性为70％、80％、90％、95％、或99％的序列。

[0018] 在一个实施例中，所述抗体包括SEQ ID NO:17、18、19、49、51或53所示的序列或与SEQ ID NO:17、18、19、49、51或53序列同一性为70％、80％、90％、95％、或99％的序列。

[0019] 在一个实施例中，所述双特异性抗体构建体的N-末端包含信号肽序列或标签序列，优选所述信号肽序列为CD5-sp信号肽，其包含如SEQ ID NO:23所示的序列。

[0020] 在一个实施例中，所述抗体包括SEQ ID NO:20、21、22、50、52或54所示的序列或与SEQ ID NO:20、21、22、50、52或54序列同一性为70％、80％、90％、95％、或99％的序列。

[0021] 在一个实施例中，重链可变区(VH)和轻链可变区(VL)之间可操作性地由$(G_4S)_n$链接，其中n为大于1的整数，优选为1至4间任意整数，例如G_4S、$(G_4S)_2$、$(G_4S)_3$或$(G_4S)_4$，例如，

[0022] 1)$VH_{抗VEGF-A}$-$(G_4S)_{m+X}$-$VL_{抗VEGF-A}$-$(G_4S)_m$-$VH_{抗ANG-2}$-$(G_4S)_{m+X}$-$VL_{抗ANG-2}$；其中m≥1，X≥2，优选为$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$；

[0023] 2)$VL_{抗ANG-2}$-$(G_4S)_m$-$VH_{抗VEGF-A}$-$(G_4S)_{m+X}$-$VL_{抗VEGF-A}$-$(G_4S)_m$-$VH_{抗ANG-2}$，其中m≥1，X≥2，优选为$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$；或

[0024] 3)$VL_{抗VEGF-A}$-$(G_4S)_m$-$VH_{抗ANG-2}$-$(G_4S)_{m+X}$-$VL_{抗ANG-2}$-$(G_4S)_m$-$VH_{抗VEGF-A}$，其中m≥1，X≥2，优选为$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$。

[0025] 进一步，本发明提供了一种核酸序列，其编码前述双特异性抗体。

[0026] 本发明还提供了一种载体，包括编码前述双特异性抗体的核酸序列。

[0027] 在一个实施例中，所述载体优选为AAV病毒。

[0028] 在一个实施例中，AAV病毒载体进一步包括：5’ITR和3’ITR、启动子和polyA序列等。

[0029] 又一方面,本发明提供了一种AAV病毒颗粒,包括如前任意的AAV病毒载体和衣壳蛋白,优选其中所述衣壳蛋白的血清型为AAV1、AAV2、AAV4、AAV5、AAV6、AAV7、AAV8、或AAV9等。

[0030] 本发明提供了一种药物组合物,包括如前所述的双特异性抗体、核酸序列、载体诸如AAV病毒载体和如前所述的AAV病毒颗粒中的至少一种,以及药学上可接受的载体。

[0031] 本发明提供如前所述双特异性抗体、核酸序列、载体诸如AAV病毒载体、如前所述的AAV病毒颗粒、或如前所述的药物组合物在制备用于治疗或预防癌症、眼内新生血管综合征、类风湿性关节炎、银屑病、增殖性视网膜病变、年龄相关性黄斑变性或糖尿病性黄斑水肿的药物中的用途。

[0032] 在一个实施例中,所述年龄相关性黄斑变性为湿性年龄相关性黄斑变性。

[0033] 在一个具体实施例中,所述药物通过玻璃体腔或视网膜下腔注射施用。

附图说明

[0034] 图1示出了XMVA01、XMVA04和XMVA09的结构示意图。

[0035] 图2示出了XMVA09的载体信息。

[0036] 图3示出了XMVA01、XMVA04和XMVA09载体转染细胞后表达VEGF165中和蛋白的含量。

[0037] 图4示出了在细胞中表达XMVA01、XMVA04和XMVA09对人视网膜微血管内皮细胞(HRMEC)在ECGS刺激下增殖的影响。

[0038] 图5示出了在细胞中表达XMVA01、XMVA04和XMVA09对HRMECs管腔形成的影响的定量图。

[0039] 图6示出了在细胞中表达XMVA01、XMVA04和XMVA09对HRMECs管腔形成的影响的细胞图。

[0040] 图7示出了XMVA10的结构示意图。

[0041] 图8示出了XMVA11的结构示意图。

[0042] 图9示出了XMVA13的结构示意图。

[0043] 图10示出了XMVA14的结构示意图。

[0044] 图11示出了XMVA15的结构示意图。

[0045] 发明详述

[0046] 以下根据实施例,并且结合附图,详细描述本发明。从下文的详细描述中,本发明的上述方面和本发明的其他方面将是明显的。本发明的范围不局限于下列实施例。

[0047] 本发明中的抗体是多特异性的、可以为人源化的、单链的、嵌合的、合成的、重组的、杂合的、突变的、以及嫁接的抗体;本发明中的抗体形式为抗体轻链可变区(VL)和抗体重链可变区(VH)拼接而成的scFv,该抗体可以结合两种不同的抗原,例如VEGF-A和ANG-2。

[0048] 抗体轻链可变区(VL)和抗体重链可变区(VH),VH和VL区可以进一步细分成:称为互补决定区(CDR)的高变区,以及穿插分布的称为框架区(FWR)的更保守区域。本发明公开的抗体和抗原结合片段的CDR由Kabat编号所定义或识别。在一个实施方案中,每个VH和VL一般包括从氨基端到羧基端按以下顺序排列的3个CDR和4个FWR:FWR1、CDR1、FWR2、CDR2、FWR3、CDR3、FWR4。本发明公开的抗体和抗原结合片段的CDR由Kabat编号所定义或识别。

[0049] 本文使用的“载体”是指包括重组多核苷酸的载体,所述重组多核苷酸包括可操作地连接至待表达的核苷酸序列的表达控制序列。

[0050] 下述实施例中的实验方法,如无特殊说明,均为常规方法。

实施例

[0051] 实例1:质粒载体的构建

[0052] 表达anti-VEGF-A/ANG-2基因的AAV载体质粒的构建

[0053] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用$(G_4S)_3$、G_4S、$(G_4S)_3$肽接头连接,组成了结构为CD5-sp-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$的开放阅读框,根据人密码子偏好设计核苷酸序列,并在5’端引入BamH I酶切位点,在3’端引入EcoR V酶切位点,根据表1、表2中各自的序列进行构建,分别命名为XMVA01、XMVA04和XMVA09(由南京金斯瑞生物科技公司合成全基因);

[0054] 用BamH I/EcoR V双酶切上述构建体和pAAV9neo-CAG质粒,通过连接、转化及克隆筛选鉴定等常规分子生物学操作分别构建了XMVA01、XMVA04和XMVA09载体,其结构示意图见图1。用无内毒素的质粒提取试剂盒(MN)获得高质量的质粒DNA备用。

[0055] 表1 XMVA09的序列信息

[0056]

产品编号	序列信息	氨基酸序列		DNA 序列	
XMVA09	VH 抗VEGF-A（G6-23）-CDR1	DYWIH	SEQ ID NO : 1	gactactggattcac	SEQ ID NO : 24
	VH 抗VEGF-A（G6-23）-CDR2	GITPAGGYTYYADSVKG	SEQ ID NO : 2	ggaatcaccccagcaggaggctacacatactatgccgacagcgtgaagggc	SEQ ID NO : 25
	VH 抗VEGF-A（G6-23）-CDR3	FVFFLPYAMDY	SEQ ID NO : 3	ttcgtgttcttcctgccatacgccatggattat	SEQ ID NO : 26
	VH 抗VEGF-A	EVQLVESGGGLVQPGGSLRLSCAASGFTISDY	SEQ ID NO : 13	gaggtgcagctggtggagagcggaggaggactggtgcagccaggaggctccctgcggctgtcttgcgc	SEQ ID NO : 27

[0057]

	（G6-23）	WIHWVRQAPGKGLE WVAGITPAGGYTYYA DSVKGRFTISADTSKN TAYLQMNSLRAEDTAV YYCARFVFFLPYAMD YWGQGTLVTVSS		cgccagcggctttaccatctccgactactggattcac tgggtgagacaggcacctggcaagggactggagt gggtggcaggaatcaccccagcaggaggctacac atactatgccgacagcgtgaagggccggttcacca tctccgccgatacctctaagaacacagcctatctgc agatgaactccctgcgggccgaggacacagccgt gtactattgcgccagattcgtgttcttcctgccatacg ccatggattattggggccagggcaccctggtgaca gtgagctcc	
	VL抗VEGF-A（G6-23）-CDR1	RASQDVSTAVA	SEQ ID NO : 4	agagcaagccaggacgtgagcaccgcagtggca	SEQ ID NO : 28
	VL抗VEGF-A（G6-23）-CDR2	SASFLYS	SEQ ID NO : 5	tccgcctctttcctgtattct	SEQ ID NO : 29
	VL抗VEGF-A（G6-23）-CDR3	KQGYANPWT	SEQ ID NO : 6	aagcagggctatgccaatccatggacc	SEQ ID NO : 30
	VL抗VEGF-A（G6-23）	DIQMTQSPSSLSASVG DRVTITCRASQDVSTA VAWYQQKPGKAPKLL IYSASFLYSGVPSRFSG SGSGTDFTLTISSLQPE DFATYYCKQGYANPW TFGQGTKVEIKR	SEQ ID NO : 14	gatattcagatgacacagtccccatctagcctgtctg ccagcgtgggcgacagggtgaccatcacatgtag agcaagccaggacgtgagcaccgcagtggcatgg taccagcagaagcctggcaaggccccaaagctgc tgatctactccgcctctttcctgtattctggcgtgcca agcaggtttagcgggtccggatctggaaccgacttc accctgacaatctcctctctgcagcctgaggattttg ccacatactattgcaagcagggctatgccaatccat ggaccttcggccagggcacaaaggtggagatcaa gagg	SEQ ID NO : 31
	VH抗ANG-2（3.19.3）-CDR1	NYGMH	SEQ ID NO : 7	aactatggaatgcac	SEQ ID NO :32
	VH抗ANG-2（3.19.3）-CDR2	VISHDGNNKYYVDSV KG	SEQ ID NO : 8	gtgatcagccacgacggcaacaacaagtactacgt ggacagcgtgaagggc	SEQ ID NO : 33
	VH抗ANG-2（3.19.3）-CDR3	EGIDFWSGLNWFDP	SEQ ID NO : 9	gagggcatcgacttttggagcggcctgaattggttc gaccct	SEQ ID NO : 34
	VH抗ANG-2（3.19.3）	QVQLVESGGGVVQPG RSLRLSCAASGFTFTN YGMHWGRQAPGKGL EWVAVISHDGNNKYY VDSVKGRFTISRDNSK NTLYLQMNSLRAEDTA VYYCAREGIDFWSGL NWFDPWGQGTLVTVS SA	SEQ ID NO :15	caggtgcagctggttgaatctggtggcggagttgtg cagcctggcagaagcctgagactgtcttgtgccgc cagcggcttcaccttcaccaactatggaatgcactg gggcagacaggccccctggcaaaggacttgaatgg gtcgccgtgatcagccacgacggcaacaacaagt actacgtggacagcgtgaagggcagattcaccatc agccgggacaacagcaagaacaccctgtacctgc agatgaacagcctgagagccgaggacaccgccgt gtactattgtgccagagagggcatcgacttttggag cggcctgaattggttcgacccttggggacagggca ccctggttacagtttcttctgcc	SEQ ID NO : 35
	VL抗ANG-2（3.19.3）-CDR1	RASQSITGSYLA	SEQ ID NO : 10	agagccagccagagcatcaccggctcttacctggc t	SEQ ID NO : 36
	VL抗ANG-2（3.19.3）-CDR2	GASSWAT	SEQ ID NO : 11	ggcgcctcttcttgggccacc	SEQ ID NO : 37
	VL抗ANG-2（3.19.3）-CDR3	QQYSSSPIT	SEQ ID NO : 12	cagcagtacagcagcagccccatcacc	SEQ ID NO : 38
	VL抗ANG-2（3.19.3）	EIVLTQSPGTLSLSPGE RATLSCRASQSITGSYL AWYQQKPGQAPRLLI CGASSWATGIPDRFSG SGSGTDFTLTISRLEPE DFAVYYCQQYSSSPITF	SEQ ID NO : 16	gagatcgtgctgacacagagccctggcacactgtc actgtctccaggcgaaagagccacactgagctgta gagccagccagagcatcaccggctcttacctggctt ggtatcagcagaagcctggacaggcccctagactg ctgatttgtggcgcctcttcttgggccaccggcattc ccgatagattttctggcagcggctccggcaccgact	SEQ ID NO : 39

[0058]

		GQGTRLEIKR		tcaccctgacaatcagcagactggaacccgaggac ttcgccgtgtactactgccagcagtacagcagcagc cccatcacctttggccagggcacaagactggaaat caagcgg	
	VH 抗 VEGF-A-(G4S)3-VL 抗 VEGF-A-G4S-VH 抗 ANG-2-(G4S)3-VL 抗 ANG-2	EVQLVESGGGLVQPGG SLRLSCAASGFTISDY WIHWVRQAPGKGLE WVAGITPAGGYTYYA DSVKGRFTISADTSKN TAYLQMNSLRAEDTAV YYCARFVFFLPYAMD YWGQGTLVTVSSGGG GSGGGGSGGGGSDIQ MTQSPSSLSASVGDRV TITCRASQDVSTAVAW YQQKPGKAPKLLIYSA SFLYSGVPSRFSGSGSG TDFTLTISSLQPEDFAT YYCKQGYANPWTFGQ GTKVE IKRGGGGSQVQLVESG GGVVQPGRSLRLSCA ASGFTFTNYGMHWGR QAPGKGLEWVAVISHD GNNKYYVDSVKGRFT ISR DNSKNTLYLQMNSLR AEDTAVYYCAREGIDF WSGLNWFDPWGQGTL VTVSSAGGGGSGGGG SGGGGSEIVLTQSPGTL SLSPGERATLSCRASQS ITGSYLAWYQQKPGQ APRLLICGASSWATGIP DRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQYS SSPITFGQGTRLEIKR	SEQ ID NO : 17	gaggtgcagctggtggagagcggaggaggactg gtgcagccaggaggctccctgcggctgtcttgcgc cgccagcggctttaccatctccgactactggattcac tgggtgagacaggcacctggcaagggactggagt gggtggcaggaatcaccccagcaggaggctacac atactatgccgacagcgtgaagggccggttcacca tctccgccgatacctctaagaacacagcctatctgc agatgaactccctgcgggccgaggacacagccgt gtactattgcgccagattcgtgttcttcctgccatacg ccatggattattggggccagggcaccctggtgaca gtgagctccggtggaggtggctccggtggcggtg gcagcggcggtggcggctctgatattcagatgaca cagtccccatctagcctgtctgccagcgtgggcga cagggtgaccatcacatgtagagcaagccaggac gtgagcaccgcagtggcatggtaccagcagaagc ctggcaaggccccaaagctgctgatctactccgcct ctttcctgtattctggcgtgccaagcaggtttagcgg gtccggatctggaaccgacttcaccctgacaatctc ctctctgcagcctgaggattttgccacatactattgca agcagggctatgccaatccatggaccttcggccag ggcacaaaggtggagatcaagaggggcggaggg ggctctcaggtgcagctggttgaatctggtggcgga gttgtgcagcctggcagaagcctgagactgtcttgt gccgccagcggcttcaccttcaccaactatggaatg cactggggcagacaggcccctggcaaaggacttg aatgggtcgccgtgatcagccacgacggcaacaa caagtactacgtggacagcgtgaagggcagattca ccatcagccgggacaacagcaagaacaccctgta cctgcagatgaacagcctgagagccgaggacacc gccgtgtactattgtgccagagagggcatcgacttttt ggagcggcctgaattggttcgacccttggggacag ggcaccctggttacagtttcttctgccggtggaggtg gctccggtggcggtggcagcggcggtggcggctc tgagatcgtgctgacacagagccctggcacactgt cactgtctccaggcgaaagagccacactgagctgt agagccagccagagcatcaccggctcttacctggc ttggtatcagcagaagcctggacaggcccctagac tgctgatttgtggcgcctcttcttgggccaccggcatt cccgatagattttctggcagcggctccggcaccga cttcaccctgacaatcagcagactggaacccgagg acttcgccgtgtactactgccagcagtacagcagca gccccatcacctttggccagggcacaagactggaa atcaagcgg	SEQ ID NO : 40
	CD5-sp-VH 抗VEGF-A-(G4S)3-VL 抗 VEGF-A-G4S-VH 抗 ANG-2-(G4S)3-VL 抗 ANG-2	MPMGSLQPLATLYLLG MLVASCLGEVQLVESG GGLVQPGGSLRLSCAA SGFTISDYWIHWVRQA PGKGLEWVAGITPAGG YTYYADSVKGRFTISA DTSKNTAYLQMNSLR AEDTAVYYCARFVFFL PYAMDYWGQGTLVTV SSGGGGSGGGGSGGG GSD IQMTQSPSSLSASVGD RVTITCRASQDVSTAVA WYQQKPGKAPKLLIY SASFLYSGVPSRFSGSG SGTDFTLTISSLQPE DFATYYCKQGYANPW TFGQGTKVEIKRGGGG SQVQLVESGGGVVQP	SEQ ID NO : 20	atgccaatggggtccctacaacccctggcaacact atatctgctaggtatgctcgtggcctcctgtttaggag aggtgcagctggtggagagcggaggaggactggt gcagccaggaggctccctgcggctgtcttgcgccg ccagcggctttaccatctccgactactggattcactg ggtgagacaggcacctggcaagggactggagtgg gtggcaggaatcaccccagcaggaggctacacat actatgccgacagcgtgaagggccggttcaccatc tccgccgatacctctaagaacacagcctatctgcag atgaactccctgcgggccgaggacacagccgtgta ctattgcgccagattcgtgttcttcctgccatacgcca tggattattggggccagggcaccctggtgacagtg agctccggtggaggtggctccggtggcggtggca gcggcggtggcggctctgatattcagatgacacag tccccatctagcctgtctgccagcgtgggcgacag ggtgaccatcacatgtagagcaagccaggacgtga gcaccgcagtggcatggtaccagcagaagcctgg caaggccccaaagctgctgatctactccgcctctttc ctgtattctggcgtgccaagcaggtttagcgggtcc	SEQ ID NO : 41

[0059]

		GRSLRLSCAASGFTFT NYGMHWGRQAPGKG LEWVAVISHDGNNKY YVDSVKGRFTISRDNS KNTLYLQMNSLRAED TAVYYCAREGIDFWSG LNWFDPWGQGTLVTV SSAGGGGSGGGGSGG GGSEIVLTQSPGTLSLS PGERATLSCRASQSITG SYLAWYQQKPGQAPR LLICGASSWATGIPDRF SGSGSGTDFTLTISRLE PEDFAVYYCQQYSSSPI TFGQGTRLEIKR		ggatctggaaccgacttcaccctgacaatctcctctc tgcagcctgaggattttgccacatactattgcaagca gggctatgccaatccatggaccttcggccagggca caaaggtggagatcaagaggggcggaggggggct ctcaggtgcagctggttgaatctggtggcggagttg tgcagcctggcagaagcctgagactgtcttgtgccg ccagcggcttcaccttcaccaactatggaatgcact ggggcagacaggcccctggcaaaggacttgaatg ggtcgccgtgatcagccacgacggcaacaacaag tactacgtggacagcgtgaagggcagattcaccat cagccgggacaacagcaagaacaccctgtacctg cagatgaacagcctgagagccgaggacaccgcc gtgtactattgtgccagagagggcatcgacttttgga gcggcctgaattggttcgacccttggggacagggc accctggttacagtttcttctgccggtggaggtggct ccggtggcggtggcagcggcggtggcggctctga gatcgtgctgacacagagccctggcacactgtcact gtctccaggcgaaagagccacactgagctgtagag ccagccagagcatcaccggctcttacctggcttggt atcagcagaagcctggacaggcccctagactgctg atttgtggcgcctcttcttgggccaccggcattcccg atagattttctggcagcggctccggcaccgacttca ccctgacaatcagcagactggaacccgaggacttc gccgtgtactactgccagcagtacagcagcagccc catcacctttggccagggcacaagactggaaatca agcgg		
-	CD5-sp 信号肽	MPMGSLQPLATLYLLG MLVASCLG	SEQ ID NO : 23	atgccaatggggtccctacaacccctggcaacact atatctgctaggtatgctcgtggcctcctgtttagga	SEQ ID NO : 42

[0060] 表2. XMVA01和XMVA04序列信息

[0061]

产品编号	序列信息	氨基酸序列	DNA 序列
XMVA01	VH 抗 VEGF-A	EVQLVESGGGLVQPGGSLRLSCTASG FSLTDYYYMTWVRQAPGKGLEWVG FIDPDDDPYYATWAKGRFTISRDNSK NTLYLQMNSLRAEDTAVYYCAGGDH NSGWGLDIWGQGTLVTVSS	gaggtgcagctggttgaatctggcggaggactggttcagcctggcg gatctctgagactgagctgtaccgccagcggcttcagcctgaccga ctactactacatgacctgggtccgacaggcccctggcaaaggacttg agtgggtcggattcatcgaccccgacgacgatccttactacgccaca tgggccaagggcagattcaccatcagccgggacaacagcaagaac accctgtacctgcagatgaacagcctgagagccgaggacaccgcc gtgtactattgtgccggcggagatcacaatagcggctggggccttga tatttggggccagggaacactggtcaccgtgtctagt
	VL 抗 VEGF-A	EIVMTQSPSTLSASVGDRVIITCQASEI IHSWLAWYQQKPGKAPKLLIYLAST LASGVPSRFSGSGSGAEFTLTISSLQP DDFATYYCQNVYLASTNGANFGQGT KLTVLG	gagatcgtgatgacacagagccccagcacactgtctgccagcgtgg gagacagagtgatcatcacatgccaggccagcgagatcatccaca gctggctggcttggtatcagcagaagcctggcaaggccctaagct gctgatctacctggcctctacactggccagcggagtgcctagcagat tttctggctctggatctggcgccgagttcaccctgaccatcagtagcc tgcagcctgacgacttcgccacctactactgccagaacgtgtacctg gccagcaccaacggcgccaattttggccagggcaccaagctgaca gtgctggga
	VH 抗 ANG-2	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTGYYMHWVRQAPGQGLEWM GWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSRLRSDDTAVYYCARSP NPYYYDSSGYYYPGAFDIWGQGTM VTVSS	caggttcagctggttcagtctggcgccgaagtgaagaaacctggcg cctctgtgaaggtgtcctgcaaggccagcggctacaccttttaccggc tactacatgcactgggtccgacaggctccaggacagggacttgaat ggatgggctggatcaaccccaatagcggcggcaccaattacgccc agaaattccagggcagagtgaccatgaccagagacaccagcatca gcaccgcctacatggaactgagccggctgagatccgatgacaccg ccgtgtactactgcgccagatctcccaatccttactactacgacagca gcgggtactactacccaggcgccttcgatatttggggccagggcac aatggtcaccgtgtctagt
	VL 抗 ANG-2	SYVLTQPPSVSVAPGQTARITCGGNNI GSKSVHWYQQKPGQAPVLVVYDDS DRPSGIPERFSGSNSGNTATLTISRVEA GDEADYYCQVWDSSSDHWVFGGGT KLTVL	agctacgtgctgacacagcctccatccgtgtctgtggctccaggaca gaccgccagaatcacatgcggcggcaacaacatcggcagcaaga gcgtgcactggtatcagcagaagcctggacaggctcctgtgctggt ggtgtacgacgacagcgatagacctagcggcatccccgagagattc agcggcagcaattccggcaataccgccacactgaccatcagcaga gtggaagctggcgacgaggccgactactactgccaagtgtgggac agcagcagcgaccactgggttttcggcggaggcacaaagctgaca

[0062]

		gtgctg
VH抗VEGF-A-$(G_4S)_3$-VL抗VEGF-A-G_4S-VH抗ANG-2-$(G_4S)_3$-VL抗ANG-2	EVQLVESGGGLVQPGGSLRLSCTASGFSLTDYYYMTWVRQAPGKGLEWVGFIDPDDDPYYATWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGDHNSGWGLDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPSTLSASVGDRVIITCQASEIIHSWLAWYQQKPGKAPKLLIYLASTLASGVPSRFSGSGSGAEFTLTISSLQPDDFATYYCQNVYLASTNGANFGQGTKLTVLGGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARSPNPYYYDSSGYYYPGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHWVFGGGTKLTVL	gaggtgcagctggttgaatctggcggaggactggttcagcctggcggatctctgagactgagctgtaccgccagcggcttcagcctgaccgactactactacatgacctgggtccgacaggcccctggcaaaggacttgagtgggtcggattcatcgaccccgacgacgatccttactacgccacatgggccaagggcagattcaccatcagccgggacaacagcaagaacaccctgtacctgcagatgaacagcctgagagccgaggacaccgccgtgtactattgtgccggcggagatcacaatagcggctggggccttgatatttggggccagggaacactggtcaccgtgtctagtggtggaggtggctccggtggcggtggcagcggcggtggcggctctgagatcgtgatgacacagagccccagcacactgtctgccagcgtgggagacagagtgatcatcacatgccaggccagcgagatcatccacagctggctggctggtatcagcagaagcctggcaaggccccctaagctgctgatctacctggcctctacactggccagcggagtgcctagcagattttctggctctggatctggcgccgagttcaccctgaccatcagtagcctgcagcctgacgacttcgccacctactactgccagaacgtgtacctggccagcaccaacggcgccaattttggccagggcaccaagctgacagtgctgggaggcggaggggggctctcaggttcagctggttcagctggttcagtctggcgccgaagtgaagaaacctggcgcctctgtgaaggtgtcctgcaaggccagcggctacaccttaccggctactacatgcactgggtccgacaggctccaggacagggacttgaatggatgggctggatcaaccccaatagcggcggcaccaattacgcccagaaattccagggcagagtgaccatgaccagagacaccagcatcagcaccgcctacatggaactgagccggctgagatccgatgacaccgccgtgtactactgcgccagatctcccaatccttactactacgacagcagcgggtactacccaggcgccttcgatatttgggccagggcacaatggtcaccgtgtctagtggtggaggtggctccggtggcggtggcagcggcggtggcggctctagctacgtgctgacacagcctccatccgtgtctgtggctccaggacagaccgccagaatcacatgcggcggcaacaacatcggcagcaagagcgtgcactggtatcagcagaagcctggacaggctcctgtgctggtggtgtacgacgacagcgatagacctagcggcatccccgagagattcagcggcagcaattccggcaatacgccacactgaccatcagcagagtggaagctggcgacgaggccgactactactgccaagtgtgggacagcagcagcgaccactggggttttcggcggaggcacaaagctgacagtgctg
	MPMGSLQPLATLYLLGMLVASCLGEVQLVESGGGLVQPGGSLRLSCTASGFSLTDYYYMTWVRQAPGKGLEWVGFIDPDDDPYYATWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGDHNSGWGLDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPSTLSASVGDRVIITCQASEIIHSWLAWYQQKPGKAPKLLIYLASTLASGVPSRFSGSGSGAEFTLTISSLQPDDFATYYCQNVYLASTNGANFGQGTKLTVLGGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARSPNPYYYDSSGYYYPGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHWVFGGGTKLTVL	CD5-sp-VH抗VEGF-A-$(G_4S)_3$-VL抗VEGF-A-G_4S-VH抗ANG-2-$(G_4S)_3$-VL抗ANG-2	atgccaatggggtccctacaaccctggcaacactatatctgctaggtatgctcgtggcctcctgtttaggagaggtgcagctggttgaatctggcggaggactggttcagcctggcggatctctgagactgagctgtaccgccagcggcttcagcctgaccgactactactacatgacctgggtccgacaggcccctggcaaaggacttgagtgggtcggattcatcgaccccgacgacgatccttactacgccacatgggccaagggcagattcaccatcagccgggacaacagcaagaacaccctgtacctgcagatgaacagcctgagagccgaggacaccgccgtgtactattgtgccggcggagatcacaatagcggctggggccttgatatttggggccagggaacactggtcaccgtgtctagtggtggaggtggctccggtggcggtggcagcggcggtggcggctctgagatcgtgatgacacagagccccagcacactgtctgccagcgtgggagacagagtgatcatcacatgccaggccagcgagatcatccacagctggctggctggtatcagcagaagcctggcaaggccccctaagctgctgatctacctggcctctacactggccagcggagtgcctagcagattttctggctctggatctggcgccgagttcaccctgaccatcagtagcctgcagcctgacgacttcgccacctactactgccagaacgtgtacctggccagcaccaacggcgccaattttggccagggcaccaagctgacagtgctgggaggcggaggggggctctcaggttcagctggttcagctggttcagtctggcgccgaagtgaagaaacctggcgcctctgtgaaggtgtcctgcaaggccagcggctacaccttaccggctactacatgcactgggtccgacaggctccaggacagggacttgaatggatgggctggatcaaccccaatagcggcggcaccaattacgcccagaaattccagggcagagtgaccatgaccagagacaccagcatcagcaccgcctacatggaactgagccggctgagatccgatgacaccgccgtgtactactgcgccagatctcccaatccttactactacgacagcagcgggtactacccaggcgccttcgatatttgggccagggcacaatggtcaccgtgtctagtggtggaggtggctccggtggcggtggcagcggcggtggcggctctagctacgtgctgacacagcctccatccgtgtctgtggctccaggacagaccgccagaatcacatgcggcggcaacaacatcggcagcaagagcgtgcactggtatcagcagaagcctggacaggctcctgtgctggtggtgtacgacgacagcgatagacctagcggcatccccgagagattcagcggcagcaattccggcaatacgccacactgac

[0063]

			catcagcagagtggaagctggcgacgaggccgactactactgcca agtgtgggacagcagcagcgaccactgggttttcggcggaggcac aaagctgacagtgctg
XMV A04	VH 抗 VEGF-A（G6-23）	EVQLVESGGGLVQPGGSLRLSCAASG FTISDYWIHWVRQAPGKGLEWVAGI TPAGGYTYYADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCARFVFFL PYAMDYWGQGTLVTVSS	gaggtgcagctggtggagagcggaggaggactggtgcagccagg aggctccctgcggctgtcttgcgccgccagcggctttaccatctccg actactggattcactgggtgagacaggcacctggcaagggactgga gtgggtggcaggaatcaccccagcaggaggctacacatactatgcc gacagcgtgaagggccggttcaccatctccgccgatacctctaaga acacagcctatctgcagatgaactccctgcgggccgaggacacag ccgtgtactattgcgccagattcgtgttcttcctgccatacgccatgga ttattggggccagggcaccctggtgacagtgagctcc
	VL 抗 VEGF-A（G6-23）	DIQMTQSPSSLSASVGDRVTITCRASQ DVSTAVAWYQQKPGKAPKLLIYSASF LYSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCKQGYANPWTFGQGTKVEI KR	gatattcagatgacacagtccccatctagcctgtctgccagcgtggg cgacagggtgaccatcacatgtagagcaagccaggacgtgagcac cgcagtggcatggtaccagcagaagcctggcaaggccccaaagct gctgatctactccgcctctttcctgtattctggcgtgccaagcaggttta gcgggtccggatctggaaccgacttcaccctgacaatctcctctctg cagcctgaggattttgccacatactattgcaagcagggctatgccaat ccatggaccttcggccagggcacaaaggtggagatcaagagg
	VH 抗 ANG-2	QVQLVQSGAEVKKPGASVKVSCKAS GYTFTGYYMHWVRQAPGQGLEWM GWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSRLRSDDTAVYYCARSP NPYYYDSSGYYYPGAFDIWGQGTM VTVSS	caggttcagctggttcagtctggcgccgaagtgaagaaacctggcg cctctgtgaaggtgtcctgcaaggccagcggctacacctttaccggc tactacatgcactgggtccgacaggctccaggacagggacttgaat ggatgggctggatcaaccccaatagcggcggcaccaattacgccc agaaattccagggcagagtgaccatgaccagagacaccagcatca gcaccgcctacatggaactgagccggctgagatccgatgacaccg ccgtgtactactgcgccagatctcccaatccttactactacgacagca gcgggtactactacccaggcgccttcgatatttggggccagggcac aatggtcaccgtgtctagt
	VL 抗 ANG-2	SYVLTQPPSVSVAPGQTARITCGGNNI GSKSVHWYQQKPGQAPVLVVYDDS DRPSGIPERFSGSNSGNTATLTISRVEA GDEADYYCQVWDSSSDHWVFGGGT KLTVL	agctacgtgctgacacagcctccatccgtgtctgtggctccaggaca gaccgccagaatcacatgcggcggcaacaacatcggcagcaaga gcgtgcactggtatcagcagaagcctggacaggctcctgtgctggt ggtgtacgacgacagcgatagacctagcggcatccccgagagattc agcggcagcaattccggcaataccgccacactgaccatcagcaga gtggaagctggcgacgaggccgactactactgccaagtgtgggac agcagcagcgaccactgggttttcggcggaggcacaaagctgaca gtgctg
	VH 抗 VEGF-A-(G4S)3-VL 抗 VEGF-A-G4S-VH 抗 ANG-2-(G4S)3-VL 抗 ANG-2	EVQLVESGGGLVQPGGSLRLSCAASG FTISDYWIHWVRQAPGKGLEWVAGI TPAGGYTYYADSVKGRFTISADTSKN TAY LQMNSLRAEDTAVYYCARFVFFLPYA MDYWGQGTLVTVSSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTI TCRA SQDVSTAVAWYQQKPGKAPKLLIYSA SFLYSGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCKQGYANPWTFGQGTKV E IKRGGGGSQVQLVQSGAEVKKPGAS VKVSCKASGYTFTGYYMHWVRQAP GQGLEWMGWINPNSGGTNYAQKFQ GRVTMTR DTSISTAYMELSRLRSDDTAVYYCAR SPNPYYYDSSGYYYPGAFDIWGQGT MVTVSSGGGGSGGGGSGGGGSSYVL TQPP SVSVAPGQTARITCGGNNIGSKSVHW YQQKPGQAPVLVVYDDSDRPSGIPER FSGSNSGNTATLTISRVEAGDEADYY CQ VWDSSSDHWVFGGGTKLTVL	gaggtgcagctggtggagagcggaggaggactggtgcagccagg aggctccctgcggctgtcttgcgccgccagcggctttaccatctccg actactggattcactgggtgagacaggcacctggcaagggactgga gtgggtggcaggaatcaccccagcaggaggctacacatactatgcc gacagcgtgaagggccggttcaccatctccgccgatacctctaaga acacagcctatctgcagatgaactccctgcgggccgaggacacag ccgtgtactattgcgccagattcgtgttcttcctgccatacgccatgga ttattggggccagggcaccctggtgacagtgagctccggtggaggt ggctccggtggcggtggcagcggcggtggcggctctgatattcag atgacacagtcccatctagcctgtctgccagcgtgggcgacagggt gaccatcacatgtagagcaagccaggacgtgagcaccgcagtgg catggtaccagcagaagcctggcaaggccccaaagctgctgatcta ctccgcctctttcctgtattctggcgtgccaagcaggttagcgggtcc ggatctggaaccgacttcaccctgacaatctcctctctgcagcctgag gattttgccacatactattgcaagcagggctatgccaatccatggacc ttcggccagggcacaaaggtggagatcaagaggggcggagggg gctctcaggttcagctggttcagtctggcgccgaagtgaagaaacct ggcgcctctgtgaaggtgtcctgcaaggccagcggctacaccttac cggctactacatgcactgggtccgacaggctccaggacagggactt gaatggatgggctggatcaaccccaatagcggcggcaccaattacg cccagaaattccagggcagagtgaccatgaccagagacaccagca tcagcaccgcctacatggaactgagccggctgagatccgatgacac cgccgtgtactactgcgccagatctcccaatccttactactacgacag cagcgggtactactacccaggcgccttcgatatttggggccagggc acaatggtcaccgtgtctagtggtggaggtggctccggtggcggtg gcagcggcggtggcggctctagctacgtgctgacacagcctccatc cgtgtctgtggctccaggacagaccgccagaatcacatgcggcgg caacaacatcggcagcaagagcgtgcactggtatcagcagaagcc tggacaggctcctgtgctggtggtgtacgacgacagcgatagacct agcggcatccccgagagattcagcggcagcaattccggcaataccgccacactgaccatcagcagagtggaagctggcgacgaggccga

[0064]

			ctactactgccaagtgtgggacagcagcagcgaccactgggttttcg gcggaggcacaaagctgacagtgctg
	CD5-sp-VH抗VEGF-A-(G4S)3-VL抗VEGF-A-G4S-VH抗ANG-2-(G4S)3-VL抗ANG-2	MPMGSLQPLATLYLLGMLVASCLGE VQLVESGGGLVQPGGSLRLSCAASGF TISDYWIIHWVRQAPGKGLEWVAGITP AGG YTYYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCARFVFFLPYAM DYWGQGTLVTVSSGGGGSGGGGSG GGGSD IQMTQSPSSLSASVGDRVTITCRASQD VSTAVAWYQQKPGKAPKLLIYSASFL YSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCKQGYANPWTFGQGTKVEI KRGGGGSQVQLVQSGAEVKKPGASV KVSCKASGYTFTGYYMHWVRQAPG QGLEWM GWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSRLRSDDTAVYYCARSP NPYYYDSSGYYYPGAFDIWGQGTM VTVS SGGGGSGGGGSGGGGSSYVLTQPPS VSVAPGQTARITCGGNNIGSKSVHWY QQKPGQAPVLVVYDDSDRPSGIPERF SGS NSGNTATLTISRVEAGDEADYYCQV WDSSSDHWVFGGGTKLTVL	atgccaatggggtccctacaaccctggcaacactatatctgctaggt atgctcgtggcctcctgtttaggagaggtgcagctggtggagagcg gaggaggactggtgcagccaggaggctccctgcggctgtcttgcg ccgccagcggctttaccatctccgactactggattcactgggtgaga caggcacctggcaagggactggagtgggtggcaggaatcacccc agcaggaggctacacatactatgccgacagcgtgaagggccggtt caccatctccgccgatacctctaagaacacagcctatctgcagatga actccctgcgggccgaggacacagccgtgtactattgcgccagatt cgtgttcttcctgccatacgccatggattattggggccagggcaccct ggtgacagtgagctccggtggaggtggctccggtggcggtggcag cggcggtggcggctctgatattcagatgacacagtccccatctagcc tgtctgccagcgtgggcgacagggtgaccatcacatgtagagcaag ccaggacgtgagcaccgcagtggcatggtaccagcagaagcctgg caaggccccaaagctgctgatctactccgcctctttcctgtattctggc gtgccaagcaggtttagcgggtccggatctggaaccgacttcaccct gacaatctcctctctgcagcctgaggattttgccacatactattgcaag cagggctatgccaatccatggaccttcggccagggcacaaaggtg gagatcaagaggggcggaggggggctctcaggttcagctggttcagt ctggcgccgaagtgaagaaacctggcgcctctgtgaaggtgtcctg caaggccagcggctacaccttttaccggctactacatgcactgggtcc gacaggctccaggacagggacttgaatggatgggctggatcaacc ccaatagcggcggcaccaattacgcccagaaattccagggcagag tgaccatgaccagagacaccagcatcagcaccgcctacatggaact gagccggctgagatccgatgacaccgccgtgtactactgcgccaga tctcccaatccttactactacgacagcagcgggtactactacccagg cgccttcgatatttggggccagggcacaatggtcaccgtgtctagtg gtggaggtggctccggtggcggtggcagcggcggtggcggctcta gctacgtgctgacacagcctccatccgtgtctgtggctccaggacag accgccagaatcacatgcggcggcaacaacatcggcagcaagag cgtgcactggtatcagcagaagcctggacaggctcctgtgctggtg gtgtacgacgacagcgatagacctagcggcatccccgagagattca gcggcagcaattccggcaataccgccacactgaccatcagcagagt ggaagctggcgacgaggccgactactactgccaagtgtgggacag cagcagcgaccactgggttttcggcggaggcacaaagctgacagt gctg

[0065] 实例2:XMVA01、XMVA04、XMVA09在细胞中的表达测定

[0066] 将XMVA01、XMVA04、XMVA09质粒分别转染HEK293T细胞,收集上清,用ELISA检测上清中蛋白的表达。具体操作如下:用含10%胎牛血清的DMEM的完全培养基重悬293T细胞后,接种至培养皿中,37℃、5%CO_2培养箱培养至细胞的汇合度达到70%-90%时,采用Lipofectamine2000(Invitrogen)促转试剂,按照其说明书转染质粒。继续培养72小时后,收集上清液,-80℃备用。

[0067] ELISA具体检测方法如下:以0.1μg/mL VEGF165(proteintech)蛋白包被酶标板(Thermo),每孔100μL,4℃过夜孵育,用含有0.05%Tween(Sangon)的PBS洗涤酶标板3次,每次3分钟。用含有2%BSA(麦客生物)的PBS 200μL/孔室温封闭1小时,再次洗涤3次。在酶标板中分别加入康柏西普(10mg/mL)标准品和XMVA01、XMVA04、XMVA09质粒转染HEK293T细胞后收集的细胞上清,标准品从第一孔以312.5ng/mL浓度开始连续8个稀释度进行倍比稀释,待测上清以1:10或1:50进行倍比稀释,数据取平均值,以未转染质粒的细胞上清液作为对照组(Control组),37℃孵育1小时,洗涤3次。每孔加入1:5000稀释的辣根过氧化氢酶标记的羊抗人IgG抗体(JacksonImmunoResearch),37℃孵育1小时,再洗涤3次。每孔加入TMB显色液(Beyotime)100μL/孔,室温避光反应6分钟,向上述孔中加入100μL/孔终止液(Beyotime)终止反应。用酶标仪在450nm处测定OD值,计算待测样品的含量,结果见图3。XMVA01、XMVA04和XMVA09载体转染细胞后能有效表达VEGF165中和蛋白,和对照组相比,具

有显著差异。

[0068] 实例3:在细胞中表达XMVA01、XMVA04、XMVA09对人视网膜微血管内皮细胞(HRMEC)增殖的影响

[0069] 具体实验如下:用含1%ECGS的ECM的完全培养基(Science Cell)调整HRMECs的细胞密度为4×10^4/mL,100μL/孔接种于平底96孔板中,将XMVA01、XMVA04、XMVA09质粒分别转染HEK293T细胞后收集的细胞上清以100μL/孔加入孔内,以未转染质粒的细胞上清液作为对照组(Control组)。37℃、5%CO_2的培养箱中培养72小时,按照Cell Counting Kit-8(CCK-8,Biosharp)说明书分别在实验组和对照组中加入20μL/孔的CCK-8的溶液,孵育4小时后,用酶标仪测定在450nm处的吸光值,结果见图4,XMVA09载体所表达的蛋白能有效抑制ECGS刺激下的HRMECs的增殖,且抑制效果显著优于XMVA01和XMVA04。

[0070] 实例4:在细胞中表达XMVA01、XMVA04、XMVA09对HRMECs管腔形成的影响

[0071] 将解冻后的Matrigel(Corning)基质胶均一地铺在平底96孔板中,50μL/孔,37℃培养箱孵育1小时;以XMVA01、XMVA04、XMVA09质粒分别转染HEK293T细胞后收集的细胞上清处理HRMECs,以未转染质粒的细胞上清液作为对照组(Control组),培养48小时后用不含生长因子和血清的ECM的基础培养基重悬,并调整细胞密度为2×10^5/mL,100μL/孔接种在含基质胶的96孔板内;于37℃,5%CO_2中培养箱中培养,每间隔2小时观察一次,4-8小时后,在显微镜下观察、拍照,记录经待测上清处理后对HRMECs管腔的形成能力的影响,结果见图5。XMVA09载体所表达的蛋白能有效抑制HRMECs管腔的形成,且抑制效果显著优于XMVA01和XMVA04。

[0072] 实例5:重组AAV病毒的制备和鉴定

[0073] 使用三质粒包装系统和纯化重组AAV病毒,辅助质粒(phelper)、AAV的Cap和Rep蛋白表达质粒(AAV2/5)、表达载体目的质粒(XMVA01、XMVA04或XMVA09)按照2:1:1的质量比,和PEI促转剂形成转染复合物,转染HEK293T细胞,进行含目的基因的AAV病毒的包装。分别于转染后第3天和第7天,进行两次上清的收集,即获得含有目的基因的AAV病毒颗粒。采用不同梯度的碘克沙醇(15%、25%、40%和60%)进行密度梯度离心(Beckman的超速离心机),获得纯化的AAV病毒。对获得的纯化的AAV病毒,通过透射电子显微电镜进行AAV质量的鉴定和qPCR进行AAV病毒滴度的定量。

[0074] 统计分析

[0075] 采用双尾分析,统计学水平设在5%或$p\leq0.05$,计算各项分析指标的平均数和标准差(Mean±SD)。上述数据按下列过程分析:

[0076] 用Levene's Test检验方差齐性;如果没有统计学意义($p>0.05$),用单因素方差分析(ANOVA)进行统计分析。如果ANOVA有统计学意义($p\leq0.05$),则进行LSD多重比较。

[0077] 如果方差不齐($p\leq0.05$),则进行Kruskal-Wallis非参数检验。如果Kruskal-Wallis非参数检验结果显著($p\leq0.05$),则进一步采用Mann-Whitney U检验进行两两比较。

[0078] 实例6:其他质粒载体的构建

[0079] 方案1

[0080] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用G_4S、$(G_4S)_3$、G_4S肽接头连接,组成了结构为CD5-sp-$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$的开放阅读框,根据人密

码子偏好设计核苷酸序列,并在5'端引入BamH I酶切位点,在3'端引入EcoR V酶切位点,命名为XMVA10(见图7)。其中抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列与XMVA09相同。

[0081] 方案2

[0082] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用G_4S、$(G_4S)_3$、G_4S肽接头连接,组成了结构为CD5-sp-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$的开放阅读框,根据人密码子偏好设计核苷酸序列,并在5'端引入BamH I酶切位点,在3'端引入EcoR V酶切位点,命名为XMVA11(见图8)。其中抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列与XMVA09相同。

[0083] 方案3

[0084] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用$(G_4S)_3$、G_4S、$(G_4S)_3$肽接头连接,组成了结构为CD5-sp-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$的开放阅读框,根据人密码子偏好设计核苷酸序列,并在5'端引入BamH I酶切位点,在3'端引入EcoR V酶切位点,命名为XMVA13(见图9)。

[0085] 方案4

[0086] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用G_4S、$(G_4S)_3$、G_4S肽接头连接,组成了结构为CD5-sp-$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$-$(G_4S)_3$-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$的开放阅读框,根据人密码子偏好设计核苷酸序列,并在5'端引入BamH I酶切位点,在3'端引入EcoR V酶切位点,命名为XMVA14(见图10)。其中抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列与XMVA13相同。

[0087] 方案5

[0088] 抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列,在N端加上分泌信号肽CD5-sp核苷酸序列,分别用G_4S、$(G_4S)_3$、G_4S肽接头连接,组成了结构为CD5-sp-$VL_{抗VEGF-A}$-G_4S-$VH_{抗ANG-2}$-$(G_4S)_3$-$VL_{抗ANG-2}$-G_4S-$VH_{抗VEGF-A}$的开放阅读框,根据人密码子偏好设计核苷酸序列,并在5'端引入BamH I酶切位点,在3'端引入EcoR V酶切位点,命名为XMVA15(见图11)。其中抗VEGF的VH氨基酸序列和VL氨基酸序列、抗ANG-2的VH氨基酸序列和VL氨基酸序列与XMVA13相同。

[0089] 通过连接、转化及克隆筛选鉴定等常规分子生物学操作构建了XMVA10、XMVA11、XMVA13、XMVA14和XMVA15载体,用无内毒素的质粒提取试剂盒(MN)获得高质量的质粒DNA备用。

[0090] 按照实施例2中所述方法,将质粒分别转染HEK293T细胞,收集上清,用ELISA方法检测上清中蛋白的表达。按照实施例3中所述的方法,在细胞中表达上述载体对人视网膜微血管内皮细胞(HRMEC)增殖的影响。按照实施例4中所述的方法,在细胞中表达上述质粒对HRMECs管腔形成的影响。按照实施例5中所述的方法,制备重组AAV病毒并鉴定。

[0091] 表3. XMVA10至XMVA15的序列信息

[0092]

产品编号	序列信息	氨基酸序列		DNA 序列	
XMVA10	VL 抗ANG-2-G4S-VH 抗VEGF-A-(G4S)3-VL 抗VEGF-A-G4S-VH 抗ANG-2	EIVLTQSPGTLSLSPG ERATLSCRASQSITGS YLAWYQQKPGQAPR LLICGASSWATGIPD RFSGSGSGTDFTLTIS RLE PEDFAVYYCQQYSSS PITFGQGTRLEIKRG GGGSEVQLVESGGG LVQPGGSLRLSCAAS GFTISDYWIIHWVRQ APGKGLE WVAGITPAGGYTYY ADSVKGRFTISADTS KNTAYLQMNSLRAE DTAVYYCARFVFFLP YAMDYWGQGTLVT VSSGGGGSG GGGSGGGGSDIQMT QSPSSLSASVGDRVTI TCRASQDVSTAVAW YQQKPGKAPKLLIYS	SEQ ID NO : 18	gagatcgtgctgacacagagccctggcacactgtcactgtctcca ggcgaaagagccacactgagctgtagagccagccagagcatca ccggctcttacctggcttggtatcagcagaagcctggacaggccc ctagactgctgatttgtggcgcctcttcttgggccaccggcattccc gatagattttctggcagcggctccggcaccgacttcaccctgaca atcagcagactggaacccgaggacttcgccgtgtactactgcca gcagtacagcagcagccccatcacctttggccagggcacaaga ctggaaatcaagcggggcggaggggggctctgaggtgcagctgg tggagagcggaggaggactggtgcagccaggaggctccctgc ggctgtcttgcgccgccagcggctttaccatctccgactactggat tcactgggtgagacaggcacctggcaagggactggagtgggtg gcaggaatcaccccagcaggaggctacacatactatgccgaca gcgtgaagggccggttcaccatctccgccgatacctctaagaaca cagcctatctgcagatgaactccctgcgggccgaggacacagcc gtgtactattgcgccagattcgtgttcttcctgccatacgccatggat tattggggccagggcaccctggtgacagtgagctccggtggagg tggctccggtggcggtggcagcggcggtggcggctctgatattc agatgacacagtccccatctagcctgtctgccagcgtgggcgac agggtgaccatcacatgtagagcaagccaggacgtgagcaccg cagtggcatggtaccagcagaagcctggcaaggccccaaagct gctgatctactccgcctctttcctgtattctggcgtgccaagcaggtt tagcgggtccggatctggaaccgacttcaccctgacaatctcctct	SEQ ID NO : 43

[0093]

		ASFLYSGVPSRFSGSGSGTDF TLTISSLQPEDFATYY CKQGYANPWTFGQG TKVEIKRGGGGSQV QLVESGGGVVQPGR SLRLSCAASGFTFTN YGMHWGR QAPGKGLEWVAVIS HDGNNKYYVDSVK GRFTISRDNSKNTLY LQMNSLRAEDTAVY YCAREGIDFWSGLN WFDPWGQGTLVTVS SA		ctgcagcctgaggattttgccacatactattgcaagcagggctatg ccaatccatggaccttcggccagggcacaaaggtggagatcaag aggggcggaggggctctcaggtgcagctggttgaatctggtgg cggagttgtgcagcctggcagaagcctgagactgtcttgtgccgc cagcggcttcaccttcaccaactatggaatgcactggggcagaca ggcccctggcaaaggacttgaatgggtcgccgtgatcagccacg acggcaacaacaagtactacgtggacagcgtgaagggcagattc accatcagccgggacaacagcaagaacaccctgtacctgcagat gaacagcctgagagccgaggacaccgccgtgtactattgtgcca gagagggcatcgacttttggagcggcctgaattggttcgaccctt ggggacagggcaccctggttacagtttcttctgcc	
[0093]	CD5-sp-VL抗ANG-2-G4S-VH抗VEGF-A-(G4S)3-VL抗VEGF-A-G4S-VH抗ANG-2	MPMGSLQPLATLYLL GMLVASCLGEIVLTQ SPGTLSLSPGERATLS CRASQSITGSYLAWY QQKPGQAPRLLICGA SSWATGIPDRFSGSG SGTDFTLTISRLE PEDFAVYYCQQYSSS PITFGQGTRLEIKRG GGGSEVQLVESGGG LVQPGGSLRLSCAAS GFTISDYWIHWVRQ APGKGLE WVAGITPAGGYTYY ADSVKGRFTISADTS KNTAYLQMNSLRAE DTAVYYCARFVFFLP YAMDYWGQGTLVT VSSGGGGSG GGGSGGGGSDIQMT QSPSSLSASVGDRVTI TCRASQDVSTAVAW YQQKPGKAPKLLIYS ASFLYSGVPSRFSGS GSGTDF TLTISSLQPEDFATYY CKQGYANPWTFGQG TKVEIKRGGGGSQV QLVESGGGVVQPGR SLRLSCAASGFTFTN YGMHWGR QAPGKGLEWVAVIS HDGNNKYYVDSVK GRFTISRDNSKNTLY LQMNSLRAEDTAVY YCAREGIDFWSGLN WFDPWGQGTLVTVS SA	SEQ ID NO：21	atgccaatggggtccctacaaccccctggcaacactatatctgctag gtatgctcgtggcctcctgtttaggagagatcgtgctgacacagag ccctggcacactgtcactgtctccaggcgaaagagccacactga gctgtagagccagccagagcatcaccggctcttacctggcttggt atcagcagaagcctggacaggccctagactgctgatttgtggcg cctcttcttgggccaccggcattcccgatagattttctggcagcgg ctccggcaccgacttcaccctgacaatcagcagactggaacccg aggacttcgccgtgtactactgccagcagtacagcagcagcccc atcacctttggccagggcacaagactggaaatcaagcggggcg gaggggctctgaggtgcagctggtggagagcggaggaggac tggtgcagccaggaggctccctgcggctgtcttgcgccgccagc ggctttaccatctccgactactggattcactgggtgagacaggcac ctggcaagggactggagtgggtggcaggaatcaccccagcagg aggctacacatactatgccgacagcgtgaagggccggttcacca tctccgccgataccctctaagaacacagcctatctgcagatgaactc cctgcgggccgaggacacagccgtgtactattgcgccagattcgt gttcttcctgccatacgccatggattattggggccagggcaccctg gtgacagtgagctccggtggaggtggctccggtggcggtggca gcggcggtggcggctctgatattcagatgacacagtccccatcta gcctgtctgccagcgtgggcgacagggtgaccatcacatgtaga gcaagccaggacgtgagcaccgcagtggcatggtaccagcaga agcctggcaaggccccaaagctgctgatctactccgcctctttcct gtattctggcgtgccaagcaggtttagcgggtccggatctggaac cgacttcaccctgacaatctcctctctgcagcctgaggattttgcca catactattgcaagcagggctatgccaatccatggaccttcggcc agggcacaaaggtggagatcaagaggggcggaggggctctc aggtgcagctggttgaatctggtggcggagttgtgcagcctggca gaagcctgagactgtcttgtgccgccagcggcttcaccttcacca actatggaatgcactggggcagacaggccctggcaaaggactt gaatgggtcgccgtgatcagccacgacggcaacaacaagtacta cgtggacagcgtgaagggcagattcaccatcagccgggacaac agcaagaacaccctgtacctgcagatgaacagcctgagagccg aggacaccgccgtgtactattgtgccagagagggcatcgacttttt ggagcggcctgaattggttcgaccctggggacagggcaccctg gttacagtttcttctgcc	SEQ ID NO：44
XMVA11	VL抗VEGF-A-G4S-VH抗ANG-2-(G4S)3-VL抗ANG-2-G4S-VH抗VEGF-A	DIQMTQSPSSLSASV GDRVTITCRASQDVS TAVAWYQQKPGKAP KLLIYSASFLYSGVPS RFSGSGSGTDFTLTIS SLQP EDFATYYCKQGYAN PWTFGQGTKVEIKR GGGGSQVQLVESGG GVVQPGRSLRLSCA ASGFTFTNYGMHWG RQAPGKGLEW VAVISHDGNNKYYV	SEQ ID NO：19	gatattcagatgacacagtccccatctagcctgtctgccagcgtgg gcgacagggtgaccatcacatgtagagcaagccaggacgtgag caccgcagtggcatggtaccagcagaagcctggcaaggcccca aagctgctgatctactccgcctctttcctgtattctggcgtgccaag caggtttagcgggtccggatctggaaccgacttcaccctgacaat ctcctctctgcagcctgaggattttgccacatactattgcaagcagg gctatgccaatccatggaccttcggccagggcacaaaggtggag atcaagaggggcggaggggctctcaggtgcagctggttgaatc tggtggcggagttgtgcagcctggcagaagcctgagactgtcttg tgccgccagcggcttcaccttcaccaactatggaatgcactgggg cagacaggccccctggcaaaggacttgaatgggtcgccgtgatca gccacgacggcaacaacaagtactacgtggacagcgtgaaggg cagattcaccatcagccgggacaacagcaagaacaccctgtacc	SEQ ID NO：45

[0094]

		DSVKGRFTISRDNSK NTLYLQMNSLRAED TAVYYCAREGIDFWS GLNWFDPWGQGTLV TVSSAGGG GSGGGGSGGGGSEI VLTQSPGTLSLSPGE RATLSCRASQSITGS YLAWYQQKPGQAPR LLICGASSWATGIPD RFSGSGS GTDFTLTISRLEPEDF AVYYCQQYSSSPITF GQGTRLEIKRGGGG SEVQLVESGGGLVQP GGSLRLSCAASGFTI SDYWI HWVRQAPGKGLEW VAGITPAGGYTYYAD SVKGRFTISADTSKN TAYLQMNSLRAEDT AVYYCARFVFFLPYA MDYWGQGT LVTVSS		tgcagatgaacagcctgagagccgaggacaccgccgtgtactat tgtgccagagagggcatcgacttttggagcggcctgaattggttc gacccttggggacagggcaccctggttacagtttcttctgccggtg gaggtggctccggtggcggtggcagcggcggtggcggctctga gatcgtgctgacacagagccctggcacactgtcactgtctccagg cgaaagagccacactgagctgtagagccagccagagcatcacc ggctcttacctggcttggtatcagcagaagcctggacaggcccct agactgctgatttgtggcgcctcttcttgggccaccggcattcccg atagattttctggcagcggctccggcaccgacttcaccctgacaat cagcagactggaacccgaggacttcgccgtgtactactgccagc agtacagcagcagccccatcacctttggccagggcacaagactg gaaatcaagcggggcggaggggctctgaggtgcagctggtg gagagcggaggaggactggtgcagccaggaggctccctgcgg ctgtcttgcgccgccagcggctttaccatctccgactactggattca ctgggtgagacaggcacctggcaagggactggagtgggtggca ggaatcaccccagcaggaggctacacatactatgccgacagcgt gaagggccggttcaccatctccgccgatacctctaagaacacag cctatctgcagatgaactccctgcgggccgaggacacagccgtg tactattgcgccagattcgtgttcttcctgccatacgccatggattatt ggggccagggcaccctggtgacagtgagctcc	
	CD5-sp-VL抗VEGF-A-G4S-VH抗ANG-2-(G4S)3-VL抗ANG-2-G4S-VH抗VEGF-A	MPMGSLQPLATLYLL GMLVASCLGDIQMT QSPSSLSASVGDRVTI TCRASQDVSTAVAW YQQKPGKAPKLLIYS ASFLYSGVPSRFSGS GSGTDFTLTISSLQP EDFATYYCKQGYAN PWTFGQGTKVEIKR GGGGSQVQLVESGG GVVQPGRSLRLSCA ASGFTFTNYGMHWG RQAPGKGLEW VAVISHDGNNKYYV DSVKGRFTISRDNSK NTLYLQMNSLRAED TAVYYCAREGIDFWS GLNWFDPWGQGTLV TVSSAGGG GSGGGGSGGGGSEI VLTQSPGTLSLSPGE RATLSCRASQSITGS YLAWYQQKPGQAPR LLICGASSWATGIPD RFSGSGS GTDFTLTISRLEPEDF AVYYCQQYSSSPITF GQGTRLEIKRGGGG SEVQLVESGGGLVQP GGSLRLSCAASGFTI SDYWI HWVRQAPGKGLEW VAGITPAGGYTYYAD SVKGRFTISADTSKN TAYLQMNSLRAEDT AVYYCARFVFFLPYA MDYWGQGT LVTVSS	SEQ ID NO：22	atgccaatggggtccctacaacccctggcaacactatatctgctag gtatgctcgtggcctcctgtttaggagatattcagatgacacagtcc ccatctagcctgtctgccagcgtgggcgacagggtgaccatcac atgtagagcaagccaggacgtgagcaccgcagtggcatggtac cagcagaagcctggcaaggccccaaagctgctgatctactccgc ctctttcctgtattctggcgtgccaagcaggtttagcgggtccggat ctggaaccgacttcaccctgacaatctcctctctgcagcctgagga ttttgccacatactattgcaagcagggctatgccaatccatggacct tcggccagggcacaaaggtggagatcaagaggggcggaggg ggctctcaggtgcagctggttgaatctggtggcggagttgtgcag cctggcagaagcctgagactgtcttgtgccgccagcggcttcacc ttcaccaactatggaatgcactggggcagacaggccccctggcaa aggacttgaatgggtcgccgtgatcagccacgacggcaacaaca agtactacgtggacagcgtgaagggcagattcaccatcagccgg gacaacagcaagaacaccctgtacctgcagatgaacagcctgag agccgaggacaccgccgtgtactattgtgccagagagggcatcg acttttggagcggcctgaattggttcgacccttggggacagggca ccctggttacagtttcttctgccggtggaggtggctccggtggcgg tggcagcggcggtggcggctctgagatcgtgctgacacagagc cctggcacactgtcactgtctccaggcgaaagagccacactgag ctgtagagccagccagagcatcaccggctcttacctggcttggtat cagcagaagcctggacaggccctagactgctgatttgtggcgc ctcttcttgggccaccggcattcccgatagattttctggcagcggct ccggcaccgacttcaccctgacaatcagcagactggaacccgag gacttcgccgtgtactactgccagcagtacagcagccccatc acctttggccagggcacaagactggaaatcaagcggggcggag ggggctctgaggtgcagctggtggagagcggaggaggactggt gcagccaggaggctccctgcggctgtcttgcgccgccagcggct ttaccatctccgactactggattcactgggtgagacaggcacctgg caagggactggagtgggtggcaggaatcaccccagcaggagg ctacacatactatgccgacagcgtgaagggccggttcaccatctc cgccgatacctctaagaacacagcctatctgcagatgaactccct gcgggccgaggacacagccgtgtactattgcgccagattcgtgtt cttcctgccatacgccatggattattggggccagggcaccctggt gacagtgagctcc	SEQ ID NO：46
XMVA13	VH抗VEGF-A（G6-31）	DYWIH	SEQ ID NO：1	gactactggattcac	SEQ ID NO：24

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	-CDR 1				
	VH 抗 VEGF-A（G6-31）-CDR 2	GITPAGGYTYYADSVKG	SEQ ID NO : 2	ggaatcaccccagcaggaggctacacatactatgccgacagcgtgaagggc	SEQ ID NO : 25
	VH 抗 VEGF-A（G6-31）-CDR 3	FVFFLPYAMDY	SEQ ID NO : 3	ttcgtgttcttcctgccatacgccatggattat	SEQ ID NO : 26
	VH 抗 VEGF-A（G6-31）	EVQLVESGGGLVQPGGSLRLSCAASGFTISDYWIHWVRQAPGKGLEWVAGITPAGGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARFVFFLPYAMDYWGQGTLVTVSS	SEQ ID NO : 13	gaggtgcagctggtggagagcggaggaggactggtgcagccaggaggctccctgcggctgtcttgcgccgccagcggctttaccatctccgactactggattcactgggtgagacaggcacctggcaagggactggagtgggtggcaggaatcaccccagcaggaggctacacatactatgccgacagcgtgaagggccggttcaccatctccgccgatacctctaagaacacagcctatctgcagatgaactccctgcgggccgaggacacagccgtgtactattgcgccagattcgtgttcttcctgccatacgccatggattattggggccagggcaccctggtgacagtgagctcc	SEQ ID NO : 27
	VL 抗 VEGF-A（G6-31）-CDR 1	RASQDVSTAVA	SEQ ID NO : 4	agagcaagccaggacgtgagcaccgcagtggca	SEQ ID NO : 28
	VL 抗 VEGF-A（G6-31）-CDR 2	SASFLYS	SEQ ID NO : 5	tccgcctctttcctgtattct	SEQ ID NO : 29
	VL 抗 VEGF-A（G6-31）-CDR 3	QQGYGNPFT	SEQ ID NO : 47	cagcagggctatggcaatccattcacc	SEQ ID NO : 55
	VL 抗 VEGF-A（G6-31）	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGYGNPFTFGQGTKVEIKR	SEQ ID NO : 48	gatattcagatgacacagtccccatctagcctgtctgccagcgtgggcgacagggtgaccatcacatgtagagcaagccaggacgtgagcaccgcagtggcatggtaccagcagaagcctggcaaggccccaaagctgctgatctactccgcctctttcctgtattctggcgtgccaagcaggtttagcgggtccggatctggaaccgacttcaccctgacaatctcctctctgcagcctgaggattttgccacatactattgccagcaggctatggcaatccattcacctttggccagggcacaaaggtggagatcaagagg	SEQ ID NO : 56
	VH 抗 ANG-2（3.19.3）	QVQLVESGGGVVQPGRSLRLSCAASGFTFTNYGMHWGRQAPGKGLEWVAVISHDGNNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGIDFWSGLNWFDPWGQGTLVTVSSA	SEQ ID NO :15	caggtgcagctggttgaatctggtggcggagttgtgcagcctggcagaagcctgagactgtcttgtgccgccagcggcttcaccttcaccaactatggaatgcactggggcagacaggcccctggcaaaggacttgaatgggtcgccgtgatcagccacgacggcaacaacaagtactacgtggacagcgtgaagggcagattcaccatcagccgggacaacagcaagaacaccctgtacctgcagatgaacagcctgagagccgaggacaccgccgtgtactattgtgccagagagggcatcgacttttggagcggcctgaattggttcgacccttggggacagggcaccctggttacagtttcttctgcc	SEQ ID NO : 35
	VL 抗 ANG-2（3.19.3）	EIVLTQSPGTLSLSPGERATLSCRASQSITGSYLAWYQQKPGQAPRLLICGASSWATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ	SEQ ID NO : 16	gagatcgtgctgacacagagccctggcacactgtcactgtctccaggcgaaagagccacactgagctgtagagccagccagagcatcaccggctcttacctggcttggtatcagcagaagcctggacaggcccctagactgctgatttgtggcgcctcttcttgggccaccggcattcccgatagattttctggcagcggctccggcaccgacttcaccctgacaatcagcagactggaacccgaggacttcgccgtgtactactgcca	SEQ ID NO : 39

[0096]

		YSSSPITFGQGTRLEIKR		gcagtacagcagcagccccatcacctttggccagggcacaagactggaaatcaagcgg	
	VH抗VEGF-A-(G4S)3-VL抗VEGF-A-G4S-VH抗ANG-2-(G4S)3-VL抗ANG-2	EVQLVESGGGLVQPGGSLRLSCAASGFTISDYWIHWVRQAPGKGLEWVAGITPAGGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARFVFFLPYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGYGNPFTFGQGTKVEIKRGGGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFTNYGMHWGRQAPGKGLEWVAVISHDGNNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGIDFWSGLNWFDPWGQGTLVTVSSAGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSITGSYLAWYQQKPGQAPRLLICGASSWATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSSSPITFGQGTRLEIKR	SEQ ID NO : 49	gaggtgcagctggtggagagcggaggaggactggtgcagccaggaggctccctgcggctgtcttgcgccgccagcggctttaccatctccgactactggattcactgggtgagacaggcacctggcaagggactggagtgggtggcaggaatcaccccagcaggaggctacacatactatgccgacagcgtgaagggccggttcaccatctccgccgatacctctaagaacacagcctatctgcagatgaactccctgcgggccgaggacacagccgtgtactattgcgccagattcgtgttcttcctgccatacgccatggattattggggccagggcaccctggtgacagtgagctccggtggaggtggctccggtggcggtggcagcggcggtggcggctctgatattcagatgacacagtccccatctagcctgtctgccagcgtgggcgacagggtgaccatcacatgtagagcaagccaggacgtgagcaccgcagtggcatggtaccagcagaagcctggcaaggccccaaagctgctgatctactccgcctctttcctgtattctggcgtgccaagcaggtttagcgggtccggatctggaaccgacttcaccctgacaatctcctctctgcagcctgaggattttgccacatactattgccagcagggctatggcaatccattcacctttggccagggcacaaaggtggagatcaagagggggcggaggggctctcaggtgcagctggttgaatctggtggcggagttgtgcagcctggcagaagcctgagactgtcttgtgccgccagcggcttcaccttcaccaactatggaatgcactggggcagacaggcccctggcaaaggacttgaatgggtcgccgtgatcagccacgacggcaacaacaagtactacgtggacagcgtgaagggcagattcaccatcagccgggacaacagcaagaacacccctgtacctgcagatgaacagcctgagagccgaggacaccgccgtgtactattgtgccagagagggcatcgactttttggagcggctgaattggttcgacccttggggacagggcaccctggttacagtttcttctgccggtggaggtggctccggtggcggtggcagcggcggtggcggctctgagatcgtgctgacacagagccctggcacactgtctactgtctccaggcgaaagagccacactgagctgtagagccagccagagcatcaccggctcttacctggcttggtatcagcagaagcctggacaggcccctagactgctgatttgtggcgcctcttcttgggccaccggcattcccgatagattttctggcagcggctccggcaccgacttcaccctgacaatcagcagactggaacccgaggacttcgccgtgtactactgccagcagtacagcagcagccccatcacctttggccagggcacaagactggaaatcaagcgg	SEQ ID NO : 57
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[0097]

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[0238] Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys

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[0244] Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala

[0245] 260 265 270

[0246] Ser Gly Phe Thr Phe Thr Asn Tyr Gly Met His Trp Gly Arg Gln Ala

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[0295] Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro

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[0306] 195 200 205

[0307] Tyr Cys Ala Arg Phe Val Phe Phe Leu Pro Tyr Ala Met Asp Tyr Trp

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[0342] 485

[0343] <210> 19

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[0356] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

[0357] 50 55 60

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[0506] 100 105 110

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[0510] 130 135 140

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[0513] Ala Ala Ser Gly Phe Thr Ile Ser Asp Tyr Trp Ile His Trp Val Arg

[0514] 165 170 175

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[0554] 485 490 495

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[0647] <210> 25

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[0649] <212> DNA

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[0655] <210> 26

[0656] <211> 33

[0657] <212> DNA

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[1058] Gln Gly Tyr Gly Asn Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu
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[1082] Thr Gly Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
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[1112] Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala
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[1114] Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Phe Val Phe Phe Leu Pro
[1115] 115 120 125
[1116] Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[1117] 130 135 140
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[1119] 145 150 155 160
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[1133] 260 265 270

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[1149] 385 390 395 400
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[1151] 405 410 415
[1152] Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
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[1154] Ser Cys Arg Ala Ser Gln Ser Ile Thr Gly Ser Tyr Leu Ala Trp Tyr
[1155] 435 440 445
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[1194] 165 170 175
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[1224] 405 410 415
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[1256] Cys Gln Gln Tyr Ser Ser Ser Pro Ile Thr Phe Gly Gln Gly Thr Arg
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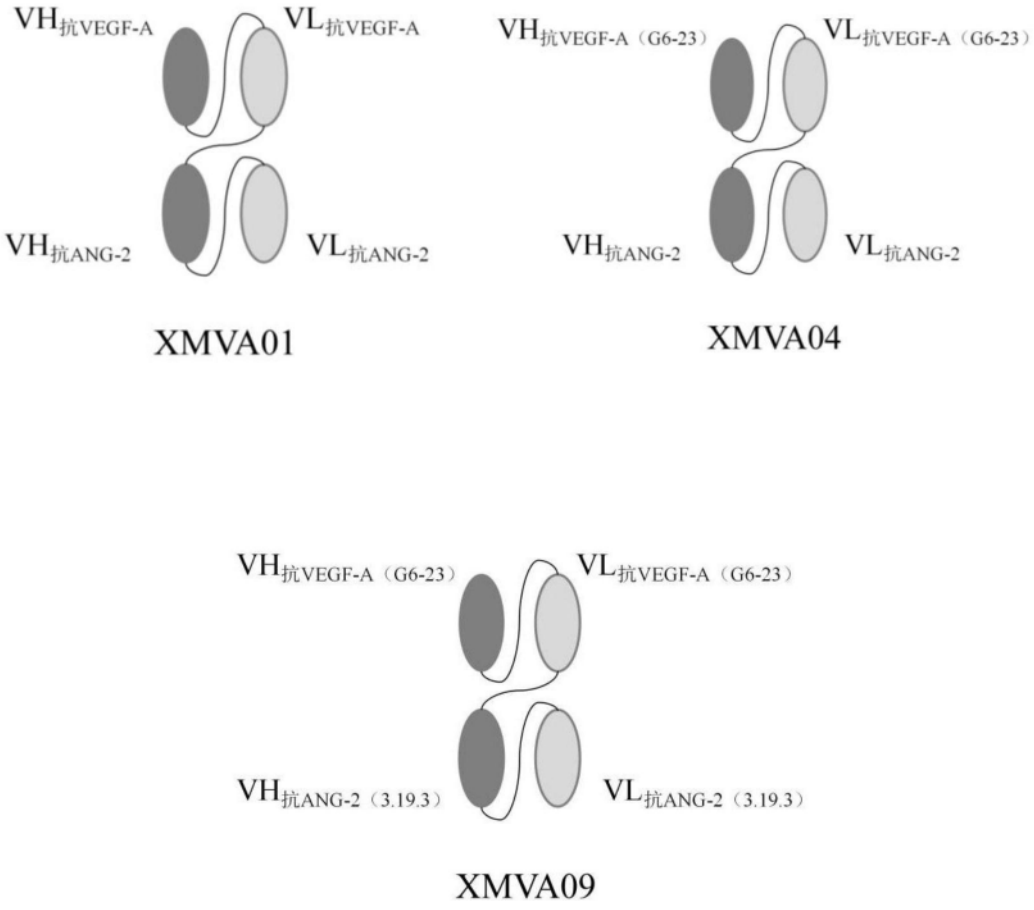

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图1

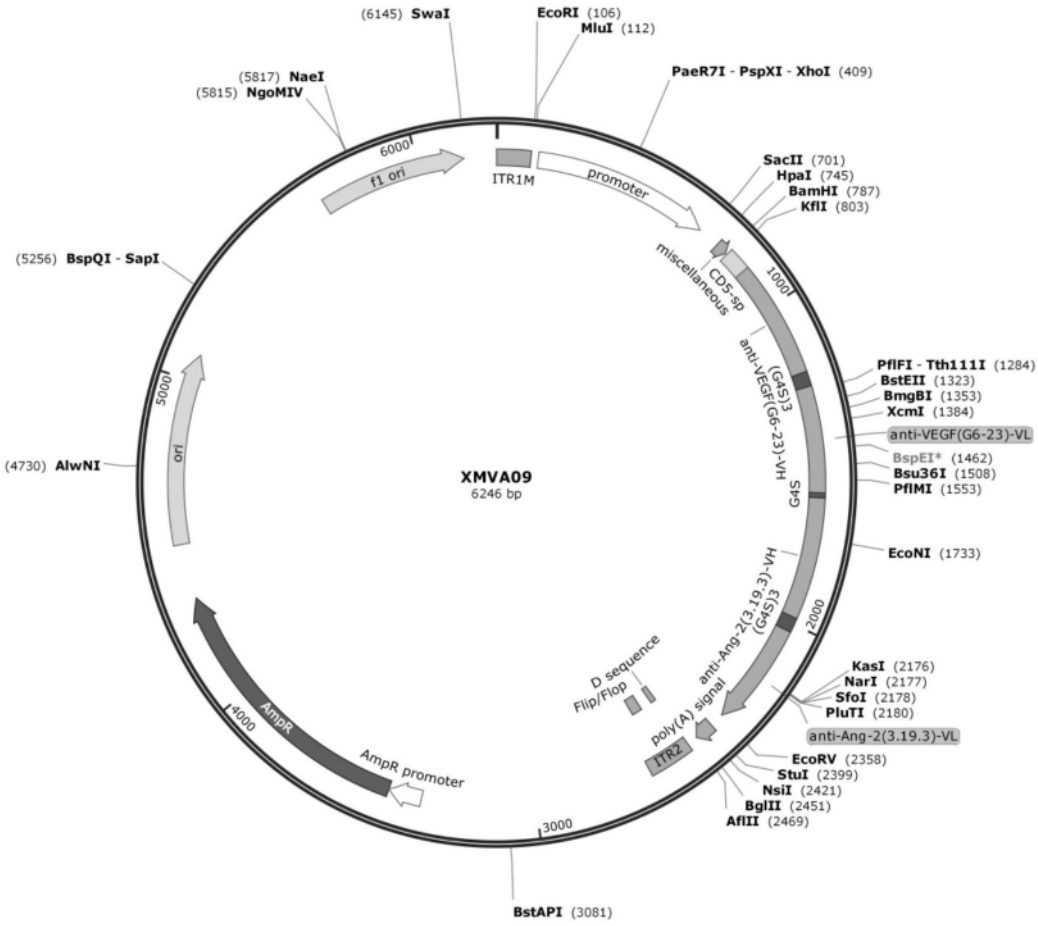

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BmgBI (1353)
XcmI (1384)
anti-VEGF(G6-23)-VL
BspEI* (1462)
Bsu36I (1508)
PflMI (1553)
(4730) AlwNI
EcoNI (1733)
KasI (2176)
NarI (2177)
SfoI (2178)
PluTI (2180)
anti-Ang-2(3.19.3)-VL
EcoRV (2358)
StuI (2399)
NsiI (2421)
BglII (2451)
AflII (2469)
BstAPI (3081)
XMVA09
6246 bp
f1 ori
ITR1M
promoter
miscellaneous
CD5-sp
anti-VEGF(G6-23)-VH
(G4S)3
G4S
anti-Ang-2(3.19.3)-VH
(G4S)3
poly(A) signal
ITR2
D sequence
Flip/Flop
AmpR
AmpR promoter
ori
1000
2000
3000
4000
5000
6000

图2

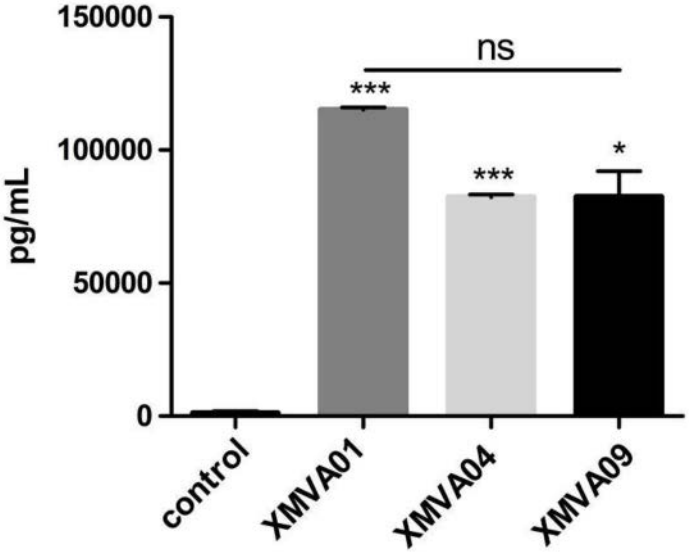

150000
100000
50000
0
pg/mL
ns
***
***
*
control
XMVA01
XMVA04
XMVA09

图3

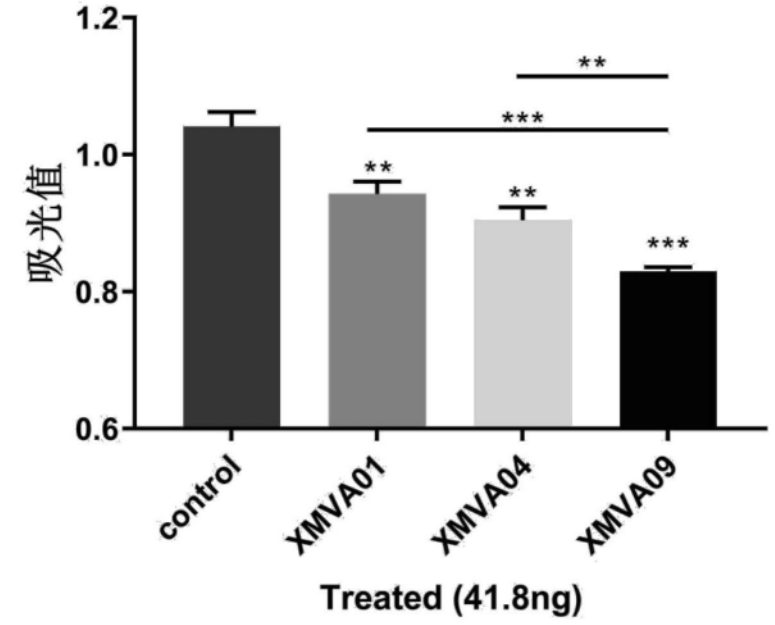

1.2
1.0
0.8
0.6
吸光值
**
***
**
**
***
control
XMVA01
XMVA04
XMVA09
Treated (41.8ng)

图4

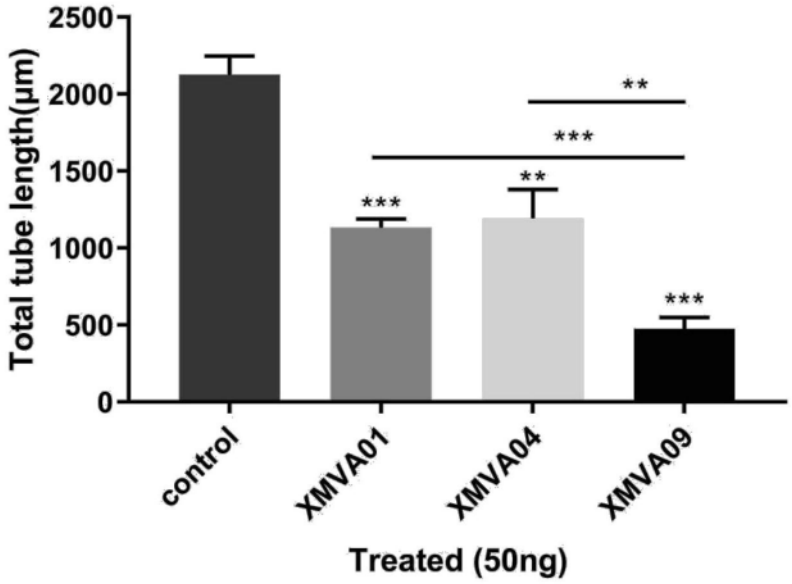

2500
2000
1500
1000
500
0
Total tube length(μm)
**
***
***
**
***
control
XMVA01
XMVA04
XMVA09
Treated (50ng)

图5

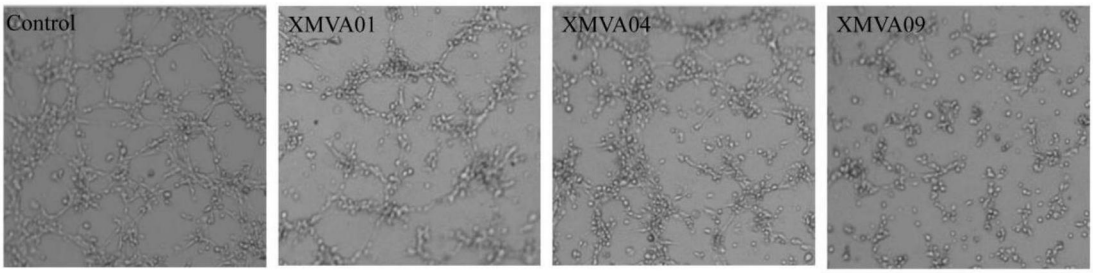
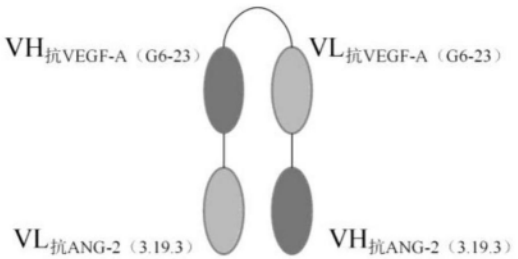
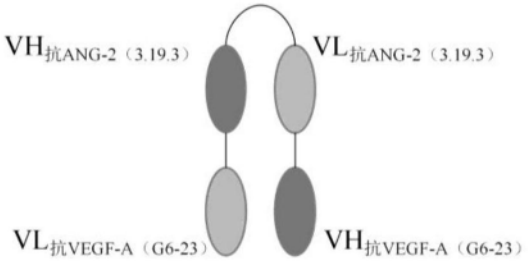


图6



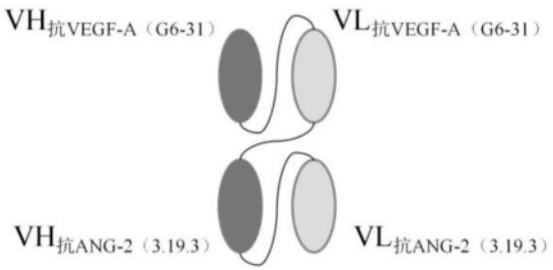
XMVA10

图7



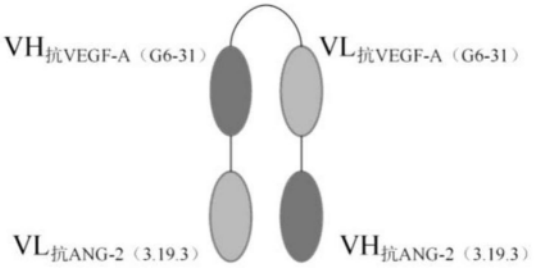
XMVA11

图8



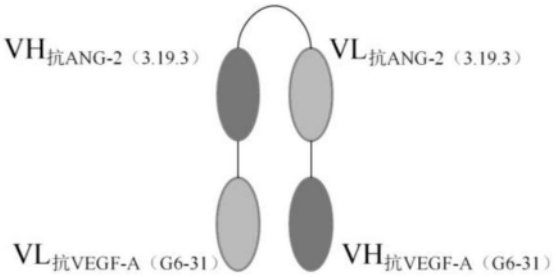
XMVA13

图9



XMVA14

图10



XMVA15

图11